Edited by VANESSA SHAW

CLINICAL Paediatric Dietetics

FIFTH EDITION

BDA The Association of UK Dietitians
Paediatric Specialist Group

WILEY Blackwell

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This edition first published 2020

Edition History
Wiley-Blackwell (4e, 2014)

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data

Names: Shaw, Vanessa, editor.
Title: Clinical paediatric dietetics / edited by Vanessa Shaw.
Description: Fifth edition. | Hoboken, NJ : Wiley-Blackwell, 2020. |
Includes bibliographical references.
Identifiers: LCCN 2020001244 (print) | LCCN 2020001245 (ebook) | ISBN
9781119467298 (cloth) | ISBN 9781119467199 (adobe pdf) | ISBN
9781119467281 (epub)
Subjects: MESH: Diet Therapy | Child
Classification: LCC RJ53.D53 (print) | LCC RJ53.D53 (ebook) | NLM WS 366
| DDC 615.8/54083–dc23
LC record available at https://lccn.loc.gov/2020001244
LC ebook record available at https://lccn.loc.gov/2020001245

Cover Design: Wiley
Cover Images: © David Crunelle/EyeEm/Getty Images, BDA logo courtesy of the British Dietetic Association

Set in 9.5/11.5pt Palatino by SPi Global, Pondicherry, India

Printed and bound by CPI Group (UK) Ltd, Croydon, CR0 4YY

10 9 8 7 6 5 4 3 2 1

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Preface

The continuing aim of this fifth edition of *Clinical Paediatric Dietetics* is to provide a very practical approach to the dietary management of children with a wide range of disorders that benefit from dietary therapy. Interventions range from nutritional support to the diet being the major or sole treatment for particular disorders. The text is relevant for professional dietitians, dietetic students and their tutors, paediatricians, paediatric nurses and members of the community health team caring for children who require therapeutic diets. The importance of nutritional support and dietary management in many paediatric conditions is increasingly recognised and is reflected in new text for this edition.

The authors are drawn from practising paediatric dietitians, with additional contributions from academic research dietitians and a psychiatrist. The need for evidence-based practice demands a thorough review of scientific and medical literature to support clinical practice, wherever possible, and this has been undertaken by the authors. Where the evidence base is lacking, expert clinical opinion is given. While the practice described is largely UK focused, the principles can be applied in other areas.

The major part of the text concentrates on nutritional requirements of sick infants, children and young people in the clinical setting. Normal dietary constituents are used alongside special dietetic products to provide a prescription that will control progression and symptoms of disease while maintaining the growth potential of the individual. Healthy eating throughout infancy, childhood and adolescence is described and underpins many clinical interventions. The trend for children to be discharge from hospital for continuing care at home makes this text a valuable resource for both acute and community-based healthcare professionals.

There has been an expansion of the range of disorders, treatments, guidelines and recommendations described in many chapters, e.g. diabetes technology, the wider use of the ketogenic diet, renal tubular disorders, refeeding syndrome and the use of blended diets in enteral nutrition, new guidelines for parenteral nutrition, irritable bowel syndrome and rare skin disorders – in addition to a thorough review of all the topics in the fourth edition. With much information presented in tabular form and with worked examples and case studies, the manual is easy to use.

The most recent information and data on dietetic products has been used in the preparation of this edition, but no guarantee can be given for validity or availability at the time of going to press.

Of particular note, the new Commission Delegated Regulation (EU) 2016/128 on food for special medical purposes (FSMP) has come into force, with the rules for infant formulas applying from 22 February 2020. Hence, there may be slight changes in some of the dilutions and compositions of formulas shown in the text.

Vanessa Shaw
May 2020

Acknowledgements

I would like to thank a number of dietitians who wrote for the fourth edition of this book whose work contributed to the following chapters:

Provision of Nutrition in the Hospital Setting: Ruth Watling
Preterm Infants: Caroline King and Kate Tavener
The Liver and Pancreas: Jason Beyers
Endocrinology: Alison Johnstone and Jacqueline Lowdon
Kidney Diseases: Julie Royle
Ketogenic Diets: Georgiana Fitzsimmons and Marian Sewell
Immunodeficiency Syndromes: Natalie Yerlett
Feeding Children with Neurodisabilities: Leanne Huxham
Epidermolysis Bullosa: Melanie Sklar and Lesley Haynes
Faltering Growth: Zofia Smith
Inherited Metabolic Disorders: Nicol Clayton, Janine Gallagher, Pat Portnoi, Jacky Stafford

About the Companion Website

The book is accompanied by a website:

www.wiley.com/go/shaw/paediatricdietetics-5e

The website features:

- Figures in PowerPoint format.
- Tables in PDF format.
- References, further reading, guidelines, support groups and other useful links.

1 Principles of Paediatric Dietetics: Nutritional Assessment, Dietary Requirements and Feed Supplementation

Vanessa Shaw and Helen McCarthy

Introduction

This text provides a practical approach to the dietary management of a range of paediatric disorders. The principles outlined in this chapter are relevant to all infants, children and young people and provide the basis for many of the therapies described later in the text. Chapter 2 describes healthy eating throughout childhood and adolescence to support normal growth and development and may inform dietetic interventions; special considerations for children from minority ethnic groups are addressed in Chapter 26. The remaining text focuses on nutritional requirements and management in the clinical setting, illustrating how normal dietary constituents are used alongside special dietetic products to allow for the continued growth of the child while controlling the progression and symptoms of disease.

Assessment of nutritional status

Assessment and monitoring of nutritional status should be included in any dietary regimen, audit procedure or research project where a modified diet has a role. Although the terms are used interchangeably in the literature, nutrition screening is a simple and rapid means of identifying individuals at nutritional risk, which can be undertaken by a range of healthcare professionals, whereas nutrition assessment is a more detailed and lengthy means for nutrition experts, i.e. dietitians, to quantify nutritional status.

Nutrition screening

While nutrition screening tools can be used to identify all aspects of malnutrition (excess, deficiency or imbalance in macro- and micronutrients), they are generally used to identify protein–energy undernutrition [1]. Despite the recommendations from benchmark standards and national and international guidelines that screening for nutrition risk be an integral component of clinical care for all [2–5], the development of nutrition screening tools for use with children has lagged behind work in the adult world. However, internationally, a number of child-specific nutrition screening tools have been developed including the Nutrition Risk Score (Paris tool), the Subjective Global Nutrition Assessment (SGNA), StrongKids and the Paediatric Nutrition Screening Tool (PNST) [6–9]. Each of these has strengths and limitations in terms of validity and reliability of the tool, the time taken to complete and the level of skill required by individuals applying the tool.

Two child-specific tools have been developed in the UK: the Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP) and the Paediatric Yorkhill Malnutrition Score (PYMS) [10, 11]. Both of these tools have been evaluated in practice and comprise a number of elements that are scored to give a final risk score (Table 1.1). The reliability of each of these tools has been published, along with a number of other studies evaluating their use in a variety of clinical settings and conditions [12–14]. The main limitation of these evaluation studies is that they rely on the dietetic assessment of nutritional status as the 'gold standard', and the findings of studies comparing the tools to date have been equivocal. A large multicentre Europe-wide study under the auspices of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has evaluated STAMP, PYMS and StrongKids in 14 centres across 12 countries. The results found only modest agreement between the three tools in identifying children at high malnutrition risk, with PYMS and STAMP classifying more children in this category than StrongKids. The authors concluded that there was still much work needed in this area and that none of the three tools evaluated could be recommended for routine clinical practice [15–17].

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Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 1.1 Child-specific screening tools developed and evaluated in the UK.

	STAMP	PYMS
Criteria utilised	Diagnosis Dietary intake Anthropometrics: weight and height centile	Diagnosis Dietary intake Weight loss Anthropometrics: BMI
Scored	High/medium/low risk	High/medium/low risk
Criterion validity		
Agreement with full nutritional assessment*	54%	46%
Positive predictive value†	55%	47%
Negative predictive value††	95%	95%
Training	30 minutes	60 minutes
Used by	Any trained healthcare professional	Registered nurses

STAMP, Screening Tool for the Assessment of Malnutrition in Paediatrics; PYMS, Paediatric Yorkhill Malnutrition Score; BMI, body mass index.
*Children identified as being at nutritional risk by tool and full nutritional assessment.
†The proportion of children identified as at risk by the tool who are actually at risk.
††The proportion of children identified as not at risk by the tool who are actually not at risk.

Table 1.2 Recommendations for routine measurements for healthy infants and children.

Weight	Length/height	Head circumference
Birth	Birth	Birth or neonatal period
In the first week of life as part of overall assessment of feeding		
8 weeks	6–8 weeks if birthweight <2.5 kg or if other cause for concern	6–8 weeks
12 weeks		
16 weeks		
1 year		
Additional weights if there are concerns: not more frequently than once a month for infants <6 months; once every 2 months from 6 to 12 months; once every 3 months over 1 year	No other routine measurement of length/height	No other routine measurement of head circumference
School entry	School entry	

Source: Adapted from Hall [18] and NICE PH11 [19].

Nutritional assessment

Nutritional assessment comprises anthropometric, clinical and dietary assessment, all of which should be used to provide as full a picture of the nutritional status of the individual as possible; no one method will give an overall picture of nutritional status. Within these areas there are several assessment techniques, some of which should be used routinely in all centres, while others are better suited to specialist clinical areas or research. This chapter provides a brief overview of the common techniques and sources of further information.

Anthropometry

Measurement of weight and height (or length) is critical as the basis for calculating dietary requirements as well as monitoring the effects of dietary intervention. It is important that all measurements are taken using standardised techniques and calibrated equipment. Ideally staff taking measurements should receive some training on how to do this accurately. There are a variety of online resources to support training in anthropometric measurement of children.

Weight

Measurement of weight is an easy and routine procedure that should be done using a calibrated digital scale. Ideally infants should be weighed naked and children wearing just a dry nappy or pants; however, this is often not possible or appropriate. In these situations, it is important to record if the infant is weighed wearing a clean dry nappy and the amount and type of clothing worn by older children. A higher degree of accuracy is required for the assessment of sick children than for routine measurements in the community. Frequent weight monitoring is important for the sick infant or child, and local policies for weighing and measuring hospitalised infants and children should be in place. Recommendations for the routine measurement of healthy infants where there are no concerns about growth are given in Table 1.2 [18]. If there are concerns about weight gain that is too slow or too rapid, measurement of weight should be carried out more frequently.

Height

Height or length measurement requires a stadiometer or length board. Measurement of length using a tape measure is too inaccurate to be of use for longitudinal monitoring of growth, although an approximate length may be useful as a single measure. Under the age of 2 years, supine length is measured; standing height is usually measured over this age or whenever the child can stand straight and unsupported. When the method of measurement changes from length to height, there is likely to be a drop in stature; this is accounted for in the UK-WHO growth charts (p. 3). Measurement of length is difficult and requires careful positioning of the infant; positioning of the child is also important when measuring standing height. It is recommended to have two

observers involved in measuring an infant or young child. It is good practice for sick infants to be measured monthly and older children at clinic appointments or on admission to hospital. Healthy infants should have a length measurement at birth, but further routine stature checks are not recommended until the preschool check [18]. Whenever there are concerns about growth or weight gain, a height measurement should be made more often.

Proxy measurements for length/height

In some cases it is difficult to obtain length or height measurements, e.g. in very sick or preterm infants and in older children with scoliosis. A number of proxy measurements can be used, which are useful to monitor whether longitudinal growth is progressing in an individual, but there are no recognised centile charts as yet, and indices such as body mass index (BMI) cannot be calculated. In younger adults arm span is approximately equivalent to height, but body proportions depend upon age, and while there is some evidence that there is a correlation in older children and adolescents, this measurement may be of limited usefulness in children. Ulna length has been demonstrated to act as a good proxy for stature in adults although evidence in children is limited [20]. Measurements of lower leg length or knee–heel length have been used and are a useful proxy for growth [21]. Total leg length is rarely measured outside specialist growth clinics and is calculated as the difference between measured sitting height and standing height. A number of other measures have been used in children with cerebral palsy as a proxy for height (p. 424), but numbers are too small for reference standards to be established [22]. Formulas for calculating stature in children from proxy measurements are available [23]. It should always be remembered that when using a proxy for length or height measurements, multiple sources of error are present, from the techniques and equipment used to obtain the measurement to calculation errors in estimation of length/height.

Head circumference

Head circumference is generally considered a useful measurement in children under the age of 2 years. After this age head growth slows and is a less useful indicator of somatic growth. A number of genetic and acquired conditions, such as cerebral palsy, will affect head growth, and measurement of head circumference will not be a useful indicator of nutritional status in these conditions. Head circumference is measured using a narrow, flexible, non-stretch tape. Accuracy is dependent on the skill of the observer, and, as such, training and practice in this technique is a requirement.

Supplementary measurements

While the measurement of weight and length or height forms the basis of routine anthropometric assessment, there are a number of supplementary measurements, which can be used. These include the proxy measurements for stature already mentioned and **mid-upper arm circumference** (MUAC). This is a useful measurement in children under the age of 5 years, as MUAC increases fairly rapidly up until this age. Increases in MUAC are less likely to be affected by oedema than body weight; they can also provide a useful method of assessing changes in children with solid tumours and liver disease. There are age-related standards for infants and children [23, 24]. Measurement of waist circumference and the index of waist to height can be helpful in the identification and monitoring of overweight and obesity [25–27]. Research has shown links with dyslipidaemias, insulin resistance and blood pressure, although the evidence for benefit using waist circumference centiles over BMI centiles is limited [27, 28].

When monitoring interventions, particularly those addressing undernutrition, it is important to determine if changes in weight are due to increases in fat mass or lean muscle mass. In order to fully differentiate between lean and fat, measurement of **skinfold thickness** (SFT) can be used. While this can be unpleasant for young children and is not used as a routine anthropometric measurement in general clinical practice, it is used in some specialist areas and can provide valuable data when taken by an experienced and practised observer. The equipment and technique are identical to those used in adults, and the measurement is subject to the same high rates of inter-observer and intra-observer error. Reference data for infants and children are available [24], and arm muscle and arm fat area can be calculated. Full details on skinfold measurements and their interpretation have been published elsewhere [23, 29].

Modern technologies can provide information on body composition. **Bioelectric impedance analysis** is easily undertaken in a clinical setting using foot-to-foot or hand-to-foot techniques. However, while studies have reported validity of this method of determining body composition in healthy populations of young children, validity in sick children and infants has yet to be fully established but may have a role in monitoring change if used on admission to hospital [30–32]. More invasive technologies for assessing body composition include **dual-energy X-ray absorptiometry** and **air displacement plethysmography**. These tend to be restricted to research assessments of body composition, and further information can be found elsewhere [23].

Interpreting anthropometric measurements

Anthropometric measurements alone confer limited information on growth, nutritional status and health and require the use of growth reference data and conversion to indices for interpretation. One of the greatest challenges, however, is the compliance with weighing and measuring infants and children, particularly when hospitalised [33, 34]. Staff training on measurement techniques and the importance of obtaining these should be reinforced regularly within all healthcare settings.

Growth charts

Measurements should be regularly plotted on a relevant growth chart. In the UK the growth charts are the UK-WHO growth chart 0–4 years and the UK growth chart 2–18 years [35]. They are based on WHO 2006 data between the ages of 2 weeks and 4 years (from the WHO multicentre longitudinal study of optimal growth in breastfed singleton births from six countries

across the world [36]) and UK 1990 data for preterm infants, for birthweights and for children over 4 years of age. They show nine centiles from the 0.4th to the 99.6th. Length data are used up to 2 years of age and standing height from age 2 onwards. The centile lines shift down slightly at the 2 years of age juncture to reflect that standing height is less than the measured length. Every child in the UK is issued with a growth centile chart as part of the personal child health record that is held by parents and completed by healthcare professionals whenever the child is weighed or measured.

Accuracy is crucial when plotting growth charts and, therefore, training is essential as a number of different professionals may be plotting on a single chart and errors could result in the misdiagnosis or non-identification of nutritional and growth problems. When assessing a child in relation to the growth charts, a number of factors need to be accounted for, including gestational age at birth and parental height. The growth charts give clear guidance on correction for prematurity and the estimation of the child's adult height.

It can be difficult to assess progress or decide upon targets where a measurement falls outside the nine centile lines (<0.4th centile or >99.6th centile). The Neonatal and Infant Close Monitoring growth chart [35] shows −3, −4 and −5 standard deviation (SD) lines to allow assessment of very small infants up to the age of 2 years. 'Thrive lines' have also been developed to aid interpretation of infants with either slow or rapid weight gain. The 5% thrive lines define the slowest rate of normal weight velocity in healthy infants. If an infant is growing at a rate parallel to or slower than a 5% thrive line, weight gain is abnormally slow. The 95% thrive lines define the most rapid rate of normal weight gain in healthy infants, and weight gain that parallels or is faster than the 95% thrive line is abnormally rapid [36]. There is also a Child and Puberty Close Monitoring Chart 2–20 years, which is a modification of the UK growth chart 2–18 years, designed to monitor unusually short, thin or overweight children. Puberty phase specific thresholds allow assessment of small children with late onset puberty and tall children with early onset puberty [35].

There are a range of resources available to support training on the plotting and interpretation of growth charts on the Royal College of Paediatrics and Child Health (RCPCH) website [35].

Some medical conditions have a significant effect on growth, and where sufficient data exist, separate growth charts have been developed. Charts for Down syndrome were jointly published by the Down Syndrome Medical Interest Group and the RCPCH in 2011 [37]. Charts for a number of other conditions including Williams syndrome, sickle cell and Turner syndrome are available from Harlow Healthcare [38].

Body mass index

A BMI measurement can be calculated from weight and height measurements: BMI = weight (kg)/height (m^2). This provides an indication of relative fatness or thinness. In children the amount and distribution of body fat is dependent on age and sex. BMI is now routinely used to identify and monitor overweight and obesity in children, on an individual and population basis, in the clinical and research environments [39]. There are limitations, however, to the use of BMI in children:

- It is not recommended in children <2 years of age as during this period BMI changes rapidly and weight gain rather than BMI has been shown to be more indicative of future overweight and obesity [40]
- In chronic undernutrition there is stunting as well as low weight for age, and thus undernutrition may be masked by using BMI
- Although BMI is a relative index of weight to height, it does not provide information about body composition; it cannot be used to distinguish between fat mass and lean mass

Paediatric BMI charts have been developed and can be used to indicate how heavy a child is relevant to its height and age [41]. The UK growth charts have a quick reference guide to estimate BMI centile on the basis of the child's weight and height centiles. More detailed BMI charts showing +3, +3.33, +3.66, +4 SD lines above the 99.6th centile and −4, −5 SD below the 0.4th centile are available from Harlow Healthcare [38].

Anthropometric indices and the classification of nutrition status

The World Health Organization (WHO) and research publications frequently report SD score or *z*-score for length/height, weight and BMI. This involves converting the measurement or index into a finite proportion of a reference or standard measurement, the calculation giving a numerical score indicating how far away from the 50th centile for age the child's measurements/index falls. For the UK growth charts, each centile space equates to 0.67 SD; therefore, a child on the 2nd centile will have a *z*-score of −2 SD, and a child on the 98th centile will have a *z*-score of +2 SD; a measurement that falls exactly on the 50th centile will have a *z*-score of 0 SD. Calculation of *z*-scores by hand is extremely laborious, but computer software is available that will enable calculation of *z*-scores from height, weight, BMI, sex and age data [38]. The *z*-score can also be used when comparing groups of children when a comparison of the measurements themselves would not be useful.

The WHO defines moderate malnutrition and obesity in children in terms of *z*-score for weight as −2 SD and +2 SD, respectively [36].

The calculations of height for age, height age and weight for height are useful when assessing nutritional status initially or when monitoring progress in children who are short for their chronological age. Table 1.3 shows examples of calculations for these indices. The Waterlow classification [42] may be of use when assessing children in the UK with severe faltering growth. An adaptation of the classification is shown in Table 1.4. Calculation of height age is necessary when determining nutrient requirements for children who are much smaller (or larger) than their chronological age.

Table 1.3 Height for age, height age and weight for height.

Worked example: 6-year-old girl with cerebral palsy referred with severe feeding problems	
Visit 1	Decimal age = 6.2 years
	Height = 93 cm (<0.4th centile)
	Weight = 10 kg (<0.4th centile)
	50th centile for height for a girl aged 6.2 years = 117 cm
	Height for age = $\frac{93}{117}$ = 79.5% height for age
	Height age is the age at which 93 cm (measured height) falls on 50th centile = 2.7 years
	50th centile for weight for 2.7 years = 14 kg
	Weight for height = $\frac{10}{14}$ = 71% weight for height
Visit 2 (after intervention)	Decimal age = 6.8 years
	Height = 95.5 cm (<0.4th centile)
	Weight = 12 kg (<0.4th centile)
	50th centile for height for a girl aged 6.8 years = 121 cm
	Height for age = $\frac{95.5}{121}$ = 79% height for age
	Height age = 3.1 years
	50th centile for weight for age 3.1 years = 14.5 kg
	Weight for height = $\frac{12}{14.5}$ = 82.7% weight for height

Conclusions: The girl has shown catch-up weight gain. Weight for height has increased from 71% to 83%. She has continued to grow in height, but has not had any catch-up height. Her height continues to be about 79% of that expected for her chronological age.

Table 1.4 Classification of malnutrition.

Acute malnutrition (wasting)	Chronic malnutrition (stunting ± wasting)
Weight for height	Height for age
80%–90% standard – grade 1	90%–95% standard – grade 1
70%–80% standard – grade 2	85%–90% standard – grade 2
<70% standard – grade 3	<80% standard – grade 3

Source: Adapted from Waterlow [42].

Clinical assessment

Clinical assessment of the child involves a medical history and a physical examination. The medical history will identify medical, social or environmental factors that may be risk factors for the development of nutritional problems. Such factors may include parental knowledge and finance available for food purchase, underlying disease, treatments, investigations and medications. Clinical signs of poor nutrition, revealed in the physical examination, only appear at a late stage in the development of a deficiency disease, and the absence of clinical signs should not be taken as indicating that a deficiency is not present.

Table 1.5 Physical signs of nutritional problems.

Assessment	Clinical sign	Possible nutrient(s)
Hair	Thin, sparse Colour change – 'flag sign' Easily plucked	Protein and energy, zinc, copper
Skin	Dry, flaky Rough, 'sandpaper' texture Petechiae, bruising	Essential fatty acids B vitamins Vitamin A Vitamin C
Eyes	Pale conjunctiva Xerosis Keratomalacia	Iron Vitamin A
Lips	Angular stomatitis Cheilosis	B vitamins
Tongue	Colour changes	B vitamins
Teeth	Mottling of enamel	Fluorosis (excess fluoride)
Gums	Spongy, bleed easily	Vitamin C
Face	Thyroid enlargement	Iodine
Nails	Spoon shape, koilonychia	Iron, zinc, copper
Subcutaneous tissue	Oedema Overhydration	Protein, sodium
	Depleted subcutaneous fat	Energy
Muscles	Wasting	Protein, energy, zinc
Bones	Craniotabes Parietal and frontal bossing Epiphyseal enlargement Beading of ribs	Vitamin D

Typical physical signs associated with poor nutrition, which have been described in children in Western countries, are summarised in Table 1.5. Physical signs represent very general changes and may not be due to nutrient deficiencies alone. Other indications such as poor weight gain and/or low dietary intake are needed in order to reinforce suspicions, and biochemical and haematological tests should be carried out to confirm the diagnosis. These include the analysis of levels of nutrients or nutrient-dependent metabolites in body fluids or tissues or measuring functional impairment of a nutrient-dependent metabolic process. The most commonly used tissue for investigation is the blood. Whole blood, plasma, serum or blood cells can be used, depending on the test. Tests may be static, e.g. levels of zinc in plasma, or may be functional, e.g. the measurement of the activity of glutathione peroxidase, a selenium-dependent enzyme, as a measure of selenium status.

Although an objective measurement is obtained from a blood test, there are a number of factors that can affect the validity of such biochemical or haematological investigations:

- Age-specific normal ranges need to be established for the individual centre unless the laboratory participates in a regional or national quality control scheme
- Recent food intake and time of sampling can affect levels, and it may be necessary to take a fasting blood sample for some nutrients
- Physiological processes such as infection, disease or drugs may alter normal levels
- Contamination from exogenous materials such as equipment or endogenous sources such as sweat or interstitial fluid is important for nutrients such as trace elements, and care must be taken to choose the correct sampling procedure

A summary of some biochemical and haematological measurements is given in Table 1.6.

Urine is often used for investigations in adults, but many tests require the collection of a 24 hour urine sample, and this is difficult in babies and children. The usefulness of a single urine sample for nutritional tests is limited and

Table 1.6 Biochemical and haematological tests.

Nutrient	Test	Normal values in children	Comments
Biochemical tests			
Protein	Total plasma protein Albumin	55–80 g/L 30–45 g/L	Low levels reflect long-term not acute depletion
	Caeruloplasmin Retinol-binding protein	0.18–0.46 g/L 2.6–7.6 g/L	Low levels indicate acute protein depletion but are acute phase proteins, which increase during infection
Thiamin	Erythrocyte transketolase activity coefficient	1–1.15	High activity coefficient (>1.15) indicates thiamin deficiency
Vitamin B_{12}	Plasma B_{12} value	263–1336 pmol/L	Low levels indicate deficiency
Riboflavin	Erythrocyte glutathione reductase activity coefficient	1.0–1.3	High activity coefficient (>1.3) indicates riboflavin deficiency
Vitamin C	Plasma ascorbate level	8.8–124 µmol/L	Low levels indicate deficiency
Vitamin A	Plasma retinol level	0.54–1.56 µmol/L	Low level indicates deficiency
Vitamin D	Plasma 25-hydroxy-colecalciferol level	30–110 nmol/L	Low level indicates deficiency
Vitamin E	Plasma tocopherol level	α-Tocopherol 10.9–28.1 µmol/L	Low levels indicate deficiency
Copper	Plasma level	70–140 µmol/L	Low levels indicate deficiency
Selenium	Plasma level	0.76–1.07 µmol/L	Low levels indicate deficiency
	Glutathione peroxidase activity	>1.77 µmol/L	Low levels indicate deficiency
Zinc	Plasma level	10–18 µmol/L	Low levels indicate deficiency
Haematology tests			
Folic acid	Plasma folate	7–48 nmol/L	Low levels indicate deficiency
	Red cell folate	429–1749 nmol/L	Low levels indicate deficiency
Haemoglobin	Whole blood	104–140 g/L	Levels <110 g/L indicate iron deficiency
Red cell distribution width	Whole blood	<16%	High values indicate iron deficiency
Mean corpuscular volume	Whole blood	70–86 fL	Small volume (microcytosis) indicates iron deficiency
			Large volume (macrocytosis) indicates folate or B_{12} deficiency
Mean cell haemoglobin	Whole blood	22.7–29.6 pg	Low values indicate iron deficiency
Percentage hypochromic cells	Whole blood	<2.5%	High values (>2.5%) indicate iron deficiency
Zinc protoporphyrin	Red cell	32–102 µmol/mol haem	High levels indicate iron deficiency
Ferritin	Plasma level	5–70 µg/L	Low levels indicate depletion of iron stores. Ferritin is an acute phase protein and increases during infection

needs to be compared with a standard metabolite, usually creatinine. However, creatinine excretion itself is age-dependent, and this needs to be taken into consideration. Stool samples can be useful in determining reasons for malabsorption if suspected. Hair and nails have been used to assess trace element and heavy metal status in populations, but a number of environmental and physiological factors affect levels, and these tissues are not routinely used in the UK. Tissues that store certain nutrients, such as the liver and bone, also provide useful materials for investigation, but sampling is too invasive for routine clinical use.

A more detailed overview of clinical assessment can be found elsewhere [24].

Dietary intake

For children over the age of 2 years, food intake is assessed in the same way as for adults: using a recall diet history; a quantitative food diary or food record chart at home or on the ward, recorded over a number of days; a weighed food intake over a number of days; or a food frequency questionnaire. These methods are not mutually exclusive, and combinations are often used to provide the greatest depth of information. There are benefits and limitations to each of these methods, and these are summarised in Table 1.7 [24, 43].

Table 1.7 Strengths and limitations of dietary assessment methodologies for individuals.

Method	Strength	Limitation
24 hour recall	Quick and easy Low respondent burden	Relies on memory May not be representative of usual intake
Estimated food diary	Assesses actual usual intake	Respondents must be literate Ability to estimate portion size Longer time frames increase respondent burden
Weighed food diary	Accurate assessment of actual intake	High respondent burden Respondents must be literate and motivated Setting may not be conducive to weighing (e.g. eating out)
Food frequency questionnaire	Quick Low respondent burden Can identify food consumption patterns: high/medium/low	Ability to quantify intakes is poor

Source: Gibson [23].

For most clinical purposes an oral history from the usual caregivers (or from the child if appropriate) will provide sufficient information on which to base recommendations. In addition to assessing the range and quantity of foods eaten, it is also useful to assess whether the texture and presentation of food is appropriate for the age and developmental level of the child. Estimation of food intake is particularly difficult in infants, as it is not possible to assess accurately the amount of food wasted through, for example, spitting or drooling. Similar difficulties occur in children with physical feeding difficulties and dysphagia. Observation of feeding can be particularly useful in these situations. Recorded intake can often be utilised at annual assessments of children with chronic conditions, in the identification of food-related symptoms (allergies and intolerances) or in the assessment of diet-related doses of medications such as pancreatic enzymes or insulin. A range of tools are available to assist with the assessment of dietary intake including pictorial portion size guides, computerised dietary analysis programmes and texture descriptors [44]. The adequacy of dietary intake is assessed in relation to the dietary reference values (DRV).

The assessment of milk intake for breastfed infants is difficult, and only very general estimations can be made. Historically infants have been test weighed before and after a breastfeed to allow the amount of milk consumed to be estimated. This required the use of very accurate scales (±1–2 g) and included all feeds over a 24 hour period as the volume consumed varied throughout the day. Test weighing should be avoided if at all possible as it is disturbing for the infant, engenders anxiety in the mother and is likely to compromise breastfeeding. Studies have shown that the volume of breastmilk consumed is approximately 770 mL at 5 weeks and 870 mL at 11 weeks of age [45]. In general an intake of 850 mL is assumed for infants who are fully breastfed and over the age of 6 weeks. Estimation of nutritional intake in a breastfed infant is further complicated by the varying composition of breastmilk [46].

Expected growth in childhood

The 50th centile birthweight for infants in the UK is 3.5 kg for boys and 3.3 kg for girls [47]. Most babies lose weight after birth while full feeding is gradually established during the first week of life (p. 19). They begin to gain weight between 3 and 5 days of age, with the majority regaining their birthweight by the 10th–14th day of life. The National Institute for Health and Care Excellence (NICE) recommends that babies are weighed at birth and in the first week of life as part of the overall assessment of their feeding. Thereafter, babies should be weighed at 8, 12 and 16 weeks and again at 1 year of age [19].

The average weight gain during the first year of life, using the 50th centile for age of the UK-WHO growth charts [35], is shown in Table 1.8. The increase in length during the first year of life is 24–25 cm. It is important to remember that the first 12 weeks of life see the most rapid postnatal growth. If length and weight measurements are static for just 2 weeks

Table 1.8 Average weight gain throughout the first year of life.

	Boys (g/week)	Girls (g/week)
First 3 months	240	210
Second 3 months	130	120
Third 3 months	80	75
Fourth 3 months	65	60

during this period, there will be a fall of one centile; if static for 4 weeks, there will be a fall of two centiles. Growth rate slows as the baby gets older.

During the second year, the toddler following the 50th centile gains 2.5–2.6 kg in weight and a further 11–12 cm in length. Average weight gain continues at a rate of approximately 2–3 kg/year. Height gain in the second year is 10 cm, steadily declining to 7 cm down to 5 cm/year until the growth spurt at puberty. Puberty in boys usually starts between the ages of 9 and 14 years. Onset of puberty before 9 years of age is considered precocious, while puberty is delayed if there are no signs by 14 years. For girls, puberty usually begins between 8 and 13 years, with the onset of puberty before 8 years considered to be precocious and puberty not present by 13 years considered to be delayed.

Dietary reference values

The 1991 Department of Health report on DRV [48] provides information and figures for requirements for a comprehensive range of nutrients and energy. The Scientific Advisory Committee on Nutrition (SACN) revised the requirements for energy in 2011 [49]. The requirements are termed dietary reference values and are for normal healthy populations of infants fed with artificial formulas and for older infants, children and adults consuming food. The 1991 DRV were not set for breastfed babies as it was considered that human milk provides the necessary amounts of nutrients when fed on demand. In some cases the DRV for infants aged up to 3 months who are formula fed are in excess of those that would be expected to derive from breastmilk; this is because of the different bioavailability of some nutrients from breastmilk and artificial formulas.

It is important to remember that these are recommendations for groups, not for individuals; however, they can be used as a basis for estimating suitable intakes for the individual, using the reference nutrient intake (RNI) for protein and other nutrients. This level of intake should satisfy the requirements of 97.5% of healthy individuals in a population group. A summary of the 1991 DRV for energy, protein, sodium, potassium, vitamin C, calcium and iron is given in Table 1.9. The DRV for other nutrients may be found in the full report. There has been a further revision for vitamin D requirements [50].

The DRV for energy is expressed as the estimated average requirement (EAR); about half of a population will need more energy than the EAR and half less. Energy requirements were revised in the SACN 2011 report [49] in the light of advancements in the methodology to measure total energy expenditure. This report gives a detailed account of the evidence that SACN used when updating the EAR for energy for infants, children, adolescents and adults in the UK. This has coincided with other revisions of energy requirements by the Food and Agriculture Organization of the United Nations, World Health Organization and United Nations University (FAO/WHO/UNU) and the Institute of Medicine (IoM) in the USA.

The revised EAR for energy has decreased for infants and children under 10 years of age and slightly increased for older children and adults. The revised EAR for energy for infants and children is shown in Tables 1.10 and 1.11.

It must be emphasised that these values are for assessing the energy requirements of large groups of people and are not requirements for healthy or sick individuals. Also, when estimating requirements for the individual sick child, it is important to calculate energy and nutrient intakes based on actual body weight and not expected body weight. The latter will lead to a proposed intake that is inappropriately high for the child who has an abnormally low body weight. In some instances it may be more appropriate to consider the child's height age rather than chronological age when comparing intakes with the DRV as this is a more realistic measure of the child's body size and, hence, nutrient requirement.

In order to make the revised EAR for energy more usable in clinical practice, it is suggested that the data given in Tables 1.10 and 1.11 are condensed and summarised (Table 1.12).

The estimated requirements for children with specific disorders are given in the relevant chapters. It is important to remember that requirements are not necessarily increased during illness. Factors to consider when estimating requirements for the individual are as follows: nutritional status prior to onset of the disease; whether the disorder is acute or chronic; is mobility affected; are there any impacts on normal feeding such as dysphagia or reduced appetite; are there increased gastrointestinal losses such as vomiting and diarrhoea; consider any urinary losses; is there an inability to metabolise dietary constituents.

A guide to increased oral and enteral (feeding by tube into the gut) requirements is given in Table 1.13.

Fluid requirements

Preterm and low birthweight infants

Chapter 7 gives a full account of the special requirements of these babies.

The newborn infant over 2.5 kg birthweight

Breastfeeding is the most appropriate method of feeding the normal infant [51] and may be suitable for sick infants with a variety of clinical conditions. Demand breastfeeding will

Table 1.9 Selected dietary reference values, 1991.

						RNI per day								
	Weight*	Energy (EAR) per day				Protein		Sodium		Potassium		Vitamin C	Calcium	Iron
Age	kg	MJ	kJ/kg	kcal	kcal/kg	g	g/kg	mmol	mmol/kg	mmol	mmol/kg	mg	mmol	mg
Males														
0–3 months	5.9	2.28	480–420	545	115–100	12.5	2.1	9	1.5	20	3.4	25	13.1	1.7
4–6	7.7	2.89	400	690	95	12.7	1.6	12	1.6	22	2.8	25	13.1	4.3
7–9	8.9	3.44	400	825	95	13.7	1.5	14	1.6	18	2.0	25	13.1	7.8
10–12	9.8	3.85	400	920	95	14.9	1.5	15	1.5	18	1.8	25	13.1	7.8
1–3 years	12.6	5.15	400	1230	95	14.5	1.1	22	1.7	20	1.6	30	8.8	6.9
4–6	17.8	7.16	380	1715	90	19.7	1.1	30	1.7	28	1.6	30	11.3	6.1
7–10	28.3	8.24	–	1970	–	28.3	–	50	–	50	–	30	13.8	8.7
11–14	43.1	9.27	–	2220	–	42.1	–	70	–	80	–	35	25.0	11.3
15–18	64.5	11.51	–	2755	–	55.2	–	70	–	90	–	40	25.0	11.3
Females														
0–3 months	5.9	2.16	480–420	515	115–100	12.5	2.1	9	1.5	20	3.4	25	13.1	1.7
4–6	7.7	2.69	400	645	95	12.7	1.6	12	1.6	22	2.8	25	13.1	4.3
7–9	8.9	3.20	400	765	95	13.7	1.5	14	1.6	18	2.0	25	13.1	7.8
10–12	9.8	3.61	400	865	95	14.9	1.5	15	1.5	18	1.8	25	13.1	7.8
1–3 years	12.6	4.86	400	1165	95	14.5	1.1	22	1.7	20	1.6	30	8.8	6.9
4–6	17.8	6.46	380	1545	90	19.7	1.1	30	1.7	28	1.6	30	11.3	6.1
7–10	28.3	7.28	–	1740	–	28.3	–	50	–	50	–	30	13.8	8.7
11–14	43.8	7.92	–	1845	–	42.1	–	70	–	80	–	35	20.0	14.8
15–18	55.5	8.83	–	2110	–	45.4	–	70	–	90	–	40	20.0	14.8

EAR, estimated average requirement; RNI, reference nutrient intake.
*Standard weights for age ranges [48].
Source: Department of Health [48]. Reprinted with permission of The Stationery Office.

Table 1.10 Estimated average requirement (EAR) for energy for infants, 2011.

	Breastfed		Breastmilk substitute fed		Mixed feeding or unknown	
Age (months)	kcal (MJ) per kg/day	kcal (MJ) per day	kcal (MJ) per kg/day	kcal (MJ) per day	kcal (MJ) per kg/day	kcal (MJ) per day
Boys						
1–2	96 (0.4)	526 (2.2)	120 (0.5)	598 (2.5)	120 (0.5)	574 (2.4)
3–4	96 (0.4)	574 (2.4)	96 (0.4)	622 (2.6)	96 (0.4)	598 (2.5)
5–6	72 (0.3)	598 (2.5)	96 (0.4)	646 (2.7)	72 (0.3)	622 (2.6)
7–12	72 (0.3)	694 (2.9)	72 (0.3)	742 (3.1)	72 (0.3)	718 (3.0)
Girls						
1–2	96 (0.4)	478	120 (0.5)	550 (2.3)	120 (0.5)	502 (2.1)
3–4	96 (0.4)	526	96 (0.4)	598 (2.5)	96 (0.40)	550 (2.3)
5–6	72 (0.3)	550	96 (0.4)	622 (2.6)	72 (0.3)	574 (2.4)
7–12	72 (0.3)	646	72 (0.3)	670 (2.8)	72 (0.3)	646 (2.7)

Source: Scientific Advisory Committee on Nutrition [49].

Table 1.11 Estimated average requirement (EAR) for energy for children, 2011.

	EAR (kcal (MJ) per day)*	
Age (years)	Boys	Girls
1	765 (3.2)	717 (3.0)
2	1004 (4.2)	932 (3.9)
3	1171 (4.9)	1076 (4.5)
4	1386 (5.8)	1291 (5.4)
5	1482 (6.2)	1362 (5.7)
6	1577 (6.6)	1482 (6.2)
7	1649 (6.9)	1530 (6.4)
8	1745 (7.3)	1625 (6.8)
9	1840 (7.7)	1721 (7.2)
10	2032 (8.5)	1936 (8.1)
11	2127 (8.9)	2023 (8.5)
12	2247 (9.4)	2103 (8.8)
13	2414 (10.1)	2223 (9.3)
14	2629 (11.0)	2342 (9.8)
15	2820 (11.8)	2390 (10.0)
16	2964 (12.4)	2414 (10.1)
17	3083 (12.9)	2462 (10.3)
18	3155 (13.2)	2462 (10.3)

*Calculated with the median physical activity ratio.
Source: Scientific Advisory Committee on Nutrition [49].

automatically ensure that the healthy infant gets the right volume of milk and, hence, nutrients. The suck–swallow–breathe sequence that allows the newborn infant to feed orally is usually well developed by 35–37 weeks of gestation. If the infant is too ill or too immature to suckle, the mother may express her breastmilk; expressed breastmilk (EBM) may be modified to suit the sick infant's requirements. If EBM is unavailable or inappropriate to feed in certain circumstances (p. 20), infant milk formulas must be used, preferably whey-based. Common brands of infant formulas available in the UK are given in Table 1.14.

A systematic review of the volumes of breastmilk and infant formula taken in early infancy [52] has revealed that formula-fed infants have a higher intake than breastfed babies (Table 1.15). While there was variation in the amount of breastmilk taken in the first few days of life, on average demand breastfed babies took only 21.5 ± 4.2 mL on day 1, whereas formula-fed babies took 170 ± 55.8 mL on day 1. By day 14, the bottle-fed babies were still taking a greater volume: 761.8 ± 18 mL vs. 673.6 ± 29 mL in the breastfed babies. Not only did the bottle-fed babies take a larger volume, but they also had a more energy-dense milk: 67 kcal/100 mL vs. 53.6 ± 2.5 kcal/100 mL for colostrum (days 1–5) and 57.7 ± 4.2 kcal/100 mL for transitional milk (days 6–14).

Most babies will need 150–200 mL/kg/day of infant formula by the end of the first week until they are 6 months old, although this will vary for the individual baby [53]. Bottle-fed babies should be allowed to feed on demand and not be encouraged to 'finish the bottle'. A suggested way to feed these babies is to offer on the first day approximately one seventh of requirements, say, 20–30 mL/kg, divided into eight feeds and fed every 2–3 hours. The volume offered should be gradually increased over the following days to appetite so that newborn babies gradually increase their intake from about 20–30 mL/kg on the first day of life to around 150–200 mL/kg by 7–14 days. Of course, more should be offered if the baby is hungry and demands more. Breastfed infants will regulate their own intake of milk.

Fluid requirements after the first few weeks

Healthy formula-fed infants should be allowed to feed on demand, although parents often wish to get them into a 'routine'. Many infants will take their feeds 4 hourly, five to six bottles per day at around 4–6 weeks of age, although many will continue to demand feeds more frequently. The infant may start to sleep longer through the night and drop a feed. A fluid intake of around 150 mL/kg should be maintained to provide adequate fluids, energy and nutrients. Infants should not normally be given more than 1200 mL of feed per 24 hours as this may induce vomiting and, in the long term, will lead to an inappropriately high energy intake. Sick infants may need smaller, more frequent feeds than the healthy baby and, according to their clinical condition, may have increased or decreased fluid requirements. Breastfed infants will continue to regulate their own intake of milk and feeding pattern.

After the age of 6 months, a follow-on milk may be used (Table 1.14). These milks are higher in protein, iron and some other minerals and vitamins than formulas designed to be given from birth and may be useful for infants with a poor intake of solids or who are fluid restricted. There is no need to change the feed from an infant formula to a follow-on milk if a baby is feeding well and growing normally.

'Growing up' milks (or young child formulas) are also on the market. Designed for children aged 1–3 years, they are not recommended for routine use, but they may increase the intake of iron, vitamin D and *n*-3 polyunsaturated acids that may be in poor supply in the toddler diet [54].

Fluid requirements in older infants and children

Once solids are introduced around the age of 6 months, the infant's appetite for milk will lessen. Breastmilk and infant formulas fed at 150 mL/kg provide 130 mL water/kg. The fluid requirements for older infants aged 7–12 months decrease to 120 mL/kg, assuming that some water is obtained from solid foods (Table 1.16). At 1 year, the healthy child's thirst will largely determine how much fluid is

Table 1.12 Guide to energy requirements in clinical practice.

	Boys			Girls		
Age	Energy (EAR) (kcal/day)	Weight†	Energy (EAR)* (kcal/kg/day)	Energy (EAR) (kcal/day)	Weight†	Energy (EAR)* (kcal/kg/day)
1–2 months		5.0	96–120		4.7	96–120
3–4		6.7	96		6.1	96
5–6		7.7	72–96		7.0	72–96
7–12		9.0	72		8.3	72
1 years	770	9.6	80	720	9.0	80
2	1000	12.2	82	930	11.5	81
3	1170	14.4	82	1080	13.9	78
4	1390	16.3	85	1290	16.0	81
5	1480	18.6	80	1360	18.2	75
6	1560	21.0	74	1480	21.0	70
7	1650	23.0	71	1530	23.0	67
8	1750	26.0	67	1630	26.0	63
9	1840	29.0	63	1720	29.0	59
10	2030	31.5	64	1940	32.0	61
11	2130	34.5	62	2020	35.9	56
12	2250	38.0	59	2100	40.0	53
13	2410	43.0	56	2220	46.0	48
14	2630	49.0	54	2340	51.0	46
15	2820	55.5	51	2390	53.0	45
16	2970	60.2	49	2410	55.3	44
17	3080	64.0	48	2460	57.0	43
18	3160	66.2	48	2460	57.2	43

1 kcal = 4.18 kJ.
* Depending on method of feeding for infants (Table 1.10).
† Median weight from the UK-WHO growth chart 0–4 years and the UK growth chart 2–18 years [35].

Table 1.13 Guide to increased oral and enteral requirements.

	Infants 0–1 year*	Children
Energy	High: 130–150 kcal (545–630 kJ)/kg/day Very high: 150–180 kcal (630–750 kJ)/kg/day	High: 120% EAR† Very high: 150% EAR
Protein	High: 3–4.5 g/kg/day Very high: maximum of 6 g/kg/day	High: 2 g/kg/day* It should be recognised that children may easily eat more than this amount
Sodium	High: 3.0 mmol/kg/day Very high: 4.5 mmol/kg/day A concentration >7.7 mmol Na^+/100 mL of infant formula will have an emetic effect	
Potassium	High: 3.0 mmol/kg/day Very high: 4.5 mmol/kg/day	

* Based on actual weight, not expected weight.
† May be better to base on height age rather than chronological age in very small children.

Table 1.14 Infant milk formulas and follow-on milks.

Whey-based infant formula	Casein-based infant formula	Follow-on milks*
Aptamil 1 First Infant Milk† (Danone)	Aptamil Hungry	Aptamil 2†
Cow & Gate 1 First Infant Milk (Cow & Gate)	Cow & Gate Hungrier Baby	Cow & Gate 2
HiPP Combiotic First Infant Milk (HiPP UK)	HiPP Combiotic Hungry Infant	HiPP Combiotic 2
Holle 1 (Holle)		Holle 2
Kendamil 1 (Kendal Nutricare)		Kendamil 2
SMA PRO 1 First Infant Milk** (SMA Nutrition)	SMA Extra Hungry	SMA PRO 2**

*Suitable from 6 months.
†Also available in Aptamil Profutura range containing long chain polyunsaturated acids and oligosaccharides.
**Also available in SMA Advanced range containing oligosaccharides.

Table 1.15 Volume of milk taken in the first 2 weeks of life.

Day of life	Breastmilk (mL)	Infant formula (mL)
1	21.5 ± 4.2	170.5 ± 55.8
2	100.3 ± 21.8	265.0 ± 67.7
7	495.3 ± 33.4	576 ± 29
14	673.6 ± 29	761.8 ± 18

Source: Hester et al. [52]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3463945/. Licensed under CC BY.

Table 1.16 Water content of foods.

Food	Percentage water content
Fruits and vegetables	80–85
Yoghurt and milk puddings	70–80
Rice and pasta	65–80
Fish	70–80
Eggs	65–80
Meat	45–65
Cheese	40–50
Bread	30–45

Source: Adapted from Grandjean and Campbell [55].

taken. There are some published fluid requirements for healthy populations (Table 1.17). These are all based on observations of water intakes and urine osmolality, not hydration status.

If all a child's nutrition comes from feed and there is no significant contribution to fluid intake from foods, then fluid requirements may be estimated using an adaptation of the Holliday–Segar formula [58]. This formula was originally

Table 1.17 Daily water requirements for infants and children.

Age	EFSA 2010* [56] Dietary reference values	IoM 2005† [57] Dietary reference intakes
0–6 months	100–190 mL/kg	700 mL
6–12	800–1000 mL	800 mL
12–24	1100–1200 mL	
1–3 years		1300 mL (900 mL from drinks)
2–3	1300 mL	
4–8	1600 mL	1700 mL (1200 mL from drinks)
9–13 (boys)	2100 mL	2400 mL (1800 mL from drinks)
9–13 (girls)	1900 mL	2100 mL (1600 mL from drinks)
14–18 (boys)	2500 mL (adult)	3300 mL
14–18 (girls)	2000 mL (adult)	2300 mL

*Includes water from beverages and food.
†Includes water from beverages, food and drinking water.

designed to calculate fluid requirements for parenteral nutrition and is based on the child's weight, using an average requirement of 100 mL water for each 100 kcal (420 kJ) of energy metabolised. If less energy is required, then less water will be needed. If nutritional requirements are met from a smaller volume of feed, then any extra fluid needed (e.g. if the child is losing more than usual fluid through breathing, sweating, vomiting, diarrhoea and passing dilute urine) may simply be given as water.

Body weight	***Estimated fluid requirement***
11–20 kg	100 mL/kg for the first 10 kg + 50 mL/kg for the next 10 kg
>20 kg	100 mL/kg for the first 10 kg + 50 mL/kg for the next 10 kg + 25 mL/kg thereafter
Worked example for a child weighing 22 kg	
100 mL/kg for the first 10 kg	=1000 mL
+50 mL/kg for the next 10 kg	=500 mL
+25 mL/kg for the final 2 kg	=50 mL
Total	=1550 mL = 70 mL/kg

Overweight children will need less fluid than the calculated volume as their actual body weight is higher than normal. It would be reasonable to estimate their weight for these calculations as the value on the centile that matches their height centile, e.g.

- 7-year-old boy with a weight of 35 kg = 99.6th centile: fluid requirement using above formula = (1000 + 500 + 375) = 1875 mL

- He is 122 cm tall = 50th centile
- Base fluid requirement initially on a body weight of 23 kg = 50th centile: fluid requirement using above formula = (1000 + 500 + 75) = 1575 mL
- Monitor fluid status and adjust accordingly. More water may be required, but not necessarily more feed

For underweight children it is important to calculate their fluid requirement based on their actual weight, not their expected weight for age or height, but as this is lower than normal, they will need increased energy and protein density in their feed to achieve catch-up growth.

Supplementing feeds for infants with faltering growth or who are fluid restricted

Supplements may be used to fortify standard infant formulas and special therapeutic formulas to achieve the necessary increase in energy, protein and other nutrients required by some infants. EBM can also be fortified using a standard infant formula powder in term babies (Table 1.18) or a breastmilk fortifier in preterm infants (p. 104). Care needs to be taken not to present an osmotic load of more than 500 mOsm/kg H_2O to the normal functioning gut; otherwise an osmotic diarrhoea will result. If the infant has malabsorption, an upper limit of 400 mOsm/kg H_2O may be necessary. Infants who are fluid restricted will need to meet their nutritional requirements in a lower volume of feed than usual, and the following feed manipulations can be used for these babies.

Concentrating infant formulas

Normally infant formula powders, whether whey- and casein-based milk formulas or special therapeutic formulas, should be diluted according to the manufacturers' instructions as this provides the correct balance of energy, protein and nutrients when fed at the appropriate volume. However, there are occasions when, to achieve a feed that is more dense in energy, protein and other nutrients, it is necessary to concentrate the formula. Most normal infant milk formulas in the UK are made up at a dilution of around 13% (13 g powder per 100 mL water). By making up the infant formula at a dilution of 15% (15 g powder per 100 mL water), more nutrition can be given in a given volume of feed, e.g. energy content may be increased from 67 kcal (280 kJ) per 100 mL to 77 kcal (325 kJ) per 100 mL and protein content from 1.3 g/100 mL to 1.5 g/100 mL. Infant formulas may be concentrated further if tolerated. Similarly, special therapeutic formulas that are usually made up at a dilution of, say, 15% may be concentrated to 17% (17 g powder per 100 mL water) or further if tolerated. This concentrating of feeds should only be performed as a therapeutic procedure and is not usual practice. The consequence of concentrating feeds is to increase the osmolality. Steele *et al*. have shown a linear relationship between feed concentration and osmolality so that the osmolality of a concentrated feed can be reliably calculated from the manufacturer's data for normal dilution, rather than necessitating the feed to be measured by osmometry in the laboratory [60]. Table 1.18 shows an example of an infant formula concentrated to 15% and 17%.

Table 1.18 Examples of energy- and nutrient-dense formulas for infants (per 100 mL).

	Energy (kcal)	kJ	Protein (g)	CHO (g)	Fat (g)	Na (mmol)	K (mmol)	Osmolality (mOsm/kg H_2O)	PE ratio
13.1% SMA PRO 1 (*normal concentration*)	67	280	1.3	7.1	3.6	1.0	1.6	296	7.8
15% SMA PRO 1	77	320	1.5	8.1	4.1	1.1	1.8	339*	7.8
17% SMA PRO 1	87	365	1.7	9.2	4.7	1.3	2.1	384*	7.8
EBM† + 3% Cow & Gate 1	84	350	1.6	8.8	4.8	0.9	1.9	–	7.6
17% Cow & Gate 1 + Maxijul to 12% CHO + Calogen to 5% fat	100	420	1.6	12.0	5.0	0.9	2.3	–	6.4
Ready-to-feed formulas									
SMA High Energy (SMA Nutrition)	99	415	2.6	10.0	5.4	1.2	2.6	377	10.5
Similac High Energy (Abbott)	100	420	2.6	10.1	5.4	1.1	2.3	333	10.4
Infatrini (Nutricia)	101	420	2.6	10.3	5.4	1.6	2.4	360	10.3

PE, protein–energy ratio; EBM, expressed breastmilk.
The Scientific Advisory Committee on Nutrition used an energy density for breastmilk of 0.67 kcal/g (2.8 kJ/g) rather than 0.69 kcal/g (2.9 kJ/g) in the revised *Dietary Reference Values for Energy*, 2011 [49].
*Calculated value.
†Holland *et al*. [59].

The protein–energy (PE) ratio of the feed should ideally be kept within the range 7.2%–12% for infants (i.e. 7.2%–12% energy from protein). For accelerated weight gain or catch-up growth [61]:

- Weight gain of 10 g/kg/day requires 126 kcal (530 kJ)/kg/day, 2.8 g protein/kg/day, 8.9% PE
- Weight gain of 20 g/kg/day requires 167 kcal (700 kJ)/kg/day, 4.8 g protein/kg/day, 11.5% PE
- Optimal PE for catch-up height is not determined, but is likely to be 11%–12%

In some clinical situations it is not possible to preserve this protein–energy ratio as carbohydrate and fat sources alone may be added to a feed to control deranged blood biochemistry, for example. In these situations it is important to ensure that the infant is receiving at least the RNI for protein.

If infants are to be discharged home on a concentrated feed, the recipe may be translated into scoop measures for ease of use. This will mean that more scoops of milk powder will be added to a given volume of water than recommended by the manufacturer. As this is contrary to normal practice, the reasons for this deviation should be carefully explained to the parents and communicated to primary healthcare staff.

Nutrient-dense ready-to-feed formulas

Nutrient-dense ready-to-feed formulas are available for hospital use and in the community (Table 1.18). They are nutritionally complete formulas containing more energy, protein and nutrients per 100 mL than standard infant formulas. They are suitable for use from birth and are designed for infants who have increased nutritional requirements or who are fluid restricted. They obviate the need for carers to make up normal infant milk formulas at concentrations other than the usual one scoop of powder to 30 mL water.

Energy and protein modules

There may be therapeutic circumstances when energy and/or protein supplements need to be added to normal infant milk formulas or special therapeutic formulas rather than increasing the concentration of the base feed. Sometimes a ready-to-feed formula does not meet the needs of the individual child, and energy and protein modules may need to be added. Energy and protein modules and their use are described below.

Carbohydrate

Carbohydrate provides 4 kcal/g (16 kJ/g). It is preferable to add carbohydrate to a feed in the form of glucose polymer, rather than using monosaccharides or disaccharides, because it exerts a lesser osmotic effect on the gut. Hence, a larger amount can be used per given volume of feed. Glucose polymers (Table 1.19) should be added in 1% increments each 24 hours, i.e. 1 g/100 mL feed per 24 hours. This will allow the concentration at which the infant becomes intolerant (i.e. has loose stools) of the extra carbohydrate to be identified. Tolerance depends on

Table 1.19 Energy modules.

Per 100 g	Ingredients*	Energy (kcal)*	kJ	Na (mmol)	K (mmol)	PO_4 (mmol)
Glucose polymer powders						
Caloreen (Nestle)	Maltodextrin	385	1610	<1.8	<0.3	0
Maxijul Super Soluble (SHS)	Dried glucose syrup	380	1590	<0.9	0.12	0.16
Polycal** (Nutricia)	Maltodextrin	384	1605	0.1	Trace	0
Vitajoule (Vitaflo)	Dried glucose syrup	380	1590	<0.9	0	0
Fat emulsions						% fat as MCT
Calogen† (Nutricia)	Canola oil, sunflower oil	450	1880	0.3	0.12	0
Liquigen (Nutricia)	Palm kernel and/or coconut oil	450	1880	2.2	<0.01	96
Combined fat and carbohydrate powdered module						
Duocal Super Soluble (Nutricia)	Hydrolysed cornstarch, corn oil, coconut oil, palm kernel oil	492	2055	<0.9	<0.1	35

MCT, medium chain triglycerides.
*As quoted by manufacturers.
**Not suitable for children <1 year.
†Unflavoured.

the age of the infant and the maturity and absorptive capacity of the gut. The addition of 2% (2 g/100 mL) glucose polymer (Super Soluble Maxijul) to infant formulas has been shown to increase the feed osmolality by 31.2 mOsm/kg H_2O [58].

As a guideline the following percentage concentrations of carbohydrate (g total carbohydrate per 100 mL feed) may be tolerated if glucose polymer is introduced slowly:

- 10%–12% carbohydrate concentration in infants under 6 months (i.e. 7 g from formula, 3–5 g added)
- 12%–15% in infants aged 6 months to 1 year
- 15%–20% in toddlers aged 1–2 years
- 20%–30% in older children

If glucose or fructose needs to be added to a feed where there is an intolerance of glucose polymer, an upper limit of tolerance may be reached at a total carbohydrate concentration of 7%–8% in infants and young children, so much less energy will be provided from the feed.

Fat

Fat provides 9 kcal/g (37 kJ/g). Long chain fat emulsions are favoured over medium chain fat emulsions because they have a lower osmotic effect on the gut and provide a source of essential fatty acids. Medium chain fats are used where there is malabsorption of long chain fat (Table 1.19).

Fat emulsions should be added to feeds in 1% increments each 24 hours, providing an increase of 0.5 g fat per 100 mL per 24 hours. Infants will tolerate a total fat concentration of 5%–6% (i.e. 5–6 g fat per 100 mL feed) if the gut is functioning normally. The addition of 2% long chain fat emulsion (Calogen) to infant formulas has been shown to increase the feed osmolality by only 0.7 mOsm/kg H_2O [58]. Children over 1 year of age will tolerate more fat, although concentrations above 7% may induce a feeling of nausea and cause vomiting. Medium chain fat will not be tolerated at such high concentrations and may be the cause of abdominal cramps and osmotic diarrhoea if they are not introduced slowly to the feed.

There is a combined carbohydrate and fat module using both long and medium chain fats (Table 1.19). Again this must be introduced to feeds in 1% increments to determine the child's tolerance of the product. The addition of 2% of a combined fat and glucose polymer powder (Duocal Super Soluble) to infant formulas increases the feed osmolality by 23.0 mOsm/kg H_2O [58].

A schedule for the addition of energy modules to infant formulas is given in Table 1.20.

Protein

Protein may be added to feeds in the form of whole protein, peptides or amino acids (Table 1.21). Protein supplementation is rarely required without an accompanying increase in energy consumption.

Table 1.20 Schedule for the addition of energy modules to infant formulas.

Day	Energy source added	Additional CHO/fat per 100 mL feed	Energy added per 100 mL (kcal)	(kJ)
1	1% glucose polymer	1 g CHO	4	17
2	2% glucose polymer	2 g CHO	8	33
3	3% glucose polymer	3 g CHO	12	50
4	3% glucose polymer +1% fat emulsion	3 g CHO 0.5 g fat	17	69
5	3% glucose polymer +2% fat emulsion	3 g CHO 1 g fat	21	88
6	4% glucose polymer +2% fat emulsion	4 g CHO 1 g fat	25	105
7	5% glucose polymer +2% fat emulsion	5 g CHO 1 g fat	29	121
8	5% glucose polymer +3% fat emulsion	5 g CHO 1 5 g fat	34	140

CHO, carbohydrate.

Table 1.21 Protein modules (powders).

Per 100 g	Type of protein	Energy (kcal)	kJ	Protein (g)	CHO (g)	Fat (g)	Na (mmol)	K (mmol)	Ca (mmol)	PO_4 (mmol)
Protifar (Nutricia)	Whole milk protein	368	1540	87.2	1.2	1.6	4.8	3.6	33.8	22.6
Hydrolysed Whey Protein/ Maltodextrin (Nutricia)		348	1455	49.8	37.2	0	19.8	16.2	9.0	3.5
Complete amino acid mix (Nutricia)		328	1370	82	0	0	0	0	0	0

Table 1.22 Vitamin supplements.

		Healthy Start Children's Vitamin Drops (NHS)	Abidec Multivitamin Drops* (Omega Pharma Ltd)	DaliVit Drops (Boston Healthcare Ltd)	Ketovite (Essential Pharmaceuticals Ltd)
		5 drops for all infants from 4 weeks to 4 years†	0.3 mL <1 year 0.6 mL >1 year**	0.3 mL <1 year 0.6 mL >1 year**	5 mL liquid + 3 tablets
Thiamin (B_1)	mg	–	0.4	1	3.0
Riboflavin (B_2)	mg	–	0.8	0.4	3.0
Pyridoxine (B_6)	mg	–	0.8	0.5	1.0
Nicotinamide	mg	–	8	5	9.9
Pantothenate	mg	–	–	–	3.5
Ascorbic acid (C)	mg	20	40	50	50
Alpha-tocopherol (E)	mg	–	–	–	15
Inositol	mg	–	–	–	150
Biotin	µg	–	–	–	510
Folic acid	µg	–	–	–	750
Acetomenaphthone (K)	µg	–	–	–	1500
Vitamin A	µg	200	400	1500	750
Vitamin D	µg	7.5 (D3)	10 (D2)	10 (D2)	10 (D2)
Choline chloride	mg	–	–	–	150
Cyanocobalamin (B_{12})	µg	–	–	–	12.5

†Children who are having 500 mL or more of formula a day do not need Healthy Start vitamins.
*Contains peanut oil.
**Values relate to 0.6 mL dose.

Protein modules are added to feeds to provide a specific amount of protein per kilogram actual body weight of the child. It is rarely necessary to give intakes >6 g protein/kg; if intakes do approach this value, blood urea levels should be monitored twice weekly to avoid the danger of uraemia developing. Modules should be added in small increments as they can very quickly and inappropriately increase the child's intake of protein. The osmotic effect of whole protein products will be less than that of peptides and peptides less than the effect of amino acids.

Vitamins and minerals

Vitamin and mineral requirements for populations of normal children are provided by the DRV [48]. Where no RNI is set, safe levels are given. The RNI for the main vitamins and minerals are shown in Table 1.9. As a quick assessment of nutritional adequacy in the well child, when there is sufficient energy, protein, calcium, iron and vitamin C in the diet, it will probably be sufficient in other nutrients. In disease states, requirements for certain vitamins and minerals will be different, and these are fully described in the dietary management of each clinical condition.

The prescribable vitamin and mineral supplements that are most often used in paediatrics are given in Tables 1.22 and 1.23.

Prescribing products for paediatric practice

Special therapeutic formulas, supplements and special dietary foods can be prescribed for specific conditions. The Advisory Committee on Borderline Substances recommends suitable products that can be prescribed for use in the community and defines their indications. Prescriptions from the general practitioner should be endorsed 'ACBS' to indicate that the prescription complies with recommendations. A list of prescribable items for paediatric use appears in the *British National Formulary for Children* under the borderline substances appendix and is available on line at bnfc.nice.org.uk [62]. Dietetic products are categorised as enteral feeds (non-disease specific), nutritional supplements (non-disease

Table 1.23 Vitamin and mineral supplements, daily dose.

		Paediatric Seravit Unflavoured powder (Nutricia)	Forceval Soluble Junior (Alliance)	Forceval Soluble Adult** (Alliance)	FruitiVits Soluble Orange flavoured powder (Vitaflo)	Phlexy-Vits Powder (Nutricia)
		14 g 0–6 months 17 g 6–12 months 25 g* 1–7 years 35 g 7–14 years	1 effervescent tablet >6 years	1 effervescent tablet >12 years	6 g sachet 3–10 years	7 g sachet >11 years
Energy	kcal (kJ)	75 (315)	8.7 (37.5)	7.5 (32.6)	2 (10)	0.2 (1)
CHO	g	18.8	0.86	0.34	0.5	0.04
Protein	g	0	0	0	0	0.2
Fat	g	0	0	0	0	0
Sodium	mg	<5	Tr	Tr	4.7	8.8
Potassium	mg	<8	96	4	4.0	<1.4
Calcium	mg	643	—	120	804	1000
Phosphorus	mg	429	—	105	502	775
Magnesium	mg	89	56	56	201	300
Iron	mg	17.3	5	12	10	15.1
Zinc	mg	11.5	5	15	10	11.1
Copper	mg	1.2	1	2	1	1.5
Iodine	µg	83	75	140	169	150
Manganese	mg	1.2	0.35	3	1.5	1.5
Molybdenum	µg	88	50	250	68	70
Selenium	µg	34	25	50	41	75
Chromium	µg	34	50	200	41	30
Vitamin A	µg	1050	375	750	500	800
Vitamin D	µg	14	5	10	15	10
Vitamin E	mg	5.4	5	10	9.3	9
Vitamin K	µg	41.5	25	0	60	70
Vitamin C	mg	100	25	60	40	50
Thiamin	mg	0.8	1.2	1.2	1.2	1.2
Riboflavin	mg	1.1	1	1.6	1.4	1.4
Niacin	mg	8.8	7,5	18	15	20
Pyridoxine	mg	0.9	1	2	1.7	1.6
Pantothenic acid	mg	4.3	2	4	4.7	5
Vitamin B_{12}	µg	2.2	2	3	2.8	5
Folate	µg	76	100	400	240	700
Biotin	µg	54	50	100	112	150
Choline	mg	88	0	0	250	0

CHO, carbohydrate.
*25 g dose.
**Also available as Forceval Capsule Adult. Same composition except for Energy 0, CHO 0, Calcium 108 mg, Phosphorus 83 mg, Magnesium 30 mg, Sodium 0 and Potassium 4 mg. Not for children <12 years.

specific), specialised formulas, feed supplements, feed additives, nutritional supplements for metabolic diseases and foods for special diets. Children under the age of 16 years in the UK are exempt from prescription charges.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

2 Healthy Eating

Judy More

Introduction

Infants, toddlers and schoolchildren need to satisfy their energy and nutrient requirements for normal growth, development and activity through eating a varied and balanced diet based on five food groups, along with a daily vitamin D supplement. Energy and nutrient requirements for healthy UK children vary with age and are found in the following documents:

- estimated average requirements (EAR) for energy: recommendations from the Scientific Advisory Committee on Nutrition (SACN) 2011 [1]
- reference nutrient intakes (RNI) and lower reference nutrient intakes (LRNI) for macro- and micronutrients: the Department of Health's Report on Dietary Reference Values (DRV) 1991 [2]
- safe intakes (SI) and revised RNI for vitamin D: SACN Report on Vitamin D and Health 2016 [3]
- fibre: SACN Report on Carbohydrates and Health 2015 [4]

In addition, SACN's 2003 Report on Salt and Health published set population goals for salt and sodium consumption for various age groups of babies and children [5] in order to tackle the longer-term problems of hypertension and cardiovascular disease found in the adult population (Table 2.1). These are not intended for individual intakes, and at only 50% above the RNI for sodium, they would be difficult to achieve in practice, despite a reduction of approximately 15% of the salt content in some commercial foods over the last few years.

UK government policies promote healthy eating for infants and children through a number of initiatives:

- promoting breastfeeding
- broadening the nutritional support for low-income families through the Sure Start and Healthy Start schemes

Table 2.1 Guideline daily amounts of sodium and salt.

Age	Reference nutrient intake [2] Sodium (g/day)	Daily recommended maximum intake [5]	
		Sodium (g/day)	Salt (g/day)
0–12 months	0.21–0.35	0.4	1
1–3 years	0.5	0.8	2
4–6 years	0.7	1.2	3
7–10 years	1.2	2.0	5
11+ years	1.6	2.4	6

- Healthy Child Programmes [6, 7]
- widening children's exposure to fruit and vegetables through the School Fruit and Vegetable Scheme [8]
- voluntary guidelines on food to be served to children in early years settings [9]
- School Food Standards, but these are non-statutory and not monitored. In England they apply to all maintained schools and academies that were founded before 2010 and after June 2014 [10]
- the Childhood Obesity Strategy [11]

Infants (0–12 months)

Infants are exclusively milk fed from birth until complementary feeding is introduced alongside milk feeding between 4 and 6 months (further details on the age for complementary feeding are given on p. 25). Breastmilk is the optimal milk feed throughout the first year of life, and the only nutritionally adequate alternatives are formula milks made according to EU regulations: infant formula from birth and from 6 months either infant formula or follow-on milk.

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Breastmilk

It is the best option as it protects the infant against certain illnesses that formula milks cannot. Breastmilk:

- contains thousands of distinct bioactive molecules that protect against infection and inflammation and contribute to immune maturation, organ development and healthy microbial colonisation [12]. It has its own microbiome and oligosaccharides that feed both the breastmilk and infant gut bacteria
- is a dynamic fluid that changes in composition from colostrum, produced in the first few days, to transitional milk – a mixture of colostrum and mature milk – and finally to mature milk from about 2 to 3 weeks of age [12]
- composition also varies with each mother and during each feed and at different feeds over the day [13]

Colostrum is high in proteins, especially immunoglobulins, which confer maternal immunity against infection. It is low in fat and energy and its provision is under hormonal control and will not be influenced by frequent suckling. Newborn babies generally take very small volumes infrequently over the first few days (21.5 ± 4.2 mL on day 1) (Table 2.2) [15]. At the same time, it is normal for infants to have a net weight loss, which is mostly fluid, of up to around 10% of their birthweight.

From about day 2–3 post-partum, the composition of breastmilk changes to **transitional milk**, which has a higher water content. This change usually coincides with the infant demanding higher volumes of milk more frequently (Table 2.2). Most mothers experience discomfort in their breasts due to this sudden increase in the volume of milk produced. They need to be advised to expect the temporary discomfort and reassured that it will only last about 24 hours as the volume produced adjusts to the amount demanded by the infant.

Some women experience a delay in this change to transitional milk, and this includes mothers who have [16]:

- poorly controlled diabetes
- had a stressful or traumatic delivery
- had a caesarean section

The delay can create anxiety and these mothers need an explanation of why there is a delay in providing a larger volume of transitional milk and reassurance that establishing breastfeeding to satisfy their infant's needs is still possible.

From this time onwards, the volume of transitional and later **mature breastmilk** is produced in response to the infant's suckling and the removal of milk from the breast during feeding or expressing the milk [16]. During the early weeks of demand breastfeeding, mothers may need to feed every 2–3 hours or 8–12 times a day. Once lactation has become fully established, the time between feeds usually increases although some infants continue to prefer smaller more frequent feeds.

Breastmilk composition

The volume of milk produced depends on the glandular tissue content in each breast and varies between a woman's two breasts and between women [17]. Breastmilk composition varies considerably between women and depends on [18]:

- beginning or end of feeding; energy and fat content increase during each feed
- duration of lactation
- time of day
- diet and body composition of the mother
- maternal genes
- possibly infant factors such as sex

The average energy composition of mature breastmilk was estimated to be 69 kcal (289 kJ)/100 mL, but a recent systematic review of data from 1088 samples of mature breastmilk showed an energy content of 65.2 ± 1.1 kcal/100 mL (273 ± 4.6 kJ/100 mL) [14] (Table 2.3). At the beginning of the feed, the milk is low in fat and higher in lactose and satisfies the infant's thirst; as the feed progresses, the fat and energy content increases and the high fat milk towards the end of a feed is more satisfying. Mothers should, therefore, be encouraged to let their infant drink as much as desired from the first breast before offering the second breast; this way the infant gets the higher energy milk at the end of feeding at each breast. Less milk (or none at all) may be taken from the second breast offered. The first breast offered should be alternated at each feed so that both breasts receive equal stimulation and drainage. Young infants may need to be woken by cuddling them upright and changing their nappy after finishing at the first breast before being offered the second breast.

Some infants demand feeds frequently, while others take larger volumes less frequently, but the total daily fat intake is not affected by the frequency of feeding nor whether one or both breasts are suckled at each feed [17].

Benefits of breastfeeding

Breastfeeding is associated with health benefits for both the infant and mother [19, 20].

Table 2.2 Average volumes (mL/day) of breastmilk consumed compared with formula milk intakes [14].

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	14 + days
Breastfeeding	21.5 ± 4.2	100.3 ± 21.8	285.3 ± 40.1	383.8 ± 17.4	457.2 ± 20.9	495.3 ± 33.4	673.6 ± 29
Infant formula	170.5 ± 55.8	265 ± 67.7	410 ± 26	493 ± 32	566 ± 30	576 ± 29	761.8 ± 18

Table 2.3 Comparison of average energy and macronutrient composition of breastmilk compared with formula milks [14].

	Energy (kcal/100 mL)	Protein (g/100 mL)	Fat (g/100 mL)	Carbohydrate (g/100 mL)
Colostrum 1–5 days	53.6 ± 2.5	2.5 ± 0.2	2.2 ± 0.2	5.6 ± 0.6
Transitional breastmilk 3–14 days	57.7 ± 4.2	1.7 ± 0.1	3.0 ± 0.1	5.9 ± 0.4
Mature breastmilk from about 14 days	65.2 ± 1.1	1.3 ± 0.1	3.8 ± 0.1	6.7 ± 0.2
Infant formula (average various UK brands)	67	1.3	3.4	7.4

Source: Licensed under CC BY 3.0.

For the infant:

- reduced incidence of non-specific gastroenteritis and lower severe respiratory infections
- reduced risk of otitis media
- fewer visits to the doctor in the first 2 years of life

For the mother:

- delay in return to menstruation allowing maternal iron stores to replenish following pregnancy and childbirth
- reduced risk of breast and ovarian cancer
- lower risk of postnatal depression

The contraindications to breastfeeding are as follows:

- The baby has classical galactosaemia, a long chain fatty acid oxidation defect or glucose–galactose malabsorption
- The mother is taking certain medications, is receiving radiotherapy or chemotherapy, is a drug abuser or takes excessive alcohol
- HIV-positive status of the mother as HIV transmission from mother to infant can occur via breastmilk; however, in developing countries, where formula feeding may greatly increase the risk of gastrointestinal infections and mortality, exclusive breastfeeding is preferable

Supporting and maintaining breastfeeding

Breastfeeding is not an entirely instinctive process and most new mothers need support and advice. At least 95% of women are able to produce sufficient milk, and, therefore, less than 5% of women will have primary lactation insufficiency [21]. Good positioning and attachment are essential for successful breastfeeding. Infants should be held so that:

- they are close to mum; the angle of the breast will determine which position is best for the baby to effectively milk the breast
- the baby's back, shoulders and neck are supported, allowing the head to easily tilt backwards
- their ear, shoulder and hip are in a line; this will ensure the neck is not twisted while they are feeding

When the baby is positioned correctly, their nose should be brought to the nipple; this will stimulate the rooting reflex and the baby will give a nice wide gape. The baby should then be brought quickly and firmly to the breast aiming to get a good mouthful of breast tissue.

Once attached to the breast, there should be more areola visible above the baby's top lip than the lower lip; the lower lip should be turned out and the tongue under the mother's nipple; the chin can be indented into the breast and the nose must be free for breathing.

If the baby is unable to suckle at birth, the mother can express her milk. Expressing 8–12 times a day will be necessary to establish a good milk supply, and considerable practical and emotional support is important for these mothers.

Provided there is no restriction on how much an infant can breastfeed (i.e. demand feeding is practised), no extra water is needed, even in very hot weather, as the infant will simply feed more frequently to obtain more fluid when thirsty.

Health professionals can support and promote breastfeeding through policy development, through the provision of environments conducive to breastfeeding and by having the knowledge and skills to give consistent practical advice and support to breastfeeding mothers. Factors that improve rates of breastfeeding include:

- *early contact between mother and baby*. Healthy infants should be placed and remain in direct skin-to-skin contact with mother immediately after delivery until the first feeding is accomplished [22]. The World Health Organization (WHO) recommends putting the baby to the breast within an hour after birth to assist in developing the suckling reflex, which is particularly strong for a short while after delivery [23].
- *extra support by trained professionals with special skills in breastfeeding* to help with good positioning and technique [24]. A good understanding of the physiology of lactation is essential for all who are involved in the care of breastfeeding mothers and can be achieved with training. The UNICEF UK Baby Friendly Initiative has developed an accreditation system for assessing higher education institutions in the UK based on the training they provide to midwives and health visitors on breastfeeding.
- *WHO/UNICEF Baby Friendly status of the maternity unit where the baby is born*. The WHO/UNICEF Baby Friendly Initiative provides a framework for the implementation of best infant feeding practice in maternity units and is represented by the *Ten Steps to Successful Breastfeeding* (Table 2.4), revised by WHO in 2018. Accredited units

Table 2.4 The 10 steps to successful breastfeeding [25].

Critical management procedures

1a. Comply fully with the *International Code of Marketing of Breast-milk Substitutes* and relevant World Health Assembly resolutions.
1b. Have a written infant feeding policy that is routinely communicated to staff and parents.
1c. Establish ongoing monitoring and data-management systems.
2. Ensure that staff have sufficient knowledge, competence and skills to support breastfeeding.

Key clinical practices

3. Discuss the importance and management of breastfeeding with pregnant women and their families.
4. Facilitate immediate and uninterrupted skin-to-skin contact and support mothers to initiate breastfeeding as soon as possible after birth.
5. Support mothers to initiate and maintain breastfeeding and manage common difficulties.
6. Do not provide breastfed newborns any food or fluids other than breast milk, unless medically indicated.
7. Enable mothers and their infants to remain together and to practise rooming-in 24 hours a day.
8. Support mothers to recognize and respond to their infants' cues for feeding.
9. Counsel mothers on the use and risks of feeding bottles, teats and pacifiers.
10. Coordinate discharge so that parents and their infants have timely access to ongoing support and care.

Source: Reproduced with permission of WHO.

Table 2.5 Summary of UNICEF UK Achieving Sustainability standard [28].

Theme	
Leadership	• A named Baby Friendly lead/team with sufficient knowledge, skills and hours to meet objectives • A mechanism for the Baby Friendly lead/team to remain up to date with education and skills • A Baby Friendly Guardian with sufficient seniority and engagement in post • Leadership structures support proportionate responsibility and accountability • Relevant managers educated to support the maintenance of the standards
Culture	• Support for ongoing staff learning • Mechanisms in place to support a positive culture (e.g. staff recognition schemes), mechanisms for staff to feedback concerns, systems to enable parents' and families' feedback to be heard and acted upon
Monitoring	• Baby Friendly audits carried out regularly according to service needs • All relevant data available and accessed • Data analysed effectively and collectively to give an overall picture • Action plans developed in response to findings • Relevant data routinely reported to the leadership team • Relevant data routinely reported to UNICEF UK
Progression	• Service demonstrates innovation and progress • Evidence to demonstrate that outcomes have improved • Needs of babies, their mothers and families are met through effective integrated working

that have successfully implemented all 10 steps have increased breastfeeding rates.
- *local peer support groups* that are particularly effective [26]. Intensive interventions from community peer support, with at least five planned contacts, have a greater effect on breastfeeding continuation than lower intensity interventions [27]. In the UK, the large nationally organised groups that provide peer support and training for counsellors are:
  - Association of Breastfeeding Mothers
  - Breastfeeding Network
  - La Leche League
  - Multiple Births Foundation
  - National Childbirth Trust
- *Family support and encouragement*
- *Supportive communities where breastfeeding is seen as the norm* and facilities are available for women to breastfeed

Both England and Scotland have legislated against discrimination towards mothers feeding infants in public places. The UNICEF UK Baby Friendly Initiative has developed standards to guide healthcare professionals through their staged Baby Friendly accreditation programme for maternity, neonatal, health visiting and children's centre services [28]. The elements of the Achieving Sustainability standard are given in Table 2.5.

Perceived barriers to breastfeeding may include:

- *too much demand on the mother's time*. Family members can provide invaluable support by helping with other children or taking over household duties.
- *embarrassment*. Some mothers are embarrassed to breastfeed in public places and even within the home for some, particularly those in lower socioeconomic groups [29]. Many women find that the attitude of other people to breastfeeding in public, coupled with the frequent lack of facilities to feed in private, make prolonged excursions outside the home difficult.
- *jealousy and lack of support from other family members*. Husbands, relatives and siblings may resent the exclusive role of the mother in breastfeeding. Involving everyone in all other aspects of caring for the infant can help alleviate this problem.
- *incompatibility with work*. Women in the UK are entitled to 12 months' maternity leave (9 months of this paid). However, many return to work within 12 months, and unless there are suitable facilities for childcare or expressing breastmilk, continuing with full breastfeeding can be difficult. Partial breastfeeding, e.g. in the mornings and evenings, is often possible on return to work and can be encouraged.

Problems and difficulties with breastfeeding

Some common problems with breastfeeding and suggestions for their management are given in Table 2.6.

Supplementary milk feeds

Breastfeeding may be supplemented with additional milk feeds if the baby cannot get enough milk from the breast for normal growth or if the mother chooses to do this. The extra

Table 2.6 Common breastfeeding problems and suggestions for their management.

Concern	Background	Action
Perceived inadequate supply A common reason cited by mothers and may be due to persistent crying or fussing of infants that are not necessarily signs of hunger	Crying in a baby does not always signal a demand for food. It may be because the baby is uncomfortable, needs a nappy change or is overtired or just bored and lonely. A breastfed baby having an adequate intake will: • Be alert and responsive and have a healthy appearance • Have 6+ feeds in 24 hours during the day and night • Have 6+ wet nappies daily • Have 2+ yellow stools daily	Check the baby is feeding for as long as she/he wishes on both breasts. More frequent breastfeeds may help establish a better supply or suit a mother who produces low volumes of breastmilk. Check mother's diet and fluid intake are adequate and that she is getting enough rest. Check medications. If available, a trained professional can observe the baby feeding and advise on how to ensure the baby is effectively transferring breastmilk
Sore nipples	Some tenderness is normal, but breastfeeding should not be painful. Pain is usually due to poor attachment and positioning. However, in some cases, it may be due to thrush (*Candida albicans*). In rare cases it may be due to Raynaud's syndrome, where nipples become blanched due to poor blood supply	Treatment from a general practitioner (GP) is necessary to resolve thrush in both the mother and infant. Heat treatment and feeding in a warm room may help in Raynaud's syndrome
Cracked nipples	Usually due to poor attachment	With improved attachment and positioning, nipples will begin to heal
Engorgement Oedema caused when the breast is full of milk and the blood and lymph flows are slow and seep into breast tissue	Usually due to poor drainage of the breast as a consequence of poor positioning and attachment and can occur when feeds are missed	Hand expressing before the feed can make it easier for the infant to suck efficiently. Advice may include: • Use of warm compresses or taking a warm shower before feeding • Frequent breastfeeding (every 1–2 hours) and encouraging the infant to suckle from both breasts • Applying an ice pack to breast and underarm after feeding until swelling decreases can also be helpful • Seek expert advice if the problem persists
Mastitis Swollen, inflamed or infected area in breast	Usually a result of engorgement or poor drainage of the breast, so it is important not to stop breastfeeding	Advise rest, frequent breastfeeds and that the mother should drink plenty of fluids. Antibiotics may be needed
Baby has poor weight gain	Less emphasis is now placed on frequently weighing healthy infants as small variations in weight centiles can cause considerable parental stress. Weight gain is not expected to be regular: • Infants often cross centiles in the first 6–8 weeks to adjust for the intrauterine environment • Thereafter variations of up to 1 centile space are normal	Check the weight chart carefully and reassure the mother if possible. Check position and feeding technique. Check the number of feeds being offered and if necessary advise an increase to stimulate breastmilk production. If top-up formula feeding is necessary in the first couple of weeks, advise the mother to give the bottle at the end of each breastfeed to encourage stimulation of breastmilk with the goal of fully resuming breastfeeding. After the infant is about 2 weeks old, advise the mother to give one bottle of formula per day and continue breastfeeding at the other feeds. Refer to the GP for assessment if growth is faltering by falling through 2 centile spaces after 8 weeks of age
Tongue tie	If severe can limit the infant's ability to suckle effectively	Refer for an assessment. Surgery resolves the problem

milk can be expressed breastmilk (EBM), infant formula or, if available, pasteurised human donor milk.

A supplementary feed can be given in a bottle, by cup or via a nursing supplementor. Infants suck against a lower pressure when sucking from a bottle teat compared with sucking from the nipple [30], and some will prefer to suck against this lower pressure, which requires less effort, if bottle feeding is offered.

There is little evidence on the best way to combine breastfeeding and bottle feeding if a top-up of EBM or formula milk is needed. There are two ways to do this:

- Mothers can feed from both breasts to stimulate breastmilk production and then offer a bottle feed if the baby still seems hungry. This may be best in the newborn period when breastfeeding is being established. However later, it can lead to a reduction in the breastmilk demanded by the infant and consequently diminishing breastmilk production.
- The infant can be given a bottle of formula milk at one feed per day and continue to breastfeed only at the other feeds. Some mothers successfully maintain breastfeeding for longer by doing this [31].

Expressing breastmilk

Once breastmilk supply is established, it can be expressed using one of three methods:

- by hand
- using a hand pump
- using an electric pump

The National Institute for Health and Care Excellence (NICE) recommends that all mothers be taught to hand express their milk [32]. EBM can be given to the baby via a bottle, cup or spoon although not all babies are happy to accept an occasional feed in this way. Bottles, containers for storage and other utensils must be sterilised until the infant is 1 year of age. EBM should be labelled and stored correctly to minimise the risk of infection. The Department of Health recommends that EBM is stored:

- in the refrigerator for up to 5 days if parents are confident that the fridge remains at 4 °C or lower. It should be stored at the back of the fridge where it is colder. A domestic fridge that is opened frequently may not maintain a low enough temperature; it is preferable to freeze EBM if it is not going to be used within 48 hours
- in the freezer compartment of a fridge for up to 2 weeks
- in a domestic freezer at –18 °C for up to 6 months

Frozen EBM should be thawed in a fridge and then used within 24 hours. It must not be reheated in a microwave oven because of the risk of 'hotspots' occurring and causing burns [33]. Standing the bottle in warm water is a suitable way of reheating milk if necessary; some babies will drink it cold from the fridge.

Table 2.7 Recommended intakes from the five food groups for lactating mothers.

Food group	Recommended daily intake
Bread, rice, potatoes and pasta and other starchy foods	Base each meal and some snacks on these foods. Use wholegrain varieties as often as possible
Fruit and vegetables	Include one or more of these at each meal and aim for at least 5 portions per day
Milk, cheese and yoghurt	2–3 portions of milk, cheese and yoghurt. Use low fat varieties if weight needs to be managed
Meat, fish, eggs, beans and nuts	2–3 portions. Two servings of fish per week are recommended, one of which should be oily fish
Butter, oils and fat spreads	Limit these to small quantities in food preparation. For those trying to lose weight, limit them ½ to 2 small portions per day
Sugary foods	Avoid for those trying to lose weight and limit to small amounts for others
Fluid intake	To satisfy thirst, but at least 6–8 drinks per day (1½–2 L). Include a drink with each breastfeed. Fluids include water, tea, coffee, milk, soup, fruit juices, squashes and fizzy drinks. More drinks may be needed in hot weather and after physical activity
Vitamin supplement	10 µg vitamin D

Nutrition for lactating mothers

The nutritional quality of breastmilk is only affected if the mother is undernourished. To support lactation higher requirements for energy, fluid, thiamin, riboflavin, niacin, vitamin B_{12}, folate, vitamins C, A and D, calcium, phosphorus, magnesium, zinc, copper and selenium are set [2]. The increased energy requirement is usually met through utilising the adipose stores deposited during pregnancy. Eating a balance of the five food groups (Table 2.7) will meet the increased nutrient requirements with the exception of vitamin D, where a daily supplement of 10 µg is recommended [3].

Vegan mothers need to plan their diets carefully and may need additional supplements of calcium, riboflavin, iodine, iron and vitamins A, B_{12} and D.

Foods to be limited or avoided

To ensure a good intake of omega-3 long chain polyunsaturated fatty acids (LCP), mothers should be encouraged to include fish in the diet, but oily fish and tuna should be limited to no more than two servings per week; marlin, swordfish and shark should be avoided [34].

Alcohol and caffeine both readily pass into breastmilk and high intakes of either should be avoided during lactation. The highest level of alcohol in milk will occur between 30 and 90 minutes after ingesting alcohol; mothers should not ingest alcohol for about 2 hours before breastfeeding and should keep alcohol intake to a minimum, e.g. 1–2 units once or twice per week. Regular or binge drinking should be avoided. Caffeine in tea, coffee, chocolate and energy drinks does not need to be avoided, but some mothers find large amounts of caffeine unsettle their baby.

Breastmilk is believed to be flavoured by foods eaten by the mother and may influence the infant's response to tastes when complementary foods are introduced [35]. There are reports that highly spiced or strong tasting foods can unsettle some infants.

Infants may become sensitised to antigens in breastmilk, e.g. cow's milk protein, eggs or nuts. If the infant reacts to the presence of these antigens in breastmilk, the mother needs to avoid these foods. If dairy products are avoided, she will need advice on dietary adequacy, which may need to include a calcium and iodine supplement.

Formula milk feeding

In contrast to the variation in breastmilk, the composition of infant and follow-on formulas is uniform, complying with EU regulations, and does not provide the antibodies that breastmilk does. These regulations are based on expert advice from the European Food Safety Authority and also implement the 1981 WHO International Code of Marketing of Breastmilk Substitutes as appropriate to the EU.

Recent research suggests that current infant formulas may contain too high an energy level for normal growth. The energy content of breastmilk may be lower than current accepted estimations, and the higher energy density of infant formulas may account for the different growth patterns seen between breastfed and formula-fed infants (Table 2.3).

Table 1.14 lists the infant formulas available in the UK. The whey-dominant formulas (whey–casein ratio of 60 : 40) have a protein ratio that is similar to that found in mature breastmilk; those with a lower whey–casein ratio (20 : 80) are more similar to the protein ratio found in cow's milk. The energy and nutrient contents are similar in both types of feed, although the casein-dominant formulas are marketed as more suitable for hungry babies; this is simply because the curd formed by the higher casein level slows gastric emptying.

Formula-fed babies should be demand fed just as breastfed babies are and offered adequate feed to satisfy their hunger and growth needs. They should be allowed to stop feeding when they signal they have had enough and not coerced to finish every bottle. An average total daily intake is around 150 mL/kg body weight/day up to about 4 months of age, although it varies with each baby. The number of feeds per day and the volume taken at each feed will vary as with breastfeeding.

Follow-on milks

These milks (Table 1.14) are only recommended from 6 months of age as they may have higher levels of protein, minerals and some vitamins than the infant formulas designed for feeding from birth. Some mothers choose to use them, but it is not generally necessary. They can be used to give additional nutrients to infants who are slow to accept complementary feeding.

Making up infant formula from powder

Tap water or bottled waters that comply with EU standards for tap water [36] may be used for making up infant formula. Up to 200 mg/L sodium is allowed in tap water, which will add 0.9 mmol sodium/100 mL feed. This extra sodium will not matter for most infants and powdered feeds on sale in the UK will still comply with the EU Directive's acceptable sodium content if made up with water containing this level of sodium. Bottled mineral waters may contain excess amounts of sodium or other electrolytes and should not be used for making up infant formula. Just as tap water must be boiled before being used for reconstituting formula feeds, so must any bottled water. Carbonated fizzy water is not suitable for making up formula feeds.

Infant formula powder is not sterile and may contain microorganisms such as salmonella and *Enterobacter sakazakii* (now known as *Cronobacter sakazakii*). Neonates, particularly those who are preterm, of low birthweight or immunocompromised, are most at risk. To minimise the risk of gastroenteritis from these bacteria:

- feeds should be made up using boiled water >70 °C (that has been left to cool in the kettle for no more than half an hour)
- this water is measured into a sterile bottle and the appropriate number of scoops of powder added (1 level unpacked scoop of powder per 30 mL/1 fluid ounce water)
- the bottle should then be sealed with a sterilised cap and shaken to mix the powder
- the feed must be cooled (by holding the sealed bottle under cold running water) and the temperature tested before giving to the baby
- bottles should be made up freshly for each feed
- any leftover milk at the end of the feed should be thrown away
- parents who require a feed for later are advised to keep water they have just boiled in a sealed flask and make up fresh formula milk when needed

If parents choose not to follow this advice and make up feeds for up to 24 hours in advance, the bottles of formula should be cooled quickly and stored in a fridge at <5 °C. These feeds can be warmed just before use by standing the bottle in a container of hot water. Microwave ovens must not be used as the milk is not uniformly heated and hotspots in the milk could burn the baby's mouth [33]. Feeds should be made up using boiled water and sterile bottles or cups until 1 year of age because of the potential for bacterial growth. This is enhanced if bottles, teats and cups are not cleaned properly.

In the case where a baby is prescribed a multi-ingredient feed, the dietitian may deem it safer, from the point of view of accuracy of feed reconstitution, for the parent to make up 24 hours' worth of feeds at one time. It is incumbent on the dietitian to give advice about scrupulous hygiene, rapid cooling and safe storage at <5 °C if feeds are to be made up in advance. Any remaining milk not consumed after 1 hour of feeding should be discarded.

Bottle feeding

Feeding position

Bottle-fed babies should be held in a supportive, semi-upright position, which encourages eye contact and bonding with the caregiver. The bottle should be angled so that the teat is always full of milk, thus minimising the amount of air consumed. It is usual to 'wind' bottle-fed babies halfway through and after a feed.

Feeding equipment

Various types of bottles are available, some with air release devices to reduce colic. The several different types of teats available have varying flow rates according to the size and number of holes, and they also vary in size and shape.

Problems preparing feeds

Lucas *et al*. [37] measured the energy content of infant formulas made up by a group of bottle feeding mothers and found the energy content ranged from 41 to 91 kcal (171–380 kJ)/100 mL, whereas the manufacturer's intended energy content was 68 kcal (284 kJ)/100 mL. One third of feeds contained less than 50 kcal (210 kJ)/100 mL and around half the feeds over 80 kcal (335 kJ)/l00 mL. These discrepancies may arise from:

- compression of the powder in the scoop or by using heaped scoops

- miscounting the number of scoops
- adding an extra scoop mistakenly believing it will be more satisfying or nourishing for the baby

Overconcentration feeds may lead to hypernatraemia with consequent dehydration and possible severe brain damage or death or to hypercalcaemia and hyperphosphataemia. Much of this potential danger has been reduced following compositional changes to modern infant formulas and the redesign of packaging to improve standards of hygiene and accuracy of mixing. The use of ready-to-feed (RTF) liquid formulas ensures the correct concentration is always given.

Overdilution of feeds may lead to excessive volumes being ingested in order to meet energy needs, and this can cause vomiting and hyponatraemia. Faltering growth and malnutrition may ensue because the capacity of the young infant's stomach cannot cope with the much larger volumes of feed required to meet nutritional requirements.

Additional fluids

Formula-fed infants may become thirsty between feeds in very hot weather, and additional drinks of cooled boiled water can be given so long as these do not interfere with the required intake of formula. Fruit juices and baby juices are not recommended; formula milks contain adequate vitamin C.

Infants with fever, diarrhoea or vomiting can dehydrate quickly and need additional fluids, and possibly electrolytes, to replace losses.

Sleeping through the night

When infants begin to sleep through the night is related to the hormonally driven development of their circadian rhythm and is not related to their energy or nutritional intake. The earliest that any infant will begin sleeping through the night is 6–8 weeks [38].

Poor appetite regulation and inappropriate weight gain

A small number of infants have genetically inherited poor appetite regulation and may demand too little or too much milk to support optimal growth patterns. After 8 weeks of age, consistent rising across the weight-for-age centiles indicates an infant has an excess milk intake and this is a risk factor for childhood obesity [39–41]. This can occur with breastfed infants, but more commonly occurs with bottle feeding [42] because the bottle teat can be held or forced into an infant's mouth even when the infant has consumed enough milk and is signalling satiation. Infants who are bottle fed in early infancy are more likely to empty the bottle or cup in late infancy than those who are fed directly at the breast [43]. A recent study has shown that 3-month-old infants taking high volumes of formula milk were at greater risk of higher body weight and overweight at 12 months than breastfed infants or those with lower formula intakes [44].

Complementary feeding

The introduction of solid foods alongside milk feeds is needed to provide a more energy and nutrient-dense diet at the time when a milk only diet becomes inadequate to support continuing growth and development. The critical nutrient is iron as it is low in breastmilk, and during the first 4–6 months of life, infants rely on the iron derived from delayed cord clamping at birth and iron stores laid down during foetal life. Recent evidence indicates that the timing of introduction of highly allergenic food during complementary feeding plays a role in the prevention of food allergy in infants (p. 340).

A time of learning new skills

During complementary feeding, infants must learn new feeding skills, and they do this as their physical coordination develops and by being given the opportunity to try, and to practise, managing food in their mouths and swallowing it. As complementary feeding progresses with a varied diet, infants will learn to like and accept the new different tastes and food textures they are offered.

When to begin

The ideal age to begin is individual as infants grow and develop at different rates. Evidence suggests beginning before 3 months of age increases the risk of respiratory infections [45] and waiting until after 6 months increases the risk of nutrient deficiencies, of iron in particular [46–48]. There is no evidence of harm in beginning complementary feeding between 4 and 6 months of age. Policies and population recommendations vary and have changed over the last two decades. Current recommendations are to begin complementary feeding:

- at 6 months (WHO Global Feeding Strategy 2003) based on the afforded protection against gastroenteritis and mortality in developing countries. They also recommend that each country interpret the age at which to begin complementary feeding depending on the health needs of their own populations [49]
- between 4 and 6 months (WHO recommendations for Europe 2003) [50]
- between 4 and 6 months (ESPGHAN 2017) for European countries where the risk of death due to gastroenteritis is very low. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends beginning complementary feeding between 4 and 6 months of age as this will cause no harm to infants and may provide benefits in terms of improved iron status [51]
- around 6 months, but not before 4 months (SACN 2018) [20]
- around 6 months, but not before 4 months (British Dietetic Association 2016) [52]

These are population recommendations and most stipulate that each infant should be considered individually due to the considerable range of growth rates and physical development between 4 and 6 months of age in term infants.

UK studies have shown that mothers of larger male infants introduce complementary feeding at an earlier age than mothers of smaller and female infants [53]. The last UK Infant Feeding Survey (IFS) (2010) reported [54]:

- 30% of infants began complementary feeding before 4 months
- 75% were having solid food by 5 months
- 94% by 6 months
- 5% after 6 months

The Diet and Nutrition Survey of Infants and Young Children (2011) reported [55]:

- 42% of infants receiving solid food by 4 months
- similar figures to the IFS at 5 and 6 months

The Scottish Maternal and Infant Survey in 2017 reported [56]:

- 3% of infants began complementary feeding before 4 months
- 54% before 6 months

Parents should therefore be encouraged to consider their infant's signs of readiness for complementary feeding and begin when they perceive their infant is ready physically and nutritionally. Signs of readiness include:

- able to sit with support and control the head to reduce the risk of choking
- putting toys and other objects in the mouth
- chewing fists
- watching others intently when they are eating
- seeming hungry between milk feeds or demanding feeds more often even though larger milk feeds have been offered

These developmental signs are generally seen between 4 and 6 months, and from this age, infants learn to accept new tastes and textures relatively quickly [57].

Sleep patterns also change around this time and infants are more likely to wake when in a light sleep mode. Waking during the night after beginning to sleep through the night has not been considered an indication to begin solids, but the EAT (Enquiring About Tolerance) study found that parents who had been randomised to begin complementary feeding from 3 to 4 months reported that their infants slept for slightly longer and woke less frequently than the parents who had been randomised to begin complementary feeding at 6 months of age [58].

Foods to offer

As infants learn new skills, they will progress through the developmental stages of complementary feeding as they are given the opportunities to learn [59]. Some progress faster than others and will begin to take more energy from food and cut down their milk intake more quickly that those whose skills develop more slowly and who will remain more milk dependent for longer. Table 2.8 gives a rough guide of the pattern of complementary feeding.

Complementary feeding usually begins with 1–2 teaspoons of a smooth mashed or puréed food being offered once a day. The addition of solids to bottles of milk is not advised in the UK; however, this is accepted practice in some other European countries.

The food given at the first attempts may come back out as the infant pushes their tongue forward, as they do when sucking from the nipple or teat. With practice infants will realise that the food stays in the mouth when the tongue moves backwards. As the infant learns to manage and swallow solid food effectively and begins to take a larger quantity, a second meal and then a third meal can be introduced. Once three meals are established, a variety of foods from the four main food groups should be included to provide a range of nutrients. Table 2.11 shows the food groups and recommended number of daily servings.

Energy and nutrient density

Meals should be nutrient dense and contain iron-rich foods [20, 62] from the beginning of complementary feeding. The best food sources of iron are meat, oily fish, pulses, eggs and nut butters. Meat and oily fish provide the haem form of iron, which is easily absorbed. Pulses, eggs and nuts contain the non-haem form of iron, and absorption is less efficient, but can be improved by combining them with a high vitamin C food.

Savoury courses for infants should ideally contain (by volume):

- ⅓ high iron foods: meat/fish/eggs/nut butter/pulses (lentils, hummus, starchy beans)
- ⅓ starchy foods: potato/rice/pasta/bread
- ⅓ vegetables

Table 2.8 Pattern of complementary feeding.

Stage	Age guide	Number of milk feeds/day	Number of meals/day	Variety of foods
1	4–6 months (17–26 weeks)	5–4	1–2	From 1 to 3 food groups (Table 2.11) Vitamin D supplement
2	6–9 months	4–3	3	3 different meals from 4 nutritious food groups 1–2 courses per meal Vitamin D supplement
3	9–12 months	3–2 Discontinue early morning feed so that more food is eaten at breakfast	3	3 different meals from 4 nutritious food groups 2 courses per meal Vitamin D supplement

This will meet the WHO recommendation that complementary foods are energy and nutrient dense providing about 80–120 kcal (335–500 kJ)/100 g food [62].

Second courses based on fruit and/or yoghurt/custard/milk pudding can be given to replace the milk feed at one and then two meals as the infant takes more food and two courses are offered at each mealtime. The amount of breastmilk or infant formula consumed by the infant will gradually reduce to about 500–600 mL/day towards the end of the first year.

Low nutrient foods high in fat and sugar do not have a place in complementary feeding.

Ingredients to avoid are:

- salt and added free sugars, although a small amount of sugar can be added to make tart or sour fruits palatable
- honey, which should not be given before 12 months as there is a small risk of infant botulism

Although recommended in the past, there is no evidence to support delaying any foods before 6 months to reduce the incidence of allergy. Evidence and policies now indicate that highly allergenic foods can be introduced from the beginning of complementary feeding [20]. Advice differs for infants at high risk of food allergy (p. 343).

Learning to like new tastes

The majority of infants will try a wide variety of tastes and textures and they learn to like the foods they are offered [63]. The frequency with which they are offered a food, rather than the amount they eat, determines how quickly they will learn to like it. By the end of their first year, infants should be eating family foods, and the more variety they have been offered by around 12 months, the wider the range of foods they will be familiar with and accept before food neophobia begins in their second year (p. 32).

Learning to manage new textures

After beginning with smooth foods, to develop confidence, offering thicker textures, lumps and soft finger foods allows infants to progress their skills [64]. Some need a lot of practice with new textures before they master eating them and are ready to move on. Others may manage soft finger foods and thicker textures from the beginning of complementary feeding. The gag reflex makes it safe for infants to try finger foods and lumps that they cannot at first process. Lumps or pieces of food that are too big to be swallowed are gagged and cleared from the back of the tongue to the front of the mouth and either spat out or reprocessed to the sides of the mouth [65, 66]. Soft finger foods early in complementary feeding offer infants the opportunity to:

- touch and play with food
- learn to visually recognise foods and to associate them with their smell and taste
- develop their self-feeding skills

Although gagging is a normal part of learning feeding skills, choking, which is not common, is not. Guidelines on treating choking in infants and children can be accessed at www.resus.org.uk/resuscitation-guidelines/paediatric-basic-life-support

> Gagging: a reflex closing off the throat and pushing the tongue to the front of the mouth
>
> Choking: a piece of food partially or completely blocking the airway, affecting breathing

Research surveys using parental questionnaires in the UK report that:

- 12% of infants were given finger foods at 4–5 months and 40% by 6 months of age [67]
- 43% of infants were eating toast before 6 months of age and 27% biscuits [68]

Infants progress in different ways and some develop a preference for self-feeding finger foods while others for spoon feeding. Therefore, it is best that each infant has the opportunity to learn and acquire both skills. Giving infants their own spoon during spoon feeding encourages independence and an opportunity to learn to coordinate transferring food from spoon to mouth. Including infants in family meals allows them to learn by copying those eating around them. There is inadequate research on outcomes for healthcare professionals to recommend only giving finger foods with no spoon feeding [69].

Table 2.9 shows the developmental stages of complementary feeding.

Responsive feeding

Responsive feeding allows each infant to decide how much solid food is eaten and how much milk is drunk. There are no set food or milk feed portion sizes for infants (under 12 months of age) because infants develop their feeding skills at different ages and grow at different rates. Most infants will

Table 2.9 Developmental stages of complementary feeding.

Stage	Age guide	Skills to learn	New food textures to introduce
1	4–6 months (17–26 weeks)	• Taking food from a spoon • Moving food from the front of the mouth to the back for swallowing • Managing thicker purées and mashed food	Smooth purées Mashed foods
2	6–9 months	• Moving lumps around the mouth • Chewing lumps • Self-feeding using hands and fingers • Sipping from a cup	Mashed food with soft lumps Soft finger foods Water in a lidded beaker or cup
3	9–12 months	• Chewing minced and chopped food • Self-feeding attempts with a spoon	Firmer finger foods Minced and chopped family foods

continue to accurately regulate their energy intake and will drink the volume of milk they need depending on how much energy they have ingested through food.

Parents may need support to recognise their infant's hunger and satiation signals. Coercing or force feeding an infant to eat or drink more when they have indicated they have had enough is counterproductive to enjoyable mealtimes and to developing a positive attitude to food. Excess energy intake through force feeding leads to excess weight gain. Hunger cues are given in Table 2.10.

Infants clearly signal to parents that they no longer want food or milk. They do this when tired from practising a new feeding skill or later when their hunger and thirst are satisfied. Signals indicating physical tiredness or hunger satiation include:

- turning their head away from the spoon
- keeping their mouth shut
- blocking their mouth with their hand or pushing away the spoon or food
- holding food in their mouth
- crying

Older infants will:

- throw food
- signal 'no' in response to unwanted food given to them
- vomit

Commercial baby foods

The energy density and composition of home-made foods for infants varies widely [71] as does the taste and texture. By contrast commercial weaning foods are more uniform in their texture and must conform to EU Directives, which govern their composition [72]. However, energy density varies and is often below WHO recommendations, particularly those comprising vegetables only. The regulations governing pesticide residues in all commercial baby foods are very strict, but most commercial baby foods purchased are now organic, which allow no pesticides to be used in their culture and preparation. Organic food regulations prohibit iron fortification, and consequently organic savoury baby foods are lower in iron content than non-organic iron-fortified savoury baby foods.

Table 2.10 Hunger cues.

Approximate age	Hunger cues
4–6 months	• Cries or fusses • Smiles, gazes at caregiver or coos during feeding to indicate wanting more • Moves head towards spoon or tries to swipe food towards mouth
5–11 months	• Reaches for food • Points to food • Gets excited when food is presented
10–12 months	• Expresses desire for specific food with words or sounds

Source: Adapted from the USDA Infant Nutrition and Feeding Guide [70].

Fluids

Once food textures have progressed to thick mash and finger foods, water should be offered from a cup or beaker with meals. This water does not have to be boiled for babies over 6 months old, but can be freshly drawn tap water or bottled water given from a clean cup.

Infants should never be left alone with cups or bottles of water or other fluids as they may choke.

The following are unsuitable fluids:

- *All sweet drinks* including fruit juices and baby juices are acidic, even when diluted, and contain free sugars; consequently they can cause dental erosion. Infants do not need fruit juices or baby fruit juices as:
  - both breastmilk and infant formula contain adequate vitamin C
  - fruit and vegetables are introduced from the beginning of complementary feeding
  - if a parent chooses to use fruit juices, they should be well diluted and served only at mealtimes in a cup or beaker, never a bottle; not be given at, or after, bedtime as during sleep saliva that buffers acid levels is not produced in the mouth; drinking times should be kept short
- *Tea and coffee* as they contain caffeine and the tannins and polyphenols present inhibit iron absorption

Vitamin D supplementation

SACN recommends an SI of 8.5–10 µg vitamin D each day from birth irrespective of feeding method. Vitamin D levels in breastmilk are low, and although infant formula is fortified with vitamin D to higher levels, a supplement is still required.

Infants whose mothers entered the pregnancy with low vitamin D levels and who did not take a vitamin D supplement during pregnancy are likely to be born with low levels of vitamin D and poor stores [73]. Exclusively breastfed infants born with low stores of vitamin D are at risk as the vitamin D content of breastmilk is normally low. It is lower still in the milk of mothers who are vitamin D deficient [74]. The level of vitamin D in formula milk appears to be inadequate for an infant born with very low stores; formula-fed infants have been diagnosed with hypocalcaemic seizures, cardiomyopathy and rickets [75].

Public Health England (PHE) recommendations for vitamin D supplements (Table 2.21) advise that infants drinking 500 mL formula milk/day do not need a supplement. However, the European Society for Paediatric Endocrinology recommends a supplement of 10 µg of vitamin D per day for all infants from birth to 12 months of age, independent of their mode of feeding, to prevent nutritional rickets [77]. The European tolerable upper intake level (UL) for infants under six months of age of 25 µg/day and 35µg/day for infants aged 6–12 months is unlikely to be reached.

Vitamin drops are best given from a spoon or syringe, not added to bottles, to ensure the full dose is taken.

Preschool children 1–4 years

Basing the diets of toddlers and preschool children on a combination of foods from the food groups in Table 2.11, along with a vitamin D supplement, will provide nutritional adequacy. Although the PHE Eatwell Guide (Figure 2.1) is not designed for children under 5 years of age, children in this age group do grow satisfactorily on the same percentage energy contributions from the macronutrients as discussed below for school-age children. However, under 5s are growing rapidly and need a nutrient-rich diet. Their diet differs from that of the infant or that of older children and adults in having:

- less milk than the infant diet
- a meal pattern of three meals with two to three planned nutritious snacks per day, as these children may only take small quantities of food at any one time

Two courses at each meal, a savoury course followed by a fruit- or milk-based second course, ensure a wider variety of foods and nutrients will be offered and consumed. Parents should be encouraged to think of the second course as a second opportunity to offer energy and nutrients and should not offer it only as a reward for finishing the savoury course.

The food groups

Bread, rice, potatoes, pasta and other starchy foods

A mixture of some white and some wholegrain varieties can be offered as the fibre load from only wholegrain cereals may be too high for some toddlers. Excess fibre can fill up the stomach and reduce food intake, thereby restricting energy and nutrient intake. Phytates in fibre reduce the absorption of certain nutrients, and excess fibre may exacerbate loose stools in some toddlers.

Fruit and vegetables

Fruit and vegetables should be offered at each meal and some snacks. Toddlers may be averse to the bitter taste of some vegetables and may eat a limited variety. This should not be a cause for concern as this age should be seen as a time for learning to like fruits and vegetables and parents should encourage their preschool children to eat these foods by setting an example and eating and enjoying these foods themselves.

Milk, cheese and yoghurt

Milk intake should reduce from 12 months of age. Three servings of milk, yoghurt and cheese per day will ensure calcium, riboflavin and iodine requirements are met. An excess of milk in the diet usually means less iron-rich foods are eaten and iron deficiency and anaemia are associated with toddler diets where there is 400 mL milk or more drunk daily [79, 80]. This is often toddlers drinking large bottles of milk during the day and/or night.

Toddlers up to 2 years of age should have whole (full-fat) milk for the extra vitamin A it contains. After 2 years toddlers can change to semi-skimmed milk if they are eating well and growing normally, but this is not necessary and the extra vitamin A in whole milk will support their immune system.

Growing up and toddler milks marketed for this age group are enriched with more iron, zinc and vitamin D than is provided in cow's milk. They can provide a nutritional safety net for toddlers who are not eating well, but a cheaper option is to give the toddler a vitamin and mineral supplement. These milks are lower in certain nutrients than cow's milk: calcium, phosphorus, iodine and riboflavin.

Substitute drinks for milk such as drinks based on soya, cereals, nuts or coconut do not have the same nutrient profile as mammalian milks and are not suitable for children as a milk substitute unless they are fortified with calcium, riboflavin, iodine and vitamin A. If unfortified versions are used, a supplement of those key nutrients should be given.

Meat, fish, eggs, nuts and pulses

Many toddlers do not like the texture of chewy meat and prefer soft tender cuts of meat products made from minced meat such as sausages, burgers and meatballs. As long as these foods are made from good quality ingredients with a high lean meat and low salt content, they will make a valuable contribution to a healthy diet. Chicken, which often has a softer texture than red meat, is popular with this age group.

Fish should be offered twice a week and one portion should be oily (p. 41). Most toddlers enjoy fish when served as fish fingers, fish cakes or fish and potato pie.

Dhal, lentils, chickpea flour in bhajis and starchy beans are commonly used by ethnic cultures and pulses can be used in soups and stews. Baked beans are popular and hummus and nut butters can be used as spreads. Finely ground nuts can be added to muesli or used in cakes, biscuits and puddings.

Butter, oils and fat spreads

Only small amounts should be used in food preparation.

Foods high in sugar

These high energy foods add flavour and enjoyment to meals. Limiting sugary foods to the amounts below will retain an average intake of around the SACN recommended maximum of 5% of energy from free sugars [4]:

- one serving per day of a nutritious sweet food such as cake, biscuits, pudding, cereal bar
- one serving per day of sweet spread such as jam or honey
- one serving per week of sweet drink or confectionery

An excess of butter, oils and fat spreads and/or foods high in sugar will increase the likelihood of obesity, which is rising in this age group.

Drinks

The use of bottles for drinks should be discontinued around 12 months as sucking on a bottle of milk can become a

Table 2.11 Food groups and recommended number of daily servings.

			Recommendations		
Food group	Foods included	Main nutrients supplied	Infants 6–12 months [60]	Toddlers and preschoolers 1–4 years	Schoolchildren 5–18 years
1. Bread, rice, potatoes, pasta and other starchy foods	Bread, chapatti, breakfast cereals, rice, couscous, pasta, millet, potatoes, yam and foods made with flour such as pizza bases, buns and pancakes	Carbohydrate B vitamins Fibre Some iron, zinc and calcium	3–4 servings a day	Serve at each meal and some snacks	4 servings per day Serve at each meal and one snack
2. Fruit and vegetables	Fresh, frozen, tinned and dried fruits and vegetables. Also pure fruit juices	Vitamin C Phytochemicals Fibre Carotenes	3–4 servings a day	Offer at each meal and some snacks and aim for about 5 small servings a day	Aim for 5 servings a day
3. Milk, cheese and yoghurt	Breastmilk, infant formulas, follow-on milks, cow's milk, yoghurts, cheese, custard and milk puddings	Calcium Protein Iodine Riboflavin Vitamin A in full-fat milk	Demand feeds of breastmilk or infant formula as main drink (about 500–600 mL/day) Some yoghurt and cheese Cow's milk in food	3 servings a day	3 servings a day
4. Meat, fish, eggs, nuts and pulses	Meat, fish, eggs, pulses, dhal, nuts, seeds	Iron Protein Zinc Magnesium B vitamins Vitamin A Omega-3 fatty acids: EPA and DHA from oily fish	1–2 servings a day 2–3 for vegetarians	2 servings a day 3 for vegetarians Fish should be offered twice per week and oily fish at least once per week*	2 servings a day 3 for vegetarians Fish should be offered twice per week and oily fish at least once per week*
5. Oils, butter and fat spreads	Cream, butter, fat spreads, cooking and salad oils, mayonnaise	Vitamin E Omega-3 fatty acids	Not required	In food preparation	In food preparation
High sugar foods and savoury snacks	Puddings, biscuits, cakes, jam, honey, syrups, chocolate, confectionery, sweet drinks, fruit juices, crisps and other high fat savoury snacks		Not required	Pudding, cakes or biscuits once per day Jam, honey or syrups once per day Chocolate, confectionery, sweet drinks, fruit juices, crisps and other high fat snacks one item once per week	Pudding, cakes or biscuits once per day Jam, honey or syrups once per day Chocolate, confectionery, sweet drinks, fruit juices, crisps and other high fat snacks one item once per week
Fluid	Drinks	Water Fluoride in areas with fluoridated tap water	Milk feeds Water with meals	6–8 drinks per day and more in hot weather or after extra physical activity	6–8 drinks per day and more in hot weather or after extra physical activity
Vitamin supplements			Vitamin D	Vitamin D	Vitamin D Folic acid for adolescent girls who could become pregnant

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
Serving sizes of food and drinks will increase as children grow. Examples of average portion sizes for different ages are shown in Tables 2.12 and 2.14.
* See p. 41.

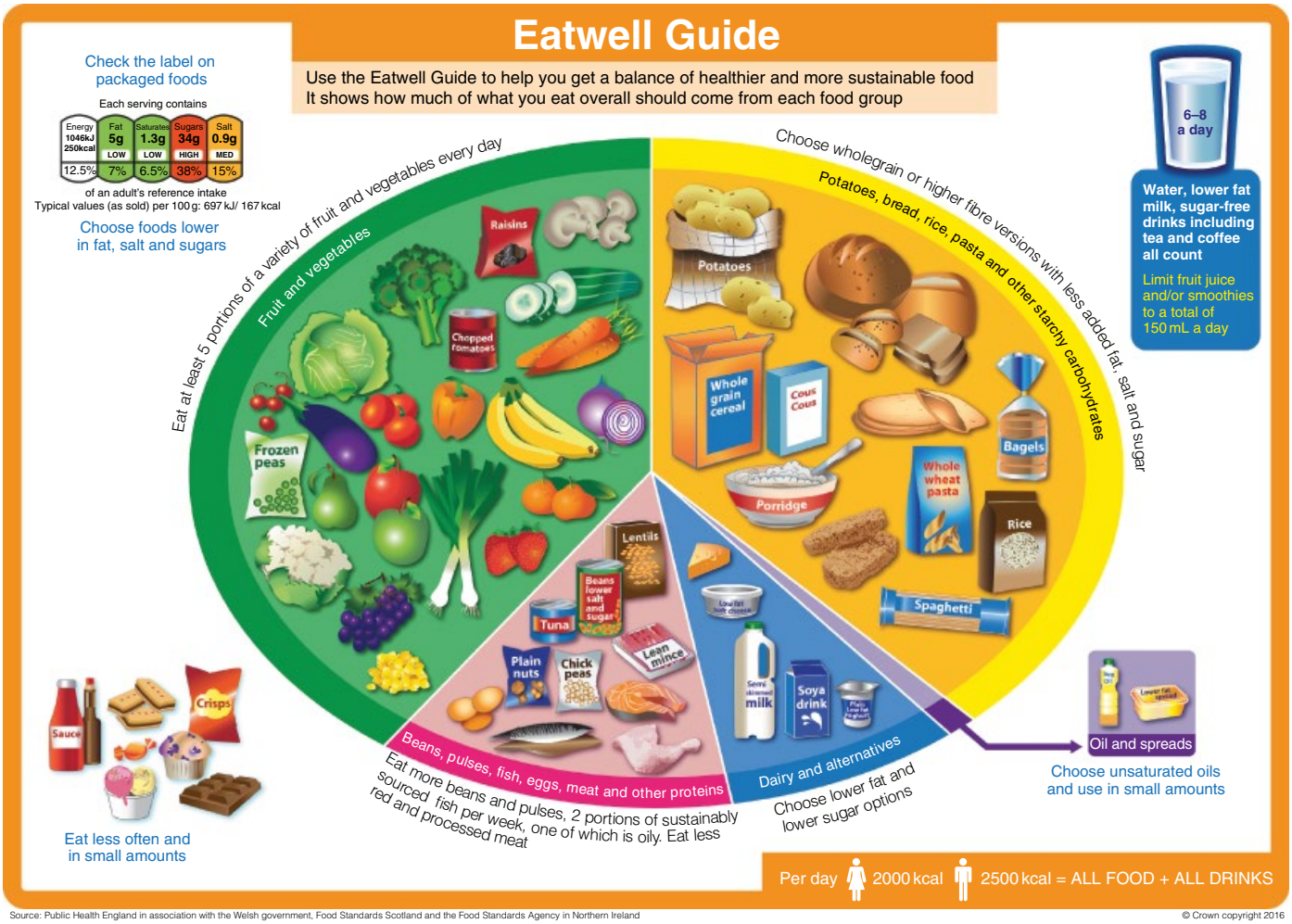

Figure 2.1 Eatwell Guide [78].

comfort habit that is hard to break. Children who drink sweet drinks from bottles have a higher risk of dental caries [61]. Water and milk are preferred drinks and should be given in a cup, beaker or glass. Six to eight drinks of about 100–120 mL can be offered throughout the day, with meals and snacks. More may be needed in very hot weather or after a lot of physical activity. Drinks containing artificial sweeteners should be kept to a minimum and be well diluted.

Portion sizes

The under 5s eat more on some days and less on other days; hence set portion sizes are not useful for them. The mid-points of the portion size ranges in Table 2.12 meet the RNI for nutrients and average energy requirement for children aged 1–4 years when combined according to the specified number of daily servings [81]. They can be used both to reassure parents of young children who eat small amounts and to limit overeating, particularly of high sugar foods.

Vitamin and mineral supplementation

A supplement of vitamin D is recommended for children up to at least the age of 5 years [3]. For preschool children who eat a balanced diet, other nutrient supplements are not required; however, some nutrients are 'at risk' in the preschool diet in addition to vitamin D, namely, iron and vitamin A (p. 38). Children who are particularly fussy eaters and exclude whole food groups may need additional supplements.

Guidance documents on food served in early years settings

The following guidelines are not mandatory and are not monitored by local authorities:

- England: The Voluntary Food and Drink Guidelines for Early Years Settings. https://app.croneri.co.uk/feature-articles/voluntary-food-and-drink-guidelines-early-years-settings
- Scotland: Setting the Table: Nutritional guidance and food standards for early years childcare providers in Scotland. http://www.healthscotland.com/documents/30341.aspx
- Wales: Food and nutrition for childcare settings. https://gov.wales/food-and-nutrition-childcare-settings-full-guidance

Table 2.12 Portion size ranges for children aged 1–4 years.

Food group	Foods	Range of portion sizes
Bread, rice, potatoes, pasta and other starchy foods • *5 servings per day*	Bread Mashed potato Pasta (cooked) Rice	½–1 medium slice 1–4 tbsp 2–5 tbsp 2–5 tbsp
Fruit and vegetables • *3 servings fruit and 3 servings of vegetables per day*	Apple/pear/peach Broccoli/cauliflower Clementine/tangerine/mandarin Sweet corn	¼–½ medium fruit 1–4 small florets or ½–2 tbsp ½–1 fruit ½–2 tbsp
Milk, cheese and yoghurt • *3 servings per day*	Cow's milk Grated cheese Yoghurt	100–120 mL or 3–4 fluid oz 2–4 tbsp 1 average pot or 125 mL
Meat, fish, eggs, nuts and pulses • *2 servings per day*	Baked beans in tomato sauce Chicken drumsticks Peanut butter Scrambled egg Tinned fish	2–4 tbsp ½–1 drumstick ½–1 tbsp 2–4 tbsp ½–1½ tbsp
Butter, oils and fat spreads • *2 servings per day*	Butter Oil	Thinly spread or 1 tsp
Foods high in sugar/savoury snacks • *1 serving per day of cake, biscuit, pudding or starchy snack* • *1 serving per day of sauces or sweet/savoury spreads* • *1 serving per week of confectionery, savoury snacks and sweet drinks*	Fruit crumble (e.g. apple or rhubarb) Ice cream Plain biscuits Honey/jam Sugar Crisps	2–4 tbsp 2–3 heaped tbsp 1–2 biscuits 1 tsp ½–1 tsp 4–6 crisps

tbsp, tablespoon (15 mL); tsp, teaspoon (5 mL).
Source: Adapted from More and Emmett [81]. Reproduced with permission of John Wiley & Sons.

- Northern Ireland: Nutrition matters for the early years: Guidance for feeding under fives in the childcare setting. https://www.publichealth.hscni.net/publications/nutrition-matters-early-years-guidance-feeding-under-fives-childcare-setting

Nursery milk

Children under 5 years are entitled to ⅓ pint (189 mL) milk per day if they attend a nursery or are with a registered childminder for more than 2 hours per day (www.nurserymilk.co.uk).

Developmental changes in preschool children

How easily parents manage to feed their young children depends to some extent on parental knowledge and parenting skills. At the same time developmental changes in toddlers affect how they respond to food and meals.

Neophobia

During their second year, toddlers develop a neophobic response to food, which means they become wary of trying new foods. The origin of this may be a survival mechanism to prevent the mobile toddler from poisoning themselves. This neophobic response usually peaks around 18 months and is more evident in some toddlers than others. If toddlers are being offered a wide variety of foods by around 12 months, then they will enter their second year with a wider range of foods they recognise, like and readily accept [82].

Disgust and contamination fears

Between 3 and 5 years, young children may develop disgust fears and stop eating foods they may have previously enjoyed [83]. They will refuse a food on sight if it resembles something they find disgusting, e.g. they may find spaghetti in sauce suddenly looks like worms. Contamination fears occur around the same time; if a disliked food is put on a plate next to a liked food, the toddler may refuse both foods.

Learning to like new foods

The neophobic response dissipates slowly throughout the rest of childhood and adolescence [84, 85]. Toddlers and young children can be helped to pass through this stage by eating in social groups, as they learn by copying adults and other children. It is, therefore, important that families eat together as often as possible and that toddlers are praised when they eat well. Toddlers may also learn to eat new foods when eating with other children at nursery or with friends. Some toddlers need to be offered a new food more than 10 times before they accept it as a liked food [82, 86].

Some toddlers have more problems than others and there are two main reasons for this in healthy individuals:

- Some become very rigid about the foods they will eat. They tend to be more emotional and more stubborn about

what they will or will not do. They do not copy other children and so will not copy other people's eating behaviour.
- Others may be more sensory sensitive and have extreme reactions to touch, taste and smell. They may be orally hypersensitive and have problems with different textures of food – they may have taken longer to progress from smooth to lumpy food and onto more difficult textures during complementary feeding. They may worry about getting their hands and face dirty and find it difficult to handle food and feed themselves.

Avoidant restrictive food intake disorder (ARFID) is the diagnosis given where there are nutritional or growth concerns with a restrictive eating pattern [87]. Toddlers who experience faltering growth need to be referred to specialists who can assess and advise.

Exacerbating food refusal

Parental anxiety when toddlers only eat a limited variety of foods can exacerbate the problem, especially if parents try to coerce or force-feed the child with food they are wary of or dislike. Until 4–5 years of age, young children's appetites are determined mainly by their energy and growth needs. They eat well at sometimes and less so at other times, and those who are not gaining excess weight should be allowed to decide the quantity they eat themselves.

Some parents expect their toddlers to eat more than they need and coerce or force-feed when the toddler is signalling they have had enough food. As mealtimes develop into a battle ground between toddler and parent, the toddler can lose their appetite just by becoming anxious as the mealtime approaches. Toddlers may use the following signals to indicate that they have had enough food:

- saying 'no'
- keeping their mouth shut when food is offered
- turning their head away from food being offered
- pushing away a spoon, bowl or plate containing food
- holding food in their mouth and refusing to swallow it
- spitting food out repeatedly
- crying, shouting or screaming
- gagging, retching or vomiting
- trying to escape from the meal by climbing out of their chair or highchair

From around 5 years of age, children learn to modify their eating according to social rules and will learn to finish what is on their plate or eat when others are eating even if they are not hungry, and they will also begin to comfort eat.

Social support for preschool children in low-income families

Healthy Start

Families who qualify for this scheme are those in receipt of certain benefits. Under the scheme they are entitled to vouchers that can be exchanged for cow's milk, fresh fruit and vegetables and infant formula (Table 2.13). Children up to 4 years in these families are also entitled to free vitamin drops containing vitamins A, C and D. Details of entitlement and how to access the scheme can be found on the Healthy Start website (www.healthystart.nhs.uk).

Table 2.13 Voucher entitlement for infants and children through Healthy Start.

	Number of vouchers valued at £3.10/week*
Term infants up to 12 months	2
Preterm infants up to 12 months after EDD	2
Children 1–4 years	1

EDD, estimated date of delivery.
* Voucher value as defined in 2020.

Sure Start children's centres

Sure Start is a government-led initiative aimed at giving every child aged 0–4 years the best possible start in life; it offers a broad range of services focusing on family health, early years care, education and improved well-being programmes. Services include advice on healthcare and child development, play schemes, parenting classes, family outreach support and adult education and advice. One aim is to help overcome the barriers to feeding young children a healthy diet, and dietitians have been involved in:

- training Sure Start workers, community food assistants and playworkers about weaning and healthy eating messages
- developing food policies with parents and staff
- developing resources with parents
- education sessions for parents on cooking, shopping and weaning. Cook and eat sessions are popular, and developing literacy skills has become part of some shopping and cooking sessions
- holiday play schemes
- clinical input and home visits

Recently many schemes have closed, but operating schemes and activities can be accessed on the Sure Start website (www.gov.uk/find-sure-start-childrens-centre).

Schoolchildren (5–18 years)

From around the age of 5 years, the principles of healthy eating that are recommended for the adult population apply. Guidance on macronutrient intakes is [2]:

- at least 50% of energy from total carbohydrates
- a maximum of 5% of energy from free sugars [4]
- a maximum of 35% of energy from fat
- a maximum of 11% of energy from saturated fat
- about 15% energy from protein

In order to satisfy the nutrient requirements of children, the recommendations need to be more specific than those given by PHE for the general population (Figure 2.1). Table 2.14 is based on recommendations from the Paediatric Specialist

Group of the British Dietetic Association, which meet the RNI for each age group when providing the EAR for energy.

Vegetarian and vegan diets

A well-planned vegetarian diet based around the same food groups shown in Table 2.11 can be nutritionally adequate. Of the group 4 foods eggs, nuts and pulses will be eaten instead of meat and fish. At least three servings are needed each day to provide an adequate iron intake as the bioavailability of iron from eggs and plant sources is much lower than that of haem iron found in meat and oily fish. Good sources of omega-3 fatty acids such as walnuts, linseeds and walnut and rapeseed oils need to be recommended.

Vegan diets are unlikely to provide adequate nutrients for optimal growth and development. Replacing milk, cheese and yoghurt with substitute drinks based on pulses

Table 2.14 Portion size ranges and food group servings per day for school-age children.

					15–18 years	
Food groups		4–6 years	7–10 years	11–14 years	Girls	Boys
Bread, rice, potatoes, pasta and other starchy foods • *4 servings per day*	Bread	36–72 g	54–108 g	72–144 g	72–144 g	108–180 g
	– medium slices	1–2	1½–3	2–4	2–4	3–5
	Potato	70–100 g	90–150 g	120–180 g	120–180 g	170–190 g
	Pasta (cooked)	70–100 g	90–150 g	120–180 g	120–180 g	180–220 g
	Rice (cooked)	65–95 g	90–150 g	120–180 g	120–180 g	170–200 g
	Dry breakfast cereal	18–32 g	25–45 g	30–50 g	30–50 g	45–55 g
	Weetabix	1–2	1½–2½	2–3½	2–3½	3–5
	Porridge, cooked	100–160 g	120–180 g	175–275 g	175–275 g	240–360 g
Fruit and vegetables • *3 servings of fruit and 3 servings of vegetables per day*	Apple/pear/orange	1 small	1 medium	1 medium	1 large	1 large
	Banana	1 medium	1 medium	1 large	1 large	1 large
	Berries/grapes	45–75 g	55–85 g	60–100 g	80–100 g	80–100 g
	Kiwi/plums/apricots	1 fruit	1–2 fruits	2 fruits	2–3 fruits	2–3 fruits
	Vegetables	30–40 g	45–60 g	60–80 g	80 g	80 g
Milk, cheese and yoghurt • *3 servings per day*	Milk	120–140 mL	140–180 mL	190–210 mL	190–210 mL	230–250 mL
	Yoghurt/lassi	125 g	130–150 g	140–160 g	140–160 g	160–240 g
	Cheese/paneer	20–30 g	25–38 g	30–45 g	30–45 g	35–50 g
	Custard	70–110 g	90–150 g	100–160 g	100–160 g	110–210 g
	Rice pudding	60–120 g	800–160 g	120–180 g	120–180 g	135–180 g
Meat, fish, eggs, nuts and pulses • *2 servings per day* • *2 portions fish/week – one of oily fish*	Meat	35–55 g	45–75 g	60–100 g	60–100 g	70–110 g
	Fish	35–50 g	45–75 g	70–110 g	70–110 g	75–125 g
	Fishcakes/fingers	35–55 g	50–70 g	65–105 g	65–105 g	110–130 g
	Eggs	1 medium	1 large	1–2 eggs	1–2 eggs	2 eggs
	Nut butter	22–27 g	30–35 g	40–50 g	40–50 g	60–70 g
	Nuts/Bombay mix	25–35 g	30–40 g	40–50 g	40–50 g	45–55 g
	Baked beans	55–95 g	75–115 g	90–150 g	90–150 g	110–170 g
	Pulses/beans (cooked)	35–65 g	60–120 g	70–130 g	75–125 g	105–175 g
Butter, oils and fat spreads • *2 servings per day*	Butter/fat spread	1½ tsp	2 tsp	3 tsp	3 tsp	4 tsp
	Oil	1 tsp	2 tsp	1 tbsp	1 tbsp	1 tbsp
	Mayonnaise	½ tbsp	½–1 tbsp	1 tbsp	1 tbsp	1-1½ tbsp
	Double cream	1 tbsp	2 tbsp	2–3 tbsp	2–3 tbsp	2–3 tbsp
Cake, biscuit, pudding • *1 serving per day*	Biscuits	1–2	2–3	3–4	3–4	3–4
	Cake/croissant	25–35 g	40–50 g	50–70 g	50–70 g	80–100 g
	Fruit-based pudding	30–60 g	45–80 g	60–100 g	60–100 g	90–120 g
	Ice cream	50–70 g	65–85 g	75–95 g	75–95 g	80–110 g
Sauces and sweet/savoury spreads • *2 servings per day*	Jam/honey/syrup	1–2 tsp	2 tsp	2 tsp	2 tsp	3 tsp
	Gravy	1½–2 tbsp	2 tbsp	3 tbsp	3 tbsp	4 tbsp
	Tomato or curry sauce	2–2½ tbsp	2½–3½ tbsp	3–4 tbsp	3–4 tbsp	4–5 tbsp
	Ketchup/savoury sauce	1 tbsp	1½ tbsp	2 tbsp	2 tbsp	2–3 tbsp
1 serving per week of either sweet drinks, confectionery or savoury snacks	Fruit juices/sweet drinks	120–140 mL	150–200 mL	200–250 mL	200–250 mL	250–330 mL
	Sweets	25 g	35 g	40 g	40 g	45 g
	Chocolate/Indian sweets	25 g	35 g	40 g	40 g	45 g
	Crisps/other packet snacks	½ small packet (25 g)	1 small packet (25 g)	1 small packet (25 g)	1 small packet (25 g)	1 packet (37.5 g)

tbsp, tablespoon (15 mL); tsp, teaspoon (5 mL).

such as soy, nuts, coconut and cereals will not provide children with the amounts of calcium, riboflavin, zinc, vitamin A and iodine found in dairy products. Micronutrient supplementation providing the RNI for iron, iodine, riboflavin, calcium, phosphorus and vitamins A, B_{12} and D is required to prevent malnutrition.

Vegan children are unlikely to achieve their full adult height potential even with micronutrient supplements as epidemiological studies show milk and meat in diets are associated with increased height [88, 89]. It is hypothesised that milk and meat proteins along with zinc, iodine and other hormonal factors exert positive effects on the growth plate of growing children [90, 91].

Neophobia

During childhood many children remain neophobic, preferring to eat foods they are familiar with. They must be motivated to taste new foods. Work in this field continues to show that the number of times children are exposed to food increases the likelihood they will try the food and then learn to like it [92].

Adolescent growth spurt

The adolescent growth spurt lasts approximately 2 years and takes place, on average, around 12 years of age for girls and 14 years for boys, but can be 2 years earlier or later. The peak height velocity can be up to 13 cm/year for boys and 10 cm/year for girls [93]. Growth rate then declines until full height is reached. During this time adolescents' energy requirements will be noticeably higher and appetite may be larger. Extra snacks often make up this increase in food intake, but their snacks are often low nutrient, high fat and high sugar foods, rather than snacks from combinations of the five food groups, which would enhance their nutrient intakes.

Good choices for snacks and drinks

These snacks are suitable for all children from 1 year of age, not just for adolescents:

- fresh fruit (dried fruit can be cariogenic when eaten as a snack so it is not advised)
- vegetable sticks, e.g. carrot, cucumber, pepper, baby corn and dips based on yoghurt, cream cheese or pulses such as hummus
- wholegrain breakfast cereals with milk
- cheese cubes and crackers or chapatti
- unsalted nuts
- sandwiches, filled rolls and pitta breads
- French toast or toast with a range of spreads, used sparingly
- slices of pizza with a plain dough base that has not been fried
- yoghurt and fromage frais
- crumpets, scones, currant buns, teacakes, Scotch pancakes and fruit muffins
- home-made plain popcorn
- cakes containing nuts or dried fruit or vegetables, e.g. fruit cake and carrot cake
- onion and vegetable bhajis

Suitable healthy drinks for meal and snack times include:

- water
- milk (plain or flavoured)
- vegetable juices
- no added sugar (sugar-free) squashes

Emotional changes in adolescents

During adolescence teenagers develop their own autonomy, rejecting their parents' values and developing their own. Values around food and meals are no exception to this, and many teenagers change their eating habits so that they are different from the rest of their family [85]. Their choices often include commercial and low nutrient snack foods. Hill [85] suggested adolescents may:

- eat more and more food outside the home and convenience may be influential in choices made
- eat according to personal ideology such as the use of vegetarian or vegan diets
- begin slimming or weight control (whether justified or not)
- choose less healthy foods as an act of parental defiance and peer solidarity
- consume certain foods or brands due to peer group pressure
- follow specific diets to enhance sporting prowess

Understanding why adolescents choose the foods they do is crucial when developing health education programmes for this age group.

Nutritional initiatives in schools

Food and drinks consumed at school can make a large contribution to a child's nutrient intake.

School food standards

These vary slightly across the four countries in the UK, and it is up to the Board of Governors for each school to ensure they are followed as there is no statutory monitoring.

England has food-based standards (www.legislation.gov.uk/uksi/2014/1603/pdfs/uksi_20141603_en.pdf).

They apply to:

- local authority maintained nursery, primary, secondary, boarding and special schools
- Pupil Referral Units
- academies that opened prior to 2010 and academies and free schools entering into a funding agreement from June 2014
- non-maintained special schools

Practical guidance is given on the School Food Plan website (www.schoolfoodplan.com). From September 2014, every child in reception, year 1 and year 2 in state-funded schools, is entitled to a free school lunch.

Wales has food-based standards (http://learning.gov.wales/docs/learningwales/publications/160226-healthy-eating-maintained-schools-en-v2.pdf).

Scotland has nutrient- and food-based standards (www.gov.scot/publications/healthy-eating-schools-guide-implementing-nutritional-requirements-food-drink-schools-9780755958306).

Northern Ireland has food-based standards (www.education-ni.gov.uk/sites/default/files/publications/de/de1-09-125640-nutritional-standards-for-school-lunches-a-guide-for-implementation-3-2.pdf).

The National Fruit and Veg Scheme

All 4- to 6-year-old children in fully state-funded infant, primary and special schools are entitled to a free piece of fruit or vegetable each school day (www.nhs.uk/live-well/eat-well/school-fruit-and-vegetable-scheme).

Subsidised school milk

This is available for primary schoolchildren. In England schools choose whether they wish to offer it, but in Wales children up to 7 years of age are entitled to ⅓ pint (189 mL) milk free per day (www.gov.uk/guidance/eligibility-for-the-school-milk-subsidy-scheme-milk-consumed-from-1-august-2017).

School breakfasts

Many schools have begun offering breakfasts, and anecdotal claims have been made that school attendance, behaviour and performance have improved as a result. However, a systematic review found that although a school breakfast is better than no breakfast, this only makes a difference in children who are malnourished. Furthermore they found that any improved academic performance may be due in part to the increased school attendance that a school breakfast encourages, rather than the food itself [94]. Children say they enjoy the social side of school breakfasts.

Packed lunches

Many children bring a packed lunch rather than have school meals that they dislike, or that their parents either cannot afford or of which they disapprove. Packed lunches can be of poor nutritional content; a survey of primary school lunchboxes showed that only 1% met all the food-based standards for school meals [95]: 85% contained a sandwich; 82% contained confectionery and/or crisps; 54% contained fruit; 19% contained vegetables.

A government leaflet on suggestions for healthy lunchboxes is available at www.healthylunch.org.uk/government. Suggestions for packed lunchboxes are given in Table 2.15. A small ice pack or a frozen drink will keep a closed lunchbox cool for a few hours.

Table 2.15 Suggestions for packed lunchboxes.

Food group	Suitable foods
Bread, rice, potatoes, pasta and other starchy foods	This should be the base of the lunch: • Breads, rolls, wraps and pittas can be filled or used for sandwiches • Crispbread or bread sticks • Pasta, rice or cooked potatoes as the base for a salad or soup • Buns, scones, tea breads
Fruit and vegetables	• Sliced in sandwiches • Combined in a salad • Sticks of raw vegetables (celery, carrots, cucumber) or small tomatoes as finger foods or crunchy alternative to crisps • Pieces of fruit or small packets of dried fruit
Milk, cheese and yoghurt	• Cheese is a popular sandwich filling • Cubes or triangles of cheese as finger foods • Pots of yoghurts, fromage frais or rice pudding are popular desserts • Cartons of milk or flavoured milk as the drink
Meat, fish, eggs, nuts and pulses	• Cold meats or flaked fish can be included in sandwiches or salads • Chicken drumsticks • Hard-boiled eggs • Falafels or vegetable bhajis • Sausages, ham and salamis are processed meats and should be limited
Combined food group foods	• Slices of quiche or pizza • Soups
Foods high in sugar	• Small cakes, plain biscuits, pancakes or muffins

Teenage girls of childbearing age

All women of childbearing age should have a nutritious diet with adequate folate content. The Department of Health recommends a supplement of 400 µg folic acid for any woman or teenager who could become pregnant. Since most teenage pregnancies are unplanned, a diet rich in folate should be recommended to all teenage girls.

Pregnancy

Pregnancy during the teenage years places extra nutritional needs on girls who may not have finished growing themselves and who will not have attained their peak bone mass. Nutrient requirements have not been specified for these young mothers, but a healthy balanced diet with folic acid and vitamin D supplementation would be a minimum requirement. For those eating poorly a multivitamin and mineral supplement (not containing retinol) could be recommended. Under the Healthy Start scheme, all pregnant girls under 18 years old are entitled to benefits regardless of their financial circumstances [96].

Nutritional needs of adolescents training as athletes

Meeting the higher energy needs for adolescents undertaking sports training is essential and may require specialist input from a registered sports dietitian. Energy requirements should be calculated to support the training programme using basal metabolic rate and physical activity level and

adding in 60–100 kcal (250–420 kJ)/day to allow for extra growth [2]. Monthly height measurement can be used to assess when the pubertal growth spurt is taking place. It is essential to meet all micronutrient requirements as sports training can have a negative effect on the immune system [97]. Adolescents in sports training should eat a high carbohydrate snack or meal, containing some protein, within an hour of finishing training to ensure good glycogen stores within muscles (as should any other athlete).

Current challenges in paediatric nutrition in the UK

Persistently high rates of obesity in UK children remain the greatest challenge and are discussed in Chapter 25. Other specific nutritional problems are discussed in other chapters: faltering weight (Chapter 24), constipation and diarrhoea (Chapter 8) and food allergy (Chapter 15).

Despite the initiatives and guidelines for healthy eating outlined above, several other paediatric nutritional challenges persist in the UK.

Breastfeeding rates during infancy are low

The last UK IFS in 2010 reported that 81% of mothers initiate breastfeeding soon after birth; however, exclusive breastfeeding declines rapidly with only 46% mothers doing so at the end of the first week, 23% at 6 weeks and 1% at 6 months [54] (Table 2.16). Similar figures were reported in the Scottish Maternal and Infant Nutrition Survey in 2017 [56]. This decline is often due to lack of support to address common problems and difficulties and a mother's perception of an inadequate breastmilk supply for her infant. NICE recommends that when mothers leave a maternity unit, they should be given contact details of breastfeeding counsellors and information on local peer support groups [32].

Free sugar, saturated fat and fibre intakes in all age groups of children do not meet recommendations

Figures from the 2018 National Diet and Nutrition Survey (NDNS) [76] show that children's current intakes of carbohydrates, total fat and protein are close to the guidelines of 50%, 35% and 15% of energy, respectively, but those of free sugars and saturated fat are higher than recommended (Table 2.17) and intakes of fibre are lower than recommendations (Table 2.18).

Foods eaten on the way to and from school make a significant contribution to schoolchildren's nutrition, particularly intakes of free sugars and saturated fats. A survey produced by a large international school caterer reported that in 2005 [98]:

- £519 million was spent by schoolchildren on their way to and from school
- Main purchases were sweets, crisps and savoury snacks, chocolate, canned fizzy drinks, chewing gum, other soft drinks, cigarettes, bottled water, chips and ice cream

Micronutrient intakes are not met in all populations of children

Preschool children

The 2018 NDNS indicates that the mean intake of the 1½–3 years population is above the RNI for all nutrients except iron and vitamin D. Less than 50% of this population met the RNI for iron and the mean intake of vitamin D was 34% RNI. More than 3% of this population did not meet the LRNI for iron, vitamin A and zinc [76] (Table 2.19). However, zinc deficiency would not be seen in this population if the UK LRNI and RNI were not set higher than in other countries, e.g. the RNI for zinc is 3 mg/day in the USA compared with 5 mg/day in the UK.

Schoolchildren

The food intakes of primary schoolchildren are fairly closely controlled by their parents and the 2018 NDNS showed that the 'at-risk' nutrients for primary-age schoolchildren (4–10 years of age) are vitamins A and D, iodine and zinc. In stark contrast older children (11–18 years), who are making more of their own food choices, have low average intakes for most micronutrients (Table 2.19).

Implications of poor teenage diets on future risk of osteoporosis

Even after the growth spurt, calcification of bones continues as peak bone mass is not reached until the early to late 20s. It is later for males than females [99]. A vitamin D supplement

Table 2.16 Incidence and prevalence of breastfeeding in the UK [54].

	% of infants in the UK receiving some breastmilk				% of infants in the UK being exclusively breastfed	
Age of infants	1995	2000	2005	2010	2005	2010
At birth	66	69	76	81	76	81
1 week	56	55	63	69	45	46
6 weeks	42	42	48	55	21	23
4 months	27	28	34	42	7	12
6 months	21	21	25	34	<1	1
9 months	14	13	18	23	–	–

Table 2.17 Macronutrient intakes of children, National Diet and Nutrition Survey [76].

	Macronutrient intakes as % energy [76]			
Age group (years)	Carbohydrates	Free sugars	Total fat	Saturated Fat
1½–3	50.5	11.3	34.4	14.5
4–10	51.6	13.5	33.4	13
11–18	50.3	14.1	33.7	12.4
Recommendation [2]	50	<5	35	<10

Source: Food Standards Agency and Public Health England 2018.

Table 2.18 Fibre recommendations and current intakes in children, National Diet and Nutrition Survey [76].

Age group (years)	Recommendations (g/day) [4]	Age group (years)	Average intakes (g/day) [76]
2–5	15	1½–3	10.3
5–11	20	4–11	14
11–16	25	11–18	15.3
16–18	30		

Source: Food Standards Agency and Public Health England 2018.

Table 2.19 Percentage of population groups with nutrient intakes from food and supplements below the LRNI, National Diet and Nutrition Survey [76].

	Age groups				
	1½–3 years	4–10 years		11–18 years	
Nutrient	Boys and girls	Boys	Girls	Boys	Girls
Vitamin A	15	13	11	19	24
Riboflavin	1	0	1	13	26
Folate	1	0	1	2	15
Iron	10	0	3	12	54
Calcium	1	2	1	11	22
Magnesium	0	0	1	27	50
Potassium	0	0	0	18	38
Iodine	3	6	4	14	27
Selenium	0	1	1	26	45
Zinc	5	9	14	18	27

LRNI, lower reference nutrient intake.
Source: Food Standards Agency and Public Health England 2018.

and three servings of milk, cheese or yoghurt daily will ensure that calcium and phosphorus requirements are being met to ensure bone deposition, but a balanced diet providing a wider range of nutrients is now considered necessary for optimal peak bone mass [100]. Calcium from dietary cow's milk is more effective than calcium supplements in preventing osteoporosis in older women [101].

Preventable dietary iron deficiency remains prevalent in 1- to 5-year-olds and adolescent girls

Iron deficiency is associated with frequent infections, poor weight gain, developmental delay and behaviour disorders. It is usually of dietary origin. Table 2.20 shows the low haemoglobin and ferritin levels of population groups from the 2018 NDNS.

Preschool children

Iron deficiency is more common in 1- to 5-years-olds than those over 5 years and is seen more in socially disadvantaged groups and in immigrant populations.

Depletion of iron stores in the second half of infancy occurs when the iron content of the weaning diet is poor [47], even though deficiency may not be evident until after 12 months of age. The early introduction of cow's milk as a main drink before 12 months of age is a risk factor [102]. Availability and choice of commercial baby foods may contribute to an iron-deficient weaning diet for Muslim families; there is a range of halal meat-based baby foods in the UK, but many families only buy or have access to low iron vegetable-only-based savoury varieties and desserts.

Overdependence on milk (consuming in excess of 400 mL/day) in toddlers and preschool children, where it replaces iron-rich foods, is another common cause [79, 80, 103].

Schoolchildren

In older children deficiency occurs most commonly in teenage girls who have begun menstruating and have high iron requirements and in children who are vegetarian or vegan or who do not eat a balanced diet.

Prevention of iron deficiency

Dietary advice should emphasise:

- the importance of regularly consuming iron-rich foods: meat, oily fish, eggs, nuts, pulses, iron-fortified breakfast cereals and dried fruit
- liver and liver products are a very rich source of iron, but because they contain very high levels of vitamin A, they should be limited to one serving per week

Table 2.20 Percentage of population groups with low haemoglobin and/or ferritin levels, National Diet and Nutrition Survey [76].

	1½–3 years	4–10 years		11–18 years	
Age	Boys and girls	Boys	Girls	Boys	Girls
Low haemoglobin levels	5	1	4	1	9
Low ferritin levels	31	9	9	2	24
Low haemoglobin and low ferritin levels	–	2	0	1	9

Source: Food Standards Agency and Public Health England 2018.

- haem iron in meat and fish is absorbed much more efficiently than non-haem iron from eggs, nuts, pulses, cereals, fruit and vegetables. Simultaneous consumption of fruits and vegetables rich in vitamin C will enhance non-haem iron absorption. This is a particularly important measure in vegetarian children
- iron uptake can be maximised by including foods rich in vitamin C and avoiding drinking tea, which hampers absorption at mealtimes

Preventable dental caries and tooth extractions are common in all ages of children due to high sugar intakes and poor oral hygiene

Children, particularly the under 5s, are more susceptible to dental caries than adults although the incidence of caries in children in the UK decreased following the introduction of fluoride toothpaste in the 1970s. However, the current high and frequent consumption of sugary foods and sugary acidic drinks contributes to:

- 23.3% of 5-year-olds in 2017 having at least one decayed, missing or filled tooth. The average was 3–4 teeth affected. The incidence ranged from 13.6% in children from the least deprived backgrounds to 33.7% from the most deprived backgrounds [104]
- the NHS spending £50.5 million on hospital-based tooth extractions for 0- to 19-year-olds in 2015–2016

The incidence of dental disease is lower in children who brush their teeth twice a day with fluoridated toothpaste and those over the age of 1 year limiting sugary and acidic food and drinks to four eating episodes per day, e.g. three meals and one snack [105]. PHE recommendations on delivering better oral health include the following [106]:

- tooth brushing should begin in infancy from the time the first tooth erupts
- teeth should be brushed twice daily with fluoridated toothpaste, once in the morning and last thing at night
- use a smear of paste containing at least 1000 ppm of fluoride up to the age of 3 years
- use a pea-sized amount of at least 1000 ppm of fluoride paste between 3 and 6 years
- use a pea-sized amount of 1350–1500 ppm of fluoride paste from the age of 7 years

Vitamin D supplements are not routinely given to all children to prevent deficiency

When body stores are low and cutaneous synthesis and dietary sources of vitamin D are limited, vitamin D deficiency can develop in rapidly growing infants, toddlers and adolescents. The number of infants and children with preventable rickets, hypocalcaemic seizures or cardiomyopathy resulting from extremely low levels of vitamin D has been rising in developed countries [107]. British paediatricians recently reported the following [108]:

- 125 cases of nutritional rickets over 2 years (March 2015 to March 2017)
- the majority were of black and South Asian origin and more boys than girls were affected
- 78% were not taking vitamin D supplements because parents had not been informed by healthcare practitioners to give them
- radiological abnormalities included bowed legs and swollen wrists
- co-morbidities included:
  - delayed gross motor development in 26%
  - fractures in 10%
  - hypocalcaemic seizures in 8%
  - dilated cardiomyopathy in four cases, of whom two died

Epidemiological studies [109] report associations between low vitamin D levels and higher rates of inflammatory and autoimmune diseases and other chronic diseases in children including:

- type 1 and type 2 diabetes
- upper respiratory tract infections
- wheeze, including asthma
- infectious diseases

Food sources of vitamin D are few in UK diets:

- Oily fish is the only significant food source
- Eggs and meat provide very small amounts
- Breastmilk provides extremely small amounts and varies depending on the mother's own vitamin D status

Some foods in the UK are fortified with small amounts of vitamin D:

- margarine, but not necessarily all fat spreads
- evaporated milk
- infant, follow-on and toddler formula milks
- some brands of breakfast cereals and yoghurts

Some countries, e.g. Finland, the USA and Canada, fortify a wider variety of foods with vitamin D such as fresh cow's milk, dairy products and fruit juices.

The 2018 NDNS [76] reports that very few children consumed the recommended SI or RNI for vitamin D through food alone (Table 2.21) and very few took the recommended supplements to ensure nutritional requirements are met (Table 2.22). Blood results from the NDNS indicate deficiency is highest in January to March when:

- 19% of children aged 4–10 years
- 37% of children aged 11–18 years

had blood vitamin D concentrations below 25 nmol/L, the threshold indicating risk of deficiency.

Over-the-counter supplements containing only vitamin D are widely available, and most multivitamin supplements for infants, children and pregnant and breastfeeding women include vitamin D. The Healthy Start vitamins are the most cost-effective supplement, but they are only available in some NHS clinics. Although NICE recommends that local authorities provide them free of charge to beneficiaries of the Healthy Start scheme and sell them

Table 2.21 Mean daily vitamin D intakes (µg/day) in children in the UK [76].

	Age groups				
	1½–3 years	4–10 years		11–18 years	
Source of vitamin D	Boys and girls	Boys	Girls	Boys	Girls
Food only	2	2.1	1.9	2.3	1.9
Food and supplements	2.9	2.5	2.8	2.5	4.6

Source: Food Standards Agency and Public Health England 2018.

Table 2.22 Public Health England recommendations for vitamin D supplementation [110] and European tolerable upper intake levels for infants, mothers and children.

Population group	Recommended daily supplement	European tolerable upper intake levels per day
Breastfed and formula-fed infants from birth	8.5–10 µg	25/35 µg*
Formula-fed infants who are drinking less than 500 mL formula milk	8.5–10 µg	25/35 µg*
Breastfed preterm infants	A vitamin supplement that includes vitamin D is usually prescribed	
Preschool children 1–4 years	10 µg	50 µg
Children 5–10 years	10 µg during autumn and winter	50 µg
Children 11–17 years	10 µg during autumn and winter	100 µg
Pregnant and breastfeeding women	10 µg	100 µg

* 25 µg for infants under 6 months, 35µg for infants 6–12 months.

to other clients, not all do this. There is no harm in school-children taking a daily 10 µg supplement all year round as the European UL (shown in Table 2.22) will not be exceeded.

Cutaneous synthesis can be the major source of vitamin D for some children, but only occurs in the UK when outside with some bare skin exposed to daylight in the summer months. Synthesis is regulated and shuts off when a particular plateau is reached so excessive amounts are not synthesised [111]. Vitamin D is stored in the body when cutaneous synthesis and dietary intakes exceed daily requirements and these stores can be used during the winter months, although stored levels may not last all winter.

The ideal time to spend outside each day to ensure adequate vitamin D levels is not defined as cutaneous synthesis varies depending on:

- season – the critical wavelength in daylight only reaches the UK between April and September; it is absorbed by the atmosphere during autumn and winter months
- latitude – less vitamin D is made in the north of the UK than in the south where more of the UVB rays are present
- weather – on a cloudy day less vitamin D is made than on a bright sunny day
- pollution in the air – reduces the critical UV light waves
- time of day – more vitamin D is synthesised when sunlight is most intense in the middle of the day compared with early morning and late afternoon
- skin type – darker skins require more time in the sun to produce the same amount of vitamin D so children with pigmented skins are at higher risk of deficiency
- lifestyles:
  - time spent outside in April to September
  - amount of bare skin exposure when outside; cutaneous synthesis is extremely limited when most skin is covered as dictated by fashion or religious and cultural traditions
- use of sunscreen – it blocks cutaneous synthesis

Conflicting advice on the use of sunscreen

Concern over the balance between having sufficient sun exposure to produce vitamin D and overexposure leading to burning of the skin and an increased risk of skin cancer has led to confusion in public health messages. To provide unified, evidence-based advice on the subject, a consensus statement on vitamin D was agreed in 2010 by several organisations with an interest in this area [112]:

> The time required to make sufficient vitamin D varies according to a number of environmental, physical and personal factors, but is typically short and less than the amount of time needed for skin to redden and burn. Enjoying the sun safely, while taking care not to burn, can help to provide the benefits of vitamin D without unduly raising the risk of skin cancer. Vitamin D supplements and specific foods can help to maintain sufficient levels of vitamin D, particularly in people at risk of deficiency. However, there is still a lot of uncertainty around what levels qualify as 'optimal' or 'sufficient'.

Inappropriate dieting leading to poor nutritional intakes

Girls as young as 9 years old, and some younger, indicate body dissatisfaction and a desire to be thinner. Similar-aged boys aspire for a more muscled body, but overweight boys and girls both desire weight loss and are unhappy with their body shape [113, 114]. Hill suggested this body dissatisfaction was a result of picking up on parental attitudes to weight and shape and the idealisation of thinness promoted in the media and peer behaviour [85].

Food safety

Good food hygiene and storage is extremely important for young children, particularly infants and children under 5 years. To offset any risks of bacterial food poisoning, meat, fish, shellfish and eggs should be well cooked right through.

Dioxin levels in oily fish

Varying levels of dioxins accumulate in the fatty tissues of oily fish, and to limit their intake, the Food Standards Agency recommends that boys have a maximum of four portions of oily fish per week. A maximum limit of two portions is set for girls to reduce the amounts they will have accumulated in their tissues as they enter their childbearing years [115].

Mercury levels in large fish

Large fish (marlin, swordfish and shark) live for many years and can accumulate high levels of mercury in their flesh. PHE recommends that pregnant women, babies and young children under 5 years do not eat these fish [115].

High vitamin A levels in liver

Although liver is a very good source of several nutrients, particularly some 'at-risk' nutrients discussed above, e.g. iron and zinc, it contains very high levels of vitamin A. SACN has recommended that no one should increase their consumption of liver beyond one portion per week [116].

Organic foods

Many parents choose to buy organic food for their infants and children despite the extra expense; the majority of commercially prepared baby foods sold are now organic. Parents do this to avoid the possible detrimental effects that pesticide residues found in foods from non-organic sources may have on the developing organs and systems. This remains a controversial issue as food safety bodies in the UK and Europe only allow pesticides at levels that are judged not to be harmful in commercial foods for infants and young children (0–3 years). However, advocates of organic food point out that there may be toxic effects of ingesting combinations of several different chemicals that may have been harmless when tested individually. Many of these chemicals are new, having only been synthesised in the last few decades, so their potential cumulative effects are unknown. Recent publications support this view and the advantage of an absence of antibiotics in organic food [117].

Studies have been published linking pesticide or synthetic chemical exposure in children with an increased incidence of cancer [118] and impaired cognitive function [119]. *In utero* exposure of the foetus to these chemicals may be the most damaging [120].

Controversial issues around nutrients and foods

Omega-3 fatty acids and learning skills

Optimum brain functioning and sight are dependent on an adequate intake of the omega-3 LCP, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), during foetal growth and early infancy [121]. They are present in breastmilk and are added to all whey-dominant and casein-dominant infant formulas (Table 1.14). Whether their presence in food or supplements for older infants and children influences brain function, behaviour or the risk of atopy remains controversial.

A weekly serve of oily fish will ensure an adequate intake of omega-3 LCP. Walnuts and linseeds as well as rapeseed, walnut, linseed and soya oils are good sources of the omega-3 essential fatty acid, α-linolenic acid. Current research has not shown that children with adequate dietary intake of omega-3 fats will benefit from extra supplements. However, omega-3 supplements and foods that have been enriched with omega-3 fats are now subject to high level marketing following limited and controversial evidence of children's reading, learning skills and behaviour improving with supplementation [122].

Food advertising

Media messages about food are targeted at children through:

- television, radio, Internet and social media advertisements
- in store displays
- child-friendly packaging including familiar cartoon characters on the packaging
- stealth marketing techniques such as embedding products in the programme content in films, online and in video games

The majority of foods advertised are high fat, high sugar and low fibre foods [123]. Packet snack foods are also high in salt. These advertisements often feature messages implying that these low nutrient foods are desirable or beneficial. These implications may confuse children and their parents about what makes a particular food a healthy choice.

Marketing experts know that toddlers and children have considerable purchasing influence and successfully negotiate purchases through 'nag factor' or 'pester power'. Requests are often made for brand-name products and food accounts for over half of total requests, with parents honouring these 50% of the time [124]. The most requested item is breakfast cereal, followed by snacks, drinks and toys. Children younger than 8 years are especially vulnerable to these marketing strategies because they lack the cognitive skills to understand the persuasive intent of television and online advertisements [125]. Older children exposed to advertising choose advertised food products significantly more often than those who are not exposed [124].

Several studies point towards the contribution of food marketing to the rising levels of childhood obesity [126]. In Australia and Canada, industry self-regulation initiatives to restrict low nutrient food advertising to children have not shown any success [127, 128].

Genetic modification

The long-term effects of genetic modification (GM) are as yet unknown and remain controversial. The nutritional contents of GM and non-GM foods sold in the UK are comparable and, therefore, do not affect infants' and children's nutritional intakes. Many parents choose not to give GM food to their children, but they may not always be aware of the extent to which GM ingredients are used in processed foods.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

3 Provision of Nutrition in a Hospital Setting

Julie Royle

Introduction

Legally binding hospital food standards were set by the government within the National Health Service (NHS) Standard Contract in 2014 to highlight the importance of nutrition and hospital food [1]. All NHS hospitals should develop and maintain a food and drink strategy. This should include the nutrition and hydration needs of all patients, healthier eating for the whole hospital community and sustainable procurement of food and catering services.

The provision of adequate and appropriate nutrition for infants, children and young people in hospital poses a significant challenge. The diverse needs of the paediatric inpatient population with respect to age, developmental stage, ethnicity and religious beliefs need to be considered. Additionally, the provision of nutrition incorporates the requirements of the nutritionally well, the nutritionally vulnerable and those requiring therapeutic diets. Dietitians will be primarily involved with the latter two groups. Recognising that the provision of nutritional care is multidisciplinary [2], dietitians must also act in an expert advisory capacity to those involved with the provision of food to the nutritionally well.

Nutrition care planning

In the Western world, the prevalence of acute undernutrition in paediatric inpatients is reported to be between 6% and 14% [3] with acute malnutrition being highly prevalent in children with an underlying disease. A nationwide study of all newly admitted children in Dutch hospitals over 3 consecutive days showed a prevalence of malnutrition in 19% of children [4]. For a child with mild illness (grade 1 clinical conditions), nutritional status can deteriorate over the course of a hospital admission [5]. In a study in the tertiary care setting, the incidence of malnutrition was higher, with 27% of children having moderate or severe malnutrition on admission, with a deterioration to 32% on discharge [6]. In chronic childhood diseases the contribution of frequent and extended admissions combined with the impact of treatment may have a negative effect on nutritional intake and consequently on nutritional status. In Pichler's study the most nutritionally vulnerable patients were those less than 2 years of age, those who had been an inpatient for more than 1 month and those who had multiple medical problems [6].

The use of a nutrition screening tool should, in theory, provide a simple and rapid means of determining those at risk and those who have specific dietary requirements. From this information a nutritional care pathway for each individual patient can be determined, implemented and monitored. There are a number of paediatric nutrition screening tools available; these are at varying stages of validation [7–9]. There is as yet no universally accepted paediatric nutrition screening tool for the assessment of paediatric inpatients, and recent work indicates variable correlation with anthropometric assessment when comparing two of the tools and a need for further validation [10].

Meticulous anthropometry identifies those who are under- or overnourished, but may not detect those at risk of developing malnutrition. For screening to be of benefit, it must identify those at greater risk of malnutrition and be linked to appropriate ensuing monitoring and intervention [11]. The implementation of nutrition support teams has been proposed to improve malnutrition diagnosis and nutritional care in paediatric inpatients [12].

In summary, individual nutrition care planning is a prerequisite to optimum nutritional provision. This needs to be undertaken in such a way that there is confidence that it can identify the significant numbers who are already malnourished, those who are at risk of becoming so and those with specific requirements, while avoiding unnecessary screening of those who are nutritionally well and undergoing a relatively short length of hospital stay.

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

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Condition-specific assessment tools, such as the one developed for children and young people with cancer (p. 375), may be a more appropriate future strategy to identify nutritional risk among paediatric inpatients [13]. Further information about nutrition screening tools may be found in Chapter 1, p. 1.

Nutritionally well inpatients

Provision of nutrition to nutritionally well inpatients should consider:

- the age and developmental stage of the patient including the level of support needed to eat and drink
- religious and cultural beliefs
- the need to provide adequate food and fluid, together with choice of both, to meet standard nutritional requirements of a healthy balanced diet
- food provided should be familiar, appetising and available to accommodate the feeding pattern of the child; a hospital admission may provide the opportunity to promote aspects of healthier eating to families

Nutritionally well infants

Paediatric inpatient facilities should endeavour to support mothers in breastfeeding their infants unless there is a clinical reason to discontinue breastfeeding. Support should include facilities for mothers to feed in comfort, respecting their privacy and dignity; support, facilities and equipment for mothers to express breastmilk; and safe and hygienic storage of expressed breastmilk (EBM). Evidence is emerging that breastfeeding can be sustained even in infants requiring significant surgical intervention [14].

For those infants who are not breastfed and not requiring a specialised infant formula, ready-to-feed (RTF) infant milks should be available. RTF milks minimise the potential infection risks that can result from reconstituting powdered infant milks at ward level and also ensure a constant composition. The availability of a variety of both whey- and casein-dominant milks will accommodate the personal preference of the family. Casein-dominant RTF formulas are less readily available in UK hospitals, and parents can be reassured that their infants' nutritional needs will be adequately met using the appropriate volume of a whey-based infant milk.

For infants 6 months of age and older, age-appropriate commercial weaning foods must be part of the catering provision. Weaning foods should include first weaning foods such as baby rice, pureed fruits and pureed vegetables as well as weaning foods with lumps.

Nutritionally well children and young people

Food standards for NHS hospitals were recommended by the government in the Hospital Food Standards Panel Report, 2014 [1]. The panel identified required standards to improve food and drink provision across the NHS for a healthier food experience where everyone needs to 'eat for good health' [1]. The food and drinks available for nutritionally well children and young people should be designed to meet their nutritional requirements and allow them to eat a healthy well-balanced diet of familiar foods.

Good eating habits can be encouraged by a well-planned hospital menu and by the availability of healthy snacks, including fresh fruit and drinks, including water. The Eatwell Guide (p. 31) can be used to inform menu planning to include the right proportions of the five food groups for children over 2 years of age. The focus of nutritional provision from hospital food should be on achievement of an adequate energy intake [15]. An average day's intake from breakfast, two main meals, two to three snacks and milk (or a suitable alternative), should meet the estimated average requirement (EAR) for energy.

The UK Department of Health Dietary Reference Values [16] and Scientific Advisory Committee on Nutrition Dietary Reference Values for Energy [17] can be used as guidelines for nutritional requirements. The *Eating Well for 5-11 Year Olds* guidelines [18] can be extrapolated to the design of hospital menus; the nutrient provision guidelines that should be worked towards are shown in Table 3.1 [15]. The high salt content of hospital meals is well recognised, and caterers should be advised to adhere to age-specific recommendations [19].

Table 3.1 Nutrient provision guidelines.

	Breakfast	Lunch	Supper	Snacks and drinks
Energy % EAR	20	30	30	20
Protein % RNI	20	30	30	20
Salt % SACN recommendations	20	30	30	20

EAR, estimated average requirement; RNI, reference nutrient intake; SACN, Scientific Advisory Committee on Nutrition.

For children, the following nutrients require special attention:

Calcium: 350–500 mL milk should be available to all children and young adults; full-fat milk for the under 2-year-olds and semi-skimmed for those older

Vitamin C: 150 mL fruit juice for all and provision of fresh fruit and vegetables

Iron: inclusion of red meat dishes, iron-fortified breakfast cereals, green leafy vegetables and pulses

Vitamin D: provision of adequate vitamin D in the diet can be a challenge; supplementation may be required in long-stay patients or those at specific risk of deficiency

A wide variety of portion sizes need to be provided to ensure that protein and energy requirements are met across the age ranges (Table 3.2). Food should be served in a manner and in an environment that encourages eating. Crockery and cutlery appropriate to the age ranges are required. Menu choices should meet the needs of vegetarians and those with specific cultural or religious beliefs (Chapter 26).

Table 3.2 Food portion sizes for age.

	1–2 years	3–5 years	10+ years	12+ years
Meal pattern	3 small meals and 3 snacks plus milk	3 meals, 2–3 snacks or milk drinks	3 meals, 1–2 snacks or milk drinks	3 meals and 2–3 snacks
Protein sources, e.g. meat, fish, eggs, pulses	20–40 g or 2–4 tablespoons or 1 small item, e.g. fish or chicken goujon, egg	50–80 g or 4–8 tablespoons or 1–3 items depending on size, e.g. 2 fish fingers, 1 egg	90–120 g or 9–10 tablespoons or 1–3 items depending on size	120 g or 10 tablespoons or 2–3 items
Dairy	20 g cheese, 1 small pot yoghurt, 1 cup milk, 5–8 tablespoons custard	20–30 g cheese, 2 small or 1 standard pot yoghurt, 1 glass milk, 8–10 tablespoons custard	30–40 g cheese, 1 standard pot yoghurt, 1 glass milk, bowl of custard	50–60 g cheese, 1–2 standard pots yoghurt, 1 large glass milk, bowl of custard
Bread and other carbohydrates	½–1 slice or ½–1 item, e.g. crumpet, bagel, 3–5 tablespoons pasta or rice, 1–2 tablespoons potato, 3–5 tablespoons breakfast cereal	1 slice or 1 item, 6–8 tablespoons pasta or rice, 2–3 tablespoons potato, 6–8 tablespoons breakfast cereal or 1–2 Weetabix	2 slices or 2 items, 10–15 tablespoons pasta or rice, 3–4 tablespoons potato, bowl of breakfast cereal or 2 Weetabix	2–3 slices or items, 10–20 tablespoons pasta or rice or 4–6 tablespoons potato, bowl of breakfast cereal or 2–3 Weetabix
Fruit and vegetables portion sizes to increase with age	5 a day	5 a day	5 a day	5 a day

1 tablespoon = 15 g.

The nutritionally vulnerable and those requiring therapeutic diets

For nutritionally vulnerable children and young people, the relative proportions of the food groups in The Eatwell Guide will not be appropriate, and a greater reliance on energy-dense foods and snacks is needed [15].

Patients in this group will require some or all of the following during the course of a hospital admission:

- adapted infant milks and specialised formulas
- enteral feeds
- parenteral nutrition (Chapter 5)
- nutrient-dense meals
- therapeutic diets

Adapted infant milks and specialised formulas

Infants and children requiring specialised formulas should receive the appropriate RTF product, where available, as these are commercially sterile in preference to powdered products [20]. In the absence of RTF products, many infants and children are prescribed individualised feeds or adapted infant milks requiring the use of a powdered formula and/or supplement. Powdered feed products are not sterile; they can be intrinsically contaminated with pathogens [21].

Powdered feeds are a food source and once reconstituted become a medium for bacterial proliferation. This concern was heightened after the increase in the notification of serious cases and outbreaks of disease caused by *Cronobacter* spp. [22]. This problem is especially serious in vulnerable infants, i.e. those who are preterm, low birthweight, immunocompromised or in the first 2 months of life [23]. To address this issue, the World Health Organization (WHO) issued guidelines for the safe preparation, storage and handling of powdered infant formula (PIF) [24] in 2007. In a hospital environment local guidelines need to be produced for making large volumes of feeds on a daily basis.

Powdered feeds must be prepared in a specific location away from the bedside with adequate space and equipment [25]. The area for the preparation of specialised feeds must ensure the preparation and delivery of safe feeds using an aseptic technique [26] as well as minimising airborne contamination (as from open windows, vents). A room that is routinely used for a function necessitating similar requirements for cleanliness and equipment can provide an acceptable work area.

Where there is a high demand for specialised feeds, as in paediatric hospitals, a separate room for the preparation and handling of powdered feeds is recommended. This is designated the Special Feed Unit (SFU) [20].

Guidelines for the preparation of adapted infant milks and specialised formulas

In the UK there are no mandatory standards for feed preparation areas in hospital settings. Feed preparation must comply with the requirements of the Food Safety and Hygiene (England) Regulations 2013 [27]; this provides for the enforcement of certain provisions of Regulation 178/2002 and for the food hygiene legislation. The Paediatric Specialist Group of the British Dietetic Association has produced best practice guidelines, and, in conjunction with the comprehensive guidelines from the American Dietetic Association, these documents provide essential reference standards for safe, effective and efficient feed making units [20, 26], which are summarised below.

Structural design of feed making areas

The area or unit should be physically isolated from direct patient care with access restricted to authorised personnel to minimise the risk of cross infection and tampering of feeds. It should be designed to be easily cleaned, prevent the entrance and harbouring of vermin and pests and operated to the highest standards of hygiene. Ideally there should be three separate areas:

- *storage area*: situated adjacent to the feed preparation area, where bulk goods are delivered, unpacked and stored. It should be large enough to accommodate adequate storage racks that are constructed and sited to permit segregation of commodities, stock rotation and effective cleaning. Items must be stored on racks or shelves above floor level. The temperature should be ambient without large shifts in temperature and be checked daily. Where the storage is integrated within the preparation area, the above criteria continue to apply. There must be a designated area for feed storage and a separate area for cleaning equipment.
- *feed preparation area*: contains a stainless steel work surface, a handwash sink with hand-free taps, antibacterial handwash and drying facilities, storage for utensils and current feeds being used and refrigerators for holding the prepared feeds. Utensils and currently used feed products should be stored in closed cupboard(s). Depending on the procedures required by the individual healthcare facility, optional equipment used in the preparation room may include a pasteuriser, blast chiller and freezer. There should be provision for water for feed preparation to meet national and institutional standards. Adequate electric outlets with sufficient power should be provided for the equipment within the room and be compliant with local standards. Electric outlets for the refrigerators and freezers should be backed by emergency generators in cases of power failure. Lights within the unit should be enclosed and allow adequate illumination for accurate feed production. Clean air should be supplied through the ventilation system. Floors, walls and ceilings should be of a material that can be easily maintained clean. The unit must be cleaned daily and deep cleaned on a weekly basis. All waste bins must be covered, foot operated and emptied daily.
- *utility area for equipment washing and administrative work*: this can be a designated area within the preparation room or in larger units situated in a separate area. In the former, the processes of preparation and clean-up must be separated by time and space. Small equipment can be cleaned in a dishwasher or sterilised in an autoclave. When a dishwasher with an 82 °C final rinse cycle is used, a single sink for pre-rinsing is sufficient [26]. If bottles are reused, a two- or three-compartment sink with bottle-washing brushes and a rinse nozzle is suggested.

Recommendations for the construction of feed units are as follows:

- *walls, floors and ceilings*: hardwearing, impervious and free from cracks and open joints. Smooth surfaces to permit ease of cleaning and coved junctions between floors, walls and ceilings to prevent collection of dust and dirt. Light-coloured sheen finish to reflect light and increase illumination.
- *doors in the production area*: self-closing with glass observation panel.
- *windows*: sealed to prevent opening.
- *mechanical ventilation to provide a clean air supply*: with temperature (and preferably humidity) control to give optimum working environment and control bacterial and dust contamination. Steam-producing equipment such as dishwashers and pasteurisers should be fitted with a canopy and exhaust fan system to draw off steam and fumes.
- *lighting level*: to allow staff to work cleanly and safely without eye strain and to expose dirt and dust. Light fixtures flush with wall or ceiling.
- *wash hand basins*: one provided in each utility and preparation area. Hot and cold water with foot- or elbow-operated taps. Hand soap and sanitiser as per local policies and single-use disposable towels or a hot air hand dryer.
- *water supply*: of potable quality from a rising main. The Department of Health has not advised against the use of tap water in the preparation of feeds. Tap water should be provided from a fixed device such as a gas or electric water boiler to dispense water >80 °C. If sterile water is used, it must be heated to >80 °C if it is used in the preparation of powdered formulas.

Equipment

All equipment and utensils used within the preparation room should be made of stainless steel or other non-absorbent material. They must be easily cleaned and decontaminated and withstand temperatures of a commercial dishwasher. Strong and persistent biofilms can form on surfaces such as steel, plastic, silicone and latex [28]. Proper cleaning and decontamination of the equipment used in feed preparation is essential to avoid *Cronobacter* spp. biofilms contaminating subsequent feeds if not removed.

Large Equipment

- Large equipment such as shelving, tables and refrigerators should be castor mounted with wheel brakes to allow easy access for cleaning. Surfaces should be smooth and impervious to allow easy cleaning and disinfection.
- Refrigerators that operate at a temperature between 1 and 4 °C; the temperature should be monitored and recorded twice daily. Commercial refrigerators are recommended in an SFU.
- Blast chillers to allow rapid cooling of all feeds to <4 °C within 15 minutes of preparation. This is advised in larger units as it is the most efficient way of cooling feeds.
- If maternal expressed breastmilk (MEBM) is stored and fortified in the feed preparation room, a freezer that holds the milk at −20 °C is needed. A commercial-grade freezer with external thermometer and alarm systems is recommended [26]. Both the refrigerator and freezer should be self-defrosting and have shelves that are easy to clean.

- Pasteurisation equipment with a range of cycles for powdered feeds and MEBM (see Feed preparation) together with a means of data logging for monitoring and recording pasteurisation cycles.
- Thermal disinfection of equipment is desirable in a small unit and essential in a large centralised SFU. This is a two-stage process achieved with a dishwasher adapted for an initial wash of bottles and equipment plus a high temperature rinse that holds a temperature of >80–85 °C for 2 minutes. This ensures a surface temperature of 80 °C for at least 15 seconds, which is an effective disinfectant. A drying cycle is useful [29].
- A feed delivery trolley either insulated or with ice packs to ensure feeds remain at <4 °C during delivery to the wards.

Small Equipment

- Mixing and measuring equipment including jugs, measures, cutlery and whisks should be made from plastic or stainless steel. They must be easily decontaminated and withstand a high temperature wash.
- Weighing equipment must be easy to clean or easy to use and of the appropriate accuracy for the task.
- Feed bottles are available in glass, polycarbonate or plastic polythene in 50–240 mL sizes. Bottles and teats are for single-use only unless they can be sterilised or decontaminated adequately [20]. Glass is a hazardous material prone to cracking and chipping; polycarbonate shrinks if autoclaved at temperatures >119 °C and the bottles become scratched or crazed with repeated use. Reusable bottles require washing, sanitising by heat or chemical means; sealing discs or caps require the same treatment. Disposable sterile polythene bottles reduce the workload in the unit. The decision to use disposable or reusable bottles necessitates a detailed cost–benefit analysis for each establishment plus a risk analysis of possible contamination from inadequately cleaned bottles. Single-use enteral feeding containers will be required for larger volumes of prepared or decanted RTF formulas.

Staffing

Feed provision is usually required every day of the year. The number of employees will depend on the volume of work within each facility. A sufficient number of trained staff should be available to provide 7-day cover for the SFU, accounting for planned and unplanned leave [20]. In large units the operational management for staff and feed preparation is usually the responsibility of the dietitian. In small areas attached to a ward, the supervision and management may be the responsibility of the nursing staff with the dietitian acting in an advisory capacity. Productivity measures for SFU staff have not been published to date.

The manager of the unit must ensure that staff are adequately trained in all aspects of food safety as it relates to feed preparation in line with the Food Safety and Hygiene Regulations 2013 [30]. All staff preparing feeds should maintain food hygiene qualifications in line with local policy. Training should cover personal hygiene, prevention of bacterial and foreign matter contamination, preparation procedures and basic knowledge of the feed composition and clinical indication.

Suitable protective uniforms and footwear are required. During feed preparation a disposable plastic apron and a disposable hat completely covering the hair should be worn.

Feed preparation

There are three key components of safe feed preparation. These are appropriate ingredients, safe and accurate preparation and limitation of microbial growth:

- All ingredients received into a feed making area should be of the required standards and specification. Goods received should be checked and stock rotated according to date. Opened tins or packets, e.g. from the patient's home, should not be accepted into the feed making area. If pasteurised cow's milk is used, e.g. to reconstitute powdered oral nutritional supplements, it should be stocked according to its dated shelf life; if opened any unused milk should be discarded at the end of the working day. MEBM will require an agreed procedure for storage and use. Any feed containing MEBM must be made up at the end of formula preparation after work surfaces have been cleaned and fresh equipment used [20].
- Details of each feed to be prepared should be in a clearly written or printed form including the patient's name, date of birth and hospital number, the weight or volume of each feed ingredient, the total fluid volume and the number and volume of each feed required. All ingredients should be weighed or measured accurately. Prepared feeds should be decanted into the appropriate number and size of bottles and each bottle labelled. The label must include details of the patient's name, ward, feed type, preparation, date and preferably advice to refrigerate and discard after 24 hours.
- Limitation of microbial growth is critical to safe feed provision. The UK Department of Health and the WHO recommend reconstituting PIF with previously boiled tap water cooled to ≥70 °C for all infants (≤12 months) [20, 24]. This fresh water should come from the cold water tap. In practice this equates to boiling 1 L of water and allowing it to cool for 30 minutes in a covered container. This evidence has been used as best practice to make up formulas for special medical purposes within the SFU in the UK. Risk assessment modelling found that reconstituting PIF with ≥70 °C water resulted in a >100 000-fold reduction in risk [30]. Such made-up feeds must be stored in the refrigerator for no longer than 24 hours from the time of reconstitution.
- For compositional reasons, several formulas for special medical purposes cannot be reconstituted with water at ≥70 °C. These include feeds with a high fat content for use in a ketogenic diet, feeds containing probiotics and pre-thickened feeds. For these products a local risk assessment needs to be undertaken, and a strict preparation technique put in place [20].

- The aseptic technique must be followed in the preparation of all feeds in healthcare settings to control the microbiological quality of the feed. Prior to feed preparation, work surfaces must be cleaned with a food-grade antibacterial sanitising solution. During feed preparation, there should be no admittance of allied staff to the feed preparation room and no other activities taking place. The aseptic technique combines hand decontamination with the no touch technique to exclude contact contamination from personnel, work surfaces, equipment and environment. Each healthcare facility should have written guidelines for the aseptic technique [20].
- Pasteurisation can limit microbial growth. There is an absence of evidence supporting or disputing the pasteurisation of specialised feeds and modified enteral feeds. Some of the larger children's hospitals in the UK have adopted the pasteurisation of feeds for at-risk groups as best practice. These include preterm infants, low birthweight infants, neonates (infants <28 days of age), immunocompromised children and those on powdered jejunal feeds. For these groups the feeds are heated to a temperature of 67 °C for 4 minutes and rapidly cooled to a safe temperature. Pasteurisers must be data logged to ensure that correct temperatures are reached [20].

  There is evidence to support the pasteurisation of donor breastmilk [20]; human milk is heated to 62.5 °C for 30 minutes and is rapidly cooled to a safe temperature.
- Blast chilling is an effective method of limiting microbial growth in prepared feeds by cooling rapidly to <4 °C within 15 minutes [20]. Following preparation and blast chilling feeds should be refrigerated at <4 °C until delivery to the wards. In small units blast chilling or pasteurisation may not be feasible, but systems must be in place for rapid cooling and refrigeration of prepared feeds.

Delivery

Transporting reconstituted feeds can increase the risk of bacterial proliferation. Local guidelines must be produced for the safe transportation of prepared feeds. Equipment that prevents contamination of feeds and maintains a safe temperature should be used to deliver feeds. If transport takes more than 30 minutes, it is recommended that feeds are transported under refrigerated conditions [24]. A cool box with ice packs or chilled trolley is suitable transportation.

Cleaning procedures

Sterilisation of small equipment (the destruction of all microorganisms and their spores) is not attainable in an SFU. Sanitation or disinfection of small equipment can be achieved by autoclaving, by a dishwasher or by chemical means.

Autoclaving, although effective, has a number of disadvantages: equipment first has to be washed, dried, packed and sealed; this is costly and time consuming. In addition water condensation forms and remains in feeding bottles, where it can induce bacterial activity.

Thermal disinfection in a dishwasher is the practical preferred option. This requires less time and the inclusion of a drying cycle will ensure that all equipment is dry and ready for storage. To achieve thermal disinfection the water in the dishwasher should reach a minimum temperature of >80–85 °C for 2 minutes [29].

Chemical disinfection, e.g. hypochlorite, reduces levels of harmful bacteria to acceptable levels and is satisfactory for small (non-metallic) equipment provided recommendations are followed.

Quality assurance

The primary infection prevention and control aim for feed preparation is to prevent any infant or child from ingesting microorganisms that can result in illness. Each establishment must have in place hazard analysis and critical control point (HACCP) guidelines for the preparation of powdered feeds and special feeds. These should address factors that influence and discourage microbial growth relating to the cleanliness of equipment, the use of the aseptic technique, storage temperatures and the handling at ward level [31]. There is no epidemiological evidence to support routine microbiological sampling of prepared feeds in healthcare facilities. Routine culturing is unlikely to detect intermittent contamination due to breaches in the preparation technique, but may be helpful in establishing trends and in evaluating root cause analysis [26].

Individual or multiple cases of infection with suspected food-borne illness from potentially contaminated feeds must be investigated and managed in line with local policies.

All premises specifically designated for feed preparation in hospitals must be inspected annually (or as deemed appropriate) by an environmental health officer.

Procedures and documentation

Clear written procedures and local guidelines are required for each phase of feed preparation. This includes guidelines from personal hygiene to procedures for ordering supplies, feed reconstitution and aseptic technique, instructions for pasteurisation and blast chilling, cleaning and disinfection, risk management, equipment maintenance and breakdown procedures.

Enteral feeds

Older children and young people at risk of malnutrition as a result of underlying disease are often dependent on nutrition support in hospital and will frequently require enteral tube feeding. The increase in the range of sterile RTF products has reduced the need to prepare powdered enteral feeds. A few remain as powdered products, and these should

be prepared to the same standards as described for adapted infant milks and specialised formulas.

Care must be taken at ward level to ensure that all prepared feeds are stored in refrigerators at <4 °C. The hanging time for feeds that are administered continuously is debatable. The UK National Institute for Health and Care Excellence (NICE) recommends that (non-sterile) reconstituted feeds should hang for no more than 4 hours. These are best practice guidelines for the prevention of healthcare-associated infections in the community; the guidelines can be adapted for local use in the hospital setting [32]. Sterile RTF enteral formulas may be hung for 24 hours if the administration system (feed reservoir and giving set) is closed.

Food for those at nutritional risk or requiring therapeutic diets

Good food and good food services for children and young adults are vital and are recognised by the Children's National Service Framework [33]. Children on therapeutic diets especially need to have the right food, at the right time, in an environment that will encourage them to eat [34]. In contrast to food provision in adult hospitals where menu coding is designed to allow patients with specific dietary requirements to choose from the main catering menu, it is preferable in large children's units to have a designated diet kitchen or diet bay. This is supported by the need for attention to detail where food items often have to be weighed very accurately; preparation of prescribed dietary food products, which demands special cooking skills to get a good result; and prevention of cross-contamination of food allergens. The exception to this is for those with higher than normal requirements for protein and energy where ordinary food from the main menu can be fortified or the provision of extra food at snacks or mealtimes may be sufficient. Consistent use of standard recipes and ingredients in food preparation in the main catering kitchen may render some items from the main menu suitable for therapeutic diets.

Patient groups can provide helpful collaboration in attempts to improve the food on offer to some of the most nutritionally at-risk groups in hospitals [33]. For some groups of children, specific initiatives have improved their food intake [13].

Staff involved in the preparation of therapeutic diets must be aware of the need for accuracy, appropriate portion size for age, consistency of nutrient content and variety. For those on a therapeutic diet, the food provided in hospital is taken as an example of what must be continued at home and must, therefore, be accurate and appetising. It is advisable that staff employed to prepare special modified diets have as a minimum qualification City and Guilds 706/2. In-service training of diet cooks by the dietitian is good practice to ensure that staff are kept up to date with changes to dietary treatment. The following points must be considered when providing a therapeutic diet service:

- The dietitian should specify to the caterer the standards of quality and suitability of provisions for use in the diet preparation area. Stocks of specific dietary products such as gluten-free and low protein products should be available, and those working in the area should be familiar with the use of these products.
- Appropriate equipment for preparation of small quantities of food must be available for the diet cooks. An industrial liquidiser, small pots and pans and accurate scales are all essential items. Freezer space is also required, as it is useful to keep frozen portions of special items, e.g. vegetable casserole for low protein diets; minimal fat snacks; and milk-, egg-, wheat- and soya-free baked goods.
- A suitable plating system for diets must be used. Where a bulk catering system is operated, individual containers, clearly labelled with relevant dietary details, are suitable for diet meals. If a plated system is in use, the individual diet meals should be clearly labelled with the patient's name and relevant dietary details.
- The dietitian should always provide the diet cooks with clear written and verbal instructions for each individual diet being prepared. The written information should include the patient's name, age and ward, the diet required and specific instructions regarding the composition of the diet.
- A diet manual within the diet preparation area should include instructions regarding commonly requested modified diets and appropriate recipes. It is also useful to include details of any patients on unusual diets if they are likely to be admitted. This manual should be regularly updated.
- To ensure consistency and accuracy and a high quality product, the provision of modified diets should be monitored regularly. The following should all be considered: the quality, freshness and suitability of the provisions, the storage methods, the preparation of raw ingredients and the presentation to the patient.

Preparation of food for neutropenic patients

Children undergoing bone marrow or haematopoietic stem cell transplantation have periods of severe immunosuppression and neutropenia. Opportunistic infection is a significant cause of morbidity and mortality in immunocompromised patients. Bacterial translocation from the gastrointestinal tract can cause significant infection and, in theory, can be decreased by reducing the potential sources of bacteria and other pathogens from food. This has been referred to as a low microbial, clean or sterile diet depending on the degree of restriction.

The evidence on the effectiveness of low microbial diets is extremely limited [35, 36]. In the absence of larger well-controlled studies, some have advocated the use of food safety guidelines for neutropenic patients [37]. The need to minimise risk from food-borne infection must, of course, be balanced with the need to support nutritional status in this vulnerable group, with the avoidance of unnecessary restrictions that may impact adversely on nutritional intake.

Current consensus suggests the use of a low microbial diet that avoids the use of raw or lightly cooked foods,

Table 3.3 Suggested foods for a low microbial diet.

Foods to avoid	Alternatives
Meats	
Raw or undercooked meat and poultry	Well-cooked meat and poultry
Smoked or cured meats	Vacuum-packed cold meats such as turkey or ham Tinned meats
Pâté	Pasteurised pâté or paste in tins or jars The Foods to avoid column will need to be realigned.
Fish	
Raw, smoked or lightly cooked fish	Well-cooked fish
Eggs	
Raw or soft-cooked eggs such as home-made mayonnaise, mousses, sauces or meringues	Hard-boiled eggs, shop-bought mayonnaise, mousses, sauces or meringues Other products made with pasteurised eggs
Milk and milk products	
All unpasteurised dairy products	Any pasteurised milk, soya milk, Jersey milk, UHT milk and cheese products
Blue-veined cheese, e.g. stilton	
Soft ripened cheeses, e.g. brie, camembert, goat's cheese, paneer	Vacuum-packed pasteurised and hard cheeses such as cheddar and edam Processed cheese
Probiotics; live, active or bio products such as live yoghurts, probiotic supplements or drinks	Pasteurised plain or fruit yoghurts
Soft ice cream	Commercial ice cream individually wrapped portions
Vegetables	
Unpeeled vegetables including salad items	Good quality vegetables that are well cooked or peeled
Damaged or overripe vegetables	UHT or long-life vegetable juices sold in cartons or jars
Unpasteurised or freshly squeezed vegetable juices or smoothies	Pasteurised smoothies
Fruit	
Unpeeled fruit	Good quality fruit that is well cooked or peeled
Raw dried fruit such as dates or raisins and products containing these such as muesli	UHT or long-life fruit juices sold in cartons or jars Pasteurised smoothies
Damaged or overripe fruit	Tinned fruit or cooked dried fruit such as in cake, flapjacks or cereal bars
Unpasteurised or freshly squeezed fruit juices or smoothies	
Herbs and condiments	
Uncooked herbs, spices and pepper	
Drinks	
Non-drinking water, bottled mineral or spring water, water from wells, coolers or drinking fountains	Cooled boiled water Sterilised water
Nuts	
All nuts	
Honey	
Unpasteurised or 'farm fresh' honey and honeycomb	Pasteurised or heat-treated honey
Miscellaneous	
Food items from 'pick and mix' or 'buffet' counters	Packets should be individually wrapped or portioned on the ward only
Deli counter	

reheated foods and foods known to contain higher levels of potential pathogens such as soft cheeses, unpasteurised products, nuts and buffet or deli counter foods. Practice varies, but a summary of common foods to avoid is given in Table 3.3 [38].

In addition strict food hygiene practices must be used in the storage, preparation and service of food to neutropenic patients requiring low microbial diets, including:

- ensuring that all preparation surfaces and equipment are clean and avoidance of wooden chopping boards and spoons
- thorough handwashing
- use of protective clothing for preparation and service of food
- cooking methods to ensure a core temperature of 70 °C in the final product
- an agreed minimum delay between the food being cooked and eaten

Table 3.4 High risk foods.

Raw and undercooked meat, fish or eggs
Soft and blue-veined cheeses
Pâté
Live and bio yoghurts
Take-away foods
Reheated food
Soft whip ice cream
Deli and buffet foods

After discharge neutrophil counts will have recovered, but there remains a risk and a small number of high risk foods should be avoided, usually for 3–6 months. These foods are outlined in Table 3.4 and food hygiene advice should be emphasised [38].

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

4 Enteral Nutrition

Tracey Johnson

Introduction

Enteral nutrition is the method of supplying nutrients to the gastrointestinal tract. Although enteral nutrition is the term often used to describe nasogastric, gastrostomy and jejunal feeding, guidelines from the European Society for Parenteral and Enteral Nutrition (ESPEN) suggest it should also include supplementary nutrition taken orally [1].

Enteral feeding is the preferred method of providing nutrition support to children who have a functioning gastrointestinal tract, with parenteral nutrition reserved for children with severely compromised gut function. It is safer and easier to administer than parenteral nutrition both in hospital and at home and can be adapted to meet the individual requirements of infants and children of all ages.

Some children receive their full nutritional requirements via a nasogastric, gastrostomy or jejunal tube, whereas others require nutrition support to supplement poor oral intake or to meet increased nutritional requirements. Enteral feeding may be short term, but for many children it can be a long-term or even lifelong method of feeding. As a result regimens need to be adaptable to ensure each child receives the essential nutrients they require for normal growth and development.

Tube feeding children requires the expert input of a paediatric dietitian who, along with a specialist multidisciplinary team, has the knowledge to use feeds and feeding equipment appropriate for the individual requirements and clinical condition of the patient. Indications for enteral feeding are given in Table 4.1.

Choice of feeds

Infants under 12 months

Many infants requiring tube feeding may be given the same feed they would otherwise be taking orally. Children who are breastfed may be able to continue breastmilk, and there are physiological and psychological advantages to this. Mother's expressed breastmilk (EBM) may be given to her own baby or pasteurised donor breastmilk may be available. The principal benefits of using breastmilk are the presence of immunoglobulins, antimicrobial factors and lipase activity. In addition, there is a psychological benefit to the mother if she is able to contribute to the care of her sick child by providing breastmilk. These benefits may be outweighed by the possible poorer energy density of EBM, particularly if the foremilk is used, which is lower in fat than the hindmilk. If the infant fails to gain weight on breastmilk alone, intake can be supplemented with a commercial human milk fortifier in preterm infants (p. 104) or with standard or high energy formulas (p. 14).

Currently there are no national guidelines for whether mother's EBM to be fed to her own baby needs to be pasteurised and individual hospitals and units have developed their own local protocols, largely influenced by the cleanliness of the collection and handling techniques of the EBM. Pasteurisation destroys some of the nutritional, antimicrobial, probiotic, hormonal and enzymic properties [2–4] of EBM, so non-pasteurisation is recommended. The evidence for the transmission of infection via EBM is limited, but there are clear guidelines from the National Institute for

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 4.1 Indications for enteral feeding.

Indication	Example
Inability to suck or swallow	Prematurity Neurological impairment and degenerative disorders Trauma and burns Tumours Critically ill child requiring ventilation
Anorexia associated with chronic illness	Cystic fibrosis Malignancy Inflammatory bowel disease Liver disease Chronic kidney disease Congenital heart disease Inherited metabolic disorders
Increased requirements	Cystic fibrosis Congenital heart disease Malabsorption syndromes (e.g. short bowel syndrome, liver disease) Trauma Severe burns
Congenital anomalies	Tracheo-oesophageal fistula Oesophageal atresia Orofacial malformations
Primary disease management	Crohn's disease Severe gastro-oesophageal reflux Short bowel syndrome Glycogen storage disease Very long chain fatty acid disorders
Refusal to eat	Anorexia nervosa Feeding aversion

Health and Care Excellence (NICE) for the processing of donor breastmilk, and pasteurisation is recommended to protect against pathological bacterial contamination [5]. In 2017 the Paediatric Specialist Group of the British Dietetic Association (BDA) published best practice guidelines for the handling of EBM (p. 45), available from www.bda.uk.com/uploads/assets/a230ba75-c66a-4157-8ff6a6ca9f2eb971/2019sfuguidelines.pdf.

Standard infant formulas are suitable for enteral feeding from birth to 12 months of age for those children with normal gut function and normal nutritional requirements. They provide an energy density of 65–70 kcal (270–290 kJ)/100 mL and meet the European Community Infant Formula Regulations [6]. An updated Regulation (EU) 2016/127 was adopted on 25 September 2015 and will start to apply on 22 February 2020. Follow-on milks may also be used after 6 months of age if their composition is thought to be more beneficial to the child. Many infants requiring enteral feeding will have increased nutritional requirements. Nutrient-dense infant formulas such as SMA High Energy, Infatrini and Similac High Energy are commercially available and have been shown to promote better growth than standard formulas with added energy supplements (glucose polymer powders and fat emulsions) [7]. Concentrating standard infant formulas achieves a feed that is more nutrient dense and retains an appropriate protein–energy ratio similar to the commercial nutrient-dense formulas (p. 13).

Standard infant formulas are based on cow's milk protein, lactose and long chain fat. Infants with impaired gut function who do not tolerate whole protein feeds frequently benefit from the use of hydrolysed protein or amino acid-based feeds. Such feeds are hypoallergenic and are free of cow's milk protein and lactose. Many of these formulas also have a proportion of the fat content as medium chain triglycerides, which can be beneficial where there is fat malabsorption, e.g. liver disease and short bowel syndrome (p. 141). If the specific requirements of an infant cannot be met by a commercial infant formula, it is possible to formulate a feed from separate ingredients. These modular feeds allow a choice of protein, fat and carbohydrate and give the flexibility to meet the needs of individual patients. However, they are expensive and time consuming to prepare, and there is a greater risk of bacterial contamination and mistakes being made during their preparation. It will take several days to establish a child on a full-strength modular feed (p. 147). Consequently, modular feeds should only be used if a complete feed is unsuitable and, in the hospital setting, should ideally be prepared in a dedicated special feed preparation area (p. 45).

Children aged 1–12 years (8–45 kg body weight)

Specialist paediatric feeds are available for children 1–12 years of age or who weigh 8–45 kg. Children have differing nutritional requirements according to their age, and consequently specifically designed feeds for these age groups are recommended to ensure provision of appropriate levels of protein, micronutrients and electrolytes to optimise growth. Although nutritional profiles of paediatric feeds are designed to meet the specific requirements of children, it is still important to assess requirements and intakes for the individual.

All feeds are categorised as Foods for Special Medical Purposes (FSMPs) and must comply with the EU Regulation (EU) 2016/128 [8], which came into effect in February 2019. The Regulation maintains the rules of the previous Directive 1999/21/EC, which lays down essential requirements on the composition of FSMPs and gives guidance for their minimum and maximum levels of vitamins and minerals, but has some additional labelling requirements and a prohibition on making nutrition and health claims. FSMPs intended for infants must now obey all rules on labelling, presentation, advertising and marketing that are applicable to standard infant formulas for healthy infants and must abide by the same rules on pesticides that apply to infant formulas and follow-on milks.

Standard paediatric enteral feeds are based on cow's milk protein, but are lactose-free, and provide three levels of energy density: 100 kcal (420 kJ)/100 mL, 120 kcal (500 kJ)/100 mL and 150 kcal (630 kJ)/100 mL. A lower energy feed, 75 kcal (315 kJ)/100 mL, is also available. A range of oral nutritional supplements are available, specifically developed for children who may benefit from a smaller volume of feed (e.g. Fortini Compact, PaediaSure Compact) (Table 12.5). These have an energy density of

Table 4.2 Paediatric enteral feeds.

	Per 100 mL			
	Age/weight	Energy kcal (kJ)	Protein (g)	Fibre (g)
Nutrini Low Energy Multi Fibre (Nutricia)	1–6 years (8–20 kg)	75 (315)	2.0	0.7
Nutrini (Nutricia)	1–6 years (8–20 kg)	100 (420)	2.7	–
Nutrini Multi Fibre (Nutricia)	1–6 years (8–20 kg)	100 (420)	2.7	0.8
PaediaSure (Abbott)	1–10 years (8–30 kg)	101 (424)	2.8	–
PaediaSure Fibre (Abbott)	1–10 years (8–30 kg)	101 (424)	2.9	0.73
Frebini Original (Fresenius)	1–10 years (8–30 kg)	100 (420)	2.5	–
Frebini Original Fibre (Fresenius)	1–10 years (8–30 kg)	100 (420)	2.5	0.75
Isosource Junior Mix (Nestle)	1–10 years (8–30kg)	120 (500)	3.6	1.0
Nutrini Energy (Nutricia)	1–6 years (8–20 kg)	150 (630)	4.0	–
Nutrini Energy Multi Fibre (Nutricia)	1–6 years (8–20 kg)	150 (630)	4.0	0.8
PaediaSure Plus (Abbott)	1–10 years (8–30 kg)	151 (632)	4.2	–
PaediaSure Plus Fibre (Abbott)	1–10 years (8–30 kg)	151 (632)	4.2	1.1
Frebini Energy (Fresenius)	1–10 years (8–30 kg)	150 (630)	3.75	–
Frebini Energy Fibre (Fresenius)	1–10 years (8–30 kg)	150 (630)	3.75	1.13
Tentrini (Nutricia)	7–12 years (21–45 kg)	100 (420)	3.3	–
Tentrini Multi Fibre (Nutricia)	7–12 years (21–45 kg)	100 (420)	3.3	1.1
Tentrini Energy (Nutricia)	7–12 years (21–45 kg)	150 (630)	4.9	–
Tentrini Energy Multi Fibre (Nutricia)	7–12 years (21–45 kg)	150 (630)	4.8	1.1

240 kcal (1010 kJ)/100 mL and can also be used for nasogastric or gastrostomy feeding if there is intolerance to high volume feeds or a fluid restriction.

Most product ranges are formulated either with or without added fibre. Those with fibre contain a mix of soluble and insoluble fibre. Constipation is common in exclusively tube-fed children, particularly those with neurological impairment [9]. A normal diet contains fibre, and, with an improved knowledge of the role of dietary fibre, it is now common practice for children to receive a fibre-containing feed as the standard. Fibre and its fermentation products (short chain fatty acids) impact on intestinal physiology and can prevent both constipation and diarrhoea [10–13].

Children with neurological impairment form the largest single diagnostic group who have long-term enteral feeding at home [14]. This group of children frequently has low energy expenditure, and, if a standard feed is provided in the necessary volume to meet recommendations for protein and micronutrients, they may show excessive weight gain. The nutritional needs of this group of children are discussed in Chapter 21.

The range of paediatric enteral feeds available for children is outlined in Table 4.2.

For children with abnormal gut function, as for infants, feeds based on hydrolysed protein and amino acids are available (Tables 8.15 and 8.16), and it is also sometimes necessary to use a modular feed (Table 8.25).

Children over 12 years (>45 kg body weight)

The requirements of children over 12 years of age may still be met by a paediatric feed designed for 7- to 12-year-olds; individual assessment is necessary. Standard adult feeds may also be used and are available with energy densities of 1 kcal (4 kJ)/mL and 1.5 kcal (6 kJ)/mL, with and without fibre. Some adult feeds have a protein content of 6 g/100 mL or more, so care should be taken when using such feeds for children, even if they are over 12 years of age, as they may provide an excessively high amount of protein. Intakes of copper, chromium, molybdenum and vitamins E, C, B_6 and B_{12} will also be high. Adult peptide-based and amino acid-based feeds can be used for children with impaired gut function, and it is also necessary in special circumstances to employ the flexibility of a modular feed.

The choice of feeds for children according to their energy requirements and gut function is given in Table 4.3.

Learning points: choice of feeds

The choice of feed depends on a number of factors:

- *age of child*
- *weight of child*
- *gastrointestinal function*
- *dietary restrictions and specific nutrient requirements*
- *route of administration*
- *prescribability and cost*

Feed thickeners

Feed thickeners are recommended by NICE as an early intervention to manage gastro-oesophageal reflux (GOR) in formula-fed infants [15]. With or without the concurrent use of anti-reflux medication, feed thickeners can help to reduce vomiting and minimise the risk of aspiration. Feed thickeners can also be added to enteral feeds that would otherwise separate out when left to stand (e.g. some modular feeds).

There is a wide range of commercial products that are suitable for thickening enteral feeds (Table 21.2). Thickened feeds may be difficult to give as a bolus via a fine bore nasogastric tube, and pump feeding may be necessary. It is

Table 4.3 Choice of feeds for enteral feeding according to energy requirements and gut function.

	Normal gut function	Impaired gut function
Infants	*Normal energy requirements* Breastmilk or standard/preterm infant formula	Hydrolysed protein formula, e.g. Aptamil Pepti-Junior (Aptamil), Nutramigen LGG 1 and 2 (Mead Johnson) Amino acid infant formula, e.g. Neocate LCP, Neocate Syneo (Nutricia), Nutramigen PURAMINO (Mead Johnson) Modular feed
	High energy requirements Breastmilk + BMF Breastmilk + standard/preterm infant formula Concentrated infant formula Nutrient-dense infant formula, e.g. Infatrini (Nutricia), SMA Pro High Energy (SMA), Similac High Energy (Abbott)	Infatrini Peptisorb (Nutricia)
1–6 years (8–20/30 kg)	*Normal energy requirements* Standard paediatric enteral feed, e.g. Nutrini (Nutricia), PaediaSure (Abbott) ± fibre	Hydrolysed protein formula, e.g. Nutrini Peptisorb (Nutricia), Peptamen Junior (Nestle) Amino acid formula, e.g. Neocate Junior (Nutricia) Modular feed
	High energy requirements High energy paediatric enteral feed, e.g. Nutrini Energy (Nutricia), PaediaSure Plus (Abbott) ± fibre	Nutrini Peptisorb Energy (Nutricia) Peptamen Junior Advance (Nestle)
	Low energy requirements Low energy paediatric feed, e.g. Nutrini Low Energy Multi Fibre (Nutricia)	
6–12 years (20–45 kg)	*Normal energy requirements* Standard paediatric enteral feed, e.g. Tentrini (Nutricia), PaediaSure (Abbott) ± fibre	Hydrolysed protein formula, e.g. Peptamen Junior (Nestle) Amino acid formula, e.g. Neocate Junior (Nutricia), E028 Extra (Nutricia) Modular feed
	High energy requirements High energy paediatric enteral feed, e.g. Tentrini Energy (Nutricia), PaediaSure Plus (Abbott) ± fibre	Peptamen Junior Advance (Nestle)
12+ years (>45 kg)	*Normal energy requirements** Standard adult enteral feed, e.g. Nutrison Standard (Nutricia), Osmolite (Abbott) ± fibre	Hydrolysed protein formula, e.g. Peptamen (Nestle), Nutrison Peptisorb (Nutricia) Amino acid feed, e.g. E028 Extra (Nutricia) Modular feed
	*High energy requirements** High energy adult enteral feed, e.g. Nutrison Energy (Nutricia), Ensure Plus (Abbott) ± fibre	Perative (Abbott), Vital (Abbott), Peptamen AF (Nestle)

BMF, breastmilk fortifier.
*Paediatric feed designed for 6–12 years old may be suitable.

also important to consider the energy contribution of some of the thickening agents. The thickeners based on modified starch given at a concentration of 3 g/100 mL may result in an increased energy content of more than 10%.

Routes of feed administration

Nasogastric feeding

Nasogastric is the most common route for enteral feeding, and unless prolonged enteral nutrition is anticipated, it would usually be the route of choice. However, passing a nasogastric tube can be distressing for both parents and children, and careful preparation is beneficial [16]. Frank discussions and a clear explanation of the procedure can help older children, and play therapy with the use of dolls, mannequins [17] and picture books has been shown to alleviate anxieties in the younger age group. Older children, particularly teenagers, are naturally sensitive about their body image, and they may be reluctant to start nasogastric feeding. Some children successfully pass their own nasogastric tube at night and remove their tube in the daytime, which can be a successful way of administering supplementary feeds without the embarrassment of a permanent nasogastric tube *in situ*.

Nasogastric feeding is a lifeline for many children, but it is not without its complications. Some of the more serious complications are related to dislodgement, poor placement and migration of tubes. Training is required to pass a

nasogastric tube. Measures need to be in place to test placement [18], and methods include measurement to predict tube insertion length [19].

Following a number of deaths, the National Patient Safety Agency published a report suggesting that conventional methods to check tube placement were inaccurate. The common method to aspirate the tube and test with blue litmus paper is not sensitive enough to distinguish between gastric and bronchial secretions; auscultation of air or observation of gastric contents is also considered ineffective. Radiology and testing of gastric aspirate with pH paper are the only acceptable methods of confirming nasogastric tube position [20].

Some feeds based on hydrolysed protein have been shown to have a pH < 4. There is a potential risk that a tube would test acidic if misplaced due to the feed pH rather than gastric contents. This has led some health professionals avoiding the use of such feeds in children.

Long-term nasogastric feeding in some children can cause inflammation and irritation to the skin where the nasogastric tube is secured to the face. Use of Duoderm or Granuflex placed onto the skin can improve this. Another common problem, particularly with fine bore tubes, is tube blockage. This may result from using the tube to administer drugs, the use of viscous formulas and inadequate flushing of the tube. Regular flushing of tubes can help to prevent this problem, and the use of carbonated liquids can clear and prevent the build-up of feed within the lumen of the tube. It may sometimes be necessary to replace the tube for one with a larger lumen.

Gastrostomy feeding

Gastrostomy is a widely used route of feeding when longer-term enteral nutrition is indicated [21]. Gastrostomy feeding is generally well accepted by children as it is more comfortable, obviates the need for frequent tube changes and is cosmetically more acceptable. Indications are not solely for long-term feeding; in certain situations gastrostomy feeding is the first route of choice. This includes children with congenital abnormalities such as tracheo-oesophageal fistula and oesophageal atresia and children with oesophageal injuries (e.g. following the ingestion of caustic chemicals). It has been suggested that a contraindication for gastrostomy is severe GOR. This can be exacerbated with the introduction of a gastrostomy tube [22], and gastrostomy placement in such children is generally done in combination with a fundoplication (p. 152).

The procedures used to place gastrostomies have significantly evolved over the past decades, and a device can be inserted by four different methods:

- surgically, using the Stamm or open technique
- using the percutaneous endoscopic approach (PEG)
- using interventional radiology (RIG)
- or by laparoscopic surgery

PEG, RIG and laparoscopic gastrostomy tube placement are minimally invasive compared with a gastrostomy performed by open surgery and are completed with a shorter anaesthetic time with fewer complications than an open surgically placed gastrostomy tube. A systematic review of insertion techniques suggests that a laparoscopic approach is associated with decreased patient morbidity when compared with an endoscopic gastrostomy insertion approach [23]. Ultimately, the technique chosen for gastrostomy tube placement will depend on individual patient's clinical condition and surgical expertise.

After about 3 months, once the tract is formed, a child can be fitted with a gastrostomy button that sits almost flush against the skin. This is far more discreet than the tubing associated with a conventional gastrostomy catheter and is a popular choice, particularly with teenagers. Primary placement of gastrostomy buttons for feeding tubes is also practised [24]. This less common intervention often leads to some minor post-operative problems, including gastrostomy site leakage.

Gastrostomy tubes and buttons require less frequent changes than nasogastric tubes. A device secured by a deflatable balloon is easier to change than one secured by an internal bumper bar or disc. If a tube is inadvertently removed, it should be replaced within 6–8 hours or the tract will start to close.

The main complications of gastrostomy feeding are wound infection, leakage and excessive granulation tissue around the exit site. Leakage of acidic gastric content can cause severe inflammation and skin irritation, and patients and parents should be taught about skin care. Infection may require treatment with topical or systemic antibiotics. There are no evidence-based guidelines on the use of prophylactic antibiotics for the insertion of PEG or other gastrostomies in children, but adult studies, including a Cochrane review, suggest a single dose of broad-spectrum antibiotics before PEG insertion reduces peristomal infections [25–27].

Feeding can be recommenced soon after endoscopic or laparoscopic gastrostomy insertion. Early feeding is well tolerated and reduces length of hospital stay, and resumption of full feeding within 24 hours is safe [28, 29].

Feeding into the jejunum

Indications for feeding into the jejunum include:

- congenital gastrointestinal anomalies
- gastric dysmotility
- severe vomiting resulting in faltering growth
- children at risk of aspiration

Placement of a nasojejunal tube and maintaining the position of the tube can be difficult. There are a number of methods of placement that include 'blind' bedside insertion, weighted tubes, fluoroscopic or endoscopic placement and the use of prokinetic agents such as erythromycin [30]. The position of the tube can be checked using pH paper. The tube can spontaneously re-site into the stomach or can be inadvertently pulled back; weighted tubes do not seem to be of much value in preventing this [31]. For longer-term feeding a surgical jejunostomy tube or a gastrojejunal tube is usually a more successful route for delivering nutrition support.

When children are fed directly into the jejunum, feed enters the intestine distal to the site of release of pancreatic enzymes and bile. Whole protein feeds are often tolerated, but if malabsorption occurs, a trial period of feeding a hydrolysed protein feed is recommended. The stomach normally acts as a reservoir for food or feed, regulating the amount that is delivered into the small intestine. Feed given as a bolus directly into the small intestine can cause abdominal pain, diarrhoea and dumping syndrome (p. 155), resulting from rapid delivery of a hyperosmolar feed into the jejunum. Feeds delivered into the jejunum should, therefore, always be given slowly by continuous infusion.

Complications can include bacterial overgrowth, malabsorption, bowel perforation and tube blockage. Stomach acid offers an antimicrobial effect that is bypassed in children receiving jejunal feeds. Like nasogastric and gastrostomy tubes, jejunostomy tubes need regular flushing to maintain patency, and it is recommended that sterile water be used.

A gastrostomy device with jejunal tube (PEG-J or G-J tube) may be used if access to the stomach and jejunum is required. These devices can be useful in children with delayed gastric emptying or those at risk of aspiration. Feed can be administered via the transgastric jejunal tube, and the gastrostomy port can be used for aspiration, decompression or administration of medicines.

The routes of enteral feeding are shown in Figure 4.1. The advantages and disadvantages of the routes of feed administration are given in Table 4.4.

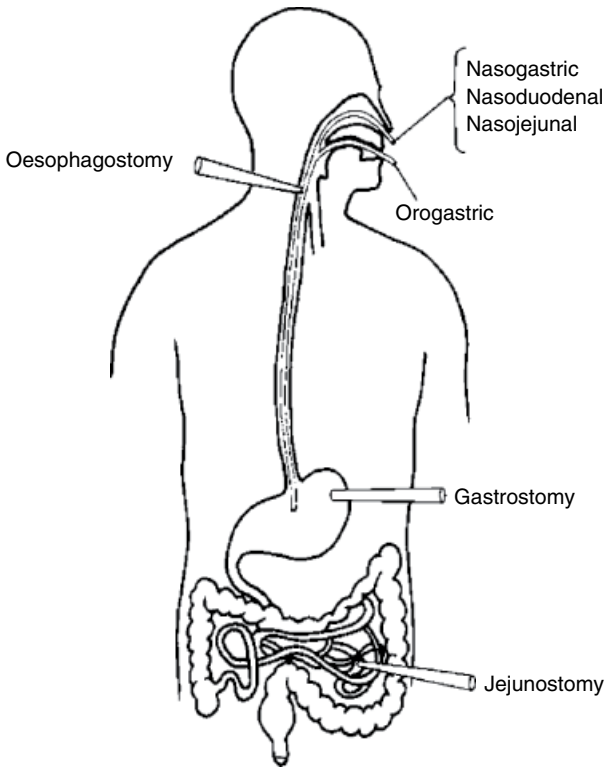

Figure 4.1 Routes of enteral feeding.

Orogastric feeding

Orogastric feeding is principally used for feeding neonates where nasal access is not feasible or where breathing would be compromised. The tube is passed via the mouth into the stomach. If all feeds are given via the orogastric tube, it can be taped in place, but if the infant is taking some breast or bottle feeds, the tube can be passed as required and removed between feeds.

Gastrostomy coupled with oesophagostomy

Following surgery in infants born with tracheo-oesophageal fistula or oesophageal atresia, it is not always possible to join the upper and lower ends of the oesophagus in continuity. If a surgical reconnection is delayed to a later date, the child will receive nutrition via a gastrostomy tube but is encouraged to feed orally to learn normal feeding skills. Any feed or food that is taken orally is collected at an oesophagostomy site and is commonly referred to as a 'sham feed' (p. 151).

Methods of feed administration

Enteral feeds can be given continuously via an enteral feeding pump, or as boluses, or a combination of both. A regimen should be chosen to meet the individual requirements of the child, and in most cases it can be tailored to the most practical method of feeding to cause minimum disruption to the child's lifestyle and that of their family. Certain situations will dictate a preferred feeding regimen, but a flexible approach should be taken wherever possible. This enables the child to maintain usual day-to-day activities and for the family to experience minimal disruption to their routines. Flexibility is especially important in children with a need for long-term tube feeding who, as time passes, will need a feed that is appropriate to their age and changing nutritional requirements and a regimen that is adaptable as they grow and develop.

Continuous feeding

Generally children will tolerate a slow continuous infusion of feed better than bolus feeds, and this method is sometimes chosen when enteral feeding is first started. Potentially there are fewer problems with intolerance when small feed volumes are infused continuously and there is a smaller time commitment for ward staff and for parents/caregivers at home. Mobility is affected but is minimised by the use of portable feeding pumps, particularly for children who are on continuous feeding for longer than 12 hours. These portable pumps can be carried by older children as backpacks and for infants can be carried by their parents/caregivers or attached to a pram or pushchair. Children under 6 years are often too small to carry a heavy backpack, yet cannot be kept still for long periods of continuous feeding. In these children the extra hours of feeding can sometimes be achieved during

Table 4.4 Advantages and disadvantages of various routes of feed administration.

Nasogastric feeds	Gastrostomy feeds	Jejunostomy feeds
Advantages	*Advantages*	*Advantages*
• No surgical procedure required • Placement can be easily taught • Non-invasive	• PEG and RIG tubes can be inserted with a short anaesthetic • No nightly insertion of tube and non-visible	• No possibility of aspiration • No nightly insertion of tube
Disadvantages	*Disadvantages*	*Disadvantages*
• Nausea • Dislodgement of tube with coughing/vomiting • Vomiting associated with coughing/reflux • Feeling of satiety • Difficulty in inserting tube • Irritation to the nose and throat • Possibility of aspiration • Visible	• Nausea • Vomiting associated with coughing and reflux • Local infection • Leakage around the exit site causing granuloma formation • Possibility of aspiration • Tube blockage	• Nausea • Tube blockage • Feeling of satiety • Placed under general anaesthesia • Increased risk of nutrient malabsorption • Leakage around the exit site causing granuloma formation • Local infection • Tube dislodgement • Micronutrient malabsorption

PEG, percutaneous endoscopic gastrostomy; RIG, radiologically inserted gastrostomy.
Source: Reprinted with permission of Anita MacDonald.

daytime sleeps and when they are occupied with quieter activities such as watching television and tablets.

There are situations where continuous feeding is essential. As previously discussed, feeds given through a nasojejunal tube or a feeding jejunostomy should always be delivered by continuous infusion. Severe GOR can be managed with a slow continuous infusion of feed as an adjunct to anti-reflux medication and positioning. Infants and children with malabsorption will also benefit from a continuous infusion of feed. This will slow transit time and may improve symptoms of diarrhoea, steatorrhoea and abdominal cramps and help to promote weight gain. In children with protracted diarrhoea and short bowel syndrome, continuous enteral feeding with a specialised formula often forms the basis of medical management; continuous tube feeding is also a treatment option for children with Crohn's disease to induce remission of disease. Infants and children with glycogen storage disease type I require a frequent supply of dietary glucose to maintain their blood glucose levels within normal limits. A continuous overnight nasogastric infusion of glucose polymer solution or standard feed will maintain blood sugars when children are asleep.

The use of nasogastric tubes for overnight feeding can achieve optimal nutritional intake but may be associated with risks of entanglement and displacement of tubes when infants and children are not closely supervised. There are currently no national guidelines for overnight nasogastric feeding of children, but some healthcare professionals no longer advocate or support overnight nasogastric feeding in the community. Development of local policies should involve risk assessments undertaken by the multidisciplinary team and should always consider the medical needs of the individual child.

Intermittent bolus feeding

Bolus tube feeding is successfully used in many children who require enteral feeding both in hospital and at home. Intermittent boluses given 3–4 hourly throughout the day via the nasogastric or gastrostomy tube mimic a physiologically normal feeding pattern, providing cyclical surges of gastrointestinal hormones that will have a trophic effect on the intestinal mucosa [32]. It is more time consuming than continuous feeding, but is the preferred method for many families with children requiring long-term feeding as it gives them greater freedom and mobility and can be adapted to fit in with family mealtimes.

There are situations where bolus feeding is recommended:

- Neonates requiring small volumes may need to be given their feed by hourly bolus as the length of tubing between the reservoir and child creates a 'dead space' holding feed; this can be particularly relevant in infants fed EBM as some fat can be lost by adherence to the sides of the burette and tubing [33]
- Children who have had a surgical anti-reflux procedure are unable to vomit; large volumes of feed from a continuous infusion can accumulate in the stomach and remain undetected in those who have gastric stasis or poor gastrointestinal motility, which can lead to gastric rupture; bolus feeding with a gravity feeding pack will prevent over-filling of the stomach as tubes are routinely aspirated before each feed; and further feed will be prevented from entering the stomach from the feeding chamber if the stomach is already full
- Children who frequently try to remove their nasogastric tube risk aspiration if the end of the tube is dislodged into the airways; they will benefit from bolus feeding as they can be constantly supervised during the feed

Table 4.5 Choosing a suitable feeding regimen.

Regimen	Example
Bolus top-up feeding	*Congenital heart disease* Bottle feeds are not completed due to breathlessness; the remaining feed is topped up via the nasogastric tube
Exclusive bolus feeding	*Long-term feeding for children with a neurological handicap* Daytime bolus feeding can allow flexibility and mobility and provide a regimen that can fit in with family mealtimes
	Post-fundoplication Bolus feeding is usually the method of choice for children following a surgical anti-reflux procedure
	Sham feeding Children who are sham fed should receive a bolus feed to coincide with oral feeds
Combination of bolus and continuous feeding	*Chronic illness* Children with anorexia associated with chronic illness may receive a large proportion of their nutrition via a nasogastric or gastrostomy tube. Daytime boluses allow for a normal meal pattern, and overnight feeding with a feeding pump reduces the time commitment at night for parents and ward staff
	Malabsorption syndromes (e.g. short bowel) Slow continuous infusion optimises absorption with additional small bolus or oral feeds to encourage normal feeding behaviour and to stimulate trophic hormones and bile
Overnight feeding only	*Supplementary nutrition* Children who require enteral feeding to supplement their poor oral intake or to meet their increased nutritional requirements are usually fed overnight only. This allows the children to maintain a normal daytime eating pattern while still providing the nutritional support they require
Continuous feeding only	*Primary disease management* Gastro-oesophageal reflux Severe Crohn's disease Glycogen storage disease

- Children with an oesophagostomy who are sham fed should preferably receive bolus feeds to coincide with their oral feeds
- The continuous delivery of enteral feeds may interfere with the absorption of medications; bolus feeding will provide periods when medication can be given on an empty stomach to allow optimal absorption

A schedule of feeding regimens is given in Table 4.5.

Enteral feeding equipment

An international standard was introduced in 2016 to govern enteral feeding devices [34]. A new global connector, ENfit, was introduced to replace the Luer connector system to ensure patient safety and prevent misconnection to intravenous lines or other types of medical device. The ENfit range includes tubes, syringes and giving sets.

Nasogastric feeding tubes

There is a wide range of paediatric feeding tubes of varying lengths and gauges to meet the requirements of children of all ages. For children, the ideal tube should be of a small gauge to make the tube more comfortable and cosmetically acceptable. Fine bore nasogastric tubes are the most commonly used tubes for children. These tubes have a small internal diameter (1–2 mm) and are flexible and available in polyvinyl chloride (PVC) and polyurethane.

PVC tubes are used for short-term enteral feeding. They are for single use only and require changing every week as the tubes stiffen over time and may cause tissue damage. These tubes are least likely to be displaced and so can be used for children who are prone to vomiting.

Fine bore polyurethane or silicone tubes are designed for longer-term nasogastric feeding and are very much softer and more comfortable than PVC tubes. Each tube comes with a guidewire or stylet to give the tube rigidity when passed. As a general guide tubes can usually remain *in situ* for 4–6 weeks, but manufacturers' instructions regarding usage should always be followed. Unlike PVC tubes that are for single use, these tubes can also be used for overnight feeding and removed during the daytime if storage and cleaning instructions are carefully adhered to.

When passing polyurethane tubes, there is a high risk of tracheal intubation in children who have an impaired swallow or who are ventilated. In these children, PVC tubes may be preferable despite the need for longer-term feeding.

Gastrostomy devices

Gastrostomy devices have evolved considerably with an increasing amount of equipment entering the specialised paediatric market. Gastrostomy tubes, whether inserted by an open surgical procedure, PEG, RIG or laparoscopic method, are manufactured from pliable biocompatible silicone. PEG and RIG tubes are held in place by a crossbar, plastic disc or bumper that anchors the device to the inside of the stomach wall, preventing inadvertent removal. They require a repeated annual procedure for change of tube, or they can be replaced with a gastrostomy button once the tract has formed. Surgically placed gastrostomy tubes are secured by an inflated balloon, which allows easy replacement of the tube. They also have a skin-level retention disc preventing migration of the tube. Foley catheters are not ideal, but may be used as gastrostomy tubes; they require strapping securely in place, as they have no retention disc and may easily migrate into the duodenum. Children requiring long-term gastrostomy feeding will usually elect to have their tube replaced by a gastrostomy button once a tract has been established. These devices are secured within the stomach by an inflated balloon, facilitating removal and replacement, and they should last 3–6 months. Parents and carers are provided with a spare button, so it can be changed immediately should it fall out.

Enteral feeding pumps

Choice of feeding pumps will depend on the requirements of individual hospitals and individual children, but there are a number of features that are either essential or desirable:

- occlusion and low battery alarms
- easy to operate
- durable
- tamper proof
- easy to clean
- low noise
- small and lightweight if designed to be portable
- long battery life if designed to be portable
- accurate flow rate setting (5%–10%)
- small flow rate increments (1 mL/hour preferable)
- option of bolus feeding
- good servicing backup

Feed reservoirs

Many sterile ready-to-feed paediatric formulas are now ready to hang (RTH) and come in pre-filled plastic bottles or flexible packs that can be connected directly to the giving set. This reduces the need for decanting and the consequent risk of bacterial contamination. If using a closed RTH system, the feed reservoir and giving set can be used for up to 24 hours and then discarded.

If it is necessary to decant a feed into a reservoir, there are many different flexible and rigid containers on the market for this purpose. Generally children require smaller reservoirs than adults, especially when using a portable system. Infants requiring small volumes of feed may have their feed decanted into a burette that has a small capacity; this is principally for hospital use.

Bacterial contamination is common [35, 36]; if there is a need to decant feeds, this should always be done in a clean environment. Sterilising and reusing feed reservoirs potentially leads to contamination and is not recommended.

The length of time a feed can safely be left 'hanging' varies. While sterile RTH feeds may be delivered over a period of up to 24 hours, local policy will determine the hanging time for reconstituted feeds. Hanging time is much shorter and is generally no longer than 4–6 hours in the hospital setting.

Home enteral feeding

When a decision is made to commence enteral feeding at home, it is important that the parents/caregivers undergo a training programme that will teach them to look after all aspects of feeding and equipment. Correct procedures and adherence to safety are paramount, and help and supervision must be given to familiarise the parents with the necessary techniques prior to hospital discharge [37]. Pictorial teaching aids may be used to help families for whom English is not their first language and those unable to read and follow written guidelines [38]. It is essential to identify and liaise with community teams who will be sharing care when a child is discharged; they will have a key role in supporting the child and family. While it is essential that the child receives adequate nutrition, the enteral feeding regimen should be planned to fit in as much as possible with the family's lifestyle.

Home enteral feeding companies can supply both feeds and feeding equipment directly to the patient's home. With more companies providing a home delivery service, the market has become competitive; they may insist on the use of their own brand of equipment and feeds, so it is important to ensure the child gets a suitable pump and feed that have been prescribed based on clinical need.

NICE gives recommendations for infection control during enteral feeding in the community [39]. These include guidelines for education of patients, their caregivers and healthcare personnel; preparation, storage and administration of feeds; and care of feeding devices. They recommend that pre-packaged ready-to-use feeds should be used in preference to feeds requiring decanting, reconstitution or dilution and that reconstituted feeds, when used, should be administered over a maximum 4 hour period. They acknowledge that the recommendations need to be adapted and incorporated into local practice guidelines.

The social and emotional aspects of tube feeding are often overlooked. Studies have shown that families experience frequent problems with enteral feeding at home related to sleep

Table 4.6 Feed intolerance.

Symptom	Cause	Solution
Diarrhoea	Unsuitable choice of feed in children with impaired gut function	Change to hydrolysed formula or modular feed
	Fast infusion rate	Slow infusion rate and increase as tolerated to provide required nutritional intake
	Intolerance of bolus feeds	Frequent, smaller feeds or change feeding regimen to continuous infusion
	High feed osmolarity	Build up strength of feeds and deliver by continuous infusion
	Contamination of feed	Use sterile commercially produced feeds wherever possible and prepare other feeds in clean environments
	Drugs (e.g. antibiotics, laxatives)	Consider drugs as a cause of diarrhoea before feed is stopped or reduced Review drugs
Nausea and vomiting	Fast infusion rate	Slowly increase rate of feed infusion or give over a longer period of time
	Slow gastric emptying Psychological factors Constipation	Correct positioning and prokinetic drugs Address behavioural feeding issues Maintain regular bowel motions with adequate fluid intakes, fibre-containing feeds and laxatives
	Medicines given at the same time as feeds	Allow time between giving medicines and giving feeds or stop continuous feed for a short time when medicines are given
Regurgitation and aspiration	Gastro-oesophageal reflux	Correct positioning, anti-reflux drugs, feed thickener, transpyloric feeding, fundoplication
	Dislodged tubes	Secure tube adequately and test position of tube regularly
	Fast infusion rate Intolerance of bolus feeds	Slow infusion rate Smaller, more frequent feeds or continuous infusion

disturbance, tube dislodgement, tube blockage and difficulties with home delivery of feed and equipment [40–42]. The additional psychosocial support needs of parents providing home enteral feeding to children with neurodisabilities must also be considered [43]. Dietitians and community nurses need to explore solutions to the common problems associated with overnight feeding. Regular review is necessary in long-term patients to continue to identify and minimise problems.

Enteral feeds are usually prescribed by the general practitioner although the costs for disposable equipment may be funded by a number of different agencies. These include hospital, community and dietetic budgets.

Feed administration and tolerance

The way in which a feed is administered ultimately depends on the clinical condition of the individual child, and there are no set rules for starting enteral feeds. Neonates may need to be started on just 0.5 mL/hour infusion rates, whereas older children may tolerate rates of 100 mL/hour. In most cases feeds can be started at full strength with the volume being gradually increased in stages, either at an increased infusion rate or as a larger bolus.

Gastrointestinal symptoms are the most common complications of enteral feeding, but with the wide choice of feeds, administration techniques and enteral feeding devices, it should be possible to minimise gastrointestinal symptoms. Some causes of feed intolerance and their resolution are given in Table 4.6.

Monitoring children on enteral feeds

Children who are commenced on enteral feeds require monitoring and review. There are at present no standards for the monitoring of children on long-term enteral feeding at home in the UK.

At the initiation of enteral feeding, goals must be set with respect to the aim of the nutritional intervention, e.g. an improvement in nutritional status, control of symptoms, palliative care and the expected growth of the child taking into account their underlying clinical disorder. Regular follow-up is required to monitor both short-term and longer-term progress. Anthropometry, blood tests and control of any symptoms should all be included in the monitoring procedure. As children gain weight and get older, their requirements change, and follow-up is essential to ensure they continue to receive adequate nutrition. The EU Regulation on Food for Specific Groups makes recommendations for the composition of FSMPs including minimum and maximum content of vitamins, minerals and trace elements [8]. A 2016 study compared the micronutrient content of 62 standard adult enteral feeds with dietary

reference values (DRVs). At a volume that met normal energy requirements, the micronutrients supplied in these enteral feeds were often above the DRV for a healthy population, but were within the range of the European standards [44]. Although enteral feeds are formulated to be nutritionally complete, it is wise to check nutritional status with biochemical monitoring, particularly if tube feeding is the sole source of nutrition [45]. There will be deterioration of vitamin content throughout the shelf life and individual variation in the absorption of micronutrients. Routine checks of albumin, electrolytes and haemoglobin are useful as well as assessment of micronutrient status. Blood tests can also be helpful in assessing response to nutritional therapy, e.g. monitoring of inflammatory markers in children with active Crohn's disease. Both hospital and community staff have a role to play in monitoring a child's progress and helping the family cope with tube feeding at home. The needs of a young infant are quite different from those of a toddler or teenager, and the individual needs of each child should be considered at different stages of their development.

Regular follow-up can be important for the family as well as the child. Home enteral feeding has a big impact on family life, resulting in both psychological and practical problems that should be addressed regularly. Good communication between the family, hospital and community teams is essential, and the family must be given a contact for professional help in the case of any emergency.

Oral feeding skills

Another important aspect of follow-up is the encouragement to maintain oral feeding skills. Children who miss out on early experiences of taste and texture are much more likely to develop feeding problems [46]. Offering a small amount of food gives children the chance to use the lips and tongue and develop their oromotor skills while experiencing a range of tastes. This is particularly important around the time of weaning when children are often more willing to accept different foods. Studies have also shown that in long-term tube-fed children, even tactile stimulation of the face and mouth alone can help re-establish oral feeding [47].

Blended diets

Internationally, blended diets for tube feeding via gastrostomy are becoming popular with families and some healthcare professionals, but in the UK the practice has been less widely advocated. A 2015 BDA policy statement endorsed the use of licensed, evidence-based sterile feeds designed specifically for enteral tube feeding as best practice [48], due to concerns regarding safety, nutritional adequacy and practical issues; the administration of blended food via a gastrostomy was not recommended. Current guidance from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) on paediatric enteral nutrition also discourages liquidised foods for tube feeding [30]. However, parents have a statutory duty of responsibility giving them the right to make fundamental decisions in their child's life including healthcare [49], and dietitians need to remain sensitive to the choices made by parents.

There is evidence of clinical benefit associated with a blended diet. One study looked at improvement in symptoms in 33 children with gagging and retching following fundoplication: 73% showed symptom reduction with a 50% increase in enteral intake [50]. Another study reported better volume tolerance and improvements in GOR and constipation when changing from commercial formula to blended diet [51]. Additional benefits relate to the impact on the family, giving them more control and allowing them to provide food for their child and include them in family mealtimes. Gastrostomy feeding is commonly required to provide nutritional support to children with complex needs, many with life-limiting neurological disorders. It is well recognised that parents of such children have a strong instinct to nurture [52]; gastrostomy feeding with a commercial formula can be seen to medicalise feeding practices [53].

A 2019 BDA policy statement [54] aims to support dietitians to ensure patients fed with a blended diet receive effective, evidence-based, equitable and quality care. For the majority of patients a commercially prepared formula remains the first choice, however, dietitians can recommend blended diet via gastrostomy where they believe there may be potential benefit. When families are considering a blended diet, it is important that dietitians provide the information necessary for them to make an informed choice, including the potential risks, tailored to the individual needs of the family.

Blended diets can be introduced at weaning age alongside breastmilk or formula and for older children either as a sole source of nutrition or in combination with commercial feeds. Despite not previously recommending blended diets, the BDA developed a toolkit in 2015 to enable dietitians to support their patients and provide practical recommendations on the use of blended diet and monitoring [55]. Further practical guidance and decision-making tools are expected in 2020.

Learning points: blended diets

- *Dietitians can recommend blended diet via gastrostomy when they believe there may be potential benefit*
- *There is some evidence of clinical benefit associated with a blended diet: reduction in gagging, retching and GOR and improvement in constipation and diarrhoea*
- *Dietitians have a duty of care to provide information to support parents who choose this method of feeding and ensure adequate training*
- *Individual risk assessment is required*

Refeeding syndrome

Refeeding syndrome is a term used to describe the metabolic complications that can arise following the introduction of nutrition to a malnourished patient. Shifts in fluids and electrolytes can lead to life-threatening complications, and the potential for refeeding syndrome should be considered whenever nutritional support is instituted orally, enterally or parenterally [55, 57].

Circumstances that put children at highest risk include feeding:

- where the child has <70%–80% weight for height
- following rapid weight loss (including in obese patients)
- after prolonged intravenous fluid therapy devoid of glucose
- when there has been minimal intake for 7–10 days
- where there are pre-existing low levels of serum potassium, phosphate or magnesium before the introduction of nutrition

Malnutrition causes an adaptive reduction in cellular activity and organ function, with fat and muscle being the major sources of energy in catabolic patients. Reintroduction of glucose for energy causes a rise in insulin and an intracellular uptake of glucose, potassium, phosphate and magnesium and fall in serum concentrations. Reactivation of carbohydrate metabolism also requires thiamin as a cofactor. In addition to biochemical changes, clinical signs of refeeding syndrome include oedema and disturbances to cardiac function [58] or respiratory failure [59].

Recommendations for the introduction of nutrition in patients at risk of refeeding syndrome vary and will depend on clinical condition, age, degree of malnutrition, route of feeding and local guidelines. The management of refeeding in the paediatric intensive care unit is described in Chapter 6 and in patients with anorexia nervosa in Chapter 19.

Before commencing nutrition, biochemical monitoring is essential with oral or intravenous correction of any electrolyte disturbances. There is no clear evidence-based guideline for the safe introduction of nutrition in children at risk of refeeding syndrome, but there is a consensus that cautious introduction of feeds, gradual increase in intake and careful biochemical and clinical monitoring are paramount. Great Ormond Street Hospital guidelines [60] recommend a starting energy intake equivalent to the basal metabolic rate (BMR) in young children, increasing in increments to the estimated energy requirement (EER) based on low physical activity [61]. For older children the guideline suggests that refeeding should be commenced at 40 kcal (165 kJ)/kg/day increasing by 200 kcal (840 kJ)/day up to EER for low physical activity. Following a review of the literature, Afzal *et al*. [57] suggest that the initial regimen should be limited to 75% of requirements and increased over 3–5 days. NICE guidelines for adult nutrition support suggest that nutritional support is introduced at no more than 50% requirements in patients who have had little intake for more than 5 days and 5–10 kcal (20–40 kJ)/kg in high risk patients; these guidelines may be relevant to adolescents [62].

During the first few days of feeding, it is recommended that potassium, phosphate and magnesium levels be monitored at least 12 hourly. This needs to be clearly documented in care plans and discussed with the medical and nursing team to ensure adherence to the regimen. In some high risk children, 8 hourly blood testing is recommended. Any electrolyte disturbances need to be corrected before further steps to increase energy intake are taken, which may mean frequent adjustment to feeding plans. Once electrolytes are stable, blood testing can be reduced to once a day.

Reactivation of carbohydrate-dependent metabolic pathways increases demand for thiamin, a cofactor required for cellular enzymatic reactions. Thiamin is a water-soluble vitamin and, therefore, is not stored in appreciable amounts so that any acceleration of carbohydrate metabolism can lead to thiamin deficiency. There are no recommendations for thiamin supplementation in paediatric refeeding, but in adults it is recommended that high dose prophylactic thiamin is given before refeeding and for the first 3–10 days [62, 63]. High dosage thiamin supplements may be given orally if tolerated or by the intravenous or intramuscular route.

Learning points: refeeding syndrome

- *It is important to identify children at highest risk*
- *Close biochemical monitoring is essential before and after introduction of feeds*
- *There is no clear evidence-based guideline for the safe introduction of nutrition in all children at risk of refeeding syndrome, but there is consensus about cautious introduction of feeds and achievement of full requirements in a stepwise fashion*
- *Refeeding regimens vary between centres, different clinical conditions and for individual children*
- *Thiamin supplementation is recommended before feeding and during the introduction of feeds*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

5 Parenteral Nutrition

Joanne Louise Price

Introduction

Although parenteral nutrition (PN) in a paediatric patient was first described in 1944 [1], it first became available for general use in the 1960s. Infusion of high concentration hyperosmolar carbohydrate solutions into peripheral veins meant that severe phlebitis limited the length of time PN could be used. However, in 1968, Wilmore and Dudrick [2] and Dudrick *et al*. [3] described the provision of intravenous nutrients to an infant via a central venous catheter (CVC). Intravenous lipids have subsequently been developed, providing improved energy density in iso-osmolar solutions. The 1970s saw the development of crystalline amino acid (AA) solutions, reducing the risk of anaphylaxis. More recently development of new lipid sources has further improved the outcome for patients requiring PN.

PN is an established therapy to which many patients of all ages owe their lives. It has transformed the outcome for many previously fatal paediatric conditions including feeding preterm infants and post-surgical neonates with short bowel syndrome [4].

The composition of PN continues to be researched, developed and refined. As with many lifesaving procedures, PN is not without its risks, and it is associated with fatal complications (Table 5.1). PN should, therefore, not be used casually, but in a disciplined and organised manner in carefully selected patients [5, 6]. Paediatric PN should be prescribed only where there is an experienced multidisciplinary team of doctors, dietitians, pharmacists and nurses contributing to the provision and monitoring of the PN therapy, preferably in an experienced paediatric centre.

However, practice among institutions varies. A report from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) of a case-based observational peer review of PN clinical practice in England, Wales and Northern Ireland found wide variability in practice [7]. Seventy children and 264 neonates in 74 hospitals (as well as 877 adults) were surveyed. Good practice, defined as 'a standard that the reviewer would accept from themselves and their trainees in their institution', was found in only 24% of those neonates surveyed. Areas of concern raised included delayed commencement of PN, inconsistent nutrient provision and inconsistent monitoring and review.

NCEPOD stated that it would be valuable to develop a team approach to parenteral nutritional support, recognising that this should be a multidisciplinary exercise with sharing of expertise. The report also recommended a large-scale national audit of PN care in children in the UK, which should be undertaken to determine the quality of PN care in this group of patients [7].

Nutrition support teams

It is generally agreed that paediatric parenteral feeding requires considerable clinical, pharmaceutical and nursing skills, with many centres now following the principle of a multidisciplinary nutrition support team (NST) facilitating treatment with PN [6, 8].

Good interdisciplinary communication is paramount if patient care is to be of the highest standard. Improvement in outcome of PN has been demonstrated where a multidisciplinary NST is involved [8, 9–12]. The following are core members of the team and their roles:

- paediatric consultant – often a paediatric gastroenterologist oversees patient care
- paediatric surgeon – inserts feeding lines and advises regarding surgical management as required; many PN-dependent children have a surgical diagnosis and will be under the overall care of a paediatric surgeon
- medical specialist paediatric registrar – advises on prescription of PN and many other aspects of care

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Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 5.1 Some complications of parenteral nutrition.

Gut related	Solution related	Line related
Villous atrophy	Over/under-delivery of nutrients	Sepsis
Decreased digestive enzyme activity	Hyperglycaemia	Catheter occlusion
Cholestasis	Hyperlipidaemia	Accidental line removal
Bacterial overgrowth/bacterial translocation	Micronutrient toxicity	Site infection
Fluid/electrolyte imbalance Metabolic bone disease	Toxic effects of non-nutrient components of solutions	
	Growth failure	
	Refeeding syndrome	
	Cholestasis	
	Metabolic bone disease	

- paediatric dietitian – role described below
- PN pharmacist – responsible for production and checking of solutions; advises regarding prescription when necessary
- PN nurse – trains caregivers and staff, coordinates patient care
- biochemist – advises on monitoring and interpretation of blood biochemistry and appropriate biochemical tests

The NST usually reviews the child's progress at least weekly, with daily reviews by some specialties as necessary. In centres where NSTs have been established, reported benefits include a reduction in mechanical line problems, reduced sepsis, fewer metabolic complications, shorter courses of PN (due to faster transition to appropriate enteral formulas) and savings on the cost of providing PN [9–11]. The NST produces protocols and procedures and organises audit and reviews of the PN service; it may be monitored by the hospital's nutrition steering committee.

Other key members of the NST to include as required are psychologists, speech and language therapists and play specialists. These have a particularly important role with children undergoing long-term PN.

The role of the dietitian

As a key member of the NST [12, 13], the dietitian ensures the child's nutritional requirements are met in order to maintain adequate growth and development. There is also a role in the development of the child's oral feeding skills. The dietitian will:

- set targets for enteral and parenteral feeding and devise a feeding plan
- monitor that correct volumes of prescribed enteral feeds/PN are received
- calculate total nutrient intake and compare with the individual's requirements
- use appropriate centile charts to plot the child's height, weight and head circumference; it is imperative that inadequate growth is recognised and discussed with the NST at the earliest opportunity
- advise regarding suitable adjustments to feeding regimens to enhance intake and absorption and, if necessary, advise on changes to feeds in cases of malabsorption or feed intolerance
- review the nutritional biochemistry and contribute to the discussion and decision making regarding nutrient intakes and adjustments to the PN

A scoping exercise was carried out by the National Institute for Health and Care Excellence (NICE) in 2017, and new guidelines for PN in neonates were published in February 2020. Guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition/European Society for Clinical Nutrition and Metabolism/European Society for Paediatric Research/Chinese Society of Parenteral and Enteral Nutrition (ESPGHAN/ESPEN/ESPR/CSPEN) have been updated and published in 2018 and will be referred to as the ESPGHAN guidelines throughout this chapter [13].

Learning points: overview of parenteral nutrition

- *PN usage is increasing and practice varies widely across the UK*
- *See neonatal PN NICE guideline 154, February 2020*
- *Research into PN lipids has improved the outcomes for PN*
- *Nutrition support teams improve outcomes in patients receiving PN*
- *Dietitians have a key role within the NST in ensuring adequate delivery of nutrients*

Indications and considerations for parenteral nutrition in children

Indications for PN are given in Table 5.2. This is not an exhaustive list. PN is a hazardous and expensive form of nutrition support in children and is indicated only where enteral nutrition cannot prevent or reverse growth failure. The timing and duration of PN is dependent upon the child's nutritional reserves, expected duration of starvation and severity of illness. PN is normally built up over 2–4 days,

Table 5.2 Indications for parenteral nutrition in children.

Intestinal failure	Other common indications	Patients requiring additional nutrition support
Short bowel syndrome	Functional immaturity in preterm infants	Trauma, burns
Surgical and gastrointestinal abnormalities, e.g. gastroschisis, intestinal atresia	Chemotherapy (leading to acute intestinal failure)	Chronic kidney disease Liver disease
Necrotising enterocolitis	Pancreatitis	Malignant disease
Protracted diarrhoea Malabsorption syndromes	Chronic aspiration due to gastro-oesophageal reflux	Pre-surgical inflammatory bowel disease
Inflammatory bowel disease		
Chronic pseudo-obstruction		

and, therefore, it is neither reasonable nor clinically indicated to routinely prescribe PN for less than 5 days [14]. Some long-term patients will require PN for several years, sometimes into adulthood. Long-term PN is generally defined as PN of >4 weeks' duration [13].

Considerations

Enteral nutrition

PN is associated with many complications, and for this reason it is widely accepted that enteral nutrition should always be given where possible. If the gut works, it should be used, even if only minimal feeds are tolerated [15]. Absence of luminal nutrients has been associated with atrophic changes in the gut mucosa, and it is well recognised that enteral feeding is the single most effective way of preventing many gut-related complications.

Nutritionally insignificant volumes of enteral nutrition have been found to have a trophic effect on the gut, encouraging intestinal adaptation, and have been linked to enhanced gut motility, decreased incidence of PN-induced cholestasis and decreased bacterial translocation [16–18]. After gastrointestinal surgery, particularly that resulting in short bowel syndrome, intraluminal nutrients and luminal substrates are essential for optimal intestinal adaptation [19]. Initiation of enteral feeding is strongly recommended early in the post-operative period.

Breastmilk or standard infant formulas are indicated unless there has been previous evidence of malabsorption or feed intolerance. Short frequent breastfeeds or small boluses of expressed breastmilk or infant formula, as little as 1–2 mL/hour, are beneficial. If there are signs of malabsorption, a hydrolysed protein feed, which is also lactose-free and has a proportion of its fat as medium chain triglycerides, may be indicated, e.g. Pregestimil Lipil and Pepti-Junior. It may be advantageous to deliver the feed continuously via an enteral feeding pump to aid absorption. (More detailed management of intestinal failure is discussed in Chapter 9.)

Growth

Malnutrition in children results in impaired growth and development. All children on PN should be weighed and measured regularly, and the measurements recorded and plotted on centile charts to ensure appropriate growth is maintained.

Nutritional requirements and demands vary considerably with age and size, with critical periods during infancy and puberty when growth is fastest. Most brain growth occurs in the last trimester of pregnancy and the first 2 years of life. Extra special care should be taken to avoid malnutrition and biochemical abnormalities at this time as poor nutrition during these critical periods not only results in slowing and stunting of growth but may also permanently affect neurological development [20, 21].

Infants are at considerable risk due to their limited energy reserves, and the commencement of PN in a small infant who cannot tolerate enteral feeds is a matter of urgency. A preterm infant weighing 1 kg has only 1% body fat and may survive for only 4 days if starved [22].

Equally adolescents are at significant risk of not achieving their growth potential if nutrient requirements are not met at the onset of and during puberty.

Cholestasis and liver disease

The pathogenesis of PN-associated liver disease (PNALD) is not completely understood. The aetiology is thought to be multifactorial and can progress to cirrhosis and end-stage liver failure in some cases [23]. With better management of PN and earlier weaning from PN to enteral feeding, the reported prevalence of PNALD in infants has reduced from around 65% [24] to around 25% [25]. The early introduction of enteral feeding and weaning from PN without compromising nutritional status is the most important measure that can be taken to help reduce the risk of cholestasis [25, 26].

In preterm neonates enteral feeding may be delayed or withheld in order to help prevent the development of necrotising enterocolitis (NEC); this has been an area of much debate. A Cochrane analysis found that delaying enteral feeds increased the length of hospital stay, prolonged use of PN and increased the incidence of cholestasis [27]. Results of a UK multicentre trial, ADEPT (Abnormal Doppler Enteral Prescription Trial), concluded that 'Early introduction of enteral feeds in growth-restricted preterm infants results in earlier achievement of full enteral feeding and does not

appear to increase the risk of NEC' [28]. Therefore, enteral feeding should be introduced as early as possible, even in preterm infants. American guidelines recommend that all preterm babies over 1000 g are commenced on minimal feeds (preferably mother's milk) by the second day of life [29].

In addition to lack of enteral feeds, pathogenesis of PNALD is associated with intrauterine growth retardation, prematurity, immature enterohepatic circulation, underlying disease, number of infections/septic episodes, number of surgical procedures and number of blood transfusions [13, 30, 31]. PN solutions themselves may have a role to play in the development of liver disease; lipid emulsions have been implicated and overfeeding of glucose has been associated with hepatic steatosis [25, 26, 31]. High risk for PNALD is also associated with PN dependency from a young age, very short bowel length and prolonged PN duration.

Cyclical, rather than continuous, PN and cycling of lipid in particular and restricting lipid to certain nights of the week afford some protection to the liver and are common practice in patients on long-term PN, particularly those who have PN at home. This usually involves giving the PN over a shorter period allowing some hours off. There are obvious implications to energy intake and tolerance of solutions, and this should be monitored carefully. Due to the implications on growth, particularly where lipid is restricted, cycling should only be used in long-term stable patients who have an experienced NST looking after them. Effective treatment and prevention of recurrent sepsis through translocation of bacteria across the gastrointestinal wall and via line infections is also known to be a significant factor in the avoidance of PNALD [31, 32]. Other therapies include the use of ursodeoxycholic acid, a synthetic bile acid [33]. Cases of PNALD that do not improve should be referred to a supraregional liver unit for assessment at the earliest opportunity [13].

In summary, increased risk of developing PNALD is found:

- in premature infants
- in those with short bowel syndrome
- where there has been long-term absence of enteral feeds
- where there is loss of enterohepatic cycling of bile salts post-operatively or due to obstruction
- where there are repeated septic episodes
- where there is intestinal bacterial overgrowth

Learning points: prevention of PNALD

- *giving early enteral feeding, even if only minimal*
- *giving some oral feeds if possible*
- *avoidance of line sepsis by rigorous line care*
- *prompt treatment of sepsis*
- *cyclical PN, particularly lipid*
- *reduction of the dose of lipid*
- *use of ursodeoxycholic acid*
- *use of lipid solutions containing ω3 PUFA in some groups (Table 5.5)*

PN-related bone disease

Children on long-term PN can develop a type of metabolic bone disease. The aetiology is multifactorial and may be related to physical inactivity, underlying disease, disordered vitamin D metabolism, hypocalcemia, hypercalciuria, raised alkaline phosphatase and hypophosphataemia.

Regular biochemical monitoring including measurements of urinary calcium, plasma calcium, plasma phosphorus, plasma parathyroid hormone, vitamin D concentrations and serum alkaline phosphatase activity along with dual-energy X-ray absorptiometry (DEXA) scanning is recommended to evaluate these children [13, 34]. Referral to an endocrine/metabolic specialist may be necessary in cases of concern.

Oral hypersensitivity

Oral hypersensitivity occurs when the oral route is not established from birth, or when there is a delayed introduction of solids, or when the oral route is not used for lengthy periods of time. Lack of oral stimulation together with unpleasant oral procedures/experiences such as intubations, suction, vomiting, choking and gastro-oesophageal reflux may lead to long-term feeding problems. Steps to prevent oral feeding aversion will help progress onto enteral feeding and subsequent reduction in PN.

Early involvement of a specialist speech and language therapist to advise regarding oral desensitisation is recommended, particularly in cases of refusal to feed or distress during feeding. A play specialist can work with children around oral desensitisation using messy play and play involving food. In addition to these specialist techniques, early and sustained oral feeding when safe to do so, use of dummies (pacifiers), sips and tastes should always be employed (where safe to do so) to maintain oral function, especially in infancy.

Learning points: considerations in children on PN

- *Their continuing growth with key stages of development*
- *They have immature liver and bowel function with inefficient enzyme production*
- *They are susceptible to PNALD*
- *Their immature immune system leads to increased susceptibility to infection*
- *They are vulnerable to central venous line infection*
- *There is a high risk of cross-contamination due to inability to self-care*
- *Oral feeding is often not established, so food aversion common*
- *There may be delayed weaning from PN due to an inability to feed orally*

Nutrient requirements and solutions

Recommended requirements vary and tend to be based on clinical experience [6, 8, 20, 34, 35]. The ESPGHAN guidelines published in 2018 [13] are the most recent regarding paediatric PN at the time of writing.

Fluid and electrolytes

Infants have immature organ systems and require high volumes of fluid in order to excrete electrolytes sufficiently. Young children are physiologically unable to concentrate urine and conserve fluid as effectively as adults. Maximum urine concentrations are 550 mOsm/L in preterm infants and 700 mOsm/L in term infants compared with 1200 mOsm/L in adults [36]. Electrolyte requirements are often higher, but dehydration and metabolic acidosis can occur if these are given without adequate fluid. Care should always be taken that fluid requirements are met.

Age, size, fluid balance, the environment and clinical conditions are all factors affecting fluid requirements. Recommendations are given in Table 5.3. Cardiac impairment, renal disease and respiratory insufficiency are examples of conditions that may limit fluid volumes, whereas high fluid losses due to diarrhoea, high output fistula/stoma and fever may all increase fluid needs. Also, additional fluid may be needed if radiant heaters/phototherapy is used.

Table 5.3 Summary of parenteral fluid and electrolyte requirements for children.

Age/weight	Fluid (mL/kg/day)	Na (mmol/kg/day)	K (mmol/kg/day)	Cl (mmol/kg/day)
<1500 g	160–180	2.0–5	1.0–2.0	2–5
>1500 g	140–160	2.0–5.0	1.0–3.0	2–5
Preterm to 2 months	140–160	2.0–5.0	1.5–5.0	2–5
2 months to 1 year	120–150	2.0–3.0	1.0–3.0	2–3
1–2 years	80–120	1.0–3.0	1.0–3.0	2–4
3–5 years	80–100	1.0–3.0	1.0–3.0	2–4
6–12 years	60–80	1.0–3.0	1.0–3.0	2–4
13–18 years	50–70	1.0–3.0	1.0–3.0	2–4

Source: Adapted from [13]. Reproduced with permission of Elsevier.

Electrolyte requirements vary with age, clinical condition and blood biochemistry. Electrolyte solutions are usually added to PN in response to each individual child's blood biochemistry.

The above requirements are a guide and are for use in stable infants and children on PN. Close daily monitoring of electrolytes should be undertaken and input adjusted accordingly, particularly in the first 5 days.

Due to very tight homeostatic mechanisms, sodium depletion is not always reflected in blood biochemistry. Sodium depletion can be a direct cause of poor growth. Monitoring of urinary sodium excretion to assess total body sodium is useful, especially in cases of high sodium losses such as high output fistula or cystic fibrosis. A low (<20 mmol/L) urinary sodium concentration indicates the need for increased enteral/parenteral sodium provision.

The available fluid volume for PN may influence the choice of nutrient solutions and the route of delivery. Some of the available fluid for PN may be taken up by medications. If concentrated PN solutions are needed to provide adequate nutrition (due to fluid restrictions), then the peripheral route for delivering the solutions may be contraindicated as there is a risk that they will cause thrombophlebitis. Children who are severely fluid restricted will only receive adequate nutrition with concentrated PN delivered via a CVC.

Macronutrients

Recommendations for macronutrient intakes are summarised in Table 5.4.

Energy

Diet-induced thermogenesis reflects the amount of energy needed for food digestion and absorption and usually accounts for about 10%–20% of daily energy needs. Generally parenteral energy requirements are approximately 10%–20% less than enteral requirements for this reason.

If energy intakes are inadequate, protein accretion falls and dietary/intravenous protein will be metabolised for

Table 5.4 Summary of recommended daily intakes of macronutrients from PN.

Energy		Amino acids		Lipid		CHO	
Age	(kcal/kg)	Age	(g/kg)	Age	(g/kg)	Body weight (kg)	(g/kg)
Preterm	90–120	Preterm	1.5–3.5	Preterm	3–4	Up to 3	Up to 17.3
0–1 year	75–85	Term	1.5–3.0	Infants	3–4	3–10	8.6–14
1–7 years	65–75	1 month to 3 years	1.0–2.5	Older children 1–18 years	2–3	11–30	4.3–8.6
7–12 years	55–65	3–12 years	1.0–2.0			31–45	4.3–5.8
12–18 years	30–55	3–18 years	1.0–2.0			>45	2.9–4.3

CHO, carbohydrate. 1 kcal = 4.18 kJ.
Source: Adapted from [13]. Reproduced with permission of Elsevier.

energy. The child may become catabolic using body tissue protein stores for fuel. This results in linear growth failure. Adequate energy intake will promote weight gain, but will not always promote linear growth in the absence of adequate protein.

Many well infants and children will achieve their expected growth rate if the energy intakes shown in Table 5.4 are provided. An appropriate gain in weight for the age, sex and size of the individual child, taking the clinical condition into consideration, is likely to indicate that the prescription is adequate.

In the disease state these requirements will vary, and research suggests that actual energy requirements for many children are less than originally thought [13, 37]. It is recommended that energy intakes should be adapted for those disease states found to increase resting energy expenditure, e.g. head injury, burn injury, pulmonary and cardiac disease [13]. Also, extremely low birthweight neonates requiring ventilation have been found to have significantly increased rates of energy expenditure [38]. Uncomplicated surgery does not significantly increase energy requirements [39, 40]. Achievement of adequate growth is a significant outcome target in the nutrition support of children. Growth presents a significant energy burden; this will vary with age and is highest in the neonatal period with 35% of energy being used for growth alone [41]. However, in the very sick child, the catabolic process inhibits growth, thereby temporarily reducing this burden.

Previous recommendations for energy did not account for this [42]. Recent research has suggested that critically ill children in the catabolic phase have better outcomes, including reduced length of stay and infection rate, if PN is withheld in the initial days [43]. However, due to the heterogenicity of the population studied, this research cannot be extrapolated to individuals. It is the job of the clinical team to prescribe PN according to the child's individual needs. Guidelines suggest that in the acute phase, intakes should be limited [13]. Further recommendations specifically relating to neonates can be found elsewhere, www.nice.org.uk/guidance/NG154 [44, 45].

Children on stable long-term PN, particularly if approaching the adolescent growth phase, should have individual energy and protein requirements calculated to maintain adequate growth. This may require an extrapolation of enteral energy requirements based on 80%–90% of the estimated average requirement (EAR) for their age.

Equations for calculation of resting energy expenditure are available (p. 87) and may also be used along with dietetic principles of calculating energy requirements. Where dietetic estimations are usually needed for those children with genetic reasons for growth failure, disability or metabolic disorders, calculated PN requirements for energy would normally be adjusted (usually downwards by 5%–10%) due to bypassing enteral absorption and its associated losses.

In all children on PN, it is essential to monitor closely to ensure appropriate growth is achieved without adverse biochemical consequences.

Lipid

Lipid preparations provide a concentrated source of energy in an isotonic solution: 2 kcal (8 kJ)/mL in a 20% lipid solution compared with only 0.8 kcal (3 kJ)/mL in a 20% carbohydrate solution. Lipid emulsions normally contribute 25%–40% of non-protein energy. Lipid emulsion, unlike high concentration dextrose solutions, can be given via a peripheral vein and helps in the provision of sufficient energy for growth, avoiding the complications associated with central venous access, and may prolong the life of peripheral lines in infants [46].

Intravenous lipid particles in solution resemble endogenously produced chylomicrons in terms of size and are hydrolysed by lipoprotein lipase. Intravenous lipids provide essential fatty acids (EFA) and improve net nitrogen balance compared with glucose alone as a source of non-protein energy [27]. Current ESPGHAN guidelines [13] specify that a minimum linoleic acid intake of 0.25 g/kg/day should be given to preterm infants and 0.1 g/kg/day to term infants and older children to prevent EFA deficiency. In premature infants, due to low stores, EFA deficiency can occur within 72 hours of birth [47] and in term infants just a few days.

Intravenous lipid emulsions available in the UK that are considered safe for use in paediatric PN are given in Table 5.5. All solutions contain glycerol and phospholipids and are available as 10% and 20% emulsions.

Higher concentration emulsions (20% or more) are advantageous where there is fluid restriction and they also deliver less phospholipid per gram of triglyceride, leading to more normal plasma phospholipid and cholesterol levels [48]. In children it is recommended that 20% or higher concentrations of lipid emulsions are used due to the higher phospholipid–triglyceride ratio found in 10% emulsions [13].

Lipid emulsions currently used are either based on long chain triglycerides (LCT) or long chain and medium chain triglycerides (MCT) combined. Both LCT and MCT/LCT solutions are considered safe to use in paediatric practice.

Soya oil emulsions have been available for many years and were the first commercially available lipid solutions; they are still commonly used. There have been some concerns over the effect of the highly polyunsaturated, unphysiological fatty acid supply from soybean oil. The development of PNALD is possibly associated with the composition of soybean oil-based lipid emulsion. There is mounting evidence that the pro-inflammatory ω6 polyunsaturated fatty acids (PUFA) most prevalent in soybean oil, along with the low ratio of antioxidants in the form of vitamin E (tocopherols), may in part have a role in the onset of liver injury [32].

Numerous 'composite' lipid emulsions have been developed over recent years, and ongoing research is extremely active in this area. A recently published systematic review [49] recommends that larger high quality trials are required to evaluate the effects of each type of lipid emulsion available.

Olive oil-containing emulsions may produce more physiological levels of linoleic and oleic acid, better antioxidant status and lower cholesterol levels [49].

Table 5.5 20% lipid emulsions*.

Name	Manufacturer	Composition	TG (g/L)	Energy (kcal/mL)	Soya oil (g/L)	Olive oil (g/L)	Fish oil (g/L)	MCT (g/L)	α-Tocopherol (mg/L)
Intralipid	Fresenius Kabi	Soya	200	2	200	0	0	0	240
ClinOleic	Baxter	80% olive 20% soya	200	2	40	160	0	0	No data
Lipofundin MCT/LCT	B Braun	50% soya 50% coconut	200	2	100	0	0	100	170 ± 40
SMOF	Fresenius Kabi	30% soya 30% coconut 25% olive 15% fish	200	2	60	50	30	60	169–225
Lipidem	B Braun	40% soya 50% coconut 10% fish	200	2	80	0	20	100	190 ± 30
Omegaven†	Fresenius Kabi	100% fish	200	2	0	0	200	0	130–296

TG, triglycerides; MCT, medium chain triglycerides; LCT, long chain triglycerides. 1 kcal = 1.48 kJ.
*Some 10% emulsions are available, but are not recommended due to the high phospholipid–triglyceride ratio [13].
†Omegaven is to be used as a supplement, not a complete source of lipid; not licensed in Europe.

Coconut oil-containing emulsions (MCT) have the advantage of carnitine-independent uptake by the mitochondria and, therefore, have a more rapid clearance from the plasma after infusion. Solutions with 50% MCT have been used in paediatric PN for many years. MCT solutions contain approximately 50% less EFA than LCT solutions alone, yet measured plasma EFA and their derivatives (linoleic and alpha linolenic acid) were similar compared with LCT solutions [49–51].

Fish oil-containing emulsions contain a significant amount of anti-inflammatory ω3 PUFA. These are probably now the most widely adopted and routinely used combinant lipids used in paediatric intestinal failure.

SMOF (Fresenius Kabi) provides just 30% and Lipedem (B Braun) 40% of the EFA contained in Intralipid due to the relatively lower soya oil content of these solutions. EFA provision will be adequate when these are given at normal volumes but may become inadequate if lipid intake is restricted.

There have been two randomised control trials to compare the short-term physiological effects of lipid preparations containing soya oil versus fish oil both in preterm and very low birthweight infants [25, 26]. There were no significant differences found in outcomes in this group of patients compared with those using soya oil-dominant lipid solutions.

In children where cholestasis is already present, there have been several paediatric case reports citing improvements in liver function tests and a drop in conjugated bilirubin and reversal of PNALD when patients were switched from soya oil solutions to fish oil-containing solutions [52–55]. An emulsion of fish oils alone (Omegaven) has been used temporarily as monotherapy, but due to risks of EFA deficiency, it cannot be recommended for long-term use (>15 days). It can be used as a 'rescue therapy' in PNALD [56].

New guidance suggests that solutions containing a combination of oils including fish oil may slow or reverse cholestasis and should be considered alongside other interventions to prevent PNALD. The guidance also suggests that paediatric PN for greater than a few days should include a lipid emulsion containing a combination of oils (with or without fish oils) [13].

It is important to note that in some children the biochemical measurement of cholestasis does not detect the degree of PN-associated liver fibrosis. There are reports that fibrosis seen on liver biopsy may persist despite the improved liver function tests after using these products [57, 58].

Serum lipid levels should be monitored to ensure adequate clearance and, hence, utilisation [59]. Clearance of lipids from the plasma is limited by the rate of activity of lipoprotein lipase. The amount of fat infused should be adapted to the lipid oxidation capacity, approximately 3–4 g/kg/day [5, 13]. Hyperlipidaemia will result if the enzyme is saturated by excessive doses of fat or by rapid infusion [60]. Gradually increasing the volume of the lipid emulsion by 1 g/kg/day over 3–4 days and maintaining a steady rate of infusion help prevent possible hypertriglyceridaemia. Tolerance of lipid emulsions has been found to be improved if given continuously in preterm infants [61], although it is usual practice to give 4 hours off the infusion per 24 hours to allow all administered fat to clear the circulation before the next infusion begins. Serum lipids should be monitored as the volume of fat given increases and should always be taken 4 hours after the infusion is completed. Peak levels of triglyceride and free fatty acids normally occur towards the end of the infusion, returning to fasting levels 2–4 hours later. Once stable, weekly monitoring is likely to be sufficient.

In malnourished children, it is good practice to assess baseline serum lipids prior to starting PN as children who have failed to thrive or lost weight due to suboptimal intake frequently have raised triglyceride levels that return to normal when sufficient energy is provided. Restricting lipid and, therefore, energy would not be beneficial in this case.

Table 5.6 Amino acid solutions.

Name	Manufacturer	Total AA (g/L)	Cysteine (g/L)	Tyrosine (g/L)	Taurine (g/L)	Comment
Primene (10%)	Baxter	100	1.89	0.45	0.6	For neonatal and infant PN
Vaminolact	Fresenius Kabi	65	1.0	0.5	0.3	For neonatal and infant PN

AA, amino acids.

A reduced lipid dose may be indicated for children with a marked risk of hyperlipidaemia, e.g. low birthweight infants, sepsis and catabolism. Reduction of the dosage of lipid emulsion can be considered if serum or plasma triglyceride concentrations during infusion exceed 3 mmol/L (265 mg/dL) in infants or 4.5 mmol/L (400 mg/dL) in older children [13].

EFA deficiency can be prevented with as little as 0.5–1.0 g/kg LCT/day [13, 62], although at this level of lipid intake there is likely to be suboptimal energy intake. As discussed above, reduction in lipid intake may improve abnormal liver function; however, this cannot be sustained over a long period due to suboptimal energy provision and a long-term effect on growth. If reducing intake for any reason, including treating PNALD, the source of lipid is an important consideration.

Some intravenous medication may be given in fat emulsions, e.g. the sedative propofol or the antifungal amphotericin. Consideration should be made of the fat (and, therefore, energy) content of this.

α-Tocopherol

Vitamin E (α-tocopherol) is the most important lipid-soluble antioxidant; it helps prevent tissue damage by free radicals produced from peroxidation of the PUFA within parenteral lipid solutions [63]. Most composite parenteral lipid solutions have α-tocopherol present in adequate amounts for this reason (Table 5.5). When these solutions are given to infants and children <11 years old, the total vitamin E intake should not exceed 11 mg/day [13].

Learning points: lipid solutions

- *MCT, fish and olive oil solutions should be considered in all patients on long-term PN*
- *Fish oil may be beneficial as part of a treatment strategy in the prevention or treatment of PNALD*
- *Pure soya oil solutions are not recommended in paediatric PN*
- *10% solutions not recommended due to the high ratio of phospholipids to triglycerides*
- *20% solutions most widely available ≡ 200 g TG/1000 mL (20 kcal [85 kJ]/100 mL)*
- *Lipids should provide 25%–40% of non-protein energy*
- *0.5–1 g/kg/day LCT is required to prevent EFA deficiency*
- *Solutions with lower LCT content will be lower in EFAs*
- *Vitamin E is protective against PNALD, but intake should not exceed 11 mg/day [13]*

Amino acids

Crystalline L-AA solutions are used as the nitrogen source for PN. Despite routine use of PN, surprisingly few clinical efficacy data are available to guide total or specific AA dosing in paediatric (and adult) patients.

Commercially available mixed AA formulations provide both essential and non-essential AA. All provide the nine essential AA (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine). They also contain varying amounts of classically non-essential AA that may become conditionally essential under certain circumstances. In children arginine, cysteine, glycine, proline, taurine, glutamine and tyrosine may be conditionally essential [13].

The products designed for infants and children are Vaminolact, which is based on the AA profile of breastmilk, and Primene, which is based on the profile of cord blood (Table 5.6). The ideal AA profile for PN solutions for infants and children is still unclear. A solution that contains insufficient quantities of essential AAs will inhibit protein synthesis and may limit growth [64–66].

Estimates of protein requirements are often based on 10%–20% of the total energy intake (Table 5.4). All nitrogen can be converted to energy (via the Krebs cycle), and where inadequate energy is provided (from fat and carbohydrate), the child may become hypoproteinaemic as nitrogen is used for energy. The child subsequently will not grow. Sufficient energy intake is 30–40 kcal (125–165 kJ)/g AA or 250 kcal (1.05 MJ)/g nitrogen [66], although in preterm infants this ratio may indeed be less: 150–200 kcal (630–835 kJ)/g nitrogen [44].

Guidelines [13] are based on amounts required to maintain nitrogen balance and growth. While it is difficult to assess if nitrogen provision is adequate, it is generally agreed that inadequate nitrogen intake is reflected by a low plasma urea level and poor linear growth. (A high plasma urea level is more likely to be attributable to dehydration than overprovision of nitrogen.)

Glutamine

Endogenous biosynthesis of glutamine may be insufficient for tissue needs in states of metabolic stress. Trials in adults have suggested that glutamine supplementation improves clinical outcomes in critically ill adults [67]. It has been suggested that glutamine supplementation may benefit preterm infants, particularly very low birthweight infants. However, a

systematic review in 2016 concluded that glutamine supplementation does not have a statistically significant effect on morbidity or mortality [68]. Currently, there is insufficient evidence to support the routine supplementation of glutamine in preterm infants, and there is no evidence for its routine use in PN in children under 2 years [13].

Carnitine

Carnitine is a nitrogen-based compound and plays a role in the beta-oxidation of long chain fatty acids and facilitates their transport across the mitochondrial membrane in the form of carnitine esters. Carnitine is present in breastmilk and formula feeds, but current PN formulations do not contain it. Carnitine can usually be synthesised in the liver from lysine and methionine, and the ability to synthesise it is age dependent [69]. Non-supplemented parenterally fed infants have very low tissue carnitine levels, and relative carnitine deficiency may impair fatty acid oxidation [70]. It is recommended that carnitine supplementation (20–30 mg/kg/day) be considered on an individual basis in premature infants or those on exclusive PN for more than 4 weeks [13].

Learning points: amino acid solutions

- *Amino acid profiles are based on cord blood or breastmilk so they are not necessarily the ideal profile for growing children*
- *They aim to provide 10%–20% of energy from protein*
- *Protein in PN is normally expressed as nitrogen (N) or amino acids (AA)*
  1 g N ≡ 7.5 g AA ≡ 6.25 g protein
- *In order to ensure efficient protein utilisation and tissue accretion, sufficient energy should be given alongside nitrogen ≡ 250 kcal (1.05 MJ)/g N*
- *Low plasma urea levels, particularly in preterm infants, may indicate inadequate nitrogen provision*

Carbohydrate

The major source of non-protein calories in PN is D-glucose (dextrose). Carbohydrate normally provides 60%–70% of the total non-protein energy intake. Glucose is an essential fuel for infants and is the most important substrate for brain cell metabolism; a continuous supply is essential for normal neurological function. For this reason, there are minimal rates of infusion that should be maintained in the absence of enteral feeding.

When the fluid volume is limited, higher concentrations (>12%) of dextrose solutions are required to meet energy requirements; this can only be achieved via a CVC.

In the acute post-operative or infectious phase, excessive intravenous glucose administration is more likely to lead to hyperglycaemia, hepatic steatosis, excessive carbon dioxide production and impaired protein metabolism [44]. Insulin resistance may occur in some situations, e.g. steroid use, very low birthweight, sepsis, trauma and stress. This is a protective mechanism to relieve the liver of excessive substrates. In this acute phase the ESPGHAN guidelines recommended that glucose infusion rates should be limited in order to prevent hyperglycaemia [13].

Glucose infusion should always be initiated gradually, increasing over 3–4 days to maximum infusion rates. Rates of glucose oxidation vary significantly with age and clinical status. In stable situations (post-acute phase), it is recommended in term neonates and children up to 2 years of age that glucose intake should not exceed 14 g/kg/day [13]. Infusion rates exceeding glucose oxidative capacity result in conversion of carbohydrate to fatty acids and can consume up to 15% of the available energy from carbohydrate [71, 72].

In cyclical PN the increased rate of glucose infusion may exceed glucose oxidation rate so the maximal infusion rate should not exceed 10 mg/kg/min [13].

Learning points: carbohydrate

- *Specific guidance for the management of the first days of PN during the acute phase is described in the ESPGHAN guidelines [13]*
- *In stable children carbohydrate should make up 60%–70% of the non-protein energy provision*
- *In stable children maximum infusion rates of 10 mg/kg/min glucose should not be exceeded*
- *Solutions given cyclically should be ramped up and down during the initial and final 2 hours of the infusion to prevent hyperglycaemia and hypoglycaemia (Table 5.10)*

Micronutrients

A summary of reasonable intakes of micronutrients for paediatric PN can be found in Tables 5.7 and 5.8. These are guidelines and should be used in conjunction with the document from which they are taken [13]. Requirements for intravenous vitamins in infants and children remain unclear. The last major publication on parenteral vitamin requirements in children was in 1988 [73]. A Cochrane review [74] in premature infants <32 weeks' gestation found an association between supply of vitamin A and a reduction in death or oxygen requirement at 1 month of age and of oxygen requirement at 38 weeks' postmenstrual age. Current knowledge is based on the historical use of available vitamin and mineral solutions and the apparent lack of deficiencies/complications associated with this. Optimal requirements in children have not been determined, and there has been little published research on this topic in the last 30 years.

Following current guidelines appears to maintain blood levels within acceptable ranges for infants and children and

Table 5.7 Vitamin solutions.

	Water-soluble	Fat-soluble		Suggested reasonable intakes Source: adapted from [13]		
Vitamin	Solvito (Fresenius Kabi) per vial (10 mL)	Vitlipid infant* (Fresenius Kabi) per vial (10 mL)	MVI paediatric (Hospira)	Preterm (/kg/day)	Infants (/kg/day)	Children (per day)
Dose	1 mL/kg/day	10 mL/day	5 mL/day			
Vitamin A (μg)	0	690 (2300 IU)	690 (2300 IU)	227–455 (700–1500 IU)	150–300 (500–1000 IU)	150 (500 IU)
Vitamin D (μg)	0	10 (400 IU)	10 (400 IU)	2–10 (80–400 IU)	10 (400 IU) (dose/day)	10–15 (400–600 IU)
Vitamin E** DL-α-tocopherol acetate (mg)	0	7 (7 IU)	7 (7 IU)	2.8–3.5 (2.8–3.5 IU)	2.8–3.5 (max 11 mg/day)	11 (max)
Vitamin K (μg)	0	200	200	10	10	200
Thiamin B_1 (mg)	2.5	0	1.2	0.35–0.5	0.35–0.5	1.2
Riboflavin B_2 (mg)	3.6	0	1.4	0.15–2	0.15–0.2	1.4
Niacin B_3 (mg)	40	0	17	4.0–6.8	4.0–6.8	17
Pantothenic acid B_5 (mg)	15	0	5	2.5	2.5	5.0
Pyridoxine B_6 (mg)	4.0	0	1	0.15–2	0.15–0.2	1.0
Cobalamin B_{12} (μg)	5.0	0	1	0.3	0.3	1.0
Vitamin C (mg)	100	0	80	15–25	15–25	80
Biotin (μg)	60	0	20	5–8	5.0–8.0	20
Folic acid (μg)	400	0	140	56	56	140

With the exception of vitamin E, no upper limits are given; care must be taken to avoid over-delivery of individual nutrients. Where nutrient mixtures are used, manufacturers' guidelines should be followed.
*In 10% Intralipid.
**Vitamin E is also added to some lipid bags (see Table 5.5).
The following single vitamin preparations are available in the European and American markets:
vitamin A, vitamin D, vitamin K, thiamin, pyridoxine, cyanocobalamin, vitamin C and folic acid.
Provision and administration of these should be arranged by a specialist pharmacist as part of a multidisciplinary team.

is based on expert opinion [5, 13, 75]. The amount of intravenous vitamins given is usually recommended to be higher than that given enterally. This is to allow for losses of the vitamins by adsorption onto the PN bag and giving set or biodegradation due to light exposure, thus reducing the available intake. Vitamin A is most affected by these problems [76]. Addition of the vitamins to the lipid bag and protecting the bag from direct sunlight is the best method of preserving the vitamin concentration. Artificial light has little effect on the stability of the vitamins [13]. Table 5.7 shows the commercially available vitamin solutions for preterm infants and neonates, none of which fully meets neonatal guidelines [13, 45]. Daily administration is recommended with the exception of vitamin K that may be given weekly [13].

Consideration should be given to cholestatic patients with obstructive jaundice as they can accumulate copper and manganese, which are normally excreted in bile [77]. Patients with renal dysfunction may not be able to excrete selenium, molybdenum, zinc and chromium [36]. High fluid losses result in greater losses of magnesium and zinc.

Calcium, phosphorus and magnesium are usually added to the PN prescription as individual solutions, and the suggested intakes are listed in Table 5.9.

Individual preparations of some (not all) trace elements are available where there is a need to exclude or increase doses of single trace elements. In cases where there is an apparent overload or deficiency, action should be taken after discussion with members of the NST.

Iron

Current commercially available paediatric mineral solutions do not contain iron (Table 5.8). Intravenous iron supplementation is controversial due to the risk of adverse side effects [78]. Parenterally administered iron bypasses the normal homeostatic mechanism of the intestine, and excess iron may lead to iron overload syndrome. Iron enhances the risk of Gram-negative septicemia [79] and has powerful oxidative properties; it may, therefore,

Table 5.8 Recommended intakes of trace elements.

		Paediatric (<40 kg)		Adult		
Trace element (atomic mass)	Requirement (ESPGHAN 2018) [13]	Peditrace (Fresenius Kabi) (µg/1 mL)	Peditrace (Fresenius Kabi) µmol/1 mL)	Tracutil (B Braun) (µmol/1 mL)	Decan (Baxter) (µmol/1 mL)	Additrace (Fresenius Kabi) (µmol/1 mL)
Iron (55.9) Not necessary in short-term PN (<3 weeks duration) Monitor carefully to avoid toxicity (p. 73)	Preterm: 250 µg/kg/day (3.58–5.37 µmol/kg/day) Infant and child: 50–100 µg/kg/day (0.895–1.76 µmol/kg/day)	0	0	3.5	0.45	2.0
Zinc (65.4) Preterm infants and children with thermal injuries may have increased requirements	Preterm: 450–500 µg/kg/day Infant 0–3 months: 250 µg/kg/day Infant >3 months: 100 µg/kg/day Child: 50 µg/kg/day (max 5 mg/day)	250	3.82	5.0	3.8	10
Copper (63.5) Requirements may increase with high gastrointestinal losses or thermal injuries. Toxicity risk in cholestasis	Preterm: 40 µg/kg/day Infant and child: 20 µg/kg/day (max 0.5 mg/day)	20	0.315	1.2	0.19	2.0
Manganese (55) In toxicity CNS deposition of manganese can occur without symptoms Monitor regularly	Max 1 µg/kg/day (max 50 µg/day)	1	0.0182	1.0	0.091	0.5
Chromium (52) A contaminant – not usually added to PN	Max 5 µg/day	0	0	0.02	0.007	0.02
Selenium (79) Optimal dose unclear	Preterm: 7 µg/kg/day Infant and child: 2–3 µg/kg/day (max 100 µg/day)	2	0.0253	0.03	0.022	0.04
Iodine (126.9)	Preterm: 1–10 µg/kg/day Infant and child: 1 µg/kg/day	1	0.0079	0.1	0.0003	0.1
Molybdenum (95.9)	LBW: 1 µg/kg/day Infant and child: 0.25 µg/kg/day	0	0	0.01	0.0065	0.02

Where upper limits are not given, care must be taken to avoid over-delivery of individual nutrients. Where nutrient mixtures are used, manufacturers' guidelines should be followed.
PN, parenteral nutrition; CNS, central nervous system; LBW, low birthweight.
Source: Adapted from [13]. Reproduced with permission of Elsevier.

Table 5.9 Suggested intakes of parenteral calcium, phosphorus and magnesium.

Age	Calcium mg (mmol)/kg	Phosphorus mg (mmol)/kg	Magnesium mg (mmol)/kg
Stable premature infant	64–140 (1.6–3.5)	50–108 (1.5–3.5)	5.0–7.5 (0.2–0.3)
0–6 months	30–60 (0.8–1.5)	20–40 (0.7–1.3)	2.4–5.0 (0.1–0.2)
7–12 months	20 (0.5)	15 (0.5)	4.0 (0.14)
1–18 years	10–16 (0.25–4.0)	6–22 (0.2–0.7)	2.4 (0.1)

Where upper limits are not given, care must be taken to avoid over-delivery of individual nutrients. Where nutrient mixtures are used, manufacturers' guidelines should be followed.
Source: Adapted from [13]. Reproduced with permission of Elsevier.

increase demand for antioxidants. Monitoring of serum ferritin and reduction/removal of iron supplementation, if levels become too high, is recommended [13]. Ferritin is a poor measure of deficiency as growing children and adolescents use most of the iron supplied almost immediately to accrete tissue and red blood cells, so they rarely have any significant iron stores. Although iron reserves should be adequate to supply red cell production for 3–5 months (much less in preterm infants), iron deficiency has been found to develop much sooner. However, this is very much dependent upon the underlying condition and if there has been a degree of blood loss due to sampling or bleeding or inter-operatively.

Iron deficiency may lead to increased blood manganese levels [77]. In the absence of iron, manganese binds to transferrin [80], and iron deficiency up-regulates both iron and manganese absorption from the intestine [81].

Oral iron supplementation when possible is preferable to intravenous iron; however, if required, iron preparations may be added to the intravenous solution or given as a separate infusion. This must be done with care due to its poor solubility, and risk of anaphylaxis; additional iron is usually given by week 4 of receiving PN.

Learning points: iron

- *Iron is not present in commercially available paediatric intravenous mineral solutions*
- *Oral supplementation should be attempted where possible*
- *Iron should be added if PN is long term (>4 weeks)*
- *Iron status (ideally transferrin and transferrin saturation) should be monitored to avoid toxicity/deficiency*

An example PN prescription is given in Table 5.10.

Administration of parenteral nutrition

A more detailed account of the techniques of PN administration is available in other publications [4, 13]. PN may be infused via a peripheral vein or a CVC. Each route has advantages and disadvantages [82, 83]. For the purpose of providing PN, it is necessary to differentiate peripheral from central venous access.

Vascular access

Peripheral lines

A needle or short catheter is placed into a subcutaneous vein to gain peripheral access. Peripheral lines are rarely associated with septicaemia. They are useful in short-term PN (7–10 days' duration) when the fluid allowance is not restricted and the concentration of PN solutions is <600 mOsm/L and when venous access is good. They are often used in neonates. One major disadvantage is the risk of thrombophlebitis caused by the hypertonic solutions used. The maximum concentration of glucose solution that should be used with these lines is 12%. Infiltration is also a common problem; the peripheral line may penetrate the surrounding tissues, resulting in leaking of the infusion. This leakage is known as extravasation and if undetected can cause tissue necrosis and severe scarring. Line sites must be inspected frequently to avoid this. Lines that fail must be re-sited quickly to avoid the risks of hypoglycaemia and suboptimal nutritional intake.

Central venous catheters

A CVC, e.g. a Broviac or Hickman catheter, is one that is tunnelled beneath the skin and inserted into the superior or inferior vena cava or outside the right atrium via a subclavian vein. It can be inserted either surgically or percutaneously. It is made of silicone that helps decrease sepsis rates and inhibits fibrin production and is, therefore, less likely to block. It has a Dacron cuff planted subcutaneously that serves to fix the line in place and inhibits the migration of microorganisms from the skin.

The maximum concentration of glucose solution that can be given via a CVC is 25%. The line can remain *in situ* for months. The major disadvantages of a CVC are the risks associated with insertion and catheter care. Complications include sepsis, occlusion, infection of the line site and accidental removal. Loss of venous access can be a life-limiting factor in PN-dependent children, e.g. those with intestinal failure. It is, therefore, imperative that these lines are well cared for. The more frequently a line is accessed, the greater the risk of infection. Only PN or fluid (not drugs) should be given via a single lumen catheter [6, 82, 83].

For the taking of blood samples or the administration of blood products or medication, separate venous access should be organised. In the case of home PN, where monitoring is less frequent, the line may be accessed as long as it is done aseptically. Multiple lumen catheters are usually inserted when frequent intravenous drug therapy is required as well as PN and where the child is critically unwell, e.g. following

Table 5.10 Case example: a parenteral nutrition prescription for a 1-year-old boy.

1-year-old boy with short bowel syndrome.
Weight = 7 kg, Length = 70 cm.
He has a CVC to provide his full requirements from PN. He requires some extra fluid due to high stool output.

Requirements
Energy = 65 kcal (270 kJ)/kg/day (non-protein calories)
AA = 2 g/kg/day
Lipid = 2.5 g/kg/day
CHO = 10 g/kg/day
Fluid = 120 mL/kg

Solution	Dose (mL)	Energy (kcal) (kJ)	CHO (g)	Lipid (g)	AA (g)
Glucose (20%)	350	280 (1170)	70		
SMOF (20%)	88	175 (730)		17.5	
Vaminolact	215	56 (235)			14
Vitlipid infant*	10	10 (40)		1	
Solivito	7				
Peditrace	7				
Water	163				
Total	840	521 (2175)	70	18.5	14
Per kg	120	66 (275) non-protein calories	10	2.6	2

*10% lipid. Electrolytes, calcium, phosphorus and iron need to be added in recommended doses.

Rates of infusion

The above is a typical PN content sheet and is supplied with the PN solutions; it is not a prescription. PN is prescribed by writing the rates of 'aqueous' and 'lipid' solutions on an intravenous (IV) prescription chart. The rates are usually specified/recommended by the PN pharmacist and are calculated as follows:

Aqueous solution (Vaminolact and 20% glucose and trace elements; could also include water, electrolytes, calcium and phosphate and any IV drugs given in the aqueous phase of the PN)

In this example volumes are calculated as follows:

Total = 380 + 215 + 163 = 728 mL = 30.3 mL/hour given for 24 hours

Lipid solution (Intralipid and vitamins; could also include any IV drugs given in the lipid phase of the PN)

In this case example volumes are calculated as follows:

Total = 88 + 10 + 7 + 7 = 112 mL = 5.6 mL/hour given for 20 hours

Lipid solution is usually given over 20 hours to allow time off for clearance of lipid from the blood prior to blood sampling.

When the boy becomes more stable, some enteral feeds are given. PN infusion rates are increased to give some hours off PN:

PN given over	Aqueous phase (mL/hour)	Lipid phase (mL/hour)
20 hours	36.4	5.6
18 hours	40.4	6.2
16 hours	45.5	7

Rates of infusion of glucose solution must be calculated and ideally should not exceed the maximum glucose oxidation rate of 10 mg/kg/min.

The PN in this case example provides 70 g glucose per 24 hours = 2.9 g glucose per hour or 10.4 mg/kg/min if given for 16 hours. With the boy's weight of 7 kg, this is just above the recommended rate.

(continued overleaf)

Table 5.10 *(continued)*

Tapering or 'ramping' PN up and down

If the PN is to be given as 'cycling PN', it is recommended that it is tapered up and down over the first and final 2–3 hours of infusion. This will steadily increase and reduce the glucose infusion in order to avoid hypoglycaemia and hyperglycaemia. For example,

How PN is given	Aqueous phase (mL/hour)	Lipid phase (mL/hour)
PN to be given over	20 × 1 hour	4 × 1 hour
a total of 18 hours	30 × 1 hour	6 × 1 hour
with a ramping up	45 × 14 hours	6.6 × 14 hours
and down for the	30 × 1 hour	6 × 1 hour
first and final 2	20 × 1 hour	4 × 1 hour
hours of the infusion	Total = 728 mL	Total = 112 mL

PN, parenteral nutrition; AA, amino acids; CHO, carbohydrate; IV, intravenous.

bone marrow transplantation or in intensive care. The rate of infection of these catheters is higher compared with single lumen catheters [82], and this is probably a reflection of more frequent catheter manipulation.

Accidental damage to, or removal of, the catheter is common. Young children will chew and pull their catheter, given the opportunity, and it is important that nursing staff and parents carefully loop and tape the catheter securely to the skin. It is then best practice to cover with a vest and other clothing to keep the line out of reach.

Portacath

A portacath is a totally implantable device that requires needle sticking for vascular access. It has limited value for PN but is useful for vascular access for frequent medications, e.g. prophylactic antibiotics in cystic fibrosis.

Learning points: central venous catheters

- *Examples are Hickman or Broviac catheters, also known as central lines*
- *Maximum glucose concentration in a CVC = 25% (12% in a peripheral line)*
- *CVC can stay in situ for years if well cared for*
- *CVC is high risk as a route of infection and source of sepsis*
- *Central venous access, or lack of it, is a life-limiting factor for children with intestinal failure*

Delivery methods

PN can be delivered by a variety of systems. Infants and children usually have a system in which AA and dextrose are mixed and delivered over 24 hours. The fat emulsion is delivered from a separate container but mixes with the AA and dextrose solution as close as possible to the peripheral or central line. All the components are compounded in a specialist pharmacy unit under aseptic conditions in an isolator. Specialist pharmacists use computer-based programmes to ensure that the nutrient content of the bag is appropriate for the child's age, condition and biochemistry. They also help to ensure that solution stability is assessed and drug–nutrient interactions are avoided [84].

Compounded PN is supplied from the manufacturing pharmacy in a premixed collapsible bag with an opaque cover to protect nutrients in the solution from photodegradation. When low rates of infusion are prescribed and the solution remains in the burette for long periods, light protective sets may also be used, although these have limited effectiveness and are most useful if solutions are exposed to direct sunlight rather than artificial light [13]. Home PN is often given during the night, thus reducing the risk of photodegradation further. Manufacturers' guidelines advise on stability, dosage and administration.

'All-in-one' mixes (containing AA and dextrose with and without lipid) are available. They are used more commonly in adults. Products that can be used in children >2 years are Oliclinomel (Baxter) and Kabiven (Fresenius Kabi).

There are two solutions (Table 5.11) that can be used from birth (whether preterm or term) to 2 years of age: Babiven (Fresenius Kabi) and Numeta (Baxter). These products do not contain vitamins or complete mineral profiles; these must be added to the bag before it is infused. Babiven does not contain lipid, which must also be given separately. Standard solutions such as these may be useful in order to increase the capacity of a busy aseptic pharmacy unit and decrease preparation time [85]. They may also help avoid some areas of risk previously identified, such as delayed PN commencement where the pharmacy capacity or ordering may delay the provision of PN. They may also avoid inadequacy in delivery of solutions as prescribing errors are minimised when 'all-in-one' bags are used at 'standard' rates.

Table 5.11 Standard paediatric parenteral nutrition bags.

Numeta G13% (preterm) (Baxter)		
	Activated 2 chamber (no lipid)	Activated 3 chamber (with lipid)
mL/kg/day	102.3	127.9
Amino acids, g/kg/day	4.0	4.0
Glucose, g/kg/day	17.1	17.1
Lipid, g/kg/day	0	3.2
Numeta G16% (term to 2 years) (Baxter)		
	Activated 2 chamber (no lipid)	Activated 3 chamber (with lipid)
mL/kg/day	72.3	96.2
Amino acids, g/kg/day	2.5	2.5
Glucose, g/kg/day	14.9	14.9
Lipid, g/kg/day	0	3.0
Babiven maintenance (Fresenius Kabi) no lipid		
mL/kg/day	100	120
Amino acids (N), g/kg/day	2.6 (0.37)	3.1 (0.44)
Glucose, g/kg/day	11.1	13.3
Lipid, g/kg/day	0	0
Babiven term (Fresenius Kabi) no lipid		
mL/kg/day	100	135
Amino acids (N), g/kg/day	2.19 (0.31)	2.96 (0.42)
Glucose, g/kg/day	11.1	15
Lipid, g/kg/day	0	0

N, nitrogen.

The stability of 'all-in-one' PN depends on the stability of the premixed nutrient solutions. The formulations cannot be varied greatly; therefore, they are not suitable for unstable patients or those with unusually low or high requirements. As the mixing of the lipid and aqueous solutions shortens the shelf life of the PN, some solutions come in separate chambers that can be rolled together and mixed just before use.

Best practice demands that children should have individually prepared PN as 'all-in-one' solutions may not contain sufficient calcium, phosphate and other electrolytes. 'All in one' is safe for use in short-term PN; however, close monitoring of biochemistry is necessary.

Equipment

A steady flow rate should be maintained when infusing PN. Hyperglycaemia and hyperlipidaemia will result if infusions are delivered too quickly. If the line blocks or the infusion stops suddenly, hypoglycaemia may occur [6]. Volumetric pumps are sufficiently accurate for use in children; these deliver measured volumes via a cassette with a syringe mechanism ensuring accuracy. Syringe pumps are used instead of volumetric pumps when small volumes are required. These have a linear drive mechanism and can be set to deliver as little as 0.5 mL/hour. Filters are needed to remove any potential bacterial or fungal contaminant and prevent air embolism and entry of particulate matter. It is considered good practice to filter PN solutions with a pore size of:

- 0.22 μm for AA and dextrose solutions; this safely removes bacteria, endotoxins, air and particles (this is not used for lipid solutions as the pore size is too small for lipid to pass through)
- 1.2 μm for 'all-in-one' bags and lipids; this safely removes *Candida*, air and particles (the pore size is large enough for the lipid to pass through); it is not a sterilising filter as it will not remove bacteria

Cyclical parenteral nutrition

This refers to the intermittent administration of intravenous fluids with a regular break in each 24 hour period. There may be advantages in terms of changes in insulin/glucagon balance and decreased lipogenesis, time off to allow for physical activity and reduction in the risk of development of liver disease [86].

Infusion rates are usually built up gradually over a period of days or weeks. Often patients on long-term PN will have infusion rates increased to enable them to have the prescribed volume of solutions delivered overnight only, leaving them free from PN during the day. However, this is very much dependent upon the age of the child, e.g. infants, particularly preterm infants, have very low glycogen stores and need an almost constant supply of glucose. Any breaks in PN require close monitoring to avoid hypoglycaemia. With increased rates of delivery, there is a risk of hyperglycaemia on commencement of PN and a risk of rebound hypoglycaemia on cessation of PN. For this reason, it is recommended that infusion tapering may be warranted, particularly in children

<2–3 years old to limit risk [87, 88]. Rates are ramped up and down over the initial and final 2–3 hours of PN (Table 5.10).

Weaning from parenteral nutrition

In order to wean the child from PN, i.e. reduce the amount of PN given, it is essential that some degree of enteral nutrition is maintained. The concentration and rate of delivery of enteral feed will be gradually increased, depending on tolerance and growth parameters. If fluid restriction is not a major issue, once enteral feeds or diet provide at least 25% of the total nutritional requirements, a corresponding reduction can be made to the PN prescription. Once 50% of requirements are met enterally, the PN can be decreased to 50%, with a further decrease to 25% once the enteral route meets 75% of requirements. When more than 75% of requirements are achieved by enteral nutrition, the PN could be stopped in most cases [88]. These reductions depend upon satisfactory growth and development of the child. Weaning from PN may take a few days where it has been used for nutritional support in the short term, e.g. following acute surgery, or be very gradual over months and sometimes years where it has been used for long-term support, such as in short bowel syndrome while waiting for gut adaptation. If the PN is provided as separate lipid and aqueous (carbohydrate and AA) solutions, it is important to decrease each solution proportionally in order to maintain an adequate nitrogen-energy ratio.

If fluid restriction is a complicating factor and the weaning period is prolonged, the PN should be made up as concentrated as possible (depending upon the route of administration and the solutions used). Thereafter, the PN will usually need to be decreased by each millilitre that the enteral nutrition is increased (although a greater fluid volume is usually tolerated via the enteral route than the parenteral route due to losses from the gut). Care and attention to actual intake is necessary in these cases to ensure maximum nutrition is achieved, as enteral feeds are often less concentrated than PN. This is especially important in infancy or for malnourished children.

Home parenteral nutrition

Although most patients discontinue PN in the acute setting, it is recommended that PN at home be considered for any patient likely to be dependent on PN for more than 3 months [89]. Home parenteral nutrition (HPN) improves quality of life for these patients and their families due to obvious psychosocial benefits. It is also associated with lower risks of catheter infection and a decreased risk of PNALD [90] and reduces the cost of caring for these children during long hospital admissions.

The demand for HPN services for children has risen over the past 30 years. Due to better understanding and management of complications, long-term survival rates on PN have improved. Published surveys show a 200% increase in patients registered on HPN since 2012 [91]. Short bowel syndrome was the most common diagnosis with an increase from 27% to 63% of cases [90]. It is widely recognised among expert practitioners in this field that a national strategy is needed to manage this expanding group of patients with chronic intestinal failure.

Patients on HPN should be managed by a specialist centre with significant expertise in this area [91]. Dedicated specialist nurses must train parents and caregivers in preparation for discharge, with community services supporting the family by providing equipment and a suitable environment for the administration of PN in the home. Home assessments must be undertaken, and, if necessary, rehousing or structural changes to housing must be made. Manufacturers of PN solutions usually provide homecare packages that may be funded by local health purchasers; contracts are often agreed on a case need basis.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

6 Nutrition in Critically Ill Children

Rosan Meyer and Luise Marino

Introduction

Data from the 2017 annual report from the Paediatric Intensive Care Audit Network (PICANet) in the United Kingdom (UK) indicate that only 150 children are admitted to a paediatric intensive care unit (PICU) per 100 000 (0.15% of all children), with the majority of those children (41.4%) being below 1 year of age (PICANet) [1]. Nutritional management of the critically ill child (CIC) is, therefore, a very specialist and challenging area in paediatric dietetic practice. In addition to minimising the effects of starvation associated with suboptimal nutrition and preventing nutritional deficiencies and excesses, its goal is to sustain organ function and prevent dysfunction of the cardiovascular, respiratory and immune systems until the acute-phase inflammatory response resolves (Table 6.1) [8]. Both under- and overnutrition have the potential to compromise this goal and significantly complicate and increase the length of hospital stay [9–11]. Overfeeding can lead to increased carbon dioxide production resulting in difficulties with weaning from mechanical ventilator support, fatty liver, as well as diarrhoea associated with electrolyte imbalances and other well documented metabolic and physiological complications [4]. Underfeeding, however, is a more common occurrence in PICU that has not improved over the last 35 years, in spite of great medical advances. Pollack *et al*. [9] found in 1981 that 16%–20% of critically ill children develop significant, acute protein energy malnutrition (PEM) within 48 hours of admission to a PICU; in 2006, Hulst *et al*. found that 24% of children have PEM [3]. More recently Valla *et al*. [12] found that 23.7% of children were either malnourished on admission or developed faltering growth during a PICU admission. In addition, children with chronic diseases such as congenital heart disease may also have persistent malnutrition, with a UK centre reporting a height for age *z*-score <–2 in 28.2% in infants <1 year of age [13]. Both malnutrition and faltering growth have been shown to have a significant effect on: muscle strength [14]; reduced wound healing due to altered immunity with increased rates of sepsis [3]; mechanical ventilation days with poorer post-operative resilience [3]; longer length of hospital stay, particularly amongst children post-surgery [12, 13, 15–17]. Ensuring optimal nutritional support in critically ill children is therefore crucial.

Learning points: incidence of critical illness

- *Mortality rates are low (4.7%) in PICUs in the West*
- *Persistent malnutrition is associated with a longer length of PICU stay*

Inflammatory and metabolic responses that impact on nutritional requirements

Endocrine and inflammatory response

Knowledge of metabolic changes and fuel utilisation during physiological stress can assist in commencing nutritional support at an appropriate time, suggesting a suitable feeding route and feed composition. Critical illness is characterised by a cascade of endocrine and metabolic reactions, affecting all major organs (Figure 6.1) [8, 18].

The reaction of the body to physiological stress changes over time and can be divided into three phases. The **acute phase** is characterised by escalating organ support, including the use of inotropes and mechanical ventilation, affecting substrate (protein, carbohydrate and fat) metabolism.

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 6.1 The effect of critical illness on the major organs.

Gastrointestinal system	Cardiovascular system	Respiratory system	Renal system
• Gastroparesis (motility affected due to medication, e.g. morphine, inotropic agents and antibiotics, as well as the disease process itself) [2] [3] • Impaired digestive enzyme secretion • Cholestasis [4, 5] • Impaired lipid metabolism due to affected liver function [5] • Increased intestinal permeability [2] • Poor gut perfusion [2]	• Tachycardia • High cardiac output [5] • Fluid shift from the intracellular, to the extracellular compartments [6]	• Respiratory deterioration leading to artificial ventilation [5]	• Renal impairment may occur during critical illness and may be as severe as acute renal failure requiring haemofiltration [7]

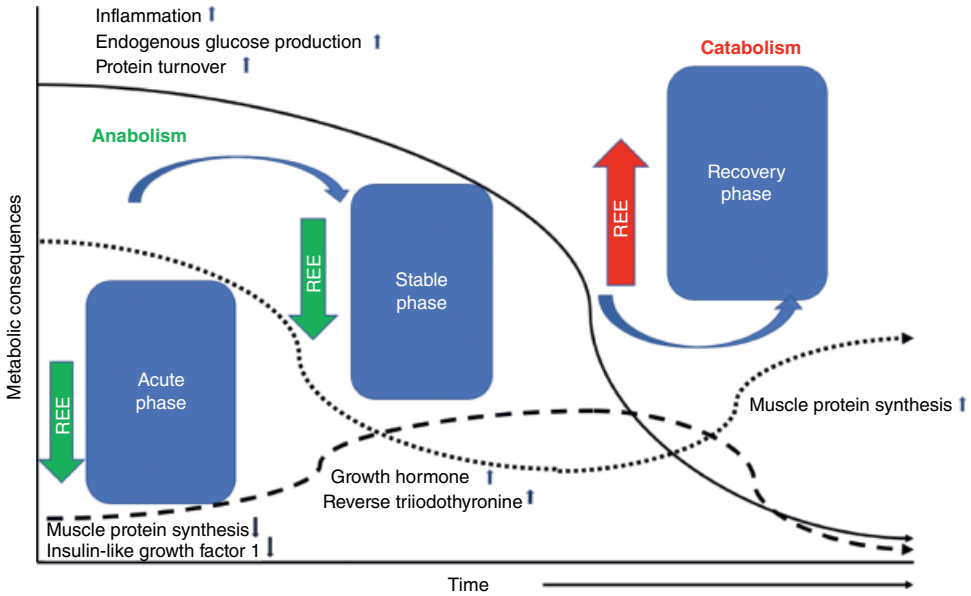

Figure 6.1 Different phases of critical illness with corresponding neuro-endocrine, immunologic and metabolic changes. REE, resting energy expenditure. Source: Adapted from Joosten [8]. Reproduced with permission of Wolters Kluwer Health.

The **stable phase** is where physiological control has been achieved, but the stress response is not completely resolved although the child is stable and there is a process of stability or weaning of vital organ support, and finally the **recovery phase** (which may not occur in PICU) involves clinical mobilisation, with normalisation of neuro-endocrine, immunologic and metabolic alterations returning to anabolism. During this phase there will be the re-accumulation of protein and fat stores, which may require a period of intensive nutritional rehabilitation [2, 8, 19, 20].

During critical illness immune cells, e.g. macrophages, lymphocytes and neutrophils, regulate the inflammatory response through the release of: cytokines (in particular interleukins (IL) such as IL-1, IL-6, IL-8, IL-10 and tumour necrosis factor alpha (TNFα); and chemokines such as heat shock protein 70 [21]. All are important mediators of the stress response (Table 6.2). Cytokines signal through receptors on the surface of target cells and organs mediating the following responses:

- up- or down-regulation of gene expression influencing wound healing and immunocompetence
- release of counter-regulatory hormones
- cell to cell signalling orchestrating the inflammatory response which affects substrate metabolism [8, 22, 23].

Learning points: pathophysiology of critical illness

There are three phases of critical illness

- *acute phase – escalating organ support, e.g. the use of inotropes and mechanical ventilation, affecting substrate (protein, carbohydrate and fat) metabolism*

Table 6.2 Cytokines involved in the acute phase of injury and possible effects on substrate metabolism and nutrition.

Cytokines	Relevant function	Interaction between metabolism, nutrition and cytokines
Pro-inflammatory cytokines		
TNFα [9, 12, 13, 22–24]	Pro-inflammatory; release of leucocytes by bone marrow; activation of leucocytes and endothelial cells	Increases glucose transport and impacts on muscle lipolysis
IL-1 [23, 25]	Involved in pyrexia; T-cell and macrophage activation	Impact on hepatic and muscle lipogenesis
IL-6 [23, 25]	Growth and differentiation of lymphocytes; activation of the acute-phase protein response	Impact on hepatic lipogenesis Increases during multi-organ dysfunction and associated with poor nutritional status
IL-8 [9, 13, 22, 23]	Chemotactic for neutrophils and T-cells	Concentrations during the first 24 hours are predictive of worsening organ dysfunction
Anti-inflammatory cytokine		
IL-10 [22, 25]	Inhibits immune function	Increases during multi-organ dysfunction and associated with poor nutritional status Both excessive and under expression of IL-10 is negatively associated with outcome Negatively correlated with resting energy expenditure: increase in IL-10 associated with lower energy expenditure Inhibits pro-inflammatory cytokine production by macrophages, monocytes, neutrophils and natural killer cells Attenuates the synthesis of TNF cell surface receptions Controlling cytokine regulating the inflammatory response

IL, interleukin; TNFα, tumour necrosis factor alpha.

- *stable phase – physiological control has been achieved, but the stress response is not completely resolved*
- *recovery phase – this phase may occur following discharge from PICU*

Energy metabolism

Although older studies have suggested a hypermetabolic state during the acute phase of illness [26], there is consensus that most children are hypometabolic during this phase. This is supported by a study by Briassoulis *et al*. [25] who found that on the first day of admission 48.6% of children were hypometabolic (<90% of predicted basal metabolic rate, BMR), 40.5% were normometabolic (90%–110% of predicted BMR) and only 10.8% were hypermetabolic (>110% of predicted BMR). A hypermetabolic pattern (or, as more recently described, the recovery phase) only emerged after 2 weeks of admission in 60% of children. This unique pattern of metabolism may be explained by a multitude of factors, including the physiological response to stress, improved medical treatment as well as the unique nature of fuel utilisation in critically ill children (Tables 6.2 and 6.3) [8, 20, 34].

In addition to the factors listed in Table 6.3 studies have found that during the acute phase, growth most probably does not take place and this energy is diverted into the recovery processes [8, 30, 35, 36]. This hypothesis is supported by the data from Hulst *et al*. [35] who found that the anabolic hormone insulin-like growth factor 1 (IGF-1) remained low until day 4 of PICU admission and T3 levels remained below normal at days 4 and 6 in 88% and 89% of the older children, respectively. It is clear that substrate metabolism varies greatly during admission and that during the early phase of illness hypometabolism is usual, whereas in the recovery phase of illness hypermetabolism predominates [8, 28]. This needs to be taken into account when calculating energy requirements and choosing feeds for these patients, which may require changes being made to prescribed energy intake during the course of a PICU stay [8].

Substrate utilisation

Several studies have focused on the relation between a CIC's metabolic state, their nutritional intake, substrate utilisation and nitrogen balance. In a similar way to critically ill adults the stress response and the severity of disease is characterised by protein catabolism. In contrast to adults, fat is the preferred fuel in children and is readily oxidised [4, 34]. Conversely carbohydrates are poorly utilised during critical illness. Gluconeogenesis is also a characteristic of paediatric critical illness and muscle mass is rapidly depleted of amino acids, such as glutamine, which are utilised in *de novo* glucose production [37, 38]. Considering glucose oxidation and production has become one of the most important factors to take into account in nutritional support in CIC as this has a direct impact on morbidity and mortality [39]. In CIC the maximal glucose oxidation rate

Table 6.3 Factors that influence energy expenditure.

Factor	Influence on energy expenditure
Sedation [27]	↓ Energy expenditure (reduced brain activity)
Muscle relaxants [27, 28]	↓ Energy expenditure, but not of clinical significance
Ventilation (with humidified air) [29]	↓ Energy expenditure, reduces the workload of breathing as well as heat loss in fully ventilated children, but where ventilatory support is minimal may have not impact
Thermoneutral environment [30, 31]	↓ Insensible losses, therefore lowers energy expenditure
Pyrexia [32]	↑ Energy expenditure (8%–12% increase in energy expenditure per 1°C above normal)
Paracetamol/NSAID [32]	↓ Energy expenditure as blunts response to fever; clinical relevance questionable
Severity of disease [28, 29, 31]	Inconclusive evidence
Diagnosis [28, 29]	No difference in energy expenditure in different diagnoses
Severity of disease [28, 29]	No significant difference in energy expenditure
Movement/activity (33)	↑ Energy expenditure

NSAID, non-steroidal anti-inflammatory drugs.

for parenteral nutrition (PN) has been found to be 5 mg/kg/min and in a study reducing this to 2.5 mg/kg/min during the acute phase reduced high glycaemic levels and increased the rate of glucose production, mainly through glycogenolysis [40, 41].

It is, therefore, important to ensure that carbohydrate intake in CIC is monitored, especially if PN is used [40]. There is no data currently published on glucose oxidation rates for enteral nutrition, however, as hyperglycaemia is an important complication, monitoring intake also from the enteral route and avoiding overfeeding is critical (see energy requirements, p. 86).

Longer term outcomes

As mortality rates continue to decline, there is an increasing focus on PICU survivorship and improving outcomes in children who are discharged. Disordered feeding is well described in children with chronic diseases such as cystic fibrosis [42], gastrointestinal disorders [43], food allergy [44] and congenital heart disease (CHD) [45] and has been reported to affect up to 22% of post-surgical infants with CHD [46], and is the cause of significant parental distress [47, 48]. However, what is not known is the extent of feeding difficulties in PICU survivors who were healthy prior to admission. Risk factors for feeding difficulties and dysphagia in adult intensive care unit (ICU) survivors are endotracheal tube intubation for longer than 48 hours, ICU associated malnutrition and muscle weakness [49–52]. Furthermore, survivors of adult critical care report significant changes to their ability to eat with reduced appetite, altered taste and food preferences lasting up to 3 months post-ICU discharge [53].

With regards to nutritional risk Hulst *et al*. considered longitudinal changes to anthropometry in critically ill infants/children (n = 293) from admission to PICU up to 6 months post-discharge. At the time of admission 24% of the cohort were undernourished. During PICU admission only infants (preterm/neonates), not older children, exhibited a decline in nutritional status. Of note at 6 months post-discharge from intensive care almost all children showed nutritional recovery with regards to weight and height [3]. This study did not consider body composition measures, so the type of nutritional rehabilitation achieved is not known, e.g. fat mass vs. lean body mass. Recent work has corroborated this finding: 2 year follow up data from the PEPaNIC study indicates that withholding early parenteral nutrition for 1 week in the PICU does not negatively affect survival, anthropometrics, health status and neurocognitive development [54, 55]. It was, however, associated with improved inhibitory control 2 years after PICU admission [56, 57]. Nutritional outcomes should be defined for future use in daily clinical work and as part of audit/research within and between organisations, to ensure variation in practice is reduced and nutritional outcomes are optimised.

Mechanism for muscle wasting

There is often an imbalance between anabolism and catabolism with protein turnover outstripping protein synthesis, leading to a net loss of muscle mass which occurs as a result of *de novo* gluconeogenesis [37, 58].

Sepsis associated muscle wasting is well described in the adult ICU, although the prevalence is not known in children. Causative factors include sepsis, muscle disuse, fasting, cancer, cardiac failure and renal dysfunction. In ICU there is often prolonged bed rest or immobilisation, use of sedatives and neuromuscular blockades, acute or chronic organ dysfunction, medication using steroids [58] and increased levels of cytokines, e.g. IL-6, IL-10, TNFα (which are associated with muscle degradation) amongst other factors [22, 58] (Figure 6.2).

Muscle wasting and ICU induced myopathy has not been described in children and it may be that the pathophysiology of paediatric critical illness does not result in this phenomenon. However, as a significant number of children admitted to PICU develop malnutrition it is likely that muscle wasting also occurs in children, although the correlation with strength and function has not yet been studied in CIC [59]. Ultrasonography of various upper and lower body muscles, in particular the

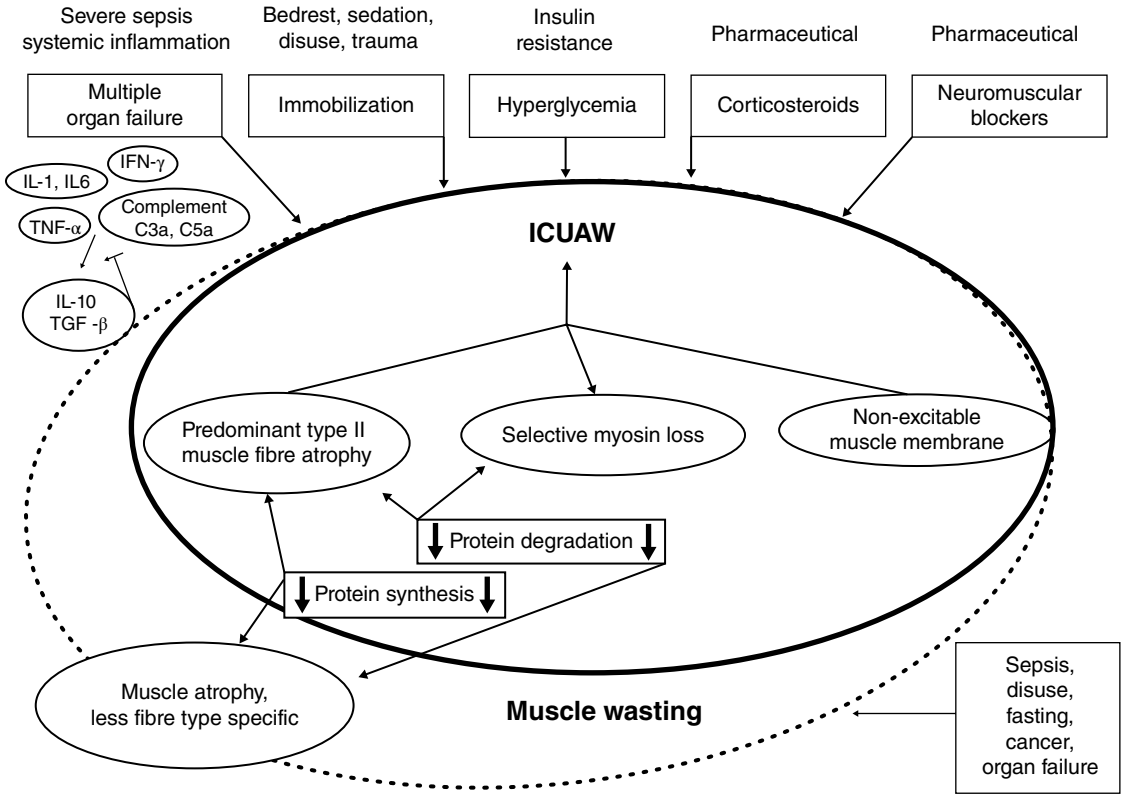

Figure 6.2 Risk factors for muscle wasting and ICU associated wasting from Schefold *et al*. with permission [58]. IFN, interferon; IL, interleukin; TNF, tumour necrosis factor; TGF, transforming growth factor; ICUAW, intensive care unit acquired weakness. Source: Reproduced with permission of John Wiley & Sons.

quadriceps femoris muscle in adults, has been studied as proxy marker of muscle wasting [59]. So, although muscle ultrasound may detect muscle wasting in CIC, the error of margin is too large for it to be used in clinical practice [59, 60].

Nutritional assessment

Growth failure is common amongst children admitted to PICU. It is, therefore, imperative to classify the type of growth impairment (i.e. wasting, stunting or faltering growth) to enable a targeted nutritional care plan. Malnutrition in this population is multifactorial and may be illness and non-illness related and it is important to identify the contributors (Figure 6.3). The multifactorial nature of malnutrition in this population makes nutritional assessment in particular challenging [62].

Anthropometry, biochemical markers, clinical and dietary review form part of the nutritional assessment in CIC [63]. This process, however, is notoriously difficult due to a multitude of factors including oedema, ascites and severity of disease, which often makes it challenging to obtain an accurate body weight. In addition, the emotional impact of having a child in PICU frequently makes the diet history from the caregivers unreliable.

A UK study found that only 20.5% of CIC had an accurate admission weight documented and it is common practice to estimate their weight on admission [64]. The Advanced Paediatric Life Support formula ([age + 4] × 2) is most commonly used to estimate weight [65], however, Luscombe *et al*. [64, 66] found that this formula underestimates the weight significantly and that a new formula (weight = 3(age) + 7) allows for a more safe and accurate estimation. A formula can, however, never replace an accurate weight measurement; it is not only used in the assessment of nutritional status and calculating nutritional requirements, but is also used for estimating fluid requirements and medication doses. Transfer and hospital notes as well as the child's personal health record (red/blue book) may have a recent accurate weight (often height and head circumference as well), which may be useful. It is important that available accurate weight, height and head circumference measurements are plotted on an appropriate growth chart [63, 67].

The use of both triceps skin fold thickness (TSF) and mid upper arm circumference (MUAC) has been documented in this population. Although MUAC is less affected by oedema, both measurements have limited use in children with a short PICU stay (4–5 days), however, should be considered for children who remain in PICU for a longer period of time (>1 week). They are most helpful when followed over time and measured by the same trained person [63, 67]. Hulst *et al*. [63] studied the feasibility of routinely performing nutritional assessments using non-invasive methods in CIC. It was found that anthropometry was reliably obtained within 24 hours of admission in 56%–91% of patients. Unfortunately, the more seriously ill patients were those where measurements were less feasible, but who might have benefited the most from having them done. Vermilyea *et al*. [68] have proposed the use of a subjective global nutritional assessment

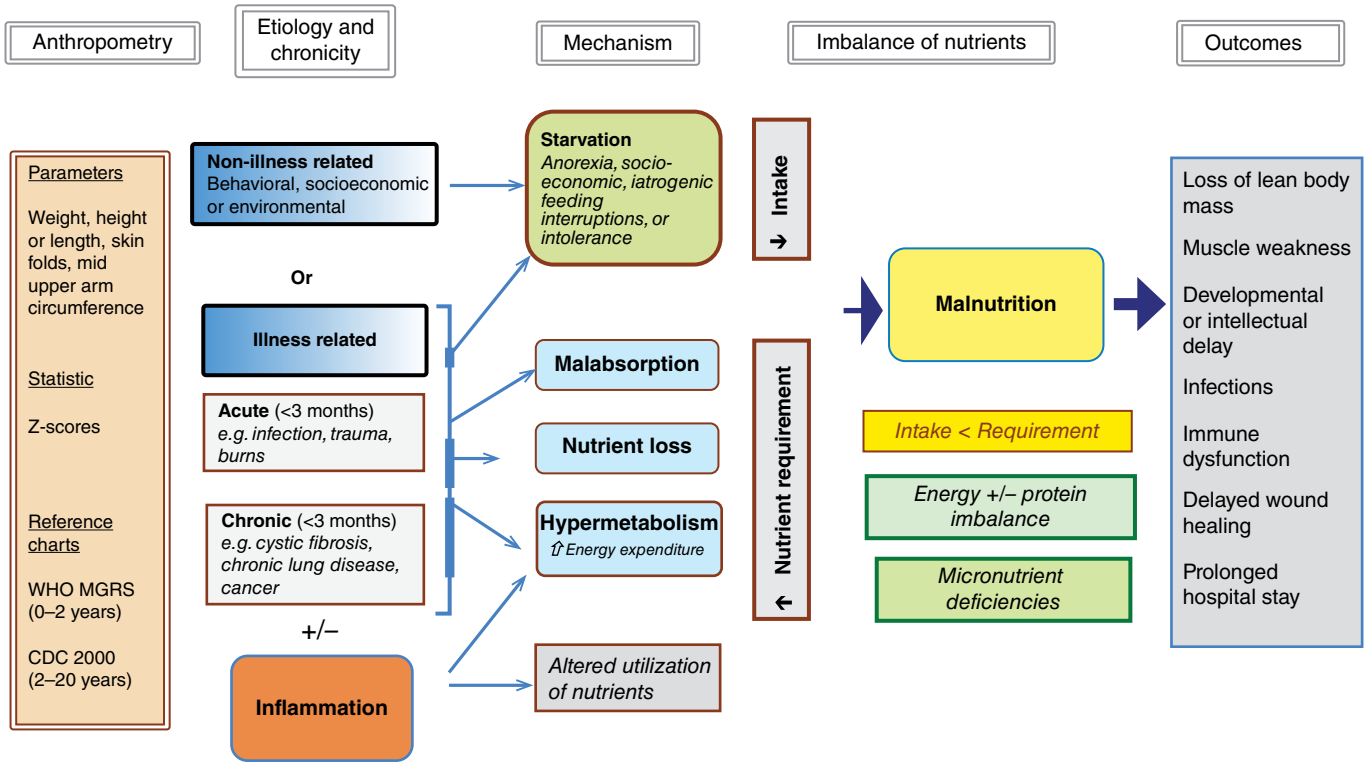

Figure 6.3 Aetiology of illness and non-illness related malnutrition in CIC [61]. Source: With permission from SAGE. Reproduced with permission of Wolters Kluwer Health.

(SGNA) tool, specifically designed for PICU. That study found, although not predictive of outcome, the SGNA was valid and strongly correlated with standard anthropometrical measurements. Although this does not replace an accurate measurement, healthcare professionals may consider this in those children where measurements are not feasible. More recently the use of bioelectrical impedance spectroscopy (BIS) in predicting nutritional risk and PICU outcomes, such as length of stay, has been investigated. A phase angle of <2.7 on day 2 in PICU following cardiac surgery for congenital heart disease was found to be associated with a four-fold risk of staying longer in PICU. A low phase angle also appeared to precede anthropometrical changes and may be a more sensitive predictor of nutrition risk [69]. Future work needs to focus on investigating the use of BIS in this setting as it may represent an inexpensive tool to identify those at risk of prolonged PICU stay, allowing for nutritional intake to more carefully managed [17, 69].

Most laboratory markers of nutritional status are affected by the acute inflammatory response, renal impairment and fluid shifts. Hypomagnesaemia (20%), hypertriglyceridaemia (25%), uraemia (30%) and hypoalbuminaemia (52%) are commonly seen in CIC [70], but an association between anthropometric measurements was only found with uraemia. Serum urea levels can indicate the degree of catabolic stress and levels of protein breakdown associated with illness, surgery and trauma. Uraemia has been shown to be negatively correlated to MUAC and weight for age on admission and discharge, as well as increased risk of mortality [71]. However, it is important to consider that serum urea levels are also influenced by impaired renal function, dehydration, polyuria and severe sweating on admission. Children with sepsis or cardiac anomalies in this study showed the highest prevalence of uraemia, which can be explained by the degree of catabolism and impairment of renal function. Although pre-albumin, retinol binding protein, transferrin and nitrogen balance studies have also been used in research on nutritional status in CIC [70], their accuracy and the value of routine use have been questioned by several authors. However, a positive nitrogen balance does not reflect protein or amino acid utilisation or stores, and although increasing amino acid intakes may result in a positive protein balance, it leads to increased endogenous glucose production and lipolysis, exacerbating insulin resistance and promoting gluconeogenesis [72, 73]. Urinary nitrogen has been used in the past as a marker of nitrogen balance. Urinary nitrogen as a biomarker is challenging to collect in clinical practice (a full 24 hours of urine is needed) and more recently the isotope tracer technique has been more commonly used to determine whole body protein balance and synthesis [20, 74, 75]. Whilst this method has been shown to be very accurate, it requires specialist equipment and expertise to conduct these studies. It is, therefore, important to select biomarkers for the assessment of nutritional status in the critically ill patient with care and interpret them accordingly (Table 6.4).

Taking a diet history often gets neglected in PICU [67]. Although manipulation of oral intake is not practical or possible, many acute and chronic nutrition related problems, e.g. food allergy, nutritional rickets, can be identified on admission and can assist in planning dietary input during

Table 6.4 Relevance of biochemical indices in critical illness.

Biochemical indices	Comment
Serum urea	• Indication of catabolism and protein breakdown associated with trauma [76] as well as impaired renal function, dehydration, polyuria or severe sweating which will impact on fluid management [70] • Although there is a link between muscle mass and urea, it is not a reliable marker to assess nutritional support
Glucose	• There is currently a great deal of interest in the use of tight glycaemic control in critically ill children. There is, however, no clear guidance on this topic from a nutritional perspective [77] • It is important to monitor glucose levels, in particular in children on IV preparations and those with PN (p. 72) [40]
Albumin	• Levels are likely to be low especially in those receiving intravenous saline • Albumin is not a good marker of nutritional status, due to a long ½ life and is more a marker of inflammation, intravascular/extravascular fluid shifts and catabolism [14, 15, 70, 76]
C-reactive protein (CRP)	• Is used as an index of the acute phase response and is usually measured serially • Serum prealbumin and CRP are inversely related, e.g. serum prealbumin levels decrease and CRP levels increase in proportion to the severity of illness, returning to normal (<5 mg/dL) once the illness has resolved • In infants a value of <2 mg/dL is associated with a return of anabolism with a concomitant rise in prealbumin levels [78]
Magnesium/calcium	• Hypomagnesaemia is commonly found in critically ill children [79] • It is strongly associated with hypokalaemia and hypocalcaemia
Phosphorus	• Hypophosphataemia (in up to 61% of critically ill children) [70, 80] and low levels of selenium, zinc [81] and manganese are also commonly found in critical illnesses [70]
Lactate	• Lactic acidosis is common in critically ill children and reflects hypoperfusion, including diabetic ketoacidosis, septic shock and cardiogenic shock • Lactic acidosis, base excess and a strong anion gap are associated with increased risk of mortality • A level of >2 mg/dL may be used as a crude proxy for cell function and a resolution of lactic acidosis is correlated with survival [82]

IV, intravenous; PN, parenteral nutrition.

the admission. The effects of long term feeding problems, e.g. obesity, constipation, can be addressed once the patient is extubated and transferred to a ward or local hospital.

Nutritional requirements

Energy requirements

Many predictive equations have been used and studied in the paediatric critical care setting to calculate energy requirements including Harris-Benedict [83], World Health Organization [84], Talbot [83], Schofield [85], Henry [86], White [87] and Meyer *et al*.'s [28] prediction equation and the simplified equation based on bedside volumetric carbon dioxide elimination method by Mehta *et al*. [88]. A recent study by Jotterand Chaparro *et al*. [89] assessed all equations specifically recommended for PICU. That study found that the equations by Mehta, Schofield and Henry had a bias <10%, however, the 95% confidence interval was large and contained values well beyond ±10% of measured energy expenditure (MEE) (Table 6.5). A subsequent systematic review assessing the accuracy of predictive equations of 2326 indirect calorimetry measurements in 1102 children found that none of the equations predicted energy requirements within the recommended ±10%, but the Schofield and Talbot equations predicted requirements within ±15% in 50% of cases.

Most authors have found that the actual energy expenditure is closer to the resting energy expenditure. These studies are summarised in Table 6.6.

Although current guidelines [1] recommend indirect calorimetry to establish energy requirements, there is a considerable cost related to running and maintaining them and most PICU units do not have access to an indirect calorimeter [20–23]. The guidelines from the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition (ASPEN) [93] and the European Society of Paediatric and Neonatal Intensive Care Society (ESPNIC) [94] recommend that in the absence of indirect calorimetry the BMR,

Table 6.5 Bias at 200 and 1000 kcal level introduced with different predictive formulas [89].

Predictive equation	Bias at 200 kcal (%)	Bias at 1000 kcal (%)	Mean bias (%)
Talbot tables	−2	−5	−2
Schofield WH	−5	9	4
Schofield W	−8	6	1
Henry W	−5	8	3
Henry WH	6	0	2
Mehta	−10	0	−3
WHO	−15	7	−1
Meyer	−18	−7	−10
White	40	−15	11
Harris Benedict infants	−40	−33	−33
Harris Benedict	175	−3	76

WH, weight and height; W, weight.

Table 6.6 Mean energy expenditure using the same indirect calorimeter (published studies since 2000).

Publication	Number of children enrolled	Diagnosis	Mean energy expenditure
Taylor *et al*. [30]	57	Mainly liver disease, some head injury and other disorders	37.2 kcal/kg (155 kJ/kg)
Martinez *et al*. [90]	43	Post-surgery, liver transplant, medical disorders	47 kcal/kg (196 kJ/kg)
De Wit *et al*. [31]	21	Post-cardiac surgery	67.8 kcal/kg (283 kJ/kg)
Botran *et al*. [91]	46	Post-surgery and medical	48.8 kcal/kg (204 kJ/kg)
Meyer *et al*. [28]	175	Respiratory, surgical, sepsis, liver and cardiac	44.6 kcal/kg (186 kJ/kg)
Mehta *et al*. [88]	94	Ventilated critically ill children (diagnoses not specified)	41 kcal/kg (171 kJ/kg) derivation data set and 55 kcal/kg (230 kJ/kg) validation data set
Jotterand Chaparro *et al*. [92]	75	Cardiac surgery, medical emergencies, ear and nose tract surgery	55 kcal/kg (239 kJ/kg)

calculated by Schofield or World Health Organization/Food Agriculture Organization/United Nations University equations, can be used using an accurate body weight without any additional stress factor (Table 6.7) [93]. The Schofield equation is used most commonly in the UK and also in 55% of European PICU [24], with some evidence of reasonable correlation with ventilated CIC. The use of physical activity factor is described by van der Kuip *et al*. [33], however, this is difficult to estimate and apply in clinical practice. It is recommended to achieve at least two thirds of calculated energy target within the first week of admission [95].

If indirect calorimetry is considered, it is important to only use validated metabolic carts. The Deltatrac II (GE Healthcare) has been validated in all populations, but is being used less as it has not been technologically updated. Several breath by breath indirect calorimeters exist, however, many are not validated and accuracy in small children (weighing <10 kg) is questionable [96]. As well as cost considerations and choosing the correct indirect calorimeter, ensuring there is sufficient resource to provide a service [97], care should be taken to perform measurements only in a resting state and to not perform any measurements if the FiO2 is >60%, or in patients with an endotracheal tube leak >10%. Dietitians need to be aware that measurements in patients on haemodialysis/haemofiltration may not be accurate [98, 99].

Learning points: energy requirements

- *acute phase – hypometabolism – energy requirements do not usually exceed BMR: Schofield equation with no activity factor*
- *stable phase – energy requirements: Schofield equation 1.2–1.4 × BMR*
- *recovery phase – energy requirements: Schofield equation up to 2 × BMR*

Table 6.7 Recommended predictive equations for calculating resting energy expenditure (REE) in critically ill children.

Name of equation	Equation (kcal/24 hours)
Schofield (if accurate weight is available)	*Males* <3 years: (59.5 × W) – 30 3–10 years: (22.7 × W) + 505 10–18 years: (17.7 × W) + 658 *Females* <3 years: (58.3 × W) – 31 3–10 years: (20.3 × W) + 486 10–18 years: (13.4 × W) + 692
Schofield (if an accurate weight and height is available)	*Males* <3 years: (0.167 × W) + (1517.4 × H) – 616.6 3–10 years: (19.6 × W) + (130.3 × H) + 414.9 10–18 years: (16.97 x W) + (137.2 x H) + 515.5 *Females* <3 years: (16.252 × W) + (1023.3 × H) – 413.5 3–10 years: (16.25 × W) + (161.8 × H) + 371.2 10–18 years: (8.365 × W) + (465 × H) + 200.0
WHO/FAO/UNU formula	*Males* 0–3 years: (60.9 × W) – 54 3–10 years: (22.7 × W) – 495 10–18 years: (17.5 × W) + 651 *Females* 0–3 years: (61 × W) – 51 3–10 years: (22.4 × W) + 486 10–18 years: (12.2 × W) + 746

W, weight (kg); H, height (m).

Protein requirements

Although there are no specific guidelines on protein requirements in ventilated CIC, research has shown that patients with an adequate energy and protein intake have a positive nitrogen balance, unlike patients that are underfed [4], although a positive nitrogen balance does not equate to protein utilisation [20, 100, 101]. Agus and Jacksic [102] suggest that the critically ill infant and child should receive 2–3

and 1.5 g/kg of protein, respectively, and in severely stressed states may require even more (≥3 g/kg). The 2017 ASPEN guidelines, based on expert opinion, recommend a minimum of 1.5 g/kg/day [95] for CIC. In contrast ESPNIC reported there was insufficient evidence to recommend a protein/amino acid intake of 1.5 g/kg or higher during the acute phase of disease and that more research is required to determine the exact threshold of protein which may be of benefit during critical illness as previous recommendations may overestimate protein/amino acid requirements during the acute phase acute critical illness [71]. Increased amounts of protein/ amino acids may be required during rehabilitation [8] Disease specific protein recommendations, e.g. for renal failure, burns also provide useful guidelines for children in PICU.

A recent study has suggested that during the acute phase amino acid intake from parenteral nutrition exceeding age related reference nutrient intakes (RNI) is associated with increased serum urea and harm [71] as well as shortened leucocyte telomere length [103]. It is important to emphasise these results arise from one large randomised controlled study and additional studies are required to confirm the association [104, 105]. These findings are in contrast from other observational studies which report that an average daily total protein intake >1.5 g/kg and energy intake of 58 kcal (242 kJ)/kg was associated with lower mortality [106], although further research is required as during the acute phase these levels may overestimate requirements during the acute phase [94]. There is insufficient data to determine the optimal structure and type of protein used in CIC [75].

It is important to note from the PEPaNIC study [107] and other studies that providing an excess of nutrients during the acute phase may be detrimental to critically ill children, particularly during the acute phase of critical illness [94, 108] and, therefore, age related nutritional requirements should not be exceeded [8, 93]. It is also important to note that substrate utilisation and effect on inflammatory mediators will vary depending on the route and type of macronutrients administered, e.g. intravenous vs. enteral [71, 109].

Learning points: protein requirements

- *Expert opinion recommends 1.5 g/kg /day as a minimum*
- *ASPEN recommends 2–3 g/kg/day*
- *PEPaNIC results suggest that it may be of benefit to withhold PN for the first 7 days of critical illness (excluding preterm infants)*

Vitamins and minerals

Vitamin and trace mineral metabolism in critically ill and postoperative paediatric patients is not a well researched area. Valla *et al*. described significantly lower plasma levels of selenium, copper, zinc, vitamin C, vitamin E and β-carotene in CIC. Low serum levels of micronutrients during the acute phase may be related to the impact of the inflammatory response on micronutrient transporters (particularly those associated with albumin), over-hydration and oxidative stress [110]. As a result there are no specific recommendations for ventilated patients in PICU [111]. The pharmacological use of vitamins and trace minerals in paediatric illness is controversial due to reports of toxicity [80, 112]. When energy and fluid requirements are met by commercial enteral tube feeds, CIC should receive sufficient vitamins and minerals to meet the RNI for both. However, many patients require additional supplementation, depending on diagnosis and treatment modality, e.g. premature infants, haemofiltration [113]. This should be done under supervision and monitored with blood biochemistry.

Nutrition care plans and outcomes

Defining energy and protein requirements is integral to any part of a nutrition care plan [114]. In addition, there is a growing focus on clinical outcomes as part of the nutrition care pathway [115]. A large multicentred retrospective study in CIC investigated whether early documentation of nutrition care plans had any effect on daily energy intake and route of nutrition support: 47.7% had energy requirements documented in the medical notes and these patients had significantly higher total daily energy intake and were more likely to be fed enterally during the first 4 days of admission to a PICU compared with those without a nutrition care plan [114]. The implementation of nutrition practice guidelines and participation of dietitians in medical rounds improved the nutritional intake in some patients [116, 117]. In another large international prospective study in adults increased intake of energy and protein was associated with better clinical outcomes [118]. As a result, the Faculty of Intensive Care Society has published minimum standards for intensive care units which recommend that a dietitian is part of an intensive care multidisciplinary team contributing to improved delivery of nutrition support to all ICU patients [119].

Nutritional management

When to commence nutrition support

The aim of nutritional support in critically ill children is not to reverse the course of illness or pre-existing malnutrition, but is to possibly minimise nutrient deficits and prevent a further decline in nutritional status [117]. Traditionally, nutrition support has been withheld in children in PICU until metabolic and cardiopulmonary stability has been established [120]. However, many units have changed their protocols and guidelines to include nutritional support at an earlier stage. Early enteral feeds can be safely initiated within 6 hours of admission and by 24 hours in CIC, including those with single ventricle cardiac physiology [120–124]. Early enteral feeing may improve nutritional delivery, particularly when used in conjunction with locally adapted feeding

protocols, and is also cost effective [117, 125]. Increasing feeds in a stepwise fashion has been shown to be an effective way to initiate and advance nutritional support until the goal volume and rate of feed delivery is achieved. [120, 123, 124, 126].

There are four main hypotheses to justify early feeding in CIC:

- Fasting has a deleterious effect on these patients
- Energy supply plays an important role in the promotion of energy metabolism
- The delivery of nutrients is important for gut maintenance
- Specific nutrients provide support for organ and system functions

The combination of decreased blood flow to the gut and interactions with drugs can lead to a reduction of nutrient absorption and gastric motility, failure of gastric acid secretion and increase in intestinal permeability and bacterial translocation [127, 128]. Early enteral nutrition support may reverse these effects by reducing catabolism, promoting wound healing and, most likely, decreasing the frequency of clinical sepsis [129].

Extracorporeal life support (ECLS), or extracorporeal membrane oxygenation (ECMO), is used in children with refractory respiratory and heart failure in order to maximise medical management. In a European survey of nutritional practices in CIC with CHD enteral nutrition support was recommended for those requiring ECLS [130]. With an increasing number of centres commissioned to provide this type of life support it is important that nutritional support during periods of ECLS is optimised in this vulnerable group of children. Previous concerns during periods of ECLS regarding the risk of decreased mesenteric blood flow and use of vasoactive medication, e.g. inotropes, resulting in intestinal ischaemia, cardiac necrotising enterocolitis and gut haemorrhage delayed the introduction of enteral nutrition [131]. Parenteral nutrition was the traditional mode of nutrition support, however, this has been associated with increased risk of catheter related line sepsis [132]; as such enteral nutrition is regarded as the preferred route of nutritional support. Ong *et al*. [133] recently completed a retrospective cohort study of children aged between 1 month and 18 years of age ($n = 51$) who required ECLS. Their average (range) intakes of energy and protein of 23.2 (16.0–35.9) kcal/kg/day and 0.8 (0.4–1.38) g/kg/day represented around 50% of estimated requirements. In this cohort intake of enteral nutrition was affected by veno-arterial compared with veno-venous cannulation and vasoactive inotropes score (VIS). Greater enteral nutrition adequacy remained associated with lower mortality after controlling for number of days of ECMO, need for continuous renal replacement therapies (CRRT) and number of vasoactive and inotropic drugs required. ASPEN have published clinical guidelines for the nutrition support of neonates/infants supported on ECLS and provide the following recommendations (levels of evidence D) [134]:

- Timely nutrition support should be provided in neonates treated with ECLS
- Neonates treated with ECLS have protein requirements of up to 3 g/kg/day
- Energy requirements in neonates treated with ECMO are equivalent to healthy subjects
- Enteral feedings should be initiated when the patient on ECMO has clinically stabilised

Due to the nature of ECLS it is not possible to use indirect calorimetry and, therefore, predictive equations, e.g. Schofield, should be used without stress factors [134]. Fluid is not usually restricted and if clinically stable it is usually possible to provide adequate amounts of enteral nutrition.

Route of feeding

Although it is an acknowledged fact that using the enteral route is more physiological and beneficial to CIC, the debate of enteral vs. parenteral nutrition in critical care has changed its focus to the delivery of nutrients in the most effective and safe way, using the most appropriate route for the individual patient [123].

Standard protocols have been shown to be useful in both improving the time taken to initiate feeding, as well as progression to full feeds [120, 135, 136]. Enteral feeding protocols guide medical and nursing staff through the choice of tube feeds, the feeding rates depending on the child's age and weight, as well as guidelines for the continuous monitoring process.

Nasogastric versus nasojejunal feeding

Nasogastric (NG) feeding is most widely used and is usually safe and well tolerated in CIC [93]. However, gastric delivery of enteral feeds may be poorly tolerated due to disordered gastric motility which may lead to aspiration. In addition, the use of gastric residual volume as a marker of tolerance of NG feeding has a poor evidence base and is often been blamed for inadequate delivery of feed [91, 137]. Horn *et al*. [138] defined delayed gastric emptying in CIC as >5 mL/kg gastric residuals every 4 hours. Although this provides some guidance, this is still an arbitrary volume and may still lead to feeds being inappropriately stopped. Therefore, interest has focused on post-pyloric feeding. Nasojejunal (NJ) feeding has been shown by several centres to be safe and effective in this subset of patients, enabling adequate delivery of nutrition in a shorter period of time in the majority of patients and so reducing the problems had PN been used: hyperglycaemia, hypertriglyceridaemia and hepatic dysfunction [139]. However, in cyanotic patients it is important to note a risk in the development of necrotising enterocolitis with enteral feeding, therefore, additional care in the monitoring of haemodynamic status is warranted when NJ feeds are given to this subgroup of patients [140]. Many units avoid post-pyloric feeding as NJ tubes are extremely difficult to place and become dislodged very easily [141]. Several blind (non-radiological guided) bedside techniques have been successfully developed using weighted or unweighted polyurethane NG tubes with hydrophilic guide wires. Meyer *et al*. [142] have shown that with continuous training and audit, a blind placement technique can be maintained at 96% success rate.

Gastric feeding is considered to be as effective as post-pyloric feeding in the majority of critically ill children and should be considered as the first choice of feeding route. However, post-pyloric feeding should be considered in those CIC at high risk of aspiration or requiring frequent fasting for surgery or procedures (e.g. severely burned children and those with traumatic brain injury or on non-invasive ventilation).

Continuous feeds versus bolus feeding

Both continuous as well as bolus feeding have been used in paediatric critical care. The pros and cons of both are well studied in the neonatal and adult setting [143, 144], but in paediatrics individual units have their preferred practice. Although bolus feeding is more physiological difficulties with monitoring the tolerance, as well as the additional nursing input, has led to many PICUs preferring continuous feeding. On the other hand, continuous feeding has been shown to delay gastric emptying in adult ICU patients [145] and reduce gallbladder contraction [146]. Horn *et al.*, however, showed gastric residual volumes did not differ between children on bolus or continuous feeds [138]. In the absence of substantial clinical evidence, consensus is that the adequate delivery of nutrition support should be the main goal in feeding CIC and should not be hampered by the feeding route. A case study of a child admitted to PICU is given in Table 6.8.

Table 6.8 Case study: a child admitted to the paediatric intensive care unit.

A 13 month old boy with meningococcal sepsis was admitted to PICU. He received fluid resuscitation and after 5 hours of admission, the doctors deem him haemodynamically stable so he can commence enteral nutrition. He is fully sedated (including muscle relaxants) and ventilated, requiring adrenalin.

Anthropometry
Weight = 11.2 kg
Length = no recent length available

Biochemistry
Electrolytes are all within normal range, but in order to achieve this he is receiving potassium and magnesium corrections. Albumin is low, urea is increased, creatinine is increased.

Clinical
Necrotic areas in all extremities: fingers and toes. Necrotic areas on the face as well.

Diet history
Parents report that he usually eats well at home and consumes 500–600 mL of full fat cow's milk, has red meat twice per week and otherwise has fish or chicken.

Nutritional requirements
Activity: physiotherapy twice per day, he is turned four times per day and is not fully ventilated.
Energy requirements:
$= (59.512 \times 11.2) - 30.4$
$= 564.72 + 10\%$
$= 636$ kcal (2.66 MJ)
Protein requirements: 2–3 g/kg/day = 22.4–33.6 g/day
Enteral feed: 1 kcal/mL (4 kJ/mL) feed with a multifibre mix
Feeding route: trial NG. Likelihood of having gastroparesis is high (adrenalin, shock) and may therefore require NJ.

NG, nasogastric; NJ, nasojejunal.

Type of enteral feed

Although there is a wide variety of types of enteral feed available, there remains a paucity of data regarding optimal enteral feed composition during critical illness in children. Feeds range from human milk and standard infant formula to various specialised infant and paediatric feeds, including energy and nutrient dense formulas with varying protein and fat sources [147–150]. However, the metabolic utilisation and assimilation of proteins, carbohydrates, fats and other nutrients during critical illness may be affected by hypoxaemia, dysbiosis and impoverishment of the microbiome [151–153], affecting absorption, tolerance and utilisation of protein [101], fats and energy [4, 19].

Traditionally polymeric enteral feeds or breastmilk are used as first line in CIC [148]. Peptide based feeds are usually considered as second line, particularly following cardiac surgery or where tolerance to polymeric feed is poor, e.g. vomiting, diarrhoea [20, 147, 148, 150]. Energy and nutrient dense whey based feeds have been successfully use in critically ill infants during the first week of admission, resulting in significantly higher *de novo* arginine synthesis and higher nutritional intakes compared to standard infant feeds [154, 155]. These feeds have also been shown to be well tolerated from day 1 of admission [149, 155, 156] and are associated with weight gain during a PICU admission [157] and, in post-surgical infants with CHD, achievement of nutritional goals of 92%–161% of BMR (51–89 kcal/kg/day) compared with 80%–100% of BMR (44–56 kcal/kg/day) in the control group [158]. However, not all infants tolerate energy and nutrient dense whey based feeds and where there is perceived feed intolerance the use of a peptide based energy and nutrient dense feed in critically ill infants with a PICU length of stay >7 days has been shown to promote weight gain and reduce the incidence of feeding interruptions due to feed intolerance to 2% [159].

There remains a paucity of data regarding optimal enteral feed composition during critical illness and further work is required regarding the type and timing of feeds, particularly as tolerance to feeds [160] or metabolic adjustments for various macronutrient sources may change throughout the acute, stable and recovery phase of critical illness [161].

Learning points: enteral feeding

- *Enteral feeds can be safely commenced within 12 hours of admission*
- *Gastric feeding is as effective as post-pyloric feeding*
- *Where there is tight fluid management, e.g. <4 mL/kg/hour, the use of an energy and nutrient dense feed from day 1 may allow nutritional targets to be met more easily*
- *Where there is poor feeding tolerance the use of a peptide based energy and nutrient dense feed may improve feeding outcomes*

Monitoring

Ideally CIC should have their nutrition monitored daily. The clinical situation can change rapidly and may impact on nutritional requirements. Nutrition is also impacted by:

- *fluid volume restriction* – the main barrier to adequate nutrition delivery. The dietitian needs to establish whether such strict fluid restriction is required in the light of inadequate nutrient delivery and to change the enteral feed (if necessary); also to negotiate whether drugs running in intravenous (IV) fluids can be made more concentrated, thus liberating volume for feeding [162].
- *procedural interruptions* – can account for 11%–57% of total interruptions affecting up to 62% of patients [137]. The most common interruptions arise from surgery, radiological procedures, attempts at extubation and the administration of medication. Often feeding rates are not increased to compensate for time lost during the interruption making it challenging to achieve nutrition goals, with the resultant large energy and protein deficits negatively impacting on weight [162, 163].
- *interruption due to gastrointestinal intolerance* – especially where there is vomiting, diarrhoea, large gastric residuals and abdominal distension which may occur in up to 57% of patients [162].
- *mechanical problems* – such as NJ tube dislodgement, NG blockage [162].

The dietitian's role is critical to improving nutrient delivery and ensuring protocols and procedures are in place to allow for optimal nutritional support [164]. Table 6.9 shows how often aspects of nutrition support need to be monitored.

Learning points: monitoring

- *Regular monitoring of anthropometry, biochemistry and nutritional intake is essential*
- *Dietetic involvement improves nutritional intake*

Table 6.9 Monitoring frequency in paediatric intensive care unit.

	Daily	2–3 times per week	Once per week
Anthropometry	X*	X*	X*
Biochemistry	X		
Recalculation of nutrient requirements		X*	X*
Evaluation of delivery of feed	X		

* Frequency depends on the age of the child.

Complications

Refeeding syndrome

As the prevalence of malnutrition within the PICU population is high, the risk for refeeding syndrome should be considered. When enteral or parenteral nutrition is commenced in children who have not received optimal nutritional support for some time, e.g. ≥3 days, it is important to ensure there is a multidisciplinary approach to determine the risk of refeeding syndrome in addition to an appropriate management strategy regarding electrolyte replacement, vitamin supplementation and energy and/or protein restriction [165–167]. Figure 6.4 provides a management outline on refeeding syndrome in PICU [168].

Baseline:

- Before starting to feed complete baseline bloods for sodium, potassium, phosphate, magnesium, corrected calcium, creatinine, glucose, particularly vitamin D, parathyroid hormone, alkaline phosphatase and albumin.
- On day 0 supplement at least 30 minutes before starting or restarting feeding.
- Give a daily dose of oral thiamin for 2 weeks: <1 year of age 50 mg daily for 2 weeks; >1 year of age 100 mg daily for 2 weeks.

During feeding (days 0 to 4–10):

- Repeat laboratory testing every 12 hours of the following: potassium, phosphate, magnesium, and as indicated: corrected calcium, albumin.
- For at least 4 days, continue if laboratory results are aberrant or show clinically relevant variations.
- Supplement with thiamin orally; if nil by mouth then thiamin should be administered intravenously as an infusion or repeated intramuscular injections. Doses in excess of 400 mg/day in adults have been associated with anaphylaxis.
- Correct any other vitamin deficiencies with therapeutic doses, e.g. vitamin D.
- Give multivitamins and trace elements complex once daily: vitamins preferably at least 200% recommended daily intake (RDI); trace elements at least 100% RDI.
- If there are no biochemical or symptomatic changes and none appear later, the feeding can be increased more quickly.
- If there is a clinical manifestation of the refeeding syndrome consider a slower approach particularly during the first week [167].

Table 6.10 shows recommended electrolyte supplementation in the management of refeeding syndrome.

Future research and unanswered questions

Immunonutrition

The use of immune enhancing enteral feeding formulas is well known in adult intensive care. In addition to the normal macro- and micronutrients, these feeds contain: a mixture of

Patients at risk for refeeding syndrome

- Any child with a history of inadequate nutritional intake pre- or post-admission to hospital – for all at risk check base line K, Ca, P, Mg levels

- If levels are low, deficits should be corrected using the appropriate age-related reference ranges as targets
- Record pulse (compensatory tachycardia/ bradycardia) and continuous ECG monitoring for arrhythmias, blood pressure and respiratory rate hourly
- Record an accurate fluid balance, weigh daily

Day 1–5 Initial refeeding – Calculate energy / protein using the table below:

- Start feeding: at 60–75% normal requirements (see below) with standard 0.67 kcal/mL feed (infants) or 0.75–1.0 kcal/mL (children)
- Calorie and protein intake should betailored to each child and the above values may need to be adjusted down by as much as 30%
- **Prescribe thiamin:** <1 year of age 50 mg daily for 1 week or >1 year of age 100 mg daily for 1 week
- **In addition to a multivitamin:** <3 years of age 0.6 mL Dalivit daily for 3 weeks or >3 years of age Santogen A-Z 1 tablet daily/Forceval Junior effervescent tablet 1–2 daily for 3 weeks
- **Biochemistry**: First 3–5 days, every 24 hours: 24 hourly U&E, Ca, P, Mg, LFTs and FBC, 4 hourly glucose

Day 1–5 initial energy

	DRV (kcal/kg)	*Enteral kcal/kg**	*PN*	*Food kcal/kg**	*Protein g/kg**
• Birth to 1 year	90–110	75% = ≈80	45–55	—	1
• 1–7 years	80–100	75% = 60–75	35	½ portions	0.6–1
• 7–10 y years	60–75	75% = 55	30–45	½ portions	0.6–1
• 11–14 years	60	75% = 45	25–30	½ portions	0.6–1
• 15–18 years	50	75% = 35	25	½ portions	0.6–1
• >18 years	25–35	75% = 18	10	½ portions	0.6–1

DRV = Dietary reference values
*Use actual body weight

Then 6–10 days:

- If blood biochemistry is stable, increase energy and protein intake to 100% of normal requirements – e.g. full enteral feeds or parenteral nutrition or full portions if eating
- As there is still a risk of refeeding syndrome with increasing nutrient intake, continue to check blood biochemistry: 4 hourly glucose, daily U&E, Ca, P, Mg, LFT & FBC
- Continue to observe for tachycardia/bradycardia, raised blood pressure, respiratory rate, positive fluid balance

Day 11 + Catch-up weight gain:

- For the younger child aim for 20 g/kg/day weight gain
- For older children aim for 1–1.5 kg weight gain per week (aim 2 500–3 000 kcal/day) — ensure protein energy ratio is achieved to promote appropriate lean body mass accretion

Catch-up no;	***Energy kcal/kg****	***Protein g/kg****	***Protein energy ratio***	***Food***
Birth to 1 year	126	2.8	10–12%	
1–7 years	126	2.8	10–12%	3 meals and 1–2 snacks/ONS
7–10 years	126	2.8	10–12%	3 meals and 2 snacks/ONS
11–14 years	80	1.5–2	15–20%	3 meals and 2 snacks/ONS
15–18 years	80	1.5–2	15–20%	3 meals and 2 snacks/ONS
> 18 years	80	1.5–2	15–20%	3 meals and 2 snacks/ONS

* Use actual body weight. Aimfor up to 10 years 20g/kg/day > 10 years 0.5 –1 –1.5 kg weight gain week
ONS = oral nutrition supplements, e.g. Fortisip

Figure 6.4 Management of refeeding syndrome in critically ill children.

Table 6.10 Recommended electrolyte supplementation in refeeding syndrome (NB adjust in case of renal insufficiency) [169].

Electrolyte	Serum level	Proposed supplementation	Frequency of testing
Phosphate	• For those children at risk of refeeding syndrome a phosphate of <0.8 mmol/L before initiating feeds should be corrected to within normal range on the day of admission		
	Mild to moderate 0.3–0.8 mmol/L	15–30 mmol/day IV or oral	Every 12 hours
	Severe <0.3 mmol/L (*with a rapid drop (>0.3 mmol/L/day) or life-threatening hypophosphataemia*)	0.25–1.0 mmol/kg over 8–12 hours IV 4.5 mmol/hour for 3 hours IV followed by 2.0–3.5 mmol/hour IV with a maximum of 90 mmol/day + frequent testing	Every 6 hours
Potassium	Mild to moderate 3.0–3.4 mmol/L	30–80 mmol/day IV or oral	Every 12 hours
	Severe <3.0 mmol/L	2–4 mmol/kg/day IV or 120–240 mmol/day IV or oral	Every 6 hours
Magnesium	Mild to moderate 0.5–0.7 mmol/L	13–34 mmol/day oral or 10–15 mmol/day IV	Every 12 hours
	Severe <0.5 mmol/L	1.5–3.0 mmol/hour IV or with very severe hypomagnesemia 4 mmol/hour IV	Every 6 hours

IV, intravenous.

omega-3 and omega-6 fatty acids (which have pro- and anti-inflammatory properties); additional arginine and/or glutamine (which become conditionally essential amino acids during increased physiological stress); and increased levels of the antioxidants selenium and β-carotene [170]. Although these enteral feeding formulas have all the ingredients to improve outcome, results in the adult population have been conflicting, as seen in a large multicentre randomised study where there have been higher mortality rates in the immunonutrition group among patients with severe sepsis or septic shock [171, 172].

There are fewer studies completed in children using immune enhancing diets. Briassoulis *et al*. [173] used an adult feed containing arginine, glutamine, omega-3 fatty acids and antioxidants (vitamin C, selenium and zinc) compared to a standard paediatric enteral feed. Mean intake after 5 days for the immune enhancing diet group was 52 ± 6 vs. 63 ± 6.3 kcal/kg in the paediatric feed group and 2.7 ± 0.4 vs. 2 ± 0.2 g/kg protein respectively. After 5 days IL-6 levels were significantly lower (11.8 ± 2.4 pg/mL vs. 38.3 ± 3.6 pg/mL $p < 0.0001$) in the immune enhancing diet group compared to the paediatric enteral feed group; IL-8 levels were significantly higher at 65.4 ± 17 vs. 21±2.5 pg/mL $p < 0.03$. There was no relationship between energy or protein intake and inflammatory mediators. There were no differences in secondary infections, duration of mechanical ventilation, length of stay or mortality rates, so although the use of an immune enhancing diet may be anti-inflammatory, this did not significantly impact on any of the outcome measures chosen.

Carcillo *et al*. [174] completed the paediatric Critical Illness Stress-induced Immune Suppression (CRISIS) comparative effectiveness trial investigating the interaction between immune enhancing nutraceuticals with intravenous (IV) metoclopramide on immune status compared to whey protein and IV saline in critically ill children In the treatment group children received enteral zinc 20 mg, an age dependent dose of selenium 40–400 µg, glutamine 0.3 g/kg and IV metoclopramide 10 mg every 12 hours. Initial analysis found no difference in the development of nosocomial infections/sepsis. A *post hoc* analysis was completed according to three categories of immune status on admission: immune competent without lymphopenia (n = 134), immune competent with lymphopenia (n = 79) and previously immunocompromised (n = 27). There was no difference in the development of nosocomial infection and sepsis in the overall population. However, there was some benefit in the immunocompromised group with fewer nosocomial infections/sepsis reported in the immune enhancing group compared to the whey group: 1.57 per 1000 days compared with 6.33 per 1000 days respectively (p = 0.01).

Jacobs *et al*. [175] considered the use of a feed enriched with γ-linoleic acid and eicosapentaenoic acid (EPA) compared to standard paediatric enteral feed. The only outcomes reported that there were significantly higher levels of plasma phospholipids of γ-linolenic acid and EPA, which would be expected.

This area of paediatric critical care nutrition is still very new and the limited evidence does not yet support routine use of immune enhancing feeds or supplementation because of possible deleterious effects. Until such data are available, specifically for CIC, the following *ad hoc* additions to feeds or future immune enhancing feeds should be used with caution.

Glutamine

Glutamine is thought to be able to alter the host response to stress [176], however, much of the work considering the use of glutamine in critical illness has been completed in adults [177–181]. Whilst initially considered to be safe and non-toxic recent studies have found that in critically ill septic adults supraphysiological levels of glutamine may increase the risk of mortality [172, 182], although a recent meta-analysis which considered the administration of glutamine dipeptide as per ESPEN (European Society of Clinical Nutrition and Metabolism) recommendations (via the parenteral route at

0.3–0.5 g/kg/day; maximum 30% of the prescribed nitrogen supply) demonstrates significant reduction in length of hospital stay, mortality and infectious complications rates [183].

Glutamine serves as a metabolic intermediate and precursor, providing carbon and nitrogen for the *de novo* synthesis of other amino acids, nucleic acids, fatty acids, nucleotides and proteins [184]. During times of stress, skeletal muscle is an active net exporter of free glutamine [37]. Glutamine's functions within the cell can be broadly classified into four main categories:

1. nitrogen transport
2. maintenance of the cellular redox state through glutathione
3. a metabolic intermediate
4. a source of energy [184].

In children, the use of glutamine remains largely undefined with paucity of data regarding the benefits of glutamine as a pharmacological agent in critical illness. Conflicting results with respect to the benefits of glutamine supplementation have been reported in preterm infants [185–190], infants with gastrointestinal disease and surgery [191, 192], burns [177, 193] and malnutrition [194–196]. Three randomised studies have been completed in CIC, two of which considered glutamine supplemented parenteral nutrition [19, 197] and one using glutamine supplemented enteral nutrition [198]. Ong *et al*. administered IV glutamine (0.4 g/kg/day), however, this study did not report any benefit with no significant difference in sepsis, however, there was a highly significant weight loss in all groups (−1.0 *z* scores to −1.3 *z* scores) suggesting that insufficient nutrients were provided to sustain growth in both study arms and this may be in part the reason for the lack of efficacy seen [199].

Jordan *et al*. investigated the effects of glutamine on heat shock protein 70 (HSP70) and inflammatory mediators in critically ill children ($n = 98$). Those children who were septic or had undergone major surgery were randomised to PN with glutamine supplementation (0.33 g/kg glutamine [= 0.5 g/kg Dipeptiven]) for a minimum of 5 days vs. standard isocaloric and isonitrogenous PN [197]. In this study glutamine supplementation upregulated the release of HSP70. These children also had significantly lower levels of IL-6, suggesting that glutamine supplementation was able to increase HSP70 release and modulate the release of pro-inflammatory mediators [197]. HSP70 is part of a family of highly conserved proteins involved in cell protection and modulation of the inflammatory response, in particular NF-κB and MAPK pathway [200, 201].

At present there is insufficient evidence to recommend the routine use of glutamine supplementation in paediatric critical illness.

Zinc

Zinc is an essential trace element which is required for the function of numerous enzymes and transcriptional factors. Zinc homeostasis maintains immune function, oxidative stress response, neurocognitive function and promotes growth and development [81]. During critical illness the expression of numerous genes either requires zinc and or has a role in regulating zinc homeostasis [202]. Critically ill children have been found to have significantly lower plasma zinc levels in the first few days of their illness which is correlated with markers of inflammation (IL-6 and CRP levels). Persistently low plasma concentrations are also associated with the severity (and number) of organ(s) dysfunction [81], increased mortality rate in septic shock [202] and pneumonia [203, 204], although the causality of this is not well understood. Yuan *et al*. [205] investigated the use of zinc supplementation in a non-blinded randomised controlled trial in critically ill infants ($n = 96$) with severe pneumonia. There was no statistical difference in lung injury score, length of hospital stay or duration of mechanical ventilation. Although zinc supplementation does not prevent infection in critically ill children, supplementation may benefit those who are found to be deficient [203, 204, 206], particularly during the recovery phase, but has not been found to be of any benefit in children who are otherwise zinc replete [204–206].

Zinc absorption occurs in the small intestine which is facilitated by zinc transporters and it is stored in the liver and kidney. Zinc is excreted from the kidney (0.5–0.8 mg/day) or is recycled back into the intestine. Zinc is vital for linear growth and is required in larger amounts during periods of nutritional rehabilitation. In severe and moderate malnutrition zinc muscle concentration is reduced from 81 to 64 mg/kg. This tissue deficit will require an additional retention of 0.57 mg/kg/day and will take approximately 30 days to replete if a child is eating a normal amount of protein in their diet [207].

Selenium

Selenium is an essential trace element with antioxidant and immunological functions. Selenium has been shown to inhibit the expression of pro-inflammatory genes, down regulating the inflammatory response. Decreased selenium levels are found in adults with systemic inflammatory response syndrome (SIRS) and multi-organ failure [208]. High doses of selenium given as an IV infusion of selenite (1000–1600 μg) has shown: to be well tolerated, significantly increasing selenium levels with resultant lower incidence of hospital acquired ventilator associated pneumonia; a reduction in infection risk; a decreased mortality in patients with severe sepsis or septic shock [209]. Selenium given enterally as a feed constituent has not been shown to be as effective, although the dose delivered was significantly lower at 300 μg [210]. There are no studies considering the efficacy of selenium in CIC.

The paediatric Critical Illness Stress-induced Immune Suppression (CRISIS) trial is currently considering the effect of an enterally administered whey protein supplemented with trace zinc, selenium and glutamine. These results are awaited with interest and may change practice in relation to glutamine, zinc and selenium supplementation [174].

Vitamin D

There are numerous reports of low vitamin D levels in critically ill children, which is associated with a greater

severity of illness [211], although the causality and the impact of vitamin D on outcomes during critical illness remain unclear [212]. Gottschlich *et al*. [213] completed a randomised controlled trial of CIC with thermal injuries ($n = 50$) aged 0.7–18.4 years, investigating the effect of vitamin D supplementation. During the acute phase the authors reported there were no significant differences in serum vitamin D levels between groups, although >10% of patients had low serum 25(OH)D levels at the point of PICU discharge. The proportion of children with vitamin D deficiency (defined as vitamin D < 30 nmol/L) increased in the group who received no vitamin D supplementation at 1-year follow up compared to those who had received D2 and D3. The prevalence of vitamin D deficiency in the groups was: no vitamin D supplementation 75%; D2 supplementation 56%; and D3 supplementation 25%. Although the study was not powered to detect changes in clinical outcomes some non-statistically significant improvements were demonstrated. A larger clinically powered randomised clinical trial is required to investigate the effect of vitamin D supplementation in CIC both during acute phase and rehabilitative phase.

McNally *et al*. [214] undertook a meta-analysis of published papers to examine and estimate prevalence of vitamin D deficiency in CIC compared to levels reported in healthy children. The average 25(OH)D levels were significantly lower in critically ill children (range 41.5–66.8 nmol/L) than in healthy children (61–99 nmol/L) with a pooled difference −17.3 nmol/L, 95% CI −14.0 to −20.6. Length of stay was evaluated in 11 studies, but only 3 published data were suitable for evaluation (1.99 days, 95% CI 0.88–3.10, $p = 0.001$). Four studies evaluated association with culture positive sepsis (pooled OR 2.02, 95% CI 1.08–3.78, $p = 0.03$). Vitamin D was associated with increased mortality (OR 1.62, 95% CI 1.11–2.36) and illness severity. Vitamin D should be supplemented with therapeutic doses in those children found to be deficient.

Probiotics

Critical illness is associated with gastrointestinal microbiome dysbiosis, with a loss of healthy commensal bifidobacteria and an overgrowth of pathogenic bacteria [215], which may in turn impact on nutrient assimilation [216]. In children there is increasing evidence that alterations in gut microbiota [217] may result in changes to the gut epithelium which may be associated with clinical outcomes in critically ill children [218].

A probiotic is a live microbial feed supplement which beneficially affects the host by improving its intestinal microbial balance [219]. Altering enteric flora is a concept gaining popularity throughout the world and the use of probiotic bacteria in PICU is developing too. Intestinal permeability is increased during critical illness particularly after burns, major trauma and sepsis. In addition, bacterial translocation has been demonstrated in patients with bowel obstruction. The administration of some probiotic strains has been associated with a reduction in bacterial translocation and intestinal inflammation [148].

In critically ill patients, the main concern remains the possibility of septicaemia related to the provision of live bacteria to patients that are relatively immunocompromised, although there are some studies showing their safety and beneficial effects in critical illness [220]. A randomised double blind placebo controlled study in CIC with severe sepsis evaluated the effect of probiotics on cytokines, duration of PICU length of day and healthcare associated costs. One hundred children with severe sepsis aged 3 months to 12 years of age were enrolled to receive VSL#3 which contains *Lactobacillus paracasei, L. plantarum, L. acidophilus, L. delbrueckii, Bifidobacterium longum, B. infantis, B. breve, Streptococcus salivarius,* maltose and silicon dioxide ($n = 50$), or a placebo of maltose and silicon dioxide ($n = 50$). Probiotics or placebo was administered in a dose of one sachet twice a day for 7 days, orally or through nasogastric/orogastric tube depending on clinical status of patients. From day 1 to day 7 the probiotic group had significantly lower levels of pro-inflammatory cytokines, IL-6, IL-12p70, IL-17 and TNFα, and higher levels of anti-inflammatory cytokines, IL-10 and transforming growth factor-β1, than the placebo group. There was a non-significant trend toward lower incidence of healthcare associated infections (14% vs. 20%) and duration of ICU stay (6.5 vs. 9 days) in the probiotic group. Mortality rates were similar in two groups. This study suggests a role for probiotics supplements in immune modulation in critically ill children. Further studies are required to confirm these results as they may be strain and geographical location dependent [221]. A recent systematic review aimed at answering the question of routine use of probiotics in CIC found that although there were positive results in some studies, routine use of probiotics cannot yet be recommended [220]. Safety also needs to be taken into account, with data pointing towards caution in extreme premature infants and those that are immunocompromised, in particular where the permeability of the gastrointestinal tract has been impaired [222].

Future Research

A number of research priorities have been identified including the: impact of malnutrition during critical illness; development of nutrition risk assessment tools and biomarkers; accurate assessment of nutritional requirements in all phases of critical illness; type and role of protein; role of immunonutrition and micronutrients; mode, type and delivery of enteral nutrition; management of feeding intolerance; role of parenteral nutrition and longer term outcomes [223].

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

7 Preterm Infants

Karen King and Lynne Radbone

Introduction

A preterm infant is one born before 37 weeks' completed gestation. An infant born <2500 g is termed low birthweight regardless of gestation, <1500 g very low birthweight (VLBW) and those <1000 g extremely low birthweight (ELBW). Categorisation of infants born smaller than expected is more contentious; however, they are often divided into small for gestational age (SGA) and/or intrauterine growth restricted (IUGR). Classification of SGA infants is usually defined as <9th centile for weight at birth (depending on the source of definition), and they constitute a heterogeneous group, i.e. those destined to be born small due to genetic influences and those who are IUGR. The former group tends to be proportionally small. Those who are IUGR will have a similarly low birthweight but may show head and/or length sparing depending on the timing of intrauterine nutrient restriction. These infants are at high risk of both perinatal and later problems [1]. This chapter will deal predominantly with the nutritional needs of preterm infants.

The early nutritional management of preterm infants may be vital to their later outcome but can be hampered by an immature or dysfunctional gastrointestinal tract and poor tolerance of parenteral and enteral nutrition.

Small term infants in general are mature with respect to oromotor function and can usually grow well if allowed breastmilk or standard infant formula *ad lib*. Only where comorbidities exist may small term infants need specialised nutritional input. It is not recommended that these infants be given any formula designed for preterm infants as there may be adverse outcomes [2, 3].

Nutritional requirements

Preterm infants have limited stores of many nutrients as accretion occurs predominantly in the last trimester of pregnancy [4]. They are born poorly equipped to withstand inadequate nutrition; theoretically, endogenous reserves in a 1000 g infant are only sufficient for 4 days if left unfed [5]. In addition, the gastrointestinal system of a preterm infant is immature; thus it is generally accepted that most infants of <30 weeks' gestation and/or weighing <1.25 kg will need some parenteral nutrition (PN), while enteral feeds are gradually increased to ensure an adequate nutritional intake. The most recent comprehensive reviews and recommendations for enteral nutritional requirements are those of Agostoni *et al*. [6] and Koletzko *et al*. [7] and for parenteral requirements are of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [8] (Table 7.1). The interested reader is advised to refer to these publications for further information.

Precise requirements for infants with a birthweight between 1800 and 2500 g are not given in these enteral feeding publications. This has led to varying interpretations of the weight cut-offs for feeding preterm formulas or fortifying breastmilk. Higher nutrient density feeds are not routinely recommended for term SGA infants, so gestational age as well as birthweight should dictate local feeding policy. In practice most infants born <2000 g and <34 completed weeks' gestation will benefit from the higher nutrient intakes recommended by Agostoni *et al*. [6] and Koletzko *et al*. [7].

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 7.1 Recommended enteral and parenteral nutrient intakes for very low birthweight infants.

Nutrient (per kg per day)	Agostoni *et al*. [6] preterm infant enteral	Koletzko *et al*. [7] preterm infant enteral	RNI (1991)* term infant enteral	ESPGHAN [8] preterm infant parenteral
Energy (kcal)	110–135	110–130	96–120**	Day 1: 45–55 Target: 90–120
Protein (g)	<1000 g: 4.0–4.5 1000–1800 g: 3.5–4.0	<1000 g: 4.0–4.5 1000–1800 g: 3.5–4.0	2.1	Day 1: 1.5 g/kg amino acids From day 2: 2.5–3.5 g/kg amino acids
Carbohydrate (g)	11.6–13.2	11.6–13.2	N/S	Day 1: 5.8–11.5 From day 2: 11.5–14.4 Maximum: 17.3
Fat (g)	4.8–6.6 (<40% MCT)	4.8–6.6	N/S	Maximum: 4.0 Minimum linoleic acid: 0.25 g
DHA (mg)	12–30	18–60	N/S	–
AA (mg)	18–42	18–45	N/S	–
Sodium (mmol)	3.0–5.0	3.0–5.0	1.9†	In stable phase >1500 g: 3.0–5.0 <1500 g: 3.0–5.0 (7.0)
Potassium (mmol)	1.6–3.3	2.0–4.9	4.2†	In stable phase >1500 g: 1.0–3.0 <1500 g: 2.0–5.0
Iron (mg)	2.0–3.0	2.0–3.0	1.3‡	2.0–2.5
Calcium (mmol)	3.0–3.5	3.0–5.0	13.1‡	In growing phase 1.6–3.5
Phosphate (mmol)	1.9–2.8	1.9–4.5	13.1‡	In growing phase 1.6–3.5
Magnesium (mmol)	8.0–15	0.3–0.6	2.2‡	0.2–0.3
Zinc (mg)	1.1–2.0	1.4–2.5	4.0‡	400–500
Selenium (μg)	5.0–10	5.0–10	0.1‡	7.0
Folic acid (μg)	35–100	35–100	50‡	56
Vitamin A (μg)	400–1000	400–1100	350‡	227–455
Vitamin D (μg/day)‡	20–25	10–25	8.5‡	5–25
Vitamin E (mg)	2.2–11	2.2–11	10‡	2.8–3.5

N/S, not specified; MCT, medium chain triglycerides; DHA, docosahexaenoic acid; AA, arachidonic acid.
Agostoni *et al*.'s recommendations are for stable growing preterm infants up to a weight of 1800 g. No recommendations are made for infants <1000 g except for protein.
Koletzko *et al*.'s recommendations presented are for fully enterally fed, growing preterm infants with a birthweight up to 1500 g.
*Reference nutrient intake (RNI) for infants aged 0–3 months [9].
**Estimated average requirement (EAR) for energy for infants aged 1–2 months [10].
†Sodium and potassium values per kg are based on weights given in [10].
‡per day, not per kg.

Interpretation of requirements

Caution must be exercised when interpreting recommendations for nutritional requirements for two reasons. First, the evidence base for nutrient requirements in preterm infants is not robust with very few randomised controlled trials (RCTs) having been undertaken, particularly in VLBW or ELBW infants. Recommendations for requirements are compiled from a variety of data sources including foetal tissue analysis, placental transfer studies, cohort studies, case reports of deficiency or toxicity, breastmilk composition and a few RCTs of controlled intake. Much of the data for infants <1000 g is extrapolated. Second, preterm infants are a heterogeneous group, and requirements are highly variable depending on post-conceptional age (inversely related), accumulated nutrient deficit (prenatally and postnatally), body composition and variations in resting energy expenditure. In addition, as with other recommendations for requirements, these are for whole populations rather than individuals.

Recommended nutrient intakes are typically greater for enterally fed compared with parenterally fed infants and greater for preterm compared with term. The following provides further information regarding certain key nutrients. Requirements refer to those via the enteral route unless specified.

Fluid

During the initial phase of adaptation to extrauterine life, fluid management is complicated, as there is a delicate balance between matching high transcutaneous losses and avoiding fluid overload due to renal immaturity (although the former should be minimised by appropriate nursing

techniques). Very sick preterm infants are often fluid restricted; therefore, nutritional intakes should always be optimised within the fluid allowed and restrictions lifted as soon as clinical condition permits. Recommendations from Agostoni *et al*. [6] suggest 135 mL/kg/day as the minimum requirement with an upper reasonable limit of 200 mL/kg/day. Between 150 and 165 mL/kg/day is likely to meet enteral requirements if an infant is fed fortified human milk or the lower end of the range if preterm formula is given.

Energy

Recommended energy intakes vary according to a baby's birthweight and postnatal age but are generally higher than term requirements [11]. There are variations in resting energy expenditure requirements between individuals with resting energy expenditure increasing over the first few weeks of life [11]. Some IUGR babies may have increased needs to facilitate catch-up growth, but this will vary between individuals and can only be established by monitoring progress and adjusting intakes accordingly. Optimising body composition is essential, and excessive energy intake may lead to excessive fat deposition. However, severity of illness rather than diet appears to be most closely linked to increased abdominal adiposity [12, 13]. It is recommended that >100 kcal (420 kJ)/kg/day is generally appropriate for enteral formula feeding as long as adequate protein, 3.0–3.6 g/100 kcal (420 kJ), is provided [6]. There are currently only three preterm formulas that meet this requirement: Nutriprem 1, Hydrolysed Nutriprem and SMA Gold Prem 1. Monitoring linear growth as a proxy for lean mass accretion is recommended.

Protein

Current recommendations for protein are significantly higher in the preterm infant than that of the term infant, due in part to increased demand for growth secondary to early delivery and relatively poor nutritional stores. In some of the sicker infants, there may be an accumulated nutrient deficit due to an inability to provide full requirements during acute episodes of illness and periods of fluid restriction. Table 7.2 shows the suggested upper limit of feed volumes to provide 4–4.5 g/kg/day protein.

The benefits of early provision of amino acids (AA) in parenterally fed preterm infants are well accepted. A staged approach is recommended by many authors [8, 14, 15] with guidance from ESPGHAN recommending starting with a minimum of 1.5 g/kg AA on day 1, increasing up to 2.5 g/kg and then a maximum of 3.5 g/kg from day 2 [8].

Fat

Fat absorption can vary between individuals, but the more immature the infant, the higher the risk of malabsorption due to low bile salt pools [16] and reduced pancreatic lipase levels [17]. Despite this, the fat component of both enteral and parenteral nutrition is crucial to attain the high energy requirements of preterm infants and to provide essential fatty acids. Feeding with non-heat-treated breastmilk has the advantage of preserving endogenous lipase (bile salt-stimulated lipase) activity, which ensures optimum fat absorption [18].

Table 7.2 Suggested upper limit of enteral feed volumes to provide 4–4.5 g/kg protein.

	Suggested maximum fluid volume (mL/kg)	Energy (kcal (kJ)/kg)	Protein (g/kg)
SMA Gold Prem 1	150	120 (500)	4.35
Nutriprem 1	165	132 (550)	4.29
Hydrolysed Nutriprem	165	132 (550)	4.29
Breastmilk with SMA Breast Milk Fortifier*	150	129 (540)	4.11
Breastmilk with Nutriprem Human Milk Fortifier*	180	151 (630)	4.32

*Using mature breastmilk.

For many years studies have investigated the theory that enteral medium chain triglycerides (MCT) lead to improved fat absorption. However, a systematic review found no consistent advantage [19]. Agostoni *et al*. [6] recommend that fat in the form of MCT should not exceed 40% of the total fat content of preterm formulas. Preterm formulas currently contain: SMA Gold Prem 1, 40% fat as MCT; Nutriprem 1, 10% fat as MCT; and Hydrolysed Nutriprem, 8% fat as MCT.

It has been recommended that the long chain polyunsaturated (LCP) derivatives of linoleic and α-linolenic acids, namely, arachidonic and docosahexaenoic acids, be provided in the diet of preterm infants [6]. However, controversy remains concerning their role, with recent reviews concluding that there were few significant benefits although no evidence of harm [19, 20]. Outcomes with respect to neurodevelopment have been inconsistent [21], which may be due to genetic variations between individuals in their ability to manufacture LCP from precursors [22]. There also appears to be risk of greater adiposity and higher blood pressure for preterm girls supplemented with LCP [23]. Conversely, research suggests that girls may show positive effects of LCP supplementation with respect to neurodevelopment [24]. Conclusions are made difficult by the heterogeneity of studies and the fact they also generally include only mature and healthy preterm infants. Despite this, all current preterm formulas are supplemented with LCP.

Enteral requirements for fat are in the range 4.8–6.6 g/kg/day [6]. Parenteral lipids should be started on day 1 of life [8], building up to a maximum of 3.5–4.0 g/kg/day of lipid [8, 14], although some extremely premature or very low birthweight infants may develop hypertriglyceridaemia; therefore, close monitoring is required. Recommendations from ESPGHAN suggest that the use of pure soya bean oil lipid emulsions should only be for the initial few days of PN and that infants who will be on PN longer than this should be given a third-generation mixed lipid source [8]. Preterm infants, particularly those born VLBW and ELBW, will

develop essential fatty acid deficiency very rapidly without an exogenous supply. This can be obtained from as little as 0.5 g/kg/day from soya bean emulsions and 1.5 g/kg/day from third-generation mixed lipid sources.

Carbohydrate

Lactase activity is present from 10 to 12 weeks' gestation and approaches levels expected at term at 36 weeks' gestation. Exposure to lactose may help to induce intestinal lactase activity. In practice, lactose malabsorption is rarely seen in the preterm infant.

A large range of oligosaccharides are present in breastmilk, with the highest concentration in colostrum and decreasing with the duration of lactation. They may help to protect against gastrointestinal problems, both by encouraging growth of a beneficial intestinal flora and by inhibiting binding of pathogens. They may improve feed tolerance and reduce stool viscosity [25]; however, a review by ESPGHAN states that more research is required before firm conclusions about their benefits can be drawn [26]. Oligosaccharides are currently added to Nutriprem 1 and Nutriprem 2 feeds.

Carbohydrate recommendations in PN are based upon the provision of a safe lower limit to prevent hypoglycaemia and the provision of an appropriate protein–energy ratio to facilitate protein accretion. Carbohydrate in the form of dextrose should be started at 5.8–11.5 g/kg/day on day 1, increasing to an upper range of 11.5–14.4 g/kg/day over a couple of days from day 2 [8]. Tolerance to carbohydrate load should be closely monitored especially in the sick or preterm infant.

Calcium, phosphorus and vitamin D

The homeostasis of calcium, phosphorus and magnesium is fundamental to the development of bone, and this in turn is regulated by factors including hormones and vitamin D. Metabolic bone disease of prematurity is a recognised comorbidity. Causes include an inadequate supply of nutrients (calcium, phosphorus, vitamin D), prolonged PN, immobilisation and medications. Immobilisation stimulates bone reabsorption, while steroids (which are occasionally used in the treatment of chronic lung disease [CLD]) reduce calcium absorption, increase urinary losses and have a direct effect on bone. Diuretics and methylxanthines such as caffeine, used to optimise respiratory status, increase renal calcium excretion. Premature infants are also born with poor reserves of calcium, phosphorus and vitamin D and have a high requirement in order to optimise bone mineralisation. Infants born IUGR or SGA are also more likely to show signs of osteopenia due to poor placental supply.

The recommendations provided by Agostoni *et al*. [6] for calcium and phosphate are similar to previous recommendations; however, vitamin D recommendations from Agostoni *et al*. are significantly higher. They argue that since the prevalence of maternal vitamin D deficiency is high, supplementation with 800–1000 IU (20–25 µg) per day is required to achieve optimal serum levels of 25-hydroxyvitamin D. There is no evidence that this higher amount of vitamin D is beneficial, and there is some evidence that these higher levels will be excessive for some infants [27]. However, babies of mothers with documented vitamin D deficiency will benefit from the higher levels as the placental supply will have been compromised. This will need to be given as a supplement as current breastmilk fortifiers (BMFs) and preterm formulas do not contain sufficient vitamin D to match this recommendation. The ratio between calcium and phosphorus is also important for adequate bone mineralisation, and Agostoni *et al*. recommend an enteral Ca–P ratio of 1.5–2.0.

In PN solutions, stability of these nutrients is a limiting factor as calcium and phosphate can bind and precipitate, although the use of organic phosphate salts has led to improved solubility and allows greater amounts to be given. The ideal Ca–P ratio should be in the region of 1:1 in PN solutions [8].

Iron

At birth there is an abrupt reduction in erythropoiesis, leading to early anaemia of prematurity, which is unresponsive to iron supplementation. Preterm iron stores are low, and infants may also lose significant volumes of blood through phlebotomy; however this may be reduced in cases where delayed cord clamping has occurred [28]. Iron in excess is toxic, and, therefore, supplementation needs to be carefully weighed up against potential overload. Infants receiving regular blood transfusions may benefit from delayed iron supplementation.

Preterm infants will become iron deplete by 8 weeks without supplementation [29]. Current recommendations are that supplements should commence between 2 and 8 weeks of age as either a supplemented formula or medicinal iron at a dose of 2–3 mg/kg/day [6]. These recommendations can easily be met by adequate volumes of currently available preterm infant formulas and SMA Breast Milk Fortifier. Nutriprem Human Breast Milk Fortifier and PN solutions do not provide iron, and, therefore, supplementation will be required if these are used.

Conditionally essential nutrients

Beta-carotene, nucleotides and inositol are present in human milk and are often added to preterm infant formulas and BMFs; however, there is currently no evidence of benefit in the preterm population.

Learning points: nutritional requirements

- *Preterm infants are those born before 37 weeks' completed gestation*
- *Accretion of nutrients occurs in the last trimester of pregnancy, and as a result preterm infants are often born with limited stores of key nutrients*
- *Preterm infants born weighing <2000 g and <34 weeks' gestation will benefit from higher nutrient intakes, as recommended in published guidelines*

Parenteral nutrition

PN has become the cornerstone of neonatal nutritional care in the very preterm infant, without which many infants would not survive. PN is required when adequate nutrients to sustain growth and development cannot be provided via the enteral route. PN should, therefore, be given to all infants with [14]:

- gestational age <30 weeks' completed gestation
- birthweight <1.25 kg
- failure to establish enteral nutrition (e.g. 100 mL/kg) by day 5 of life regardless of gestation or birthweight
- inability to tolerate enteral nutrition for a period likely to result in a significant nutritional deficit

PN can be started safely and effectively within the first 24 hours after birth in the preterm infant [8, 14, 30]. The aqueous AA solutions used are the same as those for term infants and have an AA profile based on either breastmilk or cord blood. PN solutions for preterm infants have improved in recent years, and there are now standardised formulations available that meet the specific needs of the majority of preterm infants. An example of a build-up regimen for PN using standard bags can be seen in Table 7.3.

Monitoring

Monitoring PN administration in preterm infants is imperative. A suggested guide for frequency of monitoring is given in Table 7.4 [14]. More frequent monitoring may be required according to the clinical condition of the infant.

Parenteral nutrition-related complications

Some of the smallest and sickest infants tolerate PN the least, while they also have the greatest nutritional needs; managing the complications of PN administration while optimising nutrition is, therefore, a significant challenge in this patient group.

Hyperglycaemia

Hyperglycaemia is common in small preterm infants and results from impaired glucose homeostasis and may be aggravated by carbohydrate provision from PN solutions or additional glucose in the form of intravenous drugs and flushes not being included in the total carbohydrate calculation. Often it is temporary, lasting only a few days, but it can significantly affect total energy provision if the glucose infusion rate or lipid rate (which can increase insulin resistance) is lowered for a period of time. Early AA infusion alongside glucose is associated with a lower incidence of hyperglycaemia [31]. Insulin can be used in these cases in order to protect nutrient provision, but glucose infusions >12 mg/kg/min should be avoided in very preterm infants as this may lead to excessive fat deposition in the liver [8].

Table 7.3 Example parenteral feeding regimen for a preterm infant using standardised PN bags.

Nutrient (per kg per day)	Day 1		Day 2		Day 3, fluid limited		Day 3, standard PN
	60 mL/kg/day		90 mL/kg/day		120 mL/kg/day		150 mL/kg/day
Volume of PN	Conc bag Aqueous vol: 50 Lipid vol: 10	Standard bag Aqueous vol: 55 Lipid vol: 5	Conc bag Aqueous vol: 80 Lipid vol: 10	Standard bag Aqueous vol: 80 Lipid vol: 10	Conc bag Aqueous vol: 100 Lipid vol: 20	Standard bag Aqueous vol: 105 Lipid vol: 15	Standard bag Aqueous vol: 130 Lipid vol: 20
Protein (g)	1.6	1.3	2.5	1.9	3.1	2.5	3.1
Nitrogen (g)	0.3	0.2	0.4	0.3	0.5	0.4	0.5
Glucose (g)	7.3	6.1	11.6	8.8	14.5	11.6	14.3
Lipid (g)	1.8	0.9	1.8	1.8	3.6	2.7	3.6
Sodium (mmol)	2.0	1.7	3.1	2.4	3.9	3.2	3.9
Potassium (mmol)	1.2	1.0	1.9	1.5	2.4	2.0	2.5
Phosphate (mmol)	1.0	0.8	1.6	1.2	2.0	1.6	2.0
Calcium (mmol)	0.9	0.7	1.4	1.0	1.7	1.4	1.7
Magnesium (mmol)	0.11	0.1	0.19	0.15	0.24	0.2	0.25
Solivito	1.0 mL/kg/day		1.0 mL/kg/day		1.0 mL/kg/day		1.0 mL/kg/day
Vitalipid infant	4.0 mL/kg/day		4.0 mL/kg/day		4.0 mL/kg/day		4.0 mL/kg/day
Peditrace	1.0 mL/kg/day		1.0 mL/kg/day		1.0 mL/kg/day		1.0 mL/kg/day
Total energy (kcal (kJ)/kg/day)	53.6 (224)	38.6 (161)	74.4 (311)	60.8 (254)	106.4 (445)	83.4 (345)	105.6 (441)

PN, parenteral nutrition; Conc, concentrated; vol, volume.

Table 7.4 Guide for biochemical monitoring on parenteral nutrition [14].

	Urea, creatinine and electrolytes	Liver function tests	Calcium and phosphate	Magnesium	Triglycerides	Glucose	Trace elements (selenium, zinc, copper, manganese) Fat-soluble vitamins (A, D, E)
First week of PN or unstable infant	Daily (or twice weekly depending on clinical status)	Daily (or twice weekly depending on clinical status)	Daily	Twice weekly	Twice weekly	Urine: 6 hourly Blood: 6–8 hourly	–
Stable PN*	Twice weekly	Weekly	Twice weekly	Twice weekly	Twice weekly	Urine: daily Blood: daily	Monthly once on PN >3 weeks

PN, parenteral nutrition.
*For very stable babies on long-term PN, all biochemical monitoring may be reduced to once weekly or less at the discretion of clinical staff.

Hypertriglyceridaemia

ELBW, SGA and septic infants have lower lipoprotein lipase activity and therefore struggle with lipid clearance, often leading to hypertriglyceridaemia. The significance of this is unclear, but based on the limited evidence, available recommendations suggest that triglyceride levels >265 mg/dL (3.0 mmol/L) should be avoided [8]. Reducing, rather than stopping, lipid infusions is advised in order to prevent essential fatty acid deficiency [32].

Weaning off PN

Once infants are tolerating adequate volumes of enteral nutrition, PN can start to be reduced. PN weaning should occur proportionally to support optimal protein–energy ratios. The rate of PN weaning will be dependent on local feeding policy and vary in speed depending upon the clinical stability of the infant. It is widely agreed that PN can be stopped once infants are on an adequate amount of enteral feeds, typically >120 mL/kg [14].

Parenteral nutrition-associated liver disease

Preterm infants are particularly vulnerable to intestinal failure-associated liver disease (IFALD) due to functional and anatomical immaturity of the liver. IFALD development is associated with increased length of time on PN, sepsis, lack of enteral feeding, overfeeding and low birthweight [33]. Practices that may limit its severity or development include:

- limiting carbohydrate infusion to <17.3 g/kg/day
- introducing and maintaining at least minimal enteral nutrition
- alternative lipid emulsions

There is currently some evidence to suggest that the type of lipid emulsion used may play a role in the development of IFALD. Lipid emulsions containing ω3 LCP, such as SMOFlipid (soya, MCT, olive and fish oils), have been developed, and small studies suggest that they may be of benefit in ameliorating the development of IFALD or even the reversal of cholestasis seen in long-term PN use in children [34]; however, further research is required in this area [35]. Evidence for using SMOF in preterm infants is limited but has been demonstrated to be safe in the short term and to improve serum fatty acid levels [36].

Significant IFALD leads to reduced bile flow resulting in fat malabsorption and poor weight gain. Enteral formulas containing MCT may be of benefit. SMA Gold Prem 1 meets the needs of the preterm infant and contains 40% MCT so, therefore, can be used first line when a formula is required for a preterm infant with conjugated jaundice. If the infant is feeding breastmilk, the use of these formulas should be clearly justified, and they need to be introduced cautiously in infants at high risk of necrotising enterocolitis (NEC) (p. 109). Maintaining a proportion of the enteral nutrition (25%–30%) as breastmilk may help with tolerance and deliver the immunological benefits of breastmilk over formula. In units where SMA Gold Prem 1 is not available, then a term formula with 50% of the fat as MCT, e.g. Pepti-Junior or Pregestimil, can be used. As usual, when using a term formula for preterm infants, the fact that they will not meet the nutritional needs of the preterm infant must be acknowledged. Term formulas should, therefore, only be used strictly as clinically indicated and stopped as soon as liver function improves. In order to optimise nutritional provision for preterm infants, these formulas should ideally be concentrated up to 15%–17% to provide a more energy- and nutrient-dense feed. In the case of infants nearer to term who have conjugated jaundice and who are struggling to grow, Infatrini Peptisorb (1 kcal (4 kJ)/mL, 50% fat as MCT) can be considered. Additional supplementation of vitamins, particularly fat-soluble vitamins, minerals and iron, will be required in order to support the requirements of the preterm infant.

Prescribing practice

PN should ideally be prescribed by an experienced healthcare professional and, where feasible, a nutrition team including a neonatal dietitian, neonatal pharmacist and neonatologist [14]. Input from other professionals including specialist nutrition nurses, gastroenterologists, hepatologists and surgeons may also be helpful. The use of standardised formulations, in order to optimise nutritional provision and facilitate early initiation of PN, continues to be a growing area of practice within the UK.

Standardised bags have been shown to improve rates of early PN administration and improve nutritional intake and

costs of care [37–39]. It is recommended that standardised PN be used wherever possible [8, 14, 40], and up to 80% of preterm infants receiving PN will grow adequately on a standardised PN bag [40]. Use of standardised concentrated formulations can support unstable and fluid-restricted preterm infants. The benefits of standard bags include:

- availability from first day of life
- consistency of nutritional care
- cost
- accuracy (the end product is tested)

Learning points: parenteral nutrition

- *PN is required in all infants <30 weeks' gestation and/or <1.25 kg*
- *PN should be started within 24 hours of birth*
- *Regular biochemical monitoring is required to monitor tolerance to the PN*
- *Proportionate weaning of aqueous and lipid PN phases is required in order to ensure maintenance of the required protein-energy ratio; consideration for stopping PN can start once an infant is having at least 120 mL/kg/day of enteral feeds*
- *Preterm infants who are on long-term PN are high risk for developing IFALD*
- *Standardised PN provision is recommended for the majority of preterm infants requiring PN*

Minimal enteral feeding

Structural development of the gut *in utero* initially commences outside the body of the foetus. At 8–12 weeks' gestation, the primitive gut rotates and returns into the abdominal cavity. Villi develop from around 12 weeks' gestation and they mature from approximately 22 weeks. Functional maturation occurs somewhat later with enzymes being produced from around 8 weeks' gestation and increasing in production from around 25 weeks. Motor function also begins to develop around 25 weeks' gestation so that structure and most functions are in place around this time [41] although immature motor function is likely to be the most common cause of enteral feed intolerance in the VLBW infant.

A lack of enteral nutrition leads to the risk of gut atrophy and impairs gut development. Minimal enteral feeding (also known as 'non-nutritive feeding', 'trophic feeding' or 'gut priming') is the process by which small volumes of milk (up to 24 mL/kg/day) are provided enterally for up to 7 days to facilitate gut adaptation, rather than for nutritive gain. It is believed that these small amounts of milk can promote intestinal maturation, stimulate enteral hormones that aid gut function and prevent or reverse the mucosal changes seen during starvation [42, 43].

When to start

Preterm infants should commence enteral feeding as early as possible after birth unless there is a clinical contraindication [44]. There is increasing evidence to suggest that it is also safe to introduce feeds early in the higher risk infant [45, 46]. There is no evidence that delaying enteral feeds (>4 days) in VLBW infants reduces the risk of NEC [47] and that the severity of NEC is greatest if an infant has never received enteral feeds before diagnosis [48]. Both these factors support the practice of introducing early enteral feeds. The ADEPT trial [46] investigated the effect of enteral feeding on the development of NEC in high risk growth-restricted preterm infants with abnormal antenatal Doppler. The authors concluded that early feeding (within 24–48 hours of birth) in this group of infants led to a reduced time to full enteral feeds compared with late feeding (within 120–144 hours of birth) without an increased risk of NEC. However, it is important to note that infants with abnormal antenatal Doppler who were born at <29 weeks' gestation in this study were approximately 4 times more likely to develop NEC irrespective of whether they were fed early or late. This group of infants may, therefore, benefit from a more prolonged period of minimal enteral nutrition and slower advancement of feeds [49].

The practice of giving oropharyngeal colostrum, where small volumes of maternal colostrum are placed directly onto the inside of the infant's cheeks, should be considered in all units. Maternal colostrum produced in the first few days after birth is rich in cytokines and other immune agents that provide bacteriostatic, bactericidal, antiviral, anti-inflammatory and immunomodulatory protection against infection [50] and has been found to be protective against clinical sepsis [51]. Giving oropharyngeal colostrum has also been associated with sustained breastmilk feeding in preterm infants [52].

What to give

See Enteral nutrition (p. 103).

How to progress feeding

A recent Cochrane review [53] examining studies looking at slow (15–20 mL/kg/day) versus rapid (30–35 mL/kg/day) advancements of feeds concluded that there was no significant difference in risk of NEC but that the slow group took longer to regain birthweight to establish full enteral feeds and may have an increased risk of invasive infection. It should be noted, however, that randomisation was at the discretion of the clinician; therefore there is a possibility that only a smaller proportion of high risk infants may have been included. In practice, evidence suggests that caution should be exercised when increasing feeds in high risk infants and continual review of the literature is recommended [54]. The initiation of trophic feeding followed by cautious increases in feeds at a limit of 20 mL/kg/day is recommended in this patient group. Evidence in lower risk infants indicates increases of 30 mL/kg/day are considered safe [48, 52]. Evidence also suggests that the number of days to full enteral feeds is reduced in VLBW infants if fed 2 hourly compared with 3 hourly [55].

Enteral nutrition

Breastmilk

The freshly expressed breastmilk (EBM) from a preterm baby's own mother is considered the optimal enteral feed [56]. Much of the evidence supporting the benefits of EBM is gathered from studies other than RCTs as it is ethically inappropriate to randomise a baby not receive their mother's own milk when it is available. No RCTs were found to meet the criteria for a Cochrane review [57], and those that do exist involved randomising babies to donor breastmilk (DBM) or formula when their mothers chose not to provide breastmilk. When risk for NEC was examined separately, it was found that breastmilk in the form of DBM did have a beneficial effect over formula milk [58]. There are a large number of observational studies to support mother's own freshly EBM as the milk of choice for preterm babies. Several studies confirm association with mother's EBM and lower risk of NEC [59–62]. There may also be long-term neurodevelopmental advantages [63–66].

Breastmilk may be nutritionally adequate in many respects for babies >34 weeks' gestation when fed in sufficient volumes (up to 180–200 mL/kg/day in well infants), although iron supplements will be needed. However, in infants <34 weeks, the provision of some nutrients will be limited from the start of feeding, e.g. phosphorus, sodium and most vitamins, particularly the fat-soluble ones, or become limited after 2–3 weeks of feeding, e.g. protein, calcium and zinc. A case study to illustrate this is given in Table 7.5.

Preterm breastmilk during the first 2–3 weeks of lactation usually has higher protein levels than later on [67, 68]. Protein fortification will eventually be needed for babies <34 weeks

Table 7.5 Case study to illustrate adequacy of enteral nutrition in a preterm infant.

Baby boy, born at 27/40, birthweight 800 g (9th centile). Spontaneous rupture of membranes, maternal antenatal steroids and magnesium sulphate given.		
Day	Narrative	Nutritional intervention
1	Mother visited by member of neonatal unit staff within 6 hours of delivery and provision of her breastmilk (BM) discussed; she is happy to express Advised on breast massage and hand expressing	Parenteral nutrition (PN) started 6 hours postnatally As soon as available oropharyngeal colostrum is started
2	Mother and father have long visits to baby Mother encouraged to express after visiting	PN given at 90–120 mL/kg Trophic feeds commenced at 10–20 mL/kg
3	Meconium passed and yellow seedy stools appear Maternal milk production >20 mL at each hand expression so instruction in mechanical expression given	PN given at 120–150 mL/kg Trophic feeds not yet tolerated so continue
5	Trophic feeds now tolerated and included in total fluid volume Maternal lactation checked: 200 mL/day and increasing	PN decreased to 130 mL/kg Expressed breastmilk (EBM) 20 mL/kg EBM increases by 20 mL/kg/day
8	Enteral feed well tolerated; minimal aspirates and bowels open 1–2 times per day Parents having skin-to-skin cuddles with baby Cotside expressing encouraged	PN decreased to 70 mL/kg EBM 80 mL/kg Sodium and phosphate supplements started based on blood biochemistry results
9	Enteral feed tolerance as above	PN decreased to <50 mL/kg and lipid component stopped EBM 100 mL/kg Supplements started: multivitamin supplement containing 400 IU vitamin D and 5000 IU vitamin A and folic acid
10	Maternal lactation checked: <600 mL/day Further advice on expressing given	PN stopped EBM 120 mL/kg and building up towards 150 mL/kg
12	Maternal lactation improving with increase to 8–10 expressions per day, including at night The need for breastmilk fortifier (BMF) discussed with parents and its use explained	EBM 150 mL/kg Breastmilk fortifier started†
14	Enteral feed well tolerated; minimal aspirates and bowels open 1–2 times per day Maternal lactation now >700 mL/day Mother doing regular skin-to-skin cuddles	EBM 150 mL/kg with full-strength breastmilk fortifier Sodium supplements kept the same Multivitamin and phosphorus supplements adjusted once on full-strength breastmilk fortifier
28	Baby now 31 weeks and beginning to nuzzle at breast during skin-to-skin contact; will begin first attempts at suckling over next few weeks Mother reports largest volumes of milk expressed after skin-to-skin contact	EBM 150 mL/kg + breastmilk fortifier Sodium supplements stopped (Iron supplement written up if infant on Nutriprem Human Breast Milk Fortifier)

†Could be half strength for 24–48 hours or full strength straight away; there is no consensus.

and <1.5 kg [69]. Some units start this routinely, while others wait until there are signs that additional protein is needed, e.g. low serum urea levels [70]. A commercial multinutrient BMF has many advantages over the addition of nutrients as separate supplements, e.g. reduced risk of excessively high osmolality, reduced risk of errors in administration and reduced nursing time. Those currently available in the UK are Nutriprem Human Milk Fortifier and SMA Breast Milk Fortifier. Typical composition of a BMF is given in Table 7.6.

A systematic review concluded that BMFs promote short-term growth and that, despite lack of longer-term outcome data, it was unlikely that further trials would be carried out with an unfortified breastmilk group [71]. The BMFs available in the UK provide nutrients sufficiently close to current recommendations [6, 7]; however, Nutriprem Human Milk Fortifier does not contain iron, so a separate supplement is necessary. Table 7.7 compares fortified breastmilk with the guidelines.

Table 7.6 Typical composition of a multinutrient breastmilk fortifier.

Protein (hydrolysed)
Carbohydrate
Calcium
Phosphorus
Sodium, potassium
Fat-soluble vitamins including vitamin E
Water-soluble vitamins including folic acid
Trace elements, e.g. zinc, selenium, copper, magnesium, iodine, manganese
Iron is provided from SMA Breast Milk Fortifier, but not Nutriprem Human Milk Fortifier

There is one commercially available protein supplement for preterm infants. Nutriprem Protein Supplement is designed to be added to Nutriprem 1 or Nutriprem Human Milk Fortifier to make up the additional protein requirements for those infants <1000 g as required. It should not be added to breastmilk without the prior addition of BMF as it does not contain complete nutrition.

Concerns around increased feed osmolality and bacterial growth with the use of BMF are not supported by current evidence [69]; neither is there evidence to suggest a link with NEC [73]. One paper suggested that the use of a fortifier based on human milk protein reduces the risk of NEC; however questions over the design of this study weaken this proposal [74]. Despite the lack of evidence, it is advisable to add BMF to the minimum amount of breastmilk possible and to feed as close as possible in time to the fortifier being added in order to avoid both prolonged storage and any potential disruption of immunological components, which has not yet been quantified. All feeds should be handled and stored according to current guidelines to avoid contamination [75].

Strategies are needed to ensure that mothers of preterm babies are able to produce milk in time for their baby's first feed and, if planning to breastfeed on discharge, to provide sufficient quantities to support the volume their baby will need in the longer term [76]. Table 7.8 shows a sample checklist that can be used to ensure mothers are given appropriate

Table 7.7 Nutrients in fortified breastmilk compared with guidelines.

Nutrient per kg	100 mL/kg mature EBM*	180 mL/kg mature EBM	150 mL/kg mature EBM + SMA BMF full strength	165 mL/kg mature EBM + Nutriprem HMF full strength	Agostoni *et al.* [6]	Koletzko *et al.* [7] (enteral)
Energy (kcal)	69 (290 kJ)	124 (520 kJ)	129† (540 kJ)	139† (580 kJ)	110–135 (460–565 kJ)	110–130 (420–545 kJ)
Protein (g)	1.3	2.3	4.1	4	3.5–4.5	3.5–4.5
Sodium (mg)	15	27	78	83	69–115	69–115
Potassium (mg)	58	104	159	134	66–132	78–195
Phosphorus (mg)	15	27	89	87	60–90	60–140
Calcium (mg)	34	61	165	165	120–140	120–200
Iron (mg)	0.07	0.1	3.1	0.1	2.0–3.0	2.0–3.0
Zinc (mg)	0.3	0.5	1.9	1.5	1.1–2.0	1.4–25
Selenium (μg)	1	1.8	7	4.5	5–10	5–10
Iodine (μg)	7	13	36	30	11–55	10–55
Folic acid (μg)	5	9	68	58	35–100	35–100
Vitamin A (μg)	58	104	657	479	400–1000	400–1000
Vitamin D (μg)	0.04	0.07	6	8.3	20–25‡	10–25‡
Vitamin E (mg)	0.34	0.6	7	4.9	2.2–11	2.2–11

EBM, expressed breastmilk; BMF, breastmilk fortifier; HMF, human milk fortifier. 1 μg vitamin A = 3.33 IU. 1 μg vitamin D = 40 IU.
*Finglas *et al.* [72]. Vitamin D level taken from 5th edition.
†Does not take account of high risk of fat loss on handling.
‡Expressed as per day not per kg.

Table 7.8 Lactation and breastfeeding check list.

1. To be completed within *6 hours* of admission; during visit to mother by a staff member	Tick when achieved/ circle as appropriate	Print name and initial	Date and time
Interpreter required	Y/N		
Ask feeding intention and record here:	❑		
Discuss the importance of colostrum as first feed and breastmilk for the preterm baby with respect to the following • Reduced risk of infection • Improved development • Improved gut tolerance • Reduced risk of NEC For mother; reduced risk of breast and ovarian cancer, osteoporosis	❑		
Breastmilk expressing pack given and explained	❑		
Advise watching Small Wonders DVD films:			
Film 3. First hours	❑		
Film 4. Expressing breastmilk	❑		
Advise mother to start expressing now even if on medication (prescribed/non-prescribed/herbal) Safety concerns can be checked before milk is given to baby. Ask pharmacist if unsure	❑		
Advise on the detrimental effects of alcohol and smoking on lactation	❑		
If baby is a candidate, get verbal consent for donor breastmilk from mother. Obtained by..... (Name)	Y/N		
Is there a reason why feed at 6 hours is not appropriate in this baby? If not give feed Reason:.....	Y/N		
Is the baby likely to feed at the breast within <u>*6 hours*</u> of delivery? If yes move to section 7	Y/N		
<u>*6 hours*</u> post-delivery: Call to midwife to check mother has expressed – in this hospital or one mother is in Name of midwife discussed with.	❑		
2. Within the first 24 hours: during mother's first visit to the unit:			
Highlight hygiene practice in relation to breastmilk expressing and skin-to-skin contact including regular bathing/showering	❑		
Importance of skin-to-skin contact with baby explained and check the mother has watched the film on the Small Wonders DVD: Film 5. Holding your baby	❑		
Breast massage and hand expressing observed and breastmilk expressing log offered	❑ Log taken Y/N		
Benefits of using colostrum and breastmilk for mouth care explained	❑		
Importance of frequent milk expression explained, i.e. 8–10 times in 24 hour (including once at night between 2 am and 4 am)	❑		
Benefits of non-nutritive sucking explained (calming, maximising CPAP, sucking practice during tube feeds) (*parent leaflet on shared drive)*	❑		
If mother unable to visit the unit within 24 hours go down to visit her to complete this section or if in another hospital phone her midwife to check expression has commenced	❑		
Check mother is taking vitamin D (10 µg or 400 IU per day)	❑		

(continued overleaf)

Table 7.8 *(continued)*

3. Day 2–4			
Safe collection and storage of expressed breastmilk explained, including guide to minimise contamination	❑		
Offer mother manual pump and demonstrate use when milk comes in	❑		
Use of electric breast pump demonstrated and breastmilk expressing log reoffered	❑ Log taken Y/N		
4. Day 5			
Check that milk has come in and the volume of expressed breastmilk is increasing. If not, give support	❑		
Record volume expressed in last 24 hours here Document support given <u>if needed</u>:.....	Volume = mL		
5. Day 10			
Check that production has increased and milk is being stored in the freezer (750 mL in 24 hours is optimal). If not, give support	❑		
Record volume expressed in last 24 hours here Document support given <u>if needed</u>:.....	Volume = mL		
6. Day 14			
Discussion regarding the possible need for breastmilk fortifier to meet a preterm baby's additional requirements (see guideline)	❑ N/A		
If appropriate advice has been given and followed by the mother but milk yield is not increasing, is she taking domperidone? Date started?:.....	Y/N		
Check frequently that mother's milk supply is being maintained. If not, offer support early			
7. Stable and ready to feed			
Support the mother to watch the film on the Small Wonders DVD: Film 7. Feeding independently	❑		
Importance of mother's availability for breastfeeding and rooming in discussed with support for any potential obstacles considered?	❑		
Breastfeeding observed, baby's position and attachment has been supported and signs of milk transfer explained	❑		
Disadvantages explained reintroduction of bottles before breastfeeding is fully established (different technique, undermines confidence in breastfeeding success)	❑		
Consent for bottles given if necessary and developmentally supportive feeding demonstrated	❑		

Source: Courtesy of Imperial College Healthcare NHS Trust Division of Neonatology.

support and information at the relevant times. Another useful resource is the booklet produced by the UK-based charity for sick and preterm babies, BLISS (see the website www.bliss.org.uk for the most recent publications).

If mothers are advised to express 8–10 times per day including once at night and to fully empty the breast of all the fat-rich hindmilk, they should produce milk of sufficient energy content to preclude the need for energy supplementation. However, human milk is prone to fat loss and should be handled carefully to avoid this. If it is felt that more energy is required, it may be useful for the baby to be preferentially fed hindmilk [77].

If mother's own milk is not available or there is a delay in obtaining it, DBM is the feed of choice to initiate enteral feeding in high risk infants as it is associated with a reduced risk of NEC than formula feeds [57]. There are guidelines from the National Institute for Health and Care Excellence (NICE) for the processing and handling of donor milk in the UK [78]. All donor milk in the UK is pasteurised to ensure microbiological safety with the preservation of as many immunological

components as possible. However, pasteurisation leads to denaturation of bile salt-stimulated lipase with subsequent reduced fat absorption and, therefore, total energy provision. In order to achieve optimal growth, babies are usually graded onto preterm formula once full feed volumes are established using DBM, if mother's milk remains unavailable [79]. Although not all units have a milk bank, any baby in the UK can have access to DBM; it can be purchased from many of the established milk banks and delivered to the requesting unit. Further information is available on the UK Association for Milk Banking (UKAMB) website (www.ukamb.org).

Preterm formulas

For those babies <2000 g birthweight and <34 weeks' gestation who do not have access to human milk, either mother's own or donor, a preterm formula is the feed of choice. However, if they are at high risk of NEC, every effort should be made to secure the use of donor milk if there is no mother's own milk available. If there is no option but formula feeding, there is evidence that preterm rather than term formula reduces the risk of later poor developmental outcome, particularly in boys [79]. Where mother's milk supply is inadequate and there is low risk of NEC, preterm formula can be used to supplement the baby's requirements. It is not advisable to mix and store human milk with formula for prolonged periods, although mixing just before feeding may help tolerance of the formula [80]. Hydrolysed protein formulas have not been found to be required routinely unless there are clear clinical indications [81].

Preterm formulas are highly specialised feeds designed to meet the increased nutritional needs of preterm infants without exceeding volume tolerance; their composition is based on major published recommendations [6, 7]. Those available in the UK are Nutriprem 1 (whole protein), SMA Gold Prem 1 (partially hydrolysed protein) and Hydrolysed Nutriprem (extensively hydrolysed protein).

There is a wide variation in practice as to the age and weight at which feeding with preterm formula is stopped. A suggested range is 1800–2000 g body weight or discharge from the neonatal unit, whichever is sooner. Babies can then be considered for standard term formula or a post-discharge formula (see Post-discharge nutrition, p. 110). It is important to remember that each baby must be assessed to decide on the optimum formula and this should not be arbitrarily based on age or weight alone.

Method of enteral feeding

Due to an immature suck–swallow–breathe pattern, preterm infants usually require at least a proportion of their feed by tube until around 35 weeks' gestation, some for longer. Methods of enteral feeding differ markedly around the world [70]. There are advantages and disadvantages to both bolus and continuous gastric tube feeding with a systematic review unable to give a firm recommendation of one method over the other [82]. Bolus feeding has been associated with less feed intolerance [83] but may lead to a deterioration in respiratory function (due to gastric distension) in very compromised infants when compared with continuous feeds [84]. Continuous feeding of human milk can lead to excessive fat loss due to adherence to tubing [85] and risk of sedimentation of added minerals. There is no evidence that there is a beneficiary effect of transpyloric feeding and that there may be some evidence of harm in the preterm infant [86].

Transition to oral feeding

For some infants, particularly those who have been very unwell, the transition to oral feeding, either to breast or bottle, can be difficult [76]. Despite inherent problems there has been an increase in babies leaving the neonatal unit breastfeeding, even the most preterm, and this has been facilitated by the use of different approaches including early support for lactation, promotion of skin-to-skin contact between baby and mother and encouraging mothers to 'room in' on the unit [76]. If a mother has chosen to breastfeed, the baby can start early feeding attempts as soon as they show cues during skin-to-skin contact. However, full nutritive oral feeding is usually not attained until at least 35 weeks and later in some infants [76]. Totally demand breastfeeding may not be possible even at 35 weeks as the baby may still have immature sleep patterns and, therefore, need to be woken to ensure at least eight breastfeeds per 24 hours. Some neonatal units discharge babies on tube feeds with support to facilitate breastfeeding and weaning off the tube at home.

Babies who develop CLD or have neurological impairment, gastro-oesophageal reflux disease or other long-term health problems can find the transition to full oral feedings particularly challenging, and the input of a speech and language therapist is recommended.

Learning points: enteral nutrition

- *Minimal enteral feeding promotes intestinal maturation and stimulates enteral hormones that aid gut function*
- *Enteral feeding should start as early as possible in preterm infants*
- *Freshly expressed mother's breastmilk is the feed of choice for all preterm infants*
- *Infants <34 weeks' gestation and <1.5 kg feeding mother's EBM alone will require breastmilk fortification*
- *Preterm formulas are designed to meet the nutritional needs of the preterm infant when mother's EBM is unavailable*

Nutritional assessment

The appropriateness and adequacy of nutritional management can be assessed through both serum biochemistry and growth.

Serum biochemistry

Protein status is difficult to assess, whereas adequacy of protein intake in the short term can be approximately assessed via measurement of serum urea levels. In healthy preterm infants, after the first 2–3 weeks, serum urea is likely to fall to <1.6 mmol/L when intake of human milk protein is <3.0 g/kg/day [87]. Adequate protein intake of 3.5–4.0 g/kg/day (up to 4.5 g/kg/day in infants <1000 g) [6] will probably be indicated by maintaining serum urea levels >2.0 mmol/L. However dehydration, renal and hepatic dysfunction, sepsis, steroid therapy and insufficient non-protein energy can all raise serum urea levels despite protein intake being <3.0 g/kg/day and should be taken into account. In some circumstances therefore, it may be appropriate to increase protein intake despite there being a urea level >2.0 mmol/L.

Calcium and phosphorus are essential for bone health; phosphorus is also needed for soft tissue deposition. Serum phosphorus levels vary more than calcium levels, but both are very useful for assessing needs. It is recommended that supplements be titrated to keep serum calcium and phosphorus within normal levels. A supplement of 0.5 mmol phosphorus twice daily has been shown to be a good starting point should serum levels drop <1.8 mmol/L [88]. Alkaline phosphatase is a marker of both bone formation and reabsorption. Sudden very large increases in serum levels may indicate a fracture or be due to increasing levels of the liver isoenzyme during an acute phase reaction. Levels that gradually increase with time, but stay below the upper normal range, usually reflect bone activity during growth and are not a concern.

It is important to monitor trace elements during long-term delivery of PN (Table 7.4), e.g. manganese and copper, as they can build up to excessive levels in the liver when bile flow is reduced. During prolonged renal dysfunction, selenium and molybdenum levels may accumulate, so it may be advisable to assess these in this circumstance.

Other parameters to check are haemoglobin and sodium. Sodium depletion has been associated with poor growth [89]. Preterm babies have higher requirements for sodium than term babies due to renal immaturity whereby they are unable to conserve sodium initially and can quickly become hyponatraemic. If they are on sodium-wasting diuretics, they are also at risk of depletion due to higher renal losses.

Growth

A healthy preterm baby's growth rate rapidly responds to both poor nutrition and nutritional rehabilitation. Accurate weight measurement is essential in the neonatal unit as it gives important information about fluid balance as well as changes in body mass. Head circumference is also routinely measured as it can alert to abnormal brain growth after certain insults as well as contributing to growth monitoring. Length measurement is carried out less frequently due to the high risk of inaccurate measurements using inappropriate equipment. A simple measure is available to take the length of preterm babies, both in incubators and in cots (the Leicester Incubator Measure available from Harlow Printing). It is accurate if used according to a protocol and by two observers and has been shown to lead to minimal disturbance of the baby [90]. The value of a length measurement is that it reflects growth of the skeleton and, therefore, body mass, including lean mass as well as adipose tissue, and is not affected by fluid balance changes. It is becoming apparent that preterm babies are often more stunted than wasted by the time they are discharged from the neonatal unit, but this can only be evaluated if length measurements are routinely carried out [91, 92].

Weekly measurements of length and head circumference are sufficient to give information on growth. Weighing may be carried out daily initially while on PN and during acute episodes to estimate fluid balance; thereafter twice weekly to weekly should be sufficient to monitor growth.

These anthropometric measurements can be plotted on a growth chart for preterm babies, the UK Neonatal and Infant Close Monitoring Chart (available from Harlow Printing). This chart is based on cross-sectional data on size at different gestational ages at birth and does not necessarily represent how babies at different gestational ages should grow. There is data showing postnatal growth of babies in North America [93] that are based on a cohort of babies from 1994. Similar data from UK babies has been published [94]; there are some striking similarities with the North American cohort of 1994 with both showing an initial loss of weight and tracking along a lower centile.

All preterm babies experience a reduction in extracellular fluid that is usually demonstrated by a weight loss in the first few days after delivery, and it is debatable whether this fluid should be regained and whether an infant's weight should rapidly go back up to their birth centile or not. The perceived benefit or detriment of catch-up growth is still being debated. There is a move towards ensuring satisfactory growth early on so that less catch-up growth is needed later on. In general it is acceptable for a baby to drop 1 or 2 weight centiles in the first few days and then grow along the new centile. Babies who are born growth restricted may cross centiles upwards even when fed according to standard preterm nutritional recommendations.

Rather than considering gains in weight, length and head circumference in isolation, it is useful to look at patterns of growth on a centile chart. There will be no loss of head circumference or length *per se*, but there may be a lag phase before these consistently follow a particular centile. It is difficult to quickly establish when growth is failing unless weight, length and head circumference are all considered together as babies may show weight faltering that is mainly due to loss of fluid rather than other tissue. Where there are concerns about growth, a wide range of possible causes need to be evaluated alongside nutrition (Table 7.9).

Table 7.9 Possible causes of poor growth in preterm infants.

Causes	Remedies
Inadequate nutrient input	• Optimise volume and composition of parenteral nutrition and enteral feeding • Ensure timely breastmilk fortification
Immature digestion and absorption	• Vomiting or diarrhoea – treat root cause • When MEBM unavailable and infant having DBM, consider introduction of preterm formula or fortification of DBM in infants at low risk of NEC • No benefit has been found in the use of medium chain triglycerides
Fluid restriction	• Ensure that fluid restriction is clinically necessary and negotiate a liberalisation of fluid input as soon as feasible
Inadequate sodium replacement	• After early postnatal diuresis has occurred, monitor serum sodium levels and supplement when necessary • Monitor serum sodium levels carefully during sodium wasting diuretic therapy
Breastmilk fat	• Ensure all steps taken to avoid loss of fat on handling, e.g. avoid decanting cold breastmilk and leaving fat residues in bottles • If continuous feeding, ensure syringe tilted upwards to deliver fat first • Consider the creamatocrit technique • Consider preferential feeding of hindmilk
Postnatal steroids	• Postnatal steroids are known to arrest postnatal linear growth; therefore caution is required to not overfeed during this period • Additional energy supplements are not recommended as there is a risk of excessive adiposity • Additional protein is not recommended as baby will be catabolic and can increase urea levels • Ensure liberalisation of nutritional input after steroids are finished to allow catch-up growth
Renal/metabolic	• Excess mineral loss due to renal immaturity – monitor biochemistry and supplement accordingly • Metabolic acidosis needs prompt treatment as it interferes with protein synthesis
Inactivity	• Not currently recommended but if further evidence shows benefit and no harm try gentle, passive exercise
Suspected increase energy expenditure	
1. Respiratory or cardiac disease	• Trial of high energy density feeding, e.g. preferential hindmilk feeding for babies being tube-fed breastmilk, and/or use of high energy formulations in the near term and term infant • Ensure adequate protein–energy ratio when using energy-enhanced formulations
2. Other causes	• Ensure that the infant is kept in a thermoneutral environment • Ensure that methylxanthine (caffeine) levels are not excessive • Ensure that infant is nursed to minimise energy expenditure

MEBM, mother's expressed breastmilk; DBM, donor breastmilk; NEC, necrotising enterocolitis.

Learning points: nutritional assessment

- *Urea levels <2 mmol/L can be indicative of an inadequate protein intake*
- *Aim to maintain phosphate levels >1.8 mmol/L to support bone development*
- *Preterm infants should have regular weight measurements (daily initially and when on PN and then 2–3 times per week to monitor growth)*
- *Head circumference and length should be monitored weekly*

Feeding issues in special conditions

Necrotising enterocolitis

Concerns regarding the introduction of enteral feeds to the preterm gut relate to the risk of NEC, and this must be balanced against the risks of not feeding. NEC is a potentially life-threatening condition, predominantly affecting preterm infants, that leads to acute inflammation of the bowel. Severity can range from low-grade mucosal damage to bowel perforation. In severe cases infants present with acute abdominal distension, feed intolerance, bloody stools and sepsis. Incidence is highly variable between units, but it affects approximately 5% of preterm infants <33 weeks' gestation [95], with one in four patients requiring surgery [96]. The aetiology is multifactorial and not well understood; however, the majority of affected infants have received enteral feeds. It appears to be triggered by a combination of one or all of the following factors: prematurity, hypoxia leading to gut ischaemia, gut bacterial overgrowth, sepsis, feeding of formula milk and rapid advancement of enteral feeds.

High risks for NEC include:

- <28 weeks' gestation
- <1000 g birthweight
- IUGR (birthweight <2nd centile)
- abnormal antenatal Doppler (absent or reversed)
- circulatory redistribution leading to potentially altered blood flow to the gut, e.g. infants with hypoxic ischaemic

encephalopathy or cardiac anomaly such as patent ductus arteriosus
- congenital gastrointestinal abnormalities, e.g. gastroschisis
- unstable, ventilated and hypotensive infants
- altered gut microflora

Medically managed NEC is bowel rest and PN with slow regrading of enteral feeds, ideally onto human milk. In the most extreme cases, infants may require surgical management and gut resection, which can result in short bowel syndrome if extensive gut resections are required. Severe NEC is associated with a poor neurodevelopmental outcome and high morbidity and mortality rates in those requiring surgery [97, 98]. Standardised enteral feeding protocols appear to reduce the incidence of NEC [99]. The use of probiotics in preterm infants in the prevention of NEC has been widely reviewed [100]; however, a recent study found no clear benefit of giving probiotics for prevention of NEC and that further research is required to identify the optimal probiotic strain [101].

Feed intolerance

Feed intolerance is extremely common in the very preterm infant and may occur independently of NEC. The more immature the infant, the higher the risk of feed intolerance; SGA, birth asphyxia and morphine administration also increase the risk.

Definition of feed intolerance is difficult with signs often described as vomiting, increased abdominal girth, abdominal tenderness, absence or quality of bowel sounds and/or the presence of abnormal stool, all of which can be observed in healthy preterm infants [102]. Historically, the volume of gastric residuals and bile stained aspirates has been the main indicator for feed intolerance and, in isolation, may not be sufficient reason to withhold feeds as these should be assessed as part of the whole clinical picture. Gastric residuals alone are an unreliable marker of feed tolerance as they are impacted by many factors including the size and position of nasogastric tubes and the infant's position between feeds. Most authors would recognise gastric residuals of more than 50% of the previous feeding as being a possible marker for feed intolerance [103–107].

While feed intolerance is almost unavoidable, in some babies the risks can be reduced by giving mother's milk [108, 109], having clearly defined parameters for feeding intolerance [110] and feeding at frequent intervals.

Chronic lung disease

CLD was first described following the survival of mechanically ventilated preterm babies. It appears that this condition is now on the decline due to a number of factors including more widespread use of prenatal steroids to help accelerate maturation of the baby's lungs, postnatal surfactant administered directly into the baby's lungs to improve compliance and, more recently, more rapid transfer from mechanical intratracheal ventilation to non-invasive airway support. It is now only the most immature and compromised at birth who develop this disease.

There is evidence for some increase in energy requirements with CLD; however, this is probably restricted to babies with severe forms of the disease [111]. Most babies today have a milder form of CLD and grow well without routine energy supplementation.

Learning points: special conditions

- *NEC affects 5% of preterm infants <33 weeks corrected age*
- *The most severe form of NEC can lead to short bowel syndrome in patients who require extensive surgical resection*
- *Feed intolerance is common in preterm infants and can be reduced by feeding mother's EBM and feeding at frequent intervals*
- *Infants with severe forms of CLD may have an increased requirement for energy*

Post-discharge nutrition

Discharge criteria for preterm infants vary greatly across the UK, and this will play a role in nutrition and feeding at the time of discharge. Infants who are discharged home with a normal weight for post-conceptional age are less likely to be at nutritional risk as opposed to those infants with suboptimal weight gain, ongoing increased requirements and/or significant nutritional deficits [112].

All mothers are encouraged to continue breastfeeding for as long as they wish after discharge from hospital. Most preterm infants attain maximal oral feeding by 35–37 weeks' gestation, and, therefore, many may be discharged home before oral feeding is fully achieved [113]. It has been common practice to stop BMF in all babies once feeding fully from the breast and the feeding tube has been removed. A recent Cochrane report found no benefit for use of BMF when used for 3–4 months' post-discharge, with no effects on neurodevelopment [114]. As healthy preterm babies reach term, their feeding skills improve and mature, allowing them to take large enough volumes to satisfy energy and possibly protein needs, precluding the need for BMF.

However, there is a small group of preterm infants who will benefit from being discharged home on a BMF. Depending on how the infant is feeding at the time of discharge will dictate how this is delivered. Infants who are still being nasogastrically fed at home continue to have the BMF delivered via the tube feeds; as the nasogastric feeds decrease, the infant correspondingly takes less of the BMF, i.e. is 'weaned off' the BMF. For infants who are feeding

orally, each sachet of BMF can be dissolved in a small amount of breastmilk and given via a teat or syringe just before a breastfeed, the aim being to avoid introducing a bottle where possible and risk any interference with breastfeeding. There is an argument that BMF could be given at half the usual dose as a 'step-down' to gradually reduce the nutritional concentration, as happens when changing from a preterm formula to a nutrient-enriched post-discharge formula (NEPDF). This approach has not been investigated in clinical trials, but has been advised by various units, and anecdotally it has been found not to interfere with breastfeeding, which has been voiced as a concern [115]. BMF is currently not prescribable in the community in the UK and depends on the individual neonatal unit to supply it.

Babies who are exclusively or predominantly breastfed (with or without BMF) will need a multivitamin preparation containing vitamin D, which should continue as long as breastmilk is the main drink. An iron supplement is also needed until around 1 year of age but may be stopped earlier if there is sufficient iron in the diet. The practice of giving a single dose of iron daily throughout the first year (e.g. 5.5 mg/day) allows the baby to gradually grow out of the dose per kilogram so that when the supplement is finally stopped, it is a relatively small dose, as the diet becomes the predominant source of iron.

Some babies will leave hospital on formula feeds whether fully feeding or as a top-up to breastfeeding. There has been much discussion recently over the appropriate formula for preterm infants at the time of discharge, with a recent Cochrane review suggesting that recommendations to prescribe NEPDF are not supported by available evidence [116]. However, the cohort in this review either lacked or underrepresented the infants at highest nutritional risk and those with additional requirements at discharge, e.g. those going home on supplemental oxygen [7].

It could be surmised then that infants with good weight for post-conceptional age and nutritional status will not require an NEPDF and should be considered for discharge home on a term formula. These infants will require additional vitamins and iron supplementation until around 6 months corrected age. However, it needs to be acknowledged that there is still a cohort of preterm infants, e.g. those high risk for nutritional deficits and with increased requirements who would still benefit from a going home with an NEPDF.

The nutritional composition of NEPDF falls between preterm and term formulas. There are two brands of NEPDF available on prescription in the UK: Nutriprem 2 and SMA Gold Prem 2. These formulas are prescribable to 6 months corrected age, which may benefit those who have accrued the greatest nutritional deficit while on the neonatal unit; for others their use up to 3 months corrected age is probably sufficient [117]. Although NEPDFs are currently prescribable for low birthweight term as well as preterm infants, there is no evidence that they are of any benefit for small term infants [2]. High energy formulas designed for term infants are not recommended for preterm babies post-discharge as they have lower nutrient density per kilocalorie (kilojoule) compared with NEPDF, so as babies tend to feed to meet their energy requirements and then stop feeding once achieved, they are at risk of having a lower nutrient intake.

After NEPDF is stopped, a term formula can be used up to 12–18 months of age. Iron status should be adequately maintained without supplementation [118], although some infants with limited dietary intakes may still need extra iron. When unmodified cow's milk is given at 12–18 months instead of formula or breastmilk, the toddler should be started on Healthy Start Children's Vitamin Drops as per Department of Health guidelines (Table 1.22).

Table 7.10 Cues for weaning healthy preterm babies.

Behaviours

- Alert and appears ready for a new type of feeding
- Shows an interest in others eating
- Leans forward and opens their mouth towards a spoon or food

Positioning

- Can hold their head in a stable position
- Can be supported easily in a sitting position on a lap, bouncy or high chair
- Caution should be taken when starting to wean preterm babies who cannot be assisted to achieve the above positioning skills

Oral skills

- Has started to bring their hands to their mouth and explore fingers and/or toys with their mouth
- Is demonstrating a 'munching' or up down jaw movement when mouthing non-food items
- Can breast, bottle or cup feed efficiently
  This is desirable although some babies who are not managing milk feeds efficiently can still be tried with weaning foods.
  A specialist speech and language assessment should be initiated for such babies

Some factors have been used in the past, but are now not recommended

- That a certain target weight is reached
- Demanding feeds more frequently; this will often be due to a growth spurt and should be managed initially by offering more milk rather than starting solid foods

Some factors may only develop once weaning has begun; their absence should not prevent a baby's progression with weaning

- Managing to clear the spoon with their lips; this skill develops with experience
- Presence of teeth, as they are not essential for chewing

Weaning onto solids

Introduction of solids is not recommended before 6 months for the general population; however, these UK government guidelines are not intended for special groups such as preterm babies [119]. There is limited evidence on weaning in preterm infants. The decision of when to start weaning is

based on observing each individual baby and following their cues for readiness for weaning, as advised in the new recommendations produced by BLISS. Table 7.10 shows some suggested cues for weaning.

Although age recommendations for weaning are still mentioned in the updated guidance, less emphasis is placed upon it in order to focus parents on developmental cues rather than starting at a particular age. The recommendations now suggest 4 months corrected age as the youngest age to start weaning. This is based upon observation data from parents and healthcare professionals, supported by a recent RCT [120].

It is important to remember, though, that these recommendations are targeted towards healthy preterm infants. Those infants with ongoing needs are likely to require more individualised advice to support them through the weaning period. Once weaning has started, it should proceed according to normal guidelines with particular attention being paid to ensuring appropriate nutrient-dense foods.

Learning points: post-discharge nutrition

- *Most preterm infants will not require breastmilk fortifier or nutrient-enriched post-discharge formula at home*
- *A small proportion with ongoing raised nutritional requirements or requiring catch-up growth may benefit from a period of supervised supplementation at home*
- *Vitamin and iron supplements should continue as per hospital policy on discharge*
- *Preterm infants should commence solids once demonstrating recognised cues for readiness to wean; this is often around 4 months corrected age*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

8 Gastroenterology

Sarah Macdonald and Joanne Louise Price

Introduction

Sarah Macdonald

Gastroenterology is one of the most interesting and challenging areas in paediatric dietetics. The medical conditions encountered are diverse and require an understanding of normal gastrointestinal (GI) function before correct dietetic advice can be given.

Manipulation of feeds and diet may be the primary treatment for the underlying condition. Careful documentation and monitoring of symptoms is needed to assess the response to alterations in the feeding regimen. It is important to work closely with the child's family to ensure that the planned feeding regimen is possible for them to continue at home. Once this is established the child's caregivers need accurate explanation and written advice for discharge. It should be recognised that GI symptoms are open to exaggeration and manipulation by the patient and their family. In perplexing cases hospital admission with close monitoring of symptoms may be needed. A multidisciplinary team (MDT) approach to the management of such cases is vital [1, 2].

Nutritional requirements

Nutritional requirements vary according to the underlying disorder. Normal requirements for most nutrients will suffice for GI disorders that do not result in malabsorption, with additional energy and protein required for catch-up growth.

When malabsorption is present, requirements for all nutrients are raised to allow for stool losses particularly fluid, energy, protein and electrolytes. Most infants with a malabsorptive condition will have high to very high requirements. Table 8.1 can be used as a guide for requirements for such infants who are fed enterally and are based on actual rather than expected weight. For all the clinical conditions described, the assessment and monitoring of the child's nutritional status is paramount. Anthropometric measurements should be plotted serially on appropriate growth charts and feeding regimens adapted as needed.

In conditions resulting in malabsorption, or in those requiring a very restrictive diet, iron indices, trace elements, vitamins (particularly fat-soluble vitamins and B_{12}) and urinary sodium levels should be monitored, with additional supplements prescribed as necessary. The inflammatory response is known to affect many micronutrient levels, and it is recommended that C-reactive protein (CRP) should also be measured at the same time to assess the accuracy of the results [3].

Disorders of absorption and digestion

Acute gastroenteritis

Acute gastroenteritis (AGE) remains one of the leading causes of childhood morbidity and mortality in developing nations, with an estimated 5–18 million deaths attributed to this each year. In industrial nations the mortality rate is much lower. Infants and children are particularly vulnerable to the effects of AGE because of their greater relative fluid requirements and their susceptibility to faecal–oral agents.

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

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Table 8.1 Suggested requirements for infants with malabsorption per day.

Energy	High	120–150 kcal/kg (500–630 kJ/kg)
	Very high	150–200 kcal/kg (630–840 kJ/kg)
Protein	High	3–4 g/kg
	Very high	Maximum 6 g/kg
Sodium	High	3.0 mmol/kg
Potassium	High	2.4–4.5 mmol/kg (age dependent)
Fluid	High	180–220 mL/kg

The causative mechanisms in the GI tract are:

- increased secretion
- decreased absorption

Often these coexist to produce an increased fluid load that exceeds the colonic absorptive capacity, resulting in diarrhoea. Both viral and bacterial pathogens can affect the gut in this way. Diarrhoea and vomiting can also be due to other infections, such as urinary tract infections, food hypersensitivity or surgical causes, which should be considered on presentation.

Transport of glucose and amino acids is an active process and requires the presence of a sodium gradient across the brush border membrane maintained by the Na^+/K^+ ATPase pump. The movement of water in the gut is a passive event driven by the movement of solute. The regulation of electrolyte transport is controlled by several mediators, and inhibition of these pathways results in poor absorption and active chloride secretion into the gut.

Infective diarrhoea may lead to loss of absorptive area and active secretion. The defective electrolyte and nutrient transport and functional impairment may be severe, and this situation is worsened by cycles of fasting and starvation commonly seen in infants and children with acute diarrhoea in developing countries.

AGE is defined as a decrease in stool consistency (loose or liquid) and/or an increase in the frequency of bowel actions with or without fever or vomiting. The diarrhoea should not last longer than 14 days. In Europe the incidence ranges from 0.5 to 2 episodes per child per year in children younger than 3 years, with rotavirus being the most frequent infective agent in countries that do not use routine vaccination programmes. Norovirus is considered to be the second leading agent of AGE [4].

Oral rehydration solutions

Reduced osmolality oral rehydration solutions (ORS) should be used as first-line therapy for the management of AGE. The sodium–glucose coupled transport mechanism stimulates water and electrolyte transport, and this process is preserved in acute diarrhoeal disorders. Flavoured versions of ORS are available; however, if the child cannot drink sufficiently, then a nasogastric (NG) tube should be passed to ensure that the oral ORS can be given [5].

Specific recommendations for the composition of ORS for European children were published by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 1992 [6]:

- Carbohydrate should be present as either glucose or glucose polymer at concentrations between 74 and 111 mmol/L
- ORS should contain 60 mmol/L sodium, compared with 75 mmol/L recommended by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) in developing countries, to minimise the risk of hypernatraemia
- Potassium should be added to replace stool losses
- Osmolality should be low (200–250 mOsm/kg H_2O) to ensure optimal water absorption

Table 8.2 Oral rehydration solutions (mmol/L).

	Na^+	K^+	Cl^-	CHO
Dioralyte* (Sanofi)	60	20	60	90 (glucose)
Electrolade* (Electrolade)	50	20	40	111 (glucose)
Dioralyte Relief*,† (Sanofi)	60	20	50	30 g (rice starch)
WHO formulation Oral rehydration salts	75	20	65	75 (glucose)

Flavoured preparations are not suitable for young infants.
*Reconstitute 1 sachet with 200 mL water.
†Not licensed for use in children under 3 months of age.

Systematic reviews have confirmed that this is still the best composition of ORS to use in children admitted to hospital with diarrhoea [7]. The ORS available in the UK are summarised in Table 8.2.

Feeding during acute gastroenteritis

For many years it was common practice to stop feeds during diarrhoeal episodes. It was thought that decreased lactase activity, chiefly associated with rotavirus gastroenteritis, would cause lactose malabsorption if milk feeds were introduced too early. There was also concern that food proteins could be transported across an impaired mucosal barrier and cause sensitisation [8]. As a consequence, bottle-fed infants with gastroenteritis were given ORS alone for 24 hours followed by the introduction of dilute feeds. This advice resulted in a reduced nutritional intake at a time when requirements were increased due to infection [9].

A multicentre European study showed that the complete resumption of a child's normal feeding after 4 hours of rehydration with ORS led to a significantly greater weight gain during hospitalisation and did not result in worsening or prolonged symptoms [10]. A meta-analysis showed the same outcomes [11]. This is especially important in developing countries where children may already be malnourished.

ESPGHAN recommendations for the management of AGE include fast oral rehydration with rapid reintroduction of normal feeding [4]. Formula dilution and gradual reintroduction of feeding is not indicated. Supplementing the usual

Table 8.3 Low lactose, cow's milk protein-based formulas.

Aptamil Lactose Free (Nutricia)
Enfamil O-Lac (Mead Johnson)
SMA LF (SMA Nutrition)

For lactose content see Table 29.7.

feeds with ORS (10 mL/kg/liquid stool) can prevent further dehydration. Breastfeeding should be continued at all times with supplementation of ORS. In addition to appropriate rehydration, administration of effective probiotic strains *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* reduces the length of hospital stay and may be considered in children admitted with AGE [12].

Use of lactose-free formula

A Cochrane review included 33 trials of 2973 children with AGE in high- and middle-income countries. It found that changing to lactose-free feeds in non-breastfed infants and children requiring hospital admission may reduce the duration of acute diarrhoea by 18 hours. These feeds may also reduce treatment failures by about one half [13]. Lactose-free formula should be recommended in children with chronic diarrhoea (>14 days) following AGE [5]. Lactose-free formulas have been shown to support normal growth in infancy [14]. Low lactose formulas based on cow's milk protein (CMP) are given in Table 8.3.

Learning points: acute gastroenteritis

- *Rehydration with a low osmolality ORS remains the mainstay of treatment of AGE*
- *An NG tube should be used if the child will not drink the ORS*
- *Breastfeeding should not be stopped*
- *Normal feeding should be introduced rapidly after rehydration*
- *In infants and children admitted to hospital with AGE, there is low quality evidence that the use of low lactose feeds reduces the duration of acute diarrhoea*
- *Administration of effective probiotic strains may also be considered in children requiring hospital admission with AGE*

Disaccharidase deficiencies

Deficiencies of disaccharidase enzymes can be primary in nature, due to a congenital enzyme defect, or secondary to some other GI insult. In the brush border of the small intestine, there are four disaccharidase enzymes with the highest level of activity occurring in the jejunum (Table 8.4). When a carbohydrate (CHO) intolerance is suspected, a careful diet history, which includes the timing of introduction of sugars into the diet and the onset of symptoms, can aid in the diagnosis of these disorders.

The net result of sugar malabsorption is to increase the osmotic load of GI fluid. This draws water into the small intestine and stimulates peristalsis, resulting in pain, bloating, abdominal distension and diarrhoea. The severity depends on the quantity of ingested CHO, the metabolic activity of colonic bacteria (which is reduced after antibiotic therapy) and the absorptive capacity of the colon for water and short chain fatty acids. The infant is at a disadvantage compared with the adult as the small intestine is shorter and the reserve capacity of the colon to absorb luminal fluids is reduced. Because of a faster gut transit time there is less time for alternative paths of CHO digestion to be effective.

Table 8.4 Brush border enzyme activity in the small intestine.

Enzyme	Substrate	Product
Sucrase-isomaltase (accounts for 80% maltase activity)	Sucrose α1–6 glucosidic bonds in starch molecule (approximately 25%) Isomaltose Maltose Maltotriose	Glucose Fructose
Maltase-glucoamylase (accounts for 20% maltase activity)	Maltose Maltotriose Starch	Glucose
Lactase	Lactose	Glucose Galactose
Trehelase	Trehalose	Glucose

Congenital sucrase-isomaltase deficiency

Congenital sucrase-isomaltase deficiency (CSID) is an autosomal recessively inherited disease, which is a rare, but frequently misdiagnosed cause of chronic diarrhoea in infants and children. It results in a deficiency in the ability to hydrolyse sucrose, maltose, short 1–4 linked glucose oligomers, branched (1–6 linked) α-limit dextrins and starch. The current gold standard method of diagnosis is measuring the intestinal disaccharidase activity in small bowel biopsy specimens, which show normal morphology.

Patients with CSID have different phenotypes and enzymatic activities that range from mild reduction of sucrase activity to complete absence. Isomaltase is the only enzyme to possess the α1–6 glucosidic activity needed to cleave the linkages present in the branch points of the α-limit dextrins found in high concentrations in amylopectin [15]. Although considered rare, the prevalence of CSID may have been underestimated, and it is likely that the disease remains undiagnosed in numerous patients with a history of chronic diarrhoea, some of whom are diagnosed with CSID as adults. The sucrase-isomaltase gene has been identified, and more than 25 mutations discovered, which raises the possibility of genetic screening in the future. Current estimates of the prevalence of CSID in the North American and European populations range from 1 in 500 to 1 in 2000 among non-Hispanic Caucasians [16].

Table 8.5 Low sucrose, low starch solids (<1 g per 100 g).

Protein	Meat, poultry, egg, fish
Fats	Margarine, butter, lard, vegetable oils
Vegetables	Most vegetables *except* potato, plantain, yam, sweet potato, parsnip, carrots, peas, onion, sweetcorn, beetroot, okra, beans and lentils [17]
Fruits	Initially use fruits <1 g sucrose per 100 g fruit (Table 8.6); most fruits contain negligible amounts of starch
Milk	Breastmilk, infant formula (free of glucose polymer and sucrose) Cow's milk, unsweetened natural yoghurt, cream
Others	Marmite, Bovril, vinegar, salt, pepper, herbs, spices, 1–2 teaspoons of tomato purée used in cooking, gelatine, essences and food colourings, sugar-free jelly, sugar-free drinks, fructose, glucose

Table 8.6 Sucrose content of some common fruits (per 100 g edible portion) [17].

<1 g sucrose	<3 g sucrose	<5 g sucrose
Avocado, bilberries, blackberries, blackcurrants, cherries, cooking apples, damsons, dates, gooseberries, grapes, lemons, loganberries, lychees, melon (cantaloupe, honeydew), pears, raisins, raspberries, redcurrants, rhubarb, strawberries, sultanas	Galia melon, grapefruit, kiwi fruit, passion fruit, plums, watermelon	Apples, apricots, oranges, clementines, satsumas

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While being breastfed or given a normal infant formula (where the sugar is lactose), the infant remains asymptomatic and thrives. The introduction into the diet of starch or sucrose in weaning foods or a change in formula to one containing sucrose or starch (sucrose is added to the extensively hydrolysed formula [EHF], Similac Alimentum, and starch is found in pre-thickened formulas) initiates symptoms. The clinical presentation of CSID is very variable. Chronic watery diarrhoea and faltering growth are common findings in infants and toddlers. A delay in the diagnosis may be related to the empirical institution of a low sucrose diet by parents, which controls symptoms. Some children attain relatively normal growth with chronic symptoms of intermittent diarrhoea, bloating and abdominal cramps before diagnosis. In older children such symptoms may result in the diagnosis of irritable bowel syndrome (IBS).

Treatment

In the first year of life, treatment usually requires the elimination of sucrose from the diet. Starch is excluded initially and then increased to tolerance (Table 8.5). The lactose in normal infant formula, breastmilk and mammalian milks is tolerated. Such a diet is very restrictive, and care needs to be taken to ensure an adequate energy and vitamin intake. It may be beneficial to continue an infant formula after 1 year of age. Oral nutritional supplements (ONS) (sip feeds) for older children should not be prescribed as these all contain sucrose as a sweetener. Fructose and glucose can be added to foods and low calorie drinks to provide extra energy if needed. Butter, margarine and oils can be added to savoury foods. All medications should be sucrose-free; Ketovite liquid and tablets are a suitable complete CHO-free vitamin supplement.

Once the infant or child is symptom-free, the tolerance for the excluded CHO should be tested by slowly increasing dietary intake; if the capacity to absorb CHO is exceeded, this will cause osmotic diarrhoea or a recurrence of abdominal symptoms. Reducing the CHO to the previously tolerated level will result in normal stool production. With increasing age the tolerance of starch and the lower sucrose-containing foods should improve until, by the age of 2–3 years, the restriction of starch may no longer be needed.

An international support group based in the USA tracks children with CSID and provides further information on this disorder (www.csidinfo.com). It has followed 7433 individuals and has identified 5 different phenotypes who can tolerate varying amounts of starch in the diet [18].

The sucrose content of fruits is shown in Table 8.6. Fruits containing higher amounts of sucrose can be added to the diet according to tolerance [19]. If children have problems tolerating starch in reasonable quantities, soy flour can be used in recipes to replace wheat flour as it only contains 15 g starch per 100 g compared with 75 g per 100 g in wheat flour. Parents need reassurance that occasional dietary indiscretions will not cause long-term problems.

Newly diagnosed older children should initially be advised to avoid dietary sources of sucrose only. Advice should be given about alternative sweeteners that are suitable. The following have been found to be tolerated: crystalline glucose, dextrose, corn syrup and crystalline fructose. None of the phenotypes identified by the CSID Parent Support Group could tolerate hydrogenated glucose syrup, galactose/maltose/malt sugar, acesulfame K, maltitol and brown rice syrup. If avoidance of sucrose does not lead to a prompt improvement in symptoms, then the starch content of the diet should be reduced, particularly those foods with a high amylopectin content such as wheat and potatoes. Glucose tablets may be included in the diet.

Enzyme substitution therapy

Sacrosidase, a liquid preparation containing high concentrations of yeast-derived invertase (sucrase), has been used with good results and is available, as Sucraid, on a named patient basis. It is stable if refrigerated and tasteless when

mixed with water. This formulation has been shown to be resistant to acidic pH. Degradation by intragastric pepsin is buffered by taking the enzyme with protein foods. Unlike human intestinal sucrase-isomaltase, it has no activity on oligosaccharides containing 1–6 glucosyl bonds.

A controlled, double-blind trial of sacrosidase in 14 patients with CSID consuming a sucrose-containing diet with ongoing symptoms (diarrhoea, abdominal cramps and bloating) resulted in the absence of, or less severe, problems. One other study showed that, in six patients with confirmed CSID, dietary advice resulted in little improvement in symptoms, whereas sacrosidase administration resulted in a marked improvement with no adverse events reported [20].

The recommended dose is 1 mL with each meal for patients weighing <15 kg and 2 mL for those weighing >15 kg. This allows the consumption of a more normal diet by children with CSID and decreases the high incidence of chronic GI complaints seen in this condition [21, 22]. It is suggested that the product is introduced when the child's tolerance of sucrose is known. Doses should be split, with half the dose given at the start and the other half midway through the meal, to maximise the enzyme's activity. Sucraid should not be heated, added to hot drinks or mixed with fruit juice. Data from 229 patients using Sucraid showed that 65% of patients were able to consume either a normal or mildly restricted diet. However, 27% is still needed to maintain a strict sucrose restriction with some level of starch restriction to maintain acceptable suppression of their GI symptoms. The addition of enzymes to enhance maltase and glycoamylase activity in the future may help these patients to cope with the continued problem of starch malabsorption [16].

Lactase deficiency

Congenital lactase deficiency is very rare, the largest group of patients being found in Finland. Severe diarrhoea starts during the first days of life, resulting in dehydration and malnutrition, and resolves when either breastmilk or normal formula are ceased and a lactose-free formula is given (Table 8.3).

Primary adult-type lactase deficiency is found in approximately 70% of the world's population. Lactase levels are normal during infancy but decline to about 5%–10% of the level at birth during childhood and adolescence. These population groups are common in East and South East Asia, tropical Africa and Native Americans and Australians. The age of onset of symptoms varies but is generally about 3 years or later and only if a diet containing lactose is offered. In the majority of Europeans, lactase levels remain high, and this pattern of a declining tolerance of lactose with age is not seen.

In ethnic groups with this problem, a moderate reduction of dietary lactose will be sufficient, using either lactose-reduced milks available from the supermarket or milk substitutes based on soya, oats and rice milks. It is important to ensure that children meet their requirements for calcium [23].

Secondary disaccharidase deficiency

Carbohydrate malabsorption can result from secondary damage to the GI mucosa and can present at any age. Examples include rotavirus-induced villus damage and enteropathies of assorted aetiologies. Lactase deficiency is a more common clinical problem than sucrase-isomaltase deficiency as its expression is restricted to the villi, whereas sucrase-isomaltase is expressed in the crypts of the small intestine.

Treatment

Treatment is to eliminate the offending CHO and treat the primary disorder causing the mucosal damage. Clinical course depends on the underlying disease, but studies in infants with rotavirus infections have shown an incidence of 30%–50% lactose intolerance that recovers 2–4 weeks after the infection.

Infants requiring a lactose-free formula and diet can use either lactose-free, CMP-based formula (Table 8.3) or soy formula if older than 6 months (Table 8.14). A milk-free diet (Table 8.17) is necessary although mature cheese can be included. Medications need to be checked as these can contain lactose as a bulking agent.

Learning points: disaccharidase deficiencies

- *Deficiencies of disaccharidase enzymes can be a primary problem or secondary to gut damage*
- *All are characterised by osmotic diarrhoea that stops when the offending carbohydrate is removed*
- *Dietary treatment of congenital CSID requires the elimination of sucrose (unless enzyme substitution therapy is given) and removal or reduction of all foods containing starch*
- *A primary adult-type lactase deficiency occurs from around the age of 3 years in approximately 70% on the world's population*

Lymphatic disorders

Intestinal lymphangiectasia

Intestinal lymphangiectasia is a congenital, acquired or inherited disorder characterised by dilated enteric lymphatic vessels, which rupture and leak lymphatic fluid into the gut, leading to protein loss. The presentation is variable, but diarrhoea, hypoproteinaemic oedema and decreased levels of immunoglobulins are commonly seen. Peripheral lymphoedema of the limbs is reported in 22% of cases. Failure to thrive can also be a significant problem. Children usually present in the first 2 years of life although cases diagnosed as late as 15 years of age are documented [24]. The diagnosis is definitively established by a small intestinal biopsy demonstrating the characteristic lymphatic abnormality although, as the lesion is a patchy one, negative biopsy does not exclude the diagnosis [25]. Techniques that

Table 8.7 Composition of minimal fat, cow's milk protein-based infant formulas per 100 mL.

	Dilution (%)	Energy (kcal)	Energy (kJ)	Protein (g)	CHO (g)	Fat (g)	Na (mmol)	K (mmol)	Osmolality (mOsm/kg H_2O)
Monogen (Nutricia)	16.8	75	315	2.2	11.6	2.2 (84% MCT)	1.6	1.8	235
Lipistart (Vitaflo)	15	69	277	2.1	8.3	3.1 (81% MCT)	1.7	1.9	180

allow visualisation of the small intestine, such as video capsule endoscopy or double balloon enteroscopy, may be required to diagnose this disorder [26].

Treatment

Treatment is by diet unless the lesion is localised and selective surgical excision is possible. A reduced long chain triglyceride (LCT) diet is needed to control symptoms. This reduces the volume of intestinal lymphatic fluid and the pressure within the lacteals. It has been recommended that the amount of LCT should be restricted to 5–10 g/day [25]. A very high protein intake with sufficient energy to ensure its proper utilisation is also recommended. Enteric protein loss can be monitored by measuring faecal α1-antitrypsin levels. Medium chain triglycerides (MCT) can be used as an energy source and to increase the palatability of the diet as these are absorbed directly into the portal system and not via the lymphatics. Supportive albumin infusions and, occasionally, parenteral nutrition (PN) may also be needed [27].

Papers reviewing nutritional treatments in this condition have shown that 63%–85% of paediatric cases having dietary intervention showed improvement in clinical symptoms and laboratory parameters. The exact composition of the diet in terms of fat and protein content is not reported [28, 29]. Suitable feeds in infancy and early childhood are Monogen or Lipistart (Table 8.7). If additional protein is needed to help maintain plasma albumin levels, protein supplements, such as Protifar or Renapro, can be added to a complete feed. The fat and electrolyte content of these products should be calculated in addition to the quantities supplied by the feed.

Minimal fat diet

Minimal fat weaning solids should initially be introduced and gradually expanded aiming to keep the total LCT intake <10 g/day, certainly in the first 2 years of life. Details of minimal fat diets are given elsewhere (p. 302). Attention needs to be given to protein intake, and extra very low fat, high protein foods should be included.

As the problem is lifelong, it is necessary to continue dietary restrictions, certainly until the end of the pubertal growth spurt. Maintaining such a low intake of fat becomes increasingly difficult as the child becomes older. There is no information about the degree of fat restriction required in older children, and some relaxation of the diet should be possible so long as symptoms are controlled and growth is adequate. Minimal fat or fat-free ONS such as Meritene shakes, which can be made up with skimmed milk, or PaediaSure Plus Juce, Ensure Plus Juce and Fresubin Jucy are useful to ensure adequate protein intake in older children (Table 12.5).

As the dietary restrictions are required long term, it is particularly important to ensure that the recommended amounts of essential fatty acids (EFA) are included in the diet once the volume of complete infant formula is reduced. Walnut oil provides the most concentrated source of EFA and can be given as a measured amount as a daily dietary supplement. Recommended amounts would be at least 0.1 mL per 56 kcal (235 kJ) provided from foods and drinks not supplemented with EFA (Table 30.4); however, there are no data as to how well this is absorbed in this disorder. It may be prudent to give double the normal amount of walnut oil as a divided dose mixed with food or as a medicine. This needs to be included in the daily fat allowance.

Fat-soluble vitamin supplements (A, D, E) to meet at least the reference nutrient intake (RNI) for age should be given separately. The above ONS are fortified with these vitamins, so separate supplementation may not be required if they are used. Blood levels should be monitored. A 4-year-old girl presenting with tetany caused by hypocalcaemia due to vitamin D deficiency has been described [30].

Congenital intestinal transport defects

Glucose–galactose malabsorption

This is an extremely rare congenital disorder resulting from a selective defect in the intestinal glucose and galactose/sodium co-transport system in the brush border membrane. Dietary intake of glucose, galactose, lactose, sucrose, glucose polymers and starch are all contraindicated. It presents in the neonatal period with the onset of severe watery, acidic diarrhoea, leading to rapid dehydration and metabolic acidosis. The diarrhoea can be so profuse and watery that it may be mistaken for polyuria [31]. Glucose–galactose malabsorption is a heterogeneous condition in its expression, and older children seem to have considerable variation in their tolerance of the offending carbohydrates.

Treatment

Initial intravenous (IV) rehydration is required. The use of ORS, all of which are glucose or starch based, is contraindicated. A fructose-based complete infant formula, Galactomin 19, should be introduced slowly to ensure tolerance, initially as quarter and half strength formula with IV carbohydrate and electrolyte support to avoid metabolic acidosis (Table 8.8).

Once the infant is established on feeds and gaining weight, it is important to discuss with the child's doctor a suitable

Table 8.8 Composition of Galactomin 19 per 100 mL.

	Dilution (%)	Energy (kcal)	Energy (kJ)	Protein (g)	CHO (g)	Fat (g)	Na (mmol)	K (mmol)	Osmolality (mOsm/kg H_2O)
Galactomin 19 (Nutricia)	12.9	69	288	1.9	6.4	4.0	0.9	1.6	407

protocol for oral rehydration should the child become unwell. Plain water or a 2%–4% fructose solution can be given, but this does not have the same effect on water absorption as ORS. Fructose is absorbed through the facilitative transporter, GLUT5, which is not coupled to sodium and water absorption. In severe infectious diarrhoea the infant will need IV fluids.

Fructose is available on prescription for this condition and can be used to sweeten foods for older children and as an additional energy source. It is important to ensure that all medicines are CHO-free.

First weaning solids should contain minimal amounts of starch, sucrose, lactose and glucose (Table 8.9). Manufactured baby foods are not suitable, and it is necessary for weaning solids to be prepared at home. All foods should be cooked without salt and initially blended to a very smooth texture. To save time parents can prepare foods in advance and freeze in clean ice cube trays.

With increasing age children gradually begin to tolerate more of the offending CHO due to colonic salvage. The foods in Table 8.10 are grouped to allow a gradual increase in the amount of glucose and galactose in the diet. These lists can be used as a guide by parents. Small amounts of new foods can be introduced cautiously and increased as tolerated. Too much of these foods will exceed the individual's tolerance and cause diarrhoea. In this situation the child should return to the diet previously tolerated, and food introductions tried again a few months later.

Infants and children are very dependent on Galactomin 19 to meet their energy requirements, and parents should be encouraged to continue this formula for as long as possible. It can also be useful for older children entering adolescence who find it difficult to meet their increased energy requirements from eating a low starch diet. If sufficient formula is taken, a vitamin supplement should not be needed.

Table 8.9 Foods allowed in children with glucose–galactose malabsorption (<1 g glucose and galactose per 100 g)*.

Protein	Meat, poultry, egg, fish
Fats	Margarine, butter, lard, vegetable oils
Vegetables	Ackee (canned), asparagus, bamboo shoots, beansprouts (canned only), broccoli, celery, cucumber, endive, fennel, globe artichoke, lettuce, marrow, mushrooms, spinach, spring greens, steamed tofu, watercress, preserved vine leaves
Fruits	Avocado pear, rhubarb, lemon juice
Milk substitute	Galactomin 19 formula
Others	Marmite, Bovril, vinegar, salt, pepper, herbs, spices, 1–2 teaspoons of tomato purée used in cooking, gelatine, essences and food colourings, sugar-free jelly, sugar-free drinks, fructose

*The lists of foods have been compiled calculating the amount of glucose and galactose as g starch + g glucose + g lactose + 0.5 g sucrose [17].
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Table 8.10 Glucose and galactose content of foods (per 100 g edible portion) [17].

1–2 g glucose + galactose	2–3 g glucose + galactose	3–5 g glucose + galactose
Protein Quorn, all 'hard' cheeses, cream cheese, brie, camembert		
Vegetables Aubergine, beans (French and runner), Brussels sprouts, cabbage, cauliflower, celeriac, courgettes, gherkins (pickled), leeks, okra, onions (boiled), green peppers, radish, spring onions, swede, tomatoes (including tinned), turnip	Carrots	Sugar snap peas, butternut squash, mange tout
Fruits Gooseberries, redcurrants	Apples (cooking, sweetened with fructose or artificial sweetener), blackberries, loganberries, melon (all types), pears, raspberries, strawberries	Apricots, blackcurrants, cherries, clementines, peaches, pineapple, grapefruit, nectarines, oranges, satsumas, tangerines
Other Ordinary mayonnaise (retail) – not reduced calorie	Double cream	Whipping cream

Source: Reproduced with permission of John Wiley & Sons.

Congenital chloride-losing diarrhoea

This is a selective defect in intestinal chloride transport in the small intestine and colon, which is inherited as an autosomal recessive trait. Lifelong secretory diarrhoea occurs with high chloride concentrations. It has been reported in most populations including the UK; however, it is most commonly seen in Finland, the Arabian Gulf and Poland [32].

In the past it generally resulted in severe lethal dehydration. Watery diarrhoea is present prenatally as polyhydramnios and after birth often goes unnoticed as the fluid in the nappy is thought to be urine. Dehydration occurs rapidly followed by disturbances in electrolyte concentration causing hypokalemia and hypochloraemia with mild metabolic alkalosis.

Treatment

As the intestinal defect cannot be corrected, treatment requires replacement of the diarrhoeal losses of chloride, sodium, potassium and water. The rationale behind this therapy is the normal jejunal absorption of these electrolytes. Initially this may need to be given IV, but this should gradually be changed to the oral route. Insufficient salt substitution causes chronic dehydration, salt depletion and activation of the renin–aldosterone system, which may lead to chronic kidney disease [33]. Dietary manipulation is not required in this disorder other than to ensure a normal intake for age in conjunction with the prescribed electrolyte and fluid therapy.

Congenital enteropathies and protracted diarrhoea

The causes of protracted diarrhoea in the first few months of life are mostly post-infectious and food allergic enteropathies. Rare, and usually early onset, congenital enterocyte disorders include microvillous inclusion disease (MVID) and tufting enteropathy (intestinal epithelial dysplasia) [34]. Congenital glucose–galactose malabsorption, congenital chloride-losing diarrhoea and congenital sodium-losing diarrhoea also manifest from birth, but villous morphology is normal in these babies.

Microvillous inclusion disease

MVID is a congenital enterocyte defect that requires PN for fluid and nutritional maintenance. Small bowel biopsy shows accumulation of secretory granules within the enterocytes, and electron microscopy confirms the diagnosis, showing the typical inclusions of microvilli in the cytoplasm. It does not manifest *in utero* with hydramnios (as a result of intrauterine diarrhoea), but commonly becomes apparent in the first few postnatal days. Early-onset MVID is almost invariably fatal without PN support. A later onset form of MVID has been described in a few patients who appear to have a better prognosis, with one reported case weaning off PN.

Early-onset MVID is characterised by secretory diarrhoea (typically 200–250 mL/kg/day) and intolerance of any oral nutrition. The management of the PN is difficult with the infants having very high fluid and electrolyte requirements and experiencing frequent complications of acute dehydration and metabolic imbalance. Some young children fail to tolerate any breaks in the administration of PN, necessitating this being administered over 24 hours. Trace mineral deficiencies have been reported, so it is important to carefully monitor nutritional parameters [35]. Trophic feeds should be offered so long as the resulting osmotic diarrhoea does not further complicate fluid balance. Many babies in this group have early-onset cholestatic liver disease. A case series of three infants with MVID and cholestasis showed improvement with the substitution of conventional IV lipid sources with an emulsion based on fish oil [36].

Small bowel transplantation is the only curative treatment in the early-onset form of the disease; however, the decision and timing should be carefully assessed due to recent improvements in PN management. A case series of 24 patients, detailing the complexity of managing these patients, has been published [37].

Tufting enteropathy

This is a rare autosomal recessive enteropathy of neonatal onset that presents with intractable diarrhoea, poor growth and intestinal failure. The intestinal histology shows 'tufts' of closely packed epithelial enterocytes due to poor enterocyte adhesion. Genetic associations include a mutation in the epithelial cell adhesion molecule (EpCAM) gene. There is a higher prevalence in areas with a high degree of consanguinity and in patients of Arabic origin [38].

Children with tufting enteropathy, also known as intestinal epithelial dysplasia, have a highly variable clinical phenotype. Infants require PN support, but there appears to be a range of severity in these disorders with some children becoming less dependent on, and even stopping, PN as they progress through childhood [39, 40]. The enteral management of tufting enteropathy is limited to the exclusion of major food allergens if there is concurrent inflammation in gut biopsies and additional tailored micronutrient supplements in cases weaning from PN.

Defects of lipolysis

Shwachman–Diamond syndrome

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder characterised by congenital abnormalities, exocrine pancreas dysfunction, bone marrow failure and a predisposition to myelodysplasia and leukaemia. It is a multisystem disorder with potential manifestations in the skeletal, hepatic, cardiac, immune and central nervous systems. Deficits in cognitive abilities across many domains of functioning are seen in the majority of individuals with this condition, although the extent of the problems varies [41]. The heterogenicity of presenting symptoms means that one American study of 37 children found that only 51% of patients presented with the classical picture of neutropenia associated with diarrhoea while 73% presented with failure to thrive. The median age at clinical presentation was 3.5 years [42].

Treatment

Children with SDS and pancreatic insufficiency (PI) have normal sweat chloride tests, unlike those children with cystic fibrosis (CF). Dietary treatment consists of enteric coated

pancreatic enzyme replacement therapy (PERT) (p. 219) in those with PI. This should be titrated with stool consistency, fat-soluble vitamin levels and weight gain. Due to the rarity of the condition and the lack of evidence-based treatment, a recent review concluded that medical treatment for malabsorption in SDS should aim to improve fat absorption and stool output; however, it is unclear whether this improves prognosis [43].

In the author's experience these children need less PERT per kg body weight than age-matched children with CF. It is appropriate to start with a small initial dose of 2000 units lipase/kg body weight/day distributed between feeds, meals and snacks containing protein, fat or complex carbohydrates. This can then be gradually increased as needed, but should not exceed the upper dosage guidelines for children with CF [41].

It is generally not necessary to teach families to titrate the dosage of PERT using fat exchanges. Advice to give a set PERT dosage with each meal and snack alongside suggestions to increase slightly if more fat than usual is consumed generally suffices. Unlike children with CF, pancreatic function may improve such that 50% children can stop their PERT as they get older. In most European centres faecal elastase is used as an indicator of PI, and this should be reassessed every few years.

Children with SDS are generally shorter than their peers, and it is thought that this is related to their skeletal problems. Some children do need additional nutritional support as sip or gastrostomy feeds to achieve normal weight gain and growth velocity, and a high number are recorded as requiring support for oral motor skills by specialist speech and language therapy [44].

Micronutrient levels, including trace elements and fat-soluble vitamin levels (A, D, E), should be monitored and appropriate supplements taken to correct any deficiencies. Prothrombin time can be used as a surrogate marker of vitamin K levels. It is important to ensure that fat-soluble vitamin supplements are taken at the same time as PERT to ensure optimum absorption. One study found that 16 of 21 children with SDS had low levels of vitamin A and 4 of 21 had a low vitamin E. A variable number also were also found to have deficiencies in zinc, copper and selenium possibly related to the abnormal GI histology seen in 7 of these children [44].

The long-term management of these children should be undertaken by an MDT that includes a gastroenterologist, haematologist and dietitian with appropriate referrals to dental services. Care should be individualised due to the heterogenicity of the underlying condition.

Immune Enteropathies

Joanne Louise Price

Coeliac disease

Coeliac disease (CD) is a systemic, immune-mediated disorder characterised by a variable combination of clinical manifestations, specific antibodies and enteropathy [45]. The onset of CD follows ingestion of gluten-containing grains in genetically susceptible individuals. The prevalence of CD in the UK is estimated to be 1 in 100. There are at least two prerequisites for developing CD: a genetic predisposition (associated with human leukocyte antigen [HLA] molecules DQ2 and DQ8 found in at least 98% of patients) and ingestion of gluten. More than one member of a family may be affected, and the incidence in families is increased to 1 in 10. There is considerable variation in the age of onset and in the mode of presentation, with an increasing number being diagnosed in adulthood as the disease may be atypical or clinically silent in apparently healthy individuals. Undiagnosed and, therefore, untreated CD is associated with an increased risk of long-term complications such as osteoporosis and infertility. There is also a higher incidence of non-Hodgkin's and Hodgkin's lymphoma and small bowel cancer, but overall rates are low.

Campaigns by a charity, Coeliac UK, to raise awareness of symptoms and the recommended use of screening by the National Institute for Health and Care Excellence (NICE) [45] are slowly increasing rates of diagnosis from only 15% 10 years ago [46], yet it is estimated that only 30% of people are clinically diagnosed today (Coeliac UK).

Symptoms associated with CD in children are:

- persistent non-specific GI symptoms
- iron deficiency anaemia
- other micronutrient deficiencies, e.g. B_{12} and folate
- chronic diarrhoea
- constipation
- prolonged fatigue
- weight loss
- skin rashes
- growth failure
- children present with an elevated or normal body mass index at diagnosis

Screening

In addition to children with unexplained symptoms as listed above, serological testing is recommended for asymptomatic children with a known increased risk of CD. These include those with type 1 diabetes mellitus, autoimmune thyroid disease, Down's syndrome and first-degree relatives of those with CD. This is summarised in the NICE guidelines [45].

Children should be consuming sufficient gluten in their diet at the time of testing (see gluten challenge p. 125). It should also be noted that a negative result on a serological screen at one point in time does not exclude CD for life; as it may develop later, repeat tests may be necessary.

CD is an immunological disorder mediated by T cells and local and systemic production of autoantibodies against

structural proteins of the small intestine mucosa and other organs, in association with a specific pattern of cell-mediated damage in the small intestine. CD-specific antibody tests measure IgA tissue transglutaminase (tTG) and IgA anti-endomysial antibodies (EMA) (the same antibody measured by different methods). These antibodies may not be raised in IgA deficient individuals, so IgA should always be measured at the same time, and most laboratories will incorporate this into their coeliac screen.

The gold standard for diagnosis was previously a small intestinal biopsy demonstrating mucosal damage followed by a clinical response to gluten withdrawal. New guidelines recommend that:

- symptomatic children can be diagnosed accurately without biopsy. Diagnosis based on a level of tTG-IgA 10 times or more of the upper normal limit, a positive result from the EMA tests in a second blood sample, and the presence of at least one symptom could avoid risks and costs of endoscopy [47]. Current guidance also suggests HLA testing, but this is no longer felt to be necessary and is likely to be removed from future guidance. New European guidelines for the diagnosis of CD in children can be found at www.espghan.org.
- for asymptomatic children and/or where tTG is raised on screening, but is less than 10 times the upper normal limit, a small bowel biopsy is still recommended to diagnose the condition; the histology should be interpreted using the Marsh grading system [47]

Learning points: diagnosis of coeliac disease

- *Adequate gluten must be consumed for all tests (see challenge guidance p. 125)*
- *A negative test result can change to positive over time*
- *In the UK only 30% of all those with CD are clinically diagnosed*
- *Symptomatic children can be diagnosed on blood tests alone if the markers are high enough*

Treatment

Currently the only treatment for CD is the exclusion of all dietary sources of gluten, a protein found in wheat, rye and barley and contaminated oats. Gluten can be divided into four subclasses: gliadin, glutenins, albumins and globulins. In wheat the injurious constituent is the prolamin fraction of α-gliadin. The equivalent in rye is secalin and in barley hordein. Oats is discussed in more detail (p. 123). Enzymatic degradation studies have suggested that the damaging fraction is an acidic polypeptide with a molecular weight <1500 Da.

Coeliac UK

This is an independent registered charity established over 50 years ago. All parents/caregivers of children with CD should be encouraged to join. The society acts as an invaluable resource on all aspects of management of the gluten-free (GF) diet, including topics as diverse as eating out to travelling abroad. It also produces many helpful publications such as the *Food and Drink Guide* in electronic and paper form plus a 'food checker' barcode scanner app for smart phones. Membership is free for the first 6 months and then costs £24 (£12 concessionary) per year or £42 for 2 years for the caregivers of a child with CD (www.coeliac.org.uk).

Table 8.11 Gluten-free diet.

Foods permitted	Foods to avoid	Check ingredients
Milk, butter, cream, cheese		Cheese spreads and savoury spreads, yoghurts, custard
Meat, fish, eggs, pulses	Products with pastry, thickened gravies and sauces, breadcrumbs, batter	Sausages, tinned meats
Rice, corn (maize), buckwheat, millet, tapioca, soya, gram flour, arrowroot	Wheat, rye, barley, bread, crumpets, cakes, biscuits, crackers, chapattis, nan bread, pasta, noodles, semolina, couscous	Oats
Special gluten-free flours, breads, biscuits and pasta	Wheat-based cereals, e.g. Weetabix, Shredded Wheat	Corn and rice-based cereals
Vegetables, potato, fruit and nuts	Potato croquettes	Flavoured potato crisps, dry-roasted nuts
Sugar, jam, honey, some chocolates	Liquorice	Filled chocolates, boiled sweets
Tea, coffee, drinking chocolate, fizzy drinks, juice, squash	Malted milk drinks, e.g. Horlicks and Ovaltine Barley water, beer	

Gluten-free diet

The diet should be followed for life. All possible sources of gluten including wheat, rye, barley and contaminated oats should be excluded from the GF diet (Table 8.11). This includes a number of staple foods such as bread, pasta, biscuits and cakes; parents will need support in finding suitable substitutes. Children tend to be high consumers of savoury snack foods and processed foods, which also need to be excluded and substituted. Wheat flour is commonly used in processed foods as a binding agent, filler or carrier for flavourings and spices, and these also need to be excluded and suitable GF substitutions made.

Commercially produced gluten-free foods

Many proprietary GF foods are available, and the standards for their manufacture are governed by the Codex Alimentarius Commission [48], established by the Food and Agriculture Organization of the United Nations (FAO) and the WHO to provide international food standards, guidelines and codes of practice to ensure the safety and quality of the international food trade.

Labelling

Gluten in foods can now be easily identified due to food labelling legislation (Regulation (EU) No. 78/2014), which means that all foods containing a source of gluten must be clearly labelled. These are usually highlighted, often written in bold on the ingredients list. Due to the low level of gluten deemed safe for people with CD, any food with 'may contain' statements should also be avoided. It should be noted that incorporating an allergy box on the label of manufactured foods is not compulsory and may not be reliable.

Ingredients made from a gluten-containing grain that is processed to remove all the gluten are exempt from the above labelling; however, sometimes manufacturers still state the grain source in the ingredient list. Parents should be reassured that glucose syrups derived from wheat or barley and wheat-based maltodextrins are safe to include in the GF diet.

The most recent guideline for the labelling of GF foods (EU Directive No. 828/2014, 30 July 2014, enforced July 2016) uses these Codex Alimentarius Commission definitions:

- gluten-free – 'the statement "gluten-free" may only be made where the food as sold to the final consumer contains no more than 20 mg/kg of gluten'
- very low gluten – 'the statement "very low gluten" may only be made where the food, consisting of or containing one or more ingredients made from wheat, rye, barley, oats or their crossbred varieties which have been specially processed to reduce the gluten content, contains no more than 100 mg/kg of gluten in the food as sold to the final consumer' (at the time of writing these foods are not marketed in the UK)

Oats

Oats, rye, barley and wheat are members of a subfamily of grains, the Pooideae. Based on the structure of the grains' storage proteins, this subfamily is further divided and includes the Triticeae (wheat, rye and barley) and Avinea (oats). The prolamin fraction of the storage protein contains gliadin in wheat and avenin in oats. Avenin has some sequence homology with gliadin, and recent studies suggest that some oat varieties may show a degree of residual toxicity *in vitro*, suggesting that there are differences between oat varieties in relation to their safety or toxicity for people with CD [49, 50].

Oats avenin is also present as only 5%–15% of total oat protein, as opposed to the prolamin content of wheat, rye and barley, which is as high as 50%. This suggests that there could also be a threshold of exposure to oats that needs to be exceeded before symptoms occur. Guidance for intakes in adults is based on this assumption [45, 51]. Oats are also often contaminated with wheat, rye or barley at various stages of production: in fields, transportation, storage, milling and processing.

There is a large body of evidence to support the safe use of oats in children with CD, summarised in a 2017 systematic review and meta-analysis [52]. Problems with early studies to determine the safety of oats in the diet included the use of contaminated oat products, small patient numbers, insensitive functional tests and intestinal biopsies that were difficult to interpret. However this meta-analysis contains some larger more convincing studies and a recent randomised double-blind paediatric study where 177 children (70% female, average age 9 years) completed the trial; oats that are specifically grown to be a non-reactive strain and are uncontaminated with other gluten-containing cereals appear to be safe to use in a GF diet [53].

NICE guidelines state that uncontaminated oats may be introduced into the diet at any time [45]. Coeliac UK recommends that the introduction of oats should be considered on an individual patient basis. At the time of writing, caution is still practised in many paediatric centres. The author's current practice is to advise initial avoidance of oats. Once the serum tTG level has fallen into the normal range and growth parameters are as expected, GF oats may be introduced. Coeliac UK produces a comprehensive list of uncontaminated oat products and GF oats. A repeat tTG could be offered if there are any concerns regarding symptoms after introduction of oats [45].

It should be noted that there is also additional legislation regarding food containing oats (EU Directive No. 828/2014, 30 July 2014):

- 'oats contained in a food presented as gluten-free or very low gluten must have been specially produced, prepared and/or processed in a way to avoid contamination by wheat, rye, barley, or their crossbred varieties and the gluten content of such oats cannot exceed 20 mg/kg'

Barley malt

Barley malt extract in malt vinegar is safe to consume as the amount of gluten in the end product is extremely small and is well below a level that is safe for people with CD. However, tests using a more sensitive analysis method have shown that some breakfast cereals containing malt flavourings derived from barley exceed the accepted threshold allowed by the international Codex Standard and are no longer considered suitable for inclusion in the GF diet. Foods suitable are listed in the *Food and Drink Guide* from Coeliac UK.

Codex wheat starch

GF wheat starch is known as Codex wheat starch. Prior to the reduction of gluten levels in foods considered safe for people with CD, there may have been a small number of 'supersensitive' individuals who appeared to be symptomatic when eating foods containing wheat starch. However, this was most probably as a result of the level of acceptable residual gluten previously set at 200 ppm. Since the 2012 legislation, Codex wheat starch complies with the international standard for GF foods for residual gluten content at <20 ppm. This level of gluten should no longer cause a problem for people with CD. In those reporting a reaction to products containing Codex wheat starch, a thorough dietary assessment is recommended to help identify any causative issues.

Cross-contamination

Cross-contamination is probably the biggest risk factor in ensuring provision of a GF diet. It should be explained that crumbs in toasters, bread boards, pots of butter and jam are all potential sources of significant amounts of gluten. Separate toasters, utensils and spreads should be provided for the GF diet. Where possible GF food should be regularly

prepared that is suitable for the whole family to enable everyone to eat together.

Eating out

Children should be taught to check with parents/caregivers before eating foods outside the home or when foods are offered by siblings or friends. Children's parties are a source of concern due to the buffet style table, high volume of wheat-based products and risk of cross-contamination. If GF food cannot be guaranteed, the child with CD should take suitable foods of their own to eat.

For eating out and takeaways, food outlets providing GF alternatives who comply with strict guidance are listed on the Coeliac UK website. This is an important aspect to consider in teenage years when adolescent children begin to socialise independently.

Travelling abroad

Insurance companies tend not to increase the cost of insurance for people with CD; however, it should still be declared. CD is very common in European countries, and local organisations may provide lists of hotels, restaurants and shops that supply GF foods. Coeliac UK also provides information on over 50 countries.

Taking sealed packs of GF products may not be necessary due to the excellent provision of these foods in Europe; however, if travelling further afield, it is advisable to contact the airline or tour operator before packing these items in luggage. Airlines may sometimes also give additional baggage allowance if requested, and a medical/dietetic letter in support of this should be provided if requested.

Learning points: labelling

- *Gluten-free means a gluten content of <20 g/kg (<20 ppm) in a food or drink*
- *Foods containing levels >21–100 ppm are labelled very low gluten, but this is not currently used in the UK*
- *Some foods with barley malt extract are suitable and some are not*
- *Uncontaminated oats can be introduced into the diet with caution*

Prescriptions

NHS England has published guidance for clinical commissioning groups (CCG) on the prescribing of GF foods in England [54]. This follows the Department of Health and Social Care (DHSC) recommendation to retain access to GF foods on prescription in England but to restrict these products to GF breads and flour mixes and to remove access to all other GF foods such as GF pasta and breakfast cereals. Currently in England only bread and GF mixes are routinely prescribed for those with a diagnosis of CD. Furthermore, in some CCG the type and brand of GF foods are also limited.

Dietary compliance is known to be enhanced by the ease with which patients can obtain suitable amounts of GF foods on prescription [55]. Several other staple foods remain prescribable for patients with CD; a complete list of prescribable GF foods can be found in the *British National Formulary* or in Coeliac UK's *Food and Drink Guide*. A dietitian may support and request additional items on prescription and should do so especially in exceptional circumstances, for example, where dietary intake is poor, income is low, there are multiple family members with CD or the child with growth failure may benefit from additional foods to supplement their diet. Foods will only be prescribed at the discretion of the general practitioner and within the limits of the local CCG.

Availability of GF foods that may be purchased in the UK has increased greatly over the past 10 years with most popular supermarket chains producing their own brands of GF foods. They cost more, with some specialist GF products 76%–518% more expensive than their gluten-containing counterparts [56]. Naturally GF foods should not be marketed to mislead the consumer by suggesting that the food possesses special characteristics when in fact all similar foods possess such characteristics; the dietitian can help parents identify these and avoid paying inflated prices.

Product taste and textures vary, and children should be encouraged to try different food items.

Some specialist GF food manufacturers will provide trial packs to newly diagnosed patients on application. Manufacturers' contact details can be found on the Coeliac UK website.

Learning points: prescriptions and products

- *Prescriptions are generally issued for bread and mixes only*
- *Other foods are still prescribable and may be requested in special cases*
- *Gluten-free manufactured products are expensive, and there may be naturally gluten-free alternatives available*
- *Coeliac UK resources can be used to identify naturally gluten-free products to buy*

Bone health

One of the main complications of CD in adults is reduced bone mineral density (BMD), leading to osteoporosis. It is unclear if this is due to calcium malabsorption for prolonged periods prior to diagnosis. One study found that while the bone mineral content of coeliac children was significantly lower than control subjects at diagnosis, after 1 year on a GF diet it had returned to normal. The calcium intake of the children was not assessed during this time [57]. Another longitudinal study found that, although there was an improvement after 1–2 years on the GF diet, BMD scores were still lower than expected for the normal population [58]; BMD has also been found to be lower in children with CD with poor dietary adherence [59]. Suboptimal vitamin D and K status may contribute to the increased risk of poor bone health in childhood CD, and careful consideration should be given to supplementation with these vitamins at the time of diagnosis [60]. Although there are no formal recommendations, it would appear sensible to ensure that children's intake is at least equal to the RNI for calcium for their age. Some GF products are fortified with calcium.

Gluten challenge

Gluten challenge may be necessary when there is some doubt at the time of initial diagnosis. This should always be preceded by HLA typing and assessment of mucosal histology and should be avoided in children under the age of 5 years and during the adolescent growth spurt, where possible [47]. Challenge may also be necessary when a patient has commenced a GF diet prior to a formal diagnosis.

For challenge purposes gluten can be introduced into the diet in two forms: either as gluten powder that can be mixed in foods such as yoghurt or as gluten-containing foods. Both need to be given daily in sufficient amounts for 4–6 weeks to ensure an adequate challenge [47]:

- 10 g gluten per day in young children
- 10–15 g per day in older children

Two to three grams of gluten is found in one medium slice of bread, two rusks or digestive biscuits, four tablespoons of cooked pasta or one Weetabix. Parents are often anxious that the inclusion of normal foods in the diet will make returning to the GF diet difficult if the diagnosis of CD is confirmed. Reassurance is required, and an explanation of the procedure to the child is very important in ensuring its success.

Associated food intolerances

Due to the gluten-induced enteropathy, a secondary disaccharidase deficiency may occur at the time of diagnosis. It is occasionally necessary to exclude lactose from the diet of a child newly diagnosed with CD. Infants may sometimes have an associated CMP intolerance and require a CMP-free formula (Table 8.15). This usually resolves with mucosal healing after commencement of a GF diet.

Eosinophilic Gastrointestinal Diseases

Sarah Macdonald

Eosinophils are customary inhabitants and key effector cells of the innate immune system within the GI tract. They protect against parasitic infections, the rate of these having decreased markedly in the developed world. It is thought that hypersensitivity reactions to allergens may now be the driving force for recruitment and activation of gut eosinophils. When activated they release multiple cytotoxic agents and immunomodulatory cytokines resulting in local inflammation and tissue damage [61].

Eosinophilic gastrointestinal diseases (EGID) are a heterogeneous group of diseases (eosinophilic oesophagitis [EoE], eosinophilic gastroenteritis, eosinophilic colitis) characterised by GI symptoms and increased eosinophils in the absence of other causes. Apart from EoE the diagnosis of these disorders is unclear due to the uncertainty as to the normal number of eosinophils seen in different parts of the GI tract and their distribution within the mucosa [62]. The latter may differ with geographical environment.

EGID are classified based on the location of the inflammatory response, even though their symptoms, prognosis and treatment vary considerably. In view of the close relationship between food allergies and some EGID, controlling antigen exposure is one of the most widely used strategies. In one study 80% of patients with EGID were found to have coexisting atopy, and anaphylaxis to foods was present in a significant number [63].

Eosinophilic oesophagitis

EoE is the most common and best described of the EGID and is seen in both children and adults. It is a chronic immune/antigen-mediated disease characterised clinically with symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation. There are high rates of concurrent asthma, allergic rhinitis, eczema and food allergy (FA)/anaphylaxis. It is more common in boys. Young children typically present with symptoms of gastro-oesophageal reflux disease (GORD), food refusal or growth faltering, while adolescents tend to present with dysphagia. It is a chronic, relapsing disease with only a small amount of long-term data available on which to assess outcomes. There is a complex relationship between EoE and GORD, and these disorders are not mutually exclusive and may exacerbate each other [64]. Complications include food impaction, oesophageal stricture formation and perforation. Serum immunoglobulin E (IgE) and skin prick tests for IgE-mediated FA are warranted to identify comorbid food-induced allergic disease. However, these tests alone are not sufficient to make the diagnosis of food allergy-driven EoE.

Treatment

The goals of treatment are symptom resolution and reversal of the histological abnormalities. First-line therapy is a trial of a protein pump inhibitor (PPI) followed by a second biopsy to assess histological response to this treatment and differentiation of the diagnosis between GORD and EoE. If symptoms fail to improve, then dietary therapy should be tried as sole treatment or in conjunction with topical swallowed corticosteroids (steroids that are usually inhaled but are taken orally).

Dietary therapy has been shown to be an effective treatment when assessing the histopathology of patients, and three different elimination regimens have been used:

- Complete amino acid-based formulas (AAF) have been shown to induce remission in 96% of patients, the majority of whom needed an NG tube to complete the treatment. The trial of feeds is followed by an extended

period of food reintroductions to identify specific allergens [65].
- Dietary restrictions based on allergy testing or the empirical exclusion of the most common food antigens have also been used. The former was successful in 69% of patients and is recommended as first-line therapy if allergy to specific foods is suspected by history and sensitisation supported by formal testing [66].
- An empirical six-food exclusion diet (cow's milk [CM], soy, wheat, egg, peanut, fish and seafood) has demonstrated a 74% success rate [67].

A retrospective case series of patients treated with one of these three elimination diets showed the greatest efficacy with complete AAF (elemental feeds) with 96% remission. Empirical removal of the most common allergens from the diet was as successful as a directed diet based on skin prick tests and patch testing alone (remission rates of 81% and 65%); however, the treatment chosen was not randomised and depended on negotiations with the family [68].

A recent paper has been published exploring the use of a step-up dietary regimen, where two foods were initially excluded and the symptomatic response assessed before further food exclusions was introduced. The authors suggest that such an approach may avoid unnecessary dietary restrictions, reduce the number of endoscopies required, and shorten the diagnostic process [69]. A similar result was found using computer modelling of reported studies of patients with EoE [70].

As with many dietary treatments, the optimal duration of elimination diet to achieve remission is unclear, and current recommendations suggest an 8–12-week therapeutic trial of the planned exclusion diet. It is also poorly defined which dietary intervention is associated with better mucosal healing of the oesophagus [64].

Current consensus recommendations suggest that the specific therapy prescribed should take into account the family lifestyle, adherence to therapy and resources [64]. Multiple food exclusions are difficult for the family to manage and expose the child to the dangers of dietary inadequacy. Careful monitoring is required with amino acid-based supplemental feeds or vitamin and mineral supplements prescribed as needed. Once the disease is in remission, foods should be reintroduced sequentially with careful monitoring so that only the foods the child is allergic to continue to be excluded. In one study CM was found to be the most common allergen followed by wheat, egg and soy [71].

Eosinophilic gastroenteritis

Eosinophilic gastroenteritis is a rare chronic inflammatory disorder of the GI tract characterised by eosinophil accumulation in the mucosa or in deeper layers of the GI wall. Symptoms vary according to the part of the intestine and the layer of the GI wall affected. Under healthy conditions the stomach and the small intestine show detectable baseline numbers of eosinophils, but their number is increased in eosinophilic gastroenteritis. Symptoms may include pain, dysmotility, nausea, vomiting, diarrhoea, blood loss, malabsorption, protein-losing enteropathy and faltering growth [72].

Treatment

There are no consensus guidelines on which to base therapies due to the rarity of this diagnosis and it depends on whether associated FA can be confirmed. Four-food exclusion diets (milk, egg, wheat and soya), few foods diets or exclusive elemental (amino acid-based) enteral feeds can be tried [73, 74]; however, a systematic review looking at the effectiveness of such treatments in inducing disease remission concluded that there was a lack of evidence to support their use [75]. If there is a limited response to these therapies, then medical treatment, usually with steroids, is unavoidable [76].

Learning points: eosinophilic gastrointestinal diseases

- *Controlling antigen exposure is a therapeutic strategy for children with EGID but is best described in EoE*
- *For patients with proven EoE, recommended first-line dietary therapy is an empirical elimination diet (milk, egg, wheat, soya, +/– peanuts and fish/shellfish)*
- *There is now some evidence that a step-up approach towards the use of dietary exclusions may be a more efficacious therapy in EoE. This practice has not yet been adopted in international guidelines and needs further evaluation*
- *In EoE exclusive enteral AAF as a treatment is reserved for treating children with multiple allergies, faltering growth, and severe disease where an exclusion diet has been ineffective or impossible to implement*

Food protein-induced enterocolitis syndrome

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated FA that typically presents in infancy with repetitive, protracted vomiting that starts 1–4 hours after food ingestion. The vomiting is often accompanied by lethargy and pallor and may be followed by watery or bloody diarrhoea. In at least 15% of cases, this can lead to shock with haemodynamic instability and hypotension. It occurs once CM-based or soy feeds and/or solid foods are introduced into the infant's diet.

The manifestations and severity of FPIES depend on the frequency and dose of the trigger food as well as the age and phenotype of the child. In acute FPIES, symptoms usually resolve within 24 hours after ingestion of the causative food, and most children with this disorder are well between episodes and grow normally. Chronic FPIES is rare and less well understood. It is seen in infants less than 4 months of age fed with CM or soya-based infant formula, and the affected infants have symptoms of chronic or intermittent vomiting, diarrhoea and poor weight gain [77].

The most common food allergens reported in this disorder are CM, soy, rice and oats although a wide array of other foods have been implicated. There are geographical differences in foods that trigger FPIES, with fish-induced FPIES being common in Italy and Spain, but less common elsewhere.

Local inflammation has been demonstrated on biopsy, and it is thought that this leads to increased gut permeability and fluid shifts resulting in emesis, diarrhoea and lethargy.

Diagnosis is primarily based on the clinical history with improvement after exclusion of the causative food. As FPIES is not an IgE-meditated process, specific IgE levels are not useful to identify food triggers. Diagnostic criteria for patients presenting with possible FPIES are listed in the recent international consensus guidelines by Nowak-Wegrzyn *et al*. [77].

Treatment

Acute FPIES should be considered a medical emergency with 15% of patients having hypovolaemic shock and needing aggressive fluid resuscitation and other supportive therapies. Once the child is stable, advice to ensure dietary elimination of the trigger food(s) and support for the family with introduction of new foods into the diet is required.

Infants with suspected CM or soy-induced FPIES should be advised to avoid all forms of these foods, unless baked and processed foods containing these proteins are already included in the diet and tolerated. In this instance it would be safe to continue the baked form of the food. If the infant is breastfed, this should continue, and, as the majority of infants with FPIES do not react to food proteins in human milk, maternal dietary elimination is only warranted if the infant remains symptomatic while exclusively breastfeeding. Most non-breastfed infants with this disorder will tolerate an EHF with only 10%–20% requiring an AAF.

In the majority of children, FPIES is caused by a single food, most commonly CM; however, one US centre reported 5%–10% children who reacted to more than three foods with some as many as six. Children with CM or soy-induced FPIES may react to both foods with a higher likelihood of this occurring if they developed symptoms in the first month of life. They also have an increased risk of reacting to a solid food, most commonly rice or oat.

A guideline for weaning these infants suggests that first solids introduced should be low risk fruit and vegetables (avoiding legumes and banana) followed by red meats and cereals made from quinoa and millet. In infants with severe CM and soy-induced FPIES, supervised oral food challenges (OFC) can be considered to support the family. Tolerance of one food from a particular food group is considered to be a favourable indicator that the child will tolerate other foods from the same group [77].

The age of development of tolerance to food triggers in this disorder is variable and depends on the type of food and country of origin of the child. There is currently no agreement about ideal timing of OFC to determine symptom resolution, and this varies considerably by country and individual preference. It is agreed that patients should be evaluated at regular intervals, and, in the USA, diagnostic OFC are usually attempted 12–18 months after the most recent reaction to a specific food. It should be noted that, in a large US cohort, 41% of patients with CM FPIES transformed into an IgE-mediated phenotype over time. Those who were sensitised to CM were also more likely to have their FPIES persist beyond 3 years of age. IgE testing may, therefore, be important for decision making about when and where to perform an OFC [78].

Food protein-induced allergic proctocolitis

Food protein-induced allergic proctocolitis (FPIAP), also known as allergic colitis of infancy, is a non-IgE cell-mediated food allergic disorder predominantly seen in infancy. The classical presentation is of blood streaked stools in an otherwise healthy child. It is a benign, transient condition and is considered to be one of the major causes of colitis under 1 year of age. Diagnosis relies on a history of rectal bleeding, exclusion of infections and other causes of rectal bleeding, and response to an elimination diet [79].

Treatment

Elimination of the causal protein is usually followed by a rapid resolution of symptoms [80]. In FPIAP the most common causal proteins are CM and soy. As a large number of infants with this disorder are breastfed, this necessitates a maternal exclusion diet [73]. Maternal ingestion of egg and corn has also been identified as potential triggers in the breastfed infant [79]. In one series of 95 breastfed infants with FPIAP, dietary exclusions were successful in 89% of cases. Of the remainder, seven responded to an EHF, and the remaining four (all of whom had eczema) needed an AAF [81]. The majority of infants with FPIAP achieve clinical tolerance of the food by 1 year of age [79].

Autoimmune enteropathies and IPEX syndrome

Autoimmune enteropathies are a heterogeneous group of disorders characterised by immune-mediated damage to the GI tract causing severe and intractable diarrhoea. Anti-enterocyte antibodies are seen in some patients with this problem, but not all. Patients may have other associated autoimmune conditions including liver, renal, endocrine, pulmonary, haematologic and musculoskeletal system involvement. Treatment with immunosuppression is usually required. These patients do not respond to dietary allergen exclusion as would those with a CM sensitive enteropathy, and some will require PN as supportive treatment to correct malnutrition [82–84].

Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome is a monogenic autoimmune disease caused by FOXP3 mutations. Type 1 diabetes and eczema are frequently seen in these children. The median age of onset is 2 months with most infants experiencing diarrhoea and faltering growth. Some children will have an extremely high blood IgE level and eosinophil infiltrate in the bowel; others will have a severe enteropathy. Treatment is with immunosuppressive therapy and nutritional support (enteral or parenteral) or with hematopoietic stem cell transplantation [85].

Inflammatory Bowel Disease

Joanne Louise Price

Paediatric inflammatory bowel disease (PIBD) encompasses a spectrum of inflammatory bowel diseases (IBD), the most prevalent being Crohn's disease (CrD) and ulcerative colitis (UC). In childhood these conditions are more extensive and associated with a more aggressive disease course than adult-onset disease. In paediatric-onset CrD the genetic component is more dominant, and, therefore, recurrence within the family is more frequent than in adults [86]. IBD is more common in urban than rural areas and in northern developed countries, though the incidence is beginning to increase in developing nations.

A genetic predisposition for IBD was first identified in 2001 on the NOD2 gene. Since then 200 other loci have been found, however, this genetic susceptibility only accounts for up to 26% of cases [87]. The aetiology of IBD is not fully understood, but is thought to involve a dysbiosis of the gut microbiota [88] and/or an abnormal response to environmental triggers such as diet, infection, drugs or other agents. Researchers have hypothesised that modification of the gut microbiota to influence the dysbiosis will induce remission, and this could be the mode of action of future treatments. Understanding that environmental factors have a more significant role to play in the susceptibility of individuals to develop PIBD is a continuously evolving area of research.

Most cases of PIBD are insidious in onset with nonspecific GI symptoms, often leading to a significant delay in diagnosis and growth failure [89, 90]. To aid diagnosis certain serological inflammatory markers (erythrocyte sedimentation rate [ESR], platelets, albumin and stool faecal calprotectin tests) can indicate the possibility of IBD. Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD. It is also used to monitor CrD [91].

Diagnosis of PIBD should always be carried out by a paediatric gastroenterologist and requires endoscopic confirmation with biopsy and histological interpretation; the presence of granuloma within the biopsies is a unique diagnostic feature of CrD and helps distinguish it from UC. Due to the preponderance of small bowel disease in CrD and its transmural pattern of inflammation, diagnosis requires full assessment of the mid gut, particularly the terminal ileum, and this is intrinsically reliant on imaging techniques. Ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are the most widely employed imaging methods [92].

It should be noted that PIBD is a systemic disease and is also associated with other inflammatory conditions affecting the joints (arthritis), skin (pyoderma gangrenosum) and eyes (uveitis and episcleritis).

The IBD team

Appropriate organisation and delivery of services are an integral part of good care in PIBD [93]. Management requires a team approach with many specialist centres developing dedicated MDT. According to published standards of care [94], the IBD team should include:

- consultant gastroenterologists
- consultant specialist surgeons
- clinical nurse specialists with a special interest and competency in IBD
- clinical nurse specialist with a special interest and competency in stoma therapy
- dietitian allocated to gastroenterology
- administrative support for IBD meetings, IBD database recording and audit
- named histopathologist with a special interest in gastroenterology
- named radiologist with a special interest in gastroenterology
- named pharmacist with a special interest in gastroenterology

In addition to the IBD team, PIBD patients will often be referred to several other specialties due to various systemic manifestations, e.g. ophthalmology, endocrinology, dermatology and rheumatology.

Ulcerative colitis

UC is a chronic, relapsing inflammatory disease of the intestine that is confined to the colonic and rectal mucosa. Childhood-onset UC has a worse disease course compared with that in adults with a 30%–40% colectomy rate at 10 years, compared with 20% in adults.

Drug therapy is used to induce and maintain disease remission. There is no evidence to support the use of enteral nutrition or diet as methods to induce remission in UC. The nutritional problems found in UC are not as severe as in CrD because of sparing of the small intestine [95]. Height velocity is usually normal unless there is excessive steroid use. As patients with PIBD are at risk of vitamin D deficiency, it is recommended that serum levels are routinely measured and supplemented when appropriate. Nutritional support is needed if there is growth failure or weight loss.

Crohn's disease

The incidence of CrD in children is increasing worldwide, ranging from 2.5 to 11.4 per 100 000 [96]. It is a chronic, transmural (infiltrating all layers of the intestinal wall) inflammatory process that may affect any part of the GI tract from the mouth to the anus. It is not usually continuous and is characterised by skip lesions. It can occur randomly, and inflammation can move from one area to another within the same individual. It is an extremely heterogeneous disorder with great anatomical and histological diversity, so no two cases are the same. However, the small

intestine, and particularly the terminal ileum, is involved in up to 90% of cases [86].

The presentation of CrD in children depends largely on location within the GI tract and extent of the inflammation. It is a chronic relapsing and remitting condition, and this aggressive cycle of inflammation and healing can lead to ulceration and fistula formation. In more chronic and severe disease, fibrosis of the bowel and strictures can occur.

Nutritional issues

Symptoms of nausea, anorexia and malabsorption result in the mean energy intake of patients with active CrD up to 420 kcal (1.75 MJ)/day lower than in age-matched controls [97]. This is associated with insufficient nutrient intake, which can contribute to both macronutrient and micronutrient deficiencies. The energy and protein deficit results in weight loss, occurring in over 80% of children with CrD, and a decreased height velocity. In addition to a reduced oral intake, pro-inflammatory cytokines are increased in CrD and have been shown to adversely affect growth [98, 99]. Growth failure occurs in 15%–40% children with CrD, and final adult height can be up to 7 cm shorter than expected [100].

Specific nutrient deficiencies, such as calcium, magnesium, zinc, iron, folate, B_{12} and fat-soluble vitamins, are common findings at diagnosis, with antioxidant trace elements and vitamins being consistently reported at suboptimal concentrations [101, 102]. As some of these levels are affected by the acute phase response in inflammatory conditions, the true significance of the findings is not understood; however, there is good evidence that IBD patients experience increased oxidative stress [103]. During periods of active inflammation, there is often enteric leakage of protein, resulting in hypoalbuminaemia. Protein requirements can be increased by 25% in some cases [102].

Accompanying this is retarded bone mineralisation and development and delayed puberty [104]. It is well recognized that children with IBD have an increased risk of reduced BMD [105–107]. Interpretation of BMD should be adjusted according to the child's bone age as it is known that these patients have delayed skeletal maturation [108]. It is prudent to supplement with calcium if estimated dietary intakes do not meet the normal requirements for age. Vitamin D should be supplemented as per normal guidelines [109].

Once in remission, self-imposed dietary restrictions among patients with PIBD are often associated with insufficient nutrient intake, which can contribute to both macronutrient and micronutrient deficiencies. A study of 78 patients with inactive or mild CrD, compared with 80 non-IBD controls, identified inadequate nutrient intake due to exclusion of various food groups, particularly grains, milk and vegetables [110].

Management of Crohn's disease

Treatment options are comprehensively presented in a 2014 consensus document from the European Crohn's and Colitis Organisation (ECCO) and ESPGHAN [111]. The aims of therapy in paediatric CrD are to induce remission and therefore relieve symptoms, prevent adverse longer-term outcomes such as stricture and fistula formation, optimise growth and improve quality of life (QoL) while minimising drug toxicity. At a cellular level achievement of sustained and deep mucosal healing is the ultimate goal of treatment.

Surgery is not curative and should only be indicated in refractory short segment ileal disease (without colonic involvement) and in those with stenotic disease unresponsive to treatment. Planning for surgery should be discussed within the MDT with a paediatric surgeon experienced in IBD. If indicated it is suggested that surgery should be completed prior to the onset of puberty to prevent complications of growth failure and give the best chance for catch-up growth and normal development [111].

Remission can be induced using exclusive enteral nutrition (EEN) or corticosteroids followed by maintenance therapy with an immunosuppressant, usually azathioprine or 6-mercaptopurine.

They act slowly over several months and may take 6–12 weeks before benefit is noticed. Methotrexate may be used and is given as an injection or a tablet each week. It can take up to 3 months before becoming effective.

In persistent relapsing disease, EEN can be repeated, and/or a combination of drugs known as biologics (anti-tumour necrosis factor monoclonal antibodies) may be commenced. They are relatively expensive and have been used increasingly and successfully over the past 15 years. The longer-term effects of biologics have yet to be seen. The original biologics are infliximab, given intravenously in hospital usually every 8 weeks; adalimumab, given via subcutaneous injection every 2 weeks that can be given at home; and vedolizumab, given intravenously in hospital usually every 8 weeks. The timings of the infusions/injections depend on response. Before a child receives any of these medications, it is necessary to test if they are clear of tuberculosis using a chest X-ray and serum QTB (QuantiFERON-TB). There are now many less expensive 'biosimilar' drugs available on the market that may also be used. Recent guidance also suggests biologics may be considered first line in children with a high risk of poor outcome and a 'top-down' approach could be used in these more difficult cases [111].

Exclusive enteral nutrition

The most recent consensus guidelines recommend EEN as first-line therapy in paediatric CrD [111] and should be used where there is involvement of the small intestine and/or colon [112]. This therapy for active CrD was initially identified in the 1970s by surgeons treating patients with nutrition support perioperatively, and finding the inflammation became quiescent [113]. It involves the administration of a liquid diet, for a defined period, with the exclusion of all other food. Since the 1970s many trials have been completed with the aim of establishing its efficacy. To date there has been no trial of EEN vs. placebo.

The mechanism by which EEN exerts a therapeutic effect is still not understood. The anti-inflammatory effect of EEN is recognised and precedes nutritional restitution [114]. The fat

content of the feed could potentially affect the production of pro- or anti-inflammatory mediators. EEN is known to induce mucosal healing in the affected GI tract, while corticosteroids do not do so [111]. EEN has been shown to improve QoL outcomes [115]. Research into this therapy is continuously evolving with the latest studies hypothesising that it is the withdrawal of a normal 'Western diet' and replacing it with enteral feeds that is the mode of action. Enteral feeds are known to alter the intestinal microbiome [116].

A 2019 systematic review of paediatric randomised controlled trials (RCT) [117] and 2018 Cochrane review [118] both concluded that EEN is the most effective treatment for inducing remission in active paediatric CrD; it also has the benefit of improving nutritional status and growth when compared with steroids. As children with CrD are often chronically malnourished, enteral feeds support nutritional repletion. Feeds are also preferable as a first-line treatment because of the deleterious effect of steroids on growth; the use of steroids in puberty results in lower adult height [119, 120].

There are many studies investigating the effectiveness of feeds with differing nutritional profiles and components. Protein content and sources (amino acids, peptides and whole protein), LCT fat and carbohydrate components have all been scrutinised. The protein composition (including the addition of glutamine) does not appear to influence the effectiveness of EEN [118], with similar efficacy demonstrated between a polymeric and elemental amino acid-based feed in a paediatric RCT [121]. Two large single-centre cohort studies with more than 100 subjects achieved approximately 80% remission rates using both polymeric and elemental feeds [122, 123].

In a 2007 systematic review, a non-significant trend was seen favouring feeds with a very low LCT content with the recommendation that larger trials are needed to explore this further [124]. The 2018 review [118] included 7 trials with 209 patients treated with EN formulas of differing fat content (low fat $<20\,g/1000\,kcal$ vs. high fat $>20\,g/1000\,kcal$); there was no difference in remission rates. Very low fat content ($<3\,g/1000\,kcal$) and very low LCT demonstrated higher remission rates than EN formulas with a higher content. No recommendations for the fat content of feeds have been made [118].

Two feeds, Modulen IBD and Alicalm, have been marketed for the treatment of CrD. The former claims immunomodulatory effects purportedly due to the presence of transforming growth factor-β, an anti-inflammatory cytokine, present in casein. The latter is an energy dense (1.35 kcal/mL, 5.6 kJ/mL) polymeric feed with 50% fat present as MCT and additional fish oil. There are no published trials comparing these feeds against standard paediatric polymeric feeds. The mean remission rate for EEN for all feed types from all published meta-analyses is approximately 70% [111, 117]. Relapse rate outcomes are less well reported, but in two separate studies in paediatric centres in the UK, 30% of patients relapsed within 1 year of completing a course of EEN; however, 60% remained in remission for at least 2 years [121, 122]. In terms of duration of feeding, most studies find remission occurs after 6–8 weeks of EEN [111].

A survey of IBD centres in the UK, Europe, the USA and Asia-Pacific showed wide variations in EEN protocols used throughout the world; 93% used polymeric formulas, with flavourings commonly added to enhance acceptability [125]. Polymeric feeds have the advantage of being more palatable and cheaper than the elemental alternatives. One centre found that the use of the former significantly decreased the need for NG tubes in their patients, and this did not affect adherence to the EEN regimens prescribed [126]. Amino acid-based feeds (elemental feeds) need only be used in individuals where CM allergy is suspected.

Partial enteral nutrition (PEN) is not currently recommended as a treatment to induce remission [111]. A randomised paediatric study compared children on EEN with children who received 50% of their nutritional requirements from feeds and were allowed to eat normally. On analysis nutritional parameters improved equally in both groups; however, blood indices of inflammation failed to improve in the PEN group, showing that a significant amount of food affects the anti-inflammatory response to enteral feeds [127].

Learning points: treatment of Crohn's disease

- *Enteral feeds promote mucosal healing and alter the bacterial flora in the bowel*
- *EEN has a steroid sparing role, avoiding the adverse effects steroids have on growth*
- *Partial enteral nutrition (PEN) should not be used for induction of remission*
- *Nutrition support is often required alongside other treatments and can enhance the effectiveness of other interventions*
- *It is usual to have a form of immunosuppressant therapy as part of treatment*
- *Biologics are expensive but are indicated in particular patients*
- *Surgery is only indicated in specific circumstances but should be carried out in a timely manner in order to preserve optimum growth and development*

Nutritional requirements and monitoring on EEN

Most studies have failed to show increased basal energy requirements in patients with CrD unless the patient has a fever [128, 129]. One study confirmed that measured resting energy expenditure (REE) in children with CrD fed with PN correlated well with the predicted REE using FAO/WHO/UNU equations and was not increased [130].

Guidelines suggest that EEN should provide 100% EAR for age for energy and the RNI for protein from the full feed [111]. It is important to check that all vitamins and minerals are present in amounts at least equivalent to the RNI. Children should be advised to take a larger feed volume than prescribed if they are still hungry. They should be weighed weekly and monitored by telephone or email contact. A follow-up appointment should be arranged approximately half way through the treatment to ensure that the patient is responding and that appropriate weight gain is achieved.

Commencement of EEN

Regardless of the type of feed, the following protocol can be applied:

- Aim 100% EAR for energy plus allow more to appetite
- Feeds should be gradually introduced over 3–5 days depending on symptoms. In severely malnourished patients, there is a risk of refeeding syndrome (p. 63), and daily biochemical monitoring with appropriate electrolyte and mineral supplementation should be instituted until the patient has reached their target nutritional intake and is metabolically stable
- In cases of severe disease symptoms, an NG tube should be used to deliver the feed more slowly or enable the feed to be established without pressure to drink. The tube can be removed in a few days or weeks once tolerance and oral intake is established
- Exclusive enteral feeds should provide complete nutrition for a 6–8-week period
- If the feed is well tolerated, the concentration of powdered feeds may be increased to lower the volume of enteral feed required
- Clear fluids, boiled sweets and chewing gum can be taken alongside the feed. There is no evidence to inform best practice, but these do not appear to have any adverse effects

As paediatric CrD presents more frequently in adolescents, this process can be particularly difficult for them, and they require a high degree of support and motivation to complete the treatment. Despite this, feeds are well tolerated by most patients, and the full 6 weeks is usually adhered to. If the patients are sure that they will be able to manage orally, feeds can be introduced at home. If an NG feeding regimen is required, this should be commenced as an inpatient.

Once the feed choice and prescribed volumes have been decided, the aim is to give as much control to the patient as possible. Feeds should be tried orally with different flavourings to enhance compliance; the daily volume required must be explained carefully so that it is understood that the prescribed volume must be completed every day. If the patient needs or chooses to have an NG tube, they can be taught to pass this each night and remove it in the morning to cause minimum inconvenience to their daily routine. Some patients choose to drink the full feed volume. Others opt for a combination approach (some orally and the remainder via the tube).

Introduction of foods

There is no agreement about the best methods of food introduction to patients completing a period of EEN. The most recent guidance document states it would appear prudent to reduce feed volume over a period of 2–4 weeks and gradually introduce a normal diet every 2–3 days, ensuring that continued weight gain is maintained [111]. Many centres exclude high fibre foods in the initial stages [125]. Atopic patients requiring an elemental feed should be advised to exclude suspected food allergens, ensuring an adequate energy and calcium intake. Patients with persistent narrow strictures, due to fibrosis rather than inflammation, may require a low fibre diet or liquid diet to control symptoms until the stricture is surgically removed.

It has been reported that continued use of supplementary feeds in addition to a normal diet is associated with prolonged periods of disease remission. A Cochrane review identified two adult RCTs that suggest supplementary enteral nutrition may maintain disease remission [131]. A retrospective study found that a subgroup of patients who are not commencing azathioprine or similar maintenance treatments can successfully continue PEN supplements following induction of remission with EEN; this can be an effective maintenance treatment [132].

Some patients require continued nutritional support by NG tube, gastrostomy or orally if appetite remains poor. The routine use of supplements to support growth, particularly in puberty, is usual practice in some UK paediatric centres.

Learning points: exclusive enteral nutrition

- *Use standard polymeric feeds for 6–8 weeks*
- *Aim for 100% EAR for energy plus allow increased volume to appetite*
- *Use NG tubes if indicated*
- *Reintroduce food over 2 weeks*
- *Amino acid-based feeds and exclusion diets should only be used in those with associated allergies*
- *PEN may be used as a maintenance therapy or as ongoing nutrition support in children, particularly during times of rapid growth or increased nutritional demands, but not for induction of remission*

Special diets for Crohn's disease

At the time of writing, special diets are not routinely used for therapeutic management of IBD or recommended in any guidance in the UK and are used for research purposes only:

- ***CD-TREAT diet*** – a trial diet undergoing research in the UK, based on the hypothesis that the aetiology of CrD is influenced by dysbiosis of intestinal flora. The diet mimics the profile of the carbohydrate in EEN, reducing the carbohydrate and fibre in the diet and increasing the protein. In preliminary studies it had similar effects to those of EEN on the gut microbiome and metabolome of healthy participants and reduced ileitis in a rat model of disease. The results of an initial study using this diet in children with active CrD were recently published [133]. In this initial small population sample, three of five paediatric patients with active CrD achieved remission after 8 weeks on the diet. Further larger studies are planned.
- ***Crohn's disease exclusion diet*** – excludes dairy, wheat and most processed foods. It has been used alone and in combination with PEN (Modulen) and in one prospective uncontrolled paediatric study showed 70% remission

rates. The published study did not include all of the details of the diet; however, in general this diet includes limited meat, rice and potatoes, fresh fruits and vegetables. There are larger studies in process [134].

- ***specific carbohydrate diet*** – restricts all carbohydrates (starch, polysaccharides and disaccharides) except monosaccharides (glucose, fructose and galactose). The diet results in a high protein and high fat intake. There have been two low quality paediatric studies with small numbers. Success was limited, and the evidence for using this diet in paediatric IBD is lacking [102, 135, 136].
- ***low FODMAP diet*** (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) – described on p. 138. The literature supports the use of this diet to treat IBS but not IBD. This diet can be helpful with those patients with IBD who have symptoms from IBS [102].

The 'Western diet' has been implicated in the aetiology of IBD. In a Canadian study, higher intakes of meats, fatty foods and desserts were found to increase the risk for developing CrD in females, whereas the consumption of vegetables, fruits, olive oil, fish, grains and nuts was associated with a decreased risk for developing CrD in both males and females [137], suggesting diet may be a significant environmental factor. A recent Australian population-based study demonstrated an increased risk for CrD with frequent consumption of fast food before diagnosis [138].

Until results of RCTs pertaining to diet become available, current best practice advice regarding diet should focus on following healthy eating guidelines with an emphasis on a reduction in processed foods and an increase in fresh fruit, vegetables and fibre (in the absence of stricturing disease) while meeting energy, protein and micronutrient requirements.

Orofacial granulomatosis

Orofacial granulomatosis (OFG) is a condition where there are granulomas in the orofacial region in the absence of any recognised systemic condition. It is a rare condition characterised by chronic disfiguring oral and facial inflammation in the form of severe lip and cheek swelling, and skin lesions are commonly seen. The incidence, geographical distribution and cause of this disease are not known, but are thought to involve an allergic component, the trigger for which is not always clear.

Three potential dietary triggers are thought to be cinnamon, benzoates and chocolate. Treatments can, therefore, include dietary avoidance of these, and when this fails, and no other trigger can be identified, immunosuppressive therapy is sometimes used.

Clinical features vary with OFG and oral CrD may be on the same disease spectrum. Some patients appear to respond to the exclusion of certain items from their diet [139]. A systematic review of the literature identified common hypersensitivities to benzoic acid, benzoates, cinnamaldehyde, cinnamon and chocolate. EEN, using an amino acid-based formula, followed by single food introductions to identify specific dietary triggers may also be successful [140]. Information sheets for professionals working with children with this diagnosis can be obtained on request from the King's College London website (www.kcl.ac.uk).

Transition

Transition should be an integral part of any IBD service, preferably with joint clinics held between adult and paediatric gastroenterology teams. However, it is a challenging process where practical realities do not always match official guidance. A tool has been developed by the Childhood Research Association (CICRA) with young people with IBD to equip them as they approach transition from paediatric to adult services. It includes a symptom tracker that helps young people become more confident about managing their condition. Generic transition guidance can be found in guideline 43 from NICE [141].

Disorders of Altered Gut Motility

Sarah Macdonald

Integration of the digestive, absorptive and motor functions of the gut is required for the assimilation of nutrients. In the mature gut, motor functions are organised into particular patterns of contractile activity that have several control mechanisms. Disturbances in this coordinated system can occur in all parts of the GI tract.

After swallowing, a bolus of milk or food is propelled down the oesophagus by peristalsis; this action differs from the motility of the rest of the intestine in that it can be induced voluntarily. The lower oesophageal sphincter relaxes to allow food or fluid to pass into the stomach, which acts as a reservoir and also initiates digestion. It has a contractile action that grinds food to 1–2 mm particle size. Gastric emptying can be modulated by feed components via hormonal secretion.

In the small intestine, motor activity is effected by smooth muscle contraction, which is controlled by myogenic, neural and chemical factors. In the fasting state the gut has a contractile activity (the migrating motor complex) that propels the luminal bacteria and food residue into the colon. Abnormalities of this phasic activity can result in bacterial overgrowth of the small intestine and malabsorption. Postprandial activity is initiated by hormones, which produce peristalsis in the gut. This allows the relaxation of the GI

muscle coats below the bolus of food and contraction above, propelling the bolus of food through the intestine.

Gastro-oesophageal reflux

Gastro-oesophageal reflux (GOR) is defined as the passage of gastric contents into the oesophagus, with or without regurgitation and vomiting. It is a normal physiological process that occurs several times a day in healthy infants, children and adults. Most episodes of GOR in healthy individuals occur after meals, last less than 3 minutes, and cause few or no symptoms [142]. Approximately 50% of infants regurgitate at least once a day, and, in the majority of children, this can be considered as an uncomplicated self-limiting condition, which spontaneously resolves by 12–15 months of age. This is due to the lengthening of the oesophagus and the development of the gastro-oesophageal sphincter. Parental reassurance is very important and should preclude the need for any further investigations or treatment [143].

More severe forms of this problem occur when an infant with regurgitation does not respond to simple treatment and develops GORD. Acid-induced lesions of the oesophagus and oesophagitis may develop and are associated with other troublesome symptoms such as faltering growth, haematemesis, respiratory symptoms, apnoea, irritability, feeding disorders and iron deficiency anaemia. GORD is a common finding in premature infants, children with neurological problems, obesity and previous oesophageal atresia and congenital diaphragmatic hernia. Recent clinical practice guidelines from the North American and European Societies for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN, ESPGHAN) describe symptoms and signs that may be associated with GORD to try and prevent under- or overdiagnosis of this condition. Diagnosis of GORD in infants and toddlers is complicated by the fact that there is no symptom or group of symptoms that is diagnostic or predicts response to therapy. Investigations that may be used to understand the underlying disorder include oesophageal pH monitoring with the aim of correlating symptoms with GOR events and to determine the effect of acid suppression therapy [142].

Treatment

Positioning

Postural treatment of infants has been demonstrated to help, and a prone-elevated position at 30° is the most successful in reducing GOR [144]. This cannot be recommended as several studies have shown an increased risk of sudden infant death syndrome in the prone sleeping position. A more practical approach is to avoid positions that exacerbate the situation. In older children head elevation or left lateral positioning can be used [142].

Feeding

The infant should not be overfed and should be offered an age appropriate volume of milk. Small volume, frequent feeds may also be beneficial by reducing gastric distension, e.g. 150 mL of formula/kg/day as 6–7 feeds [145]. In practice frequent feeds may be difficult for parents to manage, and reduced feed volumes may cause distress in a hungry baby.

Commercial anti-regurgitation (AR) formulas and feed thickeners decrease visible regurgitation episodes, but the impact on non-regurgitation symptoms is less clear [142]. Although the actual number of reflux episodes may not decrease with AR formulas, the reduction in regurgitation may improve QoL for caregivers.

There are four pre-thickened infant formulas based on CMP available in the UK (Aptamil Anti-Reflux, Cow & Gate Anti-Reflux, Enfamil AR with Lipil, SMA Staydown). They contain either a high amylopectin pre-gelatinised rice starch, precooked cornstarch or carob (locust) bean gum. The manufacturers' instructions should be followed when reconstituting these feeds. Feeds containing starch thicken on contact with the acid pH of the stomach, while those containing carob bean gum thicken on mixing. The EC Scientific Committee for Food has accepted the addition of starch to a maximum of 2 g/100 mL in infant formula.

A variety of feed thickeners are available on prescription, based either on locust (carob) bean gum or modified maize starch (Table 8.12). Locust bean thickeners are approved for use in infants after 42 weeks' gestation.

Table 8.12 Feed thickeners.

	Thickening agent	Suggested dilution (g/100 mL)	Added energy per 100 mL	
			(kcal)	(kJ)
Instant Carobel (Cow & Gate)	Locust bean gum (carob)	1–3	3–8	13–33
Thick and Easy (Fresenius Kabi)**	Precooked maize starch	1–3	4–12	17–50
Thixo-D (Sutherland Health)*				
Vitaquick (Vitaflo)*				
Multi-thick (Abbott)*				
Nutilis Powder (Nutricia)**				
Resource ThickenUp (Nestle)*				

*Only prescribable for children <1 year of age in cases of failure to thrive.
**Only prescribable for children over the age of 3 years.

These can cause the passage of frequent loose stools in a minority of infants; however, they have the flexibility of being able to be mixed as a gel and fed from a spoon before breastfeeds.

Where there is faltering growth a maize-based thickener can be used to provide extra energy. These products are classified as 'not suitable for children under 1 year except in cases of failure to thrive'. Their use in infants should be under the supervision of a healthcare professional. The lowest amount of thickener recommended should be added initially, and the amount gradually increased to the maximum level if there is no resolution of symptoms. Feeding through a teat with a slightly larger hole, or a variable flow teat, is recommended.

Other treatments

Non-pathological reflux is normal and does not require treatment. PPI are recommended as first-line treatment of reflux-related erosive oesophagitis in infants and children with GORD. H_2 receptor analogues may be used if PPI are contraindicated. Infants and children prescribed with these medications should have regular assessment with the aim of stopping the medication as soon as tolerated.

Symptoms of GORD, particularly in infants, may be confused with those of FA as these infants may also experience regurgitation, vomiting and distress. 30%–40% of infants with GORD resistant to treatment have CM allergy, with symptoms significantly improving on a CMP-free diet [146, 147]. Although the mechanism is still poorly understood, Borrelli *et al*. suggest that foregut dysmotility is affected by neuro-immune interactions induced by food allergens [148]. In food allergic children, CM has been shown to cause gastric dysrhythmia and delayed gastric emptying that may exacerbate GORD and induce reflex vomiting [149]. When GORD fails to respond to simple treatment, a therapeutic change of formula to EHF or AAF can be tried for 2–4 weeks followed by reintroduction of CMP to see if symptoms reoccur. Breastfed infants should have a trial of maternal CM exclusion [142].

In extreme cases that do not respond to the above treatment transpyloric/jejunal feeding should be considered as an alternative to surgery [142]. Anti-reflux surgery includes fundoplication that wraps the fundus of the stomach around the lower oesophageal sphincter (p. 152). A gastrostomy is usually inserted for venting gas from the stomach and, occasionally, for feeding purposes. There can be considerable morbidity associated with this operation.

Feeding problems in GORD

Feeding difficulties are not uncommon in this disorder, especially when the reflux has an allergic aetiology. They are characterised by food refusal, distress during feeding, poor appetite, and negative feeding experiences by the caregivers [150]. Infants with GORD are significantly more demanding and difficult to feed and have been found to ingest significantly less energy than matched infants without GORD [151]. These problems often persist after medical or surgical treatment.

Where there are severe feeding problems, it may be necessary to instigate NG or gastrostomy tube feeding to ensure an adequate nutritional intake. Wherever possible an oral intake, however small, should be maintained to minimise later feeding problems. The child's feed should be administered as oral or bolus day feeds or with continuous feeds at a slow rate to avoid feed aspiration. The feed volume may need to be reduced below that recommended for age to ensure tolerance, with feeds fortified in the usual way to ensure adequate nutrition for catch-up growth. If using a fine bore NG tube to administer bolus feeds, thickening agents should be kept to the minimum concentration recommended to prevent the tube blocking and an inappropriate length of time being taken to administer the feed. Transpyloric feeding can be tried where GORD continues to be a problem; however, one study showed that reflux can still occur during feeding times and aspiration events and reflux-related hospital admissions are still possible [152].

The requirement for tube feeding can continue for prolonged periods of time, as long as 36 months [153]. Parents of infants with feeding problems secondary to GORD need a great deal of support. Optimal management should employ a multidisciplinary feeding disorder team including a psychologist with experience of children with these problems, a paediatrician, a dietitian and a speech and language therapist.

Paediatric intestinal pseudo-obstructive disorder

Paediatric intestinal pseudo-obstructive disorder (PIPO) is characterised by the chronic inability of the GI tract to propel its contents, mimicking mechanical obstruction in the absence of any lesion occluding the gut. It is an extremely rare disorder, and children with PIPO experience significant morbidity and repeated hospital admissions. Half to two thirds of patients present within the first year of life.

A recent expert group published consensus-based recommendations to aid consistent definition, diagnosis and management of the disorder. It is hoped that this will contribute to a better understanding of the problem and more effective treatments in the future [154]. Primary causes of PIPO include sporadic or familial forms of myopathy, neuropathy or abnormal development of the interstitial cells of Cajal, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) and total intestinal aganglionosis. The urinary tract may also be involved.

Stasis of intestinal contents is common, and the chronic dilatation leads to decompensation and elongation of the bowel, further impairing motility. Dehydration and malnutrition are often not recognised, and the child's weight may be unreliable due to significant amounts of fluid pooling within distended gut loops. The management goals for this disorder are to improve GI motor activity where possible, relieve symptoms and restore nutrition and hydration.

Treatment

Nutritional support is vital for these children. In one series of 44 patients, 72% required PN for a relatively long period of time, 7 children died of PN-related complications with a further 10 remaining dependent on long-term home PN [155]. In a second series of 105 children, only 18 were able to be enterally fed throughout their illness, and 11 patients died [156]. Nutritional management of these children is challenging and has a poor evidence base. The ability to maintain an oral intake is influenced by the extent of GI disease. Children with gastroparesis are more likely to have difficulty eating food than those with predominantly small bowel involvement [157]. In children fed via the gastric route, it is known that a number of factors influence gastric emptying including the type of protein, amount and type of fat, energy density and osmolality. A recent meta-analysis of the available literature suggests that breastmilk has a faster gastric emptying rate than any infant formula. Whey-dominant formulas empty more rapidly than casein-dominant feeds due to the predominance of β-lactoglobulin. This remains soluble in the stomach and, therefore, transits more rapidly into the small intestine. The effect of protein hydrolysis on the gastric emptying of feeds remains unclear [158].

Oral diet and gastric and jejunal feeds tailored to the individual child should all be trialled. In the long term one third of patients with PIPO require PN (partial or total), one third will need feeds via an artificial device, and one third will be able to tolerate sufficient nutrition orally. For those that can manage oral diet, it would appear prudent to recommend small frequent meals and snacks avoiding high fibre foods that can result in bezoar formation. Such children are advised to eat low residue and bite and dissolve foods and soft diets to minimise the contractile activity needed for digestion [154]. High fat foods may need to be avoided in order to limit delay in GI transit.

Some children with PIPO have an ileostomy fashioned to decompress the gut. The loss of sodium-rich effluent through the stoma can result in high sodium requirements, and this needs careful monitoring. Enteral feed can be pooled in the intestine for a prolonged period of time before passing through the stoma, resulting in a lack of appreciation of the relatively high fluid requirements of these children. When unwell, children often need additional IV fluids to prevent dehydration. In certain children (especially those with impaired gastric motor function), jejunal feeding may be successful if a trial of gastric feeds has failed [159]. QoL has been shown to be poor with a reduction in school attendance and GI pain being common findings. Parents' QoL is affected by having to be vigilant in assessing their child's fluid balance and the need to follow complicated and time-consuming nutritional support protocols [160].

Where there are life-threatening complications of PN such as loss of IV access, end-stage liver disease or an intolerable QoL, multivisceral transplantation is an option. Early discussion with a transplant centre combined with an MDT approach to decide about the optimal timing of assessment is recommended.

Learning points: paediatric intestinal pseudo-obstructive disorder

- *Liquids are easier for the dysmotile gut to process than highly textured foods; it may be beneficial to minimise the intake of solids even if tolerated, although long-term evidence of outcomes is currently lacking*
- *Enteral feeds are more likely to be tolerated as a continuous infusion than as bolus feeds*
- *Feed constituents influence gastric emptying; it would appear prudent to avoid casein-dominant feeds in children with gastroparesis*
- *Care should be taken to ensure that enteral feeds are made as cleanly as possible to prevent the introduction of microorganisms into the gut, which could contribute to bacterial overgrowth; in older children the use of sterile feeds is preferable*
- *Fluid balance and sodium requirements should be accurately assessed, and supplements given as needed*
- *Foods that are low in fibre with a semi-solid or bite-dissolvable consistency are more likely to be tolerated as non-bite-dissolvable foods may increase the risk of bezoar formation*
- *Additional anthropometric measurements should be taken in this group of children to assess and monitor nutritional status*

Functional gastrointestinal disorders

Functional gastrointestinal disorders (FGID) are a heterogeneous group of symptom based conditions that cannot be explained on an organic basis. They are usually classified according to their predominant presenting symptoms and the age of the child [161, 162]. They are recognised by morphological and physiological abnormalities that often occur in combination and that can include motility disturbances, visceral hypersensitivity, altered mucosal and immune function, altered GI microbiota and altered central nervous system processing [163]. They include infantile colic, regurgitation, constipation, functional diarrhoea, functional abdominal pain (FAP), cyclical vomiting syndrome, rumination syndrome and IBS. FGID have a complex aetiology that includes biological and psychosocial factors. A recent meta-review reported that worldwide prevalence of the two most common FGID in infants, regurgitation and functional constipation (FC), is approximately 25% and 18%, respectively [164].

Most of the algorithms devised for practical management of these conditions are based on parental support, reassurance and nutritional advice. Despite this there is evidence of discrepancies between these guidelines, what physicians recommend and what parents may do, resulting in many different treatments and approaches to the management of these conditions. This comes at a considerable financial cost to parents and healthcare systems and a decreased QoL reported by parents [165, 166].

The nutritional status of children with FGID may be affected with one study of 102 children showing that those

with IBS were more likely to be overweight, while children with FAP were more likely to be underweight compared with reference data [167].

The Rome Foundation is an independent not-for-profit organisation that provides support for activities to assist in the diagnosis and treatment of FGID. It has published textbooks to update knowledge and diagnostic criteria of these disorders with the 2016 Rome IV series being the most recent; all functional disorders in infants and toddlers are included [168]. Only three of the functional GI disorders are described here.

Functional constipation

Constipation is a symptom rather than a disease and can be caused by anatomical, physiological or histopathological abnormalities. FC is not related to any of these abnormalities and is thought to be most often due to the intentional or subconscious withholding of stool after a precipitating acute event. Peak incidence occurs at the time of toilet training with an increased prevalence in boys. Constipation has been found to account for 3% of visits to general paediatric outpatient clinics and 10%–25% of visits to a paediatric gastroenterologist [162].

Average stool frequency in children has been estimated to be four stools per day in the first week of life, two per day at 1 year of age, decreasing to the adult pattern of between three per day and three per week by the age of 4 years. Within these patterns there is a great variation. The Rome III criteria for diagnosis are used in the evidence-based ESPGHAN and NASPGHAN guidelines published in 2014 [169] and are based on history and physical examination. FC is defined as the occurrence of two or more of the following characteristics for at least 1 month in children up to the age of 4 years and at least 2 months in children older than 4 years:

- less than two bowel movements per week
- at least one episode of faecal incontinence per week after the acquisition of toileting skills
- large stools in the rectum or palpable on abdominal examination
- passing of stools so large they obstruct the toilet
- a history of excessive stool retention
- a history of painful or hard bowel movements, retentive posturing and withholding behaviour in a child older than 4 years [169]

In FC prolonged stretching of the rectal walls, associated with chronic faecal retention, leads to an atonic and desensitised rectum. This perpetuates the problem as large volumes of faeces must be present to initiate the call to pass a stool. Faecal incontinence (previously described as encopresis or soiling) is mostly as a result of chronic faecal retention and rarely occurs before the age of 3 years.

Treatment

The 2010 NICE guidelines (updated in 2017) and 2014 ESPGHAN/NASPGHAN guidelines emphasise that dietary interventions alone should not be used as first-line treatment; FC should be treated with laxatives and a combination of age-appropriate behavioural interventions. Treatment should involve disimpaction with polyethlyene glycol or enemas if needed, followed by maintenance therapy. Movicol Paediatric Plain (Norgine), containing polyethylene glycol '3350' with electrolytes, should be first-line treatment with a stimulant laxative (senna, docusate sodium, bisacodyl, sodium picosulfate) added as required [169, 170].

Dietary fibre can be classified into water-soluble and water-insoluble forms. The former includes pectins, fructo-oligosaccharides (FOS), gums and mucilages that are fermented by colonic bacteria to produce short chain fatty acids. This has been shown to increase stool water content and volume. Insoluble fibre mainly acts as a bulking agent in the stool by trapping water in the intestinal tract and acting like a sponge. Both soften and enlarge the stool and reduce GI transit times.

Surveys have shown that constipated children often eat considerably less fibre than their non-constipated counterparts. Even when advised to increase their fibre intake by a physician, the fibre intake was only half the amount of the control population. It appears that families can only make the necessary changes with specific dietary counselling [171, 172]. Behavioural intervention can significantly increase dietary fibre intake at 3 months, but this increase is not sustained at 6 months and 1 year [173], confirming the difficulties initiating and maintaining high fibre diets in children. Children with FC have been shown to have lower energy intakes and a higher incidence of anorexia. It is difficult to know if this was pre-existing and predisposed to the condition or whether it is caused by early satiety secondary to constipation [174]. No RCT has shown an effect on stools in constipated children of any of the above dietary measures. The fact that FC is uncommon in societies that consume a high fibre diet has been used to justify this treatment.

The Scientific Advisory Committee on Nutrition (SACN) recommends daily amounts of dietary fibre: 15 g for 2- to 5-year-olds, 20 g for 5- to 11-year-olds, 25 g between the ages of 11 and 16 years and 30 g from the age of 16 years (Table 2.18).

In infancy and childhood it is important to ensure that adequate fluids are taken. As a guide, children should have 6–8 drinks a day, preferably as water. For children who drink insufficient amounts, foods with a high fluid intake should be encouraged such as ice lollies, jelly and sauces. Fruit, vegetables and salad have a high fluid content as well as being desirable because of their fibre content. The ESPGHAN/NASPGHAN guidelines recommend that normal fibre, fluid and physical activity levels should be achieved in children with FC but that additional fluid or fibre supplements such as glucomannan or cocoa husk should not be recommended. There is also no evidence to support the use of pre- or probiotics [175] or MDT working, involving a dietitian or psychologist, in the treatment of FC [169].

In a select group of children with constipation who fail to respond to conventional treatment, CMP-free diets have been shown to be beneficial [176]. Motility studies in these

patients have indicated that the delay in faecal passage is a consequence of stool retention in the rectum and not of a generalised motility disorder [177]. It has, therefore, been proposed that all children with chronic constipation who fail to respond to normal treatment as outlined above should be considered for a 2–4-week trial of a CMP-free diet (Table 8.17) [169]. One study showed that, of 52 patients with chronic constipation, 58% had an eosinophilic proctitis caused by an underlying FA. The response to dietary exclusion was confirmed by double-blind food challenges. The majority of children were allergic to CMP only; however, six patients had multiple food allergies identified by the use of a few foods diet [178]. A systematic review concluded that the available evidence does support a causal link between CMP and FC in some children [179].

For children with FC referred to a paediatric gastroenterologist, 50% will recover and not be taking laxatives after 6–12 months of treatment. A total of 80% of children have recovered after 10 years with most no longer taking medication [169].

Functional diarrhoea

Functional diarrhoea, previously known as toddler diarrhoea, is the most frequent cause of chronic diarrhoea in children between the ages of 1 and 5 years of age. Symptoms include more than four watery stools, often containing undigested foodstuffs, in a child who is otherwise well and thriving [168]. These children will usually have rapid gastric emptying before the foods have been ground completely in the stomach and will often need to open their bowels during a meal. It is a disease of exclusion, and treatable causes such as post-enteritis syndrome, infections, CD and IBD should be considered. Despite the children generally presenting in a good nutritional state, parental anxiety is high. The diarrhoea ceases spontaneously, generally between 2 and 4 years of age [180]. A primary problem has still not been identified. Children with this disorder are known to have a rapid GI transit time, and intestinal motility is generally thought to be abnormal, although it is unsure whether this is due to a reduced colonic transit time or a disturbance of small intestinal motility.

Carbohydrate malabsorption, particularly of fructose, has been extensively investigated in this disorder. Fructose is known to be slowly absorbed in the small intestine and is often present in large amounts in fruit juice. Young children may have an increased amount of fruit squash and fruit juices as their drink of choice [181]. Apple juice, particularly, has been implicated in causing toddler diarrhoea, and studies have been completed using hydrogen breath tests to measure carbohydrate malabsorption. What seems to be evident is that non-absorbable monosaccharides and oligosaccharides, such as galacturonic acid, are produced by enzymatic treatment of the fruit pulp in clear fruit juices, including apple, grape and bilberry juices. It is thought that these may cause problems in sensitive individuals, rather than fructose [182].

Treatment

All sources agree that parental reassurance is of primary importance. The role of diet in this disorder is controversial [183]. Advice is needed to correct any dietary idiosyncrasies. Excessive fluid intake, particularly of fruit juices and squash, should be discouraged. Fibre intake has frequently been reduced by parents in an attempt to normalise stools; therefore, increasing this to normal levels should be recommended. Often parents try excluding foods from the child's diet, mistakenly believing the problems to be due to food hypersensitivity. Once the diagnosis is established, these foods should be reintroduced.

Abdominal pain-related functional gastrointestinal disorders

Abdominal pain-related functional gastrointestinal disorders (AP-FGID) are defined as chronic or recurrent abdominal pain, not explained by an underlying organic disorder. They are thought to affect up to 20% children worldwide and include functional dyspepsia, IBS, abdominal migraine and FAP. They have a significant impact on QoL, daily functioning and school attendance and can have long-term psychological implications. Children and adolescents with these problems are at risk of the symptoms continuing into adulthood [184]. It is thought that paediatric AP-FGID are associated with stress and psychological disorders such as anxiety and depression and are found in children who have a lower coping strategy than those of healthy children.

Treatment

A recent review looking at the role and prevalence of CMP and other food allergies in FGID found limited data to support their role in the pathogenesis of these disorders. The authors concluded that an elimination diet could be trialled for a limited period to verify if the symptoms improve, followed by OFC [185]. A systematic review looking at pharmacological interventions for recurrent abdominal pain in childhood found no evidence to support the use of medications as treatment in these disorders [186]. High quality studies of non-pharmacological treatment in these disorders are lacking, and the first step in management is reassurance and education. In the 30% of children who continue to experience symptoms hypnotherapy, cognitive behavioural therapy [187] or probiotics (*Lactobacillus GG* and VSL#3) can be considered [184].

Irritable bowel syndrome

Irritable bowel syndrome is the name given to a longstanding functional GI disorder that consists of frequent abdominal discomfort and bowel symptoms that cannot be explained by any other disease. The symptoms include abdominal cramps, bloating, diarrhoea and constipation.

Treatment

In adults it has been demonstrated that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) can be beneficial in treating the symptoms of IBS [188]. FODMAPs are short chain carbohydrates (e.g. fructans, galacto-oligosaccharides, polyols, fructose and lactose) that are poorly absorbed in the small intestine. Ingestion of FODMAPs leads to alterations in fluid content and bacterial fermentation of carbohydrate in the colon triggering functional gut symptoms in susceptible individuals.

The low FODMAP diet originated at Monash University, Melbourne, Australia. It has been successfully adapted in the UK by researchers at King's College London and implemented in the adult population at Guy's and St Thomas' NHS Trust in London. Removing FODMAPs from the diet has been shown to be effective at improving the symptoms of adults with IBS. There have been numerous systematic reviews looking at the diet's efficacy in adults, the most recent including nine RCTs of 596 subjects comparing their symptoms with others consuming habitual, Western or other diets recommended for IBS. The conclusion was that short-term efficacy and safety was shown in adults; however, there need to be more studies looking at the long-term effects of following this diet [189]. One potential hazard of following a low FODMAP diet is altering the gut microbiome with studies showing a reduction in *Bifidobacteria* species concentration, the long-term effects of this on colonic health being unknown [190].

The only published study in children by Chumpitazi *et al*. enrolled 52 children with only 33 completing the trial. The study evaluated symptoms after 48 hours on a low FODMAP diet compared with the same length of time on a typical American diet, with a 5-day washout period between the two diets. All the meals were provided for the families, and the diet analysis showed no difference in macronutrient provision other than the low FODMAP diet being lower in carbohydrate. The study diet appeared to ameliorate GI symptoms in the children; however, they only followed the diet for 48 hours, which would not be long enough to see the full effect [191]. There is concern that such a restricted diet may lead to inadequate nutritional intake in children and also the development of poor eating behaviour with so many dietary exclusions involved [192]. Further studies are needed to show outcomes in the paediatric population. Resources for health professionals interested in the low FODMAP diet are available to purchase via the King's College London website (www.kcl.ac.uk).

Learning points: functional gastrointestinal disorders

- *FGID are a mixed group of disorders based on symptoms where no organic cause can be found*
- *They have a complex aetiology that includes biological and psychosocial factors*
- *Management guidelines are based on reassurance, parental support, and, in some cases, nutritional advice*
- *A low FODMAP diet has been shown to be beneficial in treating IBS symptoms in adults; however, there is scant data to show its efficacy in children; care is needed to ensure nutritional adequacy*

Food allergy in gastroenterology

A food allergy is defined as a reproducible immune-mediated adverse reaction to a specific food. Food allergies are most common in childhood due to the immaturity of the gut mucosal barrier and immune system. Allergic sensitisation involves a failure to develop oral tolerance and an immunologic response induced by food proteins in contact with the gut-associated lymphoid tissue. One common cause of this is the post-enteritis syndrome where a loss of barrier function and the breakdown of normal immune tolerance follow a GI infection. Deficiency of immunoglobulin A (IgA), which is involved in the immune defence of mucosal surfaces, is a common associated finding in allergic infants. The prevalence and prognosis of FAs in childhood is described elsewhere (p. 334). FA is classified on the basis of the involvement of IgE antibodies in the allergic pathophysiology, either as classic IgE, mixed pathophysiology (EoE or EGID), or non-IgE-mediated FA [193]. Lack of awareness of non-IgE-mediated gastrointestinal food allergies (non-IgE GI FA) often results in delayed diagnosis; however, care is needed to avoid overdiagnosis as there are currently no definitive biomarkers and GI manifestations attributed to these disorders [194]. Pathological inflammatory changes can be seen in the GI tract. Cells and mediators of the immune system such as eosinophils and lymphocytes may be found in biopsies of inflamed sites.

Non-IgE GI FA are characterised by subacute and/or chronic symptoms and include FPIES, FPIAP and food protein-induced enteropathy (FPE). FA may also be considered in a subset of children with constipation, GORD, abdominal pain, colic, dysphagia, food impaction, protein losing enteropathy, faltering growth and non-coeliac wheat sensitivity refractory to optimal medical management [193, 195]. Allergic reactions can affect GI secretion, absorption (with or without mucosal damage) and motility. Interactions between the allergic cells and the mucosal nervous system are important in mediating alterations in GI secretion and motility. Both interleukin-5 (IL-5) (a Th2-produced cytokine) and the chemokine, eotaxin, play a role in allergic responses that can present as delayed gastric emptying, GOR and constipation [196]. GI conditions that may be caused by allergic reactions to dietary proteins are summarised in Table 8.13.

In the clinical setting dietary manipulations may be used to treat symptoms before any formal GI investigations are carried out. The current tests available (skin prick tests, patch tests and specific IgE) are of limited use in identifying food allergens causing GI disease. Diagnosis is based on an allergy focused history that includes a first-degree family history of atopy (hay fever/allergic rhinitis, asthma, eczema), allergies and organ-specific autoimmunity

Table 8.13 Gastrointestinal disorders that can be caused by allergy to dietary proteins.

Eosinophilic oesophagitis (EoE)
Eosinophilic gastroenteritis
Food protein-induced enterocolitis syndrome (FPIES)
Gastro-oesophageal reflux (GOR)
Food protein-induced enteropathy (FPE)
Food protein-induced allergic proctocolitis (FPIAP)
Constipation

combined with the age at presentation of symptoms and food intake at that time. Diet history is often an unreliable indicator of the offending allergen(s) due to the delayed reaction to the food. The efficacy of the exclusion of a particular food antigen should be evaluated, and, when there is symptom improvement, an OFC should be performed to see if symptoms reoccur [197]. If there is no improvement on an exclusion diet, a normal diet should be reintroduced. In non-IgE GI FA, this diagnostic pathway is generally undertaken at home and relies on accurate parental reporting of symptoms [198].

Although the most common foods to cause GI FA problems are CM, egg, wheat and soya, any food ingested could be allergenic [199]. Sometimes a number of dietary manipulations need to be tried before the correct dietary restriction for the individual is achieved. In the presence of multiple food allergies, a few foods diet (p. 320) or exclusive use of a hypoallergenic feed may be needed.

The timing of symptom resolution varies between a few hours for acute FPIES to several weeks for FPE. A review of symptom response to the exclusion diet followed by OFC to confirm the diagnosis needs to be undertaken by the clinician or dietitian [200]. A 4-week dietary trial has been shown to be sufficient to determine symptom improvement in 98% of children with non-IgE-mediated FA responding to dietary antigen exclusion [198]. When multiple foods are excluded from the diet, it is important to sequentially challenge the excluded foods (p. 325) to identify those the child is reacting to in order to avoid overrestricting the diet.

While there are internationally recognised guidelines on the management of cow's milk allergy (CMA), these do not encompass children with possible multiple food allergies [201–203]. It is known that unnecessary food exclusions can lead to nutrient deficiencies as well as affecting QoL. One study showed that the families of children with non-IgE GI FA had worse scores in emotional and physical domains than families of children with intestinal failure [204]. It is, therefore, important that children are diagnosed and correctly managed on as few dietary exclusions as possible.

Exclusion diets are difficult to manage at home and are expensive. Selection of suitable patients is important. The use of anti-allergic or anti-inflammatory drugs as a therapeutic alternative to dietary restriction should be considered in situations where the family will not cope with a strict exclusion diet.

Removal of dietary antigens as treatment for GI allergic disorders

Exclusion of cow's milk protein

CMP is the most common food protein to cause a reaction in infant. The natural history of CMA is described elsewhere (p. 334).

Alternative infant formulas

It is vital that an infant is given a nutritionally complete milk substitute to replace a CMP-based formula. Except in FPIES, the maternal diet in breastfed infants should be modified by the removal of CMP and any other foods allergenic to the infant. Care needs to be taken to ensure that the maternal diet continues to include adequate amounts of calcium, vitamin D, energy, protein and fluid. It has been found that breastfed infants can be sensitised to multiple allergens including egg, soy, wheat and fish [205]. Recommendations from ESPGHAN are that the dietary trial should be continued for up to 14 days if delayed GI reactions are suspected. If there is no improvement, then the infant should be further evaluated. If multiple food allergies are suspected, then an EHF or AAF can be tried. The mother should be encouraged to express her milk while the clinical response to the hypoallergenic feed is evaluated [202, 206].

Mammalian milks

Mammalian milks are not suitable to be used as an infant feed without modification due to their high renal solute load and inadequate vitamin and mineral content. The proteins in goat's and sheep's milks share antigenic cross-reactivity with CMP [201, 206]. Infant formulas based on goat's milk are not recommended for use in GI FA [207].

Soy protein-based formulas

Soy formulas are based on soy protein isolate supplemented with L-methionine to give a suitable amino acid profile for infants. They are lactose-free with glucose polymer as the most common source of carbohydrate. The fat is a mixture of vegetable oils that provide long chain fatty acids, including EFA. Feeding soy formulas to infants is associated with normal growth, protein status and bone mineralisation [208, 209].

In the UK the use of soy formulas in infants under the age of 6 months has been advised against by the Chief Medical Officer due to their high phytoestrogen content, unless there is a specific medical indication [210]. There appears to be less risk to the infant after 6 months of age as the reducing dependence on formula decreases the amount of isoflavones, per kilogram body weight, ingested. The infant's potentially vulnerable organ systems are also likely to have matured by that age.

Soy protein has a very large molecular weight and after digestion can generate a large number of potential allergens. Severe GI reactions to soy protein formula have been described for more than 30 years and include enteropathy, enterocolitis and proctitis. In FPIES caused by CMP, 25%–50% of children in the USA had concomitant soy-induced

Table 8.14 Composition of soy infant formula per 100 mL.

	Dilution (%)	Energy (kcal)	Energy (kJ)	CHO (g)	Protein (g)	Fat (g)	Osmolality (mOsm/kg H_2O)
SMA Wysoy (SMA Nutrition)	13.2	67	280	6.9	1.8	3.6	204

enterocolitis, which responded to the use of hypoallergenic feeds. This frequency of sensitisation is not reported in other countries [77]. It has been suggested that an intestinal mucosa damaged by CMP allows increased uptake and increased immunological reaction to soy protein. Conversely, one study of children with CMA (both IgE and non-IgE mediated) found that soy formula was tolerated by 90% of children [211]. The American Academy of Pediatrics (AAP) states that soy formulas are not recommended in the management of CMP enteropathy or enterocolitis; however, most children can resume soy protein consumption safely after 5 years of age [208]. EPSGHAN concluded that the use of EHF (or AAF if EHF is not tolerated) should be preferred to soy protein feeds and the latter should not be used before the age of 6 months. If soy formulas are used therapeutically after the age of 6 months, tolerance to soy protein should first be established by clinical challenge [212]. The more recent ESPGHAN and European Academy of Allergy and Clinical Immunology (EAACI) guidelines for the management of CMA both state that soy formulas may be tolerated after the age of 6 months [202, 213].

Soy formula has the benefit of being at least half the cost of EHF and is much more palatable. Prospective studies looking at the incidence of soy allergy in patients with GI conditions are required. The soy infant formula available in the UK is given in Table 8.14.

Feeds based on protein hydrolysates

Infants with CMA need an alternative infant formula to ensure nutritional adequacy. The allergenicity or antigenicity of a particular protein is a function of the amino acid sequences present and the configuration of the molecule. An epitope is the area of a peptide chain capable of stimulating antibody production. During the manufacture of a hydrolysate, the protein is denatured by heat treatment and hydrolysed by proteolytic enzymes, leaving small peptides and free amino acids. The enzymes are then inactivated by heat and, along with residual large peptides, are removed by filtration [214]. The proteins used to make a hydrolysate vary, and production methods also differ between manufacturers. The profile of peptide chain lengths between different feeds will not be identical, even when the initial protein is the same.

Potential problems with hydrolysate formulas

Despite the rigorous conditions employed in the manufacture of these feeds, there are still potential sequential epitopes present that can be allergenic to a sensitised infant. EHF vary considerably in their molecular weight profile and hence in their residual allergenic activity (Table 15.6). Feeds with peptides >1500 Da have been demonstrated to have residual allergenic activity [215, 216]. The degree of hydrolysis does not predict the immunogenic or the allergenic effects in the recipient infant. It has been recommended that dietary products for treatment of CMP allergy in infants should be tolerated by at least 90% of infants with documented CMA [207].

Table 8.15 shows the composition of EHF available in the UK. Feed choice may be influenced by:

- palatability, which is affected by the presence of bitter peptides. This is particularly important in infants older than 3 months of age
- coexisting fat malabsorption, where a feed with some of the fat as MCT may be indicated
- cost, some hydrolysates being twice as expensive as others
- religion and culture, where parents do not wish their children to be given products derived from pork

Introduction of hydrolysate formulas

These feeds may need to be introduced slowly to infants with severe GI symptoms as they have a higher osmolality than normal infant formulas. If severe diarrhoea is present in an older infant, it is preferable to stop all solids while a new feed is being introduced to assess tolerance.

In an outpatient setting, where symptoms will be less severe, full strength formula can usually be introduced from the outset. In infants older than 6 months, there may be an advantage in initially mixing one part EHF to three parts of the usual formula to slowly introduce the new taste and encourage acceptance. The proportion of EHF can be increased over the next three days when full strength feeds are achieved. Milkshake flavourings at 2%–4% concentration (2–4 g per 100 mL) can also be used in this age group if sucrose is not contraindicated.

If an infant refuses to drink the EHF, an NG tube needs to be passed to ensure adequate volumes are taken. Where faltering growth coexists, feeds can be fortified in the usual manner by increasing formula concentration or the judicial use of carbohydrate and fat modules [217] (p. 13). All changes should be made slowly to ensure they are tolerated.

Amino acid-based infant formulas

Only pure amino acid mixtures are considered to be non-allergenic as there are no peptide chains present to act as epitopes. In infants who fail to tolerate an EHF, this is the next

Table 8.15 Extensively hydrolysed infant formulas per 100 mL.

	Dilution (%)	Energy (kcal)	Energy (kJ)	CHO* (g)	Protein (g)	Fat† (g)	Na (mmol)	K (mmol)	Osmolality (mOsm/kg H_2O)
Casein									
Nutramigen 1 with LGG‡,[a] (Mead Johnson)	13.6	68	280	7.5	1.9	3.4	1.4	2.1	287
Pregestimil Lipil (Mead Johnson)	13.5	68	280	6.9	1.9	3.8 (55%)	1.3	1.9	279
Similac Alimentum (Abbott)	12.8	68	283	6.6 20% sucrose	1.9	3.8 (33%)	1.3	1.8	274
Whey									
Aptamil Pepti-Junior (Nutricia)	12.8	66	275	6.8 trace lactose	1.8	3.5 (45%)	0.8	1.7	210
Aptamil Pepti 1^ (Nutricia)	13.6	67	280	7.0 41% lactose	1.6	3.5	0.9	2.0	280
SMA Althera (Nestle)	13.2	67	280	7.3 52% lactose	1.7	3.4	0.9	1.8	281
Infatrini Peptisorb§ (Nutricia)	—	100	420	10.3 trace lactose	2.6	5.4 (50%)	1.4	2.8	350

*Carbohydrate is present as glucose polymers unless otherwise stated.
†Figures in parentheses indicate the percentage of fat present as medium chain triglycerides (MCT).
‡Nutramigen 2 with LGG is available for infants >6 months of age.
[a]Feed contains probiotic *Lactobacillus rhamnosus GG*. Care is needed in certain infant groups where live bacteria may be contraindicated. Water to reconstitute the feed should be <40°C.
^Aptamil Pepti 2 is available for infants >6 months of age.
§Liquid feed, designed for infants <9 kg body weight requiring a nutrient-dense feed. Not suitable for cow's milk allergy.

Table 8.16 Infant formulas based on amino acids per 100 mL.

	Dilution (%)	Energy (kcal)	Energy (kJ)	CHO (g)	Protein (g)	Fat (g)	Na (mmol)	K (mmol)	Osmolality (mOsm/kg H_2O)
Neocate LCP (Nutricia)	13.8	67	279	7.2	1.8	3.4 (4% MCT)	1.1	1.8	340
Neocate Syneo* (Nutricia)	14.7	68	286	7.2	1.9	3.4 (4% MCT)	1.2	1.9	360
Puramino (Mead Johnson)	13.6	68	286	7.2	1.9	3.6 (33% MCT)	1.4	1.9	350
Alfamino (SMA)	13.8	70	291	7.9	1.9	3.4 (24% MCT)	1.1	2.0	332

*Feed contains a synbiotic (pre- and probiotic). Care is needed in certain infant groups where live bacteria may be contraindicated. Water to reconstitute the feed should be <40 °C.

logical step, so long as there is no coexisting fat or carbohydrate intolerance; in this circumstance a modular feeding approach should be used (p. 145). Infant AAFs available in the UK are summarised in Table 8.16. Neocate Spoon, which contains highly refined rice starch as a thickener, can be offered as a nutrient-dense hypoallergenic weaning food if required.

For the majority of infants with non-IgE gastrointestinal FA, an EHF would be the first-line treatment, with an AAF used if the child fails to tolerate this feed There are differences between the EHF and AAF brands that are shown in Tables 8.15 and 8.16. An EHF that contains *Lactobacillus rhamnosus GG* has been shown to reduce the time taken for a child

Table 8.17 Milk-free diet.

Foods permitted	Foods to be excluded	Check ingredients
Milk substitute Vegetable oils Custard made with milk substitute, sorbet	All mammalian milks, cheese, yoghurt, fromage frais, ice cream, butter	Margarines
Meat, poultry, fish, shellfish (fresh or frozen), pulses		Sausages, pies, foods in batter or breadcrumbs Baked beans
All grains, dry pasta, flour Most breads, most breakfast cereals	Pasta with cheese or milk sauce, milk bread, nan bread Cream cakes, chocolate cakes	Tinned pasta Bought cakes or biscuits
Fruit and vegetables		Instant mashed potato
Plain crisps, nuts		Flavoured crisps
Sugar, jam, jelly Marmite	Milk chocolate, toffee	Plain chocolate Ketchup, salad dressings, soups
Milkshake syrups and powder Fizzy drinks, juice, squash	Malted milk drinks	

to acquire oral tolerance of CMP (p. 337). There is a difference in cost between EHF and AAF with the latter being more than twice as expensive. It should be noted that one retrospective study found that up to 30% of food allergic infants, many with delayed reactions to foods, were intolerant of EHF [199]. Intolerances to hydrolysate formulas, resulting in GI disturbances have also been described by Vanderhoof *et al*. [216].

Learning points: cow's milk-free formulas for infants

- *Soy-based formulas should not be used under the age of 6 months, but may be tolerated by a significant number of infants with CMA over this age*
- *Consideration when selecting an EHF for an infant with CMA would include cost, enzymes used in manufacture and taste in the older in infant*
- *AAF are at least twice as expensive as EHF and, in most cases, should only be used when a trial of EHF fails*
- *The addition of selected pre- and probiotics may influence outcomes in infants with CMA*

Milk-free diet

It is important that the caregivers of infants requiring a CMP-free feed are given appropriate advice to enable them to exclude CM from solid foods. Weaning should take place at the usual age. EU law (Directive 2003/89/EC, November 2005) regarding labelling of ingredients ensures that products containing CMP are clearly identifiable. Exceptions include foods that are not pre-packed such as bread from a bakery. Many manufacturers print an allergy statement on their packaging, but, as this is not compulsory, caregivers should always be advised to check the ingredients. Foods labelled 'may contain' do not generally need to be avoided by children with non-IgE GI FA. Parents need clear advice about this due to the increasing number of foods carrying this label (p. 329). For foods manufactured outside the EU, it is still necessary to teach families about the following ingredients that indicate the presence of CM in a manufactured food: casein, hydrolysed caseinates, whey, hydrolysed whey, lactose, milk solids, non-fat milk solids and butter fat. Milk-free dietary information is summarised in Table 8.17.

Exclusion of soy protein

In conditions where soy allergy is present in addition to CMA, foods containing soy and milk protein should be excluded from the diet (Tables 8.17 and 8.18). Vegetable or soy oils and soya lecithin are normally tolerated by individuals sensitive to soy protein and should not need to be excluded except in severely affected individuals [218, 219].

Milk, egg, wheat and soy exclusion diets

In conditions where a simple exclusion diet has not worked or where there is a diet history suggestive of multiple food intolerances, this empirical dietary regimen may be tried.

Table 8.18 Foods containing soya protein.

All soy-based products including tofu, tempeh and soy sauce
Texturised vegetable proteins
Breads, biscuits and cakes containing soy flour
Baby foods containing soy protein
Soy margarines

Table 8.19 Milk, egg, wheat and soya-free diet.

Foods permitted	Foods to be excluded	Check ingredients
Milk substitute Vegetable oils	All mammalian milks and products, soya milks and soy products, shredded suet Eggs	Margarines
All meat, poultry, fish, shellfish (fresh or frozen), pulses	Meat or fish dishes with pastry, breadcrumbs or batter Tofu, tempeh, soy beans, Quorn	Sausages, beef and vegetarian burgers, hot dogs, ready meals
Rice, rice noodles or pasta, maize, corn pasta, cornflour, tapioca, sago, arrowroot, buckwheat, barley, oats, gram flour, potato flour, rye, ground almonds, carob, teff, amaranth, millet	Wheat, rye and soya flour, spelt flour, wheat bran or germ, semolina, couscous, tabouleh, pancakes, batter, pizza, stuffing mixes, ordinary pasta, e.g. spaghetti	Gluten free bread, cakes, biscuits, pasta Oatcakes
Breakfast cereals made from rice, corn and oats, rice and corn cakes	Wheat based breakfast cereals Bread, crispbreads, crackers, chapatti, croissants, biscuits, cake	Poppadoms
Jelly, plain custard powder, rice, tapioca or sago pudding (made with milk substitute)	Pies, pastries, mousse, trifle, cheesecake, instant desserts	Sorbet, blancmange powders
Fruit and vegetables	Potato croquettes	Vegetables in dressing, e.g. coleslaw, potato waffles, instant mashed potato
Plain crisps		Flavoured potato crisps
Marmite, Bovril	Ordinary mayonnaise, salad creams, soy sauce	Stock cubes, gravy mixes, soups, sauces
Sugar, jam, honey, syrup, plain fruit lollies, milkshake syrup and powder, cocoa	Chocolate spread, lemon curd, milk chocolate, instant milk drinks	Plain chocolate, jelly sweets, marshmallows, baking powder, drinking chocolate, malted drinks

Soy, eggs and wheat are also covered by EU law (Directive 2003/89/EC, November 2005) and must be clearly labelled on all pre-packed foods. Families need a lot of help and information about commercial foods to enable them to adhere to this regimen. Suitable wheat-free products that are available via the Advisory Committee on Borderline Substances (ACBS) for CD cannot be prescribed for wheat allergy. Many of these products contain milk, egg or soya, so families need help to identify suitable substitutes. Supermarkets produce many foods suitable for exclusion diets that can help families to expand the diet. For foods manufactured outside the EU, it is still necessary to teach families about the following ingredients that indicate the presence of egg, wheat and soya in manufactured foods: egg albumin, wheat flour, wheat starch/bran, edible starch, modified starch, hydrolysed wheat protein, rusk, batter, breadcrumbs, thickener (unless specified as being made from another cereal), soy protein isolate, soya grits, tofu, hydrolysed/spun/textured vegetable protein, miso and tempeh (Tables 8.19 and 15.8).

Suitable feeds for older children

A suitable infant formula should be continued for as long as it is nutritionally indicated in children on an exclusion diet and is preferable under the age of 2 years [201]. One study showed significantly better micronutrient intake if a hypoallergenic feed was continued until the age of 2 years [220]. In situations where a large percentage of the child's nutrition comes from a formula, it will either need fortification to meet nutritional requirements, or a feed designed for older children should be used. If an infant formula is modified, care needs to be taken to ensure an appropriate protein to energy ratio. Rather than addition of energy supplements, it is often preferable to concentrate the feed. This should be done slowly, taking into account individual tolerance [217]. When a concentrated infant formula is used to feed an older child, consideration should be given to the sodium intake, especially where there are increased stool or stoma losses. Most feeds in Table 8.20 have been designed to meet the requirements of older children requiring hypoallergenic feeds. Adult feeds based on soy or hydrolysed protein should be used with care in older children and may require modification or vitamin and mineral supplementation. Not all the feeds are categorised as EHF, and care needs to be taken when selecting a feed for children with CMA.

Children over the age of 2 years consuming a balanced diet and tolerating soy protein may be given liquid soy drinks as an alternative to CM. Those with added calcium and vitamins help to ensure nutritional adequacy. For children intolerant of soy and CM, there are alternative drinks made from foods as diverse as oat, nut and coconut. Many brands of rice drinks are available, but these are not recommended for children under the age of 5 years due to

Table 8.20 Hydrolysate and amino acid-based feeds for older children per 100 mL.

	Dilution (%)	Energy (kcal)	Energy (kJ)	CHO* (g)	Protein (g)	Fat† (g)	Na (mmol)	K (mmol)	Osmolality (mOsm/kg H_2O)
Whey hydrolysates									
Peptamen Junior~‡ (Nestle)	22	100	420	13.8	3	3.8 (60)	2.9	3.6	370
Peptamen Junior Advance~f‡ (Nestle)		150	631	18	4.5	6.6 (60)	4.1	4.6	450
Nutrini Peptisorb§ (Nutricia)	—	100	420	13.6 trace lactose	2.8	3.9 (46)	2.5	2.8	345
Nutrini Peptisorb Energyf§ (Nutricia)		150	630	16.7 trace lactose	4.2	6.6 (55)	4.1	4.3	510
Amino acid feeds									
Neocate Junior¶ (unflavoured) (Nutricia)	21.1	100	420	12	2.8	4.6 (35)	2.6	2.9	600
Elemental 028 Extra¶ †† (unflavoured) (Nutricia)	20	89	374	11.8	2.5	3.5 (35)	2.7	2.4	502
Emsogen¶ †† ‡‡ (unflavoured) (SHS)	20	88	370	12	2.5	3.3 (83)	2.6	2.4	580

*All present as glucose polymer.
†Figures in parentheses show percentage fat present as MCT.
‡Also available as a liquid feed.
§Liquid feed.
¶Flavoured versions also available.
†† Use with caution for children between 1 and 5 years.
‡‡Patients who are receiving a significant proportion of their nutrition from Emsogen may need to supplement their intake of α-linolenic acid to meet UK DRV 1991 guidelines [221].
~Protein is not extensively hydrolysed, therefore not suitable for cow's milk allergy.
fContains fibre.

concerns about their arsenic content [222]. These alternative drinks are available in supermarkets and health food shops and can be useful as a social replacement for CM.

Most of these drinks contain very little protein. Although fortified with calcium and vitamins, calcium supplements may need to be given if the RNI is to be achieved [221]. Calcium intakes below recommended amounts have been identified in a number of children who are limiting CM in their diet, and this may affect bone density [223]. A study in Norway showed that children aged between 31 and 37 months following CMP free diets had significantly lower intakes of energy, fat, protein, calcium, riboflavin and niacin than age-matched controls [224]. Careful monitoring of dietary adequacy and supplementation with calcium and vitamins, if needed, is required together with ensuring adequate energy and protein intake from food. Suitable calcium supplements may be found in Table 29.10. Iodine status should also be considered in children on a CMP-free diet who are not having a complete feed. One study found reduced iodine levels in breastfed infants following a CMP-free diet [225], and it is likely that this may be a problem in older children as well. Optimal dietetic management of exclusion diets ensures that these do not significantly impact on a child's growth parameters [226].

Learning points: formulas and milks for older children

- *For children under 2 years of age who do not take a hypoallergenic formula, a detailed dietary assessment is needed, and appropriate nutritional supplementation given as necessary*
- *Formulas based on partially hydrolysed proteins are not suitable for children with CMA*
- *EHF and AAF for the older child have very different nutritional profiles and should be carefully selected for the individual*
- *Alternative drinks to cow's milk, such as soy, coconut and oat 'milks', can be included in the diet of the older child and, if fortified, are a useful source of calcium*

Modular feeds for intractable diarrhoea and short bowel syndrome

Intractable diarrhoea can be defined as chronic diarrhoea in the absence of bacterial pathogens of greater than 2 weeks' duration, together with failure to gain weight. Some infants with severe enteropathy, allergic GI disorders or short bowel syndrome fail to respond to feed manipulation using EHF or AAF, as previously described, and a modular feed is necessary [227]. This allows individual manipulation of ingredients resulting in a tailor-made feed for a child. Careful assessment and monitoring is important to prevent nutritional deficiencies and to evaluate the response to feed manipulation. The grading of stools using the Bristol stool chart is important to help assess the response to feed alterations [228]. The use of modular feeds can also assist in the diagnosis of the underlying problem.

Feed ingredients

Some of the possible choices of feed ingredients and their advantages and disadvantages are listed in Tables 8.21–8.24. Before starting there needs to be a discussion with the medical staff regarding the appropriate feed composition for the individual infant and to establish good medical support for the dietitian managing the baby's nutrition. The aim is to produce a feed that is well tolerated and meets the infant's nutritional requirements. The following parameters need to be considered:

- total energy content and appropriate energy ratio from fat and carbohydrate
- protein, both type used and quantity
- EFA intake
- full vitamin and mineral supplementation, including trace elements
- suitable electrolyte concentrations
- feed osmolality

Practical details

- Accurate feed calculation and measurement of ingredients is required to make the necessary small daily feed alterations. Scoop measurements are not accurate enough, and ingredients should be weighed on electronic scales.
- Infants with protracted diarrhoea or short bowel syndrome will tolerate frequent small bolus feeds given one to two hourly, or continuous feeds via an NG tube, better than larger bolus feeds.
- Attention needs to be given to the combination of ingredients as these will affect the feed osmolality. The smaller the molecular size, the greater the osmotic effect. Most hospital chemical pathology laboratories will analyse feed osmolality on request.

Table 8.21 Protein sources for use in modular feeds.

	Protein type	Suggested dilution* (g/100 mL)	Protein equivalent (g/100 mL)	ACBS prescribable	Comments
Hydrolysed Whey Protein/ Maltodextrin Mixture (SHS)	Hydrolysed whey	4	2	N	At this dilution: 1.5 g glucose polymer, 0.8 mmol Na, 0.6 mmol K
Complete Amino Acid Mix (Nutricia)	L-amino acids	2.5	2.0	N	Amino acids increase feed osmolality No electrolytes

ACBS, Advisory Committee on Borderline Substances; SHS, Scientific Hospital Supplies.
*This is a suggested dilution only. Quantities can be varied according to the desired protein intake, age of child, and feed tolerance.

Table 8.22 Carbohydrate sources for use in modular feeds.

	Suggested concentration (g/100 mL)	ACBS prescribable	Comments
Glucose polymer*, e.g. Maxijul (Nutricia), Polycal (Nutricia), Vitajoule (Vitaflo)	10–12	Y	Carbohydrate of choice as has the lowest osmolality
Glucose	7–8	Y	Use when glucose polymer intolerance is present
Fructose	7–8	Y	Monosaccharides will increase final feed osmolality A combination of the two monosaccharides can be used to utilise two transport mechanisms

ACBS, Advisory Committee on Borderline Substances; SHS, Scientific Hospital Supplies.
* Intolerance to glucose polymers has been documented in the literature. This may be due to a deficiency of pancreatic amylase or of the disaccharidase glucoamylase. Monosaccharides become the carbohydrates of choice in this situation. It may be possible to use sucrose as an alternative carbohydrate.

Table 8.23 Fat sources for use in modular feeds.

	Suggested concentration* (g/100 mL)	Comments
Calogen (canola, sunflower oil emulsion) (Nutricia)	6–10	50% LCT emulsion Contains linoleic acid (C18:2) + α-linolenic acid (C18:3) in a 5:1 ratio
Liquigen (coconut, palm kernel oil emulsion) (Nutricia)	4–8	50% MCT emulsion MCT increases feed osmolality Does not contain EFA If used in a modular feed, consider a separate supplement of EFA rich oil, e.g. walnut
Vegetable oils, e.g. olive, sunflower†	3–5	Not water miscible An emulsion can be prepared by mixing 50 mL oil with 50 mL water and liquidising with 1–2 g gum acacia

MCT, medium chain triglycerides; LCT, long chain triglycerides; EFA, essential fatty acids.
*The amount of fat used will depend on tolerance and nutritional aim.
†These ingredients are not Advisory Committee on Borderline Substances listed.

Table 8.24 Vitamin and mineral supplements that may be used in modular feeds.

Paediatric Seravit (Nutricia)	Contains glucose syrup which may be contraindicated Does not contain electrolytes (Table 1.23)
Phlexy-Vits (Nutricia)	Designed for children >11 years Reduced dose to be given for younger children May need additional vitamins and minerals prescribed separately according to requirements Does not contain electrolytes (Table 1.23)
FruitiVits (Vitaflo)	Designed for children aged 3–10 years of age 0.5 g maltodextrin per 6 g sachet Contains orange flavouring and artificial sweeteners acesulfame K, sucralose Does not contain electrolytes (Table 1.23)

- Infants requiring a modular feeding approach may have high requirements for all nutrients depending on the underlying disorder.
- Vitamin and mineral supplements used in conjunction with a fat emulsion, such as Calogen or Liquigen, cause the fat to separate out. For feeds given as a continuous infusion, it is recommended that these products are administered separately.
- There is no carbohydrate-free complete vitamin and mineral supplement for infants in the UK. If intolerance of glucose/glucose polymer is suspected, then Paediatric Seravit cannot be used. Phlexy-Vits could be used in small quantities with specific nutrients added according to individual requirements.

Introduction of modular feeds

Depending on the clinical situation, feeds are often introduced very slowly, and the concentration of the individual components is gradually increased (Table 8.25). Occasionally, if an infant is already taking a full strength complete feed such as Neocate LCP and the necessary dietary change is to use a modular feed with, say, a different fat source (in this case wholly MCT instead of the mainly LCT found in Neocate LCP), then the full strength modular feed can be introduced more rapidly:

- Before starting a modular feed, it is necessary to assess the infant's symptoms and current nutritional support. If PN is not available, feeds should be introduced rapidly to prevent long periods of inadequate nutrition.
- In the absence of IV glucose, the carbohydrate content of the feed should never be less than 4 g/100 mL because of the risk of hypoglycaemia. A higher percentage of energy from fat than from carbohydrate may result in excessive ketone production.
- An example of the slow introduction of an amino acid-based modular feed (the case study detailed in Table 8.25) can be applied to other protein sources. Suggested incremental changes can take place every 24 hours. If well tolerated this process can be accelerated.
- The infant's response to each change of feed should be assessed daily before making any further alterations. Where possible making more than one change at a time should be avoided.
- Feed changes should be avoided during intercurrent infections as these tend to worsen GI symptoms and make it difficult to assess feed tolerance.

Preparing and teaching for home

After a period of time on a modular feed, a nutritionally complete feed should be tried again to see if this is now tolerated. The formula nearest in composition to the modular feed should be chosen and challenged slowly, either by substituting one or two small feeds or by regrading over 4 days, starting with a quarter strength complete feed mixed with three quarter strength modular feed. If this is not possible or the complete feed is not tolerated, the aim should be to simplify feed ingredients as much as possible in readiness for

Table 8.25 Case study: a female infant requiring a modular feed.

Anthropometry: Baby girl born at term, weight = 3.2 kg (25th centile). On admission to hospital at 2.5 weeks of age, she has failed to regain her birth weight and current weight = 2.8 kg.
Biochemistry: On admission her biochemical results show her to be dehydrated and have severe metabolic acidosis.
Clinical: The baby is started on IV fluids and is allowed 20 mL/kg of Dioralyte orally. On this regimen she has 4 stools per day, grade 6 on the Bristol stool scale. Stool samples are sent to the lab to rule out an infectious cause of the diarrhoea, and these come back negative. An endoscopy is planned.
Dietary: A careful feeding history shows that mum has breastfed the baby at home. When she failed to gain weight, she changed her to a standard infant formula. This was not been tolerated (diarrhoea resulting in acidosis). After rehydration and correction of the acidosis, the focus is to nutritionally rehabilitate the infant and find an enteral feed that she can tolerate. A central venous catheter is inserted to start PN. The constituents are increased slowly over 5 days with careful biochemical monitoring because of the risk of refeeding syndrome. After the PN is established, a trial of small volumes of an AAF results in increased stool output.
Environment: The baby is the second child of consanguineous parents. The sibling has known autoimmune enteropathy.
Focus: The aims of the dietetic intervention are now to ensure normal growth and weight gain and to find an enteral feed that the infant can tolerate that will allow the PN to be gradually reduced and stopped. As she has failed a trial of AAF and no specific abnormalities are found on her small bowel biopsy that can be treated, it is decided to trial a modular feeding approach. The older sibling had previously done well on this method of feeding. The introduction of her modular feed based on Complete Amino Acid Mix is shown.
Slow introduction of modular feed based on Complete Amino Acid Mix.

Time	Complete Amino Acid Mix	NaCl and KCl	Glucose polymer, e.g. Maxijul	Fat	Volume
Days 1–3	½ strength increasing to full strength	Full strength	2%	Nil	20 mL/kg
Days 4–9	Full strength	Full strength	Increase in 1% increments daily to total of 7%	Nil	No change
Days 10–12	Full strength	Full strength	7%	Calogen is added in 2% increments to 6%	No change
Day 12+	Full strength	Full strength	7%	6%	Increase volume and titrate with PN reduction

An age appropriate vitamin and mineral supplement, Paediatric Seravit, is added as a separate medication when the PN is reduced to half volume to ensure nutritional adequacy of the regimen. It is not added to the feed as this will result in the fat emulsion separating. Her full strength modular feed based on Complete Amino Acid Mix is shown.
Full strength modular feed using Complete Amino Acid Mix per 100 mL.

	Energy		Protein	CHO	Fat	Na	K
	(kcal)	(kJ)	(g)	(g)	(g)	(mmol)	(mmol)
2.5 g Complete Amino Acids	8	34	2	–	–	–	–
10 g Maxijul	38	160	–	9.5	–	–	–
6 mL Calogen	27	113	–	–	3	0.1	–
1.4 mL NaCl (1 mmol/mL)	–	–	–	–	–	1.4	–
0.8 mL KCl (2 mmol/mL)	–	–	–	–	–	–	1.6
Final feed per 100 mL	73	307	2	9.5	3.0	1.5	1.6
Paediatric Seravit administered separately							

Outcome
The baby does well on the modular feed, which she takes orally from a bottle, and the PN is successfully stopped. Before she is discharged, an alternative AAF to the one offered initially is trialled again. This is because of the complexities of making modular feeds in the home environment, and it is hoped that, now she is more clinically stable, she will tolerate an appropriate complete formula.

The new feed is introduced very slowly (¼ strength AAF mixed with ¾ strength modular feed for 24 hours, then ½ strength AAF mixed with ½ strength modular feed, etc.). Once the full strength AAF is introduced she starts to vomit, her stool frequency increases, and the amount of oral feed she is taking decreases. As a result she loses weight. She has no other cause for her GI symptoms to deteriorate such as an intercurrent infection, teething, etc. She is, therefore, changed back to her modular feed, and the GI symptoms settle again, and the parents are taught to make this feed at home.

Discharge from hospital
She is discharged at 16 weeks of age, weight = 5 kg (2nd to 9th centile), length = 60.4 cm (25th centile). Her parents are advised not to introduce solids until she is 6 months old, and these are to be started slowly, one hypoallergenic food at a time, until her tolerance to these can be established.

Management at home
In the first few weeks at home, the dietitian keeps in touch with the family regularly to ensure the feed is being made correctly and that she is taking enough. The infant is weighed weekly by her health visitor and plotted on a centile chart to ensure appropriate weight gain. Her micronutrient levels and urinary sodium levels are monitored monthly at the hospital to ensure that no additional supplements are required and that she is receiving adequate amounts of electrolytes, vitamins and minerals.

IV, intravenous; PN, parenteral nutrition; AAF, amino acid formula; GI, gastrointestinal.

discharge home. Many preparation errors in the home environment have been noted including poor recipe adherence, incorrect use of measuring equipment, and errors in ingredient measurement [229]:

- Electronic scales should be used that measure in 1 g increments. If this is not possible to arrange at home, ingredients need to be converted into scoop measurements, using the minimum number of different scoops possible to avoid confusion.
- Syringes need to be supplied for accurate measurement of electrolyte solutions.
- A 24 hour recipe should be given to reduce inaccuracies in feed reconstitution, paying due care to issues of hygiene and refrigeration of feed until it is used. It is important to demonstrate the method for making the feed to the infant's caregivers on at least one occasion before discharge.
- A laminated recipe and wipe-off pen for home is useful so that parents can tick off ingredients as they are added.
- Not all the suggested ingredients for modular feeds are ACBS listed. A separate letter to the child's general practitioner will be needed to arrange a supply of the product. A supply of these items may need to be given from the hospital.

Introduction of solids in infants on modular feeds

Where possible solids should be introduced after the infant or child is established on a nutritionally complete feed. The restrictions imposed will depend on the underlying diagnosis. If this is not practical, then two or three items should be chosen, and these should be allowed daily without variation. Often it is necessary to introduce food items singly to determine tolerance of different foods.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

9 Surgery in the Gastrointestinal Tract

Danielle Petersen and Tracey Johnson

Congenital Malformations

Danielle Petersen

Introduction

There are a number of congenital malformations that require surgery during the neonatal period. These malformations may affect the oesophagus, stomach and small and large intestines. The type of feed and the method by which it is administered will be determined by the area of gut affected, the surgery performed to correct the defect and the condition of the remaining gut.

Oesophageal atresia and tracheo-oesophageal fistula

Oesophageal atresia (OA) is one of the most common congenital gut malformations and has a prevalence of 1 in 2500 to 1 in 4500 births [1–3]. The oesophagus ends blindly in a pouch, resulting in a non-continuous route from the mouth to the stomach. Diagnosis is made antenatally or at time of birth. At birth infants are unable to swallow properly and have excessive salivation and feeding difficulties. Aspiration of saliva or feed may cause choking and cyanotic attacks and requires surgical correction within 24–48 hours [2]. The majority, 69%–86%, of infants with OA also have a distal tracheo-oesophageal fistula (TOF) where the proximal end of the distal oesophagus is confluent with the trachea (Figure 9.1). In this case any reflux of stomach contents will enter the trachea and hence the lungs. Isolated 'pure' OA, where there is no fistulous connection with the trachea, occurs in 7%–26% of infants and the rarer presentation of a tracheo-oesophageal fistula without OA ('H' fistula) occurs in approximately 4%. The aetiology of OA is unknown with environmental and ethnic differences suggested to play a role [2, 4].

OA is associated with other anomalies, associations or syndromes in 50%–66% of cases [2]. Pedersen *et al*. [1] conducted a population-based study using data from a large European database for the surveillance of congenital anomalies over 20 years; 1222 cases of OA were identified. The most common associated anomalies in these infants were congenital heart defects (29.4%), urinary tract anomalies (16.4%), other gastrointestinal anomalies (15.5%) and limb anomalies (13.1%). VACTERL association (vertebral, anorectal, cardiac, tracheo-oesophageal, renal and limb defects) occurred in 9.6% of the infants and CHARGE syndrome (coloboma, heart defects, choanal atresia, retarded growth and development, genital hypoplasia and ear abnormalities) in 1% of infants. Stoll *et al*. [5] found similar incidences of anomalies from data collected over 29 years, with 116 cases of OA identified. Associated anomalies were seen in 46.6% of infants, chromosomal abnormalities in 7.8% (including VACTERL in 10.3% and CHARGE syndrome in 1.7%), congenital heart defects in 25%, gastrointestinal anomalies in 22.4% and urinary anomalies in 15.5%.

Over the last 60 years the mortality rate of infants with OA has decreased dramatically due to improvements in surgical, anaesthetic and neonatal care. Infants with a birth weight greater than 1500 g and with no major cardiac problems should have a near 100% survival rate. In those infants with a very low birth weight (<1500 g) or a major cardiac anomaly,

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

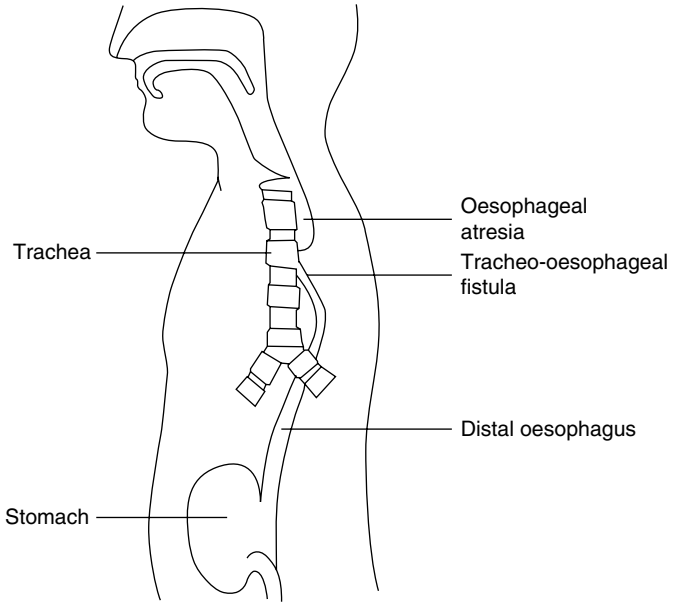


Figure 9.1 Oesophageal atresia and tracheo-oesophageal fistula.

the survival rate is reduced to 82%, and in those with a very low birth weight and a major cardiac problem, the survival rate is 50% [6, 7]. A prospective, multicentre cohort study of all infants born with OA in the UK and Ireland in 2008 and 2009 found that after 1 year the mortality rate was 8.6% [8].

Following diagnosis, the upper pouch should be suctioned using a Replogle tube to reduce the risk of aspiration. Treatment of OA, whether associated with TOF or not, is undertaken soon after birth. In most cases it involves the repair of the oesophagus by anastomosing the upper and lower ends, after closing any TOF if present, so that both the oesophagus and trachea are separate and continuous. Until the lesion is corrected surgically, the infant cannot be fed orally. Depending on the length of the gap and the surgical management, either enteral or parenteral nutrition (PN) (p. 52, 68) will be commenced [6].

Surgical interventions and feeding in the first months of life

Primary repair

A primary anastomosis is performed when the distance between the proximal and distal ends of the oesophagus is short enough for the two to be joined in one procedure. This is possible in the majority of patients, especially when a distal fistula is present. Most surgeons pass a transanastomotic tube (TAT) that allows gastric decompression in the early post-operative period and a route for nasogastric feeding. It has also been suggested that feeding via a TAT leads to reduced duration of PN [9, 10].

Feeds are often started 48–72 hours after corrective surgery and may be given orally once the infant is swallowing saliva [4]. Ideally, breastfeeding should be initiated or expressed breast milk (EBM) given. If this is not possible, then a standard infant formula is used.

Zani *et al*. [9] conducted an international survey among 178 surgeons, including 18 trainees, regarding practices in the treatment of OA (78% of respondents were from European countries). Results showed that post-operatively 90% left a TAT *in situ*. Only 2% of respondents created a gastrostomy at the time of initial repair, and PN was routinely used by 54% of surgeons. Enteral feeding via the TAT was started on or before day 2 post-operatively in 40% of respondents, day 3–4 post-operatively in 35% and day 5 or later in 25% of respondents. The majority of surgeons (89%) started oral feeds after post-operative day 5.

A recent retrospective review of 57 infants with OA and TOF seen at a single institution between 2005 and 2015 found that 61.4% of infants were discharged home on full oral feeds. Predictors for full or supplementary enteral tube feeding being necessary on discharge were having a structural cardiac anomaly and younger corrected gestational age at discharge. Only 46% of infants with a structural cardiac anomaly were discharged home on full oral feeds versus 79% without a cardiac anomaly. This study showed that a significant number of children (31.6%) with OA and TOF were discharged home receiving some or full enteral nutrition and 3.6% continued to require PN at discharge [10].

Delayed or staged repair

In infants with long-gap OA, the oesophageal repair is more complicated, and delayed repair is often necessary as the two ends of the oesophagus are too short to be anastomosed initially. There is no consensus in the literature regarding the definition of long-gap OA. Van der Zee *et al*. [11] define it as any OA that has no intra-abdominal air; therefore no distal tracheo-oesophageal fistula. Typically, the distance between the upper and lower ends of the oesophagus exceeds more than three vertebrae. The optimal surgical repair for infants with such long-gap OA remains controversial, with no clear consensus, and practices differ between centres [6, 11, 12]. In the study by Zani *et al*. [9], only 80 of the 178 surgeons and trainees provided accurate data for long-gap OA. Results showed that for surgical repair of long-gap OA:

- 60% of surgeons delay primary anastomosis and insert a gastrostomy without oesophagostomy
- 24% attempt primary anastomosis (no gastrostomy or oesophagostomy)
- 16% delay primary anastomosis and form an oesophagostomy and gastrostomy

The median age of the infant when delayed anastomosis is performed is 3 months. In long-gap OA, 47% of surgeons attempt elongation of the oesophagus, with the following interventions most commonly used: 43% use growth by traction (Foker technique), 41% serial dilation with bouginage, 8% suture both ends to encourage spontaneous fistula formation, 5% fashion an oesophagostomy for external elongation of the upper end and 3% perform a circular myotomy of the proximal oesophagus. If the gap between the two ends of the oesophagus is 4–7 cm long, 67% of surgeons would always attempt an oesophageal anastomosis. The other 23%

would not attempt an anastomosis, but would rather perform oesophageal replacement surgery [9].

In a small number of cases, the oesophagus is temporarily abandoned, and a cervical oesophagostomy is formed. This allows the infant to safely swallow saliva, and a gastrostomy is inserted for feeding [4]. In these infants the oesophagus is left for a few months before attempting to join the upper and lower ends. Although cervical oesophagostomy prevents growth in the upper pouch of the oesophagus, the lower pouch hypertrophies and shortens the distance between the two ends. However, a recent position paper on long-gap OA suggests that a cervical oesophagostomy should be avoided as it may increase the difficulty of a delayed primary anastomosis or jejunal interposition [11].

If primary oesophageal anastomosis is not possible, then an oesophageal replacement technique (p. 152) is used [11]. Feeding infants undergoing a delayed or staged repair often presents more of a challenge than in those with a primary anastomosis.

Feeding the young infant

When corrective surgery is delayed and the oesophagus is not joined up, the infant must be fed by gastrostomy. Either EBM or infant formula can be used and given at the same volume and frequency as the infant would receive had they been fed orally. Infants with cervical oesophagostomies should start sham feeding as soon as possible, which will allow the infant to experience normal oral behaviour. To facilitate normal development and coordination, the sham feed should be of the same volume as the gastrostomy feed, and the feed should be of the same duration and frequency so that the baby learns to associate sucking with hunger and satiety. Ideally the feed that is offered with sham feeding should have the same taste as that being put down the gastrostomy so that there is no refusal of feeds on the grounds of taste once the infant has a continuous oesophagus later. However, it is more common practice for mothers who choose to give their babies breastmilk to express and give EBM via the gastrostomy and infant formula by mouth for the sham feed. The sham feed seeps out of the oesophagostomy, along with saliva, and is usually managed by wrapping a towel or other absorbent material around the infant's neck. There are, however, problems with sham feeding:

- It is difficult to coordinate holding the baby, feeding from a bottle and mopping-up feed from the oesophagostomy while giving a gastrostomy feed. This event may defeat nursing staff let alone the mother coping single-handedly at home.
- One-third of infants with OA suffer from cardiovascular complications and may need ventilating, making sham feeding impossible.
- Infants may tire quickly and not be able to suck for long enough to take the same volume orally as is going through the gastrostomy.
- Many infants have small stomachs and initially require small volumes of gastrostomy feed frequently, e.g. 2 hourly, making it difficult to coordinate sham with gastrostomy feeding. However, this problem rapidly corrects itself when the feed volume is increased.

If an oesophagostomy was not formed, there would be no route for sham feeding, and infants would be deprived of oral feedings for the first few weeks to months of life. This should not be a major problem if oral feeding is established within 2–3 months of life, but if oral feeding is delayed longer than this, it may be associated with feeding difficulties. Infants who are not used to oral feeds often initially experience gagging and vomiting and may avert their head at the very sight of the breast/bottle or push out the nipple/teat with their tongue. Desensitisation to this oral aversion is a long, slow process, and it is important to remember that feeding does not only provide nutrition; infants are very alert at feeding time and develop cognitive and motor abilities while feeding as well.

Infants with OA with or without TOF can grow well on breastmilk and standard infant formulas, if adequate volumes are taken. If there is a problem with weight gain, feeds can be concentrated or a high energy formula used (Table 1.18).

Feeding the older infant and toddler

To promote normal development, infants with OA should be weaned at the recommended age of around 6 months. When a primary repair is performed soon after birth without complications, feeding is initiated early, and normal feeding progression should be achieved. However, in infants with long-gap OA, the primary anastomosis is often delayed, and these infants often experience feeding difficulties. The change from receiving full enteral nutrition to maintaining an adequate intake orally is slow, and there is often a long period where the child needs supplementary enteral feeds while learning to eat and drink orally. If gagging is experienced when solids are introduced, oral intake may be reduced to just tastes of food rather than giving large amounts in order to dispel the association between solid food and gagging. Foods need to be moist, and fibrous foods should be avoided. It may also take infants longer to take foods with chunks, and certain foods, such as white bread, can be problematic. Infants with feeding difficulties should remain on 'stage 2' foods (puree with soft lumps) for longer than usual to reduce the risk of choking. Feeding should also be done under close supervision to reduce the risk of coughing and choking. Fluid should be given at mealtimes to help food move down the oesophagus. Both mother and child need to build up confidence about eating. As the infant or child's oral intake increases, enteral feeds should slowly be reduced while monitoring intake and growth closely. Standard infant formulas and high energy formulas (SMA High Energy, Infatrini or Similac High Energy) may safely be used up to the age of 1 year or so but will need to be replaced by a more nutritionally adequate feed such as PaediaSure, Nutrini or Frebini to promote optimal growth in the older child if enteral feeds continue (Table 4.3). If the infant is still sham fed, weaning solids should also be sham fed and a nutritionally adequate feed given via the gastrostomy.

Oesophageal substitution procedures

Long-gap OA occurs in about 10% of infants with OA. Repairing the continuity of the oesophagus in these infants is more complex than those with distal tracheo-oesophageal fistulas. There is consensus among centres that the first choice in correction is to preserve the native oesophagus and perform a primary repair, with delaying primary anastomosis or using traction/growth techniques to achieve anastomosis if needed. If primary anastomosis is not possible, various oesophageal replacement techniques are used. These include jejunal interposition and, more commonly, colonic interposition and gastric pull-up/interposition, with no clear evidence regarding which has better outcomes [11, 12]. In the study by Zani *et al*. [9], results showed that 51% of surgeons perform gastric interposition, 36% colonic interposition, 9% jejunal interposition and 4% gastric tube reconstruction.

Gastric interposition

In gastric interposition the whole stomach is mobilised and moved into the chest. The proximal end of the oesophagus is joined to the top of the stomach in the neck. Advantages of this technique are that the blood supply is excellent, and only one anastomosis is required; therefore the rate of leakage and strictures is low [11, 13]. Disadvantages of this technique, gastro-oesophageal reflux (GOR), dumping syndrome (p. 155) and poor gastric emptying, are often seen in the short term; and Barrett's esophagitis may develop in the long term [13]. A single institution review of gastric interposition in 236 children (177 with OA) reported that more than 90% of patients were highly satisfied with the procedure, and there did not appear to be any long-term deterioration in function. Anastomotic leak was seen in 12% of patients, strictures developed in 20%, delayed gastric emptying was a problem in 8.9% and 3% developed dumping syndrome. Post-operatively, 55 patients (23%) had significant swallowing difficulties, of which 47% was classified as moderate and 53% severe. Follow-up showed that height was normally distributed, and weight was in the lower centiles for age. There was a 2.5% procedure-related mortality rate [13].

Colonic interposition

Colonic interposition involves removing a piece of the colon and transposing it into the chest between the oesophagus above and the stomach below. The advantages are that the required length of the graft is available, and the diameter of the lumen of the transposed colon is appropriate for joining to the oesophagus. The disadvantages of this procedure are that the blood supply to the colon is poor; the transposed colon does not have very good peristaltic function to propel food down to the stomach; with time the transposed colon may lose its muscular activity, and there is a high rate of anastomotic leaks and strictures [13].

Jejunal interposition

The jejunum can also be used for oesophageal replacement. This interposition has the advantage that the graft grows at a similar rate as the child; it has a similar diameter to the oesophagus and maintains intrinsic motility well. In the long term, the risk of GOR is less than that seen in gastric and colonic interposition. However, the main disadvantage is that the blood supply is often precarious [11, 13].

Feeding post-oesophageal substitution

The oesophagostomy, if present, is closed at the time of the oesophageal substitution. If a gastric transposition is performed, the pre-existing gastrostomy can no longer be used and is removed with a jejunostomy formed as a route for enteral nutrition. Gastrostomy feeding can continue if colonic or jejunal interposition has been performed. Oral nutrition is introduced as soon as possible, but supplementary overnight gastrostomy/jejunostomy feeds may be indicated until an adequate intake is taken by mouth. Oesophageal replacement procedures may have their problems when feeding recommences. The advantage of the gastric transposition is that there is only one anastomosis in the gastrointestinal tract, but the stomach is now sited in a much smaller place in the thorax than it usually occupies in the abdomen. The volume of feed or meals that can be taken comfortably may be greatly reduced, imposing a feeding regimen of little and often. The problem with colonic interposition is that two areas of the gut have undergone surgery and anastomosis. Over time the transplanted colon makes a rather 'baggy' oesophagus because of the nature of its musculature, and the repaired oesophagus may not have normal peristaltic function. The colon may suffer temporary dysfunction because of surgical trauma and malabsorption may ensue, necessitating a change to a hydrolysed protein feed (Table 8.15). The end result of these most commonly used surgical interventions may be oesophageal continuity, but not necessarily normal oesophageal function.

Problems with oesophageal function following repair

Gastro-oesophageal reflux

Gastro-oesophageal reflux (GOR) is the most common gastrointestinal tract complication following repair, with a reported incidence of 22%–45% [14–17]. Medical management may include the administration of proton pump inhibitors (PPI) and H2 receptor antagonists, the thickening of fluids (Table 8.12) and positioning the baby appropriately after feeding. PPI, e.g. omeprazole and lansoprazole, are recommended as first-line therapy for acid-related GOR due to their acid blocking abilities. The reduction in gastric acid output is beneficial as reflux is then less damaging to the oesophageal mucosa. If GOR is severe and unresolved by these methods, surgical correction may be considered by performing a fundoplication [17]. Literature suggests that a fundoplication is performed in 10%–45% of patients with OA [18].

Anti-reflux operations may be either a partial (Thal, Toupet or Belsey) or a complete fundoplication (Nissen) [18]. The choice depends on what the surgeon believes to be the best procedure for the individual child. The Nissen

fundoplication is the most common and involves mobilising the fundus of the stomach and wrapping it around the lower oesophagus, thus fashioning a valve at the junction of the oesophagus and stomach. In particular children with long-gap OA and recurrent anastomotic strictures may benefit from such surgery [17].

Anti-reflux surgery is, however, not without its post-operative complications. Children who experience poor motility and oesophageal clearance prior to the surgery may find their symptoms get worse after a fundoplication. This is due to increased oesophageal stasis and decreased gravity-driven oesophageal clearance, which may also worsen respiratory symptoms, including aspiration. Therefore, the decision to perform a fundoplication for respiratory symptoms only should be made with caution [17]. Holschneider *et al*. [19] found that following fundoplication children with OA had higher rates of post-operative dysphagia and/or stenosis than children without OA (17.2% vs. 6.5%). While preventing reflux into the oesophagus, the fundoplication may also stop the child from burping, and gas bloat can be very uncomfortable in the stomach. Parents should be taught how to 'wind' their child through the gastrostomy tube if they have one. Although the child should not be able to vomit, they often experience severe retching, which is very distressing for both child and parent, but this usually disappears after a few weeks or months. Fundoplication can also cause dumping (p. 155). Sometimes the wrap performed during the fundoplication weakens over time (commonly after 1.5–2.5 years but occasionally after a few months), and GOR returns. If this cannot be managed medically, the fundoplication has to be 'redone'. It has been suggested that between 20% and 45% of fundoplications fail [18]. Koivusalo *et al*. [20] reviewed data from 262 patients with OA who received fundoplication. In 31% of patients the fundoplication failed, with 15% undergoing a redo operation. The failure rate was highest in those with long-gap OA. Transpyloric feeding may also reduce reflux and retching. Studies have shown similar rates of reflux and retching between those who had a fundoplication and those who received jejunal feeds [21].

Eosinophilic oesophagitis

It is suggested that children with OA may have a higher risk of developing eosinophilic oesophagitis (EoE) than the general paediatric population [17]. One study of 103 patients reported an incidence of 17% from the retrospective review of biopsies, compared with 1 in 10 000 children in the general paediatric population. They also reported that the risk of developing EoE is much greater among those with long-gap OA [22]. Possible reasons for the increased risk of EoE within the OA population include genetic associations, impairment of oesophageal mucosal barrier function by acid reflux and prolonged exposure to acid-suppressive medication [17].

Strictures

Anastomotic strictures are also a common post-operative complication in OA [8, 17]. After repair, whether the child has undergone a primary repair in the first few days of life, a delayed repair or a staged procedure, a circular scar will form where the upper and lower segments of the oesophagus are sutured together. With perfect healing the scar will have the same diameter as the oesophagus and will grow with the child. However, if there is a long gap between the upper and lower oesophageal ends, the tissues will have been stretched to meet, and the repair will be put under tension. This tension is thought to increase the risk of an anastomotic stricture developing. Some studies also suggest that GOR is a major factor for recurrent anastomotic strictures, as the reflux of acidic stomach contents back up into the oesophagus can inflame the healing scar [17]. The presence of an oesophageal stricture has been reported in 52% of patients with GOR as opposed to 22% of patients with no reflux [23].

Other factors that have been suggested to influence stricture formation include a reduced blood supply in the lower oesophagus following repair, the type of suture material used and the suture pattern employed [6]. Allin *et al*. [8] reported that of 105 infants with OA/TOF, 39% had post-operative complications of oesophageal strictures within the first year of life, with most infants requiring multiple dilatations. Legrand *et al*. [14] had similar findings, reporting that of 57 patients with OA and TOF, 46% presented with anastomotic stenosis, which required dilatation. These strictures prevent the normal passage of food with bread, meat, poultry, apple and raw vegetables being the foods most often cited as getting stuck. Children with these problems will often show difficulty in feeding and a reluctance to swallow; they will choke and splutter. Strictures require repeated dilatations to soften the scar tissue and allow the easier passage of solid food [17]. The oesophagus may also go into spasm at the site of the anastomosis, and particular foods like mince and peas may get stuck.

Dysphagia

Dysphagia is common in infants, children and adolescents with OA following repair of the oesophagus. The reported incidence ranges from 21% to 85% and may remain a problem for many years following repair [17, 21]. Little *et al*. [24] reported that within a group of 69 patients with OA, 45% had dysphagia after 5 years, 39% at 5–10 years and 48% after more than 10 years, indicating that dysphagia may not decrease over time. It has also been suggested that the incidence of dysphagia may be higher than that reported as children in particular may not identify their symptoms as abnormal [17]. Children with OA will often eat very slowly or drink large quantities of water with their food. These and other significant changes to their eating habits have been reported in 73% of patients with dysphagia. The nutritional management of dysphagia includes the adaptation of feeding habits to help manage symptoms, and gastrostomy feeds may need to be considered in some cases [17].

Feeding difficulties following surgical repair

Prior to being joined up, the child will not have experienced the sensation of a bolus of food passing the entire length of

the oesophagus. Although the child may have been exposed to sham feeding, this method of feeding does not always lead to successful swallowing. Therefore, many children panic when offered any food other than in liquid form, and the establishment of normal feeding has to proceed through stages of gradually altering the consistency of foods, from purées to finely minced and mashed foods and then to a normal diet. The frightening experience of repeated choking and/or possible delayed introduction of solids may lead to fraught mealtimes that both parents and children come to dread.

Feeding difficulties such as dysphagia, coughing, choking, aspiration, vomiting during meals, food aversion, excessive fluid intake with meals and slow eating are seen in up to 75% of patients with OA. The reasons for these may include dysmotility, GOR, anatomic abnormalities, oesophageal outlet obstruction, oesophageal inflammation, anastomotic stenosis, laryngeal clefts, vocal cord paralysis or paresis, neuromuscular dyscoordination and developmental delay in swallowing function [17, 21]. Infants who are at risk of aspiration or those with retching or oropharyngeal dysphagia may benefit from a thickened formula [21].

Menzies *et al*. [25] conducted a retrospective review of all 75 children attending their multidisciplinary OA clinic from 2011 to 2014. Median age at initial appointment was 3.7 years. Twenty-eight percent of children had an associated syndrome, and 96% had at least one associated gastrointestinal or respiratory complication: most commonly GOR disease in 87%, chest infections in 67% and EoE in 38%. Twenty-four children (32%) had a history of gastrostomy feeding, and 10 children (13%) were still using their gastrostomy at the time of the initial appointment (median age 15 months). At the initial appointment 18% of children were wasted (weight for age), 9% were malnourished (weight for length/BMI), 9% were stunted (height for age) and 3% were overweight. Results showed that infants had poorer growth than children >1 year old. Other risk factors for poor growth included having had a fundoplication, those at risk of aspiration or children who had had an additional surgery (other than OA repair) in the first year of life. Regarding eating behaviour 54% of children did not consume age-appropriate textures (most commonly seen in those <2 years old), 29% demonstrated extreme food selectivity (<20 foods in diet) and 25% had lengthy mealtimes (>45 minutes). Results may, however, be falsely elevated in this study as children were reviewed from a specialist clinic and not a general OA population, therefore possibly containing a higher proportion of more complex cases.

Mealtimes can become very antisocial as choking and vomiting are common when eating, and children may need hefty pats on the back to dislodge food that has become stuck. Eating can be a very slow process for the child, as foods have to be thoroughly chewed before swallowing can be attempted. Parents understandably feel inhibited about eating out of the home, which curtails the social experience of the child. It is often difficult for parents and carers to understand the problems with swallowing following repair of OA, and force feeding the child may be a temptation.

Adequate nutrition can usually be achieved with small frequent meals that are energy dense and the provision of fluids at mealtimes to help wash down the food. Such are the problems associated with eating that families need help, advice and encouragement from all professionals with appropriate experience, including dietitians, speech and language therapists, clinical psychologists and medical and nursing professionals. The Tracheo-Oesophageal Fistula Support Group (TOFS) is a self-help organisation where carers of these children can share their experiences and offer advice.

Outcomes

Growth studies within the OA population are often limited by a lack of adjustment for comorbidities, e.g. cardiac, genetic or neurological, which may have a large impact on growth. Early nutritional support and advances in neonatal and surgical care of these infants and children have decreased the prevalence of long-term growth faltering in this population [17].

A review in 2006 of 15 children with OA and TOF who had primary repair at birth found that all were between the 50th and 75th centile of expected growth at 12 years of age [26]. A later review in 2012 of 57 children with OA and TOF (mean age 13 years) found that 75% had experienced normal growth patterns, 9% of patients were underweight and 16% were overweight, according to weight/height *z*-scores [14]. Vergouwe *et al*. [27] reviewed 96 children with OA at 5 years of age (genetic syndromes associated with growth disorders were excluded). Stunting (>2 SD below normal height for age) was present in 5%–8% of children depending on their age, and wasting (>2 SD below normal weight for height) in 3%–12%. In children 1–8 years old, weight and height were significantly lower than the general population, but by 12 years of age, it had normalised in most children. Low birth weight and fundoplication were found to be negatively associated with growth.

Due to improvements in surgical and post-surgical care, the focus of research in these patients has more recently been on quality of life (QoL) issues; OA is not just a neonatal problem, but can often cause lifelong issues [17]. Ongoing gastrointestinal problems are frequently reported in adults. Studies have found that 39%–85% of adults reported symptoms of dysphagia and 29%–63% experienced symptomatic reflux [17].

Legrand *et al*. [14] studied 81 patients with OA and TOF who were treated in their institution from 1989 to 1998. In 2008, 57 of these patients returned for nutritional status, digestive and respiratory symptoms and QoL assessments. The mean age was 13.3 years: 61% had dysphagia; 35% had GOR disease and only 19% of patients had no digestive symptoms. Their QoL was good but was lower than in healthy controls and was lower in patients born prematurely, with symptoms of GOR disease and a barky cough. The association between complaints of dysphagia and GOR disease, oesophageal function and QoL was also investigated in 25 adults who had previously undergone correction of OA [15]: 48% reported complaints of dysphagia and 33% of

GOR. Manometry showed low oesophageal contractions in 20% of patients, and pH measurements showed pathological reflux in 14%. Patients reporting dysphagia more often had disturbed motility and appeared affected by these symptoms in their QoL. No association was found between QoL and GOR complaints. The authors' hypothesis was that this may be because these patients had grown up with these symptoms and had got used to them.

Dellenmark-Blom *et al*. [28] conducted a literature review regarding health-related quality of life (HRQOL) studies among children and adults with OA. Overall HRQOL was found to be reduced in five out of seven studies comparing overall HRQOL in OA with a healthy reference population. Reports of the impact of OA on physical, psychological and social HRQOL differed between studies, and no conclusions could be drawn.

Dumping syndrome

Following oesophageal replacement

Dumping syndrome is often seen in infants and young children following gastric transposition. Studies have shown that children with OA often have abnormal gastric emptying. This alone, or together with damage to the vagus nerve during oesophageal anastomosis, is thought to cause dumping syndrome [17, 29].

Ravelli *et al*. [30] studied gastric emptying in 12 children who had undergone gastric transposition using electrical impedance tomography. Gastric emptying was normal in one patient, delayed in seven and accelerated in four. Like the repaired oesophagus, the transposed stomach does not behave normally. The stomach retains its function as a reservoir, but its emptying is extremely irregular. Spitz [29] found that the dumping experienced in the early post-operative period was short lived, although it lasted for as long as 6 months in some children and recurred periodically in one child. Michaud *et al*. [31] reported two children who underwent primary repair of their OA and presented a few months later with dumping syndrome. Neither child had undergone anti-reflux surgery nor had known precipitating factors. They suggested that dumping syndrome can occur after primary anastomosis of OA without anti-reflux surgery, and it should be considered in children with OA when they present with gastrointestinal symptoms, faltering growth or refusal to eat.

Following Nissen fundoplication

Dumping can also occur in children following Nissen fundoplication for severe GOR. Holschneider *et al*. [19] found that following fundoplication dumping syndrome was seen in 18.3% of children with OA post-operatively compared with 1.6% in the non-OA group. Pacilli *et al*. [32] measured gastric emptying in eight children before and after laparoscopic Nissen fundoplication. Their results showed that gastric emptying was accelerated in all but one patient and concluded that gastric emptying for liquids is accelerated following Nissen fundoplication. When gastric emptying is accelerated, the result is that hyperosmolar foodstuffs leave the stomach very rapidly and hence draw large quantities of fluid into the small bowel. This produces the 'early' symptoms of distension, discomfort, nausea, retching, tachycardia, pallor, sweating and dizziness. This may be associated with hyperglycaemia. 'Late' symptoms may occur from 1 to 4 hours later as a result of hypoglycaemia and may be indistinguishable from early symptoms [33].

Dietary interventions

There are no large studies on children with dumping syndrome, and most of the published papers are case histories; all report it as difficult to treat. Various dietary interventions have been tried to overcome the symptoms of dumping, but no one treatment has been agreed on. The aim is to avoid swings in blood sugar levels. Some children respond to a combination of treatments. In summary these are:

- giving small frequent meals [29, 33]
- taking fluids separately from solid foods [29, 34]
- avoiding a high glucose intake [29, 34]
- adding uncooked cornstarch to feeds at a concentration of 3.5%–7% [31] or 50 g/L of feed [35]
- adding pectin to the diet: 5–10 g (<12 years) or 10–15 g (>12 years) divided into six doses [34]
- administering continuous feeds with added fat (both long-chain and medium-chain fats are used) or small frequent meals enriched with fat [35–37]

Borovoy *et al*. [38] described eight children with dumping syndrome fed by gastrostomy and found that uncooked cornstarch controlled glucose shifts, resolved most of the symptoms, allowed bolus feedings and enhanced weight gain. A guideline for the administration of uncooked cornstarch could be taken from the treatment of glycogen storage disease (p. 612).

Learning points: oesophageal atresia

- *Surgical repair of the OA and/or TOF needs to be performed before oral feeding can commence*
- *The first choice in correcting OA is to preserve the native oesophagus and perform a primary repair*
- *Infants with long-gap OA often have a delayed introduction of oral feeds and commonly experience more long-term feeding difficulties than other children with OA*
- *GOR, anastomotic strictures and dysphagia are common post-operative complications in children and adults*
- *Infants should be weaned onto solids at the recommended age of around 6 months and weaning modified according to tolerance and symptoms*
- *Other associated anomalies occur in 50%–66% of infants with OA, over 50% of infants with duodenal atresia, 23% of infants with Hirschsprung's and 17% of infants with gastroschisis*

Duodenal atresia

Duodenal atresia (DA) is a cause of congenital intestinal obstruction and occurs in about 1 in 10 000 births [39]. In most cases the atresia occurs below the ampulla of Vater. Radiography demonstrates the typical 'double bubble' of the dilated stomach and duodenum proximal and distal to the atresia. DA most often presents as bilious vomiting with secreted bile unable to pass down the intestine. Less common presentations include feeding difficulties, faltering growth, gastric distension, aspiration and delayed passing of meconium. The obstruction is corrected by cutting the blind end of the duodenum and connecting it to the lower intestine. There are other anomalies associated with this atresia: Down's syndrome, structural cardiac defects, tracheo-oesophageal fistula, imperforate anus and malrotation occur in over 50% of infants with duodenal atresia [40, 41]. Mortality is related to the severity of the associated anomalies, and the prognosis for this condition has significantly increased since early 1970s. Mooney *et al*. [42] reported an improvement in survival from 72% in 1973 to 100% in 1983. Burjonrappa *et al*. [40] reported a 100% survival rate in a review of 59 infants with DA born between 1983 and 2008. Choudhry *et al*. [41] reported a 96% survival rate in 61 infants born between 1995 and 2004.

Following corrective surgery PN is often used to feed these infants (p. 68), until enteral feeds are established. Post-operatively a nasogastric (NG) tube will be left on free drainage, and once gastric aspirates decrease (indicating that the lower gut is patent), enteral feeds can commence via the NG tube. PN is then titrated down as enteral feeds are slowly increased. Bairdain *et al*. [43] found that median time to establish full enteral feeds was 12 days and that delayed transition to full enteral nutrition was more likely to occur in patients who also had congenital heart disease, malrotation or prematurity. A TAT may sometimes be passed post-surgery to help in the delivery of feeds [44]. In a study of 17 babies undergoing upper gastrointestinal surgery (10 with DA, six with malrotation and one with jejunal atresia), enteral feeding was started via transgastric transanastomotic feeding jejunostomy tubes by day two post-surgery in 14 cases; the authors concluded that this method of feeding was well tolerated and preferable to PN [45]. However, complications have also been reported with the use of these tubes, and they have been associated with increased time to reach full feeds and/or longer hospital stay [44]. Bishay *et al*. [44] conducted a retrospective study of 54 children who underwent surgery for DA (35 patients) and duodenal stenosis (19 patients). They found that in 19 children (35%) PN was commenced within 3 days of surgery, 13 (24%) received delayed PN that was commenced on average 7 days post-operatively and 22 (41%) never received PN. Children who never received PN reached full feeds quicker and had a significantly shorter hospital stay than those who did receive PN. At the last follow-up (median 19 months), the children who initially started PN and those who never started PN regained their baseline growth centiles, but those who received delayed PN had not yet regained their baseline centiles. They concluded that children with DA and stenosis can successfully be managed without PN; however, in their study a third of these infants received delayed PN and experienced a significant decrease in weight *z*-scores (from the time of surgery to full feeds being established), with poor catch-up weight gain following discharge. This highlights the need for ongoing nutritional management and weight monitoring, ensuring that either feeds or PN is started soon after surgery, helping to optimise growth.

Breastfeeding is often possible within a week of surgery. If bottle fed, EBM or standard infant formula should be given and, if administered correctly, should provide adequate nutrition. If weight gain is poor, the usual methods of feed fortification can be used (Table 1.18). These same feeds should be used if enteral feeding needs to be continued.

Feeding problems post-surgery

The feeding problems following repair of DA are usually associated with the motility of the duodenum. *In utero*, the duodenum proximal to the atresia is stretched because ingested material cannot get past the atretic area of gut. The musculature may not function properly once the obstruction is removed, resulting in a baggy proximal duodenum. The infant may feed normally, but milk will accumulate in the lax duodenum rather than continuing its passage down the gut. This can result in large vomits, up to 200 mL at a time. Feeds need to be small and frequent to overcome this problem.

If GOR is present, feeds can be thickened, and the baby should be positioned correctly after feeding. As the gut grows and matures with the infant, problems should resolve so that the older child should feed normally.

Hirschsprung's disease

Hirschsprung's disease (HD), also known as congenital megacolon or aganglionic megacolon, is a congenital disorder where there is an absence of ganglion cells in the affected part of the large intestine. This results in a loss of peristalsis and causes functional distal intestinal obstruction. In the majority of cases, only the rectum or sigmoid is involved, but in about 10% of infants, a longer segment of colon is affected, which can often be the whole colon, referred to as total colonic aganglionosis. A population-based cohort study of all live born infants with HD born in the UK and Ireland between October 2010 and September 2012 identified an incidence of 1 in 5500 live births. Results showed that the male to female ratio was 3:1, and 23% of infants had an associated anomaly. Of these 15% had a recognisable syndrome with Down's syndrome being the most prevalent [46]. These results are similar to those reported from other studies [47]. The aganglionic parts of the colon cannot pass faeces; therefore, infants commonly present around 48 hours of life with bilious vomiting, abdominal distension and failure to pass meconium. Some infants and children can present later with a history of constipation, abdominal distension, vomiting, diarrhoea and/or poor growth [47]. Following diagnosis of HD, the initial supportive management would include either rectal washouts or the formation of a stoma to maintain

colonic decompression. A pull-through procedure would then be performed by resecting the aganglionic colon and anastomosing the ganglionic bowel to the anorectum [46]. Zani *et al*. [48] found that 33% of surgeons would perform a pull-through at diagnosis and 67% would delay this until the infant was 4 months old or weighing >5 kg. Bradnock *et al*. [46] found that in 305 infants with HD, 86% were initially managed with rectal washouts and 13% with stoma formation. Of those having rectal washouts, 27% failed this management plan and required a delayed stoma. Therefore, a total of 40% ended up requiring a stoma [46]. This study confirms what other studies have shown that rectal washouts and then a primary pull-through procedure has become the preferred method of management [46, 48].

Following surgery many infants and children continue to have long-term problems with bowel function. Jarvi *et al*. [49] assessed bowel function and gastrointestinal QoL among 92 adults with previously operated HD. These patients reported increased incidence of inability to hold back defaecation (40% vs. 17% in controls), faecal soiling (48% vs. 22%), constipation (30% vs. 9%) and social problems related to bowel function (29% vs. 11%). Gastrointestinal QoL, however, was only slightly lower in the Hirschsprung's group than the control group. Collins *et al*. [50] studied QoL in 60 children with HD (median age 6.4 years). They found that they experienced significantly lower psychosocial QoL and significantly higher levels of faecal incontinence compared with healthy children. Increasing age, increasing severity of faecal incontinence, constipation and dysfunctional elimination negatively affected QoL. However, there were no significant differences in physical and total QoL between healthy children and those with HD.

Most infants and children follow a normal diet and require no dietary restrictions. However, Stathopoulos *et al*. [51] recently studied 10 patients who presented with long-term persistent faecal incontinence. Anatomical defects were excluded and rapid intestinal transit was proven by nuclear transit studies. Eight of these children (mean age 9.6 years) underwent a hydrogen breath test for fructose and/or lactose malabsorption and seven tested positive. Exclusion diets for protein allergens, lactose or fructose were then trialled, and resolution or improvement in faecal incontinence was seen in nine of the 10 children. This study suggests that reactions to food may contribute to poor bowel function in some patients and dietary restrictions should be considered in those with rapid intestinal transit.

In long segment Hirschsprung's disease (the most severe form of HD), there is small bowel involvement. Resection of all aganglionic bowel is necessary, often leaving the infant with a shortened length of small bowel. The dietary management for this condition is as described for short bowel syndrome (SBS) (p. 159).

Abdominal wall defects

Exomphalos and gastroschisis are not abnormalities of the gastrointestinal tract but are abdominal wall defects involving the exposure of the infant's intestine, and in some cases other organs, to the outside world.

Exomphalos

The overall incidence of exomphalos in England and Wales over the 7-year period 2005–2011 was 1 in 2600 births. Thirty-seven percent of these are isolated cases of exomphalos, 31% occur with other anomalies and 32% with a chromosomal abnormality. The most common anomalies associated with exomphalos are Edwards' syndrome, congenital heart defects and nervous system anomalies [52]. Springett *et al*. [52] reviewed 234 infants born in England and Wales between 2005 and 2011 and found the overall 1-year survival rate of all live born cases was 84%. The 1-year survival of infants born with isolated exomphalos was 92% compared with 81% for those with multiple anomalies and 27% for chromosomal cases.

An exomphalos can be small or large and occurs when the lateral folds of the abdominal wall fail to meet *in utero*, resulting in incomplete closure of the abdominal wall and herniation of the midgut. Not only bowel but also solid viscera like the liver, spleen, ovaries or testes may be exposed, contained in a translucent membrane composed of amnion and peritoneum. Surgery is necessary soon after birth to place the intestine and other organs back into the abdomen. If the exomphalos is small, a primary closure can be performed: the bowel is placed back inside the abdomen, and the abdominal wall is then closed and a navel fashioned. If the exomphalos is too large for this procedure, a staged repair is performed. The exposed intestines and other organs are covered with a prosthetic mesh sac ('silo') to protect them. The silo is suspended above the child and is tightened regularly as the intestine gradually moves back into the abdominal cavity by gravity. The abdomen is then closed and a navel fashioned [53].

Gastroschisis

The overall birth prevalence of gastroschisis is 1 in 2380 total births in the UK [54]. An increasing incidence has been seen worldwide and is associated with younger maternal age, low socioeconomic status, poor nutrition, smoking and substance abuse [53, 54]. Gastroschisis is classified as either simple or complex. Complex gastroschisis occurs in approximately 17% of cases and is commonly associated with at least one of the following: intestinal atresia, perforation, necrosis or volvulus. In simple gastroschisis, none of the above associations are seen, and the bowel is intact, uncompromised and continuous [55]. A study of 301 infants with gastroschisis showed a 96% survival rate after the first year of life [56].

In gastroschisis, a rupture of the umbilical cord *in utero* in early pregnancy allows the intestine to escape outside the abdominal wall; in this case, unlike in exomphalos, the intestine has no covering membrane. Surgical strategies for closing the defect consist of primary or staged and operative or non-operative techniques. In a staged closure, the defect is reduced by a preformed silo, and the abdomen is later closed either with operative or non-operative techniques [56, 57]. There is limited evidence or consensus between experts regarding which approach has more favourable outcomes. A study involving all 28 surgical units in the UK and Ireland identified 393 cases of gastroschisis born between October

2006 and March 2008. Eighty-five percent had simple gastroschisis, 11.5% complex and 3% not categorised. Within the simple gastroschisis group, 51% of infants underwent operative primary closure, and 36% staged closure after a preformed silo had been placed. Outcomes for infants with complex gastroschisis were significantly poorer than those with simple gastroschisis [57]. Bradnock *et al*. [56] found that infants managed with preformed silos took on average 5 days longer to reach full enteral feeding compared with those managed with primary closure. Other outcome measures for both groups were similar.

Feeding the infant with abdominal wall defects

Impaired gastrointestinal function is common in infants with abdominal wall defects, especially in those with gastroschisis. The pressure of the silo or the closed abdominal wall forces the intestine back into the abdomen, but this continual pressure may upset normal intestinal function, including intestinal motility, resulting in a prolonged functional ileus. Most of these infants will need PN (p. 68) for several weeks or months before bowel function returns.

Enteral feeding is considered when bowel sounds return, and nasogastric aspirate has decreased. Expressed breast milk or infant formula is usually tolerated if given as small frequent boluses or as a continuous feed. Large boluses are not tolerated as the intestinal tract is under constant pressure and cannot accommodate a large amount of fluid at once. If the baby can be handled normally and does not need to be nursed flat, breastfeeding is possible. In one study 70% of babies with gastroschisis were breastfed on discharge, 28% were bottle fed and 2% were taking solids (median hospital stay was 24 days, range 6–419 days) [58]. If there is malabsorption, then a hydrolysed protein feed is indicated (Table 8.15).

Burge *et al*. [59] conducted a retrospective review of 111 infants with gastroschisis. In 50 infants (45%), symptoms suggesting non-IgE-mediated cow's milk protein allergy (CMPA) were recorded and resulted in the feed being changed. Median age of diagnosis of suspected CMPA was 44 days. In 44 infants follow-up data was available. All experienced improvement in symptoms after their feed was changed to either an extensively hydrolysed formula, an amino acid-based formula or breastmilk while the mother was taking a cow's milk protein-free diet. The majority showed a significant reduction in symptoms within 2 weeks of this feed change. This study suggests that infants with gastroschisis and symptoms suggestive of CMPA may benefit by changing to a milk-free formula.

A retrospective study of 79 infants with simple gastroschisis found that those exclusively fed with breastmilk (28%) had a significantly shorter time to reach full enteral feeds (median 5 vs. 7 days) and a shorter time to discharge after feeds where initiated (median 7 vs. 10 days) compared with non-exclusive breastmilk fed infants. Interestingly, the same benefits were not seen in infants receiving a mixture of breastmilk and formula, suggesting that the use of exclusive breastmilk is most beneficial for infants with simple gastroschisis [60].

Kitchanan *et al*. [61] found that neonates with gastroschisis had significant delays in reaching full enteral feeds compared with those with exomphalos (24 vs. 8 days) and required prolonged support with PN (23 vs. 6 days). The age at which the infant with gastroschisis is first given enteral feeds affects the length of stay in hospital and the duration of PN; each day delay in starting enteral feeds was associated with an increase hospital stay of 1.05 days and increased PN duration of 1.06 days. Median day of first enteral feeds was day eight post-surgery (range 3–40 days) [58]. A follow-up study of 301 infants found that infants with complex gastroschisis required PN for an average of 51 days, compared with infants with simple gastroschisis who required PN for an average of 23 days. Mean length of stay was 84 days for complex gastroschisis and 36 days for simple gastroschisis [56]. Bergholz *et al*. [55] found that infants with complex gastroschisis were started on enteral feeds later, took longer to reach full feeds and therefore continued PN for longer than infants with simple gastroschisis. Their risk for sepsis (possibly PN related), SBS and necrotising enterocolitis was also higher. Infants with complex gastroschisis also had longer hospital stays and were more likely to be sent home on enteral feeds and PN.

A recent study of 50 infants with exomphalos found that 37% of infants with exomphalos major and 17% with exomphalos minor still required nasogastric feeding at discharge [62].

Outcome

Henrich *et al*. [63] followed up 22 survivors of gastroschisis and 15 of exomphalos who were treated between 1994 and 2004. Developmental delays were rapidly made up after treatment, and 75% of these children had no gastrointestinal problems or suffered from these rarely. Most children were of normal weight and height, with physical and intellectual development delay seen in a third. The initial gastrointestinal problems and developmental delays were most often made up during the first 2 years of life, and, except for those with severe defects, the children had good QoL scores.

Fifty infants with gastroschisis were followed up at a median age of 9 years (5–17 years); of these 10 infants 20% had complex gastroschisis. Growth data was available for 42 children. Most children showed significant catch-up growth from birth to follow-up. At follow-up one child (2%) was underweight, 10 children (24%) overweight and four children (9.5%) obese. Bone mineral density was measured in 41 children, and results suggested that three children (7%) had significant bone density deficiency. Laboratory investigations showed the most prevalent micronutrient deficiencies were iron deficiency anaemia (12%), vitamin D (13%) and vitamin B_{12} (6%, both children having lost significant small bowel) and fasting cholesterol was elevated in 24% of children, with no correlation to BMI. This study supports what others have suggested that good catch-up growth is seen in older children with gastroschisis [64].

Twenty infants with gastroschisis (four complex) born between October 2006 and August 2011 were reviewed.

Mean gestational age was 35.7 weeks and mean birth weight 2.29 kg. Fourteen underwent primary closure, three silo reduction and three multiple staged closure. Median duration of PN was 21.5 days and median time to start feeds 7.5 days. Growth and development were reviewed in 18 infants at 1 year of age. Weight was <10th centile in 28% of children compared with 50% at birth, and there was no significant difference in development between the study and control group. Infants born <10th centile for weight did however have significant receptive and expressive language delay. This study suggests that neurodevelopmental outcomes at 1 year of age are associated more with being small for gestational age than having gastroschisis [65].

Intestinal atresia occurs in 10%–20% of infants with gastroschisis, and they may also develop intestinal necrosis. This may lead to SBS, the management of which is described below.

Learning points: abdominal wall defects and Hirschsprung's disease

- *In infants with exomphalos 37% are isolated cases, 32% have a chromosomal abnormality and 31% have other abnormalities*
- *Infants with gastroschisis have significant delays in reaching full enteral feeds compared with those with exomphalos*
- *Complex gastroschisis is associated with longer durations of PN, delayed introduction of enteral feeds and longer hospital stays than simple gastroschisis*
- *In Hirschsprung's disease rectal washouts followed by a primary pull-through procedure are the preferred method of management*
- *Long-term problems with bowel function are commonly reported in children and adults with previous operated Hirschsprung's disease*

Short Bowel Syndrome

Tracey Johnson

Introduction

SBS is a collection of disorders where a loss of intestinal length has occurred that compromises the ability to digest and absorb nutrients. Accurate estimates of SBS incidence are difficult to determine due to variation in the definition of SBS. SBS in children may occur at any age, but the majority of cases result following extensive bowel resection in the early neonatal period. Resection may be required in infants born with congenital abnormalities, e.g. gastroschisis, bowel atresias and malrotation, or in infants who develop necrotising enterocolitis. In older children SBS may result from extensive resection following volvulus, trauma, intestinal malignancy or Crohn's disease. Even in the absence of resection, children may have conditions leading to a 'functional short bowel' including long segment Hirschsprung's disease, gastroschisis without resection and radiation enteritis.

After an extensive bowel resection, there are many factors determining outcome. All these factors will have a bearing on the management of the individual patient.

Infants are born with a small bowel length of 250 ± 40 cm [66]. Loss of intestinal length results in loss of surface area for absorption and loss of digestive enzymes and transport carrier proteins, leading to malabsorption. In general, loss of up to 50% of small bowel can be tolerated without any major nutritional problems, and clinical features of SBS usually result when more than 75% of the small intestine has been resected. The small bowel length doubles in length in the last 15 weeks' gestation, which gives preterm babies a physiological advantage as their bowel has great potential to increase in length [67].

Although it is important, the length of remaining bowel is not the only factor determining outcome; the quality of the remaining gut, the site of resection, the presence or absence of the ileo-caecal valve (ICV), the presence or absence of colon, the primary diagnosis and any ensuing complications will also influence the prognosis.

The key to survival after an extensive small bowel resection is the ability of the remaining bowel to adapt and take over the functions of the resected segment of bowel. Adaptation begins within 24–48 hours after resection. The remaining small bowel hypertrophies, increasing the surface area and the absorptive function. The absorptive functions of the jejunum and ileum are given in Table 9.1.

Although the jejunum is the site of absorption of the majority of nutrients, the loss of jejunum is better tolerated than the loss of ileum. The reasons are as follows:

- The ileum has a greater capacity for adaptation than the jejunum; the ileum can adapt and compensate for the absorptive functions of the jejunum, but the jejunum does not have the same potential for adaptation and cannot develop the specialist functions of the ileum, namely, bile salt and vitamin B_{12} absorption
- Transit time in the ileum is slower than in the jejunum, allowing luminal contents to be in contact with the mucosa for longer periods of time
- The ileum has the capacity to absorb fluid and nutrients against an osmotic gradient, leading to favourable absorption compared with the jejunum

The presence or absence of the ICV also has an important part to play in determining outcome in patients with SBS.

Table 9.1 Absorptive functions of the jejunum and the ileum.

Jejunum	Ileum
Glucose	Vitamin B_{12}
Disaccharides	Bile salts
Protein	Fluid
Fat	Electrolytes
Calcium	
Magnesium	
Iron	
Water soluble vitamins	
Thiamin	
Riboflavin	
Pyridoxine	
Folic acid	
Ascorbic acid	
Fat soluble vitamins	
Vitamin A	
Vitamin D	
Vitamin E	

The valve slows transit time, which increases the duration of contact of luminal nutrients with the mucosal surface and minimises fluid and electrolyte losses. It also serves as a barrier to prevent bacterial overgrowth that can interfere with nutrient and fluid absorption.

The colon has a crucial role in absorption of fluid and electrolytes. In patients with no or minimal colon in continuity, fluid losses slow progression with enteral feeds.

Residual disease may worsen the prognosis of infants following small bowel resection, e.g. after resection for necrotising enterocolitis, the remaining bowel may not be of good quality. This may affect function and reduce the potential for adaptation. A diagnosis of gastroschisis may be associated with intestinal dysmotility resulting in poor feed tolerance, even in infants with a good length of bowel.

Dependence on PN appears to be most governed by the remaining intestinal length and absence of the ICV. This was first recognised by Wilmore in 1972 [68] and has since been confirmed by other studies [69–72]. It has also been shown that enteral autonomy is more likely to be achieved in patients with necrotising enterocolitis as their underlying diagnosis and when there is a multidisciplinary approach to intestinal rehabilitation [72–74]. Rehabilitation programmes utilise the skills of different healthcare professionals important in managing intestinal failure. Good education, individualised nutritional support and early treatment of complications improve health outcomes and QoL.

Nutritional support

The aims of management are to maintain nutritional status, facilitate adaptation of the remaining bowel, control diarrhoea and minimise complications. Nutritional therapy needs to be tailored to the individual child and is ideally managed by a multidisciplinary nutrition team comprising a paediatric gastroenterologist, dietitian, pharmacist, specialist nurse and biochemist.

Learning points: factors determining outcome of short bowel syndrome

- *length of bowel*
- *quality of bowel*
- *jejunum versus ileal resection*
- *presence or absence of ICV*
- *presence or absence of colon*
- *complications*

The development of PN is the most significant factor in the improved survival of children with SBS. PN assures adequate balanced nutrition to maintain hydration and nutritional status (p. 68) and allows time for intestinal adaptation to occur. Although PN provides essential fluid and energy, prolonged exclusive PN can lead to complications, so it is important to aim to give PN in the longer term as nutritional support rather than as the total source of nutrition.

Enteral feeds may not be nutritionally significant, but intraluminal nutrients are the single most important factor in promoting intestinal adaptation in SBS [75]. Trophic feeds, which may be as little as 1 mL/hour, should therefore be commenced as soon as the post-surgical ileus has resolved. Enteral feeds:

- promote pancreatic secretions, hormones and bile
- are important in preventing intestinal failure related liver disease [76]
- may also help to prevent bacterial translocation [77]

Although children with SBS may require PN for long periods, there is potential for progression to full enteral nutrition. Figure 9.2 illustrates the progression from parenteral to enteral nutrition. Managing this transition is challenging as progression can be both prolonged and unpredictable. As feeds are increased, PN can be reduced with the ultimate aim of independence from PN. The process may take months or even years to complete and can involve changing feeds and trials with trophic factors.

The ability to advance enteral feeds results from the process of intestinal adaptation. There are various strategies that can help this process. As already discussed it is important to put some feed into the bowel, and if the distal bowel is not in continuity, this should include feeding stoma effluent into a distal mucous fistula to maintain function. The recycled proximal content stimulates mucosal growth, intestinal adaptation and absorption and prevents atrophy of the distal bowel [78]. There is an associated risk of sepsis due to

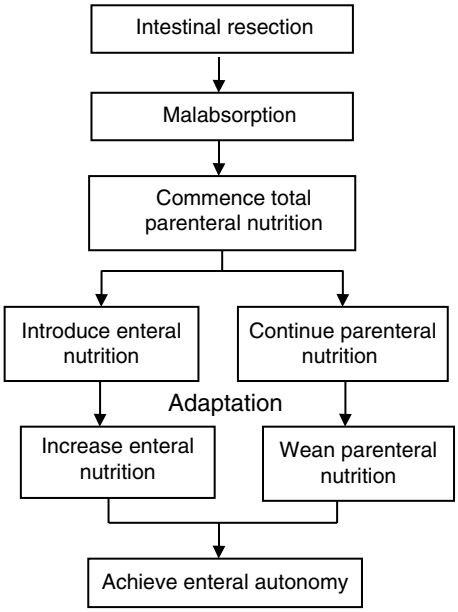


Figure 9.2 Progression from parenteral to enteral nutrition.

high levels of pathogenic bacteria in effluent samples, and it is recommended the effluent should not be used beyond 90 minutes from collection [79].

Learning points: nutritional support

- *Nutritional support needs to be tailored to the individual child*
- *Nutritional support requires the skills of a multidisciplinary nutrition team*
- *PN is essential to maintain hydration and nutritional status*
- *Enteral feeds are the single most important factor in promoting adaptation and should be started early, although they may provide insignificant nutrition*

Choice of feed

The choice of nutrients may be important. Complex nutrients, especially long-chain triglycerides (LCT), stimulate adaptation better than simple nutrients, the hypothesis being that the more work the bowel has to do to digest a nutrient, the greater the stimulus to adapt [80]. There is no consensus regarding the best formula for infants with SBS. Two systematic reviews of nutritional therapies in paediatric SBS showed the evidence was limited and of poor quality [81, 82]. There is a lack of randomised trials, and most human data on the nutritional management of SBS are derived from retrospective analysis of case series. As a result, in individual centres, practices depend more on years of personal experience than on research.

Protein

Infants with SBS might be expected to benefit from an extensively hydrolysed protein feed because of the insufficient luminal surface area for digestion and absorption, but protein digestion and absorption is completed in the upper small gut and is generally not a significant problem in SBS. There is probably little absorptive benefit from using amino acid-based or hydrolysed protein feeds [83], and complex proteins may in fact be superior in stimulating adaptation. However, cow's milk protein intolerance can occur in surgical neonates and has also been reported in SBS, so there may be a role for extensively hydrolysed protein or amino acid-based feeds when inflammation is present [84, 85]. Children with SBS, especially young infants, may have a risk of secondary non-IgE-mediated intestinal allergic disease. Secondary protein intolerance is a common phenomenon after mucosal injury [86], and increased permeability to food antigens in SBS may lead to an enteropathy or inflammatory colitis [87].

Fat

A similar compromise is needed when considering dietary fat. LCT has the greatest potential for stimulating adaptation, is a source of long-chain polyunsaturated fatty acids and essential fatty acids and has a lower osmolarity than medium-chain triglycerides (MCT). However, many children with SBS have significant fat malabsorption, and feeds with a high content of LCT may result in steatorrhoea. In contrast MCT is water soluble and, therefore, efficiently absorbed. The disadvantage of MCT is its higher osmolarity, and experimental evidence has shown that formulas containing MCT stimulate less intestinal adaptation than those containing LCT [88]. A mixture of LCT and MCT, to combine the physiological advantage of MCT and the positive effects of gut adaptation from LCT, may be the best compromise [89].

Carbohydrate

Carbohydrate has the greatest intraluminal osmotic effect but potentially can be well absorbed as brush border enzyme activity can be induced according to the composition of the feed. Feeds containing sucrose will induce sucrase, and those containing glucose polymer will induce isomaltase [90]. The exception to this is lactose.

Monosaccharides need no digestion, but have a higher osmotic load than polysaccharides. Just as with protein and fat, it can be suspected that polysaccharides may stimulate intestinal adaptation better than monosaccharides. Intact starch can also be fermented to short-chain fatty acids in the colon, stimulating sodium and water absorption and providing a primary energy source for the colonocytes.

Breastmilk

Breastmilk may not seem the ideal feed as it contains whole protein and lactose; however, it is associated with good gastrointestinal tolerance. In addition to the psychological benefits for the mother of using her breastmilk, it contains high levels of IgA, nucleotides, epidermal growth factor (EGF) and leucocytes [91]. Glutamine, LCT and growth hormone in breastmilk may play a role in intestinal adaptation, and there may also be benefits associated with protective colonic bacteria. Importantly, studies have shown that the use of breastmilk correlates highly with a shorter duration of PN and that highly specialised formulas confer no advantage over breastmilk [92]. It is the practice in most centres managing infants with SBS to use mother's EBM in the initial stages of feeding. In the early stages of enteral feeding, expressed milk is usually preferred so it can be given in the small measured amounts that are tolerated, but breastfeeding can usually be introduced when feed volumes are increased and if the infant is at least 35 weeks' gestation.

Formula feeding

It is important to have a flexible approach to feeding, and knowledge of gut anatomy and physiology allows informed decisions about nutritional management to be made. In the absence of EBM, or when there is intolerance of EBM, the most appropriate feed to try would be a protein hydrolysate feed with approximately 50% of the fat as MCT [89]. Suitable feeds would be Aptamil Pepti-Junior and Pregestimil Lipil (Table 8.15).

As feed volumes are advanced, malabsorption frequently occurs. It may be helpful to formulate a feed to suit the individual child with a choice of ingredients not predetermined by the composition of a commercial formula. A modular feeding system allows this flexibility giving a choice of protein, fat and carbohydrate so that ingredients can be manipulated individually to find a feed composition that is tolerated. Modular feeds can be successfully used in the management of children with SBS, leading to improved absorption, advancement of enteral feeds and ultimate independence from PN [93].

Tables 8.21–8.23 show some of the components that may be used in a modular feed. The protein source can be a whole protein, hydrolysed protein or amino acids. The carbohydrate source may be polysaccharides, disaccharides (sucrose, lactose) or monosaccharides (fructose, glucose), and in practice a combination of carbohydrate sources may be beneficial so as not to saturate the capacity of a single brush border enzyme. The ratio of LCT to MCT can also be manipulated to tolerance. Electrolytes and micronutrients are added to make the feed nutritionally complete (Table 8.24). An example modular feed is shown in Table 8.25.

Establishing a modular feed involves systematic stepwise changes to feed concentration and volume. Careful description of volume and consistency of stools needs to be documented, and serial analysis of stool or stoma fluid for reducing sugars, pH and fat is crucial to make informed decisions about feed composition.

Learning points: choice of feed

- *Breastmilk is recommended when feeds are first introduced*
- *If breastmilk is not available or not tolerated, a protein hydrolysate feed with 50% fat as MCT is usually recommended*
- *Amino acid-based feeds are not indicated unless inflammation is present*
- *Feed changes should be guided by stools/stoma fluid: quantity, consistency, reducing sugars, pH and fat*
- *Modular feeds can be used to establish a feed that is tolerated*

Trophic factors

There are few studies conducted in infants and children regarding trophic factors, and, like other aspects of managing SBS, more controlled studies are required to justify their widespread use. Their current use is based on trial and error, but as a non-invasive inexpensive intervention, a trial of pectin or glutamine may be useful.

Pectin is a water-soluble fibre. In animal experiments pectin has been shown to slow gastric emptying, slow transit through the small bowel and enhance adaptation. Following fermentation to short-chain fatty acids by colonic bacteria, pectin may also improve colonic absorptive function [94–97]. Slower transit allows a longer nutrient contact time with the intestinal mucosa, and in children with a preserved colon, pectin may also stimulate water and sodium absorption [98]. A dose of 1 g/100 mL feed has been suggested [99]. Pectin is no longer manufactured by pharmaceutical companies in the UK. Suitable products designed for use in the catering industry can be obtained and need to be free from added sugar and tested for microbiological safety.

Partially hydrolysed guar gum has also been shown to reduce stool frequency in children with SBS when added to enteral feeds and solids [100].

Glutamine (available as Adamin G) is considered to be an important energy source for rapidly dividing cells such as the cells of the intestinal mucosa. The benefit is unclear, but glutamine supplements may enhance adaptation, have an anabolic effect on body tissues and improve enterocyte glucose absorption [101, 102]. The ideal dose is unclear, but animal studies suggest that increasing the glutamine content of feeds to 25% total amino acids may enhance adaptation [98].

Route of feeding

Continuous tube feeding

Infants and children with SBS frequently tolerate continuous enteral feeds better than oral bottle or enteral bolus feeds. A slow infusion of feed allows constant saturation of brush border enzymes and carrier proteins, leading to improved absorption. Luminal nutrients are the single most important

stimulus for adaptation, so maximising the time during which nutrients are in contact with the intestine will optimise the potential for adaptation. While continuous enteral feeding can be associated with improved tolerance, excessive feeding by this route could lead to abdominal distension and small bowel bacterial overgrowth if unabsorbed feed collects in dilated bowel loops [103]. It is, therefore, important not to push feeds beyond the limit of tolerance.

Oral feeding

Continuous feeding allows for maximum nutrient absorption, but infants need to learn to suck, swallow and chew. Small intermittent breast or bottle feeds should be initiated to maintain oral feeding skills and to lessen the likelihood of feeding difficulties commonly seen in children who are tube fed for extended periods [104]. Oral feeding will also stimulate gall bladder contraction and perhaps, therefore, contribute to a reduced risk of intestinal failure-associated liver disease. Oral feeding will also promote the release of EGF, increasing gastrointestinal secretion of trophic factors [105].

Solids should be introduced at the appropriate time around 6 months of age. There is no consensus on the type of solids offered, but it seems sensible when infants are receiving a special formula that they are cow's milk protein and lactose-free. There is no evidence to support the avoidance of other foods such as egg, gluten, wheat or disaccharides, but in individual cases it may be necessary to exclude other foods if intolerance is suspected.

Learning points: feeding route

- *Continuous feeding allows for maximum nutrient absorption*
- *Oral feeding skills need to be maintained with intermittent breast or bottle feeds*
- *Solids should be introduced around 6 months of age*

Pharmacological agents

H_2 receptor antagonists and proton pump inhibitors

Gastric hypersecretion frequently occurs after massive bowel resection. This will increase gastric aspirates and stool and stoma output but more importantly can impair absorption by inactivation of pancreatic enzymes. Treatment with drugs such as ranitidine and omeprazole is frequently required. Gastric hypersecretion is a transient phase, and treatment with these drugs should cease once hypersecretion has resolved; it is important to restore an acid environment in the stomach to inhibit the growth of microorganisms.

Anti-diarrhoeal agents

Loperamide can be used to slow transit time and control diarrhoea.

Cholestyramine

Resection of the terminal ileum can result in bile salt malabsorption. Bile salts are conjugated to bile acids by colonic bacteria, leading to diarrhoea. Cholestyramine may help to bind the bile salts. Improvement will be seen within 24–48 hours.

Growth factors

Growth factors can be used to facilitate intestinal adaptation after surgery in patients with SBS, thus enhancing fluid, electrolyte and micronutrient absorption.

Growth hormone has been used to promote intestinal autonomy, but there is little evidence to support its use to improve weaning from PN. Reduced dependence on PN has been shown in some patients, but further evaluation is required [101, 102, 106].

Teduglutide is an analogue of endogenous human glucagon-like peptide-2 (GLP-2), which has recently been used in the management of SBS. Following surgery, the concentration of endogenous GLP-2 is decreased, which may contribute to the reduced digestive and absorptive function of the remaining intestine. Exogenous GLP-2, given by daily subcutaneous injection, has been shown in adults to improve fluid and nutrient balance by stimulating intestinal adaptation [107]. Paediatric trials have shown teduglutide is well tolerated and is associated with a trend towards reduction in PN requirement [108]. The National Institute for Health and Care Excellence (NICE) is currently evaluating the benefits and costs of teduglutide for national commissioning by NHS England for adults and children with SBS.

Short bowel syndrome in older children

It has been estimated that 20% of SBS in the paediatric population develops outside of the neonatal period [109] and children acquiring SBS require nutritional management and enteral feeds appropriate to their age. A paediatric protein hydrolysate feed with 50% fat in the form of MCT is often used in this age group.

Children born with congenital abnormalities will usually achieve enteral autonomy. Intestinal adaptation begins 24–48 hours after resection and can continue for up to 3 years. As children get older, their feeds need to be reviewed regularly: feeds need to be age appropriate and always given at the maximum level of tolerance. Children often have voracious appetites, particularly after PN is stopped, and will consume vast amounts of food to compensate for malabsorption. It is often impossible for children to consume adequate nutrition in their waking hours, and for this reason overnight tube feeds are often continued to provide additional nutritional support via nasogastric tube or gastrostomy.

Weaning from parenteral nutrition

The transition to full enteral nutrition may take many months or years to complete, but the majority of children with SBS can eventually be weaned from PN. It is important

to always provide the maximum amount of enteral nutrition and minimum amount of PN while maintaining hydration and nutritional status. This requires careful adjustment as advancing enteral nutrition too quickly will result in malabsorption and osmotic diarrhoea. In this circumstance feeds can be reduced to the level at which they were tolerated and attempts made to advance again in subsequent days and weeks. Failure to attempt to advance feeds may lead to longer dependence on PN with the risk of associated complications.

As feed tolerance improves PN can usually be reduced. Initially the number of hours on PN and the volume infused are reduced, aiming to deliver the PN at night over 12–14 hours. With time it is usually possible to reduce the number of nights children receive their PN, providing adequate enteral fluid is tolerated to maintain hydration. Careful monitoring is required during the period of transition both to ensure optimal growth and to prevent micronutrient deficiencies.

Complications

Intestinal failure-associated liver disease

PN has improved the outcome for children with SBS, but paradoxically it is associated with many potentially fatal complications. These complications include intestinal failure-associated liver disease (IFALD). The prevalence of IFALD is unknown. Two cohort studies report an incidence of 22%–23% [110, 111], but an incidence of 40%–60% of children on long-term PN has also been reported [112]. The cause of liver disease in children on PN is multifactorial with risk factors including:

- prematurity [113]
- nutrient excess
- bacterial infection [114]
- failure to tolerate enteral feeds [115]
- failure to establish continuity of the gut

Prevention and management of IFALD involves aggressive use of enteral nutrition, prevention of line sepsis, the use of ursodeoxycholic acid and 'cycling' of PN to reduce the number of hours, or days, that a child receives PN (p. 67). There has been recent interest in the use of novel intravenous lipid sources containing fish oil to treat IFALD. There are no randomised controlled trials looking at these lipid sources (SMOF lipid, Omegaven), but several case series report reversal of cholestasis and suggest a potential benefit in preventing and treating IFALD in young children [116–118].

Small bowel bacterial overgrowth and D-lactic acidosis

Small bowel bacterial overgrowth (SBBOG) occurs commonly in SBS. It results from anatomical and physiological changes associated with the condition where there is dilatation of the small bowel associated with the adaptation process and changes in motility. Patients with SBBOG typically develop symptoms of nausea, bloating, vomiting and diarrhoea resulting from nutrient malabsorption and an increased number and/or type of bacteria in the small intestine [119]. It can be controlled with antibiotics that are frequently given in 'cycles', changing the antibiotic given at regular intervals.

D-Lactic acidosis presents as a severe metabolic acidosis with neurological manifestations that can include slurred speech, ataxia, irritability and drowsiness. In patients with SBS carbohydrates can reach the colon in undigested or partially digested form and are fermented there to produce organic acids. This results in a progressive decrease in intraluminal pH, which favours the overgrowth of acid-resistant bacteria such as *Lactobacillus acidophilus*. These bacteria produce D-lactate, which is poorly metabolised in humans. Antibiotic treatment can resolve the acidosis by treating the bacterial overgrowth, but it may also be necessary to modify the type and/or amount of carbohydrate in the diet.

Monitoring

Monitoring is an important part of the management of children with SBS receiving PN and is even more important as they are weaned from PN. As previously mentioned assessment of stool output is crucial to monitor feed tolerance. This is the best indicator to assess the potential to increase enteral feeds and reduce PN.

Serial anthropometric measurements are useful to evaluate nutritional status and track progress. These should include not just weight and length but head circumference, mid-upper arm circumference and skinfold measurements.

Nutritional blood tests are also needed. Micronutrients may be poorly absorbed, and deficiencies are commonly seen in children who are weaning from PN and in those who are exclusively enterally fed. The most common deficiencies seen are fat-soluble vitamins, calcium, magnesium, zinc, iron and selenium. Oral supplements should be started to avoid clinical signs of deficiency.

Vitamin B_{12} receptors are restricted to the terminal ileum, and if this has been resected, children will require lifelong injections of B_{12} to prevent deficiency. Regular monitoring is needed to assess the appropriate time for commencement of vitamin B_{12}.

Sodium depletion can also occur in children with either high stoma output or watery diarrhoea and is a common cause of poor weight gain. Urinary electrolytes are a good indicator of sodium status and should be measured regularly, aiming to maintain a urinary sodium concentration >20 mmol/L and a sodium–potassium ratio of approximately 2:1.

Home parenteral nutrition

Many children with SBS can eventually be weaned from PN. However, if PN is required for extended periods of time, it is appropriate to continue the treatment in the home

environment, and there is good evidence that catheter sepsis is reduced when children are discharged home [120] and mortality is low [121].

Surgery

Non-transplant surgery

A number of surgical interventions have been tried to alter intestinal transit and promote adaptation in children with SBS. The aim of surgery is not only to improve nutrient absorption by increasing food contact time with the intestinal lumen but also to reduce stasis and bacterial overgrowth. Procedures require a dilated segment of small bowel to be present and include longitudinal intestinal lengthening and tailoring (Bianchi procedure) and serial transverse enteroplasty procedure (STEP) [122, 123].

Transplant surgery

Some children who develop end-stage liver disease as a result of IFALD, but have the potential to eventually achieve independence from PN, may benefit from isolated liver transplantation [124].

Small bowel transplantation has developed over the past 20 years to become a lifesaving option for children with SBS who develop the complications of intestinal failure. For children with an extremely short bowel, permanent intestinal failure is almost inevitable. Long-term PN remains the treatment of choice for this group, but intestinal transplantation may be indicated for those children who develop irreversible liver disease or impaired venous access. In 2015 the International Transplant Registry reported on 3067 patients, including 1697 children: the 10-year graft survival was 40%–60%. Advances in surgical techniques and immunosuppression have improved the outcome of intestinal transplantation with a consistent improvement in the survival of children transplanted within the last 10 years, but the survival rate does not yet justify transplantation for children who can be safely managed on PN with low mortality and good QoL [121, 125].

The graft usually comes from a size-matched child that results in a long waiting time on the transplant list. The small bowel can be transplanted alone or with the right colon if the disease also involves the colon; this occurs in congenital enteropathies and motility disorders rather than SBS. Combined liver and small bowel transplant is necessary in cases of intestinal failure-associated liver disease [126].

Feeding protocols vary between transplant centres, but enteral feeds are commenced as soon as possible and delivered either into the stomach or, if necessary, into the jejunum. The lymphatic circulation of the graft takes time to re-establish, and a feed containing at least 50% MCT is recommended. There is a risk that food antigens may increase the risk of acute graft rejection, so protein hydrolysate feeds are usually used initially [127], but normal diet and independence from nutritional support is possible.

Learning points: longer-term management

- *Home parenteral nutrition is the treatment of choice*
- *Enteral feeds should be reviewed regularly and always given at the maximum level of tolerance as most children can be weaned from PN*
- *Monitoring of anthropometry, nutritional biochemistry, stool/stoma output and sodium balance is essential*
- *Monitoring for associated complications is important*
- *Bowel lengthening procedures can alter intestinal transit and promote adaptation*
- *Small bowel transplant may be indicated when irreversible complications occur, and home PN is no longer possible*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

10 The Liver and Pancreas

Sara Mancell

The Liver

Introduction

The nutritional management of an infant or child with liver disease depends on whether the disease is acute, chronic or metabolic. Potential problems warranting nutritional attention occur when there is a disturbance in the usual metabolic functions of the liver. These include glucose homeostasis, protein synthesis, bile salt production, lipid metabolism and vitamin storage. Dietary therapy is primarily aimed at managing the consequences of these disturbances.

Nutritional assessment

Patients with liver disease require regular nutritional assessment. The frequency of assessment is determined by the stage and severity of liver disease, the age of the child and nutritional status.

Anthropometry

Children with liver disease require frequent measurements of weight and height and head circumference if under 2 years of age. As organomegaly and ascites may affect weight measurements in liver disease, additional measures such as abdominal circumference, mid-upper arm circumference (MUAC) and triceps skinfold (TSF) should be included in the assessment (p. 3). Abdominal circumference measurements can be used to help interpret weight measurements, while MUAC and TSF measurements can be useful measures of nutritional status as they are not affected by organomegaly or ascites.

Biochemistry

Liver function tests and other blood tests routinely used to investigate the liver are described in Table 10.1.

Clinical

The clinical assessment of a child with liver disease should include signs of malnutrition (muscle wasting), cholestasis (dark urine, pale/oily stools, micronutrient deficiencies), the clinical condition, the presence of ascites or organomegaly and the impact of medications on nutrition, e.g. cholestyramine. Scans and procedures commonly used in the clinical assessment of a child with liver disease are described in Table 10.2.

Dietary

Dietary assessment should explore how symptoms of liver disease may be impacting on intake, absorption and utilisation of nutrients. Examples of symptoms that may cause nutritional difficulties include nausea, vomiting, diarrhoea, pale/oily stools, pruritus (itching), organomegaly and ascites.

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 10.1 Blood tests used to investigate the liver.

Test		Reference range*	Explanation
ALP	Alkaline phosphatase	62–209 IU/L	An enzyme found in the osteoblast cells of the bone and in liver cells. It is excreted via the biliary tract. High levels can indicate bile duct inflammation; however, as it is not specific to the liver, abnormal levels can be due to processes occurring in other parts of the body (e.g. raised due to bone growth)
ALT	Alanine transaminase	5–55 IU/L	An enzyme predominantly found in the liver. Used to detect hepatocellular injury. It is most specific in the detection of acute hepatitis from viral, toxic or drug induced causes. The serum level can rise to 20 times the normal level in these cases. The level may be mildly to moderately elevated in cases of obstructive jaundice, cirrhosis and liver tumours
AST	Aspartate transaminase	3–35 IU/L	An enzyme found in the heart, but also highly concentrated in the liver. A raised AST can indicate liver inflammation. Isolated increases are more characteristic of hepatitis. A raised AST in a transplanted patient may indicate rejection
GGT	Gamma-glutamyl transferase	1–55 IU/L	A biliary enzyme found in the kidney, liver and pancreas. High levels can indicate bile duct inflammation or obstruction. It can provide information about bile production
APPT	Activated partial thromboplastin time	0.85–1.15 ratio	A medical test of blood clotting. Also used to monitor treatment effects with heparin, a drug that reduces blood's tendency to clot
INR	International normalised ratio	0.9–1.20 ratio	A measure of the time needed to form a clot. Clot formation is dependent on coagulation factors, of which four are dependent on vitamin K. Raised levels may mean there is less vitamin K due to obstructive jaundice or poor utilisation of vitamin K due to liver damage
Bilirubin		3–20 µmol/L	Raised unconjugated bilirubin occurs when the liver is unable to conjugate the bilirubin, usually due to excessive red blood cell haemolysis. Raised conjugated bilirubin is where the total serum bilirubin is raised and the conjugated fraction is >20% of the total bilirubin (normally <5%). Raised conjugated bilirubin indicates reduced flow of bile out of the liver
Albumin		35–50 g/L	This is the major circulating protein and is synthesised in the liver. It is responsible for maintaining plasma osmotic pressure. Hypoalbuminaemia is found in advanced chronic liver disease. Low levels may be due to decreased synthesis in the liver or through losses in the stool
Total protein		60–80 g/L	A test used to determine the concentration of protein in the plasma. Liver disease is one source of abnormal values, but there are many more
Globulin		25–35 g/L	This refers to a group of globulin proteins. The two affected by liver disease are alpha globulin and gamma globulin
AFP	Alpha-fetoprotein	<7k IU/L	These levels are useful in the diagnosis of primary hepatocellular cancer because only primary liver tumours secrete AFP
Cholesterol		1–5 mmol/L	Levels may become increased in chronic biliary obstruction, especially intrahepatic bile duct hypoplasia
Ammonia		12–50 µmol/L	Ammonia is formed from protein metabolism and protein degradation by colonic bacteria. The liver converts ammonia to urea. Increased levels indicate that there is liver damage or an underlying metabolic condition
Bile acids		<14 µmol/L	Bile acids are formed in the liver from cholesterol, enter the intestine via bile and are reabsorbed into the portal circulation and returned to the liver. In liver disease serum levels may be high because of reduced hepatocytes (which are able to extract bile acids from the blood) or shunting of blood past hepatocytes

*Ranges may vary according to age.

Learning points: nutritional assessment of liver disease

- *Nutritional management will depend on whether the liver disease is acute, chronic or metabolic*
- *Measurement of MUAC, TSF and abdominal girth may aid in assessment where there is organomegaly or ascites*
- *Clinical assessment of the child with cholestasis should include assessment for jaundice, dark urine, pale/oily stools and micronutrient deficiencies*
- *Dietary assessment should explore how liver disease symptoms impact on nutrition*

Table 10.2 Common liver investigations.

Procedure	Description
Liver ultrasound	Non-invasive scan measures dimensions of the liver, spleen, portal vein, gallbladder, cysts, stones or tumours. Blood flow in portal vein, hepatic artery and hepatic veins can be assessed using a Doppler attachment
HIDA (hepatobiliary iminodiacetic acid) scan	A dye is injected by nuclear medicine and a series of scans are then performed to examine bile excretion
CT (computerised axial tomography)	A 2D scan of the liver and any focal lesions, e.g. tumours, abscess, cysts or bleeding. A radioactive dye may be injected to demonstrate gastrointestinal tract, blood vessels, bile ducts and kidneys
MRI (magnetic resonance imaging)	A 3D scan using magnetic frequency to obtain cross-sectional images of the liver
Liver biopsy	A small piece of liver is taken with a needle and sent for analysis
PTC (percutaneous transhepatic cholangiography)	Dye injected under X-ray control showing the flow through the liver and biliary tracts to evaluate biliary duct obstructions. Debris and stones can be flushed out
ERCP (endoscopic retrograde cholangio-pancreatography)	An endoscope is passed through to the duodenum and contrast medium is injected into the common bile and pancreatic ducts to examine the structure and identify obstructions/narrowing/debris/stones. It can help diagnose problems such as sclerosing cholangitis or pancreatitis
MRCP (magnetic resonance cholangio-pancreatography)	A 3D scan of the hepatobiliary and pancreatic systems including the liver, gallbladder, bile ducts, pancreas and pancreatic duct
Angiography	An invasive test that uses an injection of contrast medium to visualise the hepatic artery, portal venous system and intrahepatic vessels
Transient elastography (FibroScan®)	A non-invasive procedure assessing how elastic (or how stiff) the liver is. An ultrasound probe is used to create a 2D picture of the liver. The level of fibrosis can be measured in relation to the stiffness of the liver (with increased stiffness indicating more fibrosis)
HARI (hepatic artery resistance index)	Used to evaluate portal venous blood pressure. A low HARI indicates reduced arterial blood flow, which may result from hepatic artery narrowing. A high HARI may result from chronic hepatocellular disease or transplant rejection
Paracentesis (ascitic tap)	A needle is used to drain ascitic fluid. A therapeutic tap is done where ascites stretches the abdomen, causing discomfort/distress/increased work of breathing. A diagnostic tap is where the fluid is sent for testing (i.e. for infection)

Acute liver failure

Acute liver failure (ALF) is the severe and sudden impairment of liver function. Damaged liver cells secrete substances that initiate a cascade of events resulting in multi-organ failure [1]. The presence of hepatic encephalopathy (HE) may indicate ALF in adults, but is a less useful marker in children as it is difficult to detect [1]. A definition developed by the Paediatric Acute Liver Failure Study Group (PALFSG) removes the need for HE to be present [2]:

- a high PT (prothrombin time) (20 seconds) or INR (1.5) not corrected by vitamin K in the presence of HE or an INR >2 regardless of whether there is HE
- evidence of acute liver injury
- no known chronic liver disease (CLD)

It can be difficult to determine the cause of ALF, particularly in infants with inherited metabolic disorders (IMD) as the liver may be sufficiently damaged to produce secondary biochemical abnormalities [3]. A thorough investigation is necessary although a cause for ALF is not always found. In one study, a cause was not determined in 47% (n = 329) of cases [4].

Common causes of ALF include:

- infective, e.g. hepatitis A, B or C and cytomegalovirus (CMV)
- IMD, e.g. haemochromatosis, galactosaemia and tyrosinaemia
- toxins/drugs, e.g. chemotherapy and paracetamol overdose
- irradiation, e.g. radiotherapy
- ischaemic, e.g. Budd–Chiari syndrome
- infiltrative, e.g. leukaemia
- autoimmune, e.g. autoimmune hepatitis and autoimmune sclerosing cholangitis
- trauma, e.g. non-accidental injury, fall from horse/bicycle and seat belt laceration

Common symptoms of ALF by disease and age group are shown in Table 10.3.

Clinical management

If the onset of ALF is rapid, there is a possibility of the critical life-threatening complication of cerebral oedema, requiring treatment in intensive care. For those with increasing levels of bilirubin, INR and APPT, despite declining AST (which at this stage often indicates

Table 10.3 Common clinical symptoms at first presentation of ALF by age group.

Age group	Common symptoms	Possible disease
Neonate	Hypoglycaemia Jaundice Poor feeding Vomiting Diarrhoea Lethargy Sepsis Lactic acidosis Haemolysis Hypotonia Seizures Liver failure	Neonatal iron storage disease Inborn error of bile acid synthesis Alpha-1-antitrypsin deficiency Niemann-Pick type C Galactosaemia Tyrosinaemia Glycogen storage disease
Infant	Hypoglycaemia Jaundice Faltering growth Vomiting Fever Cataracts Hepatosplenomegaly Deranged liver function tests Chronic liver disease	Fructosaemia Cystic fibrosis Progressive familial intrahepatic cholestasis Alpha-1-antitrypsin deficiency Alagille's syndrome
Child/ adolescent	Hepatomegaly Faltering growth Developmental delay Short stature	Wilson's disease Autoimmune hepatitis

increasing hepatocyte necrosis), there is a poor prognosis. These patients may be placed on the super urgent liver transplant (LT) list. LT is the only proven treatment that may improve outcomes in ALF [1]. Table 10.4 illustrates the biochemical profiles of two different presentations of ALF. These examples show the blood biochemistry results in the days prior to and at 1-week post-LT when there is a return to normal (or near normal) levels.

Learning points: clinical management of ALF

- *The definition by PALFSG removes the need for HE to diagnose ALF*
- *It can be difficult to determine the cause of ALF and often a cause is not found*
- *Liver transplant is the only proven treatment that may improve outcomes in ALF*

Dietetic management

The clinical presentation of ALF varies and requires specific dietary treatment. If presentation is rapid, infants and children are often well nourished. In children with severe ALF, nutrition support will be managed in the intensive care unit, and adjustments to ventilation, sedation and fluid allowance will be needed. If there is no evidence of dehydration, a fluid restriction (⅔ maintenance) is generally used to avoid cerebral oedema. Dietetic management is focused on avoiding hypoglycaemia, avoiding the build-up of toxic by-products of metabolism and maintaining nutritional status until there is some clinical improvement.

A child with a suspected IMD may be protein restricted initially, aiming for full requirements in the first 24–48 hours depending on advice of the metabolic team. Where a disorder of amino acid metabolism is diagnosed, the metabolic team will advise on the upper tolerable limit of the offending amino acid to limit toxic by-products. In practice, a standard formula or feed is usually used to provide up to the first 1 g/kg protein. Glucose polymer is added to meet the glucose oxidation rate (Table 10.5).

The nutritional requirements in ALF are outlined in Table 10.5.

Hypoglycaemia

Hypoglycaemia may be present in 40% of patients with ALF [5] due to increased plasma insulin levels secondary to reduced glucose uptake and gluconeogenesis. The aim in ALF is not only to avoid hypoglycaemia but also to help prevent catabolism (and the associated accumulation of toxic metabolites). In the presence of hypoglycaemia, if there is no suspicion of an IMD, a standard or high energy feed may be started (depending on whether fluids are restricted), and a glucose polymer may be added if blood sugar levels are low. If normoglycaemia cannot be achieved by continuous feeding, or it is contraindicated, a continuous intravenous (IV) dextrose infusion is started. Once feeds are commenced, they may then be gradually titrated against the IV infusion.

If an IMD is suspected, an emergency regimen (ER) is started (p. 673) using either IV dextrose or a glucose polymer added to water for enteral use. Following the ER phase, a suitable formula can be used for the suspected condition on the advice of the metabolic team. Glucose management for ALF is as described in Table 10.6.

Hepatic encephalopathy

HE is where there is brain dysfunction ranging from minor changes such as confusion to coma. As it is due, in part, to altered ammonia metabolism, treatment aims to reduce ammonia production and absorption from the gut. Almost half of the body's ammonia is endogenously produced by gut flora and is primarily managed with medical interventions (e.g. sodium benzoate). A dietary protein restriction is not recommended [1] as it could result in increased endogenous ammonia production from protein catabolism. Sufficient energy from other macronutrients needs to be supplied with close consideration to the protein–energy ratio to prevent protein breakdown. Branched chain amino acid (BCAA) supplementation may be beneficial in encephalopathy as BCAAs detoxify ammonia and limit the efflux of aromatic amino acids across the blood–brain barrier [6]. BCAAs are discussed further in the section on faltering growth in CLD.

Table 10.4 Examples of biochemistry results pre- and post-liver transplant.

	3-year-old female unknown aetiology					10-year-old male unknown aetiology				
	Day 1	Day 2	Day 3	1 week post-LT	Range	Day 1	Day 3	Day 5	1 week post-LT	Range
Albumin	31	25	24	46	35–50 g/L	30	26	26	35	35–50 g/L
Bilirubin	330	300	344	38	3–20 mmol/L	268	291	327	47	3–20 mmol/L
AST	1140	328	474	80	8–43 IU/L	1513	894	469	100	7–36 IU/L
GGT	35	32	34	76	1–55 IU/L	66	55	55	218	1–55 IU/L
ALP	315	312	350	106	129–291 IU/L	830	783	802	138	120–488 IU/L
ALT	1763	944	750	–	5–55 IU/L	1931	–	940	–	5–55 IU/L
INR	3.04	7.6	8.75	1.10	0.9–1.2 ratio	2.76	4.60	3.40	1.18	0.9–1.2 ratio
APPT	1.590	2.060	2.230	0.970	0.85–1.15 ratio	1.51	1.60	1.65	1.02	0.85–1.15 ratio
Ammonia	122	–	140	–	12–50 µmol/L	108	126	164	–	12–50 µmol/L

LT, liver transplant; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; INR, international normalised ratio; APPT, activated partial thromboplastin time.

Table 10.5 Nutritional requirements in acute liver failure.

Energy	120%–150% EAR Intensive care: basal metabolic rate with/without stress factors depending on ventilation
Glucose	Glucose oxidation rates: • Infants: 8–9 mg/kg/min • Toddlers and children: 7 mg/kg/min • Adolescents: 4 mg/kg/min
Protein	100%–120% RNI (avoid excessive protein) If severe ALF may need to limit to 1.5 g/kg If inherited metabolic disorder (IMD) suspected: • Start at 0.8–1 g/kg and increase according to metabolic team • May need to avoid specific amino acids
Fat	If no IMD meet age-appropriate requirements If IMD suspected maximise according to metabolic team recommendations If cholestatic use age appropriate medium chain triglyceride formula (Table 10.9)

EAR, estimated average requirement; RNI, reference nutrient intake.

Table 10.6 Glucose management in ALF.

Steps to take

10–20%* IV dextrose is started immediately

If no IMD is suspected

- If able to feed give standard/high energy feed ± glucose polymer and wean IV fluids

If IMD is suspected

- Glucose polymer in water or oral rehydration solution may be used
- Once able to feed give suitable formula on advice of metabolic team

Increase the amount of glucose slowly according to tolerance

Monitor blood glucose hourly and then 4 hourly once stable

Aim for target blood glucose level of 4–8 mmol/L

Example: Formula-fed infant weighing 3.5 kg, fluid restricted to 100 mL/kg on intensive care

Give 100 L/kg of 12.5% dextrose via a central vein until feeds start

Start high energy feed and gradually titrate with IV fluids

If blood glucose <4 mmol/L either add 1%–3% glucose polymer to feed (1–3 g/100 mL of feed) or increase dextrose concentration in IV fluids

*Dextrose concentrations >10% require central venous access due to risk of thrombophlebitis.

Dietetic management

- The ER should be initiated, if necessary, aiming to keep blood glucose levels between 4 and 8 mmol/L (and meeting the glucose oxidation rate)
- Nasogastric (NG) feeding should be introduced as soon as possible
- Adequate energy intake must be ensured:
  Feeds can be concentrated or energy supplements added
- Adequate protein must be ensured:
  Initially a minimum of 1 g/kg
  Protein intake maximised as soon as possible to prevent catabolism
  Consideration of using a formula with supplementary BCAAs

Learning points: dietetic management of ALF

- *Children with ALF are often well nourished if presentation is rapid*
- *Management is focused on avoiding hypoglycaemia, avoiding the build-up of toxic by-products of metabolism and maintaining nutritional status*
- *A protein restriction is not recommended for HE due to its impact on nutritional status and the risk of increasing ammonia production through catabolism*
- *BCAAs may be beneficial as they detoxify ammonia and limit the efflux of aromatic amino acids across the blood–brain barrier*

Table 10.7 Case study: a young child with acute liver failure.

Chronology	
Admission	A male aged 2 years and 9 months, previously well and healthy Weight = 15.5 kg (75th–91st centile), height = 95 cm (<75th centile) **Presentation history:** Deranged liver function, INR of 6.0 with acute liver failure, grade 1–2 encephalopathy, jaundice, pale stools, dark urine, lethargy, loss of appetite **Impression:** Post-viral hepatic failure with encephalopathy and neutropenia **Acute interventions:** Admitted to intensive care, intubated and sedated **Clinical concerns:** Blood glucose = 3.3 mmol/L. Raised bilirubin, INR rapidly increased along with a declining AST indicating hepatocellular death. Albumin declined indicating worsening synthetic liver function. Listed for super urgent liver transplantation
Management on intensive care unit	
Day 1	Blood glucose levels 3.3–4.0 mmol/L on $^{2}/_{3}$ fluid restriction of 70 mL/kg 10% IV dextrose. IV dextrose increased to 12.5%
Day 2	Continued on 12.5% dextrose. Energy requirements for ventilation calculated as 58 kcal (240 kJ)/kg (BMR, Schofield*). Started standard paediatric 1 kcal (4 kJ)/mL feed via NGT at 10 mL/hour and increased by 10 mL/hour every 6 hours. Target fluid = 37 mL/hour per 24 hours
Day 3	Feeds held at 20 mL/hour due to high gastric aspirates. Continued on 12.5% IV dextrose. Then made NBM for probable liver transplant
Day 4	Liver transplantation performed. Returned to intensive care intubated and sedated
Post-transplant	
Day 1–5	On IV fluids. NBM due to new Roux loop surgery. Extubated day 2
Day 5	Weight = 14.7 kg (50th–75th centile). Energy requirements for extubation calculated as 82 kcal (343 kJ)/kg (EAR). Started standard 1 kcal (4 kJ)/mL feed via NGT at 10 mL/hour and increased by 10 mL/hour every 6 hours. Target fluid = 53 mL/hour. Target energy 82 kcal (343 kJ)/kg
Day 6	Transferred to high dependency unit on continuous NG feeding
Day 7	Chyle fluid in abdominal drain confirmed in lab. Chyle leak secondary to chylous ascites. Changed to 80% medium chain triglyceride (MCT) feed via NG
Day 8	Allowed oral intake. Commenced sips of fat-free fluids and restricted long chain triglyceride diet alongside high MCT feed via NG
Day 10	Transferred to liver ward. NG feeding overnight to allow appetite for solid foods in the day
Week 2	Weight = 14.7 kg (50th–75th centile). Chylous ascites resolved. NGT removed as taking oral diet well. Fat content of diet liberalised
Week 4	Weight = 15.4 kg (>75th centile). Discharged with advice about short-term high energy/protein snacks and meals as not yet eating full meals. Given advice regarding monitoring for excessive weight gain in view of nutrient-dense diet and steroids
Outpatient clinic	
3 months	Weight = 16.0 kg (75th–91st centile). Growing well. No longer on nutrient-dense diet
1 year	Weight = 18.0 kg (75th–91st centile). Doing well. No concerns

INR, international normalised ratio; AST, aspartate aminotransferase; IV, intravenous; BMR, basal metabolic rate; NGT, nasogastric tube; NBM, nil by mouth; EAR, estimated average requirement.
*Schofield equation (p. 87).

A case study of the management of a young child with ALF is given in Table 10.7.

Chronic liver disease

CLD involves a process of progressive destruction and degeneration of the liver leading to fibrosis and cirrhosis. Children with CLD are at risk of malnutrition, which is strongly linked to morbidity and mortality [7]. Common factors contributing to malnutrition in CLD are listed in Table 10.8.

Learning points: malnutrition in CLD

- *There is a high risk of malnutrition in CLD*
- *Malnutrition in CLD is strongly linked to morbidity and mortality*
- *Malnutrition may be due to malabsorption, reduced intake, increased requirements and altered metabolism*

CLD manifests as a range of symptoms shared by different types of liver disease and can be grouped into the complications below. These symptoms may either be the direct result

Table 10.8 Potential causes of malnutrition in chronic liver disease.

Causes	Factors that may contribute
Malabsorption	Reduced or absent bile flow/bile salts Pancreatic insufficiency Portal hypertension-related enteropathy Malnutrition-related villous atrophy
Reduced nutrient intake	Anorexia Nausea and vomiting Early satiety as a result of ascites, enlarged liver/spleen Behavioural feeding problems Hospitalisation-related depression Unpalatable diet/feeds Taste changes Fluid restriction Timing of medication interfering with meal times Fatigue, prolonged sleeping
Increased nutrient demands	Respiratory effort increased due to organomegaly or ascites Stress such as infection Increase in metabolically active cells [8]
Altered metabolism	Increased oxidation of fat and protein stores Reduced glycogen storage Insufficient protein synthesis Impairment of gluconeogenesis

of disordered metabolism or a physiological manifestation of liver disease [9].

Jaundice

Jaundice, a condition that causes the complexion and whites of the eyes to appear yellow, is classified as either unconjugated or conjugated. Unconjugated jaundice is characterised by a jaundiced appearance without bilirubin in the urine. This may be physiological in the newborn due to an increase of bilirubin production, decreased bilirubin clearance or a combination of both. Dietetic intervention is not usually required. In contrast, conjugated jaundice or conjugated hyperbilirubinaemia (CHB) represents cholestatic liver disease and requires dietetic intervention. It results when bile is reduced either due to an obstruction (e.g. biliary atresia [BA]) or reduced bile formation (e.g. progressive familial intrahepatic cholestasis [PFIC]). Normally, conjugated bilirubin is made water soluble by the addition of glucuronide in the liver and enters the bile. If there is an absence or reduction in bile, the conjugated bilirubin glucuronide passes into the serum and is then excreted as dark urine, and as a result the stools lack pigment.

Dietetic management

For unconjugated jaundice:

- No dietetic intervention is required

For conjugated jaundice:

- Dietetic management is as described for fat malabsorption

Fat malabsorption

The absence or shortage of bile results in malabsorption of long chain triglycerides (LCT) from the gastrointestinal (GI) tract. If left untreated, it can result in faltering growth, fat-soluble vitamin deficiency and essential fatty acid (EFA) deficiency. Many cholestatic infants compensate for the loss of energy from fat malabsorption by consuming high volumes of breastmilk or infant formula. Intakes can be more than twice normal fluid requirements. Where there is fat malabsorption, medium chain triglycerides (MCT) should be given as they do not require emulsification by bile; their partial water solubility allows them to diffuse easily into intestinal cells for direct absorption into the bloodstream. As MCT is not a source of EFA, it is important that children continue to have LCT in the diet. There is a lack of evidence for the ideal MCT content of formulas, but most contain approximately half of their total fat content as MCT (Table 10.9).

Dietetic management

- Infants – dietetic management is described in Table 10.10
- Toddlers and children – normal solids with MCT supplementation as formula/oral nutritional supplements (ONS)/emulsion/oil
- Fat-soluble vitamins should be provided in order to prevent deficiency (Table 10.11).
- Although there is limited research on the need for supplementing water-soluble vitamins, twice the recommended daily allowance may be required due to altered hepatic metabolism [7]. This may be achieved with ONS.

Learning points: fat malabsorption

- *Fat malabsorption is due to the absence of bile, which is required for fat emulsification*
- *MCT does not require emulsification as it is partially water soluble*
- *Infants may compensate for fat malabsorption by increasing consumption of breastmilk/formula*
- *As MCT does not contain essential fatty acids, the diet should continue to include some LCT*
- *There is limited evidence on the ideal MCT content of formulas; most formulas contain 50% fat as MCT*
- *Fat-soluble vitamins are routinely given in CLD*

Pancreatic enzyme insufficiency

Some types of liver disease (Alagille's syndrome, PFIC, choledochal cysts) may be accompanied by pancreatic enzyme deficiency that aggravates malabsorption. Since bile salts are required to activate pancreatic lipase, a functional deficiency may be present in cholestasis. The finding of a low stool elastase may support a deficiency.

Table 10.9 Formulas and supplements high in medium chain triglycerides (per 100 mL).

Product	% fat as MCT	Energy kcal (kJ)	CHO (g)	Fat (g)	Protein (g)	Protein type	Age/weight	Comments
Heparon Junior	49	86 (360)	11.6	3.6	2	Whole	0–3 years	Supplemented with BCAA
Pregestimil Lipil	55	68 (285)	6.9	3.8	1.89	Peptide	0–1 year	Clinically lactose-free (<5 mg lactose/100 mL)
Aptamil Pepti-Junior	46	66 (275)	6.8	3.5	1.8	Peptide	0–1 year	
Puramino	33	68 (290)	7.2	3.6	1.89	Amino acid	0–1 year	
Peptamen Junior	60	100 (420)	13.2	4.0	3.0	Peptide	1–10 years	
PaediaSure Peptide	50	100 (420)	13.0	4.0	3.0	Peptide	8–30 kg	
Infatrini Peptisorb	50	100 (420)	10.3	5.4	2.6	Peptide	0–18 months or <9 kg	
Nutrini Peptisorb	46	100 (420)	13.7	3.9	2.8	Peptide	1–6 years or 8–20 kg	
Monogen	84	74 (310)	11.6	2.2	2.2	Whole	0–1 year*	Used for chylous ascites
Lipistart	80	69 (290)	8.3	3.1	2.1	Whole	0–10 years	Used for chylous ascites
Emsogen	83	88 (368)	12	3.3	2.5	Amino acid	>1 year**	Used for chylous ascites for those needing a milk-free diet
Liquigen	96	450 (1880)	0	50	0	n/a	From birth	MCT emulsion. Not a sole source of nutrition
MCT Oil	100	855 (3575)	0	95	0	n/a	From birth	MCT oil. Useful in cooking, low smoke point. Not a sole source of nutrition
Betaquik	95	189 (777)	0	21	0	n/a	>3 years	MCT emulsion. Not a sole source of nutrition
MCTprocal	96	703 (2907)	20.6	63.5	12.2	Whole	>3 years	Use in cooking/baking or add to foods/drinks. Not a sole source of nutrition

MCT, medium chain triglyceride; BCAA, branched chain amino acids.
*Complete for age <1 year or can be used as a supplement to diet for age >1 year.
**Not suitable as sole source of nutrition for 1- to 5-year-olds.

Table 10.10 Summary of dietetic management for infantile conjugated hyperbilirubinaemia/cholestatic jaundice.

1. Is galactosaemia suspected?
   - **No**, proceed to step 2 below
   - **Yes**, change to clinically lactose-free MCT formula* (Table 10.9). Stop breastfeeds and give advice on how to maintain milk supply while awaiting diagnosis. If diagnosed with galactosaemia change to soya infant formula and refer to a metabolic centre. If galactosaemia excluded, proceed with step 2 below
2. Is the infant breastfed?
   - **No**, use MCT formula
   - **Yes**, either breastfeed with 3–5 mL Liquigen × 8 per day OR
   - Give 100 mL/kg MCT formula with remainder as breastmilk in the following way:
     - Give MCT formula at the beginning of each feed and top-up with breastfeed
     - Breastfeed at every third feed
     - Breastfeeds overnight and MCT formula during the day
3. Is cholestasis resolving?
   - **No**, remain on above regimen
   - **Yes**, stop MCT formula and give full breastfeeds and/or a suitable infant formula
4. Are blood sugar levels maintained?
   - **No**, consider adding glucose polymer up to 3% concentration. Feed 2–3 hourly day and night or continuously via pump if necessary. N.B. the addition of energy supplements reduces the protein–energy ratio
   - **Yes**, continue management
5. At weaning
   - Encourage normal weaning
   - Add MCT formula when making up dried baby foods instead of water or cow's milk
   - Add cream/butter/cheese and/or glucose polymer/fat supplement to increase energy content of foods
6. If there is faltering growth, is the child taking an adequate volume of feed?
   - **No**, commence NG feeding and give advice regarding promoting oral feeding
   - **Yes**, increase the nutrient density, e.g. increasing concentration of formula, adding high energy/protein supplements and foods to diet
7. Continue to review and monitor closely

*Caution. For preterm infants receiving breastmilk who are at high risk of necrotising enterocolitis, await a definitive diagnosis of galactosaemia before stopping breastmilk. If diagnosed with galactosaemia, liaise with metabolic team.

Table 10.11 Practice guide for vitamin supplementation at King's College Hospital, London.

Vitamin	Product	Age	Daily oral dose
Multivitamins (containing A and D)	Abidec/Dalivit (Abidec preferred as lower vitamin A content. Dalivit used if patient has peanut allergy)	Birth–1 year	0.6 mL
		>1 year	1.2 mL
	Forceval capsule	>12 years	1 capsule
Vitamin E	Alpha-tocopheryl	Birth to 12 years	10 mg/kg up to 100 mg/kg (max 200 mg/kg/day)
		>12 years	1 capsule (286 mg vitamin E) (max 200 mg/kg/day)
Vitamin K	Phytomenadione	<1 year	1 mg
		1–5 years	2 mg
	Menadiol tablets	5–12 years	5 mg
		>12 years	10mg
Vitamin D	Colecalciferol	1–12 months	1000 IU (max 3000 IU daily)
		1–12 years	6000 IU in solution or 6400 IU if can swallow capsules (max 25 000 IU daily)
		>12 years	9600 IU daily (max 40 000 IU daily)
	Alfacalcidol (second line or in severe cholestatic liver disease)	<1 month	20 ng/kg
		1 month–12 years	<20 kg: 15–30 ng/kg (max 500 ng/day) >20 kg: 250–500 ng (max 500 ng/day)
		>12 years	250–500 ng
	Ergocalciferol (intramuscular)	n/a	Dose based on Vitamin D level (nmol/L): <10: 60 000 units 10–20: 45 000 units >20 < 50: 30 000 units >50: use oral supplementation

Dietetic management

Pancreatic enzyme replacement therapy (PERT) should be started and continued if a clinical benefit is seen (refer to p. 219 for PERT dosing).

Hypoglycaemia

Hypoglycaemia may occur in CLD as the liver's ability to store glycogen and mobilise glucose during fasting is impaired. Muscle glycogen homeostasis may also be disrupted. An acute-on-chronic presentation may require an ER (p. 673) to control blood sugar levels while a feeding regimen is established. Frequent or even continuous feeds may be required with a high carbohydrate content to ensure blood glucose levels are maintained. For some infants care is needed to avoid giving excess glucose, which can lead to hyperinsulinaemia.

Dietetic management

To manage hypoglycaemia, a consistent supply of exogenous glucose needs to be ensured:

- infants – 2–3 hourly breast or bottle feeding
- children – regular meals and snacks with low glycaemic index carbohydrates
- uncooked cornstarch (UCCS) may be useful for children over 2 years (p. 613)
- consider NG continuous feeding

Carbohydrate content of feeds should be increased using a glucose polymer:

- starting with the addition of 1% and increasing in 1% increments thereafter
- beware of rebound hypoglycaemia due to high glucose load

Faltering growth

In CLD there may be faltering growth with wasting of lean body mass and fat stores, despite aggressive nutrition support. Supplementation of the branched chain amino acids leucine, valine and isoleucine has been shown to improve nutritional status in liver disease [10]. Unlike other amino acids they are metabolised in muscle and, therefore, are available for protein synthesis even when there is poor hepatic function. Leucine, as a ketogenic acid, may be used preferentially as an energy substrate, while valine and isoleucine are diverted towards gluconeogenesis [11]. The result is preservation of precious reserves of fat and lean body mass. There is little evidence on the ideal amount of BCAA supplementation in liver disease. The only formula currently available with supplementary BCAA in the UK is Heparon Junior, which contains 30% BCAA.

Dietetic management

The main points are to:

- aim for increased energy and protein intakes (Table 10.12)
- increase nutrient density of the diet

Table 10.12 Energy and protein requirements for chronic liver disease.

	Energy	Protein
Infants	120–150 kcal/kg (500–630 kJ/kg)	3–4 g/kg
Older children	130%–150% of the estimated average requirement for age	3–4 g/kg

- use a formula supplemented with BCAA (Table 10.9)
- give aggressive and early nutrition support with NG feeding or parenteral nutrition (PN) if necessary

Learning points: branched chain amino acids

- *Leucine, valine and isoleucine are branched chain amino acids*
- *BCAA may improve nutritional status as they are metabolised in muscle and are available for protein synthesis even when there is poor hepatic function*
- *There is limited evidence for the ideal amount to include in the diet in chronic liver disease*

Portal hypertension

Portal hypertension is where a hardening of the liver (fibrosis) results in increased resistance to blood flow from the intestines and spleen into the liver through the portal vein. It can also occur when there is a thrombus in the portal vein (portal vein thrombosis). There may be an associated enteropathy and malabsorption due to an increased pressure in the mesenteric venous system, i.e. oedema of the mucosa of the small intestine. Oesophageal varices, splenomegaly, ascites and thrombocytopenia are clinical and biochemical features of portal hypertension and can accelerate the need for liver transplantation if uncontrolled.

Dietetic management

Portal hypertension may be managed by considering:

- using a peptide-based feed (Table 10.9)
- continuous rather than bolus feeds
- PN if there is severe malabsorption

Oesophageal varices

Oesophageal varices develop when blood flow to the liver is blocked, causing blood to flow into smaller blood vessels (such as those in the lower oesophagus), which can leak or rupture. This may result in haematemesis or melaena. Oesophageal varices are not a contraindication to oral feeding. Where varices are large and bleed frequently, NG tube placement may be contraindicated, and PN may be needed. Following sclerotherapy or oesophageal banding, a soft diet is usually initiated in the first 24 hours.

Dietetic management

This will depend on the extent of the varices:

- continue to feed orally where possible
- a soft diet is recommended following sclerotherapy/oesophageal banding
- consider PN if unable to feed enterally for an extended period

Hepatosplenomegaly and ascites

Hepatosplenomegaly (enlarged liver and spleen) and ascites (fluid retention in the abdomen) are features of decompensated liver disease. As portal hypertension worsens, the pressure in the portal vein (which connects the liver and spleen) increases, causing the spleen to enlarge. This increased pressure, as well as a reduced ability of the liver to make albumin, results in ascites. The most profound effect on nutritional status from hepatosplenomegaly and ascites is loss of appetite and early satiety due to abdominal discomfort and reduced gastric capacity. Ascites is managed with diuretics in preference to fluid restriction in order to allow adequate nutritional intake. Therapeutic paracentesis may be required (Table 10.2), usually resulting in immediate improvement of appetite secondary to the reduction of intra-abdominal pressure on the stomach. The discouragement of salty foods may help to reduce thirst. A rigid restriction is not recommended as it is difficult to impose and may result in a corresponding reduction in oral intake.

Dietetic management

This will centre on the degree of abdominal discomfort:

- a change to small, frequent, nutrient-dense meals and snacks may help
- considering NG bolus feeds or continuous feeding if oral intake is poor
- concentrating feeds or using a high energy formula/ONS if there is a fluid restriction
- limiting sodium intake in feeds and avoiding salty foods

Cirrhosis

Cirrhosis represents the end stage of CLD. CLD results in a repetitive sequence of cell injury and repair, resulting in necrosis and fibrogenesis and irreversible damage. The liver can compensate for the damage such that the cirrhosis is asymptomatic. Decompensated cirrhosis occurs when damage within the liver causes blood flow to be impaired, resulting in symptoms such as portal hypertension, ascites and varices. As decompensation occurs, there is likely to be a decline in nutritional status despite maximal nutritional support, and this may highlight the need for transplantation. Malnutrition adversely affects the outcome of liver transplantation [12], and improving nutritional status prior to transplant can help to reduce

complications [13]. Once a decision is made to consider a child for transplantation, a detailed assessment (including a full nutritional review) is carried out to determine whether the child should be placed on the transplant waiting list. Waiting time on the transplant list is unpredictable and depends on the potential recipient's severity of disease, disease type and blood type. The median (95% CI) waiting time to LT for children in the UK between 2013 and 2016 was 107 (29–135) days [14].

Dietetic management

Management for cirrhosis is as described for CLD above, depending on the symptoms that the child presents with. For those being considered for transplant:

- a detailed nutritional assessment is carried out
- pre- and post-transplant nutrition information is discussed with the family/caregivers:
  - the importance of good nutritional status prior to transplant
  - the timing and type of nutrition initiated after transplant
  - possible post-transplant complications (e.g. chylous ascites)
- close monitoring of progress is required

Learning points: cirrhosis

- *Cirrhosis represents the end stage of liver disease*
- *Compensated cirrhosis is where the liver compensates for liver damage so that cirrhosis is asymptomatic*
- *Decompensated cirrhosis occurs when liver damage causes blood flow to be impaired, resulting in symptoms such as portal hypertension, ascites and varices*
- *Nutritional status is likely to decline despite maximum nutrition support*

Liver transplantation

LT may be from a deceased or a living donor. Survival rates have been reported as 95% at 1 year, 93% at 2 years and 92% at 5 years (2010–2012) [15]. The types of LT are outlined in Table 10.13.

The biliary ducts are either rerouted directly to the small bowel (i.e. a new Roux loop is formed), or if the graft liver has an intact bile duct, it may be surgically joined to the native bile duct. Following transplant there is usually a period of between 3 and 5 days nil by mouth (NBM): 5 days NBM where a new Roux loop is formed due to the risk of small bowel perforation. The clearing of long-standing jaundice, reduction in abdominal pressure and the introduction of high dose steroids (as antirejection treatment) can play an important role in promoting good appetite. In children with pre-existing oral aversion, NG feeding may be required for an extended period after transplant, and referral to a specialist feeding clinic may be required.

Table 10.13 Types of liver transplants.

Type of transplant	Description
Partial graft	• A split liver is the most common transplant. The donor liver is split into two lobes, with the right lobe going to an adult or older child and the left lobe or a left lateral segment (part of the left lobe) going to a young child • A cut down or reduced graft is where there is one recipient. The liver is cut down to size to fit the child
Whole liver	• More common in children over 5 years • The whole liver may be used if it is the right size for the child
Auxiliary	• A partial donor liver graft is transplanted onto a resected native liver • Used where there is a possibility of the native liver recovering, e.g. in acute liver failure, some metabolic diseases
Hepatocyte	• Novel technique used in some metabolic disorders and acute liver failure • Hepatocytes are infused into the liver engraft and support liver function

Liver transplantation can be curative for many metabolic diseases, enabling a normal diet after transplant. For those patients who have been on a lifelong dietary protein restriction, self-restriction of protein intake following transplantation is common [16]. For conditions where transplant is not curative (e.g. propionic acidaemia and methylmalonic acidaemia), continued dietary restriction may be required [17]. In these patients PN is usually given initially to avoid catabolism and limit production of toxic metabolites, e.g. ammonia and organic acids.

Dietetic management

This depends on whether an LT is curative or not.

Where transplant is curative:

- after 3–5 days NBM a standard NG formula or feed is started
- some older children are able to commence a normal diet without tube feeding

Where transplant is not curative (i.e. for some metabolic conditions):

- PN is given while NBM immediately after transplant with 1.0–1.5 g/kg protein restriction
- once enteral feeing is started, PN is gradually weaned down
- in some cases it may be necessary to continue dietary protein restriction either immediately post-transplant or at a later stage. The metabolic team caring for the child should be consulted

Learning points: liver transplant

- *Survival figures for liver transplant are very high, with 92% survival at 5 years*
- *There are different types of liver transplant: partial graft, whole liver, auxiliary and hepatocyte*
- *Feeds are usually started between 3 and 5 days after transplant*
- *For methylmalonic acidaemia and propionic acidaemia, PN is given immediately after transplant, and there may be a continued need for a protein-restricted diet*

Complications after liver transplant

Bowel perforation

The risk of bowel perforation after transplant is higher in children with BA who have had surgery previously and may be linked to malnutrition, portal hypertension, CMV enteritis, sepsis, steroids and use of inotropes [18]. Where there are GI complications, an extended period of NBM is likely to be required, and PN may be needed.

Chylous ascites

Chylous ascites may develop as a result of damage to lymph vessels during transplant surgery. The leaking chyle, a triglyceride-rich fluid, has a milky appearance in the abdominal drain fluids and can resolve spontaneously. A low LCT diet (ideally <20% total fat as LCT) is generally required for 1–2 weeks in order to reduce the flow of lymph (p. 302). This may be achieved with 80% MCT formulas (Table 10.9) in young children or very low fat foods in older children. Fat-free and MCT supplements may be needed to meet requirements. If a strict low LCT diet is given for an extended period of time, walnut oil may be needed to ensure adequate provision of EFA (p. 648).

Learning points: chylous ascites

- *A chyle leak may occur due to damage to lymph vessels during transplant*
- *A low LCT diet and/or formula is used (80% MCT formula)*
- *The ideal amount of time to remain on a low LCT diet is not clear, but in practice is usually 1–2 weeks*

Immunosuppression

The commonly used antirejection medication tacrolimus (and to a lesser extent cyclosporin) can present nutritional challenges. Tacrolimus is preferentially used but can be nephrotoxic or contraindicated by cardiac complications. The pharmacokinetics of tacrolimus is affected by the presence of food in the gut; therefore, consistency with the timing of meals and taking the medication is needed.

Both cyclosporin and tacrolimus lower serum magnesium levels. Serum magnesium needs to be monitored, and supplementation may be required, as much as 0.5–1 mmol/kg/day orally. Once serum tacrolimus levels are consistently within the therapeutic range, the need for magnesium supplementation generally resolves at around 6 weeks' post-transplantation. Magnesium supplements are typically not well tolerated initially, causing diarrhoea; protein-bound magnesium is better tolerated. Grapefruit (including juice), pomegranate and blood oranges need to be avoided as they may induce toxicity.

Safe food handling is necessary (p. 51) and must be adhered to lifelong due to immunosuppression.

Infection

Infection is the most common cause of post-transplantation mortality and morbidity. Epstein–Barr virus (EBV), CMV and herpes simplex virus are the primary viral infections. A majority of paediatric liver recipients are seronegative to EBV and CMV and often receive a liver from donors who are seropositive for these viruses. GI perforation and bleeding are severe consequences of EBV and CMV infection. Depending on the virus, medical management is successful in the majority of cases. However, if unsuccessful, and in the case of EBV infection, post-transplant lymphoproliferative disorder (PTLD) can result. Treatment for advanced PTLD includes chemotherapy and radiotherapy, further exacerbating poor nutritional status, delaying growth and significantly increasing mortality risk.

Rejection

Moderate to severe acute rejection after transplant is treated with steroid boluses [18]. In the event of hyperglycaemia due to high dose steroids, a short-term reduction in sugary foods and advice about low glycaemic index foods may be required. A positive side effect of steroids may be an increase in appetite. Chronic rejection occurs less frequently and is often treated with adjustments to immunosuppression, however, if unsuccessful retransplantation may be required. If there is progressive cholestasis, MCT supplementation may be required.

Donor size mismatching

The nutritional management of small-sized recipients can be a challenge in the immediate period post-transplantation. The sheer bulk of a large piece of liver can mean that much of the intra-abdominal cavity is occupied, which can delay abdominal closure. The associated risks of an open abdomen, such as slower weaning off ventilation, an increased risk of gut ischaemia, portal hypertension and friable gut integrity, can all delay transition onto enteral feeding. These children are at higher risk of being NBM for more than 5 days, increasing the risk of gut bacterial translocation, decreased bile flow and subsequent compromised graft hepatic function. Where PN is used, some enteral feeds should also be given where possible.

Transplant-acquired food allergy

Transplant-acquired food allergy (TAFA) is seen in up to 17% of children post-transplant [19], which is approximately double that seen in the general paediatric population and may occur days or months after transplant [20]. The mechanism for TAFA is not known, but may be related to Th2 skewing, the transfer of lymphocytes or IgE or increased intestinal permeability secondary to immunosuppressant medication [20]. While some children have been reported to develop tolerance to some TAFA over time, other children may need a long-term dietary restriction [21].

Obesity

There is a risk of obesity with post-transplant metabolic syndrome (PTMS) thought to be associated with the use of corticosteroids, calcineurin inhibitors and immunosuppressants and risk factors such as non-alcoholic fatty liver disease (NAFLD) [22]. Monitoring after transplant is important and should include diet and lifestyle advice for overweight children [22].

Nutrition support in liver disease

Nasogastric tube feeding

NG feeding has been shown to improve body composition in paediatric liver disease [23] and should be commenced early to optimise nutritional status. Feeds may be administered as boluses, top-up feeds or continuous pump feeding. It is important to promote oral feeding alongside tube feeding to reduce the risk of oral aversion.

Gastrostomy feeding

The placement of a gastrostomy is often not possible in CLD. There is an increased risk of bleeding during tube placement due to portal hypertension or intra-abdominal varices [24] and a risk of puncture if the liver/spleen is enlarged. There is also a risk of inadequate tract formation with ascites [24]. It may also create potential problems with access to the abdominal cavity (due to adhesions) during liver transplantation. However, placement of a percutaneous endoscopic gastrostomy (PEG) has been successful where there is no portal hypertension, ascites or varices [25].

Parenteral nutrition

PN may be beneficial in children with advanced end-stage liver disease who are listed for LT, where the risk of PN exacerbating the liver disease is outweighed by improvement in nutritional status prior to transplantation [26, 27]. The nutrition support team plays an important role in optimising PN and promoting enteral nutrition [28].

Intestinal failure-associated liver disease

Intestinal failure-associated liver disease (IFALD) is a common complication for children on long-term PN (p. 66). IFALD may present at an early stage when it may still be possible to reverse it through intestinal rehabilitation or at an advanced stage resulting in end-stage liver disease. It is the main indication for intestinal transplantation in children [29]. The exact pathogenesis of IFALD remains unknown; it may be due to the toxic effects of PN or the underlying aetiology of intestinal failure [30]. The main risk factors for IFALD include prematurity, catheter-related bloodstream infections, PN management and lack of enteral nutrition [30].

Dietetic management for the prevention of IFALD is described on pp. 67 and 164. Where IFALD has progressed to end-stage liver failure, the dietetic management is as described for CLD above, in consultation with the intestinal failure team caring for the child.

Common disorders leading to chronic liver disease

There are many disorders that lead to CLD and the most common causes are described below.

Causes presenting in infancy:

- metabolic, e.g. glycogen storage disease, urea cycle defect and galactosaemia
- genetic, e.g. alpha-1-antitrypsin deficiency, Alagille's syndrome and PFIC
- infections, e.g. hepatitis
- biliary malformations, e.g. BA, choledochal cysts and inspissated bile syndrome
- vascular lesions, e.g. hepatocellular carcinoma and haemangioma

Causes presenting in older children:

- immune related, e.g. sclerosing cholangitis and autoimmune hepatitis
- genetic, e.g. Wilson's disease
- biliary malformations, e.g. choledochal cyst
- lifestyle disorders, e.g. NAFLD and non-alcoholic steatohepatitis (NASH)

Neonatal hepatitis

Neonatal hepatitis is inflammation of the liver in the first few months of life. The cause is most often unknown or suspected to be from a virus. Severity varies and rarely results in cirrhosis, with bile flow usually resolving with time.

Galactosaemia

Galactosaemia is a metabolic disorder resulting from the inability to metabolise galactose (p. 599). As a common clinical presentation of galactosaemia is conjugated jaundice, all

infants with CHB are screened for this condition. Where galactosaemia screening is not done at birth, the blood galactose-1-phosphate uridyltransferase (Gal-1-PUT) is measured. If the infant has received a blood transfusion within six weeks of testing, a false result can occur, in which case both parents will need testing.

Biliary atresia

BA is the inability to excrete bile due to obstruction, destruction or absence of the extrahepatic bile ducts, which leads to bile stasis in the liver with progressive inflammation and fibrosis. It is a rare progressive disease occurring in 1 in 9000–16000 births [31] but is the most frequent hepatic cause of death and requirement for transplantation [12]. At least 50% of children with this condition are likely to receive LT in the first 2 years of life [32] with a further 20%–30% likely to require a transplant later in life [26]. Up to two thirds of BA survivors who have not received liver transplantation may develop portal hypertension but maintain adequate growth [33].

Bile drainage can be restored by the Kasai operation, which involves bypassing the blocked ducts. Native liver survival rate and jaundice clearance are reported to be improved when the Kasai procedure is performed earlier than 60 days of age, with outcomes showing better results the earlier the Kasai is performed [34]. A late Kasai operation, i.e. after 60 days of age, is associated with a poor prognosis [35]. A Kasai procedure is considered to have been successful if jaundice has cleared and LFTs have normalised 3 months after the procedure.

Given the high requirement for transplantation, a focus on nutrition is extremely important in these patients. They require close monitoring and aggressive nutrition support as studies have shown that improvement of nutritional status in the pre-transplant period may improve outcomes after transplantation [31, 33]. Their management is as described for CLD.

Learning points: biliary atresia

- *BA is the most frequent hepatic cause of death and requirement for transplantation*
- *A Kasai operation can restore bile flow and should be performed in the first 8 weeks of life*
- *A Kasai operation is considered to have been successful if jaundice has cleared and LFTs have normalised 3 months after the procedure*
- *Close monitoring is required due to the high likelihood of transplantation*

Alpha-1-antitrypsin deficiency

Alpha-1-antitrypsin deficiency is an IMD that can cause varying degrees of liver disease in infancy and can present with cholestasis. Liver disease is secondary to the failure to export the glycoprotein alpha-1-antitrypsin from hepatocytes, resulting in hepatic inflammation and eventually cirrhosis [36]. The severity of this condition, degree of liver involvement and nutritional management vary significantly.

Alagille's syndrome

This syndrome is a genetic autosomal recessive condition and can present as a spectrum of disorders including intrahepatic biliary hypoplasia (paucity of the intrahepatic bile ducts) and cardiovascular, skeletal, facial and ocular abnormalities. It is a rare condition that is typically diagnosed in 7% of all neonatal cholestasis cases [37]. Infants present with CHB followed by pruritus and finally, if severely affected, xanthelasma (yellowish deposits of fat underneath the skin, usually on or around the eyelids), which usually appears by 2 years of age. Some children have cyanotic heart disease as their main problem.

The nutritional management of Alagille's syndrome can be challenging. Frequent problems include poor growth, vomiting, appalling appetite (fussy eating), pancreatic insufficiency, malabsorption, severe itching and renal acidosis. Malnutrition and severe itching may be the main indications for transplantation.

Learning points: Alagille's syndrome

- *A rare genetic condition presenting as a spectrum of disorders including lack of intrahepatic bile ducts*
- *Growth is a major problem and most children require NG feeding*
- *Malnutrition and severe pruritus may be the main indications for transplantation*

Haemangioma

Haemangiomas are benign vascular tumours of the liver. If large in size, they are supplied by wide blood vessels taking a large proportion of the cardiac output, resulting in immediate medical treatment to decrease blood pressure, increase cardiac output and reduce the risk of fluid overload. In young infants where cardiac failure develops, hepatic artery ligation is essential to restrict the tumour's blood supply. If surgical intervention is not curative or where ligation cannot be performed, liver transplantation may be required. These cases may be dramatic, presenting with hepatomegaly and worsening cardiac function; these children may struggle to meet nutritional requirements.

Inspissated bile syndrome

Inspissated bile syndrome is where a plug of thick bile blocks the bile ducts and causes conjugated jaundice.

Table 10.14 Types of progressive familial intrahepatic cholestasis.

	PFIC 1 *Familial intrahepatic cholestasis (FIC 1) or Byler's disease*	PFIC 2 *Bile salt export pump (BSEP) deficiency*	PFIC 3 *Multi drug resistance 3 (MDR3) disease*
Disease progression	Progresses quickly to cirrhosis in infancy	Cirrhosis often before age 10 years. Higher incidence of hepatocarcinoma	Slow progression of cirrhosis and liver disease
Symptoms	Jaundice, severe pruritus, diarrhoea, poor growth, gallstones. Some have pancreatic insufficiency	Severe pruritus, diarrhoea, poor growth, gallstones	Pruritus tends to be milder, gallstones, high risk portal hypertension
Biochemical or functional hallmarks	Normal GGT, high serum bile acids	Normal GGT	Elevated GGT, normal bilirubin, low phospholipids in bile

GTT, gamma-glutamyl transpeptidase.

Resolution may occur naturally with time, or with the help of ursodeoxycholic acid (enhancing bile flow), or under percutaneous transhepatic cholangiography (PTC) (Table 10.2), or in rare cases surgical excision. The syndrome often occurs in infants who have been NBM, e.g. after surgery and long courses of PN.

Choledochal cysts

Choledochal cysts are dilatations of all or part of the extrahepatic biliary tract. They may occur in infants (and can be detected *in utero*) and children. They may remain undiagnosed for years. Ursodeoxycholic acid improves bile flow and may enable a small cyst to disappear requiring no further treatment, while other cysts may require surgical removal. Indeed some are so large and invasive that the extrahepatic bile ducts have to be removed and a Kasai procedure has to be performed. Post-surgery, any required catch-up growth, should occur quickly, negating further nutritional intervention.

Progressive familial intrahepatic cholestasis

PFIC is a group of liver diseases involving a defect in the membrane transport proteins required for the formation of bile (Table 10.14). It is a rare disorder affecting 1 in 50 000–100 000 births. Pruritus is a major symptom, especially for PFIC 1 and 2, due to the increased level of bile acids in the blood. Itching is very difficult to control and may disturb sleep and contribute to fatigue, irritability, reduced appetite, nausea and vomiting. Several surgical procedures may be used to manage itching, but these may cause diarrhoea and worsening of malabsorption (Table 10.15). Growth is a major problem, and most children have short stature and reduced muscle and fat mass. Fat malabsorption may occur in PFIC without significant jaundice due to an inability to produce bile salts.

Table 10.15 Surgical procedures used to manage itching and possible nutritional consequences.

Procedure	Description
Partial external biliary diversion	Stoma created from gall bladder to remove some of the bile produced. This may worsen malabsorption and vitamin deficiencies
Partial internal biliary drainage	Similar to external diversion except a piece of bowel connects the gall bladder to the large intestine (no stoma). Diarrhoea may result as bile enters the large intestine
Internal ileal exclusion	A bypass is created around the distal ileum (where bile salts are usually reabsorbed) to reduce reabsorption. Diarrhoea may result and there may be nutrient malabsorption
Liver transplant	Most will eventually require a liver transplant. In PFIC1 the defective gene is also expressed in organs outside the liver, and therefore symptoms may persist after transplant

Learning points: PFIC

- *Growth is a major problem and most children require NG feeding*
- *Fat malabsorption may occur without significant jaundice due to lack of bile salts in bile*
- *Where there is diarrhoea an MCT formula with hydrolysed protein may be helpful*
- *Pruritus can be difficult to manage and impact on nutrition*
- *PFIC1 is also expressed in organs outside the liver, and therefore the response to liver transplant may be poor*

Autoimmune hepatitis

Children who present with autoimmune hepatitis are typically older with good nutritional status. Remission is achieved in 80% of children with prednisolone in combination with

azathioprine [38] and rarely necessitates dietetic intervention, unless associated with inflammatory bowel disease. Some of these children will need liver transplantation due to failure to prevent progression to CLD secondary to cirrhosis.

Wilson's disease

Wilson's disease is a genetically inherited disease where there is a defect in copper metabolism. It leads to an accumulation of copper in the liver, brain, kidney and cornea. Accumulation can take years and, hence, presentation is delayed. In advanced disease or acute onset, LT may be required. Oral chelating agents, e.g. penicillamine, bind dietary copper and negate the need for a copper-restricted diet. There is no conclusive evidence that a lifelong dietary restriction of copper is beneficial in patients whose serum transaminases (ALT, AST) have normalised and who are compliant with drug therapy. A strict low copper diet may negatively impact on the nutritional value of the diet and should be reserved for patients who are uncompliant with or unresponsive to drug therapy [39].

Learning points: Wilson's disease

- *A copper-restricted diet should be followed until there is remission of symptoms and normalisation of liver enzymes*
- *Chelating agents negate the need for a copper-restricted diet*

Cystic fibrosis-related liver disease

Liver disease is a known complication of cystic fibrosis (CF). Signs of CLD are seen in 25% of CF patients, but fewer than 10% will progress to cirrhosis [40]. Significant portal hypertension and associated malnutrition are characteristic of severe cystic fibrosis-related liver disease (CFLD). Jaundice is rarely seen. Liver function tests are not reliable markers for disease severity.

Liver tumours

Tumours rapidly infiltrate the liver whether benign or malignant. Medical management includes the use of steroids and chemotherapy to reduce tumour size. Resection may then be possible allowing the liver to regenerate; otherwise, transplant may be the only option and is regarded as a successful treatment in those without extrahepatic disease [41].

Bone marrow transplantation: immune deficiency disorders

Immune deficiency causing liver destruction has led to a need for bone marrow transplantation followed by liver transplantation, in some cases. The main nutritional complications include severe vomiting and diarrhoea.

Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

NAFLD may result in mild fatty infiltration of the liver and mild inflammation, advancing to NASH, which leads to cirrhosis and eventually end-stage liver failure [42]. It is typically diagnosed around 12 years of age in children with obesity. With the increase in childhood obesity, prevalence of NAFLD may range from 36% [43] to 80% [44].

Weight reduction through diet and exercise is the main treatment but can be difficult to achieve for many patients [45]. The aim is to correct metabolic disturbances by reversing insulin resistance, reducing visceral fatness and reducing oxidative stress and inflammation [46]. Evidence for other treatment options including metformin, vitamin E and anti-inflammatory fats [47] have thus far produced equivocal results.

Learning points: NAFLD/NASH

- *NAFLD is fatty infiltration and inflammation of the liver*
- *NASH is a serious condition that can progress to cirrhosis*
- *The prevalence of NAFLD is increasing alongside rising obesity levels*
- *Treatment is weight loss through diet and exercise*

The dietetic management of these common disorders leading to CLD is summarised in Table 10.16.

A case study describing the management of a baby with CLD is given in Table 10.18.

Transition to adult care

The transition from paediatric to adult services can be difficult for many young people with liver disease [48]. Non-adherence to medications and appointments post-transplant is more prevalent in adolescents than young children; it has been reported to be >50% in adolescents [49]. They may find it difficult to plan due to the unpredictable time of adolescent life and may not have a clear view of the future [50]. This should be considered when setting nutritional goals. Adolescents require consistent and ongoing education, and the communication between staff of both paediatric and adult services needs to be seamless [51]. Institutions should provide a pre-transition clinic that takes place in the adult service [52–54].

Table 10.16 Dietetic management of common disorders leading to chronic liver disease.

Disorder	Dietetic management
Neonatal hepatitis	Ensure adequate growth: • Breastmilk (with fortifier if appropriate) or preterm/high energy formula • Some MCT formula may be required in order to optimise weight gain and growth Where jaundice persists after discharge from hospital: • Dietetic management is as for infantile CHB (Table 10.10)
Galactosaemia	While awaiting the Gal-1-PUT result to exclude galactosaemia: • Stop breastfeeds and give advice to mother on how to maintain breastmilk supply • Commence a lactose-free MCT formula (Table 10.9) If the test is positive for galactosaemia: • Change to a soya infant formula • A lifelong galactose restriction will be required (p. 602)
Biliary atresia	• Initial dietetic management is the same as described in Table 10.10 • Following the Kasai operation, feeds are gradually introduced as described in Table 10.17
Alpha-1-antitrypsin deficiency	• Some children require no nutritional intervention and are clinically well • Severely affected children (who may come to transplantation before the age of 1 year): dietetic management is as described for CLD
Alagille's syndrome	If there is faltering growth without symptoms of CLD: • Consider NG feeding • Consider PEG feeding in the absence of organomegaly and portal hypertension • In children severely affected with xanthelasma, there is no evidence to restrict saturated fats If there is faltering growth with advancing CLD: • Dietetic management is as described for CLD
Haemangioma	For a small haemangioma: • Nutrition intervention is often not required For a large haemangioma: • There is likely to be a fluid restriction • Energy and nutrient density of the diet should be increased • In severe cases continuous NG feeding will be required
Inspissated bile syndrome	Supplementing the diet with MCT may be necessary until PTC is performed
Choledochal cysts	Infants or children with significant CHB or fat malabsorption: • MCT supplementation Those requiring a Kasai procedure: • Infants – see the post-Kasai procedure (Table 10.17) • Children – age-appropriate diet (MCT supplementation may be required)
Progressive familial intrahepatic cholestasis	For symptoms of fat malabsorption: • MCT supplementation is required when bile flow is poor • MCT supplementation may also be required where there is good bile flow, but poor bile quality due to a lack of bile salts • Where medication is given to bind bile acids (cholestyramine), MCT and fat-soluble vitamin supplementation is required For symptoms of diarrhoea: • There may be benefit from an MCT formula based on hydrolysed protein (Table 10.9) When there is faltering growth: • NG feeding may be needed • Gastrostomy tube feeding should be considered Consideration of pruritus: • The nutrition plan should take into account that itching may cause general irritation and distraction from eating, and feeding tubes may become dislodged due to scratching

Table 10.16 *(continued)*

Disorder	Dietetic management
Autoimmune hepatitis	Presenting symptoms that may need dietetic input range from faltering growth and malabsorption to obesity aggravated by steroid therapy

Wilson's disease	On diagnosis and initiation of drug therapy or where there is poor compliance with drug therapy [39]:
	• Avoidance of foods high in copper until there is remission of symptoms and raised liver enzymes:
	  ○ Offal, particularly liver
	  ○ Animals/fish eaten whole (which contain the liver, e.g. shellfish)
	  ○ Mushrooms
	  ○ Cocoa, chocolate
	  ○ Energy drinks
	Once there is remission of symptoms and normalising of serum transaminases (ALT, AST):
	• Normal diet

Cystic fibrosis-related liver disease	Assessment and treatment needs to take into account that: • Body mass index (BMI), the standard measure of nutritional status in CF, may be affected by ascites or organomegaly • An increase in malabsorption with progressive CFLD is most likely to be as a result of portal hypertension enteropathy. Increases in PERT above 10 000 units lipase/kg are thus unlikely to be helpful • High feed volumes may not be tolerated due to organomegaly and ascites • Restriction of sodium intake may not be needed as requirements are greater in CF • A peptide-based MCT formula should be used where portal hypertension enteropathy is suspected Dietetic management is further described on p. 232
Liver tumours	Nutritional support and monitoring is required throughout the course of treatment
Bonemarrowtransplantation–immune deficiency disorders	Nutrition support in the form of enteral and parenteral nutrition may be required throughout the critical course of treatment
Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis	• Energy-restricted diet • Incorporate regular physical activity

MCT, medium chain triglycerides; CHB, conjugated hyperbilirubinaemia; Gal-1-PUT, galactose-1-phosphate uridyltransferase; CLD, chronic liver disease; NG, nasogastric; PEG, percutaneous endoscopic gastrostomy; PTC, percutaneous transhepatic cholangiography; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PERT, pancreatic enzyme replacement therapy.

Table 10.17 Post-Kasai protocol.

Day post-Kasai	Management
Day 1–2	IV fluids
Day 3	Commence hourly feeds of Dioralyte, gradually increasing to 120 mL/kg
Day 4–5	1. Change to 120 mL/kg of feed* 2. Change to 2 hourly feeds 3. Increase volume by 5 mL every 4 hours up to 150 mL/kg feed 4. Progress to 3 hourly feeds if good tolerance and maintaining blood sugars
Day 6	Allow demand feeding Give target volume of feed to aim for each day
Worked example	Infant weighing 4 kg. Day 4 post-Kasai and has been tolerating 20 mL Dioralyte hourly (120 mL/kg). Mum has EBM available and wishes to breastfeed. • Change to feed* and give 20 mL for one feed (120 mL/kg) • Then 40 mL × 2 hourly for two feeds (120 mL/kg) • Then 45 mL × 2 hourly for two feeds (135 mL/kg) • Then 50 mL × 2 hourly for two feeds (150 mL/kg) • Then 75 mL × 3 hourly for two feeds (150 mL/kg) • Finally, allow demand feeding aiming for minimum 400 mL/day MCT formula (100 mL/kg) and remainder as EBM/breastfeeding

IV, intravenous; EBM, expressed breastmilk.
*Feed should be 100 mL/kg MCT formula and the remainder as EBM if available. If mum wishes to breastfeed, wait until the infant is taking 150 mL/kg in order to demonstrate tolerance. Feeds can then be changed to 100 mL/kg MCT formula and the remainder as breastfeeds.

Table 10.18 Case study: an infant with chronic liver disease.

Chronology	
Admission	An 8-week-old female with conjugated hyperbilirubinaemia, dark urine and pale stools. Weight = 3.75 kg (<2nd centile) **Presentation:** Excessive feeding on breastmilk and standard infant formula = 260 mL/kg. Galactosaemia excluded **Impression:** Possible biliary atresia Changed to 100 mL/kg MCT formula and breastfeeding Kasai operation performed
Management post-Kasai	
Day 1–2	NBM, on IV fluids
Day 3	Commenced hourly feeds of Dioralyte, gradually increasing to 120 mL/kg
Day 4–5	Changed to feeds and gradually increased to 150 mL/kg MCT formula. Once tolerating, changed to 100 mL/kg MCT formula and breastfeeds
Day 7	Discharged home with advice to call liver team weekly to discuss progress and provide a weight measurement
Readmitted after 8 weeks	
Admission	17 weeks old. Increased abdominal girth, remained jaundiced. Increased HARI, splenomegaly and ascites. Paracentesis performed
Day 1	Weight = 5.78 kg (<25th centile) MUAC = 11 cm (<2nd centile). Weight affected by increased girth. Feeding: 100 mL/kg MCT formula via bottle and breastmilk in addition
Day 2–3	Not managing full feed volume, so NG tube inserted to provide top-up feeds. Breastfeeding continued
Day 4–7	Kasai procedure considered to have failed in view of worsening liver disease. Liver transplant assessment completed (to determine suitability for transplant). Taking 100 mL/kg via bottle with NG top-ups. Mum breastfeeding
Day 8	18 weeks old. Weight = 5.8 kg (9th–25th centile) MUAC = 10.8 cm (0.4th centile). Listed for transplant. Discharged from hospital on bottle feeding and NG top-ups providing 150 mL/kg. Formula concentration increased to provide 1 kcal (4 kJ)/mL. Mum breastfeeding occasionally
Outpatient management	
Week 1	**Telephone review.** 19 weeks old. Weight = 5.8 kg (9th–25th centile), static. Only managing 130 mL/kg feed. Advised to take 150 mL/kg by increasing NG top-ups. Occasional breastfeeds
Week 2	**Telephone review.** 20 weeks old. Weight = 5.8 kg (>9th centile), static, increased abdominal girth, poor appetite, early satiety. Unable to tolerate more than 130 mL/kg feed. Arranged to see in clinic
Week 3	**Clinic.** 21 weeks old. MUAC = 10.3 cm (<0.4th centile). Rapid progression of end-stage liver failure. Continued on bottle feeds with NG top-ups. Still only managing 130 mL/kg feed. Formula concentration increased to 1.2 kcal (5 kJ)/mL. Mum no longer breastfeeding
Week 4	**Clinic:** 22 weeks old. Weight = 5.82 kg (9th centile) MUAC = 10.2 cm (<0.4th centile). Poor oral feeding tolerance due to organomegaly and ascites. Not always managing 130 mL/kg feed. Formula concentration increased to 1.5 kcal (6 kJ)/mL. Started on complementary foods
Week 5	**Admission:** 23 weeks old. Received liver transplant

NBM, nil by mouth; IV, intravenous; HARI, hepatic artery resistance index; MUAC, mid-upper arm circumference; NG, nasogastric.

The Pancreas

Introduction

The pancreas is involved in three primary functions associated with digestion and regulation of macronutrients:

- production of bicarbonate fluid to neutralise gastric acid in the duodenum
- synthesis and secretion of digestive enzymes
- production of hormones to regulate nutrient use and storage

Inflammation within the parenchyma of the pancreas leads to pancreatitis, and this impacts on all of the above pancreatic functions. Dietetic management of pancreatitis depends on the type of disease, which may be acute, acute-recurrent or chronic.

Diagnosis

Diagnostic criteria for acute, acute-recurrent and chronic pancreatitis [55] are outlined in Table 10.19. Ranges of serum levels of enzymes used in the diagnosis and monitoring of pancreatitis are given in Table 10.20.

Table 10.19 Diagnostic criteria for pancreatitis.

Type of pancreatitis	Diagnostic criteria
Acute pancreatitis	*Requires at least 2 of 3 criteria*: Lipase/amylase greater than three times the upper normal limit Epigastric/abdominal pain Imaging findings compatible with acute pancreatitis
Acute-recurrent pancreatitis	*Requires 2 distinct episodes of acute pancreatitis*: Complete resolution of pain ≥1 month between episodes OR Complete normalisation of serum amylase/lipase between episodes with resolution of pain symptoms irrespective of time interval between episodes
Chronic pancreatitis	*Requires at least 1 of 3 criteria*: Abdominal pain consistent with pancreatic origin and imaging suggesting pancreatic damage Exocrine or endocrine pancreatic insufficiency and suggestive pancreatic imaging findings Surgical or pancreatic biopsy showing histopathological features of chronic pancreatitis

Table 10.20 Serum enzymes used in pancreatitis.

Test	Reference range*	Explanation
Serum amylase	25–125 IU/L	Amylase is used to diagnose acute pancreatitis as it is elevated when the pancreas is inflamed
Serum lipase	5–65 IU/L	Lipase is used to diagnose acute pancreatitis as it is elevated when the pancreas is inflamed
Faecal elastase	>200 µg/g	Used for the diagnosis or exclusion of pancreatic exocrine insufficiency that can be caused by chronic pancreatitis, cholelithiasis (gallstones) and pancreatic tumour (should be performed on a formed stool as it may be falsely low with a watery stool)

*Ranges may vary according to age.

Causes of pancreatitis

Causes for pancreatitis in children differ from those of adults where lifestyle factors such as alcohol and smoking are common. Common causes of pancreatitis in children are:

- idiopathic
- drugs and toxins, e.g. valproic acid and azathioprine
- biliary tract, e.g. gallstones, biliary tract malformations choledochal cysts, pancreas divisum, pancreatic ductal abnormalities and annular pancreas
- genetic, e.g. mutations in PRSS1, CFTR and SPINK1
- autoimmune
- metabolic disorders, e.g. glycogen storage disease and hypertriglyceridaemia
- trauma, e.g. non-accidental injury, fall from horse/bicycle, seat belt laceration and endoscopic retrograde cholangio-pancreatography (ERCP) complication

Nutrition assessment

Patients with pancreatitis require regular nutritional assessment. The frequency of assessment is determined by the type and severity of pancreatitis.

Anthropometry

Routine anthropometric measurements should be undertaken for children with chronic pancreatitis including weight, height and BMI with screening for signs of impaired growth every 3–6 months [56].

Biochemistry

Blood tests routinely used to investigate the pancreas are shown in Table 10.20.

Clinical

The clinical assessment of a child with pancreatitis should include signs of malnutrition, the clinical condition (severity and type of pancreatitis), the presence and severity of abdominal pain, diabetes and pancreatic exocrine insufficiency. It is recommended that screening for diabetes and pancreatic exocrine insufficiency occur every 6–12 months [56, 57]. Many of the scans and procedures used as part of the clinical assessment for the child with pancreatitis are as described for liver disease (Table 10.2).

Dietary

Dietary assessment should explore how symptoms of pancreatitis may be impacting on intake and absorption of nutrients. Examples of symptoms that may cause

nutritional difficulties include nausea, vomiting, abdominal pain and steatorrhoea (if there is pancreatic exocrine insufficiency).

Learning points: nutritional assessment of pancreatitis

- *Nutritional management will depend on whether the pancreatitis is acute, acute-recurrent or chronic*
- *Anthropometric measurements (weight, height, BMI) should be repeated every 3–6 months*
- *Assessment should include signs of malnutrition, diabetes, pancreatic exocrine insufficiency, the clinical condition (severity and type of pancreatitis) and the presence and severity of abdominal pain*
- *Dietary assessment should explore how pancreatitis symptoms are impacting on nutrition*

Acute pancreatitis

Acute pancreatitis is sudden inflammation of the pancreas. Children commonly present with abdominal pain, weight loss and nausea or vomiting on eating. Management depends on the severity of pancreatitis, which may range from mild to severe (Table 10.21). Severe acute pancreatitis is associated with increased morbidity in children [56]. Acute pancreatitis can present initially with mildly elevated serum markers and low levels of pain but can worsen rapidly due to surgical interventions or the natural course of the disease. Most children recover from acute pancreatitis with the pancreas returning to normal [58]. The main aims of treatment are to manage pain and restore metabolic homeostasis.

Nutrition support is particularly important in acute pancreatitis caused by trauma. Trauma severity can range from minor lacerations to complete transection of the pancreas and damage to the main pancreatic duct [59]. There may also be injuries to other structures including the liver, intestine, spleen and kidneys [59]. Depending on the type and extent of trauma, surgery may be required, resulting in an extended period of NBM, which may impact on nutritional status.

Dietetic management

The practice of treating patients with acute pancreatitis with a period of NBM to suppress pancreatic enzyme secretion, thus 'resting' the pancreas, has been shown to provide no benefit [60–63]. In addition, the risk of bacterial overgrowth and gut translocation due to prolonged periods of NBM may exacerbate pancreatic infection risk [64]. Enteral nutrition has been reported to be well tolerated in mild acute pancreatitis and is associated with shorter length of stay, reduced critical care admissions and reduced progression to severe acute pancreatitis [65]. In severe acute pancreatitis enteral nutrition has been associated with reduced complications and mortality [66]. Recommendations are to commence early enteral nutrition (oral/NG/nasojejunal) following any necessary fluid resuscitation and to commence PN only in children unable to tolerate enteral nutrition [56, 57]. Table 10.22 shows the dietetic management of acute pancreatitis.

Table 10.21 Severity of acute pancreatitis.

Mild	No organ failure No local or systemic complications Resolves in first week
Moderately severe	Transient organ failure resolving in <48 hours, or exacerbation of co-morbid disease or local complications
Severe	Organ failure for >48 hours

Acute-recurrent pancreatitis

Acute-recurrent pancreatitis is where there are at least two episodes of acute pancreatitis with resolution of pain or normalisation of measured serum enzyme levels between episodes. PERT, previously used in acute-recurrent pancreatitis, is not recommended as these patients are, by definition, pancreatic exocrine sufficient [56].

Dietetic management

The dietetic management of the acute pancreatitis episodes is as described in Table 10.22. For children with acute-recurrent pancreatitis caused by hypertriglyceridaemia, a low fat diet is required [67]. Otherwise a normal fat-containing diet should be given, with a low fat diet only being used if there is vomiting or abdominal pain [56]

Table 10.22 Dietetic management of acute pancreatitis.

Timing of initiating nutrition	In mild acute pancreatitis: within 48 hours In severe acute pancreatitis: within 72 hours
Route of nutrition	Commence oral/nasogastric feeding Consider nasojejunal feeding if oral/nasogastric feeding not tolerated Consider parenteral nutrition alongside enteral nutrition if enteral not well tolerated
Type of nutrition	If oral feeding • Normal oral diet • A fat restriction is not recommended If tube feeding • Standard feed If receiving parenteral nutrition • Standard PN should be given (p. 67)
Surgical interventions	ERCP (Table 10.2): NBM for 1–2 days may be required Puestow procedure (anastomosis of pancreatic duct to jejunum): NBM for 5 days may be required

ERCP, endoscopic retrograde cholangio-pancreatography.

Table 10.23 Dietetic management between episodes of acute pancreatitis.

Timing of initiating nutrition	A regular diet should be started within one week after the onset of acute pancreatitis
Type of nutrition	A diet with normal fat content should be initiated A low fat diet should be initiated if: • There is abdominal pain/vomiting on a normal fat diet • Pancreatitis is caused by hypertriglyceridaemia

Table 10.24 Dietetic management of chronic pancreatitis.

Type of nutrition	Normal oral diet
Pancreatic exocrine insufficiency	Require: • Pancreatic enzyme replacement therapy • More frequent follow-up to monitor for malnutrition
Consequent diabetes	Require: • Specialist diabetes input • More frequent follow-up to monitor for malnutrition and complications

Table 10.25 Case study: an adolescent with pancreatitis.

Chronology	
Admission	A 15-year-old male. Fell off bike onto handlebars, vomited once, then vomited upon eating meal at home with significant abdominal pain. CT scan: tear in tail of pancreas. MRI scan: swelling with fluid around tail of pancreas **Presentation:** Active and physically fit with good nutritional status. Wt = 52.3 kg (25th–50th centile) Ht = 160.5 cm (9th–25th centile) BMI = 20.3 kg/m^2 (9th–25th centile) **Impression:** Acute pancreatitis secondary to abdominal trauma **Acute interventions:** IV fluids and standard analgesia **Dietetic intervention:** Normal oral diet started
Week 1	Wt = 49.9 kg (25th centile). Amylase level increasing, no pain on standard analgesia. Poor appetite, eating less than half of meals. Started on two cartons ONS per day
Week 2	Wt = 46.3 kg (9th–25th centile). Amylase level increased to 1400 IU/L, but no abdominal pain. Appetite slightly improved. Having half of meals. Discharged on two cartons ONS per day with advice to have high energy/protein foods
Readmitted a week later	
Week 3	Wt = 45.3 kg (>9th centile) (13% weight loss since injury). Amylase level >1700 IU/L, severe abdominal pain. Poor appetite and pain on eating. Made NBM Received stenting to tail of pancreas. Remained NBM Two days later started NG feeding using 1.5 kcal (6 kJ)/mL polymeric feed at 10 mL/hour, increasing by 10 mL/hour every 4 hours to target of 67 mL/hour × 24 hours: 1600 mL, 2400 kcal (10 MJ), 96 g protein/day Did not tolerate NG so changed to NJ feeding after 1 day
Week 4	Wt = 46 kg (>9th centile). Started normal oral diet alongside NJ feeding, but made NBM again due to pain on eating
Week 5	Wt = 46.5 kg (>9th centile). Vomiting and increased pain. Pancreatic collection identified. NJ feeds stopped. PN commenced providing 2000 mL, 2320 kcal (9.7 MJ), 81 g protein/day
Week 6	NJ feeding restarted at 5 mL/hour increasing by 10 mL/hour every 4 hours. PN titrated down as feeds increased. Kept NBM
Week 7	Wt = 49 kg (<25th centile). PN stopped as NJ feeds at full rate of 100 mL/hour × 16 hours. NBM
Month 2	Discharged to local hospital on full NJ feeds. NBM as trials of eating causing pain
Outpatient management	
Month 3	**Clinic:** Wt = 52.5 kg (25th–50th centile). Having 1600 mL NJ feeds at home. Started normal oral diet the week before with no pain or vomiting. NJ feeds reduced to 800 mL/day. Advised to remove NJ within 1 month if eating well
Month 5	**Clinic:** Wt = 54 kg (25th–50th centile). NJ tube removed following previous clinic appointment. Tolerating normal diet with no abdominal pain

CT, computerised tomography; MRI, magnetic resonance imaging; BMI, body mass index; ONS, oral nutritional supplement; NBM, nil by mouth; NG, nasogastric; NJ, nasojejunal; PN, parenteral nutrition.

(Table 10.23). There is little evidence on how restricted in fat the diet should be. Low fat diets can increase the likelihood of weight loss as fat is such a significant source of energy, and as a result these children may require high energy low fat nutritional supplements or advice on increasing the energy density of the diet.

Chronic pancreatitis

Chronic pancreatitis is the result of irreversible damage to the anatomy and function of the pancreas. It initially presents as acute pancreatitis manifesting into recurring episodes before progressing to irreversible fibrosis as a result

of long-standing inflammation [55]. Exocrine insufficiency may be seen in one third of children due to a loss of acinar cells [68], and there is an increased risk of type 3c diabetes due to a loss of islet cells [69]. The endocrine defect is insufficient insulin secretion (the abnormality in type 1 diabetes) rather than insulin resistance (as in type 2 diabetes) [57].

Dietetic management

Children with chronic pancreatitis are at increased risk of malnutrition [70, 71]. This may be due to a higher resting energy requirement; however, there is limited evidence for this in children. Children with chronic pancreatitis should have a normal fat-containing diet. Those with pancreatic exocrine insufficiency are at risk of fat malabsorption, micronutrient deficiencies and poor bone health and should have PERT [56] (p. 219). Fat-soluble vitamin levels should be measured every 6–12 months, and bone mineral density should be measured in children with malnutrition and persistently low serum vitamin D levels or a history of fractures [56]. It is recommended that children with pancreatic exocrine insufficiency and/or diabetes have more frequent follow-up due to the high risk of malnutrition and micronutrient deficiencies [56].

The dietetic management of chronic pancreatitis is summarised in Table 10.24.

A case study of an adolescent with pancreatitis is described in Table 10.25.

Future research needs/unanswered questions

- the ideal MCT content of formulas/feeds for liver disease
- extent of copper restriction required for Wilson's disease
- ideal amount of BCAA to use in formula and the impact on nutritional status in liver disease
- the extent of fat restriction and the duration a fat-restricted diet required for chylous ascites
- the ideal route of feeding for pancreatitis (NG, oral or jejunal feeding)
- the impact of a low fat diet vs. a normal diet on outcomes and pain in pancreatitis
- early enteral nutrition vs. delayed nutrition in pancreatitis
- the resting energy expenditure of children with pancreatitis

Acknowledgements

Thank you to the authors of previous versions of this chapter: Stephanie France and Jason Beyers. A special thank you to King's College Hospital, London paediatric dietitians: Gillian Geaney, Helen Mortimer, Karishma Manwani and Kate Arnold for their support and helpful feedback on the chapter.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

11 Endocrinology

S. Francesca Annan and Sarah Price

Diabetes Mellitus

S. Francesca Annan

Introduction

Diabetes mellitus describes a collection of complex metabolic disorders resulting from defects in insulin production and secretion, insulin action or both. Diabetes is classified into the following forms:

- **type 1:** β-cell destruction, usually leading to absolute insulin deficiency; may be immune mediated or idiopathic
- **type 2:** insulin resistance with relative insulin deficiency, leading to hyperglycaemia
- **other specific types:** for example, monogenic forms of diabetes; neonatal diabetes; genetic defects of insulin secretion; drug-induced forms of diabetes; secondary to other genetic syndromes; exocrine pancreatic diseases, e.g. cystic fibrosis-related diabetes (CFRD) and endocrinopathies

A detailed explanation of all forms of diabetes in childhood can be found in the International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Practice Guidelines [1].

In childhood the commonest form is type 1 diabetes [1]. The latest reported data from England and Wales collected in the National Paediatric Diabetes Audit (NPDA) [2] shows that overall prevalence rates for type 1 diabetes have been stable since 2013/2014. Prevalence of type 1 diabetes under 15 years of age was 194.2 per 100 000 population; a new diagnosis incidence rate of 25.4 cases per 100 000 was reported in 2016–2017. Scottish data [3] from 2017 reports the new diagnosis incidence as 18 per 100 000 for children under 5 years and 45 per 100 000 in 5- to 9-year-olds. There were 715 reported type 2 diabetes cases in England and Wales, with an increase in the number of newly diagnosed reports. Other forms of diabetes make up a very small percentage of the total numbers of children with diabetes.

The 2017 International Diabetes Federation (IDF) Diabetes Atlas [4] reports worldwide incidence and prevalence for type 1 diabetes; the UK is in the top 10 countries in the world with 40 300 cases of diabetes in under 20-year-olds.

Key practice recommendation documents

The following publications are essential reading for dietitians practising in the care of children and young people with diabetes:

- National Institute for Health and Care Excellence (NICE). *Diabetes (type 1 and type 2) in children and young people: diagnosis and management*, *NG18* [5]
- International Society of Pediatric and Adolescent Diabetes (ISPAD). *Clinical practice consensus guidelines compendium 2018* [6]
- American Diabetes Association (ADA). *Standards of Medical Care in Diabetes 2019* [7]
- Scottish Intercollegiate Guidelines Network (SIGN). *Management of Diabetes, A National Clinical Guideline, SIGN 116* [8]

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

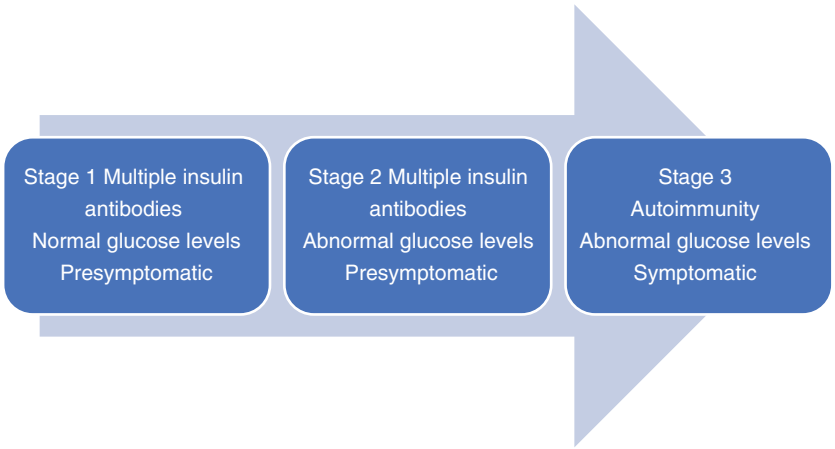


Figure 11.1 Stages of type 1 diabetes.

Table 11.1 Summary of current national and international glucose and HbA1c targets.

	NICE 2015 [5]	ISPAD 2018 [6]	ADA 2019 [7]
Waking/preprandial glucose	4–7 mmol/L	4–7 mmol/L	5–7.2 mmol/L
Postprandial glucose	5–9 mmol/L	5–10 mmol/L	N/a
Bedtime/overnight glucose	4–7 mmol/L	4.4–7.8 mmol/L	5–8.3 mmol/L
HbA1c	<48 mmol/mol	<53 mmol/mol A lower goal of 48 mmol/mol if achievable without increase in hypoglycaemia or during honeymoon phase	<58 mmol/mol A lower goal of <52 mmol/mol may be applicable if achievable without increased risk of hypoglycaemia

N/a, not applicable.

Overview of type 1 diabetes management

Type 1 diabetes is now described in stages with increased recognition of the process through which a person with increased genetic risk progresses through to diagnosis [9]. TrialNet [10] is an international collaboration, leading the work on early detection and trials to prevent or delay the development of type 1 diabetes. At the current time there are no nutritional recommendations for stages 1 and 2. The stages of type 1 diabetes are shown in Figure 11.1.

The management of type 1 diabetes in childhood is changing rapidly; development of insulin pumps and closed-loop/artificial pancreas systems, using both single (insulin) and dual hormones (insulin and glucagon) along with improvements in glucose sensing technology and the development of smart insulin pen devices, will continue rapidly over the next 2–3 years. In addition to the systems currently being researched worldwide, there has been an increased use of do it yourself (DIY) artificial pancreas systems, with families building their own systems based on open-source algorithms [11].

The increased use of continuous glucose monitoring (CGM) has had a significant impact on the understanding of how food affects glycaemia [12] and has resulted in recognition of the need for whole food approaches to education that account for the impact not only of carbohydrate amount on glucose levels but also carbohydrate type and quality, along with meal composition [13]. Increased understanding of glucose responses to food has also created groups of healthcare professionals who believe a low carbohydrate diet should be used to lower glycated haemoglobin (HbA1c) [14]. There is currently no evidence to recommend low carbohydrate diets for children with type 1 diabetes.

To provide safe and effective nutrition advice, paediatric diabetes dietitians need to be familiar with current and future technology and incorporate its use into routine clinical practice [13].

Current treatment options

There are recommendations from a number of bodies, including NICE [5], ISPAD [6] and ADA [7]. There is broad consensus worldwide that the optimal insulin replacement is one which mimics normal physiology as closely as possible.

Glycated haemoglobin and glucose targets

The recommended HbA1c target in England was lowered by NICE [5] in 2015 to 48 mmol/mol or 6.5%. The HbA1c

Table 11.2 Commonly used insulin preparations in the UK and expected insulin action profiles.

Name	Manufacturer	Onset of action	Peak action	Duration of action	Licensed for use
NovoRapid (insulin aspart)	Novo Nordisk	15 minutes	60–90 minutes	3–5 hours	Age 2 years and over
Humalog (insulin lispro)	Lilly				Age 2 years and over
Apidra (insulin glulisine)	Sanofi				6 years and over
Lantus (insulin glargine)	Sanofi	2–4 hours	8–12 hours	22–24 hours*	Age 2 years and over
Levemir (insulin detemir)	Novo Nordisk	1–2 hours	4–7 hours	20–24 hours*	Age 1 year and over
Toujeo (insulin glargine U300)	Sanofi	2–6 hours	No peak	30–36 hours	Age 18 years and over
Tresiba (insulin degludec)	Novo Nordisk	0.5–1.5 hours	No peak	>42 hours	Age 1 year and over

*Insulin action may be considerably shorter.

level in a person without diabetes is <42 mmol/mol. To achieve this target level of glycaemic management, an average blood glucose level of 8 mmol/L or below is needed. Current recommendations for the assessment of glycaemic management are moving towards measuring time spent in target glucose levels with a focus on minimising exposure to both hypoglycaemia (<3.9 mmol/L) and hyperglycaemia (>10 mmol/L) [15].

A number of glucose target recommendations are available and are summarised in Table 11.1.

Glucose monitoring

NICE guidelines recommend that blood glucose levels should be checked a minimum of five times a day [5]. International recommendations [16] based on more recent data suggest 6–10 glucose checks are required a day. They also recommended that a meter with an integrated bolus calculator is provided to children using intensive therapy (p. 199) [13, 16, 17].

CGM is currently not uniformly widely accessible across the UK. NICE guideline 18 provides guidance on when CGM should be offered in England. The use of CGM allows a child/family to have information about glucose levels every 5 minutes with the additional benefit of alarms and alerts to indicate the onset of hypoglycaemia (p. 200). CGM may be real time, the use of which has been demonstrated to improve time in target range for people using both insulin pump therapy and multiple daily injections (MDI) when used for more than 90% of the time [17–19]. Intermittent use of CGM does not lead to sustained benefits beyond the period of use. Flash glucose systems (p. 200) are also available that allow glucose to be measured without finger prick calibration, but do not offer alarms and alerts. The currently available system requires the sensor to be read at least every 8 hours for the information about glucose levels to be reviewed [18].

Insulin management

It is recommended that intensive insulin regimens (intensive therapy) are introduced from diagnosis [5, 20, 21]: either multiple daily insulin injections, using a combination of a long-acting insulin given once or twice a day, in addition to injections of fast-acting insulin with food and for the management of high glucose levels (correction doses); or insulin pump therapy. Twice daily and three times daily (split evening insulin) regimens are not recommended for routine use in clinical care. Commonly used insulin preparations and their expected action profiles are given in Table 11.2.

Newer insulin pump technologies, described as hybrid closed-loop systems, are currently undergoing clinical trials in the newly diagnosed child. Hybrid closed loop integrates the glucose sensor information into an insulin dosing algorithm, which adjusts insulin according to sensor glucose levels of every 5 minutes. These systems currently require meals to be 'announced', and carbohydrate counting and meal boluses remain essential parts of management [22]. The use of insulin pump therapy from diagnosis is recommended by ISPAD for children under the age of 7 years [23]. The use of pumps from diagnosis has been reported to be associated with improved treatment satisfaction, but not glucose management. A 2016 study comparing the use of insulin pump therapy between three large paediatric registries, namely, England and Wales (NPDA), Germany and Austria (DPV registry) and the USA (T1Dexchange), showed a much lower percentage of the population with type 1 diabetes in the NPDA registry using insulin pump therapy, 14%, compared with 41% and 47% in DPV and T1Dexchange, respectively [24]. However, the use of insulin pumps in 2017 in England and Wales was 32.2% and in Scotland was 35.7%, representing an increase in use over the last 2 years.

Care delivery and teamwork

It is recommended that children and young people with type 1 diabetes attend a specialist children's clinic and are cared for by an appropriately trained paediatric multidisciplinary diabetes team (MDT), providing ongoing integrated education and support [25, 26]. This team should include a paediatric endocrinologist or diabetologist, diabetes nurse specialists and a paediatric diabetes dietitian; children and young people should have access to psychological services and social workers in addition to services offered in primary care. The MDT should work collaboratively with the child and their family to optimise diabetes management while

enabling them to deal with their diabetes day to day and reduce the risk of acute and long-term complications.

Teamwork and target setting have been shown to have a greater impact on clinic outcomes than the treatment regimen used [27]. Teams that are consistent with the messages and information given by all team members, in addition to aiming for lower blood glucose and HbA1c targets, have better outcomes and have a greater influence on parental expectations.

To be successful, nutrition education must be tailored to the individual clinical, social, psychological, cultural and economic needs of the child and family, and dietitians should convert the scientific knowledge about food into practical, feasible advice that can be delivered by the whole MDT. Current guidance recommends regular review of nutrition and growth as part of multidisciplinary clinics, with an additional annual review [13]. Annual review is recommended for all children with diabetes, and the following additional investigations are usually performed: liver function tests, renal function, urine albumin to creatinine ratio, lipid profile, thyroid screening, screening for coeliac disease (CD) and retinopathy screening from age 12 years. Children with abnormal lipid levels will need additional advice about management of dyslipidaemia. Positive coeliac screening will require further investigation for the diagnosis of CD.

Nutritional management of type 1 diabetes

Across the UK consensus guidelines published by the International Society for Pediatric and Adolescent Diabetes (ISPAD) are used to guide clinical practice. Nutrition guidelines are published by Diabetes UK for adults only [28].

A key recommendation of the ISPAD guidelines is that more research and evidence on the role of nutrition and specific paediatric diabetes dietary management and education is required. However, there is robust evidence for the nutritional requirements of children on which the nutrition recommendations from ISPAD are based. Food choices appropriate for health and growth and development are a key part of nutrition advice.

Aims of management

The aims of management (adapted from ISPAD) are:

- to encourage healthy lifelong eating habits and appropriate eating behaviour within the context of the social, cultural and psychological well-being of the child and family
- to establish or maintain eating routines based on a wide range of nutritious foods and provide a framework for regular meals with minimal snacking to allow regular monitoring of glucose levels and administration of insulin doses
- to meet the energy and other nutrient requirements for normal growth, development and good health
- to avoid restrictive eating behaviours that may impact on growth and psychosocial well-being
- to achieve and maintain an appropriate body mass index (BMI)
- to balance food intake and insulin action profiles to optimise glycaemic management
- to reduce the risk of micro- and macrovascular complications, particularly cardiovascular disease
- to develop a supportive relationship to facilitate behaviour change
- to use diabetes technology to aid education about nutrition and inform insulin adjustments for food and activity management

Distribution of macronutrients

Children with diabetes have the same overall nutritional requirements as their peers. Energy requirements will depend on age, sex, size and activity levels. Individual assessment of energy requirements will support education about the appropriate amount and distribution of carbohydrate in the diet. The suggested macronutrient distribution is:

- carbohydrate 45%–55% energy with moderate sucrose intake up to 10% total dietary energy
- fat 30%–35% energy with <10% from saturated and trans fatty acids
- protein 15%–20% energy

Energy intake

It is important to ensure that total energy intake matches requirements and growth is regularly reviewed. Following diagnosis there is usually a period of weight gain to correct the loss of weight in the period prior to diagnosis. Appetite may be increased for 2–4 weeks. Providing a guide to appropriate portion sizes along with promotion of regular physical activity should help prevent excess weight gain. It is important to monitor energy intake and growth to identify when advice on prevention of overweight and obesity is needed. The rate of overweight and obesity reported for children aged 10–11 years in the latest National Paediatric Diabetes Audit (NPDA) report was 35.3% compared with 34.3% in the national child measurement programme in England [2].

Carbohydrate amount and type

Carbohydrate requirements in childhood should be individually determined based on weight, height, sex and activity levels. Calculation of energy needs allows determination of a target daily carbohydrate intake.

Example:

Boy aged 10 years (50th centile weight and height)
Dietary reference value for energy [29]
= 1935 kcal (8.1 MJ)/day
Expected carbohydrate intake (45%–55% energy)
= 217–266 g/day

Regular monitoring of growth should include advice on maintaining an age- and activity-appropriate intake. Healthy

sources of carbohydrate including wholegrains, legumes, fruit and vegetables and low fat dairy products should be promoted.

Education about carbohydrate counting allows the adjustment of prandial insulin to achieve post-meal glucose targets. Carbohydrate accounts for about 80%–90% of the glucose response to a meal when preprandial insulin is given [30]. Carbohydrate management education should include information about glycaemic index (GI) to facilitate understanding about the differing glucose responses families may observe when consuming the same quantity of carbohydrate from different food sources [5, 13]. Foods with a lower GI have been shown to decrease post-meal hyperglycaemia and improve overall glucose management [31, 32].

GI is a ranking of the effect of a carbohydrate food on blood glucose levels. The reference food is glucose, which has a numerical value of 100. Foods ranked as high GI > 70 impact glucose levels quickly, medium GI 55–70 less so, and foods ranked as low GI < 55 impact glucose levels the least quickly. As GI is influenced by a number of factors, including the amount of fat and protein in the food, type of sugar, type of starch and type of fibre, the body's processing of a low GI food is not always the same as the processing of a 'healthy' food. Perceived 'healthy' foods do not always have a low GI. Foods with a lower GI value may be swapped for higher GI foods. Families should receive guidance in how to use GI to understand glucose responses, swaps to make to improve glucose responses, and when to use high GI foods, e.g. in the treatment and prevention of hypoglycaemia [33]. Ideas for families for swapping low GI foods are given in Table 11.3.

Carbohydrate education should also cover the role of fat and protein on both glucose responses to mixed meals and overall dietary quality. Children should be encouraged to have carbohydrate sources that are lower in saturated fat. There is evidence from Europe and the USA that a focus on carbohydrate amount alone can result in food choices that are higher in saturated fat and meal and snack patterns that carry a greater risk of dyslipidaemia [34–36].

Table 11.3 Low glycaemic index (GI) food swap ideas.

Breakfast	Choose lower GI cereals or porridge; have fruit and yoghurt in place of cereal. Swap to wholegrain and sourdough breads. Add fruit to breakfast cereal
Lunches	Use pitta, wraps and flatbreads for sandwiches. Swap to oat-based crackers. Try pasta and rice salads, use homemade cereal bars that include oats and seeds in place of bought snacks. Have fruit and vegetable sticks as extras
Main meals	Swap sweet potato or new boiled potato for baked or mashed potato. Use more pasta and noodles and rice. Add beans and pulses to cooked dishes, replace some meat with beans and lentils
Snacks	Fruit all types, vegetable sticks, low fat yoghurt and popcorn as alternatives to biscuits and crisps If a bedtime snack is needed, swap to milk, yoghurt and yoghurt drinks

Carbohydrate counting

Carbohydrate counting is a recognised teaching strategy to enable insulin to be adjusted to the amount and type of carbohydrate eaten. Introduction of intensive therapy with carbohydrate counting from diagnosis has been shown to improve outcomes. A number of methods of carbohydrate counting education are used internationally. Studies in children and adolescents have shown that accuracy and consistency are important, meal routines and avoidance of grazing should be encouraged and quality of carbohydrate food choice matters [37–39]. The three methods of carbohydrate counting commonly described are:

- counting in grams
- 15 g exchanges
- 10–12 g carbohydrate portions

No differences in outcome have been demonstrated between the methods. The commonly used method in the UK is counting in grams.

Studies have shown that families are able to carbohydrate count very accurately when food is labelled and packaged and less accurately when foods are 'loose', for example, rice, pasta and potato [38]. It is important that whichever method is used, families are enabled to calculate carbohydrate in homemade/freshly prepared foods and do not feel they need to make changes to usual food choices to enable carbohydrate counting. Families should be taught to be consistent as both precision and consistency impact on glycaemic outcomes.

In addition to the methods recognised above, there are also innovative ways being developed in less resourced countries to support children and families with assessment of carbohydrate, using hand size and local utensils to measure foods. A number of these methods are currently being evaluated.

Carbohydrate counting is used alongside an insulin to carbohydrate ratio (ICR) to allow insulin dose adjustment. There are a number of methods for calculating ICR [40]. A number of rules have been proposed to assist calculation of ICR. The rules use current total daily dose (TDD) of insulin to derive the amount of carbohydrate covered by 1 unit of rapid-acting insulin. The original work on these rules comes from adults converting from MDI to pump therapy. To calculate the ICR the number from the rule is divided by TDD. The commonly used rule in adult practice is the 500 rule, which is usually insensitive in the paediatric population [40].

Alternative rules in paediatric practice are 150, 200 and 250 rules in younger children and the 300 and 350 rules in older children and adolescents.

Younger children have higher bolus insulin requirements and usually need relatively bigger insulin doses with food than older adolescents and adults [40]. The amount of bolus insulin and the strength of the ratio will be affected by the amount of basal insulin used. It is recommended that 30%–50% of the insulin should be basal insulin with an increasing body of evidence indicating that lower total basal insulin is linked to improved outcomes [41]. It is usual for ICR to vary

Table 11.4 Impact of adjusting ICR on actual dose delivery according to device.

Meal amount (CHO)	Ratio	Calculated dose (units)	Pen delivery (0.5 unit pen)	Pen delivery (1 unit pen)	Pump delivery
30 g	1 unit to 15 g	2	2	2	2
30 g	1 unit to 12 g	2.5	2.5	2 or 3	2.5
30 g	1 unit to 10 g	3	3	3	3
30 g	1 unit to 8 g	3.75	3.5 or 4	3 or 4	3.75
30 g	1 unit to 6 g	5	5	5	5

ICR, insulin to carbohydrate ratio; CHO, carbohydrate.

across the day, reflecting the pattern of insulin sensitivity seen. Typically, ratios are stronger on waking for breakfast and weaker at midday and bedtime. Care is needed in explaining ratio adjustment. In most pump and meter bolus calculators, ratios are expressed as 1 unit to cover an amount of carbohydrate, e.g. 1 unit to 8 g carbohydrate. To increase insulin dose the carbohydrate value is lowered, and to reduce the insulin dose, the carbohydrate value is increased. The ability to deliver the actual calculated dose will depend on the treatment regimen as illustrated in Table 11.4.

Fat and protein

Population-based recommendations for fat intake are 30%–35% total dietary energy. The goal of management is to ensure that saturated, trans and total fat intake fall within recommendations for the population. There is an association between high saturated fat intake and increased insulin requirements, as well as increased risk of cardiovascular disease and obesity [34, 42]. Children should be encouraged to reduce saturated fat intake. Where appropriate this can be replaced with unsaturated fats; consumption of oily fish two to three times a week should be promoted.

Protein requirements for growth are the same as for the general population, and intake will vary with age and rates of growth. There is likely to be benefit from encouraging vegetable protein sources, such as legumes, as part of a healthy diet. Detailed information about advice on fat and protein can be found in the ISPAD guidelines chapter on nutrition [13].

Education about the impact of fat and protein on postprandial glycaemia should also be given. There is clear evidence that meals higher in total fat and/or protein increase insulin requirements for at least 5–6 hours after eating [42–44]. A number of post-meal glucose effects have been observed and studied; the commonly reported issues by families are a post-breakfast glucose spike around 60–90 minutes after eating and raised glucose levels overnight after meals eaten in the evening [12].

Mealtime insulin dosing based solely on amount of carbohydrate is likely to be insufficient to maintain postprandial glycaemia for many [42]. Significant individual differences exist in the requirement for additional insulin, and, therefore, advice should be based on observation of effect of meals. Initial education should raise awareness of the foods likely to create an issue, and individual review of management of mealtime insulin can be provided based on results seen by families.

Fat has been shown to produce delayed hyperglycaemia when consumed with carbohydrate [42]. The impact of high protein or high fat with carbohydrate is less than the combined impact of high fat and high protein [43]. Protein, when consumed with carbohydrate, blunts the rise in glucose levels at 90 minutes and causes a delayed rise in glucose levels between 2 and 5 hours [44]. Protein consumed in the absence of carbohydrate has also been shown to cause a delayed rise in glucose levels when consumed in high quantities, 75 g or more protein per serving [45]. The impact of fat and protein is likely to be more noticeable when smaller amounts of carbohydrate are consumed. It is suggested that meals containing more than 20 g fat and 25 g protein per serving may cause delayed postprandial hyperglycaemia and will require additional food insulin dosing [13]. Examples of meals that can cause these problems include pizza, pasta with creamy sauces, fish and chips, rice with curry, fish pie and takeaway foods.

A variety of methods of calculation of additional insulin have been proposed:

- Pańkowska *et al*. [46–48] suggested the use of a formula to calculate fat and protein units (FPU) to determine both increase in insulin dose and duration of insulin delivery for patients using insulin pump therapy.
- The food insulin index (FII) has also been proposed as an alternative to carbohydrate counting in adults [49].
- A recent study comparing carbohydrate counting, FPU formula and FII demonstrated increased time in target range for blood glucose levels with the FPU formula and increased incidence of later hypoglycaemia [50].
- Data from the studies suggests that at least 20% more insulin is needed for the higher fat/protein meals. Increases of 60% are associated with increased hypoglycaemia incidence [51].
- For all mixed meals, insulin delivered using a combination bolus on insulin pump therapy has been demonstrated to be more effective at controlling postprandial glycaemia [52–55].
- For patients using MDI it is suggested that a second injection is given after the meal to provide the additional insulin needed [56].

Practical advice for managing post-meal glucose levels is given in Table 11.5.

Table 11.5 Practical advice for managing post-meal glucose levels.

Use a combination bolus with at least 60% immediate bolus and extended over 3 hours
Give an additional dose of insulin 20% for meals causing delayed hyperglycaemia. Increase carbohydrate amount used in a bolus calculator by 20% on pump therapy. Give an additional injection of 20% of calculated insulin dose on MDI
Reduce saturated fat content of meals to improve glucose profiles
Add low fat protein sources to breakfast to blunt postprandial glucose spike

MDI, multiple daily injections.

Fibre

Children's diets should contain a variety of fibre containing foods including fruit, vegetables, wholegrains and legumes. Both soluble and insoluble fibre sources should be consumed. High fibre diets are associated with reduced risk of cardiovascular disease and improved digestive health. Dietary fibre modulates bowel function, fermentation and effects of the gut microbiota. Eating an age-appropriate amount of fibre is important for glycaemic management, gut health and reduction in cardiovascular risk. Children with diabetes should be encouraged to meet the current UK population guidelines on fibre intake (Table 2.18) [57]. Practical ways do this include higher fibre breakfast cereals, addition of beans, pulses and lentils to cooked dishes and the use of raw vegetables and fruits as between meal snacks.

Sucrose

Sucrose can be consumed within the context of a healthy diet. Isocaloric quantities of sucrose and starch increase glucose levels by the same amount. Foods containing high amounts of sucrose should be discouraged as a regular component of the diet in line with population guidelines. Routine use of sugar-sweetened beverages should be avoided except for the treatment and prevention of hypoglycaemia.

Sweeteners and specially labelled products

Non-nutritive sweeteners used commercially can assist in reducing total sucrose intake. Advice should be given to avoid excessive consumption, and water should be encouraged as the first-choice drink rather than diet fizzy drinks. Fructose is not recommended as a sweetener in place of sucrose. Recent changes to UK food taxation have reduced the sugar content of drinks, though in some cases this has resulted in increased use of non-nutritive sweeteners to maintain a sweet taste. Reduced sugar products are widely available and can be useful.

Internationally, products labelled 'diabetic' are not recommended for routine use in the diets of children. They are often expensive, contain sweeteners that have a laxative effect (sugar alcohols) and are higher in fat than the product they are replacing.

Salt

Children with diabetes should follow the same recommendations for salt intake as the general population (Table 2.1).

Education and review

It is recommended that all children receive a process of education from diagnosis through the ages and stages of development so that the young person has the necessary knowledge and diabetes self-management skills as they transition to adult services [26].

A number of studies have looked at the impact of education programmes on glycaemic outcomes. These studies were all conducted in children and adolescents with established diabetes and had little or no impact in terms of improving HbA1c, but reported some benefit to quality of life [58, 59]. No studies have evaluated the same education processes from diagnosis. Both NICE and ISPAD [5, 26] have recommendations for education at diagnosis with ongoing review. Nutrition education is part of the wider diabetes education package. Education that embeds solution focused and motivational interviewing techniques is beneficial [60].

Structured education packages for use from diagnosis have been developed using educational theory and offer a variety of learning styles, but not all of these have been evaluated by clinical trials. These are summarised in the box below.

GOALS of diabetes education (Novo Nordisk) – education curriculum available from www.novonordisk.co.uk/content/dam/UK/AFFILIATE/www-novonordisk-co-uk/Home/Health%20Care%20Professionals/Documents/GoDe_Book_v7_INTERACTIVE.pdf

SEREN structured education programme (Welsh Paediatric Diabetes Network) – details available from www.cypdiabetesnetwork.nhs.uk/regional-pages/wales/network-projects/seren-structured-education-programme/

Deapp diabetes digital education – details available from http://deapp.nhs.uk/home

Management at diagnosis

Education about nutrition and diabetes management should begin as soon as possible post-diagnosis. Withholding education and information can lead to increased anxiety and difficulties with glucose management. Surveys conducted by the Families with Diabetes National Network highlight the importance of education about food, and specifically management of carbohydrate, on receiving the diagnosis of diabetes [61]. Education may occur within the hospital setting

or at home depending on local practice. The Delivering Early Care in Diabetes Evaluation (DECIDE) study compared management at home vs. management in hospital at diagnosis; this showed no difference in outcomes and explored parent preferences. Education can be successfully delivered in either setting [62].

Education at diagnosis is the beginning of a process and should enable a family to understand the role of amount and type of carbohydrate, calculate insulin doses for carbohydrate in meals, understand the importance of timing of insulin and meal routines, appreciate the impact of the whole meal on postprandial glucose levels, introduce GI and support the management of food and activity in school. In addition, for children commencing pump therapy at diagnosis education about bolus type is needed. The use of diabetes education checklists can help to provide consistency of education as well as a record of teaching for both the family and diabetes healthcare team. An example of the nutrition components of an education programme at diagnosis is given in Table 11.6. A case example of a girl newly diagnosed with diabetes is given in Table 11.7

Ongoing review

Ongoing management depends on the age and developmental stage of the child or young person. General recommendations encourage at least 3 monthly contact with a dietitian as part of MDT review in addition to annual educational review. Key points for education for both the family and child/young person are at transition to nursery, primary school, secondary school and university and how to manage exam times. Age-specific considerations are given below.

Table 11.6 Example of nutrition components of an education programme at diagnosis.

Topic	Date	Sign
Food and carbohydrate counting • Assess usual dietary habits • Check ward carbohydrate counting information available at bedside • Explain role of food in diabetes management How carbohydrate, protein and fat impact of glucose levels Recommend changes if needed, e.g. replace sugar-containing drinks with water/no added sugar drinks, timing of sweets/treats • Introduce principles of lower fat, lower GI wholegrain food choices • Explain carbohydrate counting including use of scales/weighing foods/food labels/portion pots • Explain use of insulin to carbohydrate ratio to calculate insulin doses • Discuss school meal management		
Observation of carbohydrate counting and insulin dose calculation on ward at mealtime before discharge		
Exercise/physical activity • Assess the 'normal' levels of physical activity undertaken across the week • Advise on regular PA as part of healthy lifestyle • Advice on extra fast-acting carbohydrate prior to/during exercise and advice on reduction of insulin as appropriate		

GI, glycaemic index; PA, physical activity.

Babies and toddlers

A detailed review of the management of preschool children can be found in the ISPAD guidelines [23]. Diabetes management in babies and toddlers is best supported by establishing eating routines. Supportive advice allows normal weaning and development of intake of solid foods. Insulin should be given preprandially or as a split dose with some insulin given before the meal and some during. Glucose levels are more difficult to manage when frequent grazing occurs [37]. Parental behaviours at mealtimes have been shown to impact on glycaemic outcomes [63]. Dietitians need to support parents to establish mealtime routines and reduce parental anxiety.

Advice on normal eating behaviours and the variability of appetite in this age group should be given. Food refusal can cause significant anxiety due to fear of hypoglycaemia [64]; it is helpful to provide guidance on appropriate carbohydrate amounts at meals to avoid issues arising from parents trying to feed too much carbohydrate to a young child. They can be advised that eating 5–7 g less or more carbohydrate than the mealtime dose calculation should not cause a significant problem. When less than half the meal is consumed, due to insulin action, there is time to offer additional carbohydrate. It is important that treats/sweets/desserts are not used as replacement carbohydrate foods. It is possible to achieve glycaemic management with both MDI and pump therapy, though there may be a preference for pump therapy due to the number of insulin injections required with MDI. Anxiety about hypoglycaemia may be helped by the use of CGM systems.

In the younger age group, it is suggested that the following 'rules' are used for calculation of insulin doses: breakfast 150/TDD and other meals 250 or 330/TDD [23]. Education and support may be needed for the management of food in nursery.

School-age child

The routine of starting school brings more structured days and mealtimes, which can help diabetes management routines. Education about food in school will be needed. The availability of information about carbohydrate content of school foods depends on the catering providers. Education is also needed about the management of activity in school. As a child begins to engage in more activities with friends, school and clubs, appropriate advice about eating away from home should be given [65]. Prior to the transition to secondary school education, to support the child to become more independent in managing their food is essential as levels of support change dramatically in secondary school for the majority of children.

Table 11.7 Case example: Management of a girl newly diagnosed with diabetes.

A 7-year-old female. Her first language is Arabic
Presentation: Admitted following GP referral with symptoms of tiredness, thirst, excessive urine production and weight loss. Blood glucose level on arrival 42 mmol/L, pH 7.32, blood ketones 5 mmol/L
Diagnosis: Type 1 diabetes
Initial medical management: Diabetes ketoacidosis protocol
Insulin treatment regimen: Multiple daily injections
Levemir 4 units morning 7 am and 4 units evening 7 pm NovoRapid
Breakfast 1 unit to 8 g carbohydrate
Midday meal 1 unit to 12 g carbohydrate
Evening meal 1 unit to 10 g carbohydrate

Nutritional diagnosis: New diagnosis type 1 diabetes, caused by autoimmune destruction of pancreatic β-cells, evidenced by presenting blood glucose and ketone levels, auto-antibodies and HbA1c on screening blood tests

Dietetic assessment: Establish family meal routines and usual foods eaten, school routines and regular activities

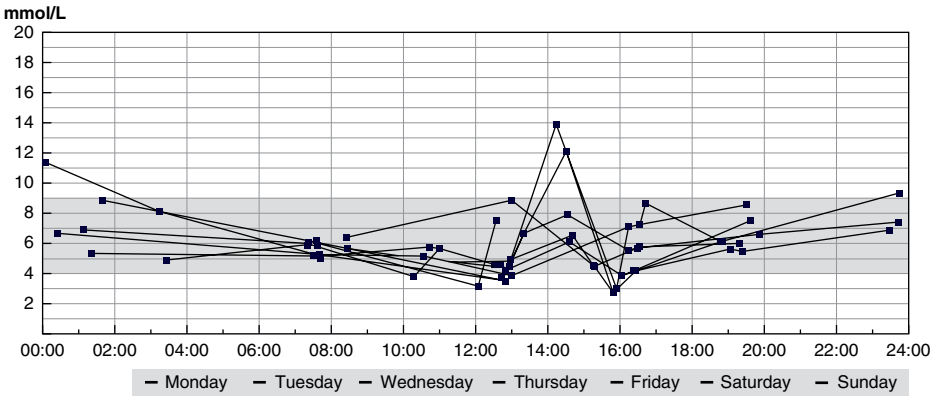
Initial management plan: Nutrition and diabetes education (days 1–6) covering:
Session 1 Food choices for health, understanding food and glucose levels, introduction to carbohydrate counting
Session 2 Review and recap session 1 plus carbohydrate counting, use of insulin to carbohydrate ratio, preprandial insulin dosing, use of insulin sensitivity factor
Session 3 Review and recap session 2 plus glycaemic index, role of fat and protein, management of activity, food in school

Follow-up 1 week post-discharge: Joint nurse and dietitian review

Follow-up 2 week post-discharge: Multidisciplinary diabetes clinic
Insulin doses at clinic review
Levemir 3 units and 3 units pm
Insulin to carbohydrate ratios:
Breakfast 1 unit to 9 g carbohydrate
Midday meal 1 unit to 12 g carbohydrate
Evening meal 1 unit to 12 g carbohydrate

Example of glucose profile at clinic review:

Glucose: Standard day



Statistics

Number of values: **59**	Values above goal (9 mmol/L): **4**	Highest value (mmol/L): **13.9**
Values per day: **7.4**	Values within goal (4–9 mmol/L): **45**	Lowest value (mmol/L): **2.7**
Period average (mmol/L): **6**	Values below goal (4 mmol/L): **10**	Standard deviation: **2.2**

Follow-up education plan:
Insulin adjustment
Review of carbohydrate counting
Education for insulin pump therapy

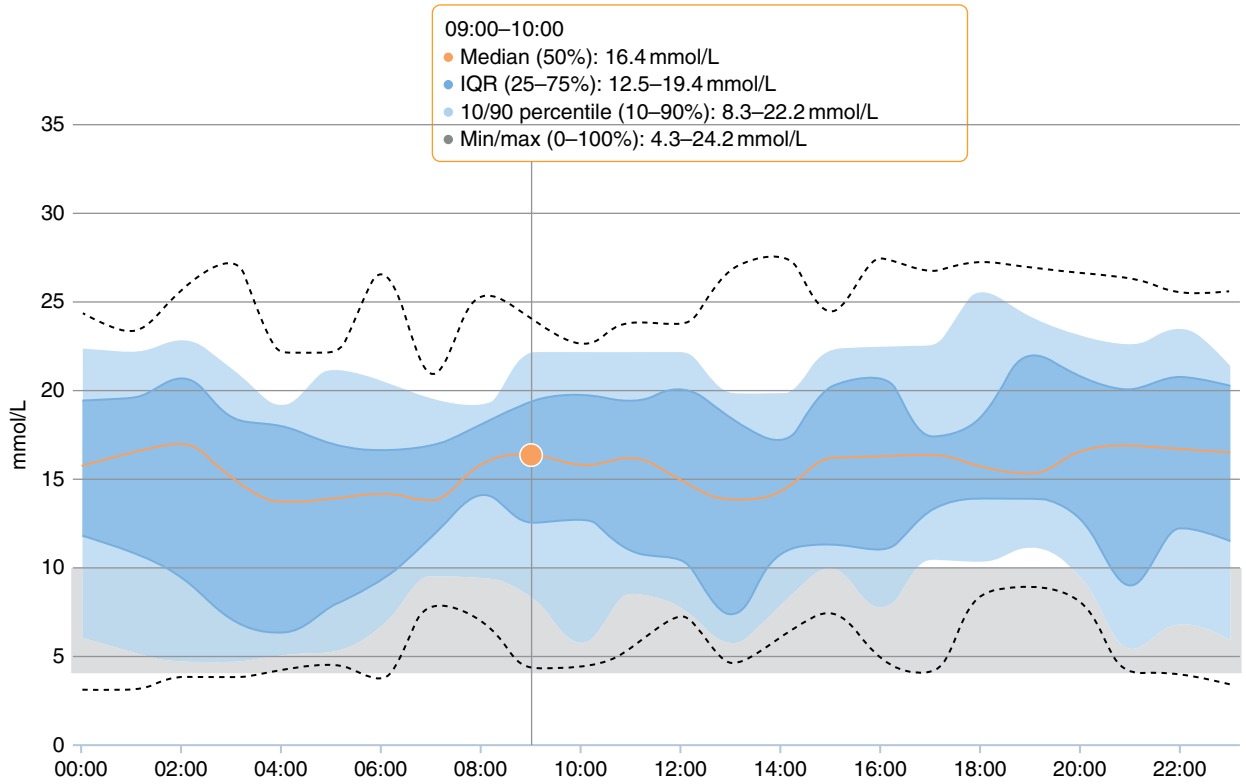


Figure 11.2 Impact of missed meal and snack injections in a 14-year-old boy on multiple daily injections.

Adolescents

During adolescence, pubertal growth challenges diabetes management. Meal routines are often disrupted by lifestyle; however, routine remains important to achieving glucose management targets. Missed meal and snack insulin boluses have a negative impact on overall glycaemia [66–68], as illustrated in Figure 11.2.

Support with the management of exams, school trips, activity, eating away from home and alcohol will be needed. Where paediatric diabetes services care for young people through to 19 years of age, advice for transition to university will be essential. This should include practical aspects of food and diabetes management including encouragement to develop cooking skills alongside carbohydrate counting ability.

Monitoring weight in this age group may identify issues with both excess weight gain and also weight loss and disordered eating behaviours. Insulin omission in order to lose weight is not uncommon in this age group. A number of screening tools are available for use in clinical settings. The risk for eating disorders increases with duration of diabetes. Frequent admissions in diabetic ketoacidosis (DKA) and deteriorating glucose levels are potential indicators of disordered eating and body image concerns.

Overweight and obesity challenge diabetes management. A pattern of increasing weight will need addressing with review of activity levels, frequency of hypoglycaemia, insulin doses and energy intake. Increased body weight is associated with increased insulin resistance; in addition to reviewing nutritional intake review of medical management and the use of insulin sensitising, therapies may be of benefit.

Management of both disordered eating and obesity will require an MDT approach that includes psychology, medical, nursing and dietetic members of the team. Specialist care may be needed for the management of eating disorders.

Festivities, fasting and special events

Lifestyle advice needs to incorporate the management of events that occur through the year in a child's/family's life: parties and special occasions, religious events and festivals including fasting. Though younger children may be exempt from fasting, they will often wish to participate in family events, and supportive advice should be provided. Often special occasions mean that different foods are eaten at different times of day to usual. Advice may need to include the impact of the types and timing of foods on glucose levels, adjustments to insulin dosing for the specific occasion and the prevention of hypo- and hyperglycaemia. Detailed management about Ramadan and fasting can be accessed from the International Diabetes Federation (IDF) Ramadan guide [69].

Different treatment regimens and continuous glucose monitoring technology

Twice daily and split evening insulin

Twice daily insulin using premixed insulin does not mimic physiological insulin production. A mix in the morning with a rapid-acting insulin for the evening meal and intermediate acting insulin before bed is also not optimal. These insulin regimens are not recommended for routine clinical care. If used then education about consistent carbohydrate intake, mealtime routines and snacks between meals and before bed to offset the risk of hypoglycaemia and match the insulin action profiles will be needed [13].

Intensive therapy

Intensive therapy delivered as both MDI and insulin pump therapy should have the following components:

- an ICR
- an insulin sensitivity or correction factor (ISF)
- a duration of insulin action or active insulin time
- a target glucose level used for calculations
- a bolus dose calculator incorporating all the above factors, which displays information about active insulin (bolus insulin already delivered)

Multiple daily injection therapy

MDI are recommended from diagnosis alongside carbohydrate counting and insulin adjustment using an ICR and insulin sensitivity factor:

- Insulin is needed for both meals and snacks. The amount of insulin should be calculated using the ICR. The smallest dose of insulin it is possible to give with an insulin pen is 0.5 unit. Families should be advised that all food containing carbohydrate, whether eaten as a meal or snack or drink, requires insulin if the calculation of dose is 0.5 unit or more.
- It is helpful to provide guidance on appropriate amounts for snacks. Children with diabetes can follow current public health guidance on the amount of food for a snack. Current analogue insulins used in MDI do not require between meal or bedtime snacks. Children should be able to omit snacks without hypoglycaemia if basal insulin doses are correct. If carbohydrate is needed to prevent hypoglycaemia between meals, this is an indication that insulin doses need reviewing.
- Advice on optimal timing of the pre-meal rapid-acting insulin should be given. Rapid-acting insulin should be given 15 minutes before eating; post-meal insulin delivery results in postprandial glucose levels that are up to 5 mmol/L higher than pre-meal dosing [70, 71]. Hypo- or hyperglycaemia, as a result of a mismatch between insulin dose and carbohydrate amount, usually takes 2 hours to occur [39]. If food refusal is a concern, parents can be reassured that additional carbohydrate can be given; in most cases a falling glucose level will cause hunger. If food refusal is a significant concern, then insulin pump therapy may be a more suitable treatment option.
- Advice to avoid post-meal insulin injection can include giving insulin split into two doses, one at the start of the meal and one towards the end of the meal.
- ICR will need to be reviewed regularly; it is usual to need different carbohydrate ratios at different times of the day as insulin sensitivity varies across the day. Usually the breakfast ratio needs to be significantly 'stronger' than those used at midday and evening meals.
- It is recommended that a glucose meter with a bolus calculator is used to reduce the burden of the family having to do the calculation and the risk of insulin stacking causing hypoglycaemia.
- The effectiveness of the ICR can be assessed by looking at the change in glucose levels. As a guide a glucose level above target (9 mmol/L) in the first hour is due to insulin timing; a raised level at 2–3 hours is likely to be due the ICR; and a raised level at 3–5 hours indicates the need for adjustment in insulin distribution for the meal type.

Insulin pump therapy

The current options for insulin pump therapy are:

1. stand-alone insulin pump with or without a continuous or flash glucose sensor (p. 200)
2. sensor-augmented insulin pump therapy
3. hybrid closed-loop insulin pump therapy

Insulin pump therapy is recommended for younger children as it offers advantages over injected insulin in the management of eating behaviour. Insulin pump therapy will require the same education about the use of ICR, timing of insulin delivery and appropriate mealtime routines as MDI. As with MDI it is important to cover all carbohydrate foods with insulin; missed meal and snack boluses are a significant cause of increased time spent in hyperglycaemic ranges. The use of an insulin pump allows mealtime insulin dosing to be more easily adjusted to the glycaemic effect of the food consumed. Nutrition education should include the use of advanced bolus techniques to help increase time spent in range post-meals. Information as previously discussed about the impact of protein and fat in meals along with strategies to manage their glycaemic effects should be discussed for families using options 1 and 2 above.

Current options for insulin delivery using a pump are a standard or normal bolus, an extended or square wave bolus and a combination bolus, illustrated in Figure 11.3. Evidence shows that the square or extended bolus is not effective in the paediatric population for dealing with meals, as insufficient insulin is active in the first 60–120 minutes [72]. For most mixed meals the combination bolus has been shown to be more effective than a standard bolus. The optimal split of

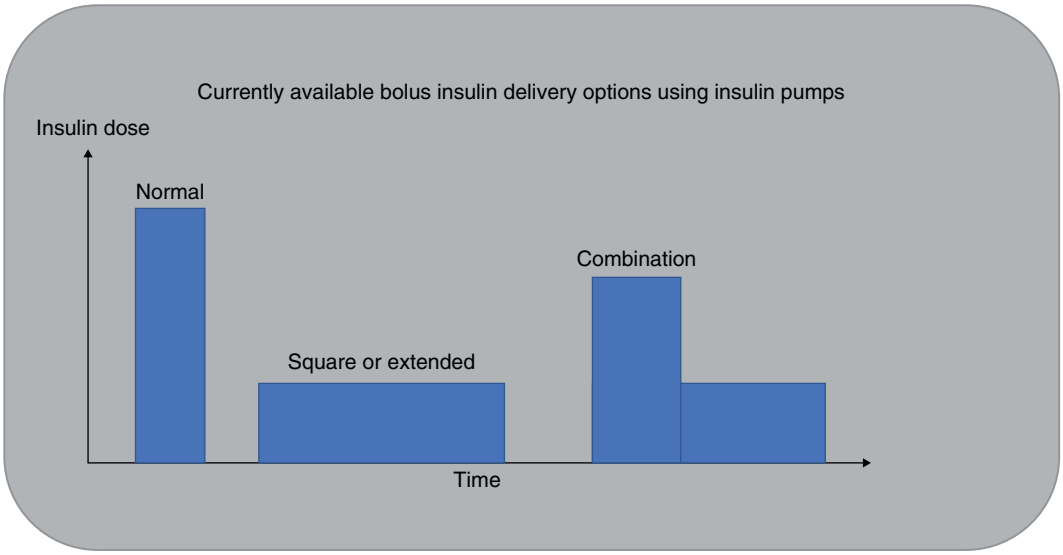


Figure 11.3 Bolus insulin delivery options.

insulin in the combination bolus varies from individual to individual. It is suggested for most children at least 50% of the insulin needs to be given in the immediate bolus, and this may be as high as 70% for some specific meals [51]. The duration of insulin delivery will also vary; however, a sensible starting point is 2–3 hours. Families should be taught how to assess the impact of meals on glucose levels and adjust bolus insulin delivery to maximise the benefits of using insulin pump therapy. The current hybrid closed-loop system does not have advanced bolus functions as basal rates are adjusted according to glucose changes post-meals.

Continuous and flash glucose monitoring

The use of real-time and intermittent CGM systems is increasing understanding of mealtime glucose responses. The effects of foods are immediately obvious to both families and healthcare professionals. As part of nutrition education, it is helpful to explain the normal glucose responses to meals in the population without diabetes. Parents and young people should understand that glucose levels fluctuate, and the aim of treatment is not a flat line. Dietitians should be able to interpret sensor downloads and provide appropriate management advice to families. Rate of change (ROC) arrows that predict the direction of change in glucose levels are increasingly being incorporated into decision making. Resources are available to help families use this information to adjust insulin doses to increase time in spent in target [73].

Physical activity and exercise management

Regular physical activity is important for long-term health. Children with diabetes aged over 5 years should be advised to achieve the World Health Organization recommendation of at least 60 minutes moderate to vigorous activity a day [74]. Specific recommendations on promotion of physical activity, including active play and movement, are also available for the under 5s. Children and young people should be doing aerobic exercise and exercise to strengthen bones and muscles daily. The health benefits of regular activity include maintenance of healthy weight, reduced cardiovascular risk, improved bone health and increased well-being. Lower levels of physical activity and physical fitness in children and adolescents with type 1 diabetes have been reported [75].

Physical activity in type 1 diabetes can be challenging as the normal physiological responses to exercise are disrupted due to the inability to adjust insulin in response to acute changes in glycaemia. Detailed explanations of exercise physiology and type 1 diabetes can be found in the Juvenile Diabetes Research Foundation (JDRF) Performance in Exercise and Knowledge (PEAK) consensus paper on exercise and type 1 diabetes management and the ISPAD guidelines [76, 77].

Activity advice should be underpinned by an understanding of exercise types, normal exercise physiology and the impact of type 1 diabetes on the usual physiological processes. Exercise can be broadly classified into three types based on the predominant energy systems used: aerobic, mixed and anaerobic exercise. The usual glucose responses in type 1 diabetes are summarised in Figure 11.4.

Children, young people and families need advice based on an understanding of how the usual physiological responses to different types of activity may impact glucose levels and factors that alter glucose responses to exercise alongside management strategies, including nutrition and glucose monitoring, to promote appropriate levels of physical activity.

Type 1 diabetes disrupts usual exercise physiology as insulin cannot be adjusted in response to activity; additionally, insulin delivered by either injection or insulin pump is delivered to the peripheral circulation, whereas pancreatic insulin production is via the portal circulation. This can produce the effect of insulin being in the 'wrong' place at key

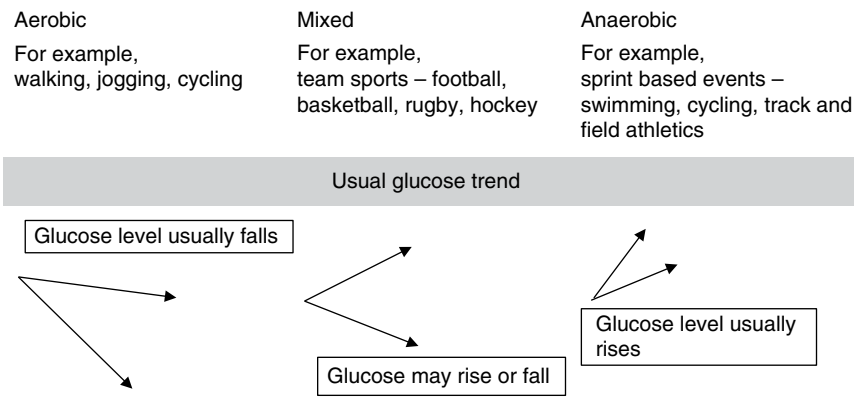


Figure 11.4 Usual glucose responses to exercise. Source: Adapted from Riddell *et al*. [78]. Reproduced with permission of John Wiley & Sons.

Table 11.8 Factors associated with the effect of activity on blood glucose levels.

Blood glucose falls	Blood glucose rises
Aerobic or low intensity exercise	Anaerobic or high intensity exercise
Excess insulin	Insufficient insulin
Prolonged duration	Short duration
Insufficient carbohydrate	Excess carbohydrate
Extremes of temperature (cold or hot environment)	Heat stress
Activity within 2 hours of unadjusted insulin bolus	Competitive nature of the sport (adrenalin will increase the blood glucose level)

points during exercise and recovery. As the duration of diabetes increases, there may a loss of glucagon production by α-cells of the pancreas; however, a study in recently diagnosed adolescents has demonstrated glucagon production during exercise at similar levels to matched controls without diabetes [78].

Hypoglycaemia is often cited as a barrier to exercise [79]; however, many young people also experience significant hyperglycaemia during exercise. Education should focus on strategies to maintain glucose levels between 5 and 10 mmol/L during activity [76]. Factors associated with the effect of activity on blood glucose levels are given in Table 11.8.

Education about physical activity management should include:

- an explanation of exercise types and the expected glucose responses; however, as studies on type of exercise report the mean responses, it is important to explain that glucose responses are individual and may differ from those expected
- a blood glucose monitoring strategy to enable understanding of the individual responses
- a nutrition strategy to prevent hypoglycaemia and support performance if appropriate
- an insulin adjustment strategy to prevent hypo- and hyperglycaemia
- management of the post-activity period

Blood glucose targets for activity

Regular glucose monitoring before, during and after activity is important to guide both insulin and nutrition adjustments. This may be done by the use of finger prick glucose checks or a glucose sensor. Trends in glucose levels help direct actions; understanding if glucose levels are stable, rising or falling will enable targeted advice to be used more effectively. A change in glucose level of more than 2 mmol/L over 30 minutes when using finger prick values indicates that glucose level is rising or falling. For glucose sensors the ROC arrows should be explained to families to allow them to interpret how glucose levels are changing. It is useful to give an example of what the change in glucose levels means in real terms. For example, if a finger prick glucose level is 7.5 mmol/L 30 minutes before exercise and 5.5 mmol/L immediately before exercise, if that pattern continues, then the glucose level will be 3.5 mmol/L in the next 30 minutes.

Families should be advised that starting exercise with a high glucose level does not protect from hypoglycaemia; in fact the opposite appears to be true. The higher the starting glucose level, the greater the fall [80]. Starting with a glucose level in target is optimal for hypoglycaemia prevention.

Children and families should be advised:

- the starting glucose level will need to be interpreted in the context of the timing of any pre-exercise food and insulin
- to start exercise with a glucose level above 5 mmol/L
- to aim for a glucose level between 5 and 10 mmol/L during exercise
- to check glucose levels before activity at least twice within the preceding hour, every 30 minutes during and immediately after activity and then 1–2 hourly, overnight if activity has been very strenuous

- to check blood ketones if glucose level is above 13.9 mmol/L
- to stop or avoid exercise if glucose level is above 13.9 mmol/L and blood ketones are above 1 mmol/L

Insulin adjustment advice for activity

Bolus insulin

Aerobic activity undertaken within 90–120 minutes of an injection or bolus of fast-acting insulin will carry an increased risk of hypoglycaemia. For this reason, it is generally recommended that insulin is reduced with any meal or snack or correction dose within 2 hours of starting exercise. The magnitude of reduction needed varies between 25% and 75% and will be influenced by the duration of the activity, and how close the insulin delivery is the start of the activity. A good starting point is to make a 50% dose reduction and keep a record of the impact of this advice for specific activities. Often if activity is anaerobic or competitive, a reduction in pre-activity meal insulin may not be needed. The insulin dose reduction may also vary with the time of day the activity is undertaken, with early morning exercise carrying a lower risk of hypoglycaemia than midday or evening exercise. Families will notice that the need for insulin adjustments will change during periods of rapid growth when insulin requirements are higher. Bolus insulin adjustments are also likely to be needed after exercise due to the increase in glucose transporters in the post-exercise period. Lower insulin doses are likely to be effective in managing both food and corrections for between 6 and 24 hours post-exercise.

If glucose levels are elevated (>10 mmol/L) immediately before exercise or during exercise, it may be appropriate to use a reduced correction dose to prevent further hyperglycaemia especially during anaerobic or competitive sports. This should be evaluated, taking into account previous insulin delivery. A high glucose level in the presence of active insulin may not require additional insulin.

Basal insulin

Prior adjustment of basal insulin is possible for planned activity on insulin pumps or twice daily long-acting basal insulin injection. The use of a temporary basal reduction can be useful for aerobic activity. Basal reductions on the insulin pump should be started at least 30 minutes and probably 60–90 minutes before the activity to produce a meaningful reduction in basal insulin levels during exercise. At the start of exercise, the increase in capillary blood flow to active muscle may mean, despite a decrease in basal insulin levels, circulating insulin levels rise transiently due to increased insulin absorption. When reductions in basal insulin are required, a starting point of 20%–50% is suggested. As with bolus adjustments these should be monitored and adjusted according to glucose responses. When exercise is undertaken in the afternoon or evening, there is an increased risk of delayed hypoglycaemia overnight. Basal insulin may need to be adjusted between 9 pm and 3 am for pump users or with a reduced night-time injection on MDI. Insulin requirements have been shown to be at least 20% lower during this period.

Nutrition advice for activity

Nutrition advice may be needed for either hypoglycaemia prevention or sports performance with the majority of studies on nutrition and activity in type 1 diabetes focusing on the former. When hypoglycaemia prevention is the priority, energy balance and the avoidance of overconsumption of energy should be considered. If weight management is a concern, then hypoglycaemia prevention should focus on insulin adjustment and appropriate adjustment of distribution of usual food around activity sessions. For sports performance an increase in energy intake may be appropriate for training and adaptation. Children undertaking the recommended 60 minutes a day of moderate to vigorous activity should not need an overall increase in energy intake compared to reference intakes for the general population. Those children/young people who undertake high volumes of activity should have an individual assessment of their energy, carbohydrate and protein intake [13]:

- Most aerobic activity lasting more than 30 minutes will need additional carbohydrate if insulin has not been adjusted:
  - Carbohydrate requirements vary between 0.5 and 1.5 g/kg body weight and depend on duration and type of activity and prior insulin adjustments.
- Carbohydrate and protein should be consumed at the meal before planned activity lasting 60 minutes or longer and post-activity to replace hepatic and muscle glycogen stores. Ingestion of protein before activity has been shown to reduce hypoglycaemia risk during the active period.
- Carbohydrate snacks for exercise should be low in fat. Fruit and dried fruit, fruit juice and low fat homemade granola bars are good options. Attention to the amount of exercise snacking is necessary to ensure that overall dietary quality is not reduced by less healthful snack choices. For many children 10–15 g carbohydrate will be sufficient to prevent hypoglycaemia.
- An isotonic drink containing 6% simple sugar such as glucose, fructose or sucrose is ideal if additional carbohydrate is required for short duration exercise. Advice about dental health should be given to reduce the impact of these drinks on the teeth.
- For some children additional pre-exercise carbohydrate may necessitate bolus insulin if the exercise is high intensity or strenuous or anaerobic [76]. Hyperglycaemia will occur during exercise if insufficient insulin is available, particularly if the exercise is anaerobic. Performance is influenced by glucose levels.
- Brief high intensity anaerobic exercise, such as sprinting, may not need carbohydrate beforehand but may result in a dramatic fall in blood glucose afterwards during muscle recovery. In this case it is preferable to prevent

hypoglycaemia by taking additional carbohydrate after the sport.
- Fluid intake should be adequate as dehydration can impair performance. High glucose levels will increase fluid requirements.
- Following moderate or intense exercise of 45 minutes duration or longer, carbohydrate stores must be replenished to lower the risk of hypoglycaemia, as insulin sensitivity remains raised for several hours.
- To minimise post-exercise hypoglycaemia lower GI foods, protein and a reduction in basal insulin, and a lower than usual bolus dose, with the post-exercise meal can be helpful.
- Hypoglycaemia treatment must be available during activity. Adults supervising children with diabetes, including teachers, coaches and activity holiday staff, should all be aware of the possibility of hypoglycaemia and know how to treat it.

Additional strategies for managing glucose levels during and after activity

10 second sprint

The 10 second sprint has been demonstrated to increase glucose levels and reduce hypoglycaemia risk [81]. Further work has shown that the order of different exercise types within an activity session can influence the pattern of glucose levels. For some young people providing advice about the order in which different exercises are performed may be helpful [82–84].

Cool down

Hyperglycaemia post-exercise is commonly reported. One of the potential causes is the production of lactate during exercise, which is not removed at the end of activity by an active cool down. Lactate is then managed through the Cori cycle and converted to glucose by the liver. Introducing 10 minutes of cool down exercise at the end of activity can be helpful in reducing post-activity hyperglycaemia [76, 77].

Insulin treatment specific considerations

Multiple daily injections

A once daily long-acting insulin makes insulin adjustment more challenging. For young people doing high volumes of activity, twice daily long-acting insulin may offer greater flexibility. To date there is only study on insulin adjustment of the ultra-long-acting analogue insulin degludec in adults, which showed insulin could be adjusted when exercise was performed two to three times per week on non-consecutive days [85].

Pumps

Exercise with the insulin pump taken off can present challenges if the exercise lasts longer than 60 minutes and is anaerobic or competitive. Where the pump cannot be worn, it may be necessary to replace missing basal insulin with a long-acting insulin analogue, for example, in multi-round competitions where performance is impacted by glucose levels rising. Post-pump disconnection, children can experience periods of hyperglycaemia, which can be managed by employing strategies to replace missing insulin; this may be by giving a bolus of half the missing basal insulin at the end of the activity or reconnecting the pump and using a higher basal rate than normal. This phenomenon may also occur when temporary basal rates are used for long periods and can be managed by returning to usual basal rates about 30 minutes before the end of activity or using a temporary basal rate increase for a period of time post-exercise.

Hybrid closed-loop pumps do not have a temporary basal rate feature, and hypoglycaemia prevention is facilitated through using higher glucose targets. It is likely that aerobic activity using these systems will still require carbohydrate to prevent hypoglycaemia during the exercise [86].

A case example of the management of exercise is given in Table 11.9.

Table 11.9 Case example: Exercise management in a 15-year-old boy.

A 15-year-old boy on insulin pump therapy He plays club football at under 18 level
Concerns: Avoiding hypoglycaemia during matches causing high blood glucose levels post-exercise overnight. HbA1c = 51 mmol/mol. Hyperglycaemia following football matches on Thursday evenings 6–9 pm. Usual management temporary basal rate (TBR): 50% set 90 minutes before the start of match until the end of the match.
Assessment and cause of issues: The team is picked on the day of match, but the boy is not told if he is starting the game or on the bench. If on the bench the TBR was not being stopped, resulting in hyperglycaemia.
Management advice: Usual insulin until 30 minutes before game. If playing check glucose, have a snack according to blood glucose level, suspend pump if below 10 mmol/L and recheck glucose at half-time. If on the bench, suspend the pump when he starts to play and have an additional snack.

Hypoglycaemia

Hypoglycaemia is a common acute complication of the treatment of diabetes, which can interfere with daily life [87]. It is often cited as a barrier to intensifying management. A review of management of children under 5 years in one large Australian centre over the last 10 years has shown both a reduction in mean HbA1c and the incidence of severe hypoglycaemia [37]. This data is supported by diabetes registries across the world, which also show a decline in rates in severe hypoglycaemia alongside an improvement in glycaemic outcomes [88–90]. The latest consensus on hypoglycaemia now defines glucose levels between 3.0 and 3.9 mmol/L as alert levels and levels below 3.0 mmol/L as an indication for

immediate action [87]. Glucose targets vary internationally, with some centres recommending near-normal glycaemia, aiming for fasting and preprandial glucose levels of 3.6–7.0 mmol/L; others recommend levels of 4.0–7.0 mmol/L. The use of technology allows safer lowering of glucose targets.

Clinical factors linked with hypoglycaemia are:

- excess insulin
- reduced food consumption
- exercise
- alcohol consumption
- sleep

The signs and symptoms of hypoglycaemia can be described as:

- autonomic (adrenergic) activation, e.g. shaking, pounding heart, pallor, cold sweatiness
- neurological dysfunction (neuroglycopenia), e.g. difficulty concentrating, disturbed vision and hearing, slurred speech, dizziness and, in severe episodes, loss of consciousness and seizure
- behavioural changes and mood swings including irritability, erratic behaviour, becoming upset and tearful
- non-specific symptoms such as hunger, headache, tiredness and nausea though these may be present when the blood glucose level is high

Children often find it difficult to describe their own symptoms but might experience shaky or wobbly legs or a 'funny' feeling.

Hypoglycaemia may be categorised as mild, moderate or severe depending on symptoms and the ability of the individual to treat the 'hypo' themselves. However, this is not applicable to younger children who are unable to self-treat.

The aim of hypoglycaemia treatment is to restore glucose levels to the euglycaemic range. While the general principles include confirming the glucose value (i.e. that blood glucose level is in the hypoglycaemic range), giving immediate treatment and checking treatment effectiveness, the treatment steps may vary with the use of technology (insulin pump therapy and CGM systems, as described below).

The amount of glucose needed for treatment of a hypo depends on the size of the child and may also depend on the severity of the hypo and ROC of blood glucose levels. The aim is to restore the blood glucose level to 5.6 mmol/L (euglycaemia) [88]. The recommended amount of carbohydrate is 0.3 g/kg body weight as glucose. It is important to avoid overtreatment of hypoglycaemia with consequent rebound high glucose levels. The amount of carbohydrate required to restore euglycaemia will also depend on the type of insulin therapy and time since its administration, recent activity and starting blood glucose level.

Figure 11.5 shows the steps for treating hypoglycaemia.

Insulin pump therapy allows the introduction of an additional treatment step of suspension of the insulin pump. Children using insulin pumps with continuous glucose sensors and a predictive low glucose suspend algorithm should be advised to either allow the system to manage the glucose level or treat and override the system. Predictive low glucose suspend algorithms stop basal insulin delivery when hypoglycaemia is predicted in the following 30 minutes. Children and families using CGM systems may also intervene to stop hypoglycaemia by giving additional carbohydrate or suspending the pump. If this is a frequent occurrence, it may indicate a need to adjust insulin doses.

Glucose is the preferred carbohydrate for the immediate treatment of hypoglycaemia as it does not require digestion or metabolism. Chocolate, milk and other lower GI items are discouraged to treat hypoglycaemia due to the slower rate of absorption of glucose they contain. Twice the amount of carbohydrate from fructose (in the form of fruit juice) has been shown to be needed compared with glucose tablets to raise blood glucose by similar amounts. Sucrose and milk also require greater amounts to provide the same rise in blood glucose.

It is advised that a rescue treatment for hypoglycaemia is available at all times. It can be useful to view the hypo rescue as a 'treatment' and to always carry glucose tablets or a glucose drink.

A guide to the amount of treatment needed based on age and average weight is given in Table 11.10. The introduction

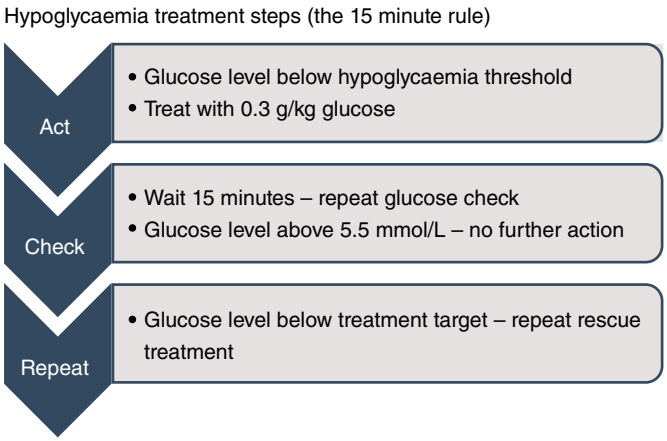


Figure 11.5 Hypoglycaemia treatment steps.

Table 11.10 Hypoglycaemia treatment amounts.

	Hypoglycaemia treatment dose (g of glucose)			
	2 g (<2 years)	5 g (2–5 years)	10 (5–10 years)	15 (>10 years)
Lucozade Energy	–	60 mL	120 mL	180 mL
Lucozade Energy tablets (3 g/tablet)	1	2	3	5
Dextrosol (3 g/ tablet)	1	2	3	5
GlucoTabs (4 g/tablet)	–	1	2 or 3	4
Lift (GlucoJuice)	10 mL	20 mL	40 mL	60 mL

of the UK government sugar tax has created a number of challenges for families in treating hypoglycaemia. As the 'sugar' content of drinks is reduced, the volume of drink required for treatment increases. The dietitian and diabetes team need to monitor changes in composition of commercially available suitable glucose containing drinks to review treatment amounts.

Severe hypoglycaemia

In the case of severe hypoglycaemia:

- parents should have access to an emergency supply of a GlucaGen HypoKit for severe hypoglycaemia
- this is a glucagon injection for use if the child is unconscious or if the parents are unable to resolve hypoglycaemic symptoms by other means

Intercurrent illness

A complete guide to the management of intercurrent illness in type 1 diabetes is available in the ISPAD guidelines [91]. Episodes of illness usually cause raised glucose levels with the exception of vomiting illness, particularly in younger children. To avoid the development of DKA, insulin should not be stopped even though children often do not wish to eat during periods of illness and infection. Instructions for the management of illness are based on glucose and ketone monitoring.

To prevent the formation of 'starvation' ketones, advice on replacement carbohydrate should be included in patient information. Suitable alternative carbohydrate sources include isotonic sports drinks, sugar-containing drinks, easily tolerated foods like soup, jelly and toast.

Insulin requirements are often increased during illness as the stress responses to illness contribute to insulin resistance. Insulin doses are adjusted based on glucose levels and blood ketone levels. Both basal/background and fast-acting insulin doses may need to be increased.

Coeliac disease

CD is more common in children with type 1 diabetes than the general population. Worldwide incidence is reported between 1.6% and 16.4% of clinic populations [92]. The NPDA [2] reported an incidence of 4.4% in England and Wales in 2016.

CD is usually picked up on annual screening, with many families reporting their children to be asymptomatic prior to diagnosis. CD may be associated with poor growth, delayed puberty, nutritional deficiency and hypo- and hyperglycaemia.

Treatment is with a gluten-free diet (GFD). The presence of CD with type 1 diabetes increases the risk of micro- and macrovascular complications, and untreated CD is linked to adverse lipid profiles. Following a diagnosis of CD, children with type 1 diabetes should receive advice on a GFD according to current management of CD guidelines. Additional advice on the potential effects on glucose levels and insulin adjustment will be required [93]. Higher postprandial glucose levels have been observed with GF alternative foods. Annual review of management of the GFD should be conducted alongside the diabetes annual review.

Type 2 diabetes

Type 2 diabetes is increasing in the paediatric population. There is little evidence for nutritional interventions in type 2 diabetes in childhood. The largest study to examine treatment options, the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study, showed that intensive diet and lifestyle support alone was not sufficient to sustain target glycaemia. Due to the relatively small numbers of children in UK with type 2 diabetes, it has been suggested that they should be managed in larger centres with access to clinical trials of newer medications [5]. Currently the only licensed drug treatments for type 2 diabetes in children in the UK are insulin and metformin. Detailed advice on the medical, psychological and nutritional management of type 2 diabetes can be found in the 2018 ISPAD Clinical Practice Guidelines [94].

The aims of management of type 2 diabetes are:

- the child and family should understand the health implications of both obesity and type 2 diabetes
- diabetes healthcare professionals should understand the health beliefs and behaviours of the family to support the development of an effective management plan and achieve optimal blood glucose levels and normal HbA1c
- to promote a healthy lifestyle through behaviour change including nutrition, weight management, activity and smoking

Specific nutritional aims are:

- to prevent further weight gain in those with a BMI between the 85th and 95th centile
- to promote weight loss for those with a BMI >95th centile with normal linear growth
- to deal with comorbidities such as hypertension and dyslipidaemia

The majority of children with type 2 diabetes are overweight; the NPDA data reported 78.6% of the children with type 2 diabetes in England and Wales to be obese [2]. A focus of nutrition intervention is, therefore, to achieve weight loss or keep weight static with normal linear growth. Education and support should encompass the whole family, as eating behaviours are reinforced in the home environment. Families should be counselled about reducing total energy intake, increasing physical activity and decreasing sedentary behaviours [13]. Older adolescents may benefit from some of the adult programmes offering very low calorie diets. Low carbohydrate diets may be appropriate in this

group. There is some evidence that substitution of low GI foods for high GI foods may help with weight control, lipid levels and control of appetite.

Strategies to lower total dietary energy intake include:

- reduction in portion size
- reduction in consumption of high fat, high sugar food and drinks. Cutting out sugary soft or fizzy drinks and fruit juices completely can make the most significant change and result in weight loss. These drinks can be replaced with water, diet drinks and sugar-free beverages.

Children needing insulin should have appropriate advice on carbohydrate counting and avoidance of hypoglycaemia.

Diabetes secondary to pancreatic disease

CFRD has a complex pathophysiology, which includes loss of pancreatic islet cells causing insulin and glucagon deficiency, variable insulin resistance, disrupted gut function and liver disease. Medication may also contribute to impaired glucose tolerance and diabetes. The use of CGM demonstrates abnormal glucose profiles in those with reported normal glucose tolerance tests. Presentation is often at times of illness or metabolic stress. The aim of management is to achieve glucose targets while following CF nutrition guidelines [95]. It has been documented that early initiation of insulin therapy may have value for growth, weight and pulmonary function. Insulin doses and types may need to be adjusted when nutritional supplements, overnight or continuous enteral feeding are being used and during times of acute infection. Dose adjustment should take priority over dietary restriction.

Dietary management includes:

- meeting CF nutritional guidelines (p. 217)
- avoiding sugary drinks/glucose loads in drinks between meals
- advice about the effect of carbohydrate on blood glucose levels and carbohydrate counting and insulin adjustment

Diabetes secondary to medication

Some drugs, such as high-dose steroids, can cause transient hyperglycaemia for the duration of the prescription, and others, such as tacrolimus and cyclosporin, may cause islet cell destruction in which case the diabetes becomes permanent. In oncology protocols some chemotherapy drugs induce diabetes, which coincides with the cyclical nature of the chemotherapy (p. 379). Following organ transplantation such as kidney transplant, diabetes most commonly occurs with the use of high dose steroids and tacrolimus (p. 266). Dietary management depends on how the diabetes is medically managed. In some instances, instruction about avoiding glucose loads, e.g. avoiding sugary drinks and foods, and healthy eating is sufficient. Other children are commenced on daily long-acting analogue insulin and require additional information about eating regularly, having a bedtime snack and hypoglycaemia prevention and management. MDI or insulin pump therapy can also be initiated, and the advice is similar to that given to those with type 1 diabetes.

Summary

The nutritional management of children and young people with diabetes is complex and reaches beyond simple carbohydrate management. As technology continues to develop, so nutrition management strategies will continue to change and develop. Increased exposure to information about glucose levels in real time will need to be supported by nutritional management strategies that allow children to eat and enjoy food as well as manage glucose responses. Both healthcare professionals and families face the challenge of keeping up to date and being able to apply the latest evidence to day-to-day management of glucose levels. Healthcare professionals should also be mindful of the recent advice about the impact of the use of language on people living with diabetes [96]; for dietitians this means following the National Health Service guidance, Language Matters, in both face-to-face consultations and in the production of written information. The role of the team in supporting families living with diabetes to achieve the best possible outcomes is well recognised. The biggest single factor in determining a clinic outcome is the teamwork and targets set by the clinical group. It is important, therefore, that the dietitian is an integral member of the diabetes MDT. However diabetes is managed, a healthy lifestyle with high quality food choices is associated with improved outcomes.

Learning points

- *Nutrition education from the point of diagnosis and thereafter should take a whole food approach*
- *Education about carbohydrate counting should happen immediately following diagnosis*
- *Physical activity should be promoted in line with recommendations for the general population*
- *Advances in technology will continue to influence and change the nutritional management of type 1 diabetes*
- *Using the right language should be central to all contact with people with diabetes*

Congenital Hyperinsulinism

Sarah Price

Introduction

Congenital hyperinsulinism (CHI) is a rare condition in which the body produces an unregulated, excessive amount of insulin, leading to severe hypoglycaemia. The condition is strongly linked with specific genetic mutations, but can also occur in response to perinatal stress and certain maternal factors. The incidence in the general population is 1 in 50 000 births but increases significantly in consanguineous parents to 1 in 2500 [97–99]. However, neither of these figures take into account those who present late (up to 10% of patients) nor those who have transient CHI [100].

Mechanism for CHI

In the healthy individual insulin is produced in response to circulating serum levels of glucose, mediated by the ATP-sensitive potassium channel K_{ATP}. The production of ATP from glucose (via the Krebs cycle) causes the closure of the K_{ATP} channel. This in turn leads to the depolarisation of the pancreatic beta cell membrane and activation of the calcium ($Ca2^{+}$) channels. The entry of $Ca2^{+}$ into the beta cells triggers $Ca2^{+}$-dependent insulin secretion [101]. In CHI this feedback regulation is dysfunctional due to errors in, or the complete absence of, the potassium channel K_{ATP}. This leads to an excessive and unpredictable production of insulin, which is disproportionate to the level of plasma glucose. The insulin is said to be blind to the amount of glucose circulating in the blood because the feedback mechanism is absent. The result is dangerously high levels of circulating insulin causing severe hypoglycaemia, the risk of which is compounded by the absence of ketone production [102].

Genetics

Mutations in the genes ABCC8 and KCNJ11 are the most common genetic causes of CHI. These genes are responsible for the function of the K_{ATP} channel and are usually recessively inherited. Whether they are inherited from the mother or the father is helpful to know in determining whether the CHI is likely to be diffuse or focal. Some genes have heterozygosity, which means there are two different alleles for the same gene, one from each parent. Where there is loss of heterozygosity, the loss of one parental allele means that areas within a chromosome will only have one copy of the allele. When a paternal heterozygous mutation in ABCC8/KCNJ11 occurs, together with a loss of corresponding maternal genes (loss of heterozygosity), the child inherits a faulty copy from one parent and loses the healthy copy in certain areas from the other parent. This results in the formation of a focal lesion [103]. In focal CHI only an isolated area of the pancreas overproduces insulin while the rest of the pancreas is normal [104]. Hyperinsulinism can also be caused by mutations in the glutamate dehydrogenase gene, GLUD1 on 10q. This causes a leucine-triggered production of ATP, which is independent of circulating glucose levels. This in turn causes closure of the K_{ATP} channel, and insulin is released. Alongside the hyposcreen bloods typical of CHI, a raised ammonia would diagnose this condition. CHI caused by GLUD1 10q mutations generally respond well to medication, and surgery is not required [105]. Other rarer genetic mutations have been identified with up to 12 known mutations. Despite this, there are a significant number of CHI patients for whom a genetic cause is never identified [106].

Whether CHI is described as diffuse or focal depends on two distinct histopathological types [107, 108]. As mentioned above a focal lesion is where a distinct area of the pancreas is enriched with insulin-producing beta cells while the rest of the pancreas is histologically and functionally normal. In diffuse disease the whole pancreas has affected beta cells [104]. This variety in types highlights the importance of genetic testing. F-DOPA positron emission tomography (PET) computerised tomography (CT) scanning can be used to identify those suspected of having focal disease [109]. Radioactive 18-fluoro-DOPA is injected into the body under general anaesthetic. In focal CHI a small area within the pancreas takes up the dye and retains it. This shows as an area of 'brightness' on the CT imaging. In diffuse CHI the whole pancreas takes up the dye, but the dye is not retained [107, 109].

It is important to identify whether a child has diffuse or focal CHI as surgery to remove the focal lesion is often curative and is, therefore, the preferred management option in these children [109, 110]. At present the scan is only available at two specialist centres in the UK: Royal Manchester Children's Hospital and Great Ormond Street Hospital for Children, London.

Learning points: genetics

- *there are two types of CHI: diffuse and focal*
- *the most common genetic mutations are ABCC8 and KCNJ11*
- *early genetic testing is important*
- *18-fluoro-DOPA PET CT scanning is crucial where genetic results indicate to distinguish between the types*
- *focal lesions can be removed by surgery, which is often curative*

Table 11.11 Risk factors for transient hyperinsulinism.

Risk factor	Mechanism
Uncontrolled gestational diabetes	The baby may or may not be macrosomic but produces too much insulin in response to the mother's high blood sugar levels. Post-birth, the infant's blood sugars usually stabilise within a week, during which time they may require additional carbohydrate to maintain their blood sugar levels
Maternal use of labetalol	The exact mechanisms are not known, but sympathetic inhibition of the infant's counter-regulatory responses may be responsible
Perinatal stress	The mechanism is not known, but anaerobic metabolism to maintain blood glucose concentration may be responsible
Small for gestational age	A small for gestational age infant will have poor glycogen stores and will therefore be more likely to drop their blood sugar below a safe level. However, why some children who are born small develop hyperinsulinism is not explained. Whether intrauterine stress plays a part in insulin overproduction remains to be seen

Presentation

Most infants present within the first few days of life, but some may present later during the first year, and, very rarely, an older child may present with hypoglycaemic symptoms. The first indications of CHI include non-specific features of hypoglycaemia including floppiness, jitteriness, reluctance to feed and lethargy [111]. If these symptoms are left unrecognised in CHI, they can lead to severe prolonged hypoglycaemia, which can result in permanent neurological damage or death.

Hyperinsulinism can also occur in response to perinatal stress and certain maternal factors. In such cases, hypoglycaemia due to hyperinsulinism is usually transient. Some of the risk factors for transient CHI are given in Table 11.11 [112, 113].

Diagnosis

Hyposcreen

Hypoglycaemia in CHI is defined as a blood sugar level of <3.0 mmol/L. The blood sugar cut-off indicating hypoglycaemia has been defined variably, with some sources relying on a level of 2.6 mmol/L. Most centres now accept that investigations should be carried out when the blood sugar drops below 3.0 mmol/L [100]. In a baby or child experiencing hypoglycaemic episodes, it is important to conduct a hypoglycaemic screen (hyposcreen) when a heel prick blood sample of <3.0 mmol/L is found in order to understand the reason for this low blood sugar. The hyposcreen measures the level of plasma glucose to confirm if the child is truly hypoglycaemic. It also measures serum levels of insulin and C-peptide, both of which would be raised in a child with CHI. In normal individuals, insulin production is suppressed at the time of hypoglycaemia. In children with CHI, insulin continues to be produced regardless of hypoglycaemia. Therefore, any insulin that is detectable at the time of hypoglycaemia suggests the diagnosis of CHI [102]. The absence of an elevated C-peptide may raise concerns over the origin of the insulin, e.g. the child could have received insulin via an injection deliberately to cause a low blood sugar level. In a hyposcreen for a child with CHI, a finding of low levels of free fatty acids and little or no ketone bodies would be expected. This is because the presence of high levels of circulating insulin suppresses lipolysis and ketogenesis [103]. Table 11.12 shows the results of hyposcreen measurements that confirm a diagnosis of CHI.

Table 11.12 Hyposcreen measurements and results to confirm a diagnosis of CHI.

Measurement	Result
Serum glucose	<3.0 mmol/L
Serum insulin	Detectable or raised
C-peptide	Detectable or raised
Free fatty acids	Low
Beta-hydroxybutarate (ketones)	Low

Glucose infusion rate

Calculating the glucose infusion rate (GIR) can be helpful in identifying babies that may have CHI. GIR is the amount of carbohydrate (CHO) expressed as milligrams (mg) required per kilogram per minute over a 24 hour period. In a full-term newborn baby, the GIR is 4–6 mg/kg/min, but in CHI this figure can be much higher [114]. A GIR > 8 mg/kg/min is a good indicator of insulin-driven hypoglycaemia [100]. GIR is both helpful at diagnosis and a useful indicator of the severity of CHI throughout the acute management phase. A reduction in GIR with stable blood glucose levels can indicate an improvement in the condition as long as other factors remain consistent, e.g. medication.

How to calculate GIR

GIR calculation for intravenous (IV) fluids alone:

$$\frac{\%\ \text{dextrose infused} \times \text{mL/hour}}{\text{weight (kg)} \times 6} = \text{mg/kg/min}$$

$$\text{Fluid rate (mL/hour)} = \frac{\text{CHO requirement (mg/kg/min)} \times \text{weight (kg)} \times 6}{\%\ \text{dextrose}}$$

GIR calculation for enteral feeds (can also be used for IV fluids if the total amount of CHO is worked out first):

$$\text{Total CHO (g)} \times 1000\ \text{(mg)} \div \text{weight (kg)} \div 24\ \text{(hours)} \div 60\ \text{(minutes)} = \text{mg/kg/min}$$

This calculation is for a 24 hour period.

Medical management of CHI

The aims of medical management are:

- prevention of hypoglycaemic brain damage, allowing for normal psychomotor development
- establishment of a normal feeding regimen appropriate for the age of the infant/child: volume, frequency, type
- ensuring normal and safe tolerance to fasting that is appropriate for age, without developing hypoglycaemia
- optimal growth
- maintenance of family unit and quality of life [115]

These aims can only be effectively achieved with the input of a multidisciplinary team of health professionals including doctors, specialist nurses, dietitians, speech and language therapists and psychologists [100].

CHI services

Early support from a specialist centre should not be undervalued and has been found to have positive effects on the neurological outcomes for patients with CHI [103]. In the UK there are two specialist centres for CHI. In the north, the Northern Congenital Hyperinsulinism Service (NORCHI) is a joint service between the Royal Manchester Children's Hospital and Alder Hey Children's Hospital in Liverpool. In the south, there is a service at Great Ormond Street Hospital for Children in London.

The management of CHI is a team effort comprising paediatric endocrinology and supporting services, of which dietetics is a key part. CHI specialist dietitians play an important part in determining feeding regimens to ensure maintenance of glucose levels. While CHI dietitians acquire knowledge and skills in the essential clinical management of hypoglycaemia in the hospital setting, they continue to provide support when children are managed at home with the support of local dietetic services.

Local dietitians may have initial contact with a newly diagnosed infant if their condition is manageable in a district general hospital or prior to transfer to a specialist centre. Upon discharge they may also have shared care with the specialist centre dietitian. Advice from the specialist dietitian should be sought early, given the complexity of the condition and acknowledging that a local dietitian's experience of CHI will usually be limited due to the rareness of the condition.

Acute management

In CHI blood glucose concentrations should be kept above 3.5 mmol/L with a consensus that neuroglycopenia can occur at level <3 mmol/L [100, 103]. In severe neonatal hypoglycaemia, oral feeds alone are unlikely to maintain safe blood glucose levels. In most instances IV access is required to provide additional CHO. An infusion of 10% dextrose at a standard volume of 90–120 mL/kg/day provides a GIR of 6–8 mg/kg/min, which again may not be enough to maintain blood glucose levels in an infant [100]. For this reason a central venous catheter should be considered to allow a higher dextrose concentration infusion (>12.5% dextrose) [116]. These IV infusions often impact on the volume of enteral feeds that can be given in the early days. Consideration must be given as to what impact this will have on the infant's nutritional status.

Despite receiving large volumes and high concentrations of IV dextrose, the infant's blood glucose levels often remain unstable. Medications are often used alongside IV dextrose, and CHO supplemented feeds in order to bring blood glucose levels into a safe stable range. A summary of the drugs used in CHI is given in Table 11.13. First-line medications are diazoxide and chlorothiazide, which are often given together due to their synergistic mechanism. Chlorothiazide is a diuretic that reduces the risk of fluid retention, a common side effect of diazoxide [100].

Blood glucose monitoring

Parents need to be taught how to measure and interpret finger/heel prick blood glucose levels, using a handheld device, prior to going home. The specialist nurse and/or ward nursing staff should help with this. It is important to carry out blood glucose monitoring prior to every feed and at other times when clinically indicated. Parents need to be advised on what is suitable for their child as management is highly individual.

The flow chart in Figure 11.6 shows the 'hypo' management advice given to the parents of children with CHI at Royal Manchester Children's Hospital, together with clear instructions on how to use it. Alongside this they are also given an 'emergency regimen' by the dietitian (p. 673). This is designed to give a solution of glucose polymer during periods of illness when the child may not be feeding/eating as normal and is, therefore, at greater risk of their blood glucose level dropping. The regimen is designed to give an amount of CHO appropriate for the child's age based on average nutritional requirements and should be used during illness with the aim of preventing (rather than treating) hypoglycaemia.

Surgical management of CHI

In focal CHI surgical removal of the lesion is the treatment of choice as this will usually resolve the hyperinsulinism with no long-term side effects [106, 108].

Children with diffuse disease should be considered for surgery (subtotal pancreatectomy) if they are unresponsive to medical treatment. Traditional opinion was that these children should be considered for surgery sooner rather than later. However, more recently there is a motion for preserving the pancreas where possible due to post-surgery and long-term side effects. In the post-operative period, a significant proportion of children with diffuse CHI continue to have hypoglycaemia due to over-secretion from the residual pancreas. In the long term, as the remnant pancreas fails, diabetes becomes inevitable, which then places a lifelong disease burden on the individual [117]. A decision for surgery should be undertaken with the input of the whole CHI team, including parents, and should be weighed up

Table 11.13 Drugs used in the management of CHI.

Drug	Mechanism	Side effects/limitations
Diazoxide – oral	Opens K_{ATP} channels and stabilises pancreatic beta cells	Fluid retention – fluid is often restricted to 120–150 mL/kg and can therefore have implications on nutritional status
		Taste changes
		Ineffective in CHI mutations where the potassium channel is absent
		Pulmonary hypertension – echocardiogram recommended prior to commencement
		Excessive hair growth
		Rarely leukopenia and thrombocytopenia
Chlorothiazide – oral	Acts synergistically with diazoxide by activating non-K_{ATP} channels	Acts as a diuretic, which helps with the side effect of fluid retention with diazoxide
		Hyponatraemia
		Hypokalaemia
Octreotide – subcutaneous injection	Activates G protein-coupled rectifier K channel	Suppression of growth hormone
		Delayed gastric motility
		Steatorrhoea
		Cholelithiasis
		Abdominal distention
		Hepatitis
		Hair loss
Sirolimus	Rapamycin (mTOR) inhibitor, beta cell suppressor	No longer in regular use in CHI due to its immunosuppressive side effects
		Used in rare cases when other treatment options have failed
Glucagon – intravenous	Increased glycogenolysis/gluconeogenesis	Nausea
		Vomiting
		Increased growth hormone
		Increased myocardial contractility
		Decreased gastric acid and pancreatic enzymes
		Helpful in allowing the reduction of IV dextrose/fluid requirement
		Not used long term as drug delivery is unreliable through subcutaneous injection

against the risks of persistent hypoglycaemia and subsequent brain damage. The quality of life for the child and family should remain central to decision making [100].

Subtotal pancreatectomy removes 95% of the pancreas. The remaining 5% is left largely due to its involvement with other major structures including the bile ducts. Post-surgery there is a higher risk of pancreatic endocrine and exocrine insufficiency.

Complications after surgery

Diabetes

Infants will often require insulin post-operatively due to hyperglycaemia, although this can usually be titrated down in the first few days. Children who have a subtotal pancreatectomy have a high risk of developing diabetes [118, 119]. Most will go on to develop insulin-dependent diabetes, usually by their teenage years [100].

Pancreatic exocrine insufficiency

Some children may become reliant on pancreatic enzyme replacement therapy (PERT) due to pancreatic insufficiency, and so faecal elastase should be measured post-subtotal pancreatectomy [120]. Some children found to be pancreatic insufficient in the immediate months following surgery have gone on to demonstrate normal exocrine function a year or two down the line. For this reason it is important to reassess exocrine function periodically. PERT is usually an area that the dietitian will lead on in terms of calculating doses and monitoring symptoms.

Chylothorax

Chylothorax is another complication that can arise in the immediate post-operative period. It can be treated conservatively using a minimal long chain triglyceride diet or feed for as long as is required (p. 299).

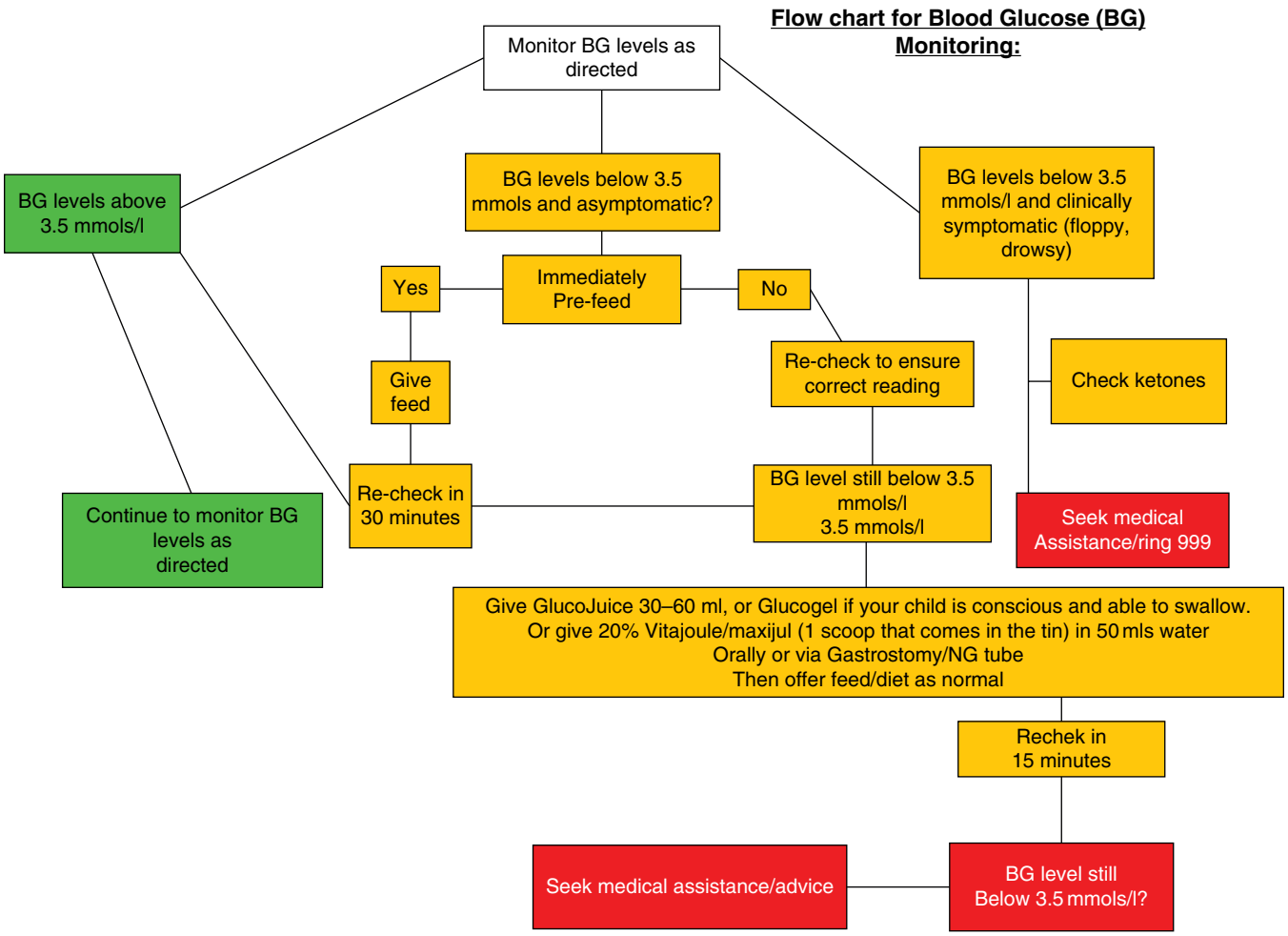


Figure 11.6 Blood glucose monitoring in CHI. Source: Reprinted with permission from Royal Manchester Children's Hospital.

Ongoing hyperinsulinism

Despite 95% of the pancreas being removed, some children still produce inappropriately high amounts of insulin from the remaining 5%. In these cases the child may still need a combination of CHO supplementation and medication to control their hypoglycaemia, although this will usually be a lot less severe and more manageable when compared with pre-surgery management [120].

Learning points: medical and surgical management of CHI

- *a hyposcreen to confirm or rule out CHI should be performed with a blood sugar level <3.0 mmol/L*
- *an infant with CHI should maintain their blood sugar level above 3.5 mmol/L*
- *surgery is the option of choice for focal CHI*
- *surgery for diffuse CHI should be considered if medical management cannot safely maintain safe blood sugar levels*
- *children with CHI become less severe over time and may eventually grow out of the condition*

Dietetic management

Acute considerations

In the acute stage of CHI management, dietetic input can be difficult due to limitations imposed by the medical management. The infant is often fluid restricted due to the commencement of diazoxide, or the fluids available for feeds are limited due to high IV dextrose volume requirements. If the infant is on 10% dextrose via a peripheral line, the placement of a central line will allow the concentration of dextrose to be increased, and, therefore, more fluid maybe become available for enteral feeds. If the infant is unlikely to meet their nutritional requirements via enteral feeds, consideration should be given to the use of parenteral nutrition (PN) alongside enteral feeds within 7 days [116]. The PN could be made to include the dextrose requirement up to a limit of approximately 25% before the stability of the bag is affected. This should be discussed with the team and pharmacist where appropriate to ensure optimal nutrition.

The frequency of feeding will depend greatly on the age of the child at presentation. Where possible the child's normal feeding/eating pattern should be maintained.

The first choice of feed should be as for normal infants, i.e. mother's breastmilk [121]. In the absence of breastmilk, a suitable standard infant formula should be used.

In the neonate feeding should be started as an hourly bolus. This may be orally or via nasogastric tube (NGT) depending on their willingness to feed. The interval between feeds should be 'stretched' equally as blood glucose levels and tolerance allow. This is usually done in hourly stages, e.g. 1 hourly, 2 hourly, 3 hourly and 4 hourly. Prior to 'stretching' an interval, the infant should receive the next interval's volume, e.g. if stretching from 1 hourly to 2 hourly, the baby should receive the 2 hourly volume 1 hour after their last feed. This is to ensure they do not go a longer period of time on the smaller feed volume, which could put the baby at risk of hypoglycaemia. Aiming for 4 hourly feeds would be the ideal for an infant prior to discharge, although this will depend on their age and size at discharge. All infants with CHI should undergo a 6 hour 'safety fast' prior to discharge to ensure they are safe to go home and maintain their blood glucose level [100].

Some infants may need to go home on a combination of daytime bolus feeding and night-time continuous feeding to achieve stable blood glucose levels. This requires a gastrostomy to be placed prior to discharge to ensure they are not at risk of tube migration during sleep. A bolus feed may need to be given soon after the overnight feed stops as the blood glucose level can drop quite quickly after the cessation of the continuous feeding period. The same rule should also be applied when starting the night-time feed after the last bolus of the day.

Quite often infants with CHI require an additional supplementation of CHO in their feed to allow the medical team to wean them off the IV dextrose. Glucose polymers such as Vitajoule, Polycal and Maxijul can be added to a feed to increase the CHO concentration [100]. The glucose polymer should be started at a small amount (1%–2.5% concentration) and increased as required/tolerated up to a maximum of approximately 5% (5 g/100 mL feed). Further increases in concentration are not tolerated due to the increase in osmotic load in the feed. This causes delayed gastric emptying, contributing to gastro-oesophageal reflux (GOR) and possibly a higher incidence of necrotising enterocolitis [122].

Consideration needs to be given to the protein-energy ratio of the feed, which should be maintained between 7.5% and 12% (p. 14). This can become easily reduced in CHI treatment with the addition of a glucose polymer and has the potential to affect growth. However, in CHI the protein-energy ratio is usually already greatly distorted through the use of IV dextrose, which to a large extent cannot be altered as it is part of the medical management. For this reason if the protein-energy ratio cannot be improved through dietetic manipulation, it is more important to ensure the child is at least meeting their safe minimum protein intake, which will vary depending on age [123].

A case study of a baby newly diagnosed with CHI is given in Table 11.14.

Some children with CHI can experience a hypoglycaemia sensitive to protein intake, particularly those with glutamate dehydrogenase deficiency. Glutamate dehydrogenase hyperinsulinism is also be known as hyperinsulinism–hyperammonaemia syndrome and is a milder form of hyperinsulinism that is more likely to present in late infancy or early childhood rather than the newborn period. In this patient group intake of protein particularly without carbohydrate can cause hypoglycaemia [105]. If, on dietary assessment, the child's protein intake is significantly above the reference nutrient intake (RNI), it may be helpful to suggest ways of reducing or spacing their protein more evenly throughout the day. Any reduction in dietary protein, which may form part of the medical treatment, must maintain at least the safe minimum protein intake so that growth and development is not compromised.

Depending on requirements for carbohydrate, energy, fluid and growth history, it may be more effective to use an energy-dense feed, e.g. Infatrini, Similac High Energy, SMA High Energy, or a standard infant formula can be concentrated to better meet their nutritional needs (p. 13).

Long-term feeding difficulties and strategies

Feeding difficulties are common and persistent in the CHI cohort: 75% will require nasogastric (NG) tube feeding, and 93% will require anti-reflux medications [124]. Recent research has found that the more severe the hyperinsulinism, the worse the feeding problems appear to be [100]. Feeding problems is a term used to encapsulate a range of difficulties, and there are a number of suggestions for their occurrence.

The presence of excessive insulin contributes to gut dysmotility, which could explain why babies with CHI often suffer from GOR and have poor tolerance of large feed volumes, with frequent vomiting. Some studies have also linked excessive insulin production with the suppression of the appetite-stimulating hormone ghrelin, which could further explain the baby's apparent reluctance to feed [125].

Although there are clear physiological explanations for poor feeding, it is well recognised that in reality feeding problems are multifactorial in origin. In the case of babies with CHI, their feeding problems are further compounded by the nature of the medical management of CHI. The adverse side effects of medication (Table 11.13) could further exacerbate feeding difficulties. Some studies found that those on a higher dose of diazoxide were more likely to have persistent feeding difficulties [124, 126]. Whether the higher dose of diazoxide is causally linked to appetite suppression or rather an indicator of the severity of CHI is unclear [124].

The use of IV fluids and need for a regimented feeding routine to maintain blood glucose levels interrupts the establishment of normal oral feeding in a newborn infant. The effect of this disruption should not be underestimated.

It is well recognised in medical conditions where there is frequent exposure to unpleasant sensory stimuli from an early age such as intubation and frequent passing of NG tubes that the infant's facial/oral sensitivity and, therefore, their oral feeding experiences are affected. Infants with CHI fit this description, and oral feed aversion is a common problem [127].

Table 11.14 Case study: Dietary management of a baby with CHI.

Anthropometry: Male born at term weighing 3.9 kg, 75th–91st centile, length 53 cm, 75th–91st centile. Growth history:
1 week, 4.2 kg, 91st centile
4 weeks, 4.8 kg, 75th–91st centile
2.5 months, 7.5 kg, <98th centile at discharge
6 months, 9.5 kg, 75th centile
11 months, 10.2 kg, 75th centile, length 75 cm, 50th–75th centile
Comments: Baby's weight increased beyond the trajectory of his birth centile due to excessive CHO intake forming part of the medical management up until 6 months of age. Weight at 11 months of age shows the rate of weight gain slowed down as the need for additional CHO had ceased

Biochemistry: Blood sugar level <2.6 mmol/L, insulin level raised, no ketones present

Clinical: Baby presented with poor feeding and lethargy in the hours after birth, which prompted a blood sugar level check at the local hospital where he was born

Dietary: Initially fed 110 mL/kg EBM, unable to increase further due to IV fluids with dextrose required to maintain blood sugar levels. At day 10 EBM was fortified with 2.5% glucose polymer to help stabilise the baby's blood sugar levels, while medication was weaned down. Mum was supported to breastfeed the baby after and in between bottle feeds. Bottle feeds given first to ensure the required volume containing the glucose polymer was taken. Baby was stretched from 3 hourly bottles to 4 hourly bottles and went home on this regimen. He started weaning at 6 months of age and stopped glucose polymer fortification at 7.5 months of age due to stable blood sugars

Environment: The baby was the first child of healthy parents. He had diffuse disease heterozygous ABCC8 mutation, which he had inherited paternally. He spent the first 2 weeks of his life on HDU before being stepped down to a medical ward for 3 months. He was then discharged home

Focus: The dietetic aims were to meet the baby's nutritional requirements while providing a dietary regimen that was safe from a blood sugar level perspective. His blood sugar levels were frequently reassessed by the dietitian once home to ensure the baby did not continue to receive an excessive CHO intake for longer than required as this would have led to further accelerating weight gain. The dietitian also maintained a focus on supporting breastfeeding throughout the baby's treatment to ensure it was considered by the medical team in their treatment planning

Age	Medical intervention	Dietetic comments
10 days	Transferred to HDU from local district general hospital neonatal unit due to uncontrolled hypoglycaemia. He had a hyposcreen performed locally, which showed high circulating levels of insulin; hence diazoxide and chlorothiazide were commenced prior to transfer Birth weight = 3.9 kg. Once on HDU he was commenced on 10% IV dextrose at 6.5 mL/hour and oral feeds of EBM 54 mL × 3 hourly, total fluid intake 150 mL/kg with 110 mL/kg as EBM *Calculation of GIR* Amount of CHO received from 10% IV dextrose: 6.5 mL/hour × 24 hours = 156 mL × 10% = 15.6 g CHO Amount of CHO received from EBM (7 g CHO/100 mL average content of EBM) 54 mL × 8 feeds in 24 hours = 432 mL × 7/100 = 30.2 g CHO Total CHO intake per 24 hours = 45.8 g GIR (mg/kg/min) = $\frac{45.8\,g \times 1000\,mg}{3.9\,kg} \div \frac{11\,744}{24\,hour} \div \frac{489.33}{60\,minutes}$ = 8.155 Round up to 8.2 mg/kg/min	This feeding regimen did not meet his nutritional requirements, but fluids could not be increased further given that he had just commenced diazoxide. Feed fortification was not considered at this point due to the potential changes in medical management
12 days	A central line was placed to obtain IV access that would allow a higher concentration than 10% IV dextrose, due his blood sugars being continually <3.5 mmol/L on the current regimen Blood sugars did not improve on diazoxide; therefore, he was commenced on octreotide and weaned off diazoxide and chlorothiazide Current regimen: 15% IV dextrose at 5 mL/hour and glucagon at 3 mL/hour to stabilise his blood sugars; feeds 50 mL EBM × 3 hourly. Current weight = 4.2 kg. *Calculation of GIR* IV fluids 15% dextrose: 5 mL/hour × 24 hours = 120 mL × 15% = 18 g CHO Feeds EBM: 50 mL × 8 in 24 hours = 400 mL × 7/100 = 28 g CHO Total CHO intake per 24 hours = 46 g GIR (mg/kg/min) = $\frac{46\,g \times 1000\,mg}{4.2\,kg} \div \frac{10\,952}{24\,hour} \div \frac{456.34}{60\,minutes}$ = 7.6 mg/kg/min	GIR had decreased due to the baby's weight increasing, but he was also on glucagon, which would have helped stabilise his blood sugar levels At this time Mum had a strong wish to breastfeed; it was agreed that he could latch on for 'comfort feeds' after the 50 mL EBM feed. This was to ensure it did not impact on his appetite for his set feed volumes via the bottle. It was important that his feed remained quantifiable given the instability of his blood sugar levels. Had he had more stable blood sugars breastfeeding may have been recommended before top-up feeds (if required depending on blood sugar levels)

(continued overleaf)

Table 11.14 *(continued)*

Age	Medical intervention	Dietetic comments
20 days	10 days after admission he was still experiencing hypos <3.5 mmol/L. The medical team discussed with the dietitian the introduction of a glucose polymer to help stabilise the blood sugar levels while weaning down the glucagon Over the next few days, with the addition of this extra CHO, he was weaned off glucagon as his blood sugars were consistently >3.5 mmol/L. This allowed the baby to be stepped down to a general ward On admission a sample had been obtained for genetic testing. When the results came back two weeks later, they showed the baby had diffuse disease heterozygous ABCC8 mutation. Despite a diagnosis of diffuse disease, the plan was for medical management as the baby's blood sugars were more stable	2.5% glucose polymer concentration was added to the EBM. To make this practical on the ward, 1 small blue SHS scoop Vitajoule (1.3 g) was added to 50 mL EBM, providing 2.6% concentration. Tolerance to this addition of CHO was monitored by stool frequency, amounts of vomits and whether the baby remained settled
24–78 days	While he was on the ward, it was planned to lengthen his feed interval from 3 hourly to 4 hourly by giving the new increased volume after a 3 hour fast, then allowing him to go 4 hourly. After the 4 hour interval, his blood sugars were on the low side (<4 mmol/L); therefore the Vitajoule in the EBM was increased to 5% rather than going back to more frequent feeds. IV fluids were stopped. Current weight = 4.8 kg *Calculation of GIR* Feeds EBM + 5% Vitajoule: 165 mL/kg × 4.8 = 792 mL Total CHO intake per 24 hours = 792 mL × 12% CHO (7% from feeds + 5% from Vitajoule) = 95.04 g GIR = $\frac{95.04}{4.8\,\text{kg}} \times \frac{1000}{24\ \text{hour}} = \frac{19\,800}{60\ \text{minutes}} = 825 = 13.75\ \text{mg/kg/min}$	His GIR had increased significantly over the course of his treatment. At this time it was important to assess his nutritional intake: *Protein intake* P:E ratio was greatly distorted at 4% due to his high CHO requirements; however, his protein intake of 1.65 g/kg was above the safe minimum protein intake of 1.3 g/kg *Energy intake* 142 kcal (595 kJ)/kg and, as is common with many babies with CHI, weight gain at a rapid rate would be expected It is important to regularly assess the stability of blood sugar levels and reduce CHO intake where possible. Dietary changes should not be made at the same time as medication changes. The baby was discharged home on this regimen at 3 months of age The parents were also given an emergency regimen to use during periods of illness when he could not tolerate his usual feeds
6 months	The baby continued on octreotide injections	The baby commenced weaning foods without any dietary manipulations and eventually stopped all CHO supplementation, which allowed Mum to solely breastfeed
11 months	The baby came back into hospital for a controlled fast off medication and demonstrated that he was now producing ketones and his CHI had become less severe and progressed to ketotic hypoglycaemia	He continued to have his emergency regimen for use during times of illness when his dietary intake may decline, and he will be at risk of a hypo

CHO, carbohydrate; IV, intravenous; EBM, expressed breastmilk; HDU, high dependency unit; GIR, glucose infusion rate.

For this reason it is important to involve a speech and language therapist from an early stage to help the family with techniques to overcome aversion or limit its development.

Anecdotally the CHI cohort has a high prevalence of cow's milk protein allergy (CMPA). Changing to an extensively hydrolysed protein formula or amino acid-based formula, where indicated, could help to alleviate some of the feeding problems such as GOR, vomiting and to a certain extent oral feed aversion. Consideration should be given to the increased gut transit time of these formulas vs. a whole protein feed and, therefore, their effect on blood glucose stability. However, if the symptoms associated with CMPA are more effectively managed through this change, it may actually lead to better blood glucose control.

Feeding difficulties often place an unbearable burden on the family of an infant with CHI. Accessible support for the family from the multidisciplinary team, including the dietitian and speech and language therapist, with a focus on feeding throughout their treatment process is crucial. Children are often in hospital for long periods of time, which adds to the stress of illness upon families. The support of a skilled and experienced psychologist is often necessary, given the burden of managing a complex medical condition over long periods of time [100].

Establishing feeding in the young infant

The infant with CHI should be given the chance to establish oral feeding as soon as possible. Although there is no published data, the NORCHI service has found through experience that the more an infant is allowed to respond to their

own feeding cues without being regimented with feeding volumes and times, the better their long-term feeding outcomes. This approach has to be weighed up against the stability of the infant's blood glucose levels so as not to compromise their safety.

Breastfeeding should be promoted and supported by the dietitian [128]. Initially, when the baby is unstable, the mother may have to express breastmilk for all the feeds. Latching on after feeds or in between for comfort should be encouraged as soon as it is safe. Expressing breastmilk is highly demanding, and steps should be taken to ensure the mother is well supported including education on optimal times and frequency of expression. Recently, continuous glucose monitors have been used in individual cases; this has allowed parents to be less regimented with the infant's feeding and has had positive outcomes in relation to oral feeding and weaning.

Weaning in infants with CHI is encouraged at around six months of age as for the normal population [129]. Early weaning may be considered in the orally averse child who does not make progress with accepting bottles to ensure that oral acceptance is encouraged through a different medium. This should be done with the supervision of a speech and language therapist and dietitian [127].

Feeding the older infant and child

As the infant gets older, every effort should be made by the dietitian to ensure their feeding progresses as expected for a child of their age, e.g. dropping a night feed if their blood glucose levels are stable enough to do so. This should be done by increasing the volume of feed prior to their nighttime fast and then stretching the period slowly by 30 minutes to 1 hour at a time while monitoring blood glucose levels over a period of days/weeks.

The older child with CHI may benefit from the introduction of uncooked cornstarch. This can be particularly helpful in stretching times between meals/feeds and snacks or to allow a longer fast period overnight. Uncooked cornstarch can help with blood glucose stability because of its structure as a complex carbohydrate and therefore slow digestion time, which ranges from 4 to 9 hours [130]. A start dose of 5 g/dose is recommended with a maximum dose of 2 g/kg/dose. It is not recommended in children under 1 year of age and may be less effective in the younger child due to the immaturity of intestinal amylase [131]. Cornstarch can be bought in the form of cornflour from most UK supermarkets. It can also be prescribed as Glycosade, although the cost implications of this should be considered. If a child is taking multiple doses of uncooked cornstarch in a day, the dietitian should give consideration to the impact this may have on their appetite and, therefore, overall nutritional intake, particularly if there are concerns regarding weight gain and growth.

As the child gets older, their condition usually becomes less severe, and they may eventually grow out of it. During this time they may progress from CHI to another form of hypoglycaemia called ketotic hypoglycaemia. This is a condition where a child's blood sugar levels may still drop, particularly during periods of illness or prolonged fasting, but they can now produce ketones, which will provide an alternative source of fuel for the brain. For children that go on to develop ketotic hypoglycaemia, their emergency regimen (p. 676) is still used for times of illness, but their eating on a daily basis is usually free from dietary manipulations.

Learning points: dietetic intervention

- *the dietitian should be involved as early as possible to ensure the impact of medical treatment on nutritional status is minimised as much as possible*
- *the aim should be for normal infant feeding while providing a regimen that is safe for the individual*
- *there is high incidence of feeding problems including gastro-oesophageal reflux, oral aversion and feed intolerance*
- *all children should have an emergency regimen to be used during times of illness, with the aim of preventing hypoglycaemia*

Acknowledgements

Thanks to the NORCHI team at Royal Manchester Children's Hospital for their comments, particularly Dr I. Banerjee and dietetic colleague Niamh Gilligan, and also to Annaruby Cunjamalay, CHI dietitian at Great Ormond Street Hospital for Children, London.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

12 Cystic Fibrosis

Carolyn Patchell and Katie Stead

Introduction

Cystic fibrosis (CF) is a recessively inherited life-limiting multi-organ disease with around 10400 people recorded as having CF on the 2017 UK Cystic Fibrosis Registry Annual Report [1]. About 1 in 25 of the UK population are carriers for the condition (www.cysticfibrosis.org.uk).

Early diagnosis, new treatments and extreme vigilance in the management of symptoms, with regular reviews by a multidisciplinary team (MDT) experienced in the management of the condition, have resulted in improvements in quality of life and life expectancy, with a larger proportion of the population surviving into adult life. 60.6% of the CF population are now adult with a median age at death of 31 years, rising from 57.6% adults and median age of death of 28 years in 2012. Predicted median survival for infants diagnosed in 2017 is 47 years, rising from 44 years in 2012, with males surviving an estimated 2–3 years longer than females [1].

CF is caused by a mutation in cystic fibrosis transmembrane conductance regulator gene (CFTR), resulting in dysfunction in the regulation of salt and water across membranes of secretory epithelial cell and thickening of secretions in all organs with epithelial cells.

There are over 2000 different genotypes that cause CF. It is possible to have two of the same (homozygous) or two different (heterozygous) mutations. The most common of these is DF508, with 89% of the UK population having one copy and 49.1% having two copies [1]. The genotype affects the production and function of the CFTR protein and, therefore, the severity of the disease. Genotypes are traditionally separated into five classes depending on the different protein defects they produce (Table 12.1). In class I, II and III production of the protein is more severely affected, so they are more likely to cause classic or more severe CF. The CFTR protein function is less affected in classes IV and V, so these are more likely to result in atypical CF; however, there is significant individual variation between patients.

Diagnosis

Newborn screening

Newborn screening for CF has been in place across the UK since 2007.

All parents of newborn infants are offered screening by heel prick test on the fifth day of life. Since screening was introduced, 93% of cases of CF are identified through this programme. Diagnosis should be confirmed by sweat test and identification of CF mutations by 4 weeks of age.

In countries that have a national screening programme, infants are diagnosed before 2 months of age [2], enabling early initiation of preventative respiratory and nutritional care and regular follow-up in a CF centre. Early instigation of treatment is recommended to delay the onset of respiratory disease [3] and to confer improved outcomes including growth, respiratory disease and survival [4–6]. The diagnosis of CF through newborn screening, however, is not always clear, and some infants are diagnosed through the screening programme whose sweat test and/or CFTR analysis is not consistent with a diagnosis of CF, nor with a negative screen. This group of infants has been classified as CF screen positive inconclusive diagnosis (CFSPID). The possible outcomes of screening are shown in Figure 12.1. The clinical outcomes of CFSPID patients are not predictable, so they will require follow-up in a CF centre. Long-term data reports good nutritional status for this group, and the majority will not require pancreatic enzyme replacement therapy (PERT) [7].

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 12.1 Classification of CF genotypes.

	Class I	Class II	Class III	Class IV	Class V
Function	No synthesis	Reduced trafficking	Reduced gating	Decreased conductance	Reduced synthesis
Mutation	Nonsense, frameshift and stop mutations: no CFTR is made due to miscoding in DNA	Poor processing; protein does not get to cell surface	On cell surface, protein unstable, chloride transport not effective	Wrong shape so chloride cannot pass through easily, but sits on cell surface	Reduced protein synthesis; reaches cell surface, but limited numbers
Genotype example	G542x	F508del	G551D	R117H	A455e

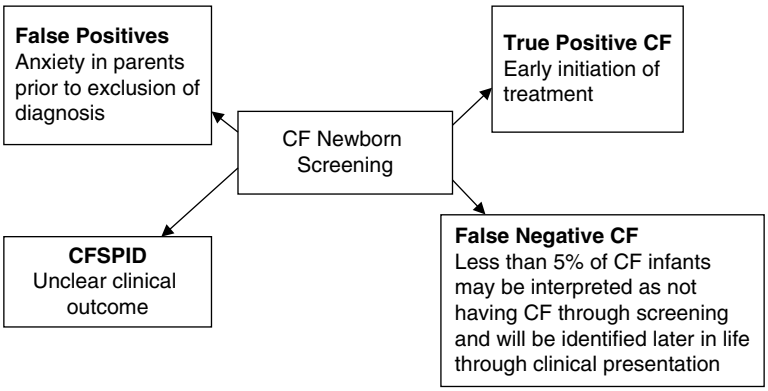


Figure 12.1 Possible outcomes of newborn screening for cystic fibrosis. CFSPID, CF screen-positive inconclusive diagnosis.

Clinical consequences of cystic fibrosis

The clinical consequences of CF include:

- chronic respiratory disease with recurrent respiratory infection, inflammation, bronchiectasis and respiratory failure
- exocrine pancreatic dysfunction (pancreatic insufficiency [PI]) affecting approximately 84% of the CF population
- nutritional consequences, including a risk of malnutrition and fat-soluble vitamin deficiency due to increased energy requirements and fat malabsorption
- bowel obstruction including meconium ileus (MI) in infants and distal intestinal obstruction syndrome (DIOS) in older patients
- impaired glucose tolerance or cystic fibrosis-related diabetes (CFRD)
- CF-related liver disease (CFLD) with or without portal hypertension
- reduced bone mineral density (BMD), osteopenia and osteoporosis
- infertility in most males
- CF arthropathy
- behavioural and psychological problems as a result of severe life-limiting disease and burden of treatment

Chronic respiratory disease

The lungs are normal at birth, but may become affected early in life due to abnormal secretions, chest infection and inflammation [8, 9]. Chest treatment aims to prevent infection and remove secretions so delaying the rate of lung damage. This is done by:

- regular chest physiotherapy
- regular surveillance of bronchial secretions and prompt treatment of infections with oral, aerosol or intravenous (IV) antibiotics
- use of bronchodilators to open up the airways
- encouragement of an active lifestyle with regular physical exercise
- cross infection measures to keep CF patients separate to avoid transmission of bacteria, which is harmful to people with CF

Overview of nutritional management

Nutritional management is an essential part of the care of people with CF. Malnutrition is a frequent co-morbidity and nutritional status is strongly associated with both pulmonary function and survival. Nutritional management should begin at diagnosis, and regular and thorough follow-up should be given by a dietitian experienced in the management of CF. A focus on detail and early intervention if there are signs of decline offer the best outcomes [10–16].

The aims of dietetic intervention are:

- achievement and maintenance of normal growth and development in childhood
- control of symptoms of malabsorption
- maintenance of normal serum vitamin levels

- maintenance of good bone health
- normal eating behaviour
- control of blood glucose levels in the presence of CFRD

The nutritional status of people with CF has improved since a high fat and high energy diet has become a standard element of care since the early 1980s.

Factors associated with poor nutrition include:

- increased stool energy losses due to PI; untreated PI will lead to significant fat, fat-soluble vitamin and, to a lesser degree, protein malabsorption leading to poor nutritional status
- reduced pancreatic bicarbonate secretion, reduced bile acid secretion and abnormal gastric and intestinal motility may also contribute to malabsorption
- increased energy requirements as a result of infections, inflammation and declining lung function; individual energy requirements vary significantly depending on the severity of the disease and requirements should be assessed on an individual basis
- reduced oral energy intake due to infection-related anorexia, sputum production leading to nausea, abdominal pain, vomiting, gastro-oesophageal reflux (GOR) and disordered eating behaviour
- co-morbidities, for example, CFRD and impaired glucose tolerance resulting in energy losses through glycosuria

Learning points: nutritional management

CF patients are at risk of malnutrition as a result of increased energy expenditure, malabsorption and poor intake.

Dietetic aims:

- *achievement and maintenance of normal growth and development in childhood*
- *control of symptoms of malabsorption*
- *maintenance of normal serum vitamin levels*
- *maintenance of good bone health*
- *development and maintenance of normal eating behaviour*

Assessment of Nutritional Status

Regular assessment of nutritional status is essential as part of clinical assessment. Longitudinal measurements should be made and measurements of growth should be plotted on age-specific growth charts: UK-WHO Growth Chart 0–4 years and UK Growth Chart 2–18 years.

Weight

All children should be weighed at each clinic visit and regularly during admission to hospital using category III electronic scales. Weight should be plotted on an age-appropriate growth chart. Factors such as ascites, organomegaly and dehydration should be taken into consideration when assessing weight.

Infants will initially require more frequent weighing, every 1–2 weeks after diagnosis to inform adjustments to feeding and treatment. This can be done in the community by the health visiting team. Once the infant is thriving and there is stability in abdominal symptoms, the frequency of weighing can be reduced.

Length/height

Supine length should be measured for children under 2 years of age at each clinic visit and admission, and the measurement plotted on the child's growth chart. Standing height, using a correctly installed and calibrated stadiometer, should be measured for all children over 2 years of age.

Head circumference

Head circumference should be measured, using a non-stretchable disposable tape measure, in infants at each clinic visit and admission throughout the first 1–2 years and plotted on the child's growth chart.

Body mass index (BMI)

The body mass index (BMI) centile is considered the most appropriate measure of nutritional status in CF, the aim being to achieve and maintain a BMI on the 50th centile.

In children, BMI centile is a sensitive marker of nutritional status; however, BMI can mask stunting, and it is important that BMI is not used in isolation, but is considered alongside height velocity. BMI cannot be used in children under 2 years of age due to a lack of reference values.

A BMI ≤20th centile has been shown to be associated with reduced lung function and a BMI ≥50th centile with better lung function [12].

Table 12.2 Frequency of measurement in infants and children.

Measurement	Infants and children up to 2 years of age	Children 2–18 years of age
Weight	Every 1–2 weeks until a stable treatment plan established, then monthly or on admission, then twice weekly	2-monthly in clinic, twice weekly on admission
Length/height	Monthly in clinic/on admission	2-monthly in clinic and on admission
Head circumference	Monthly in clinic/on admission	n/a
BMI	n/a	Each clinic visit and on admission

n/a, not applicable; BMI, body mass index.

Assessment of body composition

Lower fat-free mass status may be associated with poor lung function [16], and body weight and BMI do not distinguish between fat and lean body mass.

Assessment of body composition is, therefore, important, but in clinical practice is difficult to do due to a lack of validated low cost equipment that is easy to disinfect between each patient's use; therefore, it is not routinely done outside of a research setting.

A summary of frequency of measurement is given in Table 12.2.

Learning points: assessing nutritional status

- *Nutritional advice and interventions are aimed at achieving and maintaining normal growth and development in infants and a BMI on 50th centile for children over 2 years of age*
- *Weight and height/length should be measured at each clinic visit and hospital admission and plotted on an age-appropriate growth chart*
- *Head circumference should be measured in children under 2 years of age at each clinic visit or hospital admission and plotted on a UK-WHO Growth Chart 0–4 years*
- *No single measurement of weight or height/length should be used to evaluate nutritional status*

Management of malabsorption

PI affects around 84% of people with CF. There is a relationship between CF genotype and pancreatic status. People with class I–III CF mutations are likely to be PI; however, there is still a requirement for objective assessment of pancreatic status. Pancreatic function can be assessed by the presence of signs of malabsorption; however, it is recommended that pancreatic function be tested formally in all newly diagnosed patients. Of the tests available, the one most routinely used in clinical practice is faecal pancreatic elastase (FPE-1). This test has a high degree of sensitivity, is easy to perform on a single stool sample and is unaffected by the presence of PERT and so can be done after PERT has been commenced, if necessary.

FPE-1 levels <100 µg/g stool are predictive of severe PI, requiring treatment with PERT; levels of 100–200 µg/g stool indicate reduced pancreatic function; and PERT should be considered if there are abdominal symptoms or growth failure.

PI develops when more than 90% of acinar cell function is lost. Damage begins *in utero*, and approximately 92% of infants are PI by 12 months of age. Secretion of pancreatic amylase, protease and lipase is reduced or absent, resulting in malabsorption of fat, protein, bile and fat-soluble vitamins.

It is important to remember that pancreatic function may deteriorate over time and regular assessment should be done in those assessed as pancreatic sufficient (PS) annually during childhood, or if there are signs of malabsorption, fat-soluble vitamin deficiency or a decline in nutritional status.

Pancreatic enzyme replacement therapy

Untreated PI will result in malabsorption of dietary fat and some dietary protein, contributing to suboptimal nutritional status and fat-soluble vitamin deficiency.

The aims of PERT are to:

- control signs of malabsorption such as loose, frequent stools, bloating, wind and abdominal pain, aiming for a normal stool frequency and consistency
- promote growth and maintenance of normal nutritional status
- achieve normal serum levels of fat-soluble vitamins and fatty acids

Types of pancreatic enzyme replacement therapy

There are a number of pancreatic enzyme preparations available in the UK.

Full details can be found on the British National Formulary website (www.BNF.org).

It is recommended that enteric-coated microspheres be used; these are acid-resistant preparations, the enteric coating reducing the effect of gastric acid on the efficacy of the pancreatic enzymes. Pancreatic enzymes are available in a range of strengths and presentations, including a granular form for infants and young children, and in capsule form for older children. Table 12.3 shows the preparations available in the UK.

Table 12.3 Pancreatin preparations available in the UK.

Preparation	Protease units	Amylase units	Lipase units
Creon 10 000 capsule, e/c granules	600	8 000	10 000
Creon Micro e/c granules (per 100 mg/1 scoop)	200	3 600	5 000
Pancrex granules (per gram)	300	4 000	5 000
Pancrex V capsule, powder	430	9 000	8 000
Pancrex V '125' capsule, powder	160	3 300	2 950
Pancrex V e/c tablet	110	1 700	1 900
Pancrex V Forte e/c tablet	330	5 000	5 600
Pancrex V powder (per gram)	1 400	30 000	25 000
Creon 25 000 capsule, e/c pellets	1 000	18 000	25 000
Creon 40 000 capsule, e/c granules	1 600	25 000	40 000
Nutrizym 22 capsule, e/c minitablets	1 100	19 800	22 000
Pancrease HL capsule, e/c minitablets	1 250	22 500	25 000

e/c, enteric coated.

Dosage recommendations and administration

All pancreatic enzyme preparations contain a mixture of lipase, protease and amylase, the strength of which degrades over time. The dose of lipase stated per capsule or scoop is a minimum taking into account degradation; capsules that are close to their use by date will have less potency than those with a longer use by date.

All pancreatic enzyme preparations are derived from pork, and currently there are no forms of PERT available that are halal or kosher. This should be discussed with families before initiation of PERT. Families can be reassured that Islam and Judaism allow the use of non-halal and non-kosher medicinal products that are lifesaving, if there is no acceptable alternative. Families may wish to discuss this with a hospital chaplain or their own religious leader before starting PERT.

Pancreatic enzyme preparations are heat sensitive and should not be stored in a hot place or mixed with hot food. Doses should be advised individually and adjustments made based on clinical symptoms, appearance and frequency of stool, presence of abdominal pain, bloating, flatulence and weight gain.

Enzyme dose

The dose of PERT should be adjusted according to the quantity and composition of the food eaten. The lower strength preparations are recommended for infants and young children to allow fine adjustment of the dose.

As the majority of lipase is secreted by the pancreas, and amylase and protease are secreted elsewhere in the gastrointestinal (GI) tract, doses are adjusted based on the fat content of the meal or snack consumed. Cohort studies [17, 18] suggest that the requirement for lipase ranges from 400 to 5000 units lipase/g of fat consumed with a mean requirement of 1800 units lipase/g fat consumed to achieve optimal absorption:

- Enzyme doses should be individually determined and adjusted based on fat intake, abdominal symptoms and weight gain; requirements will vary considerably between patients
- Parents and caregivers should receive practical advice to manage their PERT dose independently. The advice should not be strictly based on lipase/g fat consumed, and there should be avoidance of an excessive focus of measuring the fat content of food due to the recognised variation in potency of enzymes, lack of accurate data on fat content of home-prepared foods and variability of appetite and intake for young children
- Other GI disorders such as coeliac disease, inflammatory bowel disease and food allergies may also occur and should be considered if there are ongoing symptoms of malabsorption despite optimising enzyme doses, timing and titration

Safety of PERT

Following a number of serious cases of fibrosing colonopathy (FC) in the 1990s, the Committee on Safety of Medicines issued some safety recommendations [19]:

- The total dose of PERT used in CF should not exceed 10 000 units lipase/kg body weight daily
- Patients developing new abdominal symptoms while using PERT should be reviewed by their specialist team to exclude the possibility of colonic damage
- High strength preparations Pancrease HL and Nutrizym 22 should not be used in children under 15 years of age
- No association with FC was found in those using Creon 25 000 and Creon 40 000
- It is important to ensure adequate hydration in those using high strength preparations

Some patients require higher doses than 10 000 units of lipase/kg body weight to achieve good control of abdominal symptoms. It is more likely to occur in infants, as they consume a higher percentage of energy from fat in their diet than older children, and in those on a very high fat diet or requiring enteral tube feeding (ETF).

Children who need high doses of PERT should be closely monitored, checking the titration relative to the fat content of the diet and ensuring that PERT is given with all fat-containing foods. Adjunctive therapies may also be required (See below). Dietary fat should not be limited to restrict the PERT dose required as this may impact on nutritional status.

Efficacy of PERT

The timing of enzyme dosing may be an important factor in maximising efficacy, and the recommendation is to split the dose throughout the meal to allow thorough mixing of the enzymes with food, although some children will achieve control of symptoms when the enzymes are all given prior to a meal.

Splitting the dose before, during and after the meal is a helpful strategy for children with variable intakes to ensure that too many enzymes are not given if the meal is refused.

Adjunctive therapies such as H2 antagonists and proton pump inhibitors (PPI) may be required to reduce gastric acid secretion to optimise PERT efficacy. Recent guidance from the UK National Institute for Health and Care Excellence (NICE) recommends that PPI should be used with caution and the use of H2 antagonists or PPI should be regularly reviewed [20].

Practical administration

Infants

Creon Micro is the most suitable PERT preparation to use in infants, although Creon 10 000 capsules may be used and the capsules opened to administer the contents. The enzyme granules should be given orally mixed with a small amount of the infant's usual feed or fruit puree on a spoon. Enzyme doses should be given before and, as necessary, during feeds of long duration. Doses will vary. A guide when starting enzymes is given in Table 12.4. Doses should then be adjusted based on volume of feed, bowel symptoms and weight gain.

Children

Points to note are the following:

- The gelatine capsule protects the pancreatic enzyme granules from gastric acid, and, therefore, they should be

Table 12.4 A guide to starting PERT in infants.

Breastfed	Formula fed	Nutrient-dense infant formula
¼–½ scoop Creon Micro for breastfeeds <20 minute duration	¼–1 scoop Creon Micro per 50–100 mL feed	½–1 scoop Creon Micro per 100 mL feed
½–1 scoop Creon Micro for breastfeeds >20 minute duration		

swallowed whole as soon as the child is able to swallow capsules (around 3–6 years of age)
- Chewing or crushing the capsules should be avoided as this reduces efficacy
- The granules should not be mixed with hot food as this reduces efficacy
- The dose should be split throughout the meal
- Suggested starting dose: 1–2 capsules Creon 10 000 per meal, 1 capsule per fat-containing snack

Pancreatic enzymes with enteral feeds
The dose and timing of enzymes depend on the timing and duration of enteral tube feeds. Feeds administered slowly by continuous infusion, either overnight or during the day, may require a lower dose of enzymes than anticipated. This is due to the stimulation of gastric lipase [21] and the slow rate of fat infusion. Pancreatic enzymes are usually given at the start and end of the infusion in a split dose [22]. Bolus feeds may require more pancreatic enzyme, similar to that required per gram of fat for meals and snacks, as a larger amount of fat is given over a short time period.

For patients unable to swallow enzyme capsules while being tube fed, e.g. those who are ventilated, a powdered preparation of pancreatic enzymes dissolved in water, or enteric-coated granules dissolved in sodium bicarbonate solution, may be used. The administration of sodium bicarbonate should be given with caution in young children due to the risk of excess bicarbonate intake. A PPI will be required if preparations are dissolved to avoid the enzymes being destroyed by gastric acid.

Learning points: pancreatic enzyme therapy

- *PERT is required for the majority of children with CF*
- *Enteric-coated microspheres should be used and given with all fat-containing drinks, snacks and meals*
- *The dose and timing of enzymes should be individually assessed and regularly reviewed by a specialist CF dietitian*
- *The presence of other conditions such as coeliac disease, food allergy and inflammatory bowel disease should be considered in those with ongoing symptoms despite adequate use of PERT*
- *Enzyme dosing advice should be used as a guideline due to the variability in bowel function and potency of enzyme preparations*
- *Adjunctive therapy should be considered in those with high enzyme requirements*

Nutritional management

Preventative nutritional advice

Dietetic advice should be given from diagnosis and at each subsequent review with the aim of achieving normal rates of weight gain, growth and a healthy BMI centile; controlling malabsorption; maintaining normal serum fat-soluble vitamin levels; and developing and maintaining normal feeding behaviours.

Infants

The majority of infants diagnosed through newborn screening will thrive well with exclusive breastfeeding for the first 6 months of life, and this should be encouraged due to the well-documented immunological and nutritional benefits breastfeeding gives. A standard infant formula can be used for infants whose mothers cannot or choose not to breastfeed.

Infants should be weighed every 1–2 weeks after diagnosis, and once adequate growth has been achieved, every month. Infants not demonstrating adequate growth and weight gain will require an increased energy intake.

Pancreatic enzymes
All infants should be screened for PI at diagnosis and those showing signs of malabsorption should be started on PERT while results are awaited. A review of bowel symptoms should be done every 1–2 weeks initially and then at each review, adjusting PERT to achieve a normal bowel habit.

Sodium supplementation
A urinary sodium–creatinine ratio (UNa–Cr) should be assessed and sodium supplementation started at a dose of 1–2 mmol/kg if UNa–Cr ratio is low (reference range 17–52) [23].

Gastro-oesophageal reflux
GOR is common in infants with CF and can contribute to poor nutritional status, increased abdominal symptoms and discomfort and increased respiratory symptoms. GOR should be managed by the use of feed thickeners (p. 133) and H2 antagonists or PPI.

Weaning
Normal weaning guidance should be followed with solid foods being introduced by 6 months of age and no earlier

than 17 weeks. Giving fruit and vegetables as first foods allows the infant to get used to feeding from a spoon in advance of Creon being required. Meat, pulses, cheese, yoghurt and cereals should be introduced at 6 months of age, with advice given on the appropriate dose of Creon to use for fat-containing solids. Salt need not be restricted and can be used in cooking; normal gravy and sauce mixes can be given.

By the age of 12 months, the infant should be weaned onto mashed and chopped family foods, maintaining a healthy balance of foods and often requiring three meals plus small mid-meal snacks. Full-fat cow's milk can be introduced as a drink at 12 months of age and should be encouraged throughout childhood to help maintain an adequate intake of calcium.

Establishment of healthy eating behaviour in infants and toddlers

Establishing healthy feeding behaviour is important, and feeding times and mealtimes should be a positive experience. Parental awareness of the need to maintain a healthy weight for their child, however, can put undue focus on eating, and food selectivity or refusal can be used effectively by the child as a means of getting attention. Advice and support should be given to minimise the duration of any feeding difficulties, and expert input from a psychologist may be needed for the more persistent cases.

Simple advice that can be given by the dietitian include:

- encouraging positive behaviour and ignoring bad behaviour
- encouraging family meals and avoiding distractions such as TV and IT devices such as phones and tablets
- making food attractive
- offering small portions; more can be given if the child eats well
- allowing the child to play with food; it is an important part of learning about food
- if the child refuses to eat, removing the food without comment and not offering an alternative
- avoiding threats and bribes at mealtimes
- limiting mealtimes to around 30 minutes, as after this time little additional food will be eaten
- all caregivers should be consistent in the management of feeding difficulties

School-age children

Normal school meals or packed lunches should be given, ideally adhering to the school food policy unless there are nutritional difficulties; the child with CF should not be made to feel any different to their peers.

Pancreatic enzymes

Most school-age children will be able to swallow their capsules whole and should be encouraged to learn the doses they require for different foods. Young children will still need guidance from school staff to administer correct doses. A care plan will be developed by the CF specialist nursing team to help support the child at school, and this will give guidance on dosing and timing of pancreatic enzymes.

Parents can request information about the school lunch menu in order to give guidance to school staff on the dose of PERT required for each meal.

Independence in self-medication should be encouraged as the child gets older. Some schools are reluctant to allow this and may need a telephone call or visit to give reassurance and advice.

Adolescents

Adolescence is a time of increased growth and nutritional requirements. There is often a clinical decline during this period, increasing nutritional requirements even further, and co-morbidities such as CFRD are more likely to develop. Many adolescents will require more aggressive nutritional management in order to achieve and maintain a healthy BMI centile.

Adolescence is also a time of increasing independence, and parents often struggle to allow the young person to become independent in the management of their diet and treatment. Young people are more likely to experiment with risk-taking behaviour including choices of food, eating patterns and adherence to treatment such as pancreatic enzymes.

Young people with chronic health conditions are more likely to develop disordered eating [24], and this is common in CF [25].

Maintaining a positive and supportive relationship with the young person is important in facilitating adherence.

Learning points: preventative nutritional advice

- *Infants diagnosed by newborn screening should be breast-fed or receive normal infant formula*
- *Infants presenting with severe growth deficit or meconium ileus will require more specialist intervention*
- *Solid foods should be introduced between 17 and 26 weeks of age and follow a normal weaning pattern*
- *Infants should be fed on a mashed or chopped family diet by the age of 12 months*
- *Regular counselling and advice should reduce the risk of behavioural feeding difficulties*
- *School-age children should be encouraged to learn about their food and enzymes*
- *Adherence difficulties in adolescents are common, and maintaining a positive and supportive relationship will help to reduce the risk or duration*

Management of moderate nutritional deficit

Early recognition and treatment of nutritional deficits is important for optimal outcomes. Addressing nutritional difficulties will require a full clinical review of not only dietary intake, but doses and timing of PERT and, in older children, screening and exclusion of CFRD.

Infants and toddlers

Infants and toddlers demonstrating poor weight gain should have the following assessment undertaken:

- feed and types of solids, amounts and timing
- PERT dose and timing
- stool frequency and description
- UNa–Cr ratio to assess the need for or adequacy of sodium supplementation in infants
- presence of GOR
- feeding behaviour

Control of malabsorption is important to optimise growth; doses of enzymes may need frequent adjustment. Assessing the presence of malabsorption based on stool description alone can be difficult; however, the presence of frequent stools with a large intake of feed per kilogram body weight, frequent feeds or meals and snacks in toddlers and inadequate weight gain would indicate that the enzyme dose needs to be increased.

Creon Micro, the enzyme preparation most commonly used in infants and toddlers, is vulnerable to the effects of gastric acid, and, in some infants and toddlers, it is difficult to control malabsorption despite a dose of Creon Micro of ≥10 000 units lipase/kg. The use of an H2 antagonist or PPI to suppress gastric acid secretion may be helpful in these situations.

Growth failure may also be due to sodium depletion; UNa–Cr should be measured in infants and sodium supplementation started or adjusted as necessary.

Significant GOR will result in growth failure and should be managed appropriately (p. 133).

Inadequate feed intakes should be addressed, and advice given on the timing and volumes to offer. Some infants will require a nutrient-dense formula to achieve adequate weight gain (Table 1.18). These are approved by the Advisory Committee on Borderline Substances (ACBS) for prescription in the community in the UK for faltering growth.

School-age children and adolescents

High energy diet

When there is poor weight gain, the dietary intervention should be 'food first'.

The energy density of the diet should be increased by the use of high fat foods, ideally offering unsaturated fats as well as saturated fats, offering small frequent meals with high energy mid-meal snacks and increasing the intake of full-fat dairy foods. The following is suggested:

- foods fried in unsaturated oils
- increased use of unsaturated spreads on bread and added to vegetables
- use of nut butters or ground nuts
- increased use of full-fat dairy foods
- addition of a high energy dessert after the main meal
- offering snacks between meals such as cheese, nuts, dried fruits, boiled egg, cereal bars, flapjacks and crisps

Oral nutritional supplements

If weight gain remains poor despite increasing the energy intake of the diet, optimising PERT, addressing eating behaviour and excluding CFRD, then oral nutritional supplements (ONS) should be offered (Table 12.5). A Cochrane review [26] demonstrated that the use of ONS should not be considered routine in the nutritional management of CF; although it is effective for some, there is a lack of consistent evidence of their efficacy.

In clinical practice ONS are often used and should be prescribed on an individual basis, and their efficacy assessed regularly. Ideally, they should be used as a short-term measure to address poor nutritional intake and stopped as soon as practical to avoid over-reliance and taste fatigue. They may be particularly helpful during acute illness to prevent weight loss. The quantity and timing of ONS is important, and they should not be given to replace meals, but as a supplement to meals.

Learning points: moderate nutritional deficit

- *Control of malabsorption, GOR and sodium depletion is important in the management of poor weight gain*
- *In infants, increased frequency of feeds or introduction of a nutrient-dense formula may be necessary*
- *A high energy diet should be encouraged in all children with poor weight gain using unsaturated fats where possible*
- *Oral nutritional supplements may be helpful; however, their efficacy should be regularly assessed, and they should be discontinued if not effective or once nutritional aims have been achieved*
- *ONS should not be used as a meal replacement, but may be helpful during acute illness to reduce weight loss*

Management of significant nutritional deficit

If nutritional status is deteriorating, or not improving, despite a high fat high energy diet and ONS being taken, then ETF should be commenced. It is widely used in CF to improve weight gain and growth; around 31% of all people with CF receive supplementary feeding via nasogastric (NG) or gastrostomy (G) tube [1].

There are a number of non-randomised studies that demonstrate the use of ETF to improve weight gain [27–30] and to stabilise or slow the rate of decline in lung function [28, 31]. Early intervention in correcting nutritional deficits is important to improve outcome, so ETF should be considered early in care where there is a worsening of nutritional status.

Routes of feeding

The route of feeding should be the choice of the patient and family unless there are contraindications to the use of any

Table 12.5 Oral nutritional supplements.

	Manufacturer	Energy (kcal)	Energy (kJ)	Protein (g)	Fat (g)	CHO (g)	Fibre (g)
Fortified ready-to-feed milkshake style ONS (per 100 mL)							
Altraplen Compact	Nualtra	240	1008	9.6	9.6	28.8	0
Aymes Complete	Aymes	150	630	6	6	18	0
Ensure Compact	Abbott	240	1008	10.2	9.35	36	0
Ensure Plus Milkshake Style	Abbott	150	632	6.25	4.9	20.2	0
Ensure Plus Yoghurt Style	Abbott	150	632	6.25	4.92	20.2	0
Frebini Energy Fibre Drink	Fresenius	150	630	3.8	6.7	18.75	1.1
Fresubin Energy	Fresenius	150	630	5.6	5.8	18.8	0
Fortini	Nutricia	153	630	3.3	6.8	18.8	0
Fortini Compact Multifibre	Nutricia	240	1005	5.7	10.9	28.5	2.4
Fortini Multifibre	Nutricia	150	630	3.4	6.8	18.8	1.5
Fortini Smoothie	Nutricia	150	640	3.4	6.4	19.0	1.4
Fortini 1.0 Multifibre	Nutricia	100	420	2.4	4.5	11.8	1.5
Fortisip	Nutricia	150	625	5.9	5.8	18.4	0.3
Fortisip Compact	Nutricia	240	1010	9.6	9.3	29.9	0
Fortisip Yoghurt Style	Nutricia	150	640	5.9	5.8	18.7	0
PaediaSure	Abbott	101	422	2.8	4.98	11.2	0
PaediaSure Compact	Abbott	240	1007	6.72	11.9	26.2	0.73
PaediaSure Plus	Abbott	150	628	4.2	7.47	16.7	0
PaediaSure Plus Fibre	Abbott	152	635	4.2	7.47	16.4	1.1
Resource Energy	Nestle	150	630	5.6	5	21	<0.5
Resource Junior	Nestle	150	631	3	6.2	21	0
Powdered high energy milkshake style ONS (estimated per 100 mL reconstituted milkshake)							
Aymes Extra Shake	Aymes	196	820	4.2	10.4	21.6	0
Foodlink Complete	Nualtra	159	671	8.8	6.3	17	0
Scandishake	Nutricia	195	820	4	9.8	9.9	0
Juice style ONS (per 100 mL)							
Ensure Plus Juce	Abbott	150	638	4.8	0	32.7	0
Fortijuce	Nutricia	150	635	3.9	0	33.5	0
Fresubin Jucy	Nestle	150	630	4	0	33.5	0
PaediaSure Plus Juce	Abbott	150	638	4.2	0	33.3	0
Fortified semi-solid supplements (per 100 g)							
Aymes Creme	Aymes	150	632	7.5	4.9	19.0	0
Ensure Plus Crème	Abbott	137	574	5.68	4.47	18.4	0
Fresubin 2 kcal Creme	Fresenius	200	840	10	7.8	22.5	0
Forticreme Complete	Nutricia	160	675	9.5	5	19.2	<0.5
Fortini Creamy Fruit	Nutricia	150	630	3.5	6.1	19.4	1.9
Nutricreme	Nualtra	180	756	10	7.2	18.8	0
Glucose polymers (per 100 g/100 mL)							
Liquid Polycal	Nutricia	247	1050	0	0	61.9	0
Polycal Powder	Nutricia	384	1630	0	0	96	0
Super Soluble Maxijul Powder	Nutricia	380	1615	0	0	95	0
Vitajoule Powder	Nestle	380	1615	0	0	95	0
High energy low volume liquid ONS (per 100 mL)							
Calogen	Nutricia	450	1850	0	50	0.1	0
Fresubin 5 kcal Shot*	Fresenius	500	2100	0	53.8	4	0.4
Pro-Cal Shot*	Vitaflo	334	1385	6.7	28.8	13.4	0
Fat and carbohydrate powder energy supplement (per 100 g)							
Duocal Powder	Nutricia	492	2061	0	22.3	72.1	0

* Not suitable for children <3 years.

particular route, e.g. the presence of gastric varices in CFLD may preclude the use of a G device. NG and G tubes are the most commonly used route of feeding. Nasojejunal and gastro-jejunal feeding can be considered in the presence of severe GOR.

Nasogastric feeding

NG feeding is usually considered a less permanent choice of feeding than other routes and is preferred by some children and young people. With concerns about their body image, some choose to remove the feeding tube for special events; some may even remove the tube daily, with replacement of the tube each night prior to commencing feeding. This needs considerable motivation to be successful. NG feeding may also be used for short episodes of feeding, such as during inpatient admissions for IV antibiotics, or to support recovery of weight following acute illness.

NG feeding tubes may be easily dislodged during coughing or vomiting and, therefore, may not be suitable for all patients. NG feeding can cause nausea, vomiting, disturbed sleep and negative changes in body image.

Local hospital policies and national guidance should be adhered to when introducing NG tube feeding.

Gastrostomy feeding

G feeding is the preferred route of feeding for many patients who require long-term ETF. Like NG feeding it can cause nausea, vomiting, disturbed sleep and negative changes in body image, although most complications are mild and short term.

Local hospital feeding policies and national guidance should be adhered to when commencing G tube feeding.

Choice of feed and administration

Most patients with CF will tolerate a high energy paediatric polymeric 1.5 kcal (6 kJ)/mL feed, with or without fibre (Table 4.3), given as a continuous infusion via an enteral feeding pump. Occasionally patients may fail to tolerate these feeds, and, in this situation, a hydrolysed protein (semi-elemental) or amino acid-based (elemental) feed can be considered (Tables 8.20), although the need for these is rare.

Administration of pancreatic enzymes with tube feeding

Pancreatic enzymes will be required with polymeric, protein hydrolysate or amino acid-based feeds. Feeds with a high medium chain triglyceride (MCT) content should be used (Table 8.20). The dose and the timing of PERT should be considered individually, taking into account the choice of feed, rate of infusion and usual enzyme requirement. Enteric-coated enzymes should be given orally and not put down the feeding tube due to the risk of blockage.

Feeds given slowly over a long period of time, e.g. overnight, may need less enzyme than those given as a bolus due to the slower infusion rate of fat.

For feeds given overnight, enzymes are usually given orally as a split dose at the start and end of the feed, although if there are signs of malabsorption using this method a smaller third dose can be given midway through the feed. The impact of disturbing sleep should be considered and children should not be woken to give enzymes.

For bolus feeds, given over a short period of time, enzymes may be given at the start of the feed only.

Other considerations

Following initiation of ETF, weight, height, BMI and abdominal symptoms should be monitored, and the feeding and enzyme plan adjusted as necessary, with the aim of increasing lean body mass, not just adipose tissue. Weight gain, therefore, should not be too rapid.

Glucose tolerance should also be carefully monitored on commencement of ETF to ensure it has not resulted in nocturnal hyperglycaemia. Blood glucose levels should be checked mid- and post-feeding and ideally repeated monthly at home with insulin being commenced if required.

Learning points: significant nutritional deficit

- *Enteral tube feeding should be introduced in patients who are failing to reach optimal BMI, despite the use of a high energy diet and ONS*
- *The choice of feeding tube and timing of feeds should be agreed for the individual child*
- *Sterile ready-to-use high energy age-appropriate polymeric 1.5–2.0 kcal (6–8 kJ)/mL feeds are suitable for the majority of patients*
- *Pancreatic enzymes should be administered with feeds; the timing and dose should be determined individually*
- *The rate of feeding and volume administered should be adjusted to ensure accrual of lean body mass; therefore, weight gain should not be too rapid*
- *Blood glucose measurements should be done at the start and midway through the feeding period to check for nocturnal hyperglycaemia; this should be repeated monthly at home*
- *Nocturnal hyperglycaemia should be treated with insulin under the guidance of a diabetes team*

Vitamins and minerals

Fat-soluble vitamins

Children with PI are at risk of malabsorption of fat-soluble vitamins, with evidence of biochemical deficiency in infants at the time of diagnosis by newborn screening [32–35]. Factors contributing to deficiencies include:

- fat malabsorption and bile salt deficiency
- suboptimal dose or poor adherence to PERT
- poor dietary intake
- inadequate dosing or poor adherence to fat-soluble vitamin supplements

- increased utilisation and poor bioavailability
- short bowel syndrome due to previous resection
- cystic fibrosis-related liver disease (CFRLD)

Avoidance of fat-soluble vitamin deficiency is important, not just in the context of overt deficiency symptoms, but in the avoidance of subclinical deficiency, which is important for optimal health outcomes.

Fat-soluble vitamin levels should be measured in all children annually. Ideally these should be done in a fasting state; however, for practical reasons, this is often not possible in paediatric patients.

Most patients with PI will require supplementation that should be taken with food and PERT to optimise absorption. Patients who are PS should be monitored closely as some will also require supplementation, despite having pancreatic function within normal limits.

Vitamin A

Vitamin A plays a role in retinal health. Low levels can result in night blindness and proceed to xerophthalmia. Vitamin A also has a role in maintenance of mucus-secreting epithelial cells and is an antioxidant. There are many reports of night blindness in CF, with both conjunctival xerosis and night vision problems reported [36]. Close monitoring and attention to maintaining normal serum levels will prevent the development of symptoms of deficiency.

Vitamin A is absorbed in the small intestine and circulates in the serum, attached to retinol binding protein (RBP). It is stored in the liver as retinol esters and serum retinol levels reflect body stores only when liver stores are severely depleted or extremely high. Serum retinol levels should be used as a guide only; however, they are the only practical assessment in the clinical setting.

Vitamin D

Dietary sources of vitamin D do not contribute significantly to vitamin D status. Exposure of 7-dehydrocholesterol present in the skin to sunlight or UV irradiation produces vitamin D3 (cholecalciferol), which impacts more on serum vitamin D levels than dietary intake. In the UK, vitamin D production usually occurs only between April and October.

Vitamin D deficiency causes rickets in children, and low levels are a contributing factor in the low BMD seen in CF. Low serum levels of 1,25-dihydroxyvitamin D increase production of parathyroid hormone (PTH), resulting in increased bone turnover and bone loss.

Vitamin D deficiency is prevalent in CF and is due to:

- reduced absorption of vitamin D due to PI
- low BMI leading to reduced ability to store vitamin D in adipose tissue
- reduced levels of vitamin D binding protein
- impaired hydroxylation in the liver
- reduced exposure to sunlight due to ill health

Vitamin D status is positively associated with lung function [37–40].

Vitamin E

Vitamin E acts as an antioxidant reducing the effect of free radicals, produced as a result of infection and inflammation, and helping to protect the cells from oxidative damage. Low levels of vitamin E have been identified in newborn screened infants, irrespective of pancreatic function [41], and vitamin E deficiency has been associated with haemolytic anaemia in infants [42], it may cause ataxia and neuromuscular degeneration [43], and it may impact cognitive function.

Vitamin K

Vitamin K plays a role in blood clotting and bone health. Deficiency can result in bleeding and may contribute to low BMD. Studies show that subclinical deficiency of vitamin K is common in CF [44, 45], and it is now recommended that all patients with CF receive a daily vitamin K supplement. This is a change in practice from that advised in previous nutritional consensus guidelines. Evidence from randomised controlled trials on the benefits of routine vitamin K supplementation for people with CF is currently weak and limited to two small trials of short duration. However, no harm was found, and until further evidence is available, the present recommendations should be adhered to [46].

The monitoring, toxicity and supplementation of fat-soluble vitamins are given in Tables 12.6 and 12.7.

Sodium and fluid intake

There is a risk of sodium depletion in CF as a result of increased losses in sweat, the risk increasing during hot weather and during exercise. Infants are also at risk due to their high surface area relative to body weight and low intake of sodium from breastmilk or formula feeds.

Sodium depletion will result in hyponatraemia, decreased appetite, nausea, vomiting, lethargy, headaches, muscle cramps and suboptimal weight gain in infants [47]. Hyponatraemia may also contribute to thicker secretions in both the lungs and bowel and may contribute to the development of DIOS [48].

In routine clinical practice, UNa–Cr should be used to assess sodium status, and supplementation given or adjusted if levels are abnormal.

Urinary sodium in isolation may be used as an approximation of status, and levels <30 mmol/L require supplementation to reduce the risk of hyponatraemia and low weight gain in infants.

All children with CF should be encouraged to have a high salt diet. Salt should be used in cooking, added to foods at the table, and salty snacks and food should be encouraged. Sodium-supplemented sports drinks may be useful. A high fluid intake should also be encouraged, especially for those requiring additional sodium supplements.

Infants

The need for supplementation should be assessed on an individual basis, taking into account sodium losses and climate. Those at risk or with low UNa–Cr should be supplemented with 1–2 mmol Na/kg daily, divided into 2–4 daily doses, added to feeds.

Table 12.6 Monitoring, toxicity and supplementation of fat-soluble vitamins.

Vitamin	Monitoring	Toxicity	Supplementation
A	Annually during a period of stability and not during an acute exacerbation. Samples should be processed promptly and protected from light to avoid degradation. If levels are low RBP, zinc and a marker of infection should be measured (e.g. CRP) as levels of vitamin A may be falsely depressed in acute infection and inflammation and in children with liver disease	Acute toxicity causes vomiting, abdominal pain, anorexia, blurred vision, headaches and irritability. Chronic toxicity causes headaches, muscle and bone pain, ataxia, alopecia, liver toxicity and dyslipidaemia	Retinol is the preferred source, starting with a low dose and increasing according to serum levels
D	Serum 25-hydroxyvitamin D levels should be measured. This need not be a fasting sample; however, seasonal variation should be taken into account when interpreting the results		There is evidence that vitamin D3 (cholecalciferol) is more effective than ergocalciferol at sustaining adequate serum levels [36]
E	Serum vitamin E levels represent only a proportion of total vitamin E, which is found mostly in cell membranes. Serum levels will vary according to levels of carrier lipoproteins so vitamin E concentrations should be reviewed in relation to serum lipid levels, which requires a fasting sample. A minimum ratio of α-tocopherol to cholesterol of 5.4 mg/g has been suggested	Hypervitaminosis E is rare and occurs only when large supplementary doses are given. It may result in bruising and bleeding and increased prothrombin time	Supplementation should be started in patients who are PI and in patients who are PS if low serum levels are seen. Supplements should be taken with food and PERT
K	Plasma vitamin K levels and deranged prothrombin time are both unreliable and insensitive markers of vitamin K status. The most reliable measure of is protein induced by vitamin K absence (PIVKA II). This is not routinely available in clinical practice and it is, therefore, difficult to routinely assess status		Vitamin K1 (phytomenadione) is considered the safest form to use. Routine supplementation is recommended for all patients who are PI

RPB, retinol binding protein; CRP, C-reactive protein; PI, pancreatic insufficient; PS, pancreatic sufficient; PERT, pancreatic enzyme replacement therapy.

Table 12.7 Recommendations for supplement doses of fat-soluble vitamins.

Vitamin	Daily supplement
Vitamin A	
<1 year	<1500 IU (0.45 mg)
>1 year	1500–10 000 IU (0.45–3.0 mg)
Vitamin D	
<1 year	400–2000 IU (10–50 µg)
>1 year	400–5000 IU (10–125 µg)
Vitamin E	
<1 year	40–80 IU
1–3 years	50–150 IU
4–7 years	150–300 IU
8–18 years	150–500 IU
Vitamin K	
<2 years	300 µg/kg
2–7 years	5 mg
>7 years	5–10 mg

Source: Adapted from www.cysticfibrosis.org.uk

Older children

Supplementation should be given:

- in hot weather
- if there are excessive GI losses, such as stoma losses or prolonged diarrhoea

Table 12.8 Recommendations for sodium supplementation [49].

Age	Daily sodium supplementation
0–12 months	1–2 up to 4 mmol/kg in those with increased losses
>1 year	Up to 4 g in divided doses
Adolescents	Up to 6 g in divided doses

- when dietary intakes are low
- before strenuous exercise
- during episodes of pyrexia
- when there is excessive sweating

Sodium supplements can be added in a liquid form to infant formula and expressed breastmilk or into fruit squash or fruit juice for toddlers. Sodium tablets are usually prescribed for older children and young people. Recommendations for sodium supplementation are given in Table 12.8.

Calcium

A number of factors affect calcium balance in CF including:

- malabsorption and increased faecal loss
- inadequate intake
- glucocorticosteroid treatment
- increased gastric acid reducing the solubility of calcium salts

Calcium deficiency will result in bone demineralisation and low BMD is a common feature in adults with CF. A high

Table 12.9 Recommendations for calcium intake.

Age	Daily calcium intake (mg)
0–6 months	210
7–12 months	270
1–3 years	500
4–8 years	800
9–18 years	1300

Source: Adapted from www.cysticfibrosis.org.uk

calcium intake is a positive predictor of bone health in adolescents with CF [45].

Intake of calcium is generally good; however, due to the factors affecting calcium absorption, a high calcium intake is advised, particularly during adolescence.

Individuals with a high intake of milk in addition to enteral feeds or calcium supplements may exceed the safe upper limit of 1500 mg/day for the healthy population. Calcium requirements in CF are higher; however, extremely high intakes should be monitored and reduced if possible. Recommendations for calcium intake are given in Table 12.9.

Learning points: calcium

- *A high intake of calcium should be encouraged for all, especially adolescents*
- *A diet rich in milk and dairy produce should be encouraged throughout childhood; intake should be assessed at each review*
- *Calcium supplements should be prescribed if dietary intakes are suboptimal*

Zinc

Zinc deficiency can result in growth retardation in children, poor appetite and impaired immune function and should be considered in children with poor oral intake and suboptimal growth. Low serum zinc levels can also contribute to secondary vitamin A deficiency, as it is required for the synthesis of RBP [50].

Fasting plasma zinc levels are the most sensitive marker of deficiency and should be assessed in those where zinc deficiency is considered, such as those with poor growth or poor oral intake. Individuals with low serum zinc levels should receive oral supplementation to correct deficiency. The North American CF Foundation recommends 1 mg zinc/kg daily in children under 2 years of age who are not growing despite a high energy intake and control of malabsorption [51].

Magnesium

Risk factors for magnesium deficiency include treatment with *N*-acetylcysteine (to treat abdominal symptoms) and diatrizoate sodium powder or Gastrografin (to treat DIOS) [52], CFRD [53] and use of PPI [54].

Serum magnesium levels should be monitored annually, and individuals identified as having low serum levels should be prescribed supplementation.

Iron

Iron deficiency is common in CF and risk factors include:

- malabsorption
- low dietary intake of iron rich foods
- chronic infection and inflammation
- use of PPI
- blood loss due to haemoptysis or GI losses

Iron status should be assessed annually and supplementation prescribed in those with low serum iron levels. All patients should be counselled regarding an adequate dietary intake of iron [49].

There have been concerns regarding iron supplementation in CF as iron can increase the virulence of bacteria, and studies suggest that increased iron may facilitate infection with *Pseudomonas aeruginosa* [55]. A randomised double-blind placebo-controlled study in which a trial of low dose ferrous sulphate was given daily for 6 weeks did not identify an increase in respiratory exacerbation or sputum microbiome [56, 57].

Water-soluble vitamins

Water-soluble vitamins are well absorbed and routine supplementation is not required.

Essential fatty acids, probiotics, antioxidants

There is no firm evidence for routine supplementation with antioxidants, essential fatty acids or probiotics in CF, and further research is required before recommendations can be made.

Case studies

A case study describing the dietetic management of an infant who screened positive for CF with newborn screening is shown in Table 12.10. A case study of a boy with significant nutritional deficit is shown in Table 12.11.

Co-morbidities

Cystic fibrosis-related diabetes

CFRD is a common co-morbidity with around 12% of children between 10 and 15 years requiring treatment, rising to around 34% of adults. The diagnosis of CFRD reduces life expectancy by an estimated of 10 years, and there is often a decline in nutritional status and respiratory function during the year prior to diagnosis [58]. CFRD shares clinical features of both type 1 and type 2 diabetes; however, it is a distinct condition [59].

Table 12.10 Case study: an infant screened positive for cystic fibrosis.

At diagnosis
A female infant 16 days old. Second child of a school teacher and an IT consultant. Older sister aged 3 years old has no medical history.
Remains under midwife care as not yet regained birthweight.
Genetics: dF508 homozygous.
Birthweight = 3.1 kg (25th centile)
Assessment
Anthropometry
Weight = 2.89 kg (2nd–9th centile) Length = 51 cm (9nd centile)
Head circumference = 36 cm (50th–75th centile)
Feeding and stools
- Breastfeeding approximately 12 times per day, feeding well at most feeds from both breasts
- 6–8 loose, yellow stools per day with visible oil

Nutritional diagnosis
- Nutritionally compromised: not regained birthweight by 14 days
- Potential for catch-up growth: head circumference centile is higher than weight and length centiles
- Malabsorption: weight loss despite frequent feeding; oily, yellow offensive stool, therefore, likely pancreatic insufficient

Management plan
PERT
- Check pancreatic function; send stool for FPE-1
- Initiate PERT based on clinical symptoms of weight loss, malabsorption, frequent stool, excessive feeding and genetics indicative of PI. This will prevent further weight faltering while waiting for FPE-1 result
- PERT dosage: ¼ scoop of Creon Micro approx. 1250 units lipase per feed, 8500 units lipase/kg
- Practical PERT advice:
  - Put Creon Micro granules on top of a drop of formula/EBM on baby weaning spoon
  - Advise not to give Creon Micro granules dry because there is a risk of inhalation
  - Give parental reassurance about dosing of Creon Micro; the scoop provided is small to allow gradual increase of dose, but precision can be difficult and it takes practice to master
  - Give parental reassurance that it is expected that feed volumes taken may reduce and stool consistency, colour and frequency may change

Feeding
- Assess attachment and positioning during a breastfeed and direct to local breastfeeding support networks if further help is needed
- Give parental reassurance that many babies with CF can successfully breastfeed. There is no need to change to infant formula or express breastmilk to enable assessment of fat intake

Micronutrients
- Provide family with fat-soluble vitamins that may be started at home before the next clinic visit, with either a home visit or telephone advice from the CF MDT; this is part of a staged introduction of CF treatments
- Check UNa–Cr to assess the need for sodium supplementation

Monitoring/follow-up
- Weekly weighing; this can be with community agencies such as the health visitor or with the CF nursing team
- Weekly telephone contact with the family to assess feeding pattern, weight gain, stool consistency and frequency, dose of PERT needed
- Increase Creon Micro by ¼ scoop per feed during phone contact if indicated by ongoing malabsorption symptoms to a maximum dose of 10 000 units lipase/kg
- Review in CF clinic appointment in 2 weeks

At second clinic visit
Infant is now 1 month old
Assessment
Anthropometry
Weight = 3.3 kg (9th centile) Length = 51 cm (9th centile)
Head circumference = 36.8 cm (50th–75th centile)
Feeding and stools
- Breastfeeding – 8 feeds per day, feeding well at most feeds from both breasts
- 4 large orange stools, mousse like consistency

PERT
- ½ scoop of Creon per feed (2500 units lipase per feed, 6250 units lipase/kg)

Biochemistry
- Urinary Na: <20 mmol/L

Nutritional diagnosis
- Nutritional status improving
- Malabsorption improved: stools less frequent, darker and less liquid. Feeding has also reduced because nutrients are being absorbed and utilised. However, stools remain abnormal
- Low urinary sodium levels

(continued overleaf)

Table 12.10 *(continued)*

Management plan
PERT
- Increase Creon to ¾ scoop per feed (3750 units lipase per feed, 9375 units lipase/kg), based on stool frequency and appearance and to promote further catch-up growth

Micronutrients
- Start sodium supplementation 2 mmol/kg, e.g. 3 mL BD 1 mmol/mL NaCl solution
- Practical advice for sodium solution:
  - Put in a bottle of EBM/formula, it can be given in one dose per day if tolerated
  - NaCl can be given undiluted via syringe, but this is not well tolerated and often causes vomiting

Monitoring/follow-up
- Continue weekly weighing in the community to monitor nutritional recovery closely
- Continue weekly phone contact to assess bowel symptoms and feeding pattern, increase Creon dose by ¼ scoop if indicated (to a maximum 10 000 units lipase/kg).
- Review at clinic appointment in 1 month

At third clinic visit
Infant is now 2 months old
Assessment
Anthropometry
Weight = 4.5 kg (9th–25th centile) Length = 55.2 cm (9th–25th centile)
Head circumference = 38.5 cm (50th–75th centile)
Feeding and stool history
- Taking fewer feeds – 6 breastfeeds per day, feeding well at most feeds from both breasts plus one bottle of EBM with added NaCl
- 2–3 orange/light brown pasty stool per day

Biochemistry
- UNa–Cr ratio: 42
- Vitamin A: 1.3 µmol/L (0.7–1.5 µmol/L), Vitamin E: 16.2 µmol/L (7–21 µmol/L), Vitamin D: 78 nmol (>50 nmol/L), figures in brackets normal range

PERT
- 1¼ scoop Creon Micro per feed (6250 units lipase per feed, 8578 units lipase/kg)
- Consider giving it in fruit purée instead of formula/EBM, as it holds granules in a gel so is easier to give

Nutritional diagnosis
- Nutritional status recovering
- Malabsorption significantly improved and excessive feeding reduced
- Sodium status normalised
- Serum vitamin levels normal

Management plan
- No vitamin adjustments needed
- Continue sodium supplementation, maintain dose at 1–2 mmol/kg, will need adjusting with weight gain
- Increase Creon Micro: 1½ scoops (7500 units lipase per feed, 10 290 units lipase/kg)

Monitoring/follow-up
- Reduce frequency of weight measurements and telephone reviews with the family because weight gain is recovering and PERT does not need adjusting as frequently

At seventh clinic visit
Infant is now 6 months old
Assessment
Anthropometry
Weight = 7.3 kg (50th centile) Length = 63 cm (25th centile)
Head circumference = 42.5 cm (50th–75th centile)
Feeding and stool history
- 4 breastfeeds per day, feeding well at most feeds from both breasts plus one bottle of EBM with added NaCl
- 2 meals of a variety of fruit and/or vegetable purée with some finger foods
- 2 light brown, soft, large stools

PERT
- 2 scoops Creon Micro per breast or bottle feed (10 000 units lipase per feed, 7024 units lipase/kg)

Nutritional diagnosis
- Nutritional status recovered
- Malabsorption improved and feeding reduced

Management plan
- Introduce fat-containing solids, e.g. meat, dairy, egg – appropriate textures
- ½ scoop Creon Micro with fat-containing solids
- Give parental reassurance that stool appearance and frequency may change with the introduction of solids, discuss signs of malabsorption and encourage parents to contact dietitian by telephone if concerned

Monitoring/follow-up
- Telephone call to parents 2 weeks after clinic to advise:
  - Titration of Creon Micro if indicated by symptoms of malabsorption
  - Progression of normal weaning
  - Review in clinic in 1 month

PERT, pancreatic enzyme replacement therapy; FPE-1, faecal pancreatic elastase; PI, pancreatic insufficient; EBM, expressed breastmilk; UNa–Cr, urinary sodium–creatinine ratio; BD, twice daily.

Table 12.11 Case study: a boy with cystic fibrosis with significant nutritional deficit.

A 9-year-old male
He lives with mum, a homemaker, and dad, a finance officer. No siblings
Genetics: Homozygous delta F508
Diagnosed by newborn screening, weight was faltering at diagnosis with his weight 2 centiles below his length. Good catch-up growth was achieved by 12 months and his weight tracked on 50th centile from then, with his height around 25th–50th centile
The CF MDT have no concerns around his CF treatment compliance. Unable to increase oral intake due to poor appetite and dislike of ONS
Lung function (FEV1) is stable around 100% predicted; no recent clinically significant pulmonary exacerbations

Assessment
- Baseline lung function (FEV1) stable: 103% predicted
- Static weight = 23 kg (9th centile) for 9 months, previously had a slow decline from 50th to 25th centile over 12 months
- 12 months ago: BMI = 25th–50th centile, 18 months ago BMI = 50th percentile, current BMI = 9th centile
- Oral nutritional strategies have been maximised, including food fortification
- Poor tolerance of ONS, currently taking 60 mL Pro-Cal Shot daily, providing 200 kcal
- No signs of malabsorption: stools described as normal, type 3 or 4 on Bristol stool chart, brown, once per day (parents agree: not excessively frequent, offensive or difficult to flush)
- No recent clinically significant pulmonary exacerbations
- Recent OGTT normal

Nutritional diagnosis
- Faltering growth despite attempts to maximise oral intake
- No malabsorption
- Glucose tolerance normal – no CFRD

Management plan
- Discuss enteral feeding with family and MDT
- Start nasogastric feeds
- Blood glucose levels should be checked mid- and post-feeding and repeated monthly at home with insulin being commenced if required

Calculating feed regimen
- EAR energy = 63 × 23 = 1449 kcal
- Aim to give approximately 50% energy using overnight feed = 725 kcal/day (500 mL standard age-appropriate energy fibre containing feed)

Calculating enzymes dose
- Feed contains 6.3 g fat/100 mL (aiming for 500 mL of feed) = 6.3 × 5 = 31.5 g fat in total feed volume
- Estimate PERT dose from average of patient's usual enzyme dosing 1 Creon 10 000 capsule/5 g fat therefore 31.5 ÷ 5 = 6.3 = 6 Creon 10 000 capsules in total

Feeding plan:
Tentrini Energy Multifibre: 55 mL/hour × 9 hours
Creon 10 000: 4 capsules at the start and 2 capsules at the end/on waking

Initial monitoring
- Stool consistency: check for any changes indicating malabsorption
- Feed tolerance: ensure no new reporting of vomiting, abdominal pain, diarrhoea or other signs of feed intolerance

Follow-up
- Check weight 1 month post-discharge; this can be in community, e.g. GP surgery or community nurse, to ensure nutritional recovery
- Review in CF clinic review every 2 months with full nutritional assessment

At 6 month clinic review

Assessment
Weight = 28.4 kg (25th centile) Height = 131.2 cm (9th centile) BMI = 50th–75th centile

Nutritional diagnosis
- Achieved catch-up growth. Can now aim for normal growth along centile

Management plan
Reduce feeds to 5 nights per week
- Likely to need long-term enteral feeding to maintain optimal nutritional status, discuss option of gastrostomy

MDT, multidisciplinary team; ONS, oral nutritional supplement; BMI, body mass index; OGTT, oral glucose tolerance test; CFRD, cystic fibrosis-related diabetes; EAR, estimated average requirement; PERT, pancreatic enzyme replacement therapy.

Table 12.12 Dietary recommendations for CFRD.

Dietary recommendations	Low BMI	BMI 25th–75th centile	Overweight/obese
Complex carbohydrate	Regular intake, include at all meals	Regular intake, include at all meals	Regular intake, include at all meals
Simple sugars	Include at meals, avoid high sugar snacks and drinks	Include at meals, avoid high sugar snacks and drinks	Avoid
Fat	No limit	No limit	Reduce intake
Carbohydrate counting	Consider in those with poor or variable appetite	Consider in those with poor or variable appetite	Consider in those with poor or variable appetite

BMI, body mass index.

The main driver of CFRD is insulin deficiency. Insulin secretion in people with CF appears to decline from childhood, even in individuals with normal blood glucose levels [59]. The insulin response to a glucose load is reduced and delayed, resulting in high glucose levels that can normalise within 2 hours. Basal insulin secretion is usually initially preserved, so fasting levels may remain normal despite a diagnosis of CFRD. Insulin sensitivity is usually normal in CF, but other factors common in CF may cause insulin resistance, e.g. infection, inflammation or systemic corticosteroid use. There is evidence that starting insulin therapy early improves respiratory and nutritional health and reduces the development of diabetes-related complications [58–61].

Collaborative MDT working between CF specialists and diabetes specialists is important to optimise outcomes.

Screening for CFRD

Annual oral glucose tolerance tests (OGTT) are advised for all children over 10 years of age as a screening tool. As significant numbers of children with CF have a degree of impaired glucose tolerance, the standard WHO OGTT may not identify all of those with a degree of impaired glucose tolerance requiring treatment. A 4-point OGTT, with blood glucose measurements taken at T0, T30, T60, T90 and T120, may be a more sensitive screening tool due to abnormalities in insulin secretion.

Abnormal glucose tolerance identified through screening should be followed by serial blood glucose monitoring or continuous glucose monitoring (CGM) (p. 191) to assess the need for treatment.

Treatment

The aim of treatment is to normalise blood glucose levels, to avoid the long-term complications of diabetes and to optimise nutritional status and respiratory function.

Insulin injection is the recommended treatment for CFRD. Control of blood glucose levels has been shown to have a positive impact on respiratory function, nutritional status and mortality [58–62]. Insulin regimens should be individualised, depending on the pattern of hyperglycaemia identified through CGM or serial blood glucose monitoring.

The dietary recommendations for type 1 and type 2 diabetes are not usually appropriate, and advice should be individualised based on nutritional status. Insulin regimens need to be modified for those receiving overnight enteral feeding to optimise glycaemic control at night and may need adjusting to account for patients who do not receive enteral feeding every night. Dietary recommendations for CFRD are given in Table 12.12. A case study describing CFRD is given in Table 12.13.

Learning points: CF-related diabetes

- *Annual OGTT is required to screen for CFRD after 10 years of age*
- *Glycaemic control should be optimised to minimise the impact on nutritional status and respiratory health*
- *Insulin injections are required and the regimen should be individualised based on the pattern of hyperglycaemia*
- *Standard dietetic advice for type 1 and type 2 diabetes is not suitable for CFRD*
- *Dietary advice depends on nutritional status and patterns of eating*
- *MDT working between the CF team and the diabetes team is important for optimal outcomes*

Cystic fibrosis-related liver disease

CFRLD includes fatty liver (steatosis), which is a relatively benign condition with no evidence that it leads onto cirrhosis, and biliary cirrhosis.

The development of steatosis is not linked to a high dietary fat intake, and there should be no dietary restrictions if BMI is either suboptimal or healthy. For patients who have a high BMI, advice should be given to reduce energy and fat intake with the aim of reducing BMI to within the healthy range.

Biliary cirrhosis is a more serious complication leading to portal hypertension in 5%–15% of cases [63–65], and

Table 12.13 Case study: an adolescent boy diagnosed with cystic fibrosis-related diabetes.

A male aged 13.5 years
Lives with mum, a florist, and brother aged 11 years
Genetics: heterozygous DF508 and G542x
Baseline lung function (FEV1% predicted): 75%
Has elective hospital admissions every 4 months for IV antibiotics
Fed via gastrostomy since infancy due to poor oral intake
At the time of review was having an overnight feed four times per week: 800 mL given over 10 hours, 2 kcal/mL (8 kJ/mL) feed

Assessment
- Weight loss of 1.5 kg over 2 months, but gradual decline of 4 kg over the past 9 months
- Weight previously on 75th centile, at time of review just below 50th centile
- BMI dropped from 50th–75th centile to 25th at time of review in 9 months
- Height tracking 75th centile
- Lung function (FEV1% predicted) slowly decreased by approx. 15% (baseline approx. 75%) to 57% over previous 6 months
- No changes in dietary intake, gastrostomy feeds, stool or PERT
- No severe respiratory exacerbations
- No malabsorption symptoms reported
- OGTT 18 months ago was normal
- Overnight hyperglycaemia on routine blood glucose monitoring

Nutritional diagnosis
- Weight faltering despite gastrostomy feeding, adequate PERT management and good oral intake
- Decline in pulmonary and clinical status without significant pulmonary exacerbations or other clinical explanation

Management plan
- To have OGTT

OGTT results:
- 0 minute: 4.5 mmol/mL
- 30 minutes: 11.0 mmol/mL
- 60 minutes: 11.7 mmol/mL
- 90 minutes: 9.0 mmol/mL
- 120 minutes: 7.2 mmol/mL

This is diagnostic of impaired glucose tolerance

Management plan
5-day CGMS to include:
- School and non-school days
- Days with and without overnight gastrostomy feeds

CGM results:
- 23% of readings >7.8 mmol/mL (see Figure 12.2)
- Demonstrating five peaks of >11.1 mmol/mL and other peaks >7.8 mmol/mL following consumption of sweets or full sugar fizzy drinks at morning break, after school and in the evening
- Readings >7.8 mmol/mL overnight, occurring on days on and off overnight gastrostomy feeds, but higher levels and longer duration when on gastrostomy feeds overnight

Joint review with endocrine consultant:
- Initiate insulin, 1 dose of long-acting insulin given in the evening
  - 4 units Levemir when not on gastrostomy feeds
  - 6 units Levemir when on overnight gastrostomy feeds
- Swap full sugar drinks for diet, zero or no added sugar alternatives
- Maximum of one portion of sweets after meals, not to be eaten in isolation
- No other dietary alterations, maintain a high energy diet

Assessment 4 months after start of insulin
- Weight tracking 75th centile (increased by 3 kg)
- Lung function back at baseline (FEV1% predicted: 75%)
- Repeat CGMS after 3 months is normalised (see Figure 12.3)
  - 4% reading >7.8 mmol/mL
  - No peaks >11.1 mmol/mL

IV, intravenous; PERT, pancreatic enzyme replacement therapy; OGTT, oral glucose tolerance test; CGMS, continuous glucose monitoring system.

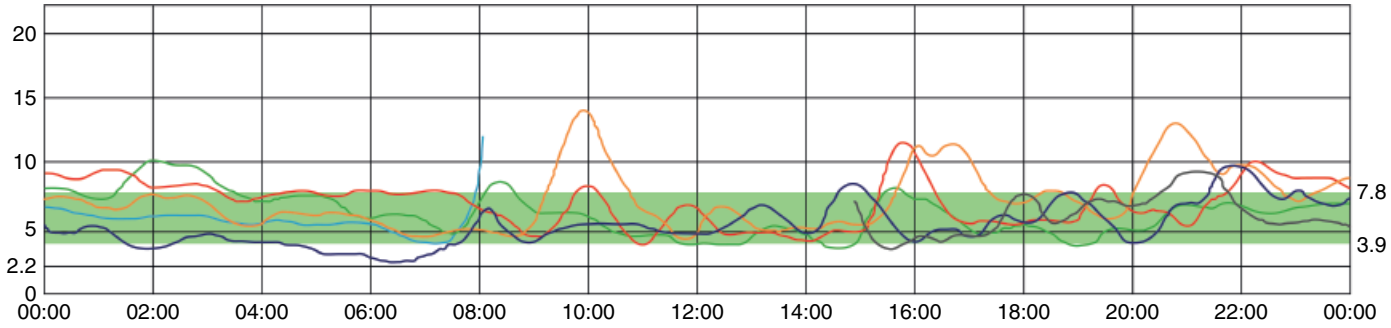


Figure 12.2 Continuous glucose monitoring before insulin started.

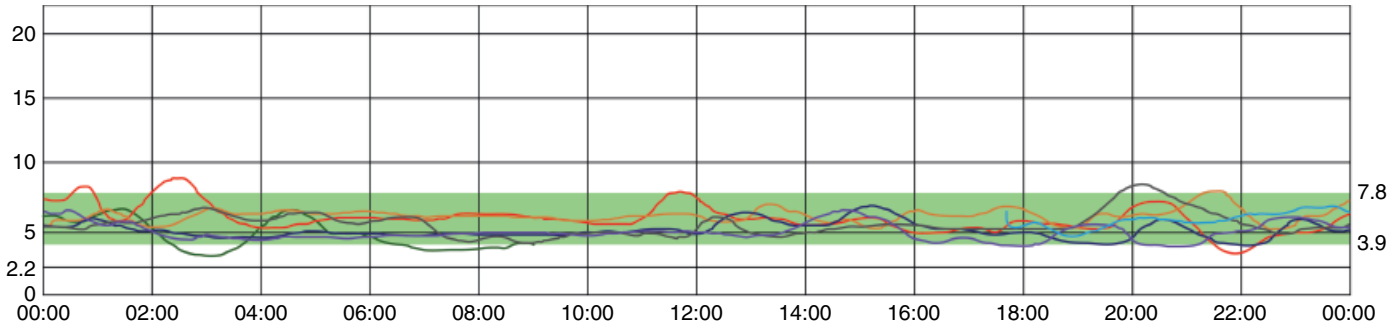


Figure 12.3 Continuous glucose monitoring 3 months after insulin started.

end-stage liver disease is a late complication affecting mainly adults. Data from the 2017 UK CF Registry [1] shows that 7.9% of all CF patients under 16 years of age have evidence of liver disease, with or without portal hypertension.

The only therapeutic option to give ursodeoxycholic acid (p. 180) has been shown to improve serum liver enzymes levels. A small proportion of CF patients will require a liver transplant.

Significant CFRLD may increase energy requirements by a further 20%–40% due to increased fat malabsorption as a result of cholestasis. This will not be improved by changes in PERT, and care should be taken to ensure that pancreatic enzyme doses are not increased inappropriately.

ETF may be required to optimise nutritional status, and advice should be taken regarding the suitability of NG or G feeding devices if oesophageal varices are present. NG feeding may be preferred if there is a risk of gastric varices.

Assessment of nutritional status should be undertaken with care as there may be ascites, oedema or significant organomegaly leading to overestimation of body weight and BMI. Serial mid-arm circumference and triceps skinfold thickness should be measured, ideally by the same observer to reduce error.

Osteoporosis/osteopenia

Patients may develop low BMD through either osteoporosis or vitamin D deficiency osteomalacia. Studies suggest that BMD is normal in well-nourished children with CF with well-preserved lung function, but many patients fail to gain bone mass normally and/or experience premature bone loss in adolescence or early adult life. Osteoporosis affects around 0.7% under 16 year olds, rising to 18.5% in adults [1].

The aetiology of low BMD is multifactorial and major risk factors include:

- overall disease severity, including links to FEV1 (forced expiratory volume in 1 second)
- the frequency and duration of IV antibiotic therapy
- corticosteroid use
- exercise tolerance and levels of physical activity
- DF508 genotype
- CFRD
- delayed puberty

Peak growth velocity is associated with high bone mass accrual, and low BMD in CF is thought to be due to suboptimal peak bone mass accrual during childhood [66]. In healthy populations, peak bone mass accrual occurs at 11.7 years in girls and 13.4 years in boys. Puberty may be delayed in CF, and this is associated with a reduction in bone age and delay in peak height velocity.

There are also nutritional factors:

- nutritional status and lean body mass
- vitamin D status may result in impaired bone mineralisation and increased loss

- vitamin K deficiency may contribute by altering the balance of bone formation and resorption
- calcium intake

Diagnosis of low BMD

European guidelines for bone mineralisation recommend that BMD should be measured in the lumbar spine from around 8 to 10 years of age [67]. Dual-energy X-ray absorptiometry (DEXA) scans should ideally be done in a centre with a clinical team experienced in performing and interpreting bone densitometry in children. These scans should be repeated every 1–5 years; serial measurements will allow for identification of peak bone mass, and this may influence treatment options if premature bone loss occurs.

Recommendations to optimise bone health

Low BMD in adults has its origins in childhood, and factors to optimise bone health should be considered in paediatric care. Dietary factors play a significant role, and it is important that patients are regularly reviewed by an experienced paediatric dietitian with the aim of achieving normal weight, height, body composition, optimal vitamin D and K status and adequate calcium intake.

Weight-bearing physical exercise and safe sun exposure should be encouraged. Children and adolescents should be encouraged to exercise for 20–30 minutes three times per week, and exercises should include high-impact weight-bearing exercises.

Glucocorticosteroid use should be minimised, and CF pulmonary exacerbations should be promptly treated to minimise the systemic inflammatory effect on bone. Pubertal delay should be recognised and treated.

Learning points: bone mineral density

- *Vitamin D levels should be monitored annually and normal serum levels maintained*
- *Advice should be given to optimise calcium intake; supplements may be required in patients who dislike milk and dairy produce*
- *Weight-bearing exercise and exposure to sunlight should be encouraged*

Gastro-oesophageal reflux

GOR is common, affecting around 6% of children with CF [1], and can compromise growth and increase respiratory symptoms. Treatment includes the use of thickened infant formula (p. 133) and reducing gastric acid secretion either with H2 antagonists or PPI, although these should be used with caution [20].

Distal intestinal obstructive syndrome

DIOS is a common complication. It is characterised by accumulation of sticky mucofaecal matter in the terminal ileum and caecum, often presenting as abdominal pain and presence of a right iliac fossa mass. Patients may present acutely with intestinal obstruction with bilious vomiting. It affects mainly patients who are pancreatic insufficient; factors predisposing to DIOS include fat malabsorption and impaired gut motility. Risk factors include poorly controlled malabsorption and dehydration.

Medical management is usually effective in treating the condition and includes rehydration with oral or IV fluids and administration of an osmotic laxative containing polyethylene glycol, administered either orally or via NG tube. In more severe cases Gastrografin enemas may be required, and in very severe cases surgery may be required.

A dietetic review should be done for patients suffering from DIOS to ensure optimal use of PERT and avoidance of dehydration.

Meconium ileus

Around 20% of infants born with CF will present with MI, where the intestine is obstructed with inspissated meconium in the small bowel [1]. It can also be associated with other complications, such as intussusception, volvulus, atresia and perforation.

Management varies according to the severity of obstruction and anatomical changes, from conservative management in the form of bowel washouts to laparotomy; in severe cases bowel resection and formation of a temporary ileostomy may be necessary.

Infants requiring surgery present significant nutritional difficulties, and it is recommended that these be managed in a tertiary CF centre post-operatively. These infants will require a period of parenteral nutrition (PN) until oral or enteral feeds can be introduced. Use of PN is associated with a number of risks in all patients and oral or enteral feeds should be introduced as soon as it is safe to do so. The choice or feed depends on whether a stoma has been formed and the position of the stoma and the extent of any bowel resection. Breastmilk, either as breastfeeds or EBM given orally or by enteral feeding tube, should be encouraged post-operatively. If breastmilk is not available, then an extensively hydrolysed infant formula containing MCT should be considered (Table 8.15).

In conservatively managed infants, breastmilk and standard infant formula are recommended.

Management of MI, either conservative or surgical, may result in suboptimal weight gain, and there may be a requirement to give higher volumes of feed or a high energy formula (Table 1.18) to optimise weight gain and ensure catch-up growth.

MI is associated with PI and all infants presenting with it will require PERT when feeds are introduced. FPE-1 levels in

the stool should be assessed to confirm the requirement; however a sample taken from stoma fluid may be too liquid for analysis.

Supplementation with sodium should be considered in infants with a stoma due to increased losses in stoma fluid.

Learning points: meconium ileus

- *Infants requiring surgery for MI should be managed in a tertiary centre specialising in neonatal surgery and CF*
- *Breastmilk and standard infant formula are recommended for infants managed conservatively*
- *Breastmilk or a hydrolysed protein formula containing MCT should be used in those requiring surgery*
- *Some infants have suboptimal weight gain during the period of management of MI and require increased volumes of feed or a high energy feed to ensure catch-up growth*
- *All infants with MI will require PERT*
- *Sodium supplementation should be considered in all infants, especially in those with a stoma*
- *If there is nutritional deficit, attention should be given to volume and type of feeds to achieve catch-up growth*

Constipation

Constipation should be differentiated from DIOS. It is defined as a reduced stool frequency and increased consistency, often with abdominal pain and distension. The aetiology is unknown, but it may be due to changes in gut motility and intestinal fluid.

There is no consensus on the cause of constipation; a high dose of pancreatic enzymes is often cited, although one study failed to find an association [68] and other studies have shown no association with fibre or fluid intake [69].

Constipation can be effectively treated with polyethylene glycol, which is well tolerated in CF.

Other nutritional considerations

Obesity and overweight

Early diagnosis, improvements in care, and new therapies have resulted in an increasing number of people with CF becoming overweight and obese. Traditionally, overnutrition has been seen in older PS patients, but it is increasingly being seen in PI and paediatric populations [70].

Preventing malnutrition has been the primary focus of nutritional care in CF because of the benefits to lung function and clinical outcomes; however, a large longitudinal study in adults demonstrated that being overweight or obese does not confer additional benefit to lung function [71]. Overweight and obesity have also been shown in a smaller paediatric study where 23% of patients had a BMI above the 90th centile [70]. The evidence is limited currently, but increased longevity may put patients with CF at risk for some of the metabolic complications due to excess body weight seen in the general population.

Individualised advice should be given to prevent excessive weight gain and ensure a well-balanced diet. It is important to ensure that height velocity is not affected by energy restriction in children and aiming for weight maintenance may be preferable before and during the pubertal growth spurt. Effective communication to the families and the wider MDT is essential to prevent conflicting advice about energy needs. It may be useful to counsel early on in treatment that dietary advice may change throughout life.

Learning points: Overweight and Obesity

- *Families should be counselled early on that the aims of dietetic management may change with time*
- *Individualised advice should be given to prevent excessive weight gain, aiming for a healthy BMI*
- *Communication about the aims of dietetic management to the wider MDT is necessary to ensure a consistent message is given*

CFTR modulator therapies

These therapies target the underlying defect in the transmembrane conductance regulator (CFTR) protein. The defect in the protein varies depending on the specific genetic mutations (genotype) that the individual has because the different genetic mutations code for different defects in the protein. This is why each modulator therapy is only effective for specific genotypes.

The two types of modulator therapies currently available are 'correctors' and 'potentiators':

- CFTR potentiators keep the chloride channel on the CFTR protein open so the chloride can pass through to the other side of the membrane.
- CFTR correctors help the CFTR protein to form the correct three-dimensional shape so that it can be trafficked to the cell surface.

Ivacaftor

Ivacaftor (Kalydeco) is a corrector molecule. Due to its mechanism of action, it is licensed for use in patients over 2 years old with one class III mutation, e.g. G551D. This accounts for approximately 6% of UK CF population [1]. It is the longest-standing modulator therapy and has been approved by NICE.

Treatment with ivacaftor has shown significantly decreased sweat chloride, improved lung function (FEV1) and much improved BMI *z*-score in children aged 6–11 years [72]. Similar improvements were seen in weight and sweat

chloride in younger children, and they additionally had an increase in faecal elastase levels [73, 74]. This suggested that starting modulator therapy in younger patients may support the recovery of exocrine pancreatic function, but further investigation is needed.

Lumacaftor/ivacaftor

Lumacaftor/ivacaftor (Orkambi) is a combination therapy containing two active molecules: ivacaftor, a corrector, and lumacaftor, a potentiator. Treatment with Orkambi has demonstrated a small significant increase in BMI *z*-score, lung function (FEV1) (by 2%–4%) and reduction in exacerbations [75, 76]. These improvements were not as substantial as those seen with ivacaftor.

Due to its mechanism of action, Orkambi is licensed in Europe for individuals aged 2 years and over who are homozygous for dF508, approximately 49% of the current UK CF population [1]. NICE has recommended Orkambi for use in the National Health Service.

There are many other modulator therapies currently in production, which offers great promise for future therapeutic options.

Practical nutritional management with modulator therapies

Modulator therapies are given as tablets or granules. They need to be taken twice a day, 12 hours apart, with fat-containing food to optimise the absorption of the drug. There is no specific recommendation for the amount of fat needed, and most families choose to give it at breakfast and a later evening meal, or with a fat-containing snack before bed.

Due to drug nutrient interactions, it is recommended to avoid grapefruit and Seville orange (found in marmalade) when on ivacaftor-containing therapies.

Some centres are choosing to regularly monitor faecal elastase levels in children <6 years of age who are started on modulator therapies.

Due to the significant weight gain in patients seen with some modulator therapies, in well-nourished individuals, weight monitoring and individualised advice to support optimal BMI may be advisable.

Learning points: CFTR modulator therapies

- *Modulator therapies should be taken with fat-containing foods every 12 hours*
- *Weight gain should be monitored and pre-emptive dietary advice given to ensure optimal BMI is maintained, especially in well-nourished individuals*
- *Monitoring faecal elastase levels is advised in younger children, initially at 6 months and then annually after starting therapy or if new abdominal symptoms are described*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

13 Kidney Diseases

Leila Qizalbash, Shelley Cleghorn and Louise McAlister

Acute Kidney Injury and Chronic Kidney Disease

Leila Qizalbash

Introduction

The kidneys play an essential role in the maintenance of homeostasis by excreting waste products, such as urea and uric acid, and purposely adjusting the urinary excretion of water and electrolytes (solute) to counter dietary intake and the body's endogenous production of these from metabolism. The kidneys have a major role in the secretion of hormones. This includes erythropoietin for red blood cell production, renin and angiotensin II affecting renal and systemic haemodynamics and hydroxylated vitamin D affecting calcium, phosphate and bone metabolism. Other functions include peptide hormone catabolism and gluconeogenesis.

A variety of diseases can affect the kidneys leading to a sudden deterioration in renal function (acute kidney injury [AKI]) or an irreversible deterioration of renal function (chronic kidney disease [CKD]). Impairment of excretory, regulatory and endocrine functions is seen as kidney function deteriorates, and the management of these impairments is the foundation of treatment.

Acute kidney injury

The definition of AKI has changed in recent years; it is defined as an abrupt decrease in kidney function that encompasses both injury to the kidney (structural damage) and kidney impairment (loss of function). Diagnosis is now mostly based on monitoring creatinine levels with or without urine output [1]. An incidence of one in three children worldwide experiencing AKI during a hospital admission has been suggested [2]. It is more common for those children requiring intensive care and is an independent risk factor for mortality and severe morbidity [3]. The incidence and causes differ between developing countries and developed countries. Premature infants are also at significant risk of AKI because of high rates of infection and exposure to nephrotoxic medications; however, the exact incidence of AKI in this population is unknown [4]. The causes of AKI in children are classified as pre-renal AKI, intrinsic AKI or obstructive AKI [5, 6] (Table 13.1).

A shift has been seen in the causes of paediatric AKI from primary renal disease, e.g. haemolytic uraemic syndrome (HUS), dehydration and burns to renal ischaemia (often after cardiopulmonary surgery), use of nephrotoxic medications and sepsis [7]. This change could be due to increased severity of illness, more complex treatments and invasive procedures [8].

Management of AKI

The initial management of AKI focuses on the correction of fluid balance and biochemical abnormalities. This includes hyponatraemia, hyperkalaemia and acidosis, which can be life threatening. Further injury to the kidney should be prevented through maintaining adequate blood pressure and avoiding nephrotoxic medication. Transfer to a tertiary nephrology centre is indicated in those children requiring renal replacement therapy (RRT), if they are failing to respond to medical management. Such indications for RRT include [9]:

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 13.1 Causes of acute kidney injury in children [5, 6].

Pre-renal AKI	Intrinsic AKI	Obstructive AKI
Loss of effective blood volume • Absolute losses: haemorrhage gastrointestinal, renal, skin • Relative losses: capillary leak, vasodilation, sepsis, antihypertensives, hypoalbuminaemia ECMO Impaired cardiac output Bilateral renal vessel occlusion Pharmacologic agents, e.g. cyclosporin, diuretics, ACE inhibitors, ARB, indometacin	Renal artery damage Renal vein damage Acute tubular necrosis Interstitial nephritis Glomerular causes • Post-infectious • IGA nephropathy • Membranoproliferative Renal vascular causes • Renal artery thrombosis • Renal vein thrombosis Myoglobinuria Intrarenal obstruction Infections (pyelonephritis) Nephrotoxins Radiation Chemotherapy Tumour infiltrate Lupus HUS	Congenital malformations Imperforate anus Urethral stricture Posterior urethral valves Urethral diverticulum Ureterocoele Megaureter Ureteropelvic junction obstruction Extrinsic compression • Carcinoma Intrinsic obstruction • Calculi • Tumour Neurogenic bladder

ECMO, extracorporeal membrane oxygenation; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; HUS, haemolytic uraemic syndrome.

- hyperkalaemia
- metabolic acidosis
- symptoms or complications of uraemia (pericarditis or encephalopathy)
- fluid overload
- pulmonary oedema
- fluid removal to allow the provision of nutrition [6]

Choice of renal replacement therapy

The selection of RRT in acutely ill children depends upon the availability of treatment modalities, ventilatory support, the patient's requirements for fluid and solute removal and haemodynamic stability. The choice is between peritoneal dialysis (PD), continuous renal replacement therapy (CRRT) and intermittent haemodialysis (IHD). Factors determining the choice of RRT include the desired outcome of therapy and clinical condition of the child as indicated in Table 13.2 [10]. PD is the preferred modality in children as it is well tolerated and there are no rapid fluid shifts. IHD is used when there is an urgent need for solute removal. For the critically ill child in the paediatric intensive care unit (PICU), CRRT is the favoured treatment.

Table 13.2 Indications for choice of renal replacement therapy in acute kidney injury.

Indication for dialysis	Clinical condition	Modality indicated
Solute removal	Stable	HD
	Unstable	CRRT, PD
Fluid removal	Stable	PD, isolated ultrafiltration on HD
	Unstable	CRRT
Solute and fluid removal	Stable/unstable	HD, PD, CRRT
Tumour lysis syndrome	Stable/unstable	HD followed by CRRT
Toxin or drug removal	Stable/unstable	CRRT, IHD for some drugs

HD, haemodialysis; CRRT, continuous renal replacement therapy; PD, peritoneal dialysis; IHD, intermittent haemodialysis.

Nutritional management of AKI

Children with AKI are highly catabolic. This is usually multifactorial manifesting as anorexia. The catabolic nature of the underlying disorder, increased breakdown and reduced synthesis of muscle protein, increased hepatic gluconeogenesis, nutrient losses in drainage fluids or dialysis and impaired access to food can all impact the child's nutritional status. Input from a paediatric dietitian with experience in renal disease is essential from the onset as the dietary prescription varies with clinical management and the stage of the illness [11].

Nutritional support aims to provide sufficient energy to avoid catabolism, starvation and ketoacidosis as well as to control metabolic abnormalities. The provision of nutrition is easier once dialysis is initiated since the fluid removed by ultrafiltration allows larger volumes of feed to be given. Nutritional intervention for children with AKI depends on:

- clinical management: conservative vs. RRT (and modality)
- biochemical assessment: serum levels of sodium, potassium, bicarbonate, urea, creatinine, albumin, glucose,

calcium, magnesium and phosphate should be regularly monitored and reviewed
- cause of AKI including the involvement of other organs
- gastrointestinal functioning
- growth parameters: height (if available) and weight plotted on a growth chart; weight recordings prior to the onset of AKI will help determine a more accurate estimation of dry weight
- dietary history: if the child is eating.

Table 13.3 shows the normal range for serum levels of creatinine.

Methods of feeding

Enteral feeding

The child with AKI may initially take oral fluids readily, driven by thirst. Some children fail to achieve nutritional targets through diet alone. As the duration of the acute illness can be prolonged, the passing of a fine bore nasogastric tube (NGT) is recommended. The tube can be passed at the time of sedation or when anaesthetised for procedures including the insertion of a PD catheter or arterial line [11]. This allows the provision of early nutritional support because anorexia, vomiting or food refusal can impair management and may increase parental anxiety.

A continuous 24 hour feeding regimen using an enteral feeding pump at a slow rate (10–20 mL/hour) is advantageous in the initial stages of treatment if vomiting is present. As oral intake improves, the transition from continuous to overnight feeding provides the outstanding nutritional prescription until appetite improves sufficiently to allow tube feeding to be discontinued. Those children with persistent diarrhoea may tolerate a hydrolysed protein-based feed (Tables 8.15 and 8.20) before considering parenteral nutrition (PN).

Parenteral nutrition

The parenteral route is only considered when enteral nutrition is not tolerated. Standard hospital PN regimens are often unsuitable for the child with AKI because of their electrolyte composition and the amount of fluid they provide. An appropriate daily nutritional prescription to meet individual requirements should be agreed by the dietitian, pharmacist and medical staff. When formulating PN, nitrogen and electrolyte modified solutions, together with increased energy from carbohydrate and fat solutions where fluid allowance is limited, need to be considered. On CRRT the loss of nutrients through filtration and dialysis needs to be compensated for in the replacement fluids (p. 243); levels need to be greater than those found in standard PN regimens. For many children PN is temporary and the enteral route is re-established as soon as gut function returns.

Table 13.3 Guidelines for normal serum creatinine values.

Age	Serum creatinine (μmol/L)
<1 week	<100
1–2 weeks	<80
2–4 weeks	<55
1 month to 1 year	<40
1–3 years	<40
4–6 years	<46
7–9 years	10–56
10–12 years	30–60
13–15 years	40–80
16 years to adult male	40–96
16 years to adult female	26–86

Ketones interfere positively. Bilirubin interferes negatively.

Nutritional considerations

There are few data on the nutritional requirements of critically ill children with AKI and on RRT. Most of the information is derived from adult data.

Energy

Little is known about the energy requirements of infants and children with AKI [12]. A minimum of the estimated average requirement (EAR) for energy [13] for healthy children of the same chronological age provides a guide. These recommendations can be difficult to achieve during acute treatment; it is important to provide the maximum energy intake tolerated within the prescribed fluid allowance. The early addition of glucose polymers to water (flavoured with squash or cordial if desired) or to drinks of choice is recommended. It is prudent to start at a concentration of 0.5 kcal (2 kJ)/mL, building up to a concentration of 1 kcal (4 kJ)/mL, or 25% carbohydrate (CHO) concentration, depending on individual tolerance. Liquid glucose polymer preparations can also be used, but require dilution with water to be tolerated by children. It is recommended to start with a 1 : 5 dilution of liquid glucose polymer, building up to a final 1 : 3 dilution. Neutral tasting preparations can be flavoured with squash or cordial. When fluid is severely restricted, ice cubes and lollies can be prepared with these energy-dense solutions and offered at frequent intervals. Energy-rich CHO drinks including original bottled Lucozade Energy (8.4%–8.9% CHO concentration) and Mountain Dew (12.3% CHO concentration) and some full sugar squashes (6%–10% CHO concentration) can be useful alternatives for those children who refuse to drink prescribed energy supplements.

A list of energy supplements that can be considered is given in Table 13.4. These can be successfully added to infant formulas to increase energy density:

- In infants up to 6 months of age, 0.85–1.0 kcal/mL (3.6–4 kJ/mL) is usually tolerated
- In infants from 6 to 12 months of age, 1.0–1.5 kcal/mL (4–6 kJ/mL) should be tolerated

In children over 12 months of age, or whose weight is >8 kg, a nutritionally complete paediatric feed can be considered and modified as necessary to meet individual

Table 13.4 Nutritional supplements.

Supplement	Suggested use
Energy	
Glucose polymers	
Powder, e.g. Polycal, Super Soluble Maxijul, Vitajoule	Add to infant formula, baby juice, cow's milk, squash, fizzy drinks, tea, milk shake, ice cubes and lollies
Liquid, e.g. Polycal	Dilute with water, cordial or fizzy drinks of choice (unless fluid restricted); add to jelly
Fat emulsion	
Calogen, Liquigen, Carbzero, Betaquik	Add to infant formula, cow's milk, nutritionally complete supplements or take as a supplement
Combined fat and carbohydrate	
Powder, e.g. Super Soluble Duocal Powder	Add to infant formula, cow's milk, nutritionally complete supplements
Liquid, e.g. Liquid Duocal	Add to infant formula, cow's milk, nutritionally complete supplements or take as a supplement
Protein	
Powder, e.g. Protifar, Renapro*, ProSource TF*	Add to infant formula, modular feed components
Liquid, e.g. Renapro Shot*	Add to cow's milk, squash, tea, milkshake, supplements, feeds, modular feed component or take as a supplement
Combined fat, carbohydrate and protein	
Powder, e.g. Pro-Cal*	Add to cow's milk, squash, tea, milkshake, milky puddings, supplements, feeds, modular feed component
Liquid, e.g. Pro-Cal Shot*, ProSource*, ProSource Plus*	Add to cow's milk, squash, tea, milkshake, supplements, feeds, modular feed component or take as a supplement
Renal specific infant formulas	
Kindergen Powder per 100 g: 7.5 g protein, 503 kcal (2104 kJ), 93 mg phosphorus, 3 mmol potassium, 10 mmol sodium 20% solution (20 g powder made up to 100 mL with water): 1.5 g protein, 101 kcal (421 kJ), 18.6 mg phosphorus, 0.6 mmol potassium, 2 mmol sodium	For infants with CKD or conservatively managed AKI Suitable from birth to 10 years of age
Renastart Powder per 100 g: 7.5 g protein, 494 kcal (2066 kJ), 92 mg phosphorus, 3 mmol potassium, 10.4 mmol sodium 20% solution (20 g powder made up to 100 mL with water): 1.5 g protein, 99 kcal (413 kJ), 18.4 mg phosphorus, 0.6 mmol potassium, 2.1 mmol sodium	Not nutritionally complete for all age groups, nutritional assessment needed
Nutritionally complete feeds	
Nutrini per 100 mL: 2.8 g protein, 100 kcal (420 kJ), 50 mg phosphorus, 2.8 mmol potassium, 2.6 mmol sodium *PaediaSure* per 100 mL: 2.8 g protein, 101 kcal (422 kJ), 53 mg phosphorus, 2.8 mmol potassium, 2.6 mmol sodium *Nutrini Energy* per 100 mL: 4.1 g protein, 150 kcal (630 kJ), 75 mg phosphorus, 4.2 mmol potassium, 3.9 mmol sodium *PaediaSure Plus* per 100 mL: 4.2 g protein, 151 kcal (632 kJ), 80 mg phosphorus, 3.5 mmol potassium, 2.6 mmol sodium	For oral or supplementary tube feeding in children >1 year and weight >8 kg Can be combined with energy supplements
Nepro HP per 100 mL: 8.1 g protein, 180 kcal (722 kJ), 72 mg phosphorus, 2.7 mmol potassium, 3.0 mmol sodium	Consider micronutrient contribution in younger children
Low electrolyte supplements (not nutritionally complete)	
PaediaSure Plus juce per 100 mL: 4.2 g protein, 150 kcal (638 kJ), 9.5 mg phosphorus, 0.49 mmol potassium, 0.32 mmol sodium *Fortijuce* per 100 mL: 4 g protein, 150 kcal (640 kJ), 12 mg phosphorus, 0.2 mmol potassium, 0.4 mmol sodium *Ensure Plus juce* per 100 mL: 4.8 g protein, 150 kcal (638 kJ), 11 mg phosphorus, 0.4 mmol potassium, 0.5 mmol sodium *Renilon 7.5* per 100 mL: 7.5 g protein, 200 kcal (835 kJ), 3 mg phosphorus, 0.6 mmol potassium, 2.5 mmol sodium *VitaBite* per 25 g bar: 0.06 g protein, 137 kcal (571 kJ), <12.5 mg phosphorus, 0.63 mmol potassium, <0.1 mmol sodium	Can be diluted with water or fizzy drinks

(contiued to overleaf)

Table 13.4 *(continued)*

Supplement	Suggested use
Low protein milk substitute	
Sno-Pro per 100 mL: 0.16 g protein, 89 kcal (371 kJ), <30 mg phosphorus, <1.3 mmol potassium, <3.3 mmol sodium, <20 mg calcium *ProZero* per 100 mL: 0 g protein, 67 kcal (278 kJ), 2.0 mg phosphorus,0.05 mmol potassium, 1.8 mmol sodium, 0.04 mmol calcium *Renamil* per 100 g: 4.6 g protein, 477 kcal (2003 kJ), 32 mg phosphorus, 0.13 mmol potassium, 1.04 mmol sodium	Use as a substitute for cow's milk to reduce protein and phosphate intakes

CKD, chronic kidney disease; AKI, acute kidney injury.
*These contain potassium/phosphate/sodium/calcium.

requirements (Table 13.4). The energy density can be built up to 1.5–2.0 kcal/mL (6–8 kJ/mL). Fat emulsions can be given as a prescribed medicine during the day.

A few children develop insulin resistance and hyperglycaemia can occur. If managed on PD, this can be exacerbated by the absorption of glucose from the PD fluid together with the intake of high CHO supplements. Insulin infusions need to be considered to control blood glucose levels before the reduction of dietary CHO.

Protein

In children with AKI who are being managed conservatively, protein should be limited to the reference nutrient intake (RNI) [11] level to minimise uraemic symptoms. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend avoiding restriction of protein intake as a way to delay RRT and recommend starting RRT early [1]. Protein intake needs to be gradually increased as tolerated if RRT is started, with its associated increased solute removal and possible protein losses. The RNI for protein is not always appropriate for the child with AKI on RRT, and requirements should be individually determined [11]. The age and weight of the child, the serum biochemistry and RRT modality, when implemented, all need to be considered. Inadequate energy intake can exacerbate high urea levels; therefore, it is beneficial to maximise energy intake.

Once RRT is established, the following increments can be used as a guide to increase protein intake to the RNI (Table 1.9). If dialysis is prolonged, an increase in protein intake above the RNI may be required:

- Exclude protein if the serum urea is ≥40 mmol/L
- Introduce 0.5 g protein/kg if the serum urea is ≥30 and <40 mmol/L
- Give 1.0 g protein/kg if the serum urea is ≥20 and <30 mmol/L
- Give the RNI for height age (infants) or chronological age (children) if the serum urea is <20 mmol/L

CRRT offers haemodynamic stability while maintaining excellent control of solutes in extracellular fluid and allows nutritional support in highly catabolic states, but contributes to nitrogen loss through the filtration of free amino acids and small peptides across haemofilters. Maxvold *et al*. [14] demonstrated that at similar blood and dialysate/prefiltered replacement fluid flow rates, there is an equivalent urea clearance with haemofiltration and haemofiltration with dialysis. A negative nitrogen balance occurred in children with AKI on PN containing 1.5 g/kg/day of protein and an energy intake 20%–30% above resting energy expenditure. An 11%–12% loss of dietary amino acids was found on both modalities. A significant daily accumulative glutamine loss may potentiate nitrogen imbalance. A dose adjustment of amino acid formulation may be needed to overcome negative nitrogen balance in children with AKI on CRRT. An adult study by Scheinkestel *et al*. [15] showed that a protein intake of 2.5 g/kg/day and meeting energy requirements increased the likelihood of achieving a positive nitrogen balance and improving survival. However, another adult study recommends a protein intake between 1.5–1.8 g/kg/day and an energy allowance of 25–35 kcal (105–145 kJ)/kg/day [16].

Nutrition therapy in AKI remains an area of many unanswered questions, especially for those managed on CRRT; Li *et al*. illustrate this in their review of AKI studies in adults [17]. A review article in paediatric intensive care patients [8] reinforces the high risk of underfeeding the critically ill child, with the presence of AKI further increasing the risk of protein–energy debt. Further paediatric studies are needed to investigate nutritional support adequacy, nutritional status and clinical outcomes [8].

Nutritional supplements, using an NGT, are frequently used to meet protein and energy requirements in the initial stages of treatment. For infants standard whey-based formulas (which are already low in electrolytes and phosphate) are recommended. These can be modified as required. Kindergen and Renastart – renal specific low phosphate, low potassium infant formulas (Table 13.4) – can be beneficial for infants not receiving RTT or receiving IHD when serum biochemistry levels are unstable. Nutritionally complete, energy-dense infant formulas (Infatrini, Similac High Energy, SMA High Energy) can be useful if blood biochemistry allows when on RTT. The phosphate content of these feeds is higher than in standard infant whey-based formulas, so serum phosphate levels should be regularly reviewed. For the older child a number of nutritionally complete supplements are available. These can be used solely or in

combinations with their protein, phosphate and potassium contents being assessed prior to use (Table 13.4). If protein hydrolysate formulas are indicated (in particular when the diarrhoeal phase is prolonged in HUS), they should be modified with respect to biochemical parameters as well as to meet individual nutritional requirements. Introduction should be gradual and delivery is usually by the nasogastric (NG) route. Once the child's appetite improves and protein intake is met through eating, energy supplemented drinks can replace nutritionally complete formulas or protein supplements.

Fluid

The volume of fluid prescribed during conservative treatment is based on insensible fluid requirements of 400 mL/m^2 body surface area (BSA)/day or approximately 20 mL/kg body weight/day, with a 12% increase for each degree Celsius above normal body temperature and a reduction if the child is ventilated. Insensible losses should be added to the previous day's urine output to give the total daily fluid allowance. Body surface area may be calculated using the formula $\sqrt{[(\text{weight kg} \times \text{height cm})/3600]}$.

On RRT, the fluid prescription is determined by monitoring the volume of fluid removed by ultrafiltration plus insensible losses. Ideally fluid removal on RRT should be flexibly managed to allow the maximum space for increased nutritional fluids. Maximal nutrient intakes using supplements should be provided within the fluid allowance and divided as evenly as possible throughout the day. A prescription plan should be provided for the ward nurses and families.

Electrolytes and minerals

The intake of electrolytes, especially potassium, is likely to be restricted in conservative management. Serum levels and the use of RRT will dictate requirements thereafter. Any dietary restrictions should be minimised to avoid compromising nutritional intake.

Potassium-rich foods including citrus fruits, fruit juices, bananas, potato crisps and chocolate are commonly brought into hospital by relatives. All caregivers should be advised about choosing foods with a low potassium content when serum potassium levels are elevated so that rich food sources are withdrawn (Table 13.5).

Once serum phosphate levels are above the reference ranges, the intake of phosphate-rich foods should be moderated. A lower phosphate intake can partly be achieved when protein intake, particularly that of dairy products, is modified (Table 13.6). Cow's milk is generally restricted or eliminated from the diet during the acute phase because of its high protein, phosphate and potassium content. Avoidance of cow's milk also reduces the potential cow's milk protein or lactose intolerance, which can follow the diarrhoeal prodrome in patients with HUS. If the milk restriction proves difficult, a low protein milk substitute, such as Sno-Pro or Renamil (Table 13.4), can be advised. Phosphate binders may also be useful (p. 253).

Reduction in sodium intake can aid compliance when fluid intake is restricted by reducing thirst. This can be achieved by the avoidance of salted snacks and a reduced or 'no added salt' diet (Table 13.7). Practical advice for families is given in Table 13.24.

The level of the above restrictions depends on each individual child and their clinical condition. They should be frequently monitored to avoid unnecessary restrictions when

Table 13.5 Potassium-rich foods and suggested alternatives.

Potassium-rich foods*	Suggested alternatives
Banana, apricots, kiwi fruit, grapes, avocado, citrus fruits, e.g. orange, grapefruit; dried fruit, e.g. raisins; tinned fruit in fruit juice; melon, plums, rhubarb, blackcurrants	Apple, pear, satsuma, blueberries, tinned fruit in syrup
Hi juice squash, fruit juices including orange, apple and tomato Instant coffee and coffee essence Malted drinks Cocoa, drinking chocolate	Squash, cordials, Lucozade, lemonade and fizzy drinks, tea
Potato crisps and potato containing snacks, nuts, peanut butter, salt substitutes, meat extract, yeast extract	Corn or rice snacks (without added potassium chloride and take account of sodium content), sweetened popcorn, jam, honey, marmalade, syrup
Jacket potatoes, chips (oven and frozen), roast potatoes	Rice (boiled or fried), spaghetti, pasta, noodles, bread, chapatti, naan, crackers
Mushrooms, spinach, tomatoes, spaghetti in tomato sauce, baked beans, pulses and hummus, tinned and packet soups	Carrots, cauliflower, swede, broccoli, cabbage
Chocolate and all foods containing it, toffee, fudge, marzipan, liquorice	Boiled sweets, jellies, mints, marshmallows
Chocolate biscuits	Biscuits: plain, sandwich, jam filled, wafer
Chocolate cake, fruit cake	Cake: plain sponge filled with cream and/or jam Jam tarts, apple pie, doughnuts, plain scones
Milk, yoghurt, evaporated and condensed milk	Low protein milk substitutes, e.g. Sno-Pro, Renamil, ProZero

*Allowance will depend on individual assessment.

Table 13.6 Phosphate-rich foods and suggested alternatives.

Phosphate-rich foods*	Suggested alternatives
Cow's milk (full cream, semi-skimmed, skimmed) Dried milk powder and other milk products	*Infants* Whey-based infant formulas, e.g., Cow & Gate 1, SMA PRO 1, Aptamil Pro Futura 1 for at least 1–2 years *Children* Reduced intake; consider low protein milk substitute (Table 13.4)
Large portions of meat, poultry and fish Processed meats containing phosphate additives	Reduced portion sizes
Yoghurt, fromage frais, mousse, ice cream, milk puddings including custard	Reduce intake Custard made with milk substitute
Evaporated milk, condensed milk, single cream	Double cream†
Cheese, e.g. Cheddar, Edam, processed cheese and cheese spread	Limit intake and/or encourage use of cottage cheese or full-fat cream cheese
Egg yolk	Meringues
Cocoa, chocolate and chocolate-containing foods, toffee, fudge	Boiled sweets, mints, dolly mixtures
Sardines, pilchards, tuna	White fish
Baked beans, pulses	Vegetables
Nuts, peanut butter, marzipan and seeds	Jam, honey, marmalade, syrup
Cola drinks and any others containing phosphoric acid	Squash, cordials, lemonade, Lucozade
Convenience and processed foods with phosphorus-containing additives (Table 13.14)	Foods with no phosphorus-containing food additives

*Allowance will depend on individual assessment.
†Caution: vitamin A content (p. 262).

Table 13.7 Sodium-rich foods and suggested alternatives.

Sodium-rich foods	Suggested alternatives
Salted crisps, nuts and savoury snacks	Unsalted crisps, unsalted nuts, rice cakes, unsalted popcorn
Tinned and packet soups	Home-made soups
Pot savouries/noodles	Sweet snacks instead of savoury
Tinned foods with added salt	*Reduced salt products, e.g. reduced salt baked beans
Bacon, sausages and other processed meats and fish	Fresh meats and fish
Cheese and cheese products	Cottage cheese, ricotta and cream cheese
Stock cubes, meat and vegetable extracts	Halve the amounts used or use reduced salt varieties; add herbs and spices in their place, use gravy powder and meat juices to make gravy
Pickles, sauces and chutneys	Reduced salt alternatives
Ready-made meals and takeaway meals	Home-made meals using fresh ingredients

See also Table 13.24.
*Many processed/manufactured foods contain high amounts of salt and even lower salt varieties can have a high salt content. A reduced salt or 'no added salt' diet, avoiding the sodium-rich foods in the table above, provides approximately 3 mmol sodium/kg body weight, assuming the child eats average food portion sizes.

their appetite is typically poor and their nutrition is easily compromised.

Micronutrients

Vitamin supplementation should be considered if dialysis treatment is prolonged. A general paediatric vitamin supplement of water-soluble vitamins should be adequate for the majority of children as appetite improves, e.g. Ketovite tablets. Iron supplementation may be indicated in some children during the recovery phase, particularly in those who had a poor diet history prior to the onset of AKI.

When on CRRT water-soluble vitamins, especially folic acid, thiamin and vitamin C are lost. Requirements when on this treatment are unknown and a minimum of the RNI [18] should be given. Patients receiving CRRT also lose magnesium and calcium; this often leads to negative balances requiring additional supplementation. Zinc is also

abnormally lost, but serum levels do not generally fall [19, 20]. Additionally Wiesen *et al*. [16] recommend selenium supplementation.

Recovery phase

As renal function improves and urine output increases, the need for RRT is reduced and stopped. Dietary restrictions, where instigated, can gradually be relaxed. Serum electrolytes and dietary intake should be monitored closely as major losses, especially of potassium, during the diuretic phase can occur.

Prior to discharge, advice should be given on returning to a normal diet as renal function continues to improve. The opportunity to educate the child and family about the principles of a well-balanced diet can also be taken if poor eating patterns were highlighted during the admission. Where appetite is slow to improve, some children may need to continue energy and vitamin supplements for a short time, with monitoring of their progress in clinic.

Outcome of AKI

The prognosis and outcome for children with AKI depends on the underlying cause. Factors associated with a poor outcome include multi-organ failure and the need for RRT and these children need secondary or tertiary follow-up.

Learning points: acute kidney injury

- *Progression of the degree of AKI is based on monitoring creatinine levels, with or without urine output*
- *Dietary prescription varies with clinical management and stage of the illness*
- *Nutritional support aims to provide sufficient energy to avoid catabolism as well as controlling metabolic abnormalities*
- *Nutritional intervention depends on clinical management, blood biochemistry levels, cause of AKI, gastrointestinal function, growth parameters and dietary intake*
- *Achieving energy requirements may be difficult during acute treatment; it is important to try to provide the maximum energy within the prescribed fluid allowance*
- *Protein should be limited to the RNI to minimise uraemic symptoms; however unnecessary protein restriction must be avoided*

Chronic kidney disease

CKD is characterised by an irreversible deterioration of renal function that can progressively decline to end-stage renal disease (ESRD) [21], evidenced by structural or functional kidney abnormalities. Renal dysfunction is defined as a continuum from mild to severe. The National Institute for Health and Care Excellence (NICE) has adopted the US National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) classification of CKD into five stages (Table 13.8) [22]. This staging does not apply to children below 2 years of age where ongoing renal maturation is seen. UK data published in 2015 reveals an incidence of established renal failure under the age of 16 years of 10.2 per million age-related population [23]. Children from minority ethnic groups displayed higher RRT prevalence rates when compared with white children, with South Asian children exhibiting the highest rates. The causes of CKD in the registry data are shown in Table 13.9 [23]. Regardless of the underlying cause, CKD is characterised by progressive scarring that ultimately affects all structures of the kidney [24]. Despite the diverse causes, once CKD develops, the subsequent response of the failing kidney is similar. Initially, the kidney adapts to damage by increasing the filtration rate in the remaining nephrons, a process called adaptive hyperfiltration. Additional homeostatic mechanisms permit the serum concentrations of sodium, calcium, phosphate, potassium and total body water to remain within the reference range, particularly among those with mild to moderate stages of CKD. Adaptive hyperfiltration, although initially beneficial, appears to result in long-term damage to the glomeruli of the remaining nephrons. This irreversibility is responsible for the development of ESRD [25].

Table 13.8 Stages of renal failure.

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	<15 or dialysis

GFR, glomerular filtration rate.

Table 13.9 Causes of chronic kidney disease in childhood in the UK.

Cause	Percentage
Renal dysplasia ± reflux	34.7
Obstructive uropathy	18.9
Glomerular disease	11.4
Congenital nephrotic syndrome	10
Tubulo-interstitial disease	6.6
Renovascular disease	4.8
Polycystic disease	4.3
Metabolic disease	3.8
Malignancy and associated disease	2.2

Management of CKD

Childhood CKD presents clinical features that are specific to paediatrics such as the impact of the disease on growth, not only influencing the health of the patient through childhood but also having an impact on the life of the adult that the child will become. Therefore, the care of this vulnerable population requires the collaborative efforts of a multidisciplinary team (MDT). The aim is to optimise the quality of life of the child and family while treating the complications of the disease, delaying or slowing the progression of the disease and preparing for RRT or preemptive transplant when the time comes. There needs to be an appreciation that the long-term consequences of CKD, e.g. cardiovascular disease (CVD), poor growth and bone disease, have a great psychosocial impact on both the patient and their family. Parents/caregivers not only fulfil a parental role but also take on many tasks that are normally the remit of nurses and doctors [26], and they are, therefore, vital members of the MDT.

Irrespective of aetiology, the sequence of events in CKD demands attention to the management of nutrition, growth, fluid and electrolyte balance, acid–base abnormalities, CKD-mineral bone disease, hypertension, slowing the progression of CKD, anaemia, CVD, medication, education and psychosocial support.

A good knowledge of biochemical and haematological parameters is essential to identify variations from normal age-specific reference ranges when formulating dietary management plans. The serum values of particular relevance include urea, creatinine, sodium, potassium, bicarbonate, albumin, calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH), glucose, cholesterol and triglycerides. Haemoglobin, ferritin and percent hypochromic cells (<10%) can be used to assess iron status in combination with serum iron and total iron binding capacity (TIBC) to calculate the percent transferrin saturation (TSAT = serum iron × 100 divided by TIBC), which should be maintained at >20%.

An assessment of the glomerular filtration rate (GFR) provides an indication of the overall level of renal function. GFR estimation by Cr51 EDTA clearance is used to predict when RRT is likely to be required. GFR should not be measured before 1 year of age as the kidney function may continue to mature during the first year of life and even beyond. GFR can be estimated using the Haycock Schwartz formula: predicted GFR = 40 × ht (cm)/serum creatinine (μmol/L).

Nutrition

The adverse effects of poor nutrition in children are manifested by their influence on the capacity to grow and develop appropriately. There is a complex interrelationship between renal dysfunction and nutrition whereby abnormalities or a decline in renal function frequently leads to changes in metabolism, as well as a poor nutritional intake complicating CKD. Malnutrition is associated with increased mortality. Early and careful nutritional therapy may improve growth, development and mortality in all ages of children with CKD [27]. The aetiology of growth delay and cachexia in children with CKD is multifactorial with inadequate energy intake, uraemic toxicity, anaemia, increased inflammatory response and metabolic and endocrine abnormalities among the foremost causes. The dietitian plays an essential role in optimising the management of these causes and needs to ensure that individualised dietary prescriptions are practical and flexible to aid adherence.

Growth

Achieving optimal growth is the most challenging problem for the dietitian in this population. The causes of growth failure in children with CKD are multifactorial (Table 13.10) [28]; the two most important factors are the severity of the CKD and young age at onset.

Normal growth in childhood occurs in four phases: foetal, infantile, mid-childhood and pubertal. Nutrition is important in all growth phases, but especially during the infantile phase when growth is at its most rapid and is less dependent on growth hormone (GH). There is a slowing of growth velocity in the mid-childhood phase when growth is more dependent on the GH/IGF-1 (insulin-like growth factor 1) axis [28]. At puberty, which is typically delayed in CKD, there is a rapid increase in growth velocity in response to sex steroids and GH; adequate nutrition is important during this anabolic phase. A third to a half of total postnatal growth occurs during the first 2 years of life and 20% during the pubertal phase.

Table 13.10 Aetiology of growth failure in children with CKD [28].

Birth-related factors:	**Genetic factors:**
Prematurity	Height of parents
Small for gestational age	Sex
Intensive care	Concurrent syndromes
Co-morbidities	
Hormonal disturbances affecting:	**Metabolic disturbances:**
Somatotropic hormone axis	Salt and water balance
PTH and vitamin D metabolism/action	Metabolic acidosis
Gonadotropic hormone axis	CKD-MBD
Gastrointestinal hormones	
Age at onset of CKD	**Severity of CKD and residual renal function in those undergoing dialysis**
Anaemia	
Malnutrition:	**Protein energy wasting:**
Anorexia	Uraemic toxins
Vomiting	Infections and inflammation
Altered taste sensation	Oxidative stress
Dietary restrictions	Inflammatory cytokines
Nutrients lost to dialysis fluids	
Infections and inflammation	
Abnormal levels of gastrointestinal hormones	

CKD-MBD, chronic kidney disease-mineral and bone disorder; PTH, parathyroid hormone.

As the infantile phase is predominantly dependent on nutrition, inadequate intake at this time can have a dramatic influence on growth with irreversible loss of growth potential. Nutritional adequacy is complicated by other factors, e.g. fluid and electrolyte balance, vomiting, infections, CKD-mineral bone disorder (CKD-MBD), acidosis and catabolic states. If these factors are adequately controlled, severe stunting can be avoided in the majority of patients (without untreatable co-morbidities) [28].

In order to maximise nutritional intake, supplementary feeding is often used via the enteral route. In a retrospective analysis of growth in infants and children with severe CKD, catch-up growth was achieved in the majority of patients with good metabolic control and enteral feeding [29]. KDOQI advises that early and intensive nutritional management will benefit nutritional status and growth [22].

In later childhood catch-up growth is rarely achieved by diet alone as the role of the GH/IGF-1 axis becomes more important [30]. Optimising nutrition, however, may still prevent further growth decline.

GH resistance is seen in CKD as well as decreased secretion when there is metabolic acidosis. This is an important factor during the peri-pubertal years and can result in a delayed growth spurt [31]. The efficacy and safety of recombinant growth hormone (rhGH) has been shown extensively in paediatrics [31]. Pre-pubertal children (conservatively managed or on RRT) treated with rhGH demonstrate increased height velocity [28]. For children with a height or height velocity for chronological age <–2 SDS, GH therapy following the optimisation of nutritional management has been shown to increase height velocity and final adult height [30].

IGF-1 production and sensitivity is also negatively affected by GH and CKD. The role of IGF-1 is vital in longitudinal growth. Treatment with rhGH stimulates IGF-1 synthesis and, therefore, promotes longitudinal growth.

As already described, in the infantile phase, nutrition has the greater impact on growth. Two studies have shown that infants treated with rhGH showed significantly greater gain in length than the control groups [27]. Early rhGH may be beneficial in those infants that, despite adequate nutrition, show growth failure since it will help achieve the body size required for renal transplant without delay [28].

Dietary and anthropometric assessment

There is no simple measure of nutritional status for children with CKD. Nutritional parameters are complicated on account of salt and water imbalances together with the inappropriateness of comparing growth to that of age-matched populations. The frequency of nutritional monitoring depends on age, stage of CKD and how well the child is thriving. Clinical guidelines for growth monitoring in children with CKD have been developed in the UK [32]. The guidelines (Table 13.1) provide recommendations for the minimum frequency of reviewing weight, head circumference, length, pubertal stage and body mass index (BMI). Some patients may need to be seen more frequently in order to prevent the development of malnutrition. This will depend on CKD stage and need for enteral nutrition [30].

In older infants and children, who may have a varied diet, a 3-day dietary diary and 24 hour recalls (for three separate periods in order to account for wide day-to-day variability) are valuable tools when estimating nutritional intakes and individual baseline requirements [33]. Information on prescribed medications, presence or absence of nausea and vomiting, diarrhoea, constipation and energy levels can be helpful in determining the child's nutritional and medical needs. Dietary intake should be communicated to members of the MDT, where appropriate, to reinforce discussions and recommendations made with the child and family.

Height and weight plotted on growth charts are used to assess nutritional status. At each clinic visit, accurate measurements of height, or supine length, and weight should be obtained. Infants with CKD have been shown to be at high risk of poor head growth [33]. Children <2 years of age should have regular measurement of their head circumference and plotted for chronological age on appropriate growth charts. Where the child is within normal centile ranges for height (>2nd centile), energy and nutrient requirements can be based on recommendations for children of the same chronological age [13, 19]. For the child who falls below the normal centile ranges for height (<2nd centile), their height age (age at which the child's height would be on the 50th centile) should be used for comparison with recommended intakes for energy and nutrients [13, 19] and adjusted accordingly thereafter. Estimated dry weights need to be used in those children retaining fluid.

Extremes of BMI are associated with increased morbidity and mortality, and children with CKD should avoid becoming overweight or obese. However, it is difficult to find a measure of body composition that is relevant for children with CKD. They may not have a normal body composition making a comparison with normal populations inappropriate. CKD may have a disproportionately greater effect on spinal growth, and children have been shown to have a low ratio of length of trunk to limb [34]. They also have a relatively high fat mass, low lean mass and increased central adiposity [35]. BMI should not be used as a measure of fatness for children <2 years of age. It can also be misleading in adolescents with CKD due to delayed sexual maturation and linear growth, which is further confounded by reduced muscle mass, reduced activity and fluid retention; if BMI is used, it is suggested that it is plotted against the child's height age [36]. Caution should be used when interpreting BMI in this patient group [33].

Mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSF) are no longer recommended as part of routine assessment, due to concerns of overestimation due to fluid overload and distorted fat and lean distribution in this patient group [22] (Table 13.11).

Table 13.11 Growth monitoring guidelines for children with chronic kidney disease.

GFR ml/min/1.73 m²	CKD stage	Measurement	Frequency of measurement	Action
>90	Stage 1	Normal childhood growth monitoring	Royal College of Paediatrics and Child Health (RCPCH) guideline	Measure, document and plot on growth chart
60–89	Stage 2	Length/height and weight	Annually	Measure, document and plot on growth chart
GFR ml/min/1.73 m²	**CKD stage 3–5**	**Measurement**	**Frequency of assessment (minimum recommended)**	**Action**
≤59	All these items for children with greater severity CKD, i.e. stages 3–5	Weight (euvolaemic, i.e. normal fluid status)	Measure every clinic visit, but for growth purposes required: Every month if aged <6 months Every 2 months if 6–12 months Every 3 months if >1 year	Measure, document and plot on growth chart
		Head circumference	Every 2 months if <1 year Every 3 months if 1–2 years	Measure, document and plot on standard head circumference curve on growth chart
		Length/height	Every 2 months if 0–1 year Every 3 months if >1 year	Measure supine length if <2 years on validated length mat, i.e. rollameter or kiddimeter Measure standing height if >2 years on wall-mounted stadiometer Document and plot on growth chart Sitting height, knee height or total leg length can be used as height proxies
		Assess pubertal stage	Annually if ≥12 years, i.e. during the older half of the normal age range of onset of puberty in girls 8–13 years, boys 9–14 years	Consider whether growth and development progress is as expected or whether concern of pubertal delay Consider using Childhood and Puberty Close Monitoring (UK CPCM 2–20 years) chart if concerns Assess 6 monthly
		Body mass index (BMI)	Only applicable if >2 years, then do so every 6 months	Calculate and plot on growth chart (UK 2–18 years) against chronological age
		Parental heights	As soon after referral as possible if able to do so	Calculate mid-parental height using information on growth chart Document in notes and on growth chart

Source: Adapted with kind permission from S. Trace [32].

Learning points: management of chronic kidney disease

- *Irrespective of aetiology, the sequence of events in CKD demands attention to the management of nutrition, growth, fluid and electrolyte balance, acid–base abnormalities, CKD-MBD, hypertension, anaemia, CVD, medication, education and psychosocial support*
- *Early and careful nutritional therapy may improve growth, development and mortality in all ages of children with CKD*
- *The cause of growth failure is multifactorial, the two most important factors being the severity of the CKD and young age at onset*

Dietary principles in CKD

Nutritional management of children with CKD requires attention to adequacy of energy intake, regulation of protein intake, fluid balance and electrolytes, regulation of calcium and phosphate intakes, correction of acid–base abnormalities and adequacy of micronutrient and iron intakes.

Dietary recommendations depend upon age, stage of CKD, clinical management and nutritional assessment. The recommended intakes of energy and protein in conservatively managed children are given in Table 13.12, based on UK dietary reference values [13, 18]. More recent recommended intakes have been proposed by the Paediatric Renal Nutrition Taskforce (see Guidelines, companion website), with similar values. Anorexia is a common feature of CKD in

Table 13.12 Nutritional guidelines for the child with chronic kidney disease.

Age	Energy (per kg body weight per day) (kcal)	Energy (per kg body weight per day) (kJ)	Protein (per kg body weight per day) (g)
Conservative management			
Infants			
Preterm	110–135	460–560	2.5–3.0
0–2 months	96–120	400–500	2.1
3–12 months	72–96	300–400	1.5–1.6
1–3 years	78–82	325–340	1.1
Children/adolescents			
4 years to puberty	Minimum of EAR for chronological age (use height age if		1.0–1.1
Pubertal	<2nd centile for height)		0.9–1.0
Post-pubertal			0.8–0.9
Peritoneal dialysis (APD/CAPD)			
Infants			
Preterm	110–135	460–560	3.0–4.0
0–2 months	96–120	400–500	2.4
3–12 months	72–96	300–400	1.9
1–3 years	78–82	325–340	1.4
Children/adolescents			
4 years to puberty	Minimum of EAR for chronological age (use height age if		1.3
Pubertal	<2nd centile for height)		1.2
Post-pubertal			1.0–1.2
Haemodialysis			
Infants			
Preterm	110–135	460–560	3.0
0–2 months	96–120	400–500	2.2
3–12 months	72–96	300–400	1.7
1–3 years	78–82	325–340	1.2
Children/adolescents			
4 years to puberty	Minimum of EAR for chronological age (use height age if		1.1
Pubertal	<2nd centile for height)		1.1
Post-pubertal			1.1

These guidelines are for the initiation of management and require adjustments based on individual nutritional assessment.
Protein intakes reflect the reference nutrient intake (RNI) in the UK [18] plus an increment to achieve positive nitrogen balance including any transperitoneal losses [22].
EAR, estimated average requirement [13]; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

infants and is a primary reason for growth failure in this patient group [33]. It can be seen in less severe CKD. Anorexia is caused by a combination of factors including nausea, vomiting, gastro-oesophageal reflux, oral aversion, delayed gastric emptying, altered taste changes, elevation of cytokine levels and changes in leptin and ghrelin hormone levels [37]. This will result in suboptimal nutritional intake. In order to optimise intake and growth, nutritional interventions either with supplements (Table 13.4) or enteral tube feeding is commonly required [28].

Energy

The energy requirements for children with CKD are the same as those of healthy children. Energy intakes below the EAR contribute to growth failure [28]. The provision of adequate energy is essential to promote appropriate weight gain and linear growth in all children with CKD and to avoid the use of lean muscle mass as an energy source. The EAR for energy for either height age (if the child's height is <2nd centile) or chronological age (if the child falls within the normal centile range) is used as baseline guidelines (Table 13.12) [13]. Raised serum urea levels in combination with increased serum potassium levels can be suggestive of catabolism and the need to increase non-protein energy intake.

High energy, low protein foods

These include sugar, glucose, jam, marmalade, honey and syrup and should be encouraged where possible. The liberal use of polyunsaturated or monounsaturated oils in cooking or margarine spread on bread or toast or added to meals and vegetables can contribute significantly to the child's energy intake. Special low protein dietary products such as bread and biscuits are rarely needed.

Energy supplements

Anorexia, nausea and vomiting are features of CKD and can be exacerbated by uraemia. These symptoms, together with an abnormal sense of taste, contribute to a reduced energy intake. Energy supplements are helpful in meeting this deficit. A number of supplements are available and enable a flexible approach (Table 13.4). Combined fat and CHO supplements or glucose polymer alone, if additional fat is not tolerated, can be successfully added to infant formulas, tube feeds and oral nutritional supplements. The concentrations of CHO and fat should be increased gradually to establish tolerance. Assuming normal gut function, the following upper limits for CHO and fat can be worked towards:

- infants <6 months: 12% CHO and 5% fat
- infants >6 months to 1 year: 15% CHO and 6% fat
- toddlers aged 1–2 years: 20% CHO and 7% fat
- older children: 32% CHO and 9% fat

Liquid glucose polymers are useful when diluted with a fizzy drink or diluted squash, and the volume used will depend on the fluid allowance. Powdered glucose polymers are useful in children who drink plenty of water or squash. Each day a target amount to use should be negotiated, and a personalised record chart can aid compliance.

Protein

Children, especially infants and young children, have a high requirement for protein per kilogram body weight because of the demands of growth. A systematic review of protein restriction for children with CKD [38] showed no significant impact on delaying progression of renal failure, and there is an association with inferior growth. The correlation between dietary protein intake and proteinuria was also insignificant.

Protein intake should be optimised to allow for the maintenance of nitrogen balance and growth, together with the preservation of lean body mass. In CKD, protein must provide at least 100% of the RNI for age to avoid protein becoming a limiting factor in growth [27]. The RNI for height age is advised when the child is <2nd centile for height. Insufficient protein will impact on body composition with a predominance of fat rather than lean tissue being laid down. Children achieve recommended protein intakes more easily than their energy requirements, and a protein intake above 3.0 g protein/kg should be avoided because of the associated phosphorus load and link with cardiovascular morbidity. Where dairy proteins have been limited to restrict phosphate intake, and adequate energy intake has been ensured to promote anabolism, further protein modification is seldom needed. However, when a child's serum urea remains persistently >20 mmol/L, a gradual protein reduction based on the child's 3-day dietary record should be initiated to lower the urea level to <20 mmol/L, aiming not to go below the RNI appropriate for the child. Protein of a high biological value should comprise 65%–70% of the total dietary protein intake.

Should protein supplements be needed, consideration should be made regarding the phosphate, calcium and potassium content of these supplements (Table 13.4).

Electrolyte and fluid balance

Sodium and fluid balance

In several causes of CKD in infancy, including obstructive uropathy and renal dysplasia, there is poor urinary concentrating capacity and sodium wasting. Sodium depletion results in contraction of the extracellular fluid volume and further impairment in renal function, as well as impairment of growth [39]. Sodium chloride supplements can be added to infant feeds or be given as a medicine. The amount should be increased until an improvement in growth is seen without the development of hypertension, peripheral oedema or hypernatraemia. Such infants typically require up to 4–6 mmol sodium/kg/day. These infants are usually polyuric and require free access to fluids in the form of supplemented feed and extra water. Their preference of water over feed/food can diminish their appetite [33].

In contrast, children with primary renal diseases exhibiting hypertension may benefit from a reduction in sodium intake and advice on a reduced salt or 'no added salt' diet (Table 13.7).

As the GFR declines in CKD stages 4 and 5, sodium and fluid retention are commonly seen. This can lead to volume overload and hypertension; dietary sodium and fluid restriction together with diuretics are instigated. Fluid restrictions are only instituted as urine output diminishes or oedema develops, more usually when the GFR falls below 15 mL/min/1.73 m^2. Fluid prescriptions are individualised to take account of insensible losses and a typical day's urine output.

Potassium

The majority of children with CKD stages 1–3 maintain potassium homeostasis. If hyperkalaemia occurs, other correctable causes including drugs such as angiotensin-converting enzyme (ACE) inhibitors, metabolic acidosis and catabolism should be excluded before initiating a potassium-modified diet (Table 13.5). A haemolysed blood sample will show a falsely high serum potassium level. In stage 5 CKD, hyperkalaemia necessitates a potassium-modified diet; any nutritional supplements used must be exchanged for low potassium varieties. Foods containing the preservative potassium sorbate should be minimised if hyperkalaemia persists; 100 g of food containing this additive can add an additional 1.0–2.5 mmol of potassium to the diet. Hyperkalaemia is the most dangerous of the electrolyte disturbances, affecting cardiac function.

Hypokalaemia is seen in renal tubular disorders such as cystinosis and Bartter syndrome (p. 272, 274). Potassium supplements are usually indicated together with medication (indometacin) that reduces renal sodium, potassium and water losses. Hypokalaemia can be seen in polyuric CKD as well as resulting from the use of some diuretics or with episodes of diarrhoea and vomiting.

Acid–base abnormalities

Acidosis can occur as early as CKD stage 2 in young children with dysplasia. It is common in all causes of CKD when the GFR falls below 25 mL/min/1.73 m^2. It is more commonly seen in children due to the consumption of base due to growth of bone and other tissues [30]. Acidosis can have substantial adverse effects on development, exacerbation of bone disease, growth retardation, increased muscle degradation, reduced albumin synthesis, resistance to the effects of insulin and acceleration of the progression of CKD. It is also associated with increased mortality [40]. Current recommendations are to maintain serum CO_2 at ≥20 mmol/L among children less than 2 years of age and at ≥22 mmol/L in children aged over 2 years of age [22].

Hyperkalaemia can be exacerbated by acidosis. Extracellular potassium shifts occur with metabolic acidosis as bicarbonate is lost through the kidney. Acidosis is corrected with the administration of sodium bicarbonate. Sodium bicarbonate supplements do not usually cause sodium retention until CKD stage 5 and, as such, have little effect on blood pressure control; they do not usually need to be included in an assessment of sodium intake. Dialysis will usually correct acidosis.

In older children a protein intake in excess of requirements, and hence an excess in intake of sulphur containing amino acids, can increase endogenous acid production. Protein intake should be modified in such instances.

CKD-mineral bone disorder

The pathogenesis of CKD-MBD is complex. Children with stage 2 CKD usually have no signs of bone abnormalities, but biochemical abnormalities can be evident. There is a fall in 1,25-dihydroxyvitamin D_3 production; this results in an increase in PTH levels and a drop in serum calcium levels, further stimulating PTH production. Phosphate retention, as a result of reduced GFR, causes hypocalcaemia and a rise in PTH. Secondary hyperparathyroidism (SHPT) causes bone resorption and a further increase in serum phosphate levels [21]. In addition to MBD, this process can lead to calcification in other tissues including blood vessels and muscle tissue as well as phosphate acting as a uraemic toxin.

Vitamin D deficiency is widely prevalent and often severe in children with chronic kidney disease and contributes to abnormalities in calcium, phosphate and PTH homeostasis [41]. The mineral dysregulation seen in CKD directly affects bone strength, mineralisation and architecture. CKD-MBD in childhood presents multiple obstacles to bone accrual, resulting in bone pain, deformities, growth retardation and fractures [41].

Management of CKD-MBD should be based on serial assessments of phosphate, calcium, PTH and vitamin D levels. Therefore, dietary management is a combination of dietary assessment and manipulation of calcium and phosphate intake and the treatment of vitamin D deficiency [42]. Hyperphosphataemia and hypocalcaemia contribute to the pathogenesis of SHPT. Optimal control of bone and mineral homeostasis is essential for preventing debilitating skeletal complications, achieving adequate growth and preserving long-term cardiovascular health.

Phosphate

Bones expend 85% of the body's phosphorus during skeletal mineralisation [43], making phosphate essential for childhood growth. Organic phosphorus is naturally found in foods that are rich in protein. Inorganic phosphorus is the main component of many preservatives and additive salts found in a variety of processed foods. The bioavailability of organic and inorganic phosphorus varies considerably [44] with 30%–80% bioavailability from organic plant, meat and dairy sources [45] and over 90% from inorganic phosphorus preservatives and additives [46]. Bioavailability is lower from plant foods, including seeds and legumes, due to the limited gastrointestinal absorption of phytate-based phosphorus. Food preservatives and additives (Table 13.13) add to the burden of the diet and need to be factored into dietary counselling.

Table 13.13 Phosphate preservatives and additives.

Phosphate additive	Food industry purpose	Examples of food
Phosphoric acid	Acid	Processed meats, cakes, chocolates, sweets, jams, vegetable fats and oils, cola drinks, beer
Sodium phosphate	Antioxidant	Processed meat, processed cheese, powdered milk
Potassium phosphate	Antioxidant	Cured meats, milk and cream powders, drinking chocolate
Calcium phosphate	Anti-caking agent	Self-raising flour, cake and pancake mixes, powdered milk drinks, instant pasta and sauces
Magnesium phosphate	Anti-caking agent	Salt substitutes, prepared mustard
Diphosphate	Emulsifier	Processed cheese, instant mashed potatoes, cakes
Triphosphate	Emulsifier	Fish fingers
Polyphosphate	Emulsifier	Dried foods and desserts
Distarch phosphate	Thickening agent	Batters for frozen foods, custards, sauces, mayonnaise, salad dressings, pies and fillings, dried foods, drinking yoghurt, flavoured milk, whipped cream, pre-cooked pasta and noodles, starch-based puddings, instant beverages

There is much debate as to when to start dietary phosphate restriction. In the past phosphate restriction was started when either serum phosphate or PTH levels were above normal; this is now felt to be too late in relation to CKD progression, advancement of CKD-MBD and the increase in risk of CVD. Consumption of a phosphate-rich diet in the early stages of CKD releases fibrin growth factor 23 (FGF-23) from the bones [47, 48]. A study in adults with ESRD proposes that FGF-23 is the earliest marker of abnormal phosphate metabolism [49] and it has been found to be an independent risk factor for CKD progression in children [50]. FGF-23 levels above the normal range have been seen as early as CKD stage 3 [51]. Raised serum phosphate levels are not normally seen until CKD stage 4 and significant CKD-MBD has already occurred by this time [50]. Therefore, reducing dietary phosphate in the early stages of CKD has been suggested as a possible strategy to slow down the progression of FGF-23 levels and, thus, delay disease progression [47, 50] and decrease mortality risk from CVD [52, 53].

Phosphate restriction

For infants, standard whey-based infant formulas are used for at least the first 1–2 years of life due to their lower phosphate content. Where hyperphosphataemia persists, Kindergen or Renastart (Table 13.4), usually in combination with standard whey-based infant formula, can be used to regulate serum phosphate levels. Consideration should be given to their lower calcium and potassium contents (and higher sodium content). In older children, cow's milk can be introduced in a controlled amount. Individualised targets should be given for cow's milk and cow's milk products. Phosphate-rich foods and alternatives also should be tailored to the individual's diet (Table 13.6) Where indicated, nutritional supplements with a lower phosphate content (Table 13.4) should be chosen and be included within the dietary allowance. Guidelines for phosphate intake are based on body weight as follows:

- infants <10 kg < 400 mg/day
- children 10–20 kg < 600 mg/day
- children 20–40 kg < 800 mg/day
- children >40 kg < 1000 mg/day

Care needs to be taken not to compromise protein intake while restricting dietary phosphate. A guide to the phosphorus content of different foods per gram of protein is given in Table 13.14. Note this is not appropriate for processed foods due to their added phosphate preservative and additive content. Dietary strategies should enable children and their caregivers to choose foods with less phosphate, but to maintain an adequate protein intake. Maintenance of serum phosphate within the normal reference values for age is desirable. During conservative management and when on haemodialysis (HD), phosphate intake will be reduced with protein

Table 13.14 Guide to the phosphorus content of foods related to their protein content.

Type of food	Phosphorus (mg/g protein)
Poultry, meat and white fish	7–9
Pulses	12–18
Tofu	12
Shell fish, oily fish, offal	15–20
Egg	16
Hard cheese	20
Milk, yoghurt	28
Peanuts	15
Almonds	26
Walnuts	48

modification. Phosphate binders may be needed in addition to dietary phosphate restriction.

Calcium

Childhood and adolescence are critical periods for bone mass accrual. Therefore, it has been advised that serum calcium levels be maintained in the age-appropriate normal range in children and adolescents; this recognises the high calcium requirements of the growing skeleton [42]. Hypocalcaemia is a feature of CKD secondary to diminished gastrointestinal uptake of calcium due to vitamin D deficiency. Calcium intake is compromised when phosphate is restricted in the diet and may need supplementation. An average of 20%–30% of the calcium in calcium-based phosphate binders is absorbed and, therefore, can be factored into calcium intake [54]. It has been suggested that total daily intake of calcium from both binders and dietary sources should be in the range of 100%–200% of the dietary reference intake for age and not exceed 1.5 g/day [22, 55]. The Paediatric Renal Nutrition Taskforce has published more recent recommendations for the dietary management of calcium and phosphate (see Guidelines, companion website).

Vitamin D and parathyroid hormone

Vitamin D deficiency is common in CKD. Therefore, it has been recommended that children with CKD stages 2–5 who have a serum 25(OH)D concentration less than 75 nmol/L be supplemented either with vitamin D_2 or D_3 [41]. A high PTH level in children with decreasing GFR can sometimes reflect vitamin D deficiency/insufficiency and not the activity of renal bone disease [56].

Vitamin D is converted to the activated form 1,25-dihydroxyvitamin D_3 in the healthy kidney. The decrease in activated vitamin D levels seen in CKD contributes to hypocalcaemia (due to decreased absorption in the small intestine), SHPT and the spectrum of CKD-MBD. Recommendations suggest that children with CKD stages 2–5 who have persistently increased serum PTH are prescribed a vitamin D analogue. Supplementation solely with native vitamin D may not adequately treat hyperparathyroidism [57]. Preparations include calcitriol (a naturally occurring form of active vitamin D), alfacalcidol (1α-hydroxycholecalciferol) and paricalcitol. The dose is based on serum calcium and PTH levels and is reduced or suspended if calcium levels are above or below the normal range [57].

The optimal level for PTH in children with CKD is not known; modest increases may represent an appropriate adaptive response to declining kidney function. KDIGO guidelines [42] have been adjusted to reflect this and stress the importance of looking at modifiable factors, such as hyperphosphatemia, hypocalcaemia, high dietary phosphate intake and vitamin D deficiency, in patients who have PTH levels that are progressively rising or persistently above the upper normal limit. Higher PTH levels are associated with a higher morbidity and mortality.

Phosphate binders

Although dietary management can control plasma levels in early CKD stages, persistent hyperphosphataemia requires the addition of oral phosphate binding drugs to block intestinal phosphate absorption (Table 13.15). Compounds use the anionic nature of phosphate for ionic exchange to form a non-absorbable compound that is excreted in the faeces [54]. Aluminium salts, although effective phosphate binders, have been abandoned in children due to their toxicity. Calcium-based binders are the first-line phosphate binder in children [59] and can be made from calcium carbonate or calcium acetate.

Calcium carbonate binders should be chewed and taken preferably just before meals/snacks as a lower pH improves binding capacity. Alternatively, calcium carbonate solution can be added to feed bottles or overnight/daytime bolus feeds. Calcium carbonate impairs the absorption of iron so should be taken separately from oral iron supplements. Approximately 20%–30% of the calcium contained in a calcium phosphate binder will be absorbed and can contribute to hypercalcaemia. Calcium acetate achieves a similar control of serum phosphate at a lower dose of elemental calcium. It is taken during meals and swallowed whole (but can be crushed and added to drinks if necessary).

Calcium-based binders can lead to an increase of the Ca × P ion product and the development of vascular and soft tissue calcification. Soft tissue calcification has been reported in 60% of autopsies of children with renal failure [60]. If a series of serum calcium measurements shows a trend towards the upper limit of normal, a combination of a calcium-based binder with a non-calcium-based phosphate binder, sevelamer, could be used having taken into account other causes of rising calcium [59]. Sevelamer hydrochloride and sevelamer carbonate are calcium-free synthetic anion exchange polymers that bind phosphate and cholesterol. Sevelamer binds to bile salts and may interfere with normal fat absorption and the absorption of fat-soluble vitamins. Therefore, it is recommended that fat-soluble vitamin and folic acid levels are monitored when sevelamer is prescribed [54]. Sevelamer carbonate reverses the negative effect of sevelamer hydrochloride on acid–base balance. If, with a mixture of phosphate binders, serum calcium rises above the age-adjusted upper limit, a switch to all non-calcium-based binders can be considered [59]. It should be noted that sevelamer is contraindicated in patients who are at risk of small bowel obstruction.

Lanthanum carbonate is another available calcium-free phosphate binder, but is not currently used in children due to a lack of data on its effect on the growing skeleton. Sucroferric oxyhydroxide is an iron-based phosphate binder. Trials in adults have demonstrated efficacy, tolerability and safety, with a reduction in pill burden from sevelamer [58]. It is not currently licensed for children as a phosphate binder. Nicotinamide (vitamin B_3) has been trialled in conjunction with a phosphate binder in adults and shown to reduce serum phosphate level further. Nicotinamide reduces phosphate absorption by inhibiting intestinal sodium–phosphate

Table 13.15 Phosphate binders.

	Elemental calcium mg (mmol) per tablet	Dose	Flavour	Estimate of potential binding power
Calcium carbonate binders				
Setlers Tums tablets (500 mg)	200 (5.0)	1–3 tds	Various fruit flavours	Approximately 39 mg phosphorus bound per 1 g calcium carbonate
Calcium carbonate (20% solution)	400 (10.0) per 5 mL	5–15 mL tds	—	
Rennie tablets	272 (6.8)	1 tds	Peppermint/spearmint	
Digestif/Spearmint (680 mg)				
Remegel tablets (800 mg)	320 (8.0)	1–3 tds	Mint	
Calcichew tablets (1250 mg)	500 (12.6)	1 tds	Orange	
Adcal (1500 mg)	600 (15.0)	1 tds	Fruit flavour	
Calcium acetate binders				
Phosex tablets (1000 mg)	250 (6.25)	1–3 tds	Designed to be swallowed whole, but can be crushed and mixed with water or other drink	Approximately 45 mg phosphorus bound per 1 g calcium acetate
Phosex tablets (500 mg) named patient basis	125 (3.1)	2–4 tds		
Renacet* tablets (475 mg)	120 (3.0)			
Renacet* tablets (950 mg)	240 (6.0)			
Sevelamer binders				
Sevelamer hydrochloride Renagel tablet (800 mg)	None	1–3 tds	Swallow whole	Approximately 26 mg phosphorus bound per 1 g sevelamer (this amount varies between 21 and 39 mg) [58]
Sevelamer carbonate Renvela tablet (800 mg) or powder (2.4 g)	None	1–3 tds or 1 sachet of powder	Powder in natural or citrus flavour	

tds, three times a day.
*Not prescribable for children.

co-transporter 2b [54]. Additional data on safety and efficacy are required before widespread use and at the time of writing a trial in adults is underway.

Calcimimetic agents

Cinacalcet is a calcimimetic agent that increases the sensitivity of calcium sensing receptors to extracellular calcium ions, thereby inhibiting the release of PTH. It is gaining use in severe cases of hyperparathyroidism. Promising results have been seen in limited paediatric trials [28, 61, 62]; however, there is still limited experience especially in the first years of life [63]. A large multicentre trial was stopped due to a severe serious event (hypocalcaemia) in one patient; caution in the use of this drug is therefore advised [28].

Hypertension

Hypertension is common in the late stages of CKD and is due to fluid overload and the activation of the renin–angiotensin–aldosteronesystem[21].Hyperparathyroidism can also contribute. Management strategies include salt restriction (Table 13.7), exercise, carefully monitored weight loss in overweight children and strict fluid control where appropriate.

Many children readily exceed the adult daily maximum recommendation for sodium intake of 100 mmol/day (6 g salt) due to their intake of salted snacks and processed foods. Dietary advice should take into account current lifestyles and the hidden salt in foods when devising targets to reduce salt intake. Advice needs to be given on interpreting food labels and giving ideas for lower salt snacks. Poor compliance with salt restriction is a common observation. The UK Scientific Advisory Committee on Nutrition (SACN) [64] gives recommendations on maximum daily salt intake for children throughout childhood, which can be used as a guideline (Table 13.16).

In the absence of fluid overload, hypotensive therapy is started when the child's systolic or diastolic blood pressures are repeatedly >90th centile for age. A systematic review in adults showed a reduction in sodium intake significantly reduced resting systolic blood pressure [65]. It would be prudent to avoid excessive sodium intakes in this group of children.

Table 13.16 Recommendations on salt consumption in children.

Age range	Target daily intake of salt and sodium	
0–6 months	<1 g	<17 mmol
7–12 months	1 g	17 mmol
1–3 years	2 g	34 mmol
4–6 years	3 g	50 mmol
7–10 years	5 g	84 mmol
11–14 years	6 g	100 mmol

Target salt intakes for infants and children have been estimated as an increase in the reference nutrient intake (RNI) by a factor of 1.5 [64] and should be considered the maximum daily intake.
To convert grams of salt to milligrams of sodium: divide the salt figure in grams by 2.5 and then multiply by 1000, e.g. 6 g
salt ÷ 2.5 = 2.4 × 1000 = 2400 mg sodium = 100 mmol sodium.

Preservation of renal function

Control of hypertension and proteinuria continues to be the strongest independent predictor for progression of renal disease [66]. The ESCAPE study group showed that strict blood pressure control slowed the progression on CKD in children [67]. The same trial also showed the benefits of the use of an ACE inhibitor on proteinuria. Proteinuria is associated with inflammatory factors in the urine, which contribute to renal disease progression.

There is clear evidence in adults that obesity is associated with increased risk of development and progression in CKD. A similar association is seen in children; however, there is a lack of large and long-term follow-up studies in paediatrics [66]. There is reluctance to recommend dietary modification in an attempt to delay the progression of chronic renal insufficiency in the early stages of CKD [68]. The lack of significant impact from protein restriction in children was considered earlier (p. 250). Some paediatric data suggest that factors such as anaemia, hypoalbuminaemia, hyperphosphataemia and hypocalcaemia might be associated with the rate of CKD progression; however, further studies are needed to confirm this [66].

Anaemia

The anaemia of CKD is associated with substantial morbidity, an increased risk of CVD, reduced quality of life, increased hospitalisations, anorexia, growth retardation, cognitive impairment and reduced exercise capacity. Anaemia can be seen as early as CKD stage 2 [69]. The blood film is a normochromic, normocytic anaemia as a consequence of inadequate erythropoietin production by the damaged kidneys. The aetiology of anaemia in CKD is multifactorial with iron and folate deficiency, reduced red blood cell survival, hyperparathyroidism-induced bone marrow suppression and gastrointestinal loss. Serum ferritin is used to assess iron status and should be >100 µg/L. Management aims are to prevent the development of iron deficiency anaemia and the maintenance of adequate iron stores. Haematology results are frequently monitored by the MDT.

Dietary assessment

Foods rich in iron, folic acid and vitamins C and B_{12} should be advised to ensure children are achieving recommended intakes for age and sex [19]. Sources of haem iron are to be recommended together with advice about non-haem iron and its potential inhibition by phytates in cereal grains and legumes; polyphenols including tannin in tea, coffee and cocoa; and calcium in milk and dairy products.

Oral iron supplements

Oral iron supplements are prescribed when dietary iron intake is insufficient to maintain adequate iron stores. As the child progresses to stage 5 CKD, intravenous iron therapy is used.

Iron preparations can be prescribed as liquid, tablet or capsule to aid compliance. Vitamin C enhances the absorption of non-haem iron. It is important to avoid over-supplementation. It can be given in two to three divided daily doses [70]. Iron is best absorbed in the absence of medications (antacids, phosphate binders), food, infant formulas, milk or nutritional supplements. Ideally, it should be taken 1 hour before or 2 hours following a feed or meal and be taken with a micronutrient supplement where prescribed. Problems with compliance are common, particularly with the potential side effects including nausea, vomiting and constipation. The ideal prescription can be impractical, and a flexible approach that is conducive to the child's feeding pattern, school and family should be advised.

Cardiovascular disease

The lifespan of children with advanced CKD remains low compared with the general paediatric population, with CVD accounting for the majority of deaths [55]. Cardiovascular abnormalities develop early in the course of CKD and progress as end stage is reached. Recognised risk factors in renal insufficiency include a pro-atherogenic state with left ventricular hypertrophy (LVH), hyperlipidaemia, hypoalbuminaemia, hypertension and dysregulated mineral metabolism. Hypertension and volume overload are associated with the development of LVH in children. There is consistent association between the length of time on dialysis and deteriorating measures of vascular function. Thickening and stiffness of the blood vessel walls have both been associated with abnormal levels of calcium, phosphorus and PTH [55]. The lifelong nature of CKD reinforces the importance of dietetic involvement in reducing CVD risks in connection with addressing the management of fluid levels, hypertension, obesity and the regulation of CKD-MBD and levels of vitamin D.

Education and psychosocial support

The conservative stage of CKD management is a time for ongoing education and preparation for the child and family by all members of the renal team in preparation for stage 5 CKD management. Progressive renal failure is disruptive to a child's schooling, social life and family life. Parents of children with CKD reported moderate health-related quality of life scores, with parents of children undergoing dialysis experiencing more limitations in quality of life [71]. To many families, nutrition can be one of the more demanding parts of management. An understanding of the psychosocial effects of feeding such children is as important as the nutritional advice [72]. Many families travel long distances to their renal unit; regular telephone contact and visits to the home, nursery and school can be invaluable supportive measures to clinic visits. Good communication is essential with other team members to help develop practice, management strategies and shared team philosophies, which ultimately lead to better patient care. There is emerging evidence regarding a positive relationship between MDT support and clinical outcomes [73]. Adequate dietetic time is crucial to provide the close and frequent assessments and support, which is required to optimise nutrition and minimise negative outcomes. These negative outcomes can lead to significant emotional, physical and financial costs to the patients and their families [73]. Attendance on ward rounds, outpatient clinics and psychosocial team meetings are essential [72].

Medication

Several of the prescribed medications in CKD are nutrition related (including phosphate binders, oral iron, sodium supplements and vitamins) and should be periodically reviewed as part of the dietary assessment. Children and their families should be advised on the correct administration and timing of medications to ensure compliance, optimise absorption and minimise potential side effects. Ongoing discussion with education and information about each medication should be routine at each dietetic review. The practicalities of taking medications, including at school, should be identified, and regimens adjusted accordingly following medical and team discussion. Adherence with medication is a significant problem, especially among the adolescent group.

Management of stage 5 CKD

For many children with established renal failure, treatment can be cyclical between dialysis and transplantation. The treatment of choice for all children with established renal failure is a successful renal transplant with pre-emptive transplantation occurring before dialysis is required. Transplantation provides superior long-term survival and quality of life. Children are usually activated on the national waiting list for cadaveric renal transplantation at NHS Blood and Transplant when their GFR falls to approximately 10 mL/min/1.73 m^2. Living donor transplantation is becoming the choice for an increasing number of families.

Pre-emptive transplantation is not always possible and is unsuitable for certain renal diseases or if the child presents in established renal failure. European guidelines recommend commencing dialysis when the estimated glomerular filtration rate (eGFR) is between 15 and 10 mL/min/1.73 m^2 unless the child is growing well and is asymptomatic [74]. The indications for starting maintenance dialysis are a combination of clinical and biochemical characteristics. The presence of fluid overload that is resistant to medical management, especially if the resulting fluid restriction makes it difficult to provide adequate nutrition, is a major factor. Subjective indictors include fatigue, drowsiness and general weakness, which decrease quality of life and educational attainment and attendance [75].

Dialysis in children can be by HD or PD. In the UK, PD is the favoured dialysis modality for children. Data from the 2015 UK Renal Registry showed that 44% of paediatric patients started RRT on PD, 33% on HD and 23% had a pre-emptive transplant [23].

Chronic dialysis

Choice of RRT modality needs to be individualised to fit the needs of the patient and their family. Factors that need to be considered are the patient's age, lifestyle choice, parental preference and assessment of whether the patient their family can adhere to a dialysis regimen at home [75].

Peritoneal dialysis

PD is the method of choice for initiating RRT in the youngest age group and has been shown to preserve residual renal function [74]. PD has numerous advantages: relaxation of dietary restriction; avoidance of vascular access, therefore preserving for future use; ability to provide RRT in the home setting; less disruptive to home and school life; and the daily ultrafiltrate (UF) allowing a more liberal fluid allowance that may be necessary to optimise nutrition. However, it is very labour intensive and gives a high level of responsibility for the family.

The procedure of PD requires a patent abdominal cavity and a functioning peritoneal membrane across which solute and fluid transport can take place. A PD catheter is inserted into the abdominal wall. PD can be performed intermittently (usually overnight) using an automated cycling machine. This automated peritoneal dialysis (APD) is the preferred option in smaller children, combining 5–10 overnight exchanges with a long daytime dwell of dialysate. Alternatively, the child may have continuous ambulatory peritoneal dialysis (CAPD) where the child or caregiver carries out 3–4 exchanges of dialysate during the day with a long overnight dwell.

Peritoneal membrane transport capacity for solutes and ultrafiltration can be estimated using a standardised

peritoneal equilibration test (PET), which is used in determining the PD prescription including dialysate dwell times. A low transporter status in the PET indicates low purification rates and potential issues in achieving creatinine clearance, but ultrafiltration is good. A high solute transport rate in the PET implies good purification, but poor UF. The reason is twofold: firstly, due to the rapid absorption of glucose, the osmotic gradient is lost, resulting in reduced UF; secondly, once the osmotic gradient is lost, the rate of fluid reabsorption is more rapid, leading to a positive fluid balance [76]. Prescriptions can be individualised based on patients' needs; the combination of dwell times and fill volumes can optimise dialysis [77]. Newer PD solutions that lessen the harmful effects caused by the exposure of the peritoneal membrane to glucose have been shown to improve membrane health and viability in adults [76]. There is no strong evidence in children; however, the Renal Association guideline group's view [76] is that the principles used in adults of minimising glucose exposure and avoiding obesity should be applied to the paediatric population. The European Society for Paediatric Nephrology (ESPN) notes some caution in their use in children due to possible hyponatraemia and risk of rebound hypoglycaemia in the daytime [74].

Peritonitis is the single most common complication of PD and requires antibiotic therapy. Anorexia can be experienced as a result of the pressure effect caused by the dialysate in the abdomen, which may decrease appetite and increase vomiting.

Haemodialysis

HD is chosen as the initial mode of RRT in infants with primary oxalosis and those with contraindications for PD (omphalocele, gastroschisis, diaphragmatic hernia, obliterated peritoneal cavity, bladder exstrophy) [74]. Conventional HD has the disadvantage of being a hospital-based treatment that disrupts the home routine, but it can relieve the family of a great responsibility and may be used to give the caregiver some respite. A child will transfer to HD if there is a loss of peritoneal access or function. No comparative studies of conventional HD and PD outcomes in children suggest that one procedure is superior to the other [78]. Intensified and home HD (HHD) is being recognised as an important strategy to improve clinical outcomes [75]. Only two centres in the UK currently provide HHD.

Conventional HD is an intermittent process lasting 4–6 hours typically three times a week; smaller children, especially anuric patients, frequently require four or more dialysis sessions a week to ensure adequate fluid removal. Small molecular weight solutes are removed from the blood by diffusion through a semipermeable membrane. Small solute clearance is typically measured by urea clearance and is dependent on the clearance characteristics of the dialyser and the blood pump flow rate [79]. The dialysis fluid composition takes into account concentrations of sodium, potassium, chloride, bicarbonate, calcium, magnesium and glucose. HD provides a greater level of small molecule mass transfer than PD. Access to the circulation is usually through a central venous catheter in younger children while an arteriovenous fistula is created in older children once blood vessels have developed sufficiently. Central venous catheters pose an infection risk.

Intensified HD, which includes short daily HD, intermittent nocturnal HD and daily nocturnal HD, has demonstrated improved control of phosphate, anaemia and blood pressure. There is less dietary restriction and room to optimise nutrition, leading to improved growth compared with conventional HD [75].

Nutrition and chronic dialysis

Children treated with dialysis require a nutritional prescription dependent on their age and treatment modality. This prescription requires regular dietetic review and includes all the points highlighted in the conservative management of CKD, together with consideration of the efficiency and demands of dialysis. Evidence-based clinical practice guidelines for all stages of CKD and related complications are published in the NKF KDOQI [22]. Nutritional guidelines for the child with stage 5 CKD based on NKF KDOQI data are given in Table 13.12.

The monitoring of dialysis prescriptions (dose of dialysis, solution(s) used, ultrafiltration) and urine output should be carried out by the nephrologist, renal nurse and dietitian and is used when formulating a nutritional prescription. Dialysis dose affects growth and nutritional status in children. Dialysis adequacy can be monitored by urea kinetic modelling, in particular by calculation of Kt/V (normalised whole-body urea clearance) and nPCR (normalised protein catabolic rate). Kt/V is termed as the minimally acceptable dose of dialysis and refers to the dose of dialysis below which a significant increase in morbidity and mortality would occur. The target Kt/V for patients on PD is >1.7 [76] and on HD is 1.2 [79]. Current guidelines recommend that the delivered daily dose be measured monthly. Kinetic modelling software programs can be used to tailor PD prescription to the individual's characteristics and needs. In contrast to adult patients, Kt/V is difficult to define in children, and scientific data demonstrating that dialysis efficacy can be predictive of morbidity and mortality are lacking [80]. Adequacy of PD in children is better expressed by the attainment of appropriate fluid balance, good electrolyte and acid–base control. The most sensitive measure of appropriate dialysis in infants is appropriate growth and development [74].

Energy

The EAR for energy is used as a guideline for requirements. This is corrected for height age if the child's height is <2nd centile (Table 13.12). There is no consistent evidence that energy requirements on dialysis are different from those for normal children. Some studies suggest that HD stimulates the release of cytokines and complement that can have the direct effect of increasing resting metabolic rate [52].

Table 13.17 Glucose absorption from peritoneal dialysate (PD).

PD solution concentration	Grams of anhydrous glucose per 1 L	1.5 L	2 L	Osmotic effect
1.36%	13.6	20.5	27.2	Weak hypotonic solution
2.27%	22.7	34.1	45.4	Intermediate
3.86%	38.6	57.9	77.2	Strong hypertonic solution

To calculate the energy obtained from glucose absorbed from PD fluid: total the grams of glucose from all the exchanges, multiply by 4 kcal (17 kJ)/g and then multiply by 60%–80%.

However, other studies have shown a deficit of energy stores in children on HD, which, when adjusted for lean body mass, gives a similar resting energy expenditure to matched healthy children [81]. Energy requirements should be calculated based on the individual needs for growth and dialysis. Subsequent adjustments for weight gain/weight loss should be made.

During PD glucose is absorbed from the dialysis fluid. It is estimated that glucose absorption from the dialysate can be 10–20 kcal (40–85 kJ)/kg/day [74]. Table 13.17 gives a guide to the energy from glucose absorbed from PD fluid. Energy intake for children on PD should be reduced when excess weight gain is seen. For those children on PD requiring additional energy intake, it is best to consider a nutritionally complete supplement (Table 13.4) in preference to a refined CHO supplement in view of the raised triglyceride levels seen in children on PD and the additional source of exogenous glucose derived from the PD fluid. These children also have increased protein requirements and, therefore, benefit from the protein content of complete supplements. The use of complex CHO foods such as bread, potatoes, rice and cereals should be encouraged. The replacement of glucose in PD fluid by glucose polymers (7.5% icodextrin) is beneficial in children with sodium and water overload; in addition the transperitoneal absorption rate is much lower than that of glucose [80] and so contributes much less energy. The quantity of toxic glucose degradation products is also reduced. Significantly, increased dialysis with an icodextrin daytime dwell in children on overnight APD showed no effect on albumin homeostasis in the short term [82], but longer-term studies are awaited. Excess weight gain is emerging as a problem in children on PD in developed countries, and dietary prescriptions need to be modified accordingly.

Protein

There are limited data to demonstrate the optimal amounts of protein for children on dialysis, and existing data do not include all age ranges. Protein intake must be no less than 100% RNI for children on dialysis, with an addition to compensate for the losses of protein and amino acids across the dialysing membrane (Table 13.12) [74].

Dietary protein restriction has led to poor growth in children on HD. A small study in adults demonstrated a loss of 0.2 g amino acid/L filtrate in an HD session [83]. Protein intake in children on HD needs to be sufficient for growth, but moderated in order to minimise large variations in blood urea levels between dialysis sessions. The aim for pre-dialysis serum urea levels should be <20 mmol/L, provided the child is not catabolic. For children on HD, an added dietary protein intake of 0.1 g/kg/day should be appropriate to compensate for dialytic losses [22].

The protein requirements of children on PD are higher than when on HD to allow for the greater reported transperitoneal losses of protein and amino acids, with the greatest losses being seen in the smaller, younger child (Table 13.12). Daily peritoneal protein losses reduce from an average of 0.28 g/kg in the first year of life to <0.1 g/kg in adolescents [84]. Dietary protein sources with a high phosphate content, including cow's milk, dairy foods and foods with phosphate additives (Tables 13.13 and 13.14), need to be restricted to reduce the dietary phosphorus load that is implicated in the pathogenesis of dialysis-associated calcifying arteriopathy [22]. Infants and children may require complete nutritional supplements either as sip or tube feeds (Table 13.4) to meet recommended protein intakes. High protein intake could negatively affect acid–base status, bone mineralisation and fat-free mass [85]; therefore, any alterations to protein intake should always be made along with ensuring an adequate energy intake. Consideration of serum urea, albumin and phosphate levels is essential in tailoring an individual's protein requirements. Hypoalbuminaemia is a marker of cachexia and protein energy wasting (PEW) and has been associated with mortality in children initiating dialysis such that each 1 g/L fall in serum albumin level has been shown to relate to a 54% increase in risk of death [86]. Rapid changes in albumin levels can, however, be attributed to non-nutritional factors including PD loss of albumin, hydration status, the presence of systemic disease, liver function and a persistent nephrotic state.

Protein requirements may be increased in patients with proteinuria, as well as during episodes of peritonitis or other intercurrent infections. Peritonitis has a catabolic effect on the body, and the permeability of the peritoneum for protein and amino acids can increase by 50%–100%. The main protein loss is albumin although other immunoglobulins are also lost. Serum albumin levels fall in these circumstances.

Amino acid-containing PD solutions have been suggested to replace transperitoneal losses and to reduce glucose load. The ESPN working group found no evidence to suggest a benefit in children [74].

There are losses of amino acids into the dialysate during HD. There are limited and small studies on the use of intradialytic parenteral nutrition (IDPN) in children receiving HD. An early study showed no improvement in amino acid levels after supplementation; another study showed weight gain in three adolescents with organic illness after 6 weeks of starting IDPN [87]. It has been suggested that in patients who do not respond to enteral supplementation, IDPN could be considered in those who have been losing >10% body weight for three consecutive months [87]. The use of IDPN

remains controversial and further clinical trials are needed. There are potential side effects: hyperglycaemia, cramps and long-term changes to liver function.

Protein energy wasting

In patients with CKD, especially those undergoing maintenance dialysis, PEW is the strongest risk factor for adverse outcomes and death [88]. Younger age, duration of CKD and time on dialysis together with the presence of inflammatory diseases are increased risk factors. PEW is characterised by the state of decreased body protein mass and fuel reserves. The PEW seen in CKD is a slow, progressive process. Initially, there is slightly impaired nutrient intake and absorption plus an increase in inflammatory markers in seemingly well-nourished children. In the second phase, depletion of tissue levels and body stores occurs with a change in biochemical and physiological functions; these changes progress with time and marked cachexia is seen [89].

PEW is the result of multiple mechanisms characteristic to CKD including undernutrition, systemic inflammation, co-morbidities, hormonal derangements, dialysis procedure and consequences of uraemic toxicity. PEW may cause infection, CVD, frailty and depression; these complications may also increase the extent of the PEW [90].

Inflammation is an important cause of cachexia and PEW in patients with CKD. An increase in pro-inflammatory cytokines, tumour necrosis factor alpha and interleukin-6 are seen [91]. These act through the hypothalamus to affect appetite and metabolic rate. In turn, poor protein anabolism results in a reduction in serum albumin and prealbumin. Levels of albumin, prealbumin and C-reactive protein (CRP) can be used to assess the degree of inflammation or illness, but should not be used as an indicator of nutritional status. Increased dietary intake of energy and protein alone is not enough to reverse the catabolism associated with inflammation. Adequate dialysis is essential. Current diet therapies in the early stages of investigation into the PEW of CKD are omega-3 fatty acids and soya protein, used for their anti-inflammatory properties [92]. A systematic review by Rangel-Huerta *et al*. reports a positive correlation between omega-3 fatty acid supplementation and lowering of plasma biomarker levels. However, they conclude that further research is required before specific recommendations can be made about the routine supplementation of omega-3 fatty acids in chronic renal disease [93]. A trial by Fanti *et al*., looking at the dietary effect of soy in adult patients with ESRD, suggests a possibility of beneficial effects on inflammatory and nutritional status of HD patients. They acknowledge that larger clinical trials are needed [94]. The treatment of inflammation to improve body composition and linear growth in children with CKD is likely to become a cornerstone in management.

Nutritional supplements

For infants to meet their energy and protein requirements, protein supplements with a lower phosphate content can be added to standard whey-based infant formulas, in combination with energy supplements (Table 13.4). Alternatively, where biochemical parameters allow, infant formulas can be concentrated progressively to provide an increased balance of all nutrients or energy-dense infant formulas can be used (Table 1.18). Biochemistry should be frequently monitored, particularly with respect to potassium, phosphate, calcium, sodium and urea. A combination of Kindergen or Renastart (renal specific low phosphate and potassium infant formulas) and a standard whey-based infant formula is used to design a feed to correct high serum phosphate and potassium levels.

Table 13.18 Case study: A young child with chronic kidney disease with a high serum potassium levels.

A 1-year-old girl, diagnosed with renal dysplasia, is running high serum potassium levels 5.6 mmol/L. Her current feed is 800 mL of a whey-based infant formula, taken orally. She currently does not take any solids.
Wt = 8.5 kg (25th centile). Ht = 72 cm (0.4th centile).
Energy requirement: 72 kcal (300 kJ)/kg. Protein requirement: 1.2 g/kg.

Feed	Energy (kcal (kJ))	Protein (g)	Na (mmol)	K (mmol)	Ca (mmol)	PO_4 (mmol)
Cow & Gate 1 per 100 mL	66 (278)	1.3	0.74	1.8	1.3	1.0
800 mL provides per kg	62 (262)	1.22	0.7	1.7	1.26	0.9

Her feed is changed to a 50:50 mixture of normal infant formula with renal specific low potassium formula, Renastart, to reduce her potassium intake. There is a beneficial increase in energy intake. Note changes in protein, Na, Ca and PO_4 intakes. Her serum biochemistry results and growth pattern will determine if further changes to the feed profile are necessary. Excellent communication with the multidisciplinary team, together with regular monitoring, is essential.

Feed	Energy (kcal (kJ))	Protein (g)	Na (mmol)	K (mmol)	Ca (mmol)	PO4 (mmol)
½ strength Cow & Gate per 100 mL	33.5 (140)	0.65	0.37	0.9	0.65	0.5
½ strength Renastart per 100 mL	45.5 (207)	0.75	1.05	0.3	0.3	0.3
800 mL provides	632 (2640)	11	11	9.6	7.6	6.4
800 mL provides per kg	74 (310)	1.3	1.3	1.13	0.9	0.75

For infants >12 months of age, or whose weight is greater than 8 kg, nutritionally complete supplements can be considered (Table 13.4). Combining feeds and supplements to achieve specific intakes of particular nutrients is a common practice to achieve nutritional and biochemical goals. A case study to show how feeds can be modified to control serum potassium levels is given in Table 13.18.

Nutritional supplements may be useful for children and adolescents depending on dialysis modality and biochemical parameters.

Carnitine

Carnitine is an amino acid derivative that has a key role in the regulation of fatty acid metabolism and adenosine triphosphate (ATP) formation. Altered carnitine metabolism is seen in CKD; limited protein intake, impaired carnitine synthesis, malnutrition and dialysis all contribute. A low serum free carnitine concentration can be seen in paediatric dialysis patients [95]. Carnitine supplements have been proposed as a treatment for symptoms or complications of dialysis including intradialytic arrhythmias, skeletal muscle cramps, hypertriglyceridaemia and anaemia. Further research to support the routine supplementation of children on dialysis is needed. In adults, a systematic review and meta-analysis reported that two out of seven trials showed L-carnitine supplementation significantly decreased the percentage of patients who experienced dialysis cramping symptoms at the end of an HD session [96]. The authors comment, however, that no definitive conclusions should be drawn due to the lack of data available. With regard to the effects of L-carnitine on haemoglobin and erythropoietin dose, the meta-analysis failed to confirm previous findings that supported supplementation. There was no significant decrease in serum LDL cholesterol levels with supplementation.

Fluid and electrolytes

Fluid

Fluid allowance is prescribed for the individual depending on insensible losses, residual urine output and dialysis modality. Insensible fluid losses are calculated as 400 mL/m^2 body surface area per day or approximately 20 mL/kg body weight/day. On PD the fluid removed by ultrafiltration is also included in formulating fluid prescriptions. Fluid weight gain between HD sessions can be problematic especially if the child is anuric; the fluid allowance is based on insensible fluid losses and fluid removal between dialysis sessions. Ideally, interdialytic weight gain should not exceed 5% of the child's estimated dry weight. Prolonged fluid overload in HD can cause cardiac problems, including cardiomyopathy. Accurate weighing of patients with careful interpretation of the intake and output of fluids can help with the interpretation of fluid balance.

In children and infants receiving enteral feeds, the fluid allowance needs to be negotiated with the medical staff to allow space for nutrition and to avoid overconcentration of feeds in order to meet nutritional requirements in a small volume of fluid.

Meticulous attention should be given to fluid management to avoid the cardiovascular complications of long-term fluid overload. Educating children about their fluid restriction should include practical ways of reducing fluid intake including using tablet rather than liquid medicines; the judicious use of foods with a high water content such as jelly, gravy, sauces, yoghurt and milky puddings; and freezing drinks and sipping the fluid as it melts. In older children sucking sugar-free boiled sweets or chewing gum may help along with drinking from small cups/glasses. Thirst prevention techniques, including reducing salt intake and good mouth care, should be considered. Involving younger children in devising fluid record charts can aid compliance. It is also better, psychologically, to talk about a fluid allowance rather than a fluid restriction. Case studies showing example feeds for children on HD and PD are given in Tables 13.19 and 13.20.

Sodium

Infants and children, especially the polyuric infant, on PD can become hyponatraemic (serum sodium <130 mmol/L) due to the sodium losses into the UF. To maintain sodium balance, medicinal salt supplements are prescribed if increasing enteral sodium intake does not correct levels. Conversely, those children on PD who are hypertensive and oedematous require education regarding a 'no added salt' diet (Table 13.7). Hypertension and excess interdialytic weight gain seen in children on HD are invariably related to salt and water overload. The importance of a sodium-restricted diet needs to be reinforced to reduce both thirst and fluid intake. An intake between 1 and 3 mmol/kg body weight/day is usually acceptable.

Potassium

A child with a good urine output can cope with a more liberal potassium intake. In anuric or anephric infants and children, dietary potassium modification is invariably indicated. In adolescents on APD, or those who are having large volumes of dialysate with CAPD, a moderate intake of potassium can usually be allowed. However, advice should be targeted at preventing overindulgence of potassium-rich foods and drinks, e.g. potato crisps may be taken occasionally, but suitable low potassium corn snacks are preferable; squash should be drunk in preference to pure fruit juices.

Although HD is very effective at clearing potassium, because of the intermittent nature of the treatment (typically three times a week), children on IHD invariably require dietary potassium advice to minimise problems with hyperkalaemia (Table 13.5). Some dialysis units allow potassium treats such as crisps or chocolate while receiving HD; these should be eaten within the first 30 minutes of HD and be given in controlled amounts so that the potassium can be cleared during the dialysis session.

Table 13.19 Case study: Meeting the nutritional requirements of a child on haemodialysis.

A boy aged 4 years and 1 month, with CKD stage 5 due to non-recovery of renal function post-cardiac transplant. He has HD three times a week.
Wt = 13.2 kg (2nd centile). Ht = 0.98 m (9th centile).
Fluid allowance 800 mL/day.
Energy requirement: 85 kcal (355 kJ)/kg. Protein requirement: 1.1 g/kg.
This young boy is on a hydrolysed protein formula as he has always experienced feed intolerance due to poor gut perfusion, a consequence of his cardiac condition. With his history of poor weight prior to starting HD, the hydrolysate formula was continued. His feed is delivered via a nasogastric tube (he has been tube fed since his was 2 weeks old). He occasionally picks at food, but has no other oral intake.
Pre-dialysis blood results: Na 136, K 4.9, Ca 2.44, PO_4 1.6, urea 17.
His feed, as shown below, is not complete for all B vitamins. The addition of more Paediatric Seravit to give a greater intake of a range of vitamins and minerals would increase the phosphate content of the feed further, hence has 1 Ketovite tablet a day to provide extra B vitamins. He also has a small dose of calcium-containing phosphate binders that provide some elemental calcium (this has helped keep his serum calcium in the acceptable range).

Feed recipe	Amount	Energy (kcal (kJ))	Protein (g)	Na (mmol)	K (mmol)	Ca mmol	PO_4 mmol
Peptamen Junior 17%	153 g	699 (2922)	21	20.2	24.3	16	13.6
Duocal 14%	126 g	620 (2592)	0	1.1	0.13	0.2	0.2
Paediatric Seravit 0.6% + water to 900 mL	5.4 g	15 (63)	0	0	0.04	3.2	2.7
Total per 100 mL		148 (619)	2.3	2.4	2.72	2.1	1.8
Total per 800 mL		1184 (4949)	18.4	19.2	21.76	16.8	14.4
Total per kg		89 (372)	1.4	1.4	1.63	1.3	1.1

CKD, chronic kidney disease; HD, haemodialysis.

Table 13.20 Case study: Meeting the nutritional requirements of a child on peritoneal dialysis.

A boy aged 3 years and 8 months, diagnosed with FSGS, thought to be secondary to tacrolimus toxicity (given as immunosuppression for previous cardiac transplant). He has a single functioning kidney and is on daily overnight PD.
Wt = 13.2 kg (9th centile). Ht = 0.93 m (2nd centile).
Fluid allowance = 800 mL/day.
Energy requirement: 82 kcal (349 kJ)/kg. Protein requirement: 1.4 g/kg.
Post-dialysis blood results: Na 146, K 4.5, Ca 2.57, PO_4 1.81, urea 13.1.
His feed is delivered via a PEG.
The feed meets the RNI for vitamins except for B_6 (95%) and niacin (77%). As a prudent measure he has 1 Ketovite tablet a day. The feed meets 57% RNI for vitamin A, serum level within normal range. The feed does not meet the RNI for Na (70%), but serum level is in the normal range and he is growing well.

Feed recipe	Amount	Energy (kcal (kJ))	Protein (g)	Na (mmol)	K (mmol)	Ca (mmol)	PO_4 (mmol)
Nutrini 75%	750 mL	750 (3135)	21.0	19.5	21.0	11.3	12.0
Duocal 11%	110 g	541 (2261)	0	0.1	0.11	0.1	0.2
ProSource TF 1.5% + water to 1000 mL	15 mL	19 (80)	4.4	0.1	0.06	1.7	1.1
Total per 100 mL		131 (548)	2.5	2.1	2.12	1.3	1.3
Total per 740 mL		969 (4052)	18.5	15.5	15.6	9.6	9.6
Total per kg		73 (305)	1.4	1.2	1.19	0.6	0.7

FSGS, focal segmental glomerulosclerosis; PD, peritoneal dialysis; PEG, percutaneous endoscopic gastrostomy; RNI, reference nutrient intake.

Hyperkalaemia can result in fatal cardiac arrhythmias. When plasma levels are >6.5 mmol/L, there is a prolongation of the PR interval and peaking of the T wave on electrocardiogram (ECG). In such instances salbutamol is prescribed to enhance cellular potassium uptake. An ion exchange resin such as calcium resonium can be used as a crisis management strategy. It can take several HD sessions following a high serum potassium level to achieve an acceptable baseline level due to the movement of potassium from the intracellular fluid.

Education about potassium intake needs to be tailored to each individual. Advice on adapting recipes at home to lower potassium content of meals may be helpful. Intake needs to be reviewed at frequent intervals together with blood

biochemistry results and dietary analysis. A photographic album of foods rich in potassium and food models can be useful educational tools. Older children need to be involved in decision making and the setting of targets when discussing serum potassium levels. Having potassium 'swaps' can also be helpful in this age group, e.g. a 5–10 mmol potassium 'treat' a day of their choice; this could be an extra piece of fruit or vegetable portion, a small portion of chocolate or some crisps.

Phosphate

Phosphate restrictions continue when on dialysis (Table 13.6). In adults 800 mg of phosphate is typically removed during each HD session and 300–400 mg/day on PD. Removal figures will be lower in children due to lower flow rates and volume of dialysate used.

As with potassium restriction advice needs to be tailored to each individual. Education and support around the taking of phosphate binders is also advisable.

Micronutrients

Little is known about the essential micronutrient requirements or biochemical status of children with CKD. It is recognised that children with CKD on dialysis are at risk of vitamin and mineral deficiencies. This may be due to inadequate intake, poor absorption and dialysis-related losses [22]. Individual dietary assessment is essential, taking into account intakes from diet, infant formulas, oral nutritional supplements and enteral feeds, the latter often being the sole source of nutrition for many younger patients. Only then can micronutrient supplements be individually and safely prescribed, where indicated [27]. Dietary assessment has numerous limitations, but can be supported with regular measurement of serum levels of vitamins and minerals that may guide when to start supplementation and what to give.

The RNI for healthy children of the same age and sex [18] provides guidelines for children with CKD [97] and should be aimed for in stages 2–5 CKD, with the exception of calcium, phosphate, magnesium, sodium and potassium, which may not bear any relation to recommended dietary reference values.

For children on dialysis a water-soluble vitamin supplement is often prescribed as a prudent measure, although a recent study measuring serum levels of B vitamins of mainly unsupplemented children on dialysis showed normal to high levels of these in all children [98]. Adult renal studies have shown that there are potential dialysate losses of vitamins C, B_6 and folic acid [99]. Published adult recommendations for these vitamins are likely to be too high for the majority of paediatric patients [100]. Excessive intakes of vitamin C should be avoided as elevated oxalate levels can lead to the development of vascular complications [101].

Vitamin A levels are invariably increased in the serum of children on dialysis as retinol binding protein levels increase with uraemia. Vitamin A is also not removed in dialysis. Elevated levels of vitamin A in CKD have been associated with hypercalcaemia, anaemia and hyperlipidaemia [102]. A study has shown that those children on exclusive or supplemental feeding received a higher vitamin A intake and had a serum vitamin A level above the upper limit of normal compared with those on diet alone [103]. It was also shown that those children on dialysis were more likely to have a higher vitamin A level relative to their vitamin A intake compared with those children not on dialysis. An excessive intake of vitamin A should be avoided. An intake close to the RNI is a sensible practice target [103]; however, this can be difficult to achieve when the vitamin A contribution from feeds and nutritional supplements is also considered.

Vitamin D has been discussed earlier (p. 253).

Homocysteine is an intermediary of methionine metabolism that, at raised levels, is a risk factor for CVD. Hyperhomocysteinaemia is common in adult patients with chronic renal insufficiency and appears to relate to reduced clearance of plasma homocysteine. Supraphysiological folic acid treatment has been used to normalise homocysteine levels in CKD, but a recent systematic review has shown that homocysteine lowering based on folic acid does not reduce cardiovascular events in people with kidney disease and should not be used as such [104]. Increased cancer outcomes have been shown for patients on high levels of folic acid [105].

Low serum zinc and copper levels were seen in a study of paediatric patients on dialysis, some of which were supplemented [106]. Zinc and copper is cleared by dialysis, which could explain the low levels in this group. Low zinc levels can result in anorexia, impaired would healing and faltering growth. Papers in adult studies discuss the theoretical risk of both deficiency and accumulation of trace elements depending on dietary intake, removal by dialysis, composition of source water and residual kidney function [107]. It is helpful to measure serum levels before starting supplementation as these trace elements have impaired clearance with reduced renal function. Further studies are needed in order to evaluate the benefit of supplementation on clinical outcomes.

Infants and children receiving nutritional support from complete feeds, usually by the enteral tube feeding route, are less likely to require extra vitamin and minerals. Older children, with an inadequate diet and poor compliance with oral nutritional supplements, may benefit from micronutrient supplements.

Micronutrient intakes can be greater than the RNI when adult renal specific feeds are used solely or in combination for children. It needs to be borne in mind that some nutrients, including pyridoxine and magnesium, can have toxic effects at high intakes. Dietary intake should be evaluated and serum levels measured where intake far exceeds the RNI for all vitamin and minerals.

To aid compliance and acceptability, the taste and presentation of micronutrient supplements are important factors. Ketovite tablets (dose 1–3 per day) are most widely prescribed.

Encapsulating peritoneal sclerosis

Encapsulating peritoneal sclerosis (EPS) is a rare, but serious complication of long-term PD. It involves the formation an inflammatory and later fibrotic 'cocoon' surrounding the gastrointestinal tract [84]. The result is abdominal inflammation and intestinal obstruction. The clinical presentation includes abdominal pain, nausea, vomiting, weight loss, low-grade fever and ultrafiltration failure [108]. The treatment is immunosuppression or surgery (partial or complete enterolysis). Post-surgery, PN is commenced. The possibility of refeeding syndrome may need to be considered (p. 63). Enteral feeds are gradually reintroduced. A 10-year study showed a prevalence of 1.5% in paediatrics, and the outcome data was significantly better then seen in the adult population [109].

Feeding problems in CKD

Improved clinical experience in dialysis techniques and renal transplantation has seen increasing numbers of infants taken onto end-stage management programmes. The ultimate goal is early transplantation; this is technically more complex in the very small child. Most units prefer to promote the growth of the child to a body weight >10 kg or length >80 cm before they are eligible for transplantation. Optimal nutrition, with or without early dialysis, is essential in the care of these infants and young children since growth is crucially nutrition dependent during the first 2 years of life. Nutrition has been one of the most important factors responsible for the improved outcomes and improved growth seen in this population [110, 111]. Data on growth, without the use of GH, and the dietetic contact necessary to manage and support children and their families receiving chronic PD and intensive nutrition support illustrates the essential role of paediatric renal dietitians in the management of such families [112]. The provision of adequate nutrition for growth requires frequent adjustments of nutritional prescriptions in accordance with blood biochemistry, especially in preschool children.

Once diagnosis is established, there may be a period of conservative management to determine if renal function improves or stabilises. Appetite is poor in the infant with CKD, vomiting is common, and there is usually a reluctance to feed spontaneously. This impacts on both growth and biochemical stability. Supplementary enteral feeding is indicated early to achieve and maintain growth and neurodevelopmental progress when oral feeding is insufficient. In addition, salt and water should not be restricted in the salt-wasting polyuric infant as this will also adversely impact on growth [27]. Initiation of enteral feeds before height deficits were noted has been associated with superior height outcomes compared with initiation after growth had faltered [113].

Tube feeding reduces some of the parental anxieties associated with oral feeding while assuring nutritional and medication prescriptions are met. It is preferable to force feeding, which can result in vomiting and/or refusal of formula or food as well as having a detrimental effect on normal oral feeding behaviour in the long term [114]. Data from the International Pediatric Peritoneal Dialysis Network (IPPN) demonstrated a benefit of gastrostomy over NGT feeding. A possible explanation is the increased vomiting associated with an NGT, which can act as a stent passing through the gastro-oesophageal junction [30]. Placement of a gastrostomy button or percutaneous endoscopic gastrostomy (PEG) tube in a child already on PD may not be ideal as it carries the risk of peritonitis. Ledermann *et al*. recommend placement prior to a PD catheter [114], while two other groups report no statistical difference with gastrostomy insertion prior to or after PD catheter insertion [115, 116].

Vomiting can be an ongoing problem for some infants; feed prescriptions should be closely monitored and altered appropriately. Some infants are sensitive to changes in their fluid balance, and this should be considered in relation to vomiting. Persistent vomiting is stressful for families, and close dietetic and team support is required in the long term [72]. Gastro-oesophageal reflux (GOR) and disturbances in gastrointestinal motility are common in infants with CKD [117], and investigations to detect and treat appropriately are essential. Advice about appropriate positioning of the baby when feeding should be initially given and a thickened feed can be tried (p. 133). Gastroparesis (delayed gastric emptying) can be treated with prokinetic agents such as metoclopramide, erythromycin and domperidone. Due to concerns with potential side effects and lack of robust evidence, these medications are prescribed with caution. Some medications, including calcium channel blockers and calcitonin, can delay gastric emptying and should be reviewed. Persistent GOR can respond to proton pump inhibitors such as omeprazole and lansoprazole [118]. In extreme cases a fundoplication may be indicated to manage persistent vomiting [74]. Caregivers, especially those of infants, need frequent reassurance that lack of interest in food and anorexia are symptomatic of renal failure.

Weaning should be encouraged at the customary recommended age to enable the development of oral feeding experiences and the reduction of sensitisation to food. The feeding problems seen in infants and young children with CKD are multifactorial. Many of these infants commonly pass large volumes of dilute urine; this creates a thirst and preference for water rather than formula. The large number and volume of prescribed medications can contribute to refusal to take adequate formula by mouth. Some of these infants have disordered taste perception and refuse energy-dense sweetened foods in preference for salty foods. They often find difficulty in swallowing lumpy foods and fail to progress from puréed baby foods to more energy-dense family foods; in extreme circumstances even puréed foods may cause choking and retching [119]. Caregivers need reassurance that it is typical for a child with CKD to only take small amounts of food and drink and that the early introduction of enteral feeding is recommended before growth failure is evident. Positive reinforcement with the use of dummies (pacifiers) and oral feeding while receiving daytime enteral bolus feeds should be

encouraged to help minimise feeding issues [120]. A review article summarises some common oral feeding challenges and offers useful strategies and interventions [121].

Enteral feeding regimens that provide a balanced fat and CHO profile to meet energy requirements do not enhance the hyperlipidaemia seen in CKD [122].

Nutritional support

Prevention of growth disturbances is a major goal of nutritional therapy. The early initiation of enteral nutritional support is considered when the child's oral intake fails to meet recommended nutritional requirements and growth velocity is affected. Prolonged trials of oral supplements should be discouraged. Brief intervals of poor growth during infancy can result in significant loss of height potential. Where oral supplementation is unsuccessful, enteral tube feeding should be instigated early before significant nutritional deficits and aversive feeding interactions have developed between the child and family.

There needs to be a discussion with the family and the MDT as to the most appropriate feeding route for each child. Essentially, a shared team philosophy of early and sustained nutritional support is required [123]. Play preparation with the use of DVDs, photograph albums, booklets and dolls can assist in teaching, while some caregivers find it helpful to talk to other families with similar experiences.

The delivery of the feeds must be tailored to the individual child and their home circumstances. Intermittent enteral tube feeding can be given as daytime boluses or serve as a top-up if oral feeds are not completed. These bolus feeds can be given as gravity feeds or given more slowly through an enteral feeding pump. Initially, slower rates may be required for more concentrated feeds to improve tolerance [112]. A continuous overnight infusion via a pump can be beneficial in those infants with more severe GOR and may reduce vomiting; however, many community healthcare professionals will not supervise this feeding method, especially if the child has an NGT rather than a gastrostomy device *in situ*. If poor tolerance of feeds is having a negative effect on growth, jejunal feeding should also be considered.

Learning points: nutritional management of chronic kidney disease

- *Considerations: adequacy of energy and protein intakes; fluid and electrolyte balance; regulation of calcium and phosphate intakes; correction of acid–base abnormalities; adequacy of micronutrient and iron intakes*
- *Dietary requirements depend upon age, stage of CKD, clinical management and nutritional assessment*
- *Prevention of growth disturbances is a major goal of nutritional therapy; early initiation of enteral nutritional support is considered when oral intake fails to meet recommended nutritional requirements and growth velocity is affected*
- *Energy requirements are the same as those of healthy children; energy intakes below the EAR contribute to growth failure*
- *Protein restriction shows no significant impact on delaying progression of renal failure and there is an association with inferior growth*
- *Protein intake should be optimised to allow for the maintenance of nitrogen balance and growth, together with the preservation of lean body mass*
- *Protein must provide at least 100% of the RNI for age to avoid protein becoming a limiting factor in growth*
- *When on dialysis additional protein may be needed to compensate for the losses of protein and amino acids across dialysing membranes*
- *Hyperkalaemia can be exacerbated by acidosis – extracellular potassium shifts occur with metabolic acidosis as bicarbonate is lost through the kidney; acidosis is corrected with administration of sodium bicarbonate*
- *Vitamin D deficiency is prevalent and often severe and contributes to abnormalities in calcium, phosphate and PTH homeostasis*
- *Management of CKD-MBD should be based on serial assessments of phosphate, calcium, PTH and vitamin D levels; dietary management: assessment and manipulation of calcium and phosphate intakes, treatment of vitamin D deficiency*
- *Reducing dietary phosphate in the early stages of CKD is a possible strategy to delay disease progression and decrease mortality risk from CVD*
- *The lifelong nature of CKD reinforces the importance of dietetic involvement in reducing CVD risks: management of fluid levels, hypertension, obesity and regulation of CKD-MBD and levels of vitamin D*
- *Nutrition can be one of the more demanding parts of management; an understanding of the psychosocial effects of feeding children is as important as the nutritional advice*

Renal transplantation

Renal transplantation is the treatment of choice for children with stage 5 CKD to restore normal or near-normal physiology and metabolic function without dialysis and minimal dietary restrictions. Survival of children with an allograft is superior compared with those remaining on dialysis. The donor kidney can come from a living related, living unrelated or deceased donor. Pre-emptive transplantation results in improved graft survival and reduced mortality compared with dialysis followed by transplantation [21]. Children on the UK cadaveric transplant waiting list are given priority over adults, and an average wait is 286 days (2016–2017 data) [124]. Living related donor (LRD) transplantation is increasing. This has the advantages of shorter waiting times and improved graft survival. Five-year paediatric allograft survival is 91% for LRD and 79% for cadaveric transplants [21]. Of the 127 transplants in the 2016–2017 data, 72 were LRD, 3 of these through the paired exchange scheme.

Post-transplantation medications aim to prevent graft rejection and include the calcineurin inhibitors cyclosporin and tacrolimus, mycophenolate and steroids. Minimising steroid exposure can improve linear growth and reduce metabolic disorders. Early steroid withdrawal has been shown to significantly help growth at 6 months post-transplant especially in pre-pubertal children [125]; improved lipid and glucose metabolism profiles were also seen. Nutritional advice continues to be an important feature of treatment post-transplant with the dietitian continuing to be involved with the ongoing management.

Initial dietary management

Immediately after transplantation, the main concerns for the recipient include the complications of rejection and infection. Feeding commences on the return of normal bowel sounds. If there are no complications, the child usually develops an appetite as renal function improves and previous dietary restrictions can be relaxed in line with biochemical results. Fluid balance is dependent on output and is assessed daily by medical staff. A high fluid intake is initially encouraged to perfuse the transplanted kidney. Serum phosphate levels typically fall below reference ranges due to the large tubular and urinary losses; dietary advice should encourage phosphate-rich foods and drinks at this stage. Invariably phosphate supplements are prescribed in the early post-transplant days to match urinary losses. Serum magnesium levels can also fall and require medicinal supplementation. Those children who experience acute tubular necrosis following a renal transplant require a period of conservative management or dialysis therapy, including appropriate dietary modification, until adequate renal function is achieved.

In infants and children receiving enteral feeds pre-transplant, concerns have been raised about a prolonged transition to exclusive oral nutrition [120]. Others have shown that long-term enteral tube feeding does not preclude the transition to normal feeding and the majority of children will eat and drink after a successful renal transplant [110]. Feeding dysfunction and impaired oromotor development appear to be more evident in infants who received NG feeding than in those who had gastrostomy buttons for feeding [126].

It is recommended to cease tube feeding, whenever possible, at the time of renal transplantation in order to stimulate appetite as renal function is restored, especially if higher doses of corticosteroids are prescribed. To do this successfully, the medical staff, dietitian and team members need to provide ongoing support to families. Most children do well and resume normal eating and drinking post-transplant [110, 126]. There will always be exceptions to this approach with some children requiring short periods of nutritional support, particularly in the first few weeks or months post-transplantation. In such patients a planned and agreed strategy to wean off enteral tube feeding must be implemented. Common experience is that some young children take time to adapt to drinking more fluids. In such cases fluid boluses delivered via the enteral feeding tube are given short term. Severe eating difficulties present in a small number of children; these may benefit from a behaviour modification approach [127].

Although a renewed appetite is positive in the initial stages of management, excessive weight gain and obesity in the long term must be avoided. Both the child and family should be reminded of this soon after transplant. The principles of a sensible, healthy eating, well-balanced diet for all the family is advised prior to discharge from hospital.

All patients on immunosuppressive therapy need to take care with food hygiene and avoid foods that carry a high risk of food poisoning organisms such as *Listeria* and *Salmonella*; this should be discussed with each child and family prior to discharge.

Hypertension can present following transplantation and antihypertensive therapy is prescribed. Early post-transplantation systolic hypertension strongly and independently predicts poor long-term graft survival in paediatric patients [128]. Arterial wall stiffness has been demonstrated in young adults with ESRD since childhood, with hypertension being the main determinant [129]. Weight control and advice regarding salt intake, as part of the healthy eating recommendations, should be encouraged.

Dyslipidaemia is seen in some children following transplantation and requires regular assessment. An evaluation 2–3 months after transplantation and annually thereafter is recommended [130]. Studies have identified that 40% of deaths in adult renal transplant patients are attributed to CVD and they occur at a younger age than in the general population [131]. There is growing evidence that dyslipidaemia hastens the progression of renal disease itself. Disordered lipoprotein metabolism results from complex interactions among many factors including the primary disease process, use of medications such as corticosteroids, the presence of malnutrition or obesity and diet [132]. All children with dyslipidaemia should follow the recommendations for therapeutic lifestyle changes [131]. Dietary modification should include advice favouring monounsaturated and polyunsaturated fats and oils in preference to saturated fats, together with encouraging the regular consumption of omega-3 fatty acids and antioxidants from fruit and vegetable intake. Moderate physical activity is recommended.

Ongoing dietary management

Children still receiving nutritional support post-transplant should be regularly reviewed in the outpatient clinic. A transition period to encourage the oral route of feeding should be agreed with families. To stimulate the appetite, a reduced volume of bolus feed should be given during the day. Vitamin and/or trace mineral preparations may be required in those children whose micronutrient intakes are poor. Iron status should also be monitored. Many younger children struggle with fluid targets post-transplant and require bolus top-ups with water.

Transplantation restores the conditions to promote more typical growth. However, (when used) corticosteroids as well as a low GFR in the graft kidney will both have growth suppressive effects. Steroids suppress growth mainly by interacting with the GH/IGF-1 axis and by affecting the growth plate [133]. A retrospective analysis of longitudinal growth in children who

had been weaned off steroids within 6 months of transplant showed improved height growth [28]. A nutritionally adequate balanced diet should be established to sustain normal growth while guarding against overnutrition.

The prevention of weight gain leading to obesity can be a difficult problem particularly for adolescents where body image is important. The patient who was anorexic prior to transplantation may not engage in discussions to modify food intake to control body weight. Adolescents who experience excess weight gain and change of body image can be susceptible to crash dieting and possible fasting to lose weight. Healthy eating and exercise should always be encouraged, including information on the health risks of alcohol and smoking. Adolescents need to be included in setting their own dietary targets. Paediatric data looking at weight status at transplant found that obese recipients were at higher risk of mortality and graft failure compared with normal weight patients. Overweight patients also had greater risk of graft failure, acute rejection and delayed graft function. Obese children either pre- or post-transplant experience higher workload within the nephrons that contributes to graft loss [134].

A small number of children develop steroid-induced diabetes mellitus post-transplant, which requires insulin therapy and appropriate dietary advice. Hyperglycaemia is also seen in a small number of children when acute rejection episodes are treated with pulses of methylprednisolone; this effect is often transitory.

Chronic rejection of the transplanted kidney will eventually result in the child returning to dialysis with appropriate dietary intervention as for CKD.

Learning points: renal transplantation

- *Nutritional advice continues to be important post-transplant; weight control and advice regarding salt intake, as part of the healthy eating recommendations, should be encouraged*
- *Studies have identified that 40% of deaths in adult renal transplant patients are attributed to CVD and they occur at a younger age than in the general population*
- *Overweight patients have a greater risk of graft failure, acute rejection and delayed graft function; obese children either pre- or post-transplant experience a higher workload within the nephrons that contributes to graft loss*

Nephrotic Syndrome and Congenital Nephrotic Syndrome

Shelley Cleghorn

Nephrotic syndrome

Nephrotic syndrome (NS) is an umbrella term for a group of clinical features: proteinuria (early morning urine protein–creatinine ratio >200 mg/mmol), hypoalbuminaemia (<25 g/L), 3+ protein on urine dipstick and oedema with or without hyperlipidaemia. The kidneys have a filtration barrier made up of a membrane and cells called podocytes with foot-like processes and a slit diaphragm. When there is disruption of the foot-like processes, the filtering membrane does not function properly, resulting in protein leakage into the urine. This results in reduced protein in the blood and lowers the plasma oncotic pressure. Water then moves from the blood vessels to the body tissues causing swelling (oedema).

Proteins have important functions in the blood. They:

- regulate the amount of water in blood vessels
- act as carriers for many substances in the blood, such as hormones and lipids
- prevent blood from clotting
- are important for the growth and development of children
- and, in the form of antibodies, are an important part of the immune system

When a large amount of protein is lost in the urine, the child can become oedematous, be prone to infections, become anaemic, suffer poor growth and be prone to blood clots.

Dyslipidaemia results from several underlying complex mechanisms including increased production of cholesterol, triglycerides and lipoproteins in the liver, decreased activity of lipoprotein lipase and reduction of the albumin transportation of cholesterol in the blood [135].

NS may be due to an inherited condition or it may be acquired due to an infection, allergy, neoplasm, drugs or another disease process such as inflammation of the blood vessels (vasculitis). It is not always possible to determine the exact cause of the NS; hence, it is termed idiopathic nephrotic syndrome (INS).

NS can be classified according to:

- age
- response to steroids
- histology
- genetics

Congenital nephrotic syndrome (CNS) is usually diagnosed in the first 3 months of life (p. 269). Infantile NS presents between 3 months of life and a year of age.

Steroid-sensitive NS (SSNS) includes frequently relapsing (FRNS) and steroid-dependent NS (SDNS). 80%–90% of children with INS will respond to treatment with steroids within 4 weeks. FRNS is when there are ≥2 relapses in 6 months or ≥4 relapses in 1 year. In the case of SDNS, the child relapses within 2 weeks of stopping steroids, or while they are still on

steroids. Steroid-resistant NS (SRNS), as the name suggests, is when the child does not respond to steroids; 10%–20% of children with INS have this type of disease.

NS results from changes in the kidneys. These changes include:

- minimal change disease (MCD) – very small changes to the glomeruli that can only be seen under an electron scanning microscope
- focal segmental glomerulosclerosis (FSGS) – some of the glomeruli are damaged and become scarred
- membranoproliferative glomerulonephritis (MPGN) – the glomeruli become inflamed

A renal biopsy is usually not necessary at diagnosis as it is the responsiveness to steroids that is more predictive of the child's outcome. Children with MCD tend to respond well to steroid treatment, and the outcome is good with minimal dietary problems. Conversely, those with FSGS tend to be less responsive to steroids and may be at more risk for progressive kidney disease and may need more dietary involvement. The finding of the recurrence of protein in the urine after a renal transplant in a child who has FSGS indicates that there are circulating factors that may play a role in the pathogenesis of NS. In this instance, plasma exchange may induce remission.

Genetic testing should be considered if a child has CNS, SRNS or a family history of NS. Genetic mutations in podocyte structure and function present most often as either CNS or SRNS [135]. Children with monogenic SRNS experience higher rates of resistance to immunosuppression, but lower rates of disease recurrence after renal transplantation [136].

Although the classifications shed little light on the understanding of the disease, they do guide management and help predict long-term outcome [135].

Treatment

The first-line treatment for NS is oral corticosteroids. It induces remission in about 80% of children [135]. Side effects of long-term steroid use in children with NS include growth impairment and weight gain as well as behavioural changes, anxiety and depression. Some children may need additional immunosuppressants including rituximab, cyclosporin, tacrolimus, cyclophosphamide (CYP) or mycophenolate mofetil (MMF), the aim of which is to reduce the number of relapses and keep them in remission longer. In the relapse phase salt restriction is essential and a key aspect of the management of oedema.

Dyslipidaemia

Dysregulated lipid metabolism leading to dyslipidaemia is a complication of persistent NS. Whereas adults with NS have a markedly increased risk of both myocardial infarction and coronary death compared with that of healthy individuals, very few data are available regarding these risks in children [137]. The use of statins for the treatment of children with NS has not been well studied; therefore, it is not current practice to treat with statins.

Dyslipidaemia and diet

Unfortunately there is very little evidence to guide on the optimal treatment of dyslipidaemia in patients with NS [137]. Dietary supplements, such as fish oils, have been poorly studied in NS. Two studies examining omega-3 fatty acids have shown some positive effects; however, the studies have a small number of patients and limited follow-up [138].

Other lifestyle changes include weight control in patients who are overweight and increased exercise. These recommendations have never been formally studied in patients with NS; however, they seem a sensible lifestyle change together with the use of monounsaturated and polyunsaturated fats and a decrease in saturated fats. Care must be taken not to compromise the energy intake of children who have poor appetites and growth.

Food allergy

Over the years there have been numerous reports suggesting an association between INS and allergies. The mechanism underlying minimal change disease is unknown, but it is believed to be immune mediated. As immunosuppression with corticosteroids is the most common treatment in NS, it is reasonable to think that impairment of the immune system plays a pathogenic role in the disease development.

Relapses have been described after exposure to allergens and patients with MCD can show increased IgE levels [139]. There are very small clinical trials and case reports on the positive effects of hypoallergenic diets, such as milk- or gluten-free diets, although the response to these exclusion diets has been inconsistent as well as the results being confounded by a lack of a control group. Research on diets as a therapeutic option in NS is limited [139, 140], though a recent case series describing the effect of a gluten-free diet on eight children with difficult to manage NS showed clinical improvement, with a reduction or discontinuation of steroid dosage [141]. The use of hypoallergenic diets is not currently recommended as more research is needed in this area.

Growth

Glucocorticoids (GC) are known for their adverse effects on skeletal health [142] and high dose steroid therapy in children is known to impair growth and increase body mass index (BMI), with these effects proportional to dose and duration of the disease and therapy. Steroid-sparing treatment strategies may improve linear growth [143, 144] and have been associated with a lower BMI [145].

Some studies suggest that progression of steroid-induced growth failure can be prevented by administration of rituximab. A study including 51 patients with complicated SDNS or FRNS showed mean height *z*-scores at 1, 2, 3, 4 and 5 years after the initial rituximab treatment were not significantly different from those at the time of initial rituximab treatment [146].

In a retrospective study looking at long-term effects of using CYP as a treatment for FRNS and SDNS in 143 children, it was found that height SDS at last follow-up was not significantly different from height SDS at time of CYP

introduction. After using CYP treatment, BMI decreased significantly [147].

A study with 60 patients evaluated the final stature of adults with childhood-onset steroid-responsive INS. INS-related issues did not prevent final stature reaching the predicted target height [148].

Vitamin D

Many small studies have documented very low total 25(OH) D levels in NS, attributed to the urinary loss of vitamin D binding protein (DBP) and albumin [149]. Children with NS and normal renal function have evidence of abnormal bone metabolism and structure, and vitamin D deficiency may be an important modifiable risk factor in this population. However, skeletal outcomes have not been addressed, and guidelines for management of bone health in this population are lacking [149]. In an incident INS cohort, all children at diagnosis had 25(OH)D deficiency. Supplemental vitamin D decreased the odds of 25(OH)D deficiency at follow-up, supporting a role for supplementation [150].

More research is needed to provide guidance about the management of vitamin D deficiency in NS.

Micronutrients

Trace elements play a significant role in several metabolic processes and often circulate in the blood bound to protein.

Anaemia is one of the complications seen in patients with persistent NS and may occur as a result of excessive urinary losses of iron, transferrin (iron transport protein), erythropoietin, transcobalamin (which binds and transports vitamin B_{12}) and/or metals. This leads to a deficiency of substrates necessary for effective erythropoiesis. Supplementation of iron and erythropoietin alone often does not lead to correction of the anaemia [151].

Copper plays a significant role in erythropoiesis, and its deficiency is known to be associated with anaemia and other haematological abnormalities. Urinary losses of ceruloplasmin, a copper carrier protein in plasma, can lead to copper deficiency and consequent anaemia in children with NS. If anaemia does not improve with iron and erythropoietin therapy, copper deficiency could be considered with measurement of serum copper levels [151].

Vitamin B_{12} (cobalamin) is transported in plasma bound to the protein transcobalamin. The role of vitamin B_{12} in erythropoiesis is well established, and its deficiency can lead to acquired megaloblastic anaemia. How much impact these urinary losses have on the development of anaemia in children with NS is not clear.

The reticulocyte count is the best laboratory marker of effective erythropoiesis, and levels are expected to be low in anaemia due to deficiencies in erythropoietin, iron, vitamin B_{12}, folate and copper [151]. In a small prospective study, plasma levels of boron, selenium and zinc were shown to be significantly lower in 14 children with NS in active phase compared with 14 healthy children [152].

A study including 48 children with NS showed elevated serum copper levels in relapse, contrasting with previous findings of depressed serum copper. Low serum copper levels, as previously reported, may occur in the early disease phase because of loss of ceruloplasmin in urine. Increased plasma levels likely reflect oxidative stress. Plasma selenium was significantly decreased in active NS compared with controls [153].

Zinc is an important antioxidant and aids growth in children. Low serum zinc levels have been seen in children in clinical practice with SRNS and CNS. Plasma zinc constitutes only 0.1% of total body zinc stores. Zinc is an important component of alkaline phosphatase (ALP) and zinc deficiency leads to a decreased serum ALP level. In a systematic review including six randomised controlled trials, zinc supplementation reduced the frequency of relapses in children with SSNS and SDNS/FRNS; however, the GRADE evidence generated was of very low quality [154].

There is very limited literature on the dose of supplementation that is needed when low levels of trace elements are found [155]. There are no recommendations for monitoring micronutrient status in NS patients. In CNS or SRNS, if there is concern about a child's growth or ongoing anaemia, measuring levels of trace elements and relevant micronutrients would seem acceptable; however, more evidence is needed to justify routine measurements of these nutrients in all patients.

Protein

Whether a high or low protein intake is necessary in NS is questionable, and there is limited evidence on protein needs for children. An old study in nephrotic rats suggested that augmentation of dietary protein stimulates albumin synthesis, but also causes an increase in glomerular permeability so that the excess albumin synthesised is lost in the urine [156]. In a further study, dietary supplementation with protein had no obvious beneficial effect on the nutritional status of nephrotic rats [157]. Low protein diets have been shown to decrease albuminuria in rats with NS [158]. In children a low protein diet carries the risk of malnutrition and is, therefore, not recommended.

Oedema

One of the primary strategies in the management of oedema is salt restriction. With severe or symptomatic oedema, fluid may need to be restricted with the addition of a loop diuretic under close medical supervision [159, 160]. In a nephrotic state, the kidneys retain salt inappropriately in the tubules, causing oedema [161]. Filtered proteins send a signal to the kidney tubules to reabsorb salt into the blood, so it is not effectively excreted in the urine, which results in salt and water retention and oedema.

Nutritional management

Nutritional assessment

At diagnosis, the child's length/height and weight should be measured. The child is likely to be oedematous, so obtaining a history from the parents/caregivers of previous

weights prior to the onset of disease is important in order to help the medical team estimate the dry weight. Length/height and dry weight should be plotted on a growth chart and used to estimate nutritional requirements. A diet history should be taken.

At follow-up appointments, the dietitian should obtain details from the medical team about how the child has responded to steroids, if they are currently in relapse or remission and whether they are oedematous. A history of the child's bowel habit should be taken, especially if they have not responded to steroids and are in a persistent nephrotic state; the gut and surrounding tissues may be oedematous and there may be consequent malabsorption. A diet history should be taken at each appointment.

Energy and protein

A balanced diet adequate in energy and protein, providing the EAR for energy and RNI for protein for the normal healthy population, is usually adequate for most children. The child's chronological age should be used for estimating requirements or their height age if their height is less than the 2nd centile.

Salt

The main nutritional management for children with NS is a reduced salt ('no added salt') diet (Tables 13.7 and 13.24) when the child is in an oedematous state. The UK Scientific Advisory Committee on Nutrition (SACN) has published daily target average salt intakes for children [64] (Table 13.16). These do not represent an optimal or ideal consumption level, but a possible achievable goal in reducing the level of salt in the diet and can be used as a guide for the dietitian in advising on a lower salt intake. Taking a detailed diet history will help to identify high salt foods that must be avoided and finding suitable alternatives.

Snacks high in salt as well as processed foods need to be reduced. Takeaway meals should be strongly discouraged. Seventy-five percent of the salt people eat is already in the food they buy. Education on reading and interpreting labels should be given to those families where appropriate. Many commercial foods have colour-coded labels indicating their high, medium or low salt content; this is a useful and simple tool; however, such labels do not appear on all packaged foods.

When the child is in remission and the oedema resolves, the salt restriction can be relaxed.

Persistent nephrotic state

If a child is resistant to steroids and is in a persistent nephrotic state, a reduced salt diet will need to be ongoing to control the persisting oedema. Children in this chronic state are likely to have reduced appetites and may have diarrhoea and malabsorption (due to oedema of the gut), so care needs to be taken to ensure diets are palatable and adequate to meet their nutritional needs. Dietary supplements, such as sip feeds (oral nutritional supplements), may be needed in these situations; for the younger child, tube feeding may be necessary. Hydrolysed feeds (partial or extensive hydrolysates) can be trialled if diarrhoea is present and malabsorption is suspected. It is likely that these steroid-resistant children will progress to end-stage kidney disease. It is important to monitor their renal blood tests, growth parameters and appetite on a more frequent basis.

Monitoring of trace elements and 25(OH)D blood levels should be considered in children who are steroid resistant and in a persistent nephrotic state. There is not any strong evidence about dosages to supplement with if the levels are low; this can be discussed with the medical teams. For zinc supplementation, dosages in the British National Formulary can be used as a guide to correct low levels. Measuring CRP is advised as levels can be affected if the child is in a state of inflammation.

Corticosteroids

Corticosteroids are known to be associated with a high BMI in children with NS [145, 162, 163]. If a child is on steroids, it is likely that their appetite and weight will increase. Early advice on weight management should be given, and weight, height and BMI should be monitored in the community. An adequate calcium intake meeting the RNI should be advised in children on long-term corticosteroids.

Learning points: nephrotic syndrome

- *Nephrotic syndrome is an umbrella term for a group of clinical features: proteinuria, hypoalbuminaemia, 3+ protein on urine dipstick and oedema with or without hyperlipidaemia*
- *In a nephrotic state, the kidneys retain salt inappropriately in the tubules, causing oedema. The main nutritional management for children with nephrotic syndrome is a reduced salt ('no added salt') diet when the child is in an oedematous state*
- *If a child is resistant to steroids and is in a persistent nephrotic state, they are likely to have reduced appetite and may have diarrhoea and malabsorption (due to oedema of the gut), so care needs to be taken to ensure the diet is palatable and adequate to meet nutritional needs; sip feeds may be useful*
- *Monitoring of trace elements and 25(OH)D blood levels should be considered in children who are steroid resistant and in a persistent nephrotic state. Supplementation should be given if levels are low. More research is needed in this area to guide management*

Congenital nephrotic syndrome

CNS is defined by hypoalbuminaemia, heavy proteinuria and oedema with or without hyperlipidaemia. CNS is diagnosed in the first 3 months of life and is more commonly an autosomal recessive inherited disease or less commonly due

to a congenital infection. An increasing number of genetic defects have been identified for their involvement in the pathogenesis of CNS, including NPHS1, NPHS2, WT1, PLCE1 and LAMB2. Mutations in the genes NPHS1 and NPHS2 are the most common causes. CNS was initially referred to as the Finnish-type nephrotic syndrome due to its high incidence in Finland, with NPHS1 mutations underlying most cases [164, 165]. These genes provide instructions for producing proteins that are found in cells of the glomerulus (filtering unit). When there is a defect of the gene, the kidney leaks protein in the urine. Infectious causes of CNS include congenital syphilis, toxoplasmosis and cytomegalovirus (CMV). Treatment with antibiotics or antivirals is sometimes curative.

Medical management

Initially management includes stabilisation of the child, controlling oedema, preventing and treating infection and thrombosis and optimising nutrition to promote growth. Daily intravenous albumin in the early weeks or months is typically required with monitoring of thyroid function and blood tests for anaemia. This may require infants to remain in hospital for many months, which can affect family life. Serum creatinine levels are typically normal in the early stages of CNS. Once the infant is stable, medications such as ACE inhibitors can be used to reduce protein loss.

Clinical symptoms can vary hugely depending on the phenotype, and there is wide variance in practice [166]. Some centres advocate regular albumin infusions, with planned unilateral or bilateral nephrectomies to reduce the huge urinary losses of protein, once a child reaches an appropriate dry weight of about 7 kg. Peritoneal dialysis is then commenced until the child is a suitable size for transplantation (weighing aproximately10 kg). Other centres are moving away from regular daily albumin, giving it on a clinical basis as required and allowing the child to progress naturally towards end-stage renal disease [166]. If the infant is discharged home without albumin infusions, they need close monitoring with frequent outpatient follow-up, initially weekly, and with telephone support by a clinical nurse specialist and specialist paediatric renal dietitian.

The decision to carry out a bilateral nephrectomy and start dialysis is dependent on the child's growth, frequency of infections and kidney function. In the majority of cases, kidney transplantation is the only curative outcome [165].

Nutritional management

Nutritional assessment

Babies with CNS are at nutritional risk due to large losses of protein, oedema and fluid restriction, poor oral feeding, vomiting and diarrhoea, increased risk of infections that further affects feeding and losses of vitamin D and trace elements.

It is important to obtain an estimated dry weight from the medical team in order to calculate requirements. Dry weight, length and head circumference should be plotted on growth charts weekly in hospital to closely monitor growth. It is not always easy to estimate the dry weight due to the oedema. The level of fluid restriction is determined by the medical team. Infants are often restricted to 100–130 mL/kg/day. However, it is important to discuss with the medical team the limit on nutrition (and hence growth) that this fluid restriction imposes; they may be able to change the medical management to control the oedema and allow more fluid to provide better nutrition.

A feeding history should be taken as well as a history on the frequency of vomiting and stool output. Stools can be loose due to malabsorption resulting from oedema of the gut.

Dietetic management

The dietetic aims are to provide adequate nutrition for growth and development, to minimise diarrhoea and vomiting and to support the parents through what is a very difficult time.

Feeds will need to be concentrated due to the fluid restriction. Exclusive breastfeeding is unlikely to be sufficient to meet nutritional requirements and in the early stages is not advised due to strict control of the fluid intake. In more stable babies, supplementary comfort breastfeeding may be allowed. Mothers are encouraged to express their breastmilk, and expressed breastmilk (EBM) can be fortified according to local policies. If there is no EBM, standard whey-based infant formulas are used and slowly concentrated depending on tolerance. In practice, infant formulas have been concentrated up to 20%–23% depending on the level of fluid restriction, tolerance and age of the child. Proprietary high energy infant formulas can be used. Extensively hydrolysed protein formulas (powdered and liquid), particularly those with a high medium chain triglyceride (MCT) content, and amino acid-based formulas may be helpful where there is diarrhoea and vomiting and feed intolerance is preventing growth. Protein powders, glucose polymers and fat emulsions can be added to feeds to help meet nutritional requirements.

Infants who cannot meet their nutritional requirements orally and are not growing adequately will need a placement of a nasogastric tube. Feeds in hospital should be given continuously at first if the baby is vomiting and slowly moved to bolus feeding as tolerated. A combination of day bolus feeds and continuous overnight feeding is a commonly used regimen. It is important to involve the family in the decision making. If tube feeding is likely to be long term, gastrostomy feeding should be discussed with the medical team and the parents. It is advisable to place the gastrostomy before peritoneal dialysis is started. A gastrostomy can be very helpful post-kidney transplant in order to give daily immunosuppressants and to meet high fluid requirements.

Normal weaning practices are encouraged. Some babies struggle to take more than tastes; however, some babies wean successfully.

There have been reports of improved growth in CNS with aggressive treatment regimens. However, it is unknown whether this improvement is related to the high protein intake

(4 g/kg/day) or other components of the regimen such as albumin infusions [167]. Infants with severe CNS have traditionally been treated with a high energy (130 kcal (545 kJ)/kg/day) and high protein (3–4 g/kg/day) diet [165, 168]. Micronutrient requirements are not known, but to aim for at least the dietary reference values [153] seems appropriate.

Due to the heavy losses of protein, which include iron transport proteins, copper carrying proteins, B_{12}-transporting proteins and the reported losses of other trace elements such as zinc and selenium, some renal units have started measuring these micronutrient levels in their babies with CNS. There is, however, very little evidence to guide on the level of supplementation needed if the serum levels are found to be low. Once supplementation is started, blood levels should be monitored together with CRP 2–3 monthly and doses adjusted accordingly. Research in this area is needed.

Renal function declines with time so the dietary management needs to be modified according to the level of CKD and blood results. If bilateral nephrectomies are performed and the child starts peritoneal dialysis or haemodialysis, the dietary prescription is altered accordingly until they receive a successful kidney transplant.

Learning points: congenital nephrotic syndrome

- *CNS is diagnosed in the first 3 months of life and is more commonly an autosomal recessive inherited disease or less commonly due to a congenital infection*
- *Babies with CNS are at nutritional risk due to large losses of protein, oedema and fluid restriction, poor oral feeding, vomiting and diarrhoea, increased risk of infections that further affects feeding and losses of vitamin D and trace elements. Regular dietetic monitoring is paramount*
- *Feeds need to be concentrated due to the fluid restrictions. A large percentage of babies with CNS will need to be tube fed to aid growth*
- *Monitoring of trace elements and 25(OH)D blood levels should be considered. Supplementation should be given if levels are low. More research is needed in this area to guide management*
- *In the majority of cases of CNS, kidney transplantation is the only curative outcome*

A case study to show the management of a baby with congenital nephrotic syndrome is given in Table 13.21.

Table 13.21 Case study: A baby with congenital nephrotic syndrome.

A 6-week-old term baby girl diagnosed with CNS is fluid restricted to 120 mL/kg.
Birthweight = 3 kg (25th centile).
Current estimated dry weight = 3.5 kg (2nd centile). Length = 54 cm (25th centile). Head circumference = 37 cm (50th centile).
Energy requirements 130 kcal (545 kJ)/kg/day. Protein requirements 3–4 g/kg/day.
Mum is not expressing any breastmilk. Feeds using whey-based infant formula were gradually increased daily to 20% concentration with 1% added glucose polymer and 1% added protein powder, as tolerated.

Feed recipe	Energy (kcal (kJ))	Protein (g)	CHO (g)	Fat (g)	Na (mmol)	Calcium (mg)
20 g SMA PRO 1	102 (427)	1.9	11	6	1.6	65
1 g Vitajoule	3.8 (16)	0	1	0	0	0
1 g Protifar	3.6 (15)	0.9	0	0	0	14
Total per 100 mL	109 (458)	2.8	12	6	1.6	79
Total per 420 mL (120 mL/kg)	458 (1924)	11.8	50.4	25.2	6.7	332
Total per kg	**131 (550)**	**3.4**	**14.4**	**7.2**	**1.91**	**95**

The following week, she became more oedematous and was vomiting frequently, and the doctors request the fluid be further restricted to 110 mL/kg. It is difficult to estimate a dry weight, due to oedema, but the medical team has decided on 3.6 kg. A more concentrated feed was calculated to provide her nutritional requirements in 110 mL/kg. To try to achieve better feed tolerance, the dietitian changed the base feed to a high energy extensively hydrolysed liquid infant formula with 5% added glucose polymer.

Feed recipe	Energy (kcal (kJ))	Protein (g)	CHO (g)	Fat (g)	Na (mmol)	Calcium (mg)
100 mL Infatrini Peptisorb	100 (420)	2.6	10.3	5.4	1.4	80
5 g Vitajoule	19 (80)	0	4.8	0	0	0
Total per 100 mL	119 (500)	2.6	15.1	5.4	1.4	80
Total per 400 mL (110 mL/kg)	476 (2000)	10.4	60.4	21.6	5.6	320
Total per kg	**132 (556)**	**2.9**	**16.8**	**6**	**1.6**	**89**

Her vomiting improved by reducing in frequency; however, she still had occasional vomits 2–3 times a week that the medical team felt was acceptable. She continued to receive daily albumin infusions and her oedema reduced. For the next couple of weeks, it was felt that her dry weight was increasing well. Close monitoring by the dietitian and liaison with the medical team continues because as she grows, she will need either an increase in her fluid allowance or a further increase in the feed concentration to continue to meet her nutritional needs.

Renal Tubular Disorders

Louise McAlister

The renal tubules play a central role in fluid, electrolyte and acid–base homeostasis. Urine composition is determined by active and passive reabsorption from the glomerular ultrafiltrate (mainly occurring in the proximal tubule) and secretion into the tubule from the surrounding blood supply. The final regulation occurs in the distal tubule and collecting duct under the influence of hormones. Defects in tubular function may be inherited or acquired and disrupt one or more of these absorptive or secretory processes, leading to potential abnormalities in electrolyte, mineral and water balance that can be life threatening.

Classification of renal tubular disorders is based on the location of the defect in the nephron and whether it is isolated (e.g. nephrogenic diabetes insipidus), generalised (as in renal Fanconi syndrome) or secondary to a more widespread disease process (such as cystinosis, tyrosinaemia or Lowe syndrome) (Table 13.22). Biochemical analysis of serum and urine assists differential diagnosis, and genetic testing can confirm the diagnosis in suspected or familial cases.

Inherited renal tubular disorders may present in the first year of life with faltering growth, polydipsia and polyuria. Dehydration can lead to symptoms of constipation, recurrent fevers and vomiting. Bone deformities (rickets) may be part of the clinical picture, suggesting loss of phosphate from the proximal tubule. The antenatal history can include polyhydramnios with infants born premature and with low birthweight. A few conditions (such as Gitelman syndrome [GS] and renal glycosuria) may not present until later in childhood or adulthood [170, 171].

The initial management for most tubular disorders involves correction of dehydration and electrolyte abnormalities and reduction of further losses by appropriate medication. Early diagnosis and initiation of therapy can improve growth and prognosis. Glomerular function is preserved in some disorders (e.g. GS), but can be severely affected in others (e.g. cystinosis and some Bartter patients), leading to chronic kidney disease (CKD). Episodes of dehydration or complications related to the original defect (e.g. renal stones in cystinuria) can also affect glomerular filtration rate (GFR). Although rare, the long-term outcome and clinical profile of many of these inherited renal tubular disorders are now being reported [170–175].

Ensuring a nutritionally adequate diet and achieving appropriate growth can be challenging. The polyuria, which is a common feature of many of these conditions, drives thirst and can result in a poor appetite, especially during infancy. The medical treatment and dietary considerations for a few of these conditions are described below.

Bartter syndrome

Bartter syndrome (BS) is not a single entity, but refers to a group (types I–V) of rare, predominantly autosomal recessive disorders, characterised by hypokalaemic alkalosis, hypochloraemia, hyper-reninaemia and hyperaldosteronism with normal or low blood pressure. The underlying renal abnormality causes high urinary losses of sodium, chloride and potassium. Males and females are affected equally.

The BS subtypes correspond to specific defective transport proteins in the thick ascending limb (TAL) of the loop of Henle caused by a variety of gene mutations. They share

Table 13.22 Disorders of tubular function.

Renal tubular disease	Location of defect	Main process affected
Hypophosphataemic rickets	Proximal tubule	Transport: phosphate
Renal glycosuria		Transport: glucose
Aminoacidurias, e.g. cystinuria		Transport: amino acid
Proximal renal tubular acidosis (pRTA)		Transport: bicarbonate
Renal Fanconi syndrome[1]		Generalised dysfunction
Bartter syndrome (BS)	Ascending loop of Henle	Transport: sodium, potassium, chloride
Distal renal tubular acidosis (dRTA)	Distal tubule	Secretion: proton (H^+)
Gitelman syndrome, EAST syndrome[2]		Transport: sodium, chloride
Pseudohypoaldosteronism	Collecting duct	Transport: sodium, potassium
Liddle syndrome		
Nephrogenic diabetes insipidus		Transport: water

[1]Primary or secondary to another disorder (e.g. galactosaemia, nephropathic cystinosis, mitochondrial cytopathies, Lowe syndrome, Wilson's disease).
[2]Epilepsy, ataxia, sensorineural deafness, tubulopathy [169].

many of the same physiological derangements, but differ with regard to the age of onset (antenatal to adulthood), presenting symptoms and size of urinary calcium and potassium losses. Polyhydramnios and prematurity are common for infants with BS types I, II and IV, together with symptoms of polyuria, dehydration, constipation, poor weight gain and nephrocalcinosis. Episodes of severe fever and dehydration may occur during the early weeks of life, and hypokalaemia can result in muscle weakness, cramping and fatigue. Type IV BS is a result of mutations of barttin protein, which is expressed in the kidney and the cochlea, and patients, therefore, also have sensorineural deafness. GS has considerable clinical overlap with BS type III, so is commonly grouped with BS, as the underlying gene is expressed in both the TAL and the distal convoluted tubule (DCT). These two conditions usually have a milder clinical picture than the other subtypes, a later age of onset (school age or adolescence) and a low urinary calcium level. Asymptomatic individuals with GS usually require minimal medical treatment and monitoring. However, both GS and BS type III patients are at risk of severe life-threatening electrolyte abnormalities during episodes of intercurrent illness (e.g. gastroenteritis). A pseudo-BS with signs and symptoms similar to BS, but no tubular dysfunction, can be caused by diuretics, severe vomiting, laxative abuse or in young children cystic fibrosis [176].

The diagnosis of BS is made in the neonatal period in about 50% of cases [177], requiring correction of dehydration and electrolyte abnormalities. Oral potassium supplementation up to 12 mmol/kg may be necessary, but this requirement reduces with age, nearing 1 mmol/kg in the teenage years [177]. However, despite supplementation, serum potassium usually remains low <2.5 mmol/L [171]. Potassium supplements are available in liquid or tablet form and are often associated with gastrointestinal (GI) side effects such as abdominal pain and diarrhoea. Sodium requirements can be very high in the first year (up to 13 mmol/kg), but by 15 years only about one quarter of individuals require supplements [171]. Other medications used to manage polyuria include non-steroidal anti-inflammatory drugs (NSAID), e.g. indometacin, ibuprofen or a cyclooxygenase-2 selective inhibitor (COX-2 inhibitor) such as celecoxib. Indometacin and ibuprofen should be taken with food or milk because of potential GI side effects including nausea, vomiting, abdominal pain and peptic ulcers. Individuals experiencing these side effects may be changed to a COX-2 inhibitor under specialist supervision.

Reduced GFR and proteinuria are seen in about 60% of patients with BS [171], with a small proportion of these progressing to CKD requiring renal replacement therapy. The mechanism for this is not clear and is likely to be multifactorial, related to prematurity, recurrent dehydration, secondary to nephrocalcinosis or due to chronic hypokalaemia. High urinary calcium levels can lead to nephrocalcinosis and calcium-containing renal stones in some BS patients, but calcium restriction is not appropriate.

Nutritional management

Growth retardation, poor weight gain, low appetite and feeding problems are all associated with BS. Walsh [171] recently reported long-term longitudinal data on 45 children with BS and GS finding that median height was low at presentation and growth remained poor during follow-up with median standard deviation scores (SDS) for height being −1.6 at presentation and −1.2 at follow-up. Similarly, Kaur in a retrospective review of 34 children from three tertiary UK paediatric nephrology centres [177] reported that a third of children had a height below the 2nd centile at 15 years of age. The exact aetiology of the short stature is unknown, although growth hormone (GH) therapy has been successful for some children [171, 178], especially if BS presents in early childhood or after a delayed diagnosis.

Dietetic input is particularly important in the first 2 years of life to ensure optimal weight gain and growth by regular monitoring of food, fluid and nutritional intake. Infants born with a low birthweight are especially vulnerable to the effects of poor nutrition. Fluid requirements can be greater than 200 mL/kg in the first 6 months of life and, if this is not achievable orally, may need to be given by a feeding tube, nasogastric (NG) or gastrostomy (G), or intravenously (IV). The fluid requirements per kilogram body weight decrease with age, depending on the control of polyuria. Kaur [177] reported that 26% of their cohort were gastrostomy fed, which enabled them to achieve adequate fluid and nutrition. Standard infant formula or age-appropriate paediatric feeds can be used for enteral feeding to provide normal nutritional requirements for age (or height age if stunted), with additional water to maintain hydration. These feeds may need the addition of extra energy modules (such as a glucose polymer or a fat emulsion) if weight gain or growth is poor.

Normal weaning onto solids can begin at around 6 months, but some infants progress slowly. For children with poor food intake, the use of oral nutritional supplements (p. 224) and energy-dense foods can be helpful to achieve an adequate nutritional intake.

Sodium supplementation is often provided in early childhood, but a high dietary salt intake may be sufficient in older children [177]. Many patients report intense cravings for high salt foods. As GI tolerance of potassium supplements is poor, encouraging high potassium foods may be appropriate. In GS hypomagnesaemia is a more prominent component, and magnesium supplementation is routinely required for life. High doses of magnesium can cause diarrhoea, so normal levels of serum magnesium may be difficult to achieve. Directing food choices for children with low appetites to try to include these electrolytes in sufficient and reliable amounts is probably unrealistic. Patient support websites [179, 180] include practical advice on dietary sources of potassium and salt (and magnesium if needed), but do acknowledge that apart from salt, this is unlikely to replace the need for medicinal supplementation.

Careful monitoring of serum urea and creatinine levels will identify any decline in kidney function, and dietetic advice would then need to be tailored accordingly (p. 249).

Learning points: Bartter syndrome

- *High fluid requirements*
- *Wean onto solids at around 6 months of age*
- *May require nutritional support to achieve adequate weight gain and growth*
- *Use standard age-appropriate feeds (oral or enteral)*
- *Allow liberal salt and potassium (and sometimes magnesium)*
- *Monitoring of renal specific serum biochemistry (particularly urea and creatinine) will identify any decline in glomerular function (and onset of CKD)*

Cystinosis

Cystinosis is a rare autosomal recessive inherited lysosomal storage disorder caused by the failure to transport cystine (the disulphide of the amino acid cysteine) out of lysosomes into the cytoplasm. This accumulated cystine can increase the content of cells by 50–100 times the normal value leading to cellular and tissue damage. Cystinosis is a systemic disease as lysosomes are present in all cells, but clinical manifestations are typically first seen in the kidneys and eyes. Corneal cystine crystals can be seen in all children from about 12 to 18 months of age and contribute to photophobia. Mutations in the CTNS gene (located on chromosome 17) are responsible for all forms of cystinosis, as the gene encodes for the protein cystinosin, which is the lysosomal transmembrane transporter for cystine.

There are three clinical forms of cystinosis with the most severe form (infantile or nephropathic) accounting for 90%–95% of cases. Cystine accumulation begins in foetal life, predominantly in the proximal renal tubules, leading to renal Fanconi syndrome in the first year. Cystinosis is the most common inherited cause of paediatric renal Fanconi syndrome. Initially, amino acids and glucose are poorly reabsorbed, but as the damage progresses, electrolytes (sodium, potassium, magnesium, calcium and phosphate), low molecular weight proteins and bicarbonate are lost in the urine. Kidney function progressively declines through childhood, despite treatment, due to chronic interstitial nephritis, leading to end-stage CKD by the age of 20 years in 90% of patients. The use of a cystine-depleting medication (such as cysteamine) substantially delays, but does not prevent, the onset of renal failure. Renal transplantation is the preferred treatment for kidney failure, but a period on dialysis may be required if a live-related donor is not available or if kidney function has declined rapidly. Paediatric cohorts report a better renal graft survival post-transplant in cystinosis patients compared with most other renal diagnoses [181]. Cystinosis does not recur in the transplanted kidney as these cells do not carry the defect, but cystine continues to accumulate post-renal transplant in other organs including the eyes, thyroid, pancreas, liver, muscle and gonads [182].

Infants with nephropathic cystinosis usually have a normal birthweight and progress in the first 3–4 months of life, but then develop poor feeding, excessive thirst, profound polyuria, vomiting, constipation, delayed growth, weakness, rickets and recurrent fevers. The typical biochemical profile includes hypokalaemia, metabolic acidosis, hypophosphataemia, low serum uric acid and carnitine. All racial and ethnic groups are affected; however, the classical child with cystinosis of Northern European descent is fair-haired and blue-eyed (possibly related to the role of cystinosin in the regulation of melanin synthesis). A single gene mutation (57 kb deletion) accounts for about 50% of all cases of nephropathic cystinosis in Northern Europe [183].

A milder form of nephropathic cystinosis (juvenile or late onset) accounts for 3%–5% of cases and is usually diagnosed later in childhood or during adolescence, but can present from the age of 2 years [184].

A third form of cystinosis, non-nephropathic or ocular, is rarely diagnosed before adulthood and only represents about 1%–2% cases. This is characterised by symptoms related to corneal cystine crystal depositions (including photophobia and an abnormal contraction or twitch of the eyelids).

Treatment for nephropathic cystinosis involves rehydration, replacement of renal loses of electrolytes, administration of bicarbonate, attention to nutrition and provision of vitamin D supplements. Maintaining normal hydration can be difficult as individuals produce large volumes of dilute urine and so free access to water (and salt) is essential. NSAID, such as indometacin, are sometimes given to control the polyuria, but there is no consensus on its routine use in cystinosis.

The only specific targeted therapy for cystinosis is the cystine-depleting agent cysteamine (also known as mercaptamine), which is started at diagnosis. This converts entrapped cystine to cysteine and cysteine–cysteamine mixed disulphide, which can then both exit the lysosomes through an alternative transporter. The most commonly used preparation has to be taken every 6 hours orally (or via a feeding tube) together with aqueous eye drops (applied 6–12 times per day) [185]. Oral medications have no influence on ocular manifestations as there is no blood supply in the cornea. Cysteamine has a strong taste and smell and binds to the oral mucosa and dental fillings. It is metabolised to volatile sulphur compounds that can cause bad breath and an unpleasant sweat odour, reducing compliance in young people [186]. Other common adverse effects of cysteamine are nausea, diarrhoea, vomiting, abdominal pain and loss of appetite [14]. These can be reduced if the medication is taken with or after food (although this may decrease absorption) and by the concurrent use of proton pump inhibitors (such as omeprazole or lansoprazole). A delayed-release enteric-coated product (Procysbi) has been developed and can control blood levels for up to 12 hours. This should aid adherence, but is not yet routinely available. The essential role of cysteamine in delaying the progression to end-stage renal disease, improving growth, reducing the severity of the extrarenal complications and improving prognosis is now well documented [187].

Routine monitoring in children includes assessment of growth and weight gain to promptly detect any deterioration in growth velocity and weight faltering. Slow growth is

multifactorial being secondary to the renal Fanconi syndrome [187], inadequate nutrition, rickets and cystine deposition in the bones and thyroid. Early initiation and compliance with cysteamine therapy can help prevent growth retardation by increasing GH release and improving metabolic status, but cannot induce catch-up growth [188]. Frequent measurement of trough leucocyte cystine levels are used to adjust cysteamine dose [189] and can help assess compliance with medication.

Hypophosphataemic rickets can be seen at a young age in cystinosis due to the large urinary losses of phosphate, calcium and vitamin D binding protein and impaired vitamin D metabolism. High doses of phosphate supplements and active vitamin D may be required to treat and prevent rickets. However, careful monitoring of phosphate and bone status (using serum phosphate, parathyroid hormone or ionised calcium levels) is necessary to detect a reduction in phosphaturia that may occur as CKD progresses. High serum phosphate levels can trigger increases in serum fibroblast growth factor-23 (FGF-23), which is associated with adverse outcomes including increasing progression of renal disease and risk of cardiovascular disease and mortality.

Urinary carnitine excretion is high in cystinosis due to the renal Fanconi syndrome, as 97% of free carnitine is normally reabsorbed by the renal tubules. This leads to low levels in plasma and muscle, although clinical signs of deficiency (such as cardiomyopathy or metabolic encephalopathy) have never been reported. In addition, the cysteamine medication may also inhibit the efficient transport of carnitine into muscle.

Carnitine levels improve with the onset of CKD and the reduction in urinary losses. The value of supplementation is debatable as it can take many years to replace muscular carnitine and it is unclear if this provides any clinical improvement [190].

High urinary copper excretion (up to four times normal) has been reported in patients with cystinosis [191] together with low serum copper and ceruloplasmin levels. Copper is a cofactor involved in maintaining normal collagen and bone structure, and so it has been proposed that copper deficiency may play a role in the connective tissue lesions that have been reported. Monitoring copper status and the use of oral copper supplements may be important to prevent these, but there is no consensus on whether copper supplements should be given [192].

Nutritional management

Infants with cystinosis are asymptomatic at birth with a normal weight and length, but by 6–12 months may be faltering [183]. Breastfeeding, EBM and infant formula are appropriate feed choices, but energy and nutritional intake should be regularly assessed along with anthropometry. If weight gain or growth is poor, the optimal feed will depend on the volumes taken or tolerated. Energy-dense infant formulas, e.g. Similac High Energy or Infatrini, may be useful or concentrating a standard infant formula with the addition of energy supplements (such as glucose polymers and a fat emulsion) if necessary. It is usually sufficient to aim for 100% of energy requirements for age (or height age if stunted) [182]. Within the first year many experience feeding difficulties including frequent vomiting, poor appetite and oral aversion. Weaning can begin at around 6 months, but progression onto solids can be slow, with an extended reliance on formula and poor acceptance of a cup rather than a bottle [193]. Extreme thirst may be a feature due to the polyuria, along with craving for high salt foods. A reduction in saliva production can compromise the ability to chew and swallow [194].

Achieving adequate nutrition and fluid intake can be difficult, and infants and children may require intensive dietetic support. Fluid requirements may be up to twice normal for weight. Young children can benefit from an NG or G tube to administer nutrition, fluid and medications, resulting in improvements in height and weight parameters [189, 195]. A questionnaire survey of 70 members of the Cystinosis Foundation [196] reported that 30% of responders had received gastric/jejunal feedings and 7% had periods on parenteral nutrition. Oral nutritional supplements can be helpful if a child's appetite is reduced. Children with poor growth, whose medical and nutritional therapy have been optimised, may benefit from the use of GH.

Despite treatment, cystine can accumulate in the oropharyngeal muscles, with many patients reporting choking, gagging and vomiting during mealtimes and poor tolerance of changes in food textures [193, 197]. A videofluoroscopy can be helpful to assess the nature, severity and aspiration risk associated with these swallowing difficulties. A wide range of GI disturbances have been reported in this patient group, including intestinal dysmotility and delayed gastric emptying [198–200].

As renal function declines, dietary intake may need to be manipulated according to serum biochemistry (p. 249). However, dietary advice requires a careful balance between compensation for renal losses and the usual dietetic management of CKD.

Learning points: cystinosis

- *Cystinosis is an inherited systemic disease*
- *95% have the severe form (nephropathic or infantile)*
- *High fluid requirements*
- *Breastfeeding and standard infant formula are usually appropriate*
- *May need nutritional support (supplementation or tube feeding)*
- *Symptoms of extreme thirst and feeding difficulties, especially in infancy*
- *Normal weaning from about 6 months of age, but often slow progression onto solids*
- *Serum copper levels may be low and could be supplemented*
- *Cysteamine medication:*
  - *improves prognosis and delays progression of CKD*
  - *has a strong taste and smell which reduces compliance*
- *90% of children with cystinosis have stage 5 CKD by age 20 years requiring renal replacement therapy*

Nephrogenic diabetes insipidus

Congenital nephrogenic diabetes insipidus (NDI) is a rare genetic condition characterised by insensitivity of the distal renal tubule to antidiuretic hormone (arginine vasopressin [AVP]) leading to an inability to concentrate urine. The most common manifestations are polyuria, polydipsia and hyposthenuria (urine with an osmolality less than that of plasma) with recurrent episodes of dehydration and fever. About 80% of cases have mutations in the gene affecting the vasopressin V2 receptor (AVPR2) in the collecting duct, an X-linked recessive disorder. Mutations in the aquaporin water channel (AQP2) in the collecting duct account for 10% with a recessive mode of inheritance (or rarely a dominant inheritance pattern). These genes code for critical compounds for the transepithelial water permeability of the collecting duct [201]. A further 10% of cases of NDI are due to unknown mutations.

The clinical presentation of NDI may be indistinguishable from central (or neurogenic) diabetes insipidus (DI), which is due to insufficient AVP production or release. In both of these conditions, the high urine output leads to an increase in serum osmolality and hypernatraemia, accompanied by an inappropriately low urine osmolality. Urine volume is often greater than 6 mL/kg/hour in neonates (or 4 mL/kg/hour in children), accompanied by a fluid intake of >2 L/m^2 BSA/day (p. 243). The nephrogenic form of DI is confirmed by administering an artificial form of AVP, 1-desamino-8-D-arginine vasopressin (DDAVP), either IV or subcutaneously. In patients with central DI, DDAVP will concentrate the urine to normalise serum osmolality, whereas in NDI there will be no response. Genetic testing (if available) can help to confirm the NDI diagnoses.

Most patients with congenital NDI have non-specific symptoms in the first weeks of life, e.g. faltering growth, recurrent vomiting, poor feeding, irritability, hypotonia, fever and constipation. Birthweight and height have been reported as normal, suggesting normal prenatal growth [202]. In a recently reported retrospective review of 36 NDI cases [174], 69% were diagnosed in the first year of life with a median age of diagnosis of 7 months. The majority (87%) of patients are diagnosed in the first 2.5 years of life [203]. Median height and weight SDS at presentation a the Dutch cohort [203] was −1.06 (range −4.94 to −1.9) and −2.1 (range −8.25 to −2.6), respectively.

Infants with NDI may need IV fluids to rehydrate and slowly normalise serum sodium in the first instance. Too rapid a decrease in serum sodium levels can risk cerebral oedema and potentially be fatal. The IV fluids should be 5% glucose, given at an infusion rate just exceeding urinary output, with careful monitoring of urine and plasma biochemistry. Only in the event of circulatory shock should a bolus of 0.9% saline be given. In other situations, the higher sodium load from 0.9% saline would worsen the hypernatraemia, exacerbating the polyuria. These IV fluids are carefully managed and monitored by the medical team. Once oral feeding is initiated, achieving an adequate fluid intake to replace urinary losses can be difficult. Lowering the renal solute load (RSL) of the feed to <15 mOsm/kg H_2O per kg body weight/day will reduce the amount of urine produced and can help to achieve feed tolerance by decreasing polydipsia.

The RSL refers to solutes of dietary and endogenous origin that need to be excreted in the urine along with water [204]. These include urea (from dietary protein metabolism), creatinine, sodium, chloride, potassium and phosphate. In practice, most of the RSL is of dietary origin, and the potential RSL of a feed can be estimated from the protein content together with the main electrolytes. Formulas for roughly calculating this are given in the literature using slightly different assumptions regarding contributions of dietary electrolytes and protein. The formula shown in Table 13.23 was devised generalising that all dietary proteins are metabolised to urea (and contribute 4 mmol to the RSL per gram of protein) with the addition of a contribution from electrolytes (by multiplying the millimolar amounts of sodium and potassium by two to allow for the accompanying anions).

The medical management of NDI usually includes the administration of a thiazide diuretic, often in combination with a potassium-sparing diuretic (amiloride) or an NSAID (such as indometacin or ibuprofen) or a COX-2 inhibitor (celecoxib) to reduce urine output. Potassium supplementation may be indicated if serum potassium levels fall below the normal range for age.

Patients have been reported to have developmental delay, attention deficit hyperactivity disorder (ADHD) and poor short-term memory [203], although these may be secondary to the feeling of constantly craving for fluids and needing to pass urine.

Nutritional management

Infants with NDI are usually fed a controlled volume of a low solute whey-based infant formula calculated to provide a RSL <15 mOsm/kg H_2O per kg body weight (Table 13.23). This infant formula may be given as a feed up to 150 mL/kg body weight, with additional fluids offered freely as water. Fluid requirements are high (up to 250 mL/kg), but can reduce substantially when urine output is controlled on medication. To achieve the EAR for energy for age, energy supplementation of the formula and also of the free water may be needed. Glucose polymers (p. 14) can be used to provide extra energy without further increasing the RSL. Tolerance and acceptance of glucose polymers varies, but between 3 and 10 g of glucose polymer powder can be added to 100 mL of the fluids, providing an additional 11–38 kcal (45–160 kJ)/100 mL. A total carbohydrate concentration of 10 g/100 mL can be trialled initially and slowly increased in increments of about 2 g/100 mL if required (up to a maximum of about 20 g total carbohydrate per 100 mL, i.e. 20% concentration). Most infants have a preference for water, so the formula should be offered first to ensure adequate nutrition. An NG tube may needed for those infants who refuse to take an adequate amount of formula orally. Within the first year of life, many infants experience feeding problems that lead to poor weight gain and growth, so regular monitoring and adjustment of feeds may be necessary.

Table 13.23 Case study showing calculation of renal solute load.

RSL (mOsm/kg H_2O) = total intake of protein (g) × 4 + 2 × [sodium (mmol) + potassium (mmol)]
Case: A 3-month-old boy diagnosed with NDI weighing 5 kg
He is unable to concentrate his urine greater than an osmolality of 70 mOsm/kg H_2O

Influence of RSL on fluid intake:
- If given a feed with an RSL of 20 mOsm/kg H_2O per kg body weight, he would receive 100 mOsm/day

To excrete this he would need 100/70 × 1000 mL of fluid = 1429 mL (286 mL/kg)
- If given a feed with an RSL of 15 mOsm/kg H_2O per kg body weight, he would receive 75 mOsm/day

To excrete this he would need 75/70 × 1000 mL of fluid = 1070 mL (214 mL/kg)
- If given a feed with an RSL of 13.8 mOsm/kg H_2O per kg body weight (see feed below), he would receive 68 mOsm/day

To excrete this he would need 68/70 × 1000 mL of fluid = 971 mL (194 mL/kg)

Feeding plan:
He is offered a normal feed volume of 150 mL/kg = 750 mL/day of a reduced RSL feed, given as 150 mL × 4 hourly × 5 feeds
In addition he is offered water freely after feeds, aiming for 40–60 mL/kg = 250 mL/day
Total fluid intake = 1000 mL
Fluid volume required to excrete the RSL = 971 mL

Feed calculation:
12% infant formula (e.g. Cow & Gate 1) + glucose polymer (Vitajoule) added up to 10% total carbohydrate concentration

	Energy (kcal (kJ))	Protein (g)	Na (mmol)	K (mmol)
90 g Cow & Gate 1	435 (1820)	8.7	4.9	12.5
28 g Vitajoule + water up to 750 mL	106 (445)		0.3	
Total	541 (2265)		5.2	12.5
Intake per kg body weight	108 (455)	1.8		

Renal solute load 8.7 × 4 + 2 (5.2 + 12.5) = 69 mOsm/kg H_2O
= 13.8 mOsm/kg H_2O per kg body weight
RSL, renal solute load; NDI, nephrogenic diabetes insipidus.

The reduced RSL feed may initially result in a shortfall in protein and micronutrient intake, but is essential to stabilise urine output and minimise thirst. Preterm infants are particularly vulnerable to the effects of poor nutrition, so it may not be possible to reduce RSL below 15 mOsm/kg H_2O per kg body weight, and a compromise of 18 mOsm/kg H_2O per kg may be more appropriate. Once an infant is thriving and medically stable, the feed RSL can be relaxed to improve protein and nutrient intake. Plasma sodium concentration and routine monitoring of paired urine and plasma osmolality can guide hydration status, although interpreting these can be difficult [205]. A plasma osmolality >300 mOsm/kg H_2O and serum sodium >150 mmol/L in an NDI infant suggests hypernatraemic dehydration and medication doses may need adjustment (to reflect an increase in body weight) or extra fluids given. Urine osmolality in NDI is rarely concentrated above 70–150 mOsm/kg H_2O, even when serum osmolality is high.

The tendency to vomit and experience constipation (due to dehydration) is commonly reported in infants and young children with NDI. The regular use of laxatives can be helpful. To control vomiting, careful positioning during feeding, the use of feed thickeners, anti-emetics and prokinetics can be tried, but are often unsuccessful. For infants with severe vomiting and faltering growth, a trial of NG tube feeding to allow a slower administration of feed volume (by gravity or pump) can be helpful. In the cohort review by Sharma, about a third of infants had required NG feeding, and 24% had had a G device inserted [174]. Tube feeding is not usually needed beyond the age of 2 years [174], although children and their families often need a lot of support to achieve a consistent oral intake and careful weaning off from the tube. A multidisciplinary approach, including the support of speech and language therapists and a specialist feeding team, can be helpful to manage this process.

To reduce urine output, lifelong control of dietary salt intake is required. In infants, initial weaning should be a low sodium diet, with a gradual relaxation to a reduced salt diet (or 'no added salt diet') by the age of 2 years. Most traditional weaning foods are low in sodium including fruit, vegetables and baby rice and manufactured baby foods (apart from those with added high salt items such as cheese, ham and bacon). A reduced salt diet provides about 3 mmol sodium/kg body weight (Table 13.7), which is similar to the healthy eating guidelines given to the general public. A web-based support group for NDI families gives detailed advice on strict adherence to a very low sodium diet irrespective of age, which is not necessary or achievable. Practical advice on achieving a reduced salt intake is given in Table 13.24.

A very strict low salt diet can contribute to growth failure despite adequate energy intake and optimal medical treatment [206]. Individual tolerance of salt varies, with parents reporting higher fluid intakes (with accompanying polyuria and bedwetting) if salty foods are taken. For this reason, many older children self-regulate their salt intake to avoid

Table 13.24 Practical advice to achieve a reduced salt diet ('no added salt diet').

General advice

- Do not add salt to your food at the table or in cooking
  This includes sea salt, rock salt, garlic salt, natural salt, table salt or salt substitutes
- Eat foods high in salt less often and in smaller amounts
- Check food labels
  Very high salt foods may have >1.5 g salt/100 g. However, salt intake from these will depend on the amount eaten and a small portion may be acceptable
- Season foods with fresh, frozen or dried herbs, black pepper, garlic, onions, chilli, lemon juice, vinegar, spices (check spice mixes for salt)
- Try baking or roasting vegetables to bring out their flavour
- It is not usually necessary to avoid cereals, bread and normal butter and spread

High salt foods	Lower salt advice
Cheese	
Especially hard and processed cheese (e.g. cheddar cheese and cheese slices or strips)	Try using a small amount of a stronger cheese or grating hard cheese to make it go further. Cream cheese, cheese spread and cottage cheese are lower salt cheeses
Processed meats/ready meals	
Bacon, sausages, hot dogs, frankfurters, ham, corned beef, beef burgers, salami, meat pies, sausage rolls, meat paté or paste Ready meals or dried pot meals (particularly if containing bacon, ham, cheese or soy sauce)	Not all processed meals are high in salt – check food labels for those with ≤0.3 g salt/100 g Replace packaged meals with freshly cooked meat, poultry and fish Replace dried pot meals with fresh or dried noodles or pasta; discard ready-mixed 'seasonings' packets and flavour with a low salt spice mix or suitable sauce Burgers can be made at home and chicken strips can be oven baked or fried in batter or breadcrumbs rather than choosing shop-bought items
Certain fish products	
These include smoked salmon or mackerel, tins or jars of fish (including anchovies, sardines and pilchards), fish paté or paste	Fresh or frozen fish
Tinned foods	
Check soups and vegetables	Prepare fresh soup or choose suitable lower salt products Use fresh, frozen or salt-free tinned vegetables and pulses in place of tinned vegetables with added salt. If you cannot find salt-free products, rinse the can's contents in a colander under running water to remove excess salt
Ready-made gravy and sauces	
These include tomato ketchup, soy, brown, barbecue, mayonnaise, pickles, mustard, tabasco, curry paste and pesto	Use these sauces sparingly or replace with a lower salt brand if available. You could make a stock and/or gravy from suitable ingredients, rather than using cubes or granules. Try apple, cranberry or mint sauces Manufactured jars of tomato-based sauces are often lower in salt than cheesy ones or those containing olives, bacon or ham. Alternatively, make a sauce with fresh ingredients such as tomatoes/tomato purée and garlic
Takeaway foods	
Including Chinese, Indian, kebabs, fried chicken, burgers and salted chips	Make pizza at home: Spread a base with salt-free tinned smooth chopped tomato and add home-cooked meat, chicken, red peppers, onions, sweetcorn and mushrooms Unsalted oven and microwave chips Go to a local restaurant or takeaway shop that will prepare your foods freshly with minimal salt, e.g. fresh meat or chicken kebab with pitta bread (not doner or kofte kebab) In a takeaway or restaurant choose plain rice, sticky or coconut rice rather than egg fried or pilau rice
Salty snacks	
Avoid most crisps, salted nuts, mini cheddars, salted or flavoured corn snacks, olives, most sun-dried tomatoes, peanut butter, pickles and some savoury spreads (including yeast extracts)	Choose salt-free crisps, some toddler finger food sticks/straws (check the label for salt content), sesame or sunflower seeds (be aware of the choking hazard for a child under 5 years) Popcorn (unsalted), dried fruit, trail mix Rice cakes, crumpets, croissants, toast Biscuits, cakes

Source: Adapted from the advice sheet produced by the nephrology dietetic team at Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.

these side effects. Free access to water during the day and at night is important, and Sharma noted in their cohort [174] that the median fluid intake at the age of 13 years in their sample was 3800 mL/m^2 BSA (range 1600–9200 mL/m^2 BSA), the mean BSA at this age being 1.4 m^2. Nocturnal enuresis is a commonly reported problem related to the high fluid intake, resolving at a median age of 11 years [174]. Conversely, the over-provision of water can drive urine output and potentially result in water intoxication [207]. The reported feeding problems, including vomiting and poor appetite, improve in early childhood with good adherence to salt control and medications. Most children take adequate nutrition orally, but regular dietary assessments through childhood can be helpful to ensure that the recommended intakes for energy, protein and micronutrients are still being met.

Providing advice on how to manage acute episodes of GI symptoms such as vomiting or diarrhoea is important. To prevent hypernatraemic dehydration, a glucose polymer solution can be offered in place of the usual oral rehydration solutions. As a precaution, clear instructions should be given on the preparation of a 10% concentration of a glucose polymer (10 g in 100 mL water) using scoop measurements or pre-measured sachets along with a very small supply of suitable product.

Growth has been reported to be suboptimal in long-term follow-up studies [203, 208], but near normal in others [174]. In the latter, median *z*-scores for weight improved from −2.1 at presentation to 0.2 at last follow-up; median height SDS remained essentially unchanged −1.06 at presentation to −0.9 at last follow-up.

Learning points: nephrogenic diabetes insipidus

- *Feeding problems are common in infancy (related to polydipsia, vomiting and constipation)*
- *Feed renal solute load in infants should be reduced to ≤15 mOsm/kg H_2O per kg body weight*
- *Allow free access to water*
- *May need tube feeding support up to 2 years of age*
- *Wean onto a low sodium diet initially*
- *Expand intake up to a reduced salt diet ('no added salt') by the age of 2 years*
- *Episodes of diarrhoea and vomiting should be managed by offering a glucose polymer solution (e.g. at 10% concentration), rather than a rehydration solution*

Renal Stones

Urolithiasis (or urinary stone disease) is a heterogeneous group of conditions where minerals crystallise to form hard solid stones, or calculi, in the urinary tract. They are typically classified by their main chemical component (calcium, uric acid, struvate or cystine) or location, e.g. nephrolithiasis (in the kidney). Stones vary in size from less than 3 mm diameter to larger stones that can block urinary flow and cause renal damage. Stones are less common in infants and children than in the adult population. A recent UK single-centre retrospective paediatric cohort of 511 patients over a 22-year period [209] reported a median age of presentation of 4.4 years for males and 7.3 years for females, but stones were reported from as young as 1 month of age. Paediatric renal stone disease is more common in males than females, especially in the first decade.

A significant proportion (20%–60%) of paediatric patients have an underlying condition that is conducive to stone formation, e.g. a metabolic disorder, urinary tract abnormality (especially if leading to urinary stasis or risk of an infection), tubular damage secondary to medications (e.g. furosemide) or frequent urinary tract infections [209]. There has been a shift over the past decades in paediatrics from predominantly infectious to metabolic causes and 30%–40% of children have a family history of stone disease [209, 210].

The prevalence of paediatric urolithiasis varies between countries, with high rates reported in Turkey, Pakistan and Saudi Arabia compared with the UK, the USA and Japan. The incidence and prevalence in developed countries appears to be increasing, particularly in adolescents [210], although this may reflect more sensitive imaging technology. The initial presentation in children differs from the classic signs of urolithiasis in adults, with less acute abdominal pain or haematuria. The large UK paediatric cohort [209] reported that 36% children presented with a urinary tract infection, 32% with abdominal pain and 27% with haematuria (especially in children <6 years) and 13% were asymptomatic (some presenting with more than one main symptom).

The medical management of children with renal stones involves alleviating acute pain, prevention of renal damage, managing infections or obstruction and facilitating passage or removal of stones. Diagnosis is confirmed by an ultrasound, enabling assessment of the size of the stone, location and degree of urinary obstruction. Kidney stones less than 3 mm ('gravel') are likely to pass spontaneously [211]. Many stones can be cleared by lithotripsy using high energy shock waves directed towards the stone. If the stones are in the middle or lower portion of the ureter, an ureteroscopy can assist in removing the stone. Larger and more complex stones (such as staghorn stones) in the upper urinary tract may require percutaneous lithotomy [212].

The majority of stones in children are composed of calcium oxalate (≥75%) or calcium phosphate (10%–20%), followed by struvite, cystine or uric acid in descending order [209, 213]. Cystinuric patients often present with larger stones and higher new stone formation rates and are more likely to require surgery [214]. Evaluation of the composition of the stone (if available), together with identification of underlying metabolic risk factors, guides treatment and directs targeted advice to prevent recurrence. Metabolic risk factors include hypercalciuria, hyperuricosuria, hyperoxaluria, cystinuria, disorders of purine metabolism and hypocitraturia, in addition to environmental factors such as diet

and fluid intake. A metabolic screen on a 24 hour urinary sample (or a spot urine sample for younger children) is usually performed along with microscopy to assess for an infective aetiology [215]. Most UK laboratories will report paediatric urinary concentrations indexed to creatinine (rather than BSA or body weight) and have age and sex reference intervals for some of these. However, there is little evidence-based published data and no universally accepted standards, so interpretation of urinary values can be difficult. Table 13.25 gives a guide to normal urinary reference values [215, 216].

Stone recurrence can be frequent in children (30%–67%) [217, 218] especially if there is an underlying metabolic abnormality, with a mean interval of 3–6 years. The prevention of recurrence focuses on improving the balance between the crystal-forming and crystal-inhibiting substances in the urine [219]. The treatment approaches in children are based largely on extrapolation of adult studies, single institution cohorts or case series in children. The main pharmacological and dietary treatment options used in relation to paediatric kidney stones are shown in Table 13.26.

Fluid

Dehydration can contribute to the formation of all forms of stones, and this may be secondary to a low fluid intake, high dermal or ileostomy losses or diarrhoea. Children with stones have been reported to have a lower 24 hour urine volume than controls [220]. An increase in fluid intake will increase urine output, preventing urine stagnation and reducing saturation of some solutes such as uric acid, calcium, oxalate and cystine molecules [221]. A minimum urine flow of 1 mL/kg/hour has been shown to reduce the urinary saturation of calcium oxalate, calcium phosphate and uric acid [222]. A very high urine output may be necessary for patients with cystinuria as the aim of treatment is to reduce the urine cystine concentration below 1 mmol/L (240 mg/L). A prospective randomised trial in 199 adult calcium stone formers [223] confirmed the importance of fluid, an intake of more than 2 L/day delaying and reducing total frequency of stone recurrence during the 5-year follow-up. A similar fluid intake (1–2 L) has been recommended for children [213, 224], but the optimal fluid intake for different

Table 13.25 Guide to normal urinary reference values.

Refer to country, age and laboratory-specific reference intervals.

Solute	24 hour excretion [216]	Spot urine [215] (from 2nd morning sample)
Calcium (Ca)	<0.1 mmol/kg (<4 mg/kg)	*Ca–creatinine ratio* (mmol/mmol) <1 year <2.2 1–5 years <1.5 5–17 years <0.8
Magnesium (Mg)	>3.6 mmol/1.73 m^2 (>88 mg /1.73 m^2)	*Mg–creatinine ratio* (mmol/mmol) <1 year <2.2 1–5 years <1.3 5–17 years <1.0
Phosphate (P)		*P–creatinine ratio* (mmol/mmol) <1 year <19 1–5 years <14 5–17 years <5
Citrate		*Citrate–creatinine ratio* (mmol/mmol) Female <0.55 Male <0.33
Oxalate	<2 mg/kg	*Oxalate–creatinine ratio* (μmol/mmol) Infant <98 Child <72
Cystine	<60 mg/1.73 m^2	*Cystine–creatinine ratio* (μmol/mmol) <3 months <35 3 months to 3 years <25 >3 years <20
Uric acid (urate)	<815 mg/1.73 m^2 <35 mg/kg	*Uric acid–creatinine ratio* (mmol/mmol) <2 years <1.96 2–6 years <1.35 6–18 years <0.85
Creatinine[1]	0.1–0.2 mmol/kg 15–25 mg/kg	

[1]Often measured in a 24 hour urine sample to check adequacy of collection.

Table 13.26 Pharmacological and dietary treatment options for paediatric renal stones.

Type of stone	Medications	Possible dietary changes
Calcium (calcium oxalate or phosphate)	Potassium citrate (increases urinary citrate) Thiazide medication (reduces hypercalciuria)	High fluid intake Adequate calcium Reduced salt diet Avoid vitamin C supplements
Uric acid	Potassium citrate Allopurinol (reduces the amount of uric acid made by the body by blocking xanthine oxidase)	High fluid intake Reduced dietary purine (probably not useful)
Struvate	Antibiotics	High fluid intake
Cystine	Potassium citrate Penicillamine or mercaptopropionylglycine (helps dissolve urinary cystine)	High fluid intake Reduced salt diet
Hyperoxaluria	Potassium citrate Pyridoxine (in some cases)	High fluid intake Low oxalate diet (probably not useful)

age groups has not been investigated. A suggested intake of at least 3 L has been proposed for children with cystinuria, 1 L of fluid for every millimole of cystine excreted [225], but compliance with this is difficult. Some adult research suggests that water, milk and fruit juices (except grapefruit, cranberry or apple juice) are all appropriate fluids [226]. However, consumption of fructose-containing drinks been shown to increase oxalate and calcium excretion in adults, increasing stone risk [227]. Extra fluids are ideally given as water, rather than fructose or sugar sweetened drinks, especially as a link between stones and obesity has been seen in adults. Prevention of dehydration is central to management, and practical advice should be given on regular drinking both day and night, during sports and exercise, during car and airplane journeys and in hot weather. Alcohol is also a risk factor causing dehydration, so young people should be cautioned about this (taking extra water alongside if appropriate).

Nutritional management

Dietary interventions may reduce urinary stone formation and recurrence, but there is no conclusive consensus in the literature regarding their effectiveness in children [221, 228]. Restrictive diets may alter urine concentration of solutes, but not necessarily translate to decreased stone formation [229]. The regulation of urine saturation and crystallisation is complex, and dietary alterations of a single component may be too simplistic an approach. An example of this has been the previous misconception that limiting oral calcium intake would reduce hypercalciuria and risk of calcium-containing stones. Paradoxically, diets low in calcium carry an increased risk of renal stones, possibly due to lower binding with dietary oxalate in the gut leading to increased oxalate absorption [230]. A Cochrane review assessing the effectiveness of diets for adults with renal stones [231] concluded that a low protein, low salt diet (with a normal calcium content) reduced oxaluria, urinary calcium oxalate saturation and, hence, risk of stone recurrence. The National Institute for Health and Care Excellence (NICE) is producing guidelines on the assessment and management of renal and ureteric stones that will include dietary and lifestyle advice [224]. Lack of clinical trial data in children means that adult data is often extrapolated by clinicians to the management in children. The role of diet in preventing paediatric renal stone recurrence is now discussed.

Salt

High dietary sodium intake decreases proximal tubular sodium and calcium reabsorption, increasing urinary calcium excretion [232]. Hypercalciuria is found in approximately 30%–50% of stone-forming children [233]. For individuals at risk of developing renal stones, a reduction in salt intake is helpful to reduce hypercalciuria [230, 234] and cystinuria [235], and this also increases urinary citrate [236]. However, the level of sodium restriction required has been debated.

Following a literature review, Tasian [213] recommended reducing sodium intake to <2–3 mmol/kg for young children and <2.4 g sodium/day (<6 g salt/day) in adolescents with hypercalciuria or calcium-based stones. The usual practice in the UK is similar, advising on a reduced salt diet (approximately 3 mmol sodium/kg; 2–6 g salt per day depending on age), achieved by omitting adding salt to meals and avoiding high salt foods such as most takeaway foods, processed meat, cheese, smoked fish, savoury snacks, ready meals and high salt soups and sauces (Table 13.24). Personalised practical advice based on a careful diet history will improve compliance. This should include education on identifying high salt manufactured foods, adaptation of standard recipes and ideas for suitable snacks. Salt taste preferences are dependent on the salt level in the diet, so it can take time for a child with a high salt intake to become accustomed to a reduced intake. The degree of salt restriction imposed can be reassessed depending on urinary composition.

Calcium

Deposition of calcium oxalate may be a result of hypercalciuria, hyperoxaluria or hyperuricuria or because of hypocitraturia. Hypercalciuria is usually defined as a calcium excretion of more than 0.1 mmol/kg (4 mg/kg/day) or a urinary calcium–creatinine ratio above 1.5 mmol/mmol [237], but this is age dependent (being highest in younger children) (Table 13.25).

Hypercalciuria is not usually due to a high calcium intake, so decreasing calcium intake is not advised. A low calcium intake actually increases stone risk, and an increase in calcium intake decreases risk of stones in adults [232]. Ensuring adequacy of calcium intake should be part of the dietary management to prevent stone recurrence.

Citrate

Hypocitraturia is a common metabolic alteration seen in about 60% of children with nephrolithiasis [238]. Low citrate excretion can also occur secondary to use of a ketogenic diet for epilepsy, renal tubular acidosis and diarrhoea. Citrate acts as an inhibitor for crystal formation and increases the solubility of stone-forming calcium salts. Most international guidelines recommend the administration of alkaline citrate medication (usually potassium citrate) to prevent stone recurrence, and this is also given prophylactically to children on ketogenic diets [239]. Citrus (lemons, oranges, grapefruit and lime) and non-citrus (melon) fruit are natural sources of citrate, and there is some low quality evidence that these fruits and/or their juices can increase urine citrate levels in adults [240, 241].

Oxalate

The most common paediatric stones are predominantly calcium oxalate, and a high urinary excretion of oxalate is a risk factor. Hyperoxaluria may be secondary to increased oxalate absorption (often called enteric hyperoxaluria) or high dietary intake or as a consequence of an inherited defect in oxalate metabolism (primary hyperoxaluria). Urinary oxalate is primarily produced from endogenous metabolism of glycine, glycolate, hydroxyproline and vitamin C, with estimates varying from 10% to 50% originating from diet [242, 243]. Oxalate is mainly consumed as plant and plant products, but their reported content varies widely reflecting different analytical techniques, processing, cooking methods, soil content and even time of harvest, along with many factors that influence its bioavailability [244–246]. Although there is no accepted definitive list, the following consistently have a high content: spinach, beetroot, okra, rhubarb, strawberries, almonds, peanuts, cashew nuts, chocolate and wheat bran. A randomised clinical trial in stone-forming adults indicated that reducing dietary oxalate lowered urinary oxalate excretion [247], but there is little evidence that reducing intake decreases stone risk [248]. Oxalate restriction is not generally recommended in children at risk from oxalate stones [213], the advice being to increase fluid intake, reduce salt, consume adequate calcium and avoid high doses of supplemental vitamin C [249].

Primary hyperoxaluria types 1, 2 and 3 (PH1, PH2, PH3) are inherited disorders of oxalate metabolism causing increased liver oxalate production and higher urinary oxalate excretion with risk of nephrocalcinosis and nephrolithiasis. Pyridoxine supplements (vitamin B_6) can reduce the urinary excretion of oxalate by over one third in about 10%–30% children with PH1. Dietary oxalate does not significantly affect urinary oxalate in PH.

Some GI conditions are linked to a higher risk of stones as a consequence of increased oxalate absorption in the gut. This can happen secondary to cystic fibrosis, biliary tract disease, inflammatory bowel disease and short bowel syndrome. In these situations, malabsorbed free fatty acids and bile salts may bind to calcium in preference to oxalate, increasing the absorption of free oxalate (secondary alimentary hyperoxaluria). The effectiveness of limiting dietary oxalate intake to reduce the risk of renal stones in these children has not been researched. It is probably more important to reduce the diarrhoea and control the malabsorption if possible.

Urate

Hyperuricosuria is an independent risk factor for calcium stones, as uric acid decreases the solubility of calcium oxalate. In addition, children can also have uric acid stones (containing xanthine or 2,8-dihydroxyadenine) due to disorders of purine overproduction, renal tubular problems or excessive purine ingestion. Purines are metabolised to uric acid. The main treatment for preventing uric acid stones is increased fluid intake, alkalinisation of the urine and allopurinol medication (if overproduction of uric acid is a problem). Dietary purine restriction has been suggested for adults with hyperuricosuria, but is not thought appropriate for children because of the efficiency of allopurinol medication [213].

Protein

High protein diets, especially from animal protein, can increase urinary calcium, decrease urinary citrate and pH and also increase urinary uric acid (being a source of purines). However, although low protein diets in adults have been shown to reduce the risk of stone formation [230], restricting protein intake in growing children is not appropriate. For intractable recurrent paediatric stones, a cautious reduction in dietary animal protein intake towards the RNI [18] may be appropriate if a dietary assessment indicates a high consumption [250].

Probiotics

Theoretically, probiotics could enhance intestinal oxalate metabolism or decrease gut absorption, reducing urinary oxalate excretion. However, there is insufficient evidence to support their use in reducing calcium oxalate stone risk [247].

Struvite stones

Calculi containing struvite (magnesium ammonium phosphate or triple phosphate stones) result from infections with urea-splitting bacteria and are usually large, sometimes filling the entire renal pelvis (known as staghorn calculi). Struvite stones have to be removed surgically and can cause serious morbidity, being more likely to result in CKD than other calculi [209, 251]. In the UK cohort [209], 26% of those who ended up with CKD also had an underlying structural abnormality, which probably contributed to the development of infection. Heilberg [252] concluded that diet has no definitive role in the prevention of struvite stones following a comprehensive literature review. However, a high fluid intake is usually advised in the presence of normal glomerular function, but the main medical management is focused on preventing further infections.

Cystine

Cystinuria is an autosomal recessive disorder arising from defective reabsorption of four amino acids (cystine, ornithine, arginine and lysine) by their common transporters in the proximal tubule of the kidney. Only cystine causes problems due to its low solubility. Patients with homozygous cystinuria may excrete up to 30 times the normal amount of cystine, and heterozygotes up to 10 times. Cystine is poorly soluble and precipitates to form cystine stones in the kidneys, ureter and bladder (accounting for about 1% of paediatric renal stones). Half of individuals with cystinuria develop their first stone by the age of 10 years and 25%–40% before 20 years [253].

To maintain cystine solubility, individuals are encouraged to have a very high fluid intake (e.g. 1.5–2 L/m^2 BSA), which should be distributed throughout the day and night ideally. The aim of treatment is to keep urinary cystine levels below 1 mmol/L. In addition, as cystine is more soluble in alkaline urine (optimal pH between 7 and 7.5), potassium citrate and bicarbonate are often given to prevent calculi forming. For some children with a high stone recurrence rate, other medications to increase cystine solubility may be given (e.g. thiols). A reduced salt diet (Table 13.24) should be advised as this will reduce urinary cystine excretion [235], as sodium and cystine transport is coupled in the renal tubule. As cystine is a non-essential amino acid synthesised from methionine, methionine (or protein) restriction theoretically can reduce urinary cystine and increase urinary pH. However, limiting protein intake is not appropriate in growing children. For recurrent intractable stones, it may be helpful to identify children with a very high protein intake and advise a reduction to nearer the RNI for age.

Learning points: renal stones

To prevent recurrence (especially for cystine stones):

- *increase fluids (2–3 L/day depending on age and diagnosis)*
- *advise a reduced salt diet*
- *ensure adequate calcium intake*
- *stop vitamin C supplements*
- *avoid very high protein intake (if very frequent stone recurrence)*
- *minimal benefit from reducing dietary oxalate or purine intake*

Hypercalcaemia

Hypercalcaemia is uncommon in children, but can be associated with long-term morbidity including renal, cardiac and neurological problems. The usual definition of hypercalcaemia is a total (albumin-corrected) plasma calcium (Ca) >2.6 mmol/L or an ionised Ca >1.3 mmol/L, severe levels being >3.0 and >1.5 mmol/L, respectively [216]. However, reference ranges vary with different laboratories and are age dependent, with higher levels in infants compared with children.

The management of hypercalcaemia involves identifying the underlying cause and initiation of treatment to lower serum calcium (including fluids, antiresorptive medications and potentially surgery). A reduction in calcium intake from enteral, parenteral, medicinal and supplemental calcium (and vitamin D) is often appropriate, particularly when increased intestinal absorption is a possible aetiology.

The causes of hypercalcaemia are diverse and may be genetic or acquired, including abnormalities of parathyroid hormone or vitamin D metabolism, malignancies, immobilisation, inherited metabolic disorders or occurring secondary to phosphate depletion (e.g. in premature or low birthweight infants) [254]. Congenital anomalies associated with hypercalcaemia include idiopathic infantile hypercalcaemia (IIH) and Williams syndrome.

Idiopathic infantile hypercalaemia

IIH is an autosomal recessive disorder resulting in high levels of active vitamin D and hypercalcaemia in infancy, often resolving by the age of 2 years. Inadequate 24-hydroxylase enzyme activity results in impaired catabolism of vitamin D, leading to high intestinal calcium absorption, decreased calcium excretion and increased osteoclastic activity [255]. Infants present in the first year with severe vomiting, dehydration, constipation, faltering growth, weight loss and lethargy, which can be exacerbated by the administration of supplementary vitamin D. Hypercalciuria and nephrocalcinosis may develop

and persist into adulthood, increasing the risk of renal stones. Treatment may be limited to simple oral hydration, discontinuation of additional vitamin D supplementation and possibly short-term dietary calcium restriction. However, more severe cases reported in the literature have required steroid, bisphosphonates and even haemodialysis [255]. If a dietary restriction is imposed, a gradual increase in calcium intake to normal levels is recommended after 6–12 months to reduce risks of rickets and poor dentition [256]. Lifelong avoidance of vitamin D supplements should be advised.

Williams syndrome

Williams (or Williams–Beuren) syndrome (WS) is a rare autosomal dominant multisystem disorder known to be associated with hypercalcaemia in infancy. It is characterised by cardiovascular abnormalities, distinct facial features (often referred to as elfin face), low muscle tone and manifestations relating to endocrine and nervous system disturbances.

Hypercalcaemia has been reported in 5%–50% patients with WS, but is often transient and mild [257–259]. The mechanisms underlying this are not known, but may be due to hypersensitivity to vitamin D, increased 1,25-dihydroxyvitamin D or defective calcitonin metabolism. Hypercalcaemia is most likely to be symptomatic in infancy, levels normalising between 2 and 4 years of age although recurrence in puberty has been reported [260]. Hypercalcaemia is clinically relevant if it leads to hypercalciuria and nephrocalcinosis. Nephrocalcinosis is rare and may improve in time, with a report from Italy finding no evidence on ultrasound in a cohort of 57 WS patients [258]. Guidelines from the American Academy of Pediatrics [260] suggest a urinalysis for total calcium 2–4 yearly, depending on baseline calcium, with spot urine calcium–creatinine ratios every 2 years. However, others suggest symptom-based testing, triggered by changes in feeding pattern and behaviour, irritability, nausea and vomiting and/or signs of dehydration [257].

In infants with WS, hypercalcaemia appears to exacerbate colic and cause extreme irritability, poor appetite, mild hypotonia and constipation, but not all infants are symptomatic [258]. The acute management of hypercalcaemia may include IV hydration (particularly in infants), to improve urinary calcium output, and the administration of loop diuretics together with a strict reduction in calcium intake and vitamin D intake. Vitamin D supplements (including multivitamin formulations) should be avoided during the stabilisation period as this will significantly increase calcium absorption. If hypercalcaemia and hypercalciuria are present, part of the dietetic review should include an assessment of fluids, advising an increase if necessary, e.g. to 160–200 mL/kg for an infant to prevent nephrocalcinosis.

Clinical practice guidelines for WS in the UK [261] suggest calcium intake may need to be reduced to equal or less than half the RNI of the child's age group [18]. However, for some infants, lowering of serum calcium is only achieved after more severe restriction [262]. Standard infant formulas or breastfeeding may need to be stopped and replaced with Locasol, a nutritionally complete formula low in calcium and vitamin D. This formula can be given to infants or used as a supplementary drink in hypercalcaemic children. When prepared using deionised or distilled water (available in the UK on prescription), Locasol provides <7 mg calcium/100 mL. The calcium content of tap water in the UK is available by contacting the relevant water suppliers (www.water.org.uk); hard water can contribute over 0.3 mmol (12 mg) calcium per 100 mL. The level of calcium restriction is determined by blood calcium levels and may need to remain low throughout infancy and early childhood, e.g. at 300 mg (7.5 mmol) daily, which is less than the RNI (or population reference intake) in most countries. However, this should be relaxed when possible, especially if serum PTH or alkaline phosphatase starts to rise. Rickets has been described in infants with WS [263] as a result of inappropriate prolonged treatment of hypercalcaemia. If serum calcium and urinary calcium–creatinine ratios are in the age-appropriate range, then dietary calcium restriction is not necessary. Breastfed infants with WS without hypercalcaemia may need additional vitamin D to prevent rickets (along with careful monitoring).

Infants are usually born at term, but often with a low birthweight [90], and gain weight poorly and may continue to have a decreased BMI and percentage body fat up until early adulthood. Conversely, a longitudinal study [264] reported that nearly 60% of their WS patients (median age 13.6 years) were overweight or obese and 25.9% and 11% patients had impaired glucose tolerance and type 2 diabetes, respectively. The weight gain in WS adults is particularly related to fat accumulation in the lower extremities, as assessed by thigh circumference [265]. Growth charts for British children with WS have been published [266] with data from 169 children and adults with an established genetic diagnosis. These allow improvement in growth monitoring and picking up growth abnormalities that may require further medical investigation.

Infants with WS may experience feeding problems from 2 to 3 months of age including feed refusal, reflux, vomiting, a sensitive gag reflex, symptoms of colic, constipation and disordered suck or swallowing patterns [256]. Weaning onto solid foods may be delayed as they may not readily accept change in textures (tactile sensory defensiveness). These feeding difficulties tend to resolve in early childhood, although gastro-oesophageal reflux may continue to be a problem. Abnormal dentition including small, widely spaced, crooked or missing teeth and malocclusion are commonly reported [267].

For children and weaned infants, a low calcium diet limits high calcium foods such as milk and milk products, tinned fish (where the bones are eaten), tofu and calcium or vitamin D fortified foods (such as orange juice, breakfast cereals and breads). Table 13.27 gives a guide for low calcium and vitamin D diet. For a 5-year-old, this would achieve a calcium intake

Table 13.27 Guide to a low calcium and vitamin D diet.

Refer to country-specific food composition tables if available.
In the UK it is mandatory to fortify all wheat flour (except self-raising flour with a calcium content ≥0.2% or wholemeal flour) with calcium carbonate, according to the Bread and Flour Regulations 1998 (SI 1998/141) (www.legislation.gov.uk/uksi/1998/141/contents/made); this addition will be declared on the ingredient list of products made from these flours. Flour milled and imported from elsewhere may not be fortified.
The calcium naturally present in wholemeal flour may be less bioavailable, due to the present of phytate.

Foods to avoid	Suitable alternatives
Water	
Tap or bottled water	Purified water (deionised or distilled)
Milk and milk products	
Infant formulas	Locasol (Nutricia)
Cow's milk – any fresh or dried (whole, semi-skimmed, skimmed, evaporated, condensed)	Unfortified (often organic): coconut, rice, soya drinks. Rice drinks are not advised under 4½ years of age
Other mammalian milks (including goat, sheep and buffalo) Calcium fortified milk substitutes, e.g. soya, oat, almond, hemp, coconut White or cheese sauce	
Yoghurt, fromage frais, rice pudding, ice cream, ready-made custard, instant custard powder mix	Jelly, sorbet, pure ice lollies, meringue
Cheese, cream, quark, crème fraiche	Make custard using custard powder and milk substitute. Non-milk, non-fortified ice cream, e.g. soya and coconut (check labels)
Oils and spreads	
Margarines and spreads fortified with vitamin D Cod liver oil	Butter, cooking fats, oils, lard
Meat	
If made with fortified flour, cheese or milk, e.g. meat pies, lasagne	All are suitable – unless made into a product with fortified flour, cheese or milk
Fish	
Oily fish or fish with edible bones, e.g. whitebait, sardines, pilchards, anchovies, salmon, mackerel, herring, anchovies, tinned tuna, trout, kippers, eel Prawns, mussels, oysters, fish paste	White fish, e.g. cod, haddock, hake, monkfish, halibut, plaice, sole, skate
Eggs	
Particularly egg yolk Egg dishes, e.g. omelette, quiche	Egg white
Flours	
Calcium fortified wheat flour or products made with this, e.g. bread, crumpets, biscuits, muffins, bagels, scones, some pasta*, noodles	100% wholemeal, granary, rye, rice, cornflour, gram flour
Self-raising flour (white, brown or wholemeal) or products made with this, e.g. cakes	Wholemeal, granary, rye, oats or wholegrain products not made with self-raising flour e.g. bread, chapattis, pitta bread and biscuits
Soya flour	Barley, rice, oats, sago, tapioca
Baking powder	
Ordinary baking powder	A substitute can be made from cream of tartar and bicarbonate of soda
Breakfast cereals	
Calcium and/or vitamin D fortified breakfast cereals	All unfortified cereals are suitable unless they have added unsuitable nuts, seeds or dried fruit
Nuts and seeds	
Almonds, brazil nuts, hazelnuts, pecans, pistachios, walnuts	Peanuts and peanut butter
Sesame seeds and sesame seed pastes, e.g. tahini	Sunflower seeds
Fortified products (with calcium or vitamin D) e.g. baby rusks, orange juice, breakfast cereals	
Fruits	
Dried figs, sultanas, raisins, currants, prunes, apricots Rhubarb, orange	All other fruit

(continued overleaf)

Table 13.27 *(continued)*

Vegetables/pulses	
Okra, kale, spinach, broccoli, spring greens, watercress, olives	All other vegetables
Tofu – especially if firm (often processed with calcium sulphate)	Small portions only of broad beans, chickpeas, baked beans, kidney beans, hummus
Malted and chocolate drinks, malted milk products	
Drinking chocolate, Horlicks, Ovaltine drinks and malted milk drinks and biscuits	Purified water (deionised or distilled) Unfortified fruit juice of allowed fruit, e.g. apple, grape, pineapple Fruit squash Sugary drinks, e.g. lemonade, cola drinks
Confectionery	
Chocolate, fudge, toffee, chocolate spread	Boiled sweets, lollies, pastilles, peppermints, jam, syrup, honey

*Pasta made from wheat flour milled in the UK is also fortified with calcium; pasta made in other countries may not be.
Source: Adapted from the advice sheet produced by the nephrology dietetic team at Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.

of less than 250 mg/day. Locasol can be used as a milk substitute at any age to ensure nutritional adequacy, but unfortified (usually organic) rice, oat or other plant-based drinks can also be offered to older children. Once serum calcium is approaching the normal range, the calcium intake can be increased gradually (e.g. by about by 120 mg at a time, equivalent to 100 mL cow's milk) as indicated by blood biochemistry. To avoid hypercalcaemia, patients are advised to use sunscreen to minimise endogenous vitamin D production.

A high incidence of decreased bone mineral density has been described in adults with WS [265, 268], which may be a consequence of a prophylactic low calcium diet, initiated by parents or professionals.

Gastrointestinal problems, including chronic constipation and colonic diverticulitis, have been reported more frequently in WS compared with the general population [269, 270], causing recurrent or acute abdominal pain. This may not be identified promptly, as WS children have been reported to have an increased pain tolerance. Acute management of diverticulitis may involve a reduction in dietary fibre, but, once in remission, incorporating adequate soluble and insoluble fibre (fruit, vegetables, oats, pulses, wholegrain cereals) and fluids may help to minimise recurrence.

Learning points: hypercalcaemia

- *Paediatric hypercalcaemia has a diverse aetiology including being secondary to abnormalities of PTH or vitamin D metabolism or status, phosphate depletion malignancy or immobilisation*
- *Williams syndrome (WS) and idiopathic infantile hypercalcaemia (IIH) are inherited disorders, usually presenting in infancy*
- *WS is a multisystem disorder with hypercalcaemia present in 5%–50%, which is usually mild and resolves by the age of 2–4 years of age*
- *IIH presentation may be precipitated by the use of vitamin D supplements*
- *Symptoms of hypercalcaemia include nausea, vomiting, irritability, poor appetite, polyuria, polydipsia, constipation, faltering weight and height in infants*
- *A low calcium and vitamin D diet may be appropriate, but is not usually needed beyond infancy*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

14 Congenital Heart Disease

David Hopkins and Luise Marino

Introduction

Congenital heart disease (CHD) in infancy and childhood refers to structural abnormalities that arise in the four main chambers of the heart itself and/or the great vessels that lead to or from the heart. The type, size and combination of lesions determine the ability of the heart and lungs to, respectively, pump and oxygenate blood. This affects the workload and energy utilisation of these organs and associated musculature that, in turn, determines the type and extent of faltering growth seen in CHD.

A glossary is given, describing cardiac anomalies and corrective procedures (p. 311–313).

Incidence

The incidence of clinically relevant moderate to severe forms of CHD in Western Europe and North America is between 6 and 8 in every 1000 live births [1, 2], accounting for a third of all congenital abnormalities [3]. In Africa the incidence is lower at around 2 cases per 1000 births [3], but this may be due to underdiagnosis. It is highest in Asia, with incidence in Taiwan at around 13 per 1000 births [4]. Eight lesions make up 80% of cases, the most common of which are ventricular septal defect (VSD), persistent ductus arteriosus (PDA), atrial septal defect (ASD) and tetralogy of Fallot. Children with genetic defects have a higher incidence: 50% in infants with Down's syndrome, presenting with ventricular or atrioventricular septal defects, and 80% in Noonan syndrome, presenting mainly with pulmonary stenosis or hypertrophic cardiomyopathy [5]. One study has implicated increasing maternal and paternal age and antenatal febrile illness with increasing incidence of CHD [6] but interestingly also highlighted the possibility of good maternal nutrition, including multivitamin preparations, in reducing CHD incidence.

Learning points: incidence of CHD

- *Incidence in the West is between 6 and 8 cases in every 1000 births*
- *Incidence is much higher in children with genetic defects*

Screening and diagnosis

Some congenital cardiac anomalies are detected by ultrasound at antenatal screening, others during the postnatal check-up, while some may present acutely with cardiogenic shock and elevated blood lactate levels or, chronically, with faltering growth. Table 14.1 summarises the pathways to diagnosis.

Prevalence of faltering growth in CHD

Faltering growth is common in CHD [7–10]. Up to a quarter of patients have weight for height < –2 SD and mean weight for age < –1 SD, and weight for age may cross down two centile bands in up to 30% of cases prior to corrective surgery [8]. In countries where diagnosis may be delayed, an even higher proportion of patients with uncorrected CHD present with faltering growth. Okoromah has described wasting (weight for height SD score < –2) in 58% of acyanotic cases and stunting (height for age SD score < –2) in 68% of cyanotic cases [11].

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 14.1 Modes of diagnosis of congenital heart disease.

	Postnatal signs and symptoms		
Antenatal	Early	Late	Confirmation
Antenatal ultrasound	Heart murmur[1]	Collapse with elevated blood lactate[4]	Echocardiography
	Absent femoral pulse[2]	Faltering growth[1,5]	Cardiac catheterisation*
	Cyanosis[3]		

[1] Ventricular or atrial septal defects (VSD/ASD) and persistent ductus arteriosus (PDA).
[2] Coarctation aorta.
[3] Cyanotic heart lesions.
[4] Coarctation of aorta.
[5] Complex heart disease.
* In very rare cases.

Learning points: prevalence of faltering growth

- *Faltering growth is common*
- *Up to a quarter of patients have marked wasting*
- *Delayed diagnosis increases the prevalence and severity of faltering growth*

Pathogenesis of faltering growth in CHD

The extent and type of growth attenuation in CHD depend on how the different lesions affect different metabolic processes. Not all CHD results in faltering growth. Some lesions, such as transposition of the great arteries (TGA), may be diagnosed on antenatal ultrasound scan, while others, such as coarctation of the aorta, may present shortly after birth. Both lesions usually undergo primary surgical repair in the neonatal period and have negligible impact on long-term growth [12]. Other lesions, such as ASD, do not cause cardiopulmonary changes that are large enough to affect energy expenditure and are repaired in early childhood [13]. Relatively mild forms of lesions that would usually result in faltering growth, such as small VSD, may either resolve with time or undergo repair having had limited effect on growth. Figure 14.1 shows the growth chart of an infant with mild tetralogy of Fallot who continued to breastfeed with minimal impact on growth until the defect was repaired (see arrow), with slight post-operative weight loss, after which he fed more avidly and weight trajectory improved.

For the healthy infant the average daily total energy expenditure (TEE) is between 60 and 70 kcal (250–290 kJ)/kg/day [14–16]. Achieving the estimated average requirement (EAR) of 96–120 kcal (400–500 kJ)/kg/day in early infancy [17] results in 35–60 kcal (145–250 kJ)/kg/day being available for growth. However, up to a third of children with CHD have an energy expenditure 120% of normal [18, 19], resulting in less energy available for growth. An understanding of the primary cardiac anatomy and the surgery involved in either repair or palliation helps to identify those who are at most risk of faltering growth. Lesions that increase cardiorespiratory workload affect growth by reducing the surplus

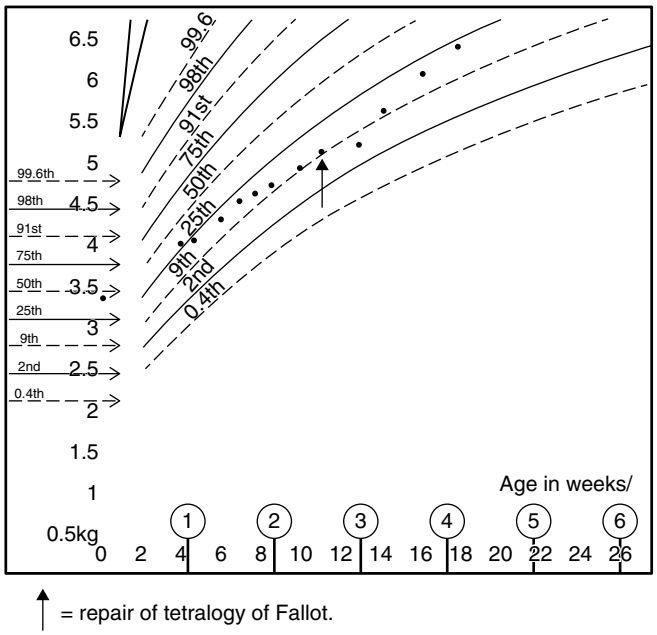


Figure 14.1 Growth chart of a breastfeed infant with mild tetralogy of Fallot.

energy available for tissue accretion, and the level of growth failure depends on the extent to which workload is increased. Examples are moderate to large VSD and atrioventricular septal defect (AVSD), and PDA. The effect on faltering growth is exacerbated if the lesion progresses to cause congestive heart failure (CHF), in which cardiac output is unable to meet the metabolic demands of the body [18].

Improving growth before surgery is considered key to improving longer-term outcomes among infants with complex heart lesions [20], especially as a high risk growth pattern has been quantified as faltering growth during the first 2 years of life with subsequent rapid catch-up growth between the ages of 2 and 15 years [21]. It is hypothesised that increased adiposity in adults with CHD may increase the risk of metabolic and cardiovascular disease later in life [22–24].

Complex CHD is associated with malnutrition and growth retardation in both infancy [11, 25–30] and childhood [11, 31].

The type of congenital cardiac defect impacts on energy expenditure and, hence, growth and can be divided into two main types: acyanotic lesions, where oxygen saturation of haemoglobin is normal, and cyanotic lesions, which cause low oxygen saturation.

Acyanotic lesions: In the normal circulation the weaker right ventricle pumps blood to the lungs at a pressure that is a third of that of the left ventricle, which pumps blood to the rest of the body, the systemic circulation. However, the vascular resistance of the lung is considerably less than that in the systemic circulation resulting in equal blood flow out of each ventricle. However, cardiac anomalies that cause a 'hole' between the left and right sides of the circulation usually result in a larger than normal volume of blood being pumped to the lungs by both the right and, the more powerful, left ventricle: a 'left-to-right shunt'. If blood flow through the shunt is high and prolonged, the elevated pressure causes pulmonary hypertension [18], resulting in inefficient gas exchange across the capillaries. Adequate tissue oxygenation is then achieved only at the expense of increased respiratory effort. This elevates the body's TEE, resulting in less energy being available for growth. The elevated pulmonary vascular resistance (PVR) [32] and TEE seen in patients with severe acyanotic lesions [16, 18, 33] correlate inversely with weight gain. This effect is illustrated in Figure 14.2 showing twins, one with a normal circulation and the other with a VSD. Severe, prolonged 'left-to-right shunts', resulting in CHF, further increases energy expenditure [18].

Cyanotic lesions: The presence of cyanosis appears to exert an independent effect on growth resulting in stunting [11, 26, 34]. The mechanism for this is uncertain, but it appears that hypoxia is a factor causing suboptimal tissue oxygenation [35]. Cardiac defects that result in both pulmonary hypertension and cyanosis appear to place patients at greatest nutritional risk, by causing both wasting and stunting [26]. Examples of a cyanotic lesion, an acyanotic lesion and tetralogy of Fallot are shown in Figures 14.3–14.5.

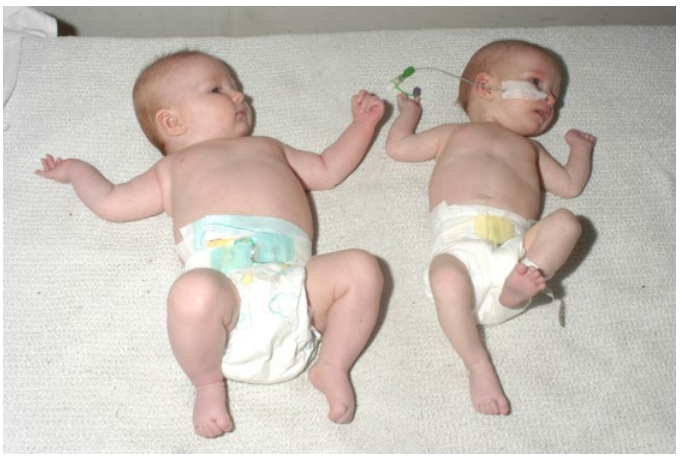


Figure 14.2 Twins, one with a normal circulation and the other with a VSD. Source: David Hopkins (Permission from parent, Bristol Royal Hospital for Children).

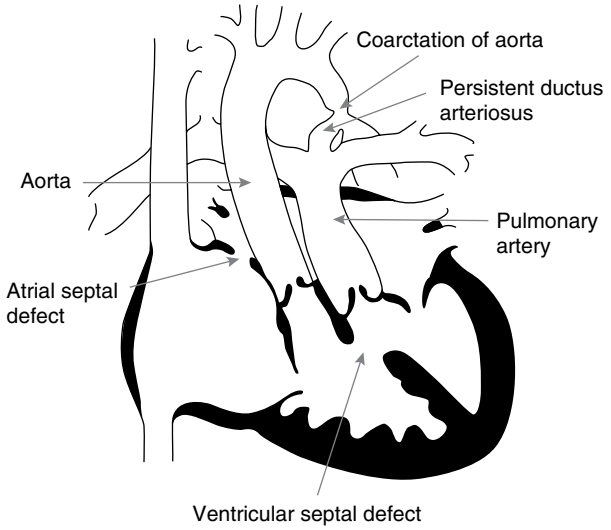


Figure 14.3 A cyanotic lesion. Transposition of the great arteries with ventricular and atrial septal defects, patent ductus arteriosus and coarctation of aorta.

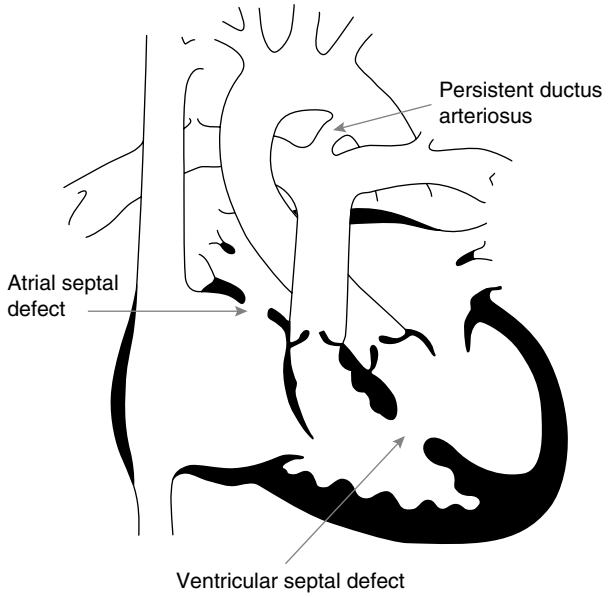


Figure 14.4 An acyanotic lesion. Atrial and ventricular septal defects with patent ductus arteriosus.

Table 14.2 shows the potential effect of the different types of lesion on growth. Table 14.3 summarises the risk that specific defects pose on growth faltering.

Cardiomyopathy: Paediatric cardiomyopathies are a heterogeneous group of disorders affecting the muscle of the heart, resulting in significant morbidity and mortality. The incidence is 1.13–1.24 per 100 000 children 18 years and younger. Nearly one third of children diagnosed with a cardiomyopathy during the first year of life will die within 1 year of diagnosis, and 40% will require a heart transplant within 2 years. Growth failure is common and the promotion of adequate nutrition is essential [36].

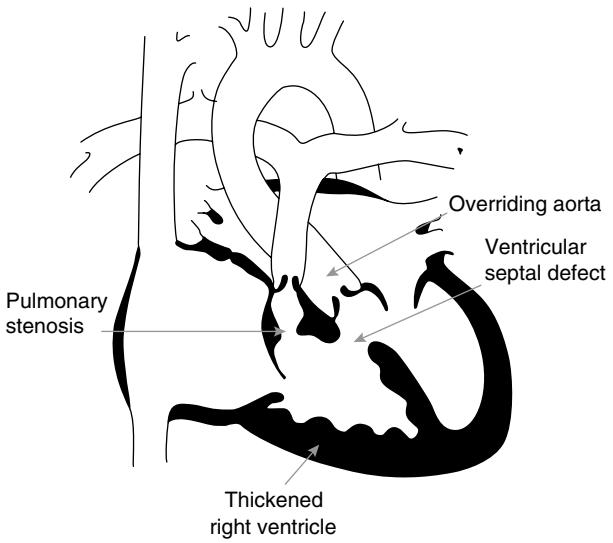


Figure 14.5 Tetralogy of Fallot illustrating the four aspects of the cardiac defect.

Learning points: pathogenesis of faltering growth in CHD

- *Not all CHD results in faltering growth*
- *Acyanotic lesions that increase cardiorespiratory workload tend to cause wasting by reducing energy available for growth*
- *Lesions that cause cyanosis tend to be associated with stunting*

Energy expenditure and energy intake in CHD

Energy expenditure

Doubly labelled water studies have been used to calculate the TEE of 'free-living' infants with a variety of cardiac lesions [16, 18, 37, 38]. However, indirect calorimetry is the recommended method of calculating energy expenditure of

Table 14.2 Effect of type of cardiac lesion on metabolic processes affecting somatic growth.

Lesion type	Metabolic effect	Effect on growth	Examples
Acyanotic	↑TEE	Wasting +	VSD, PDA, AVSD
Acyanotic with CCF	↑↑TEE	Wasting ++	Persisting large VSD, AVSD
Cyanotic	Poor tissue oxygenation	Stunting	TOF, TGA, hypoplastic left heart
Cyanotic with pulmonary hypertension	↑↑TEE + poor tissue oxygenation	Stunting with wasting	Truncus arteriosus

TEE, total energy expenditure; VSD, ventricular septal defect; PDA, patent ductus arteriosus; AVSD, atrioventricular septal defect; CCF, congestive cardiac failure; TOF, tetralogy of Fallot; TGA, transposition of the great arteries.

Table 14.3 Risk of different congenital cardiac defects affecting long-term growth.

Low			
Repaired soon after presentation	Limited effect on growth	Variable/moderate	High
Coarctation of the aorta	Atrial septal defect (ASD)	Pulmonary atresia*	Aortopulmonary window
Cor triatriatum		Tetralogy of Fallot*	Atrioventricular septal defect (AVSD)
Patent ductus arteriosus (PDA) (if early closure)			Ebstein's anomaly*
Pulmonary stenosis*			Hypoplastic left heart (HLH)*
Total anomalous pulmonary venous drainage (TAPVD)*			Partial anomalous pulmonary venous drainage (PAPVD)*
Transposition of the great arteries (TGA)*			Patent ductus arteriosus (PDA)¶
			Tricuspid atresia*
			Truncus arteriosus*
			Ventricular septal defect (VSD), moderate to large
			Double outlet right ventricle (DORV)

*Cyanotic lesions.
¶ If PDA is large and/or if surgery is delayed.

Table 14.4 Effect on energy expenditure according to congenital heart defect.

Lesion	Lesion type	Total energy expenditure, TEE (kcal/kg)		
		Healthy control	Pre-operative	Post-operative
VSD [16, 18, 19, 37, 41]	Acyanotic	61 [18] 62 [16]	71–97 [41] 77 [18] 78–157 [37] 84–123 [19] 87 [15]	
VSD (with CHF) [18]	Acyanotic	61	92 ± 20	
ASD [19]	Acyanotic		77–168	54–92
AVSD [41]	Acyanotic		91 [19] 98 [41]	
TOF, TAPVD, complex CHD [38]	Cyanotic	60* 72**	73* 94**	
TGA [37]	Cyanotic		78	
TOF [37]	Cyanotic		101–185 [19] 104 [37]	79–105 [19]
		Resting energy expenditure, REE (kcal/kg)		
				Post-operative
Hypoplastic left heart [44]	Cyanotic			43
Mixed CHD [45]	Acyanotic			70
Mixed CHD [45]	Cyanotic			66
Mixed CHD [45]	Requiring bypass			74

*At 2 weeks of age.
**At 3 months of age.
VSD, ventricular septal defect; CHF, congestive heart failure; ASD, atrial septal defect; AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot; TAPVD, total anomalous pulmonary drainage; CHD, congenital heart disease; TGA, transposition of the great arteries.

ventilated post-operative patients [39]. One study has shown that congestive cardiac failure (CCF) may increase energy expenditure in infants as young as 1 month old [40] although good diuretic control may negate this effect [41]. Malnutrition itself reduces ventricular mass and cardiac output, which may exacerbate an already compromised circulation [42]. The elevated energy expenditure causing growth failure in lesions resulting in large 'left-to-right shunts' and some cyanotic cases [16, 18, 25, 26, 37, 38, 42, 43] is summarised in Table 14.4.

Energy intake

Most studies show pre-operative energy intakes of patients with CHD are near normal [16, 18, 30, 38, 46, 47]. In one study where mean daily intake at 6 months of age was able to be measured, an average intake of 91.1 ± 38.9 kcal/kg and 2.5 ± 0.9 g/kg protein was similar to that of healthy controls: 89.4 ± 16.9 kcal/kg and 2.2 ± 0.55 g/kg [47]. However, some authors report low energy intakes [26] of the order of 80%–90% of that recommended [37, 48, 49], although the methodology for nutritional data collection in some of these studies is unclear [26, 49]. Children with cardiac defects resulting in both cyanosis and pulmonary hypertension have been reported as having significantly lower energy intakes than those with pulmonary hypertension or cyanosis alone [26, 49], and these patients may warrant more frequent nutritional review.

Any child with faltering growth whose energy intake is normal or above normal warrants cardiac assessment as part of further clinical investigations. The dietitian's role may be key in highlighting suspicion if growth failure continues following optimisation of nutritional intake.

Learning points: energy expenditure and intake in CHD

- *Most studies report normal energy intakes in most cases of CHD*
- *Elevated energy expenditure is the cause of faltering growth in most cases*
- *Energy intake may be reduced in infants whose cardiac defects result in both pulmonary hypertension and cyanosis*

Other factors affecting nutritional intake and growth

Delayed diagnosis and additional investigations

Where diagnosis is delayed, nutritional deficits become exacerbated, one study showing over 90% of cases having weight for age Z score (WAZ) < −2 SD and 60% having WAZ < −3 SD [11]. Repeated investigations such as cardiac catheterisation or computed tomography scans, requiring patients to be nil by mouth, interfere with feeding regimens often with limited scope to catch up with additional feeds. In addition, beliefs around the effect of prostaglandin infusions, indwelling umbilical catheters and cardiac drugs on the ability to tolerate feeds may limit intake [50]. Poor pain control may prolong the catabolic response to surgery, having detrimental effects on healing [51], and may delay progression to oral feeding.

Endocrine

Hypermetabolism is thought to reduce insulin-like growth factor 1 (IGF-1) synthesis in children with VSD, with lower serum levels correlating with increasing size of the 'left-to-right shunt' and reduced body mass index (BMI) [46]. Elevated levels of norepinephrine and renin are also associated with increasing respiratory rate in children with acyanotic CHD [32].

Metabolic

Lipid metabolism has been shown to be disturbed in infants with CHD with those with cyanotic lesions having a decreased ability to oxidise fatty acids [52]. Cardiopulmonary bypass (CPB) is known to cause the release of inflammatory mediators with the raised levels of catecholamines and cortisol, resulting in a degree of insulin resistance [53]. In the acute post-operative period amino acids, required for wound healing, may be obtained from muscle breakdown, but replenishment of these is needed to optimise growth in the medium to longer term.

Digestive

Nutritionally compromised infants are more susceptible to infections [54], and if these are frequent, the use of antibiotics may affect gut flora. Patients who develop infected post-operative sternal wounds may have antibiotic therapy resulting in diarrhoea, which may transiently affect absorptive capacity.

Infants with CHD have been found to have delayed gastric emptying [55]. Vomiting, diarrhoea, bloating, constipation and gastro-oesophageal reflux (GOR) are common [49]. Persisting or increasing vomiting frequency may hamper progression to higher energy feeds [32]. Prolonged use of prostaglandin infusions to keep the ductus arteriosus open has been linked to transient pyloric stenosis, resolving when the infusion is stopped [56]. Table 14.5 summarises the additional factors that have potential to impact on growth in CHD.

Pre-surgical nutrition to improve outcomes in high risk patients

Faltering growth and surgical outcome

Several studies have linked measures of malnutrition to poorer post-operative outcomes. These are summarised in Table 14.6. Most importantly malnutrition is associated with increased post-operative mortality risk at 1 month of age [69], 3 months of age [67, 73] and at 1 year [67].

Pre-surgical nutrition

Lesions that cause marked 'left-to-right shunts' and/or cyanosis that require staged repairs carry the highest risk of growth failure. After diagnosis, stabilisation and/or initial palliative surgery, some patients are discharged home to undergo a period of growth prior to correcting the primary defect or undergoing further palliation. This results in a gap of several weeks or months and, in the case of hypoplastic left heart syndrome (HLHS), years before the final operation. Table 14.7 summarises the stages of repair of some lesions.

Table 14.5 Additional factors affecting nutritional intake and growth in CHD.

Procedural	Digestive	Endocrine	Metabolic
Delayed diagnosis [11]	Gastro-oesophageal reflux [32, 57]	Insulin resistance [53]	Elevated energy expenditure [16, 18, 38]
Prolonged respiratory support [58]	Pyloric stenosis [56]	Reduced insulin-like growth factor [46]	Hypoxia [26]
Repeated operations [9]	Diarrhoea (antibiotic/infective)	Elevated norepinephrine [32]	Increased inflammatory markers [53]
Pain [51]	Chylothorax [59]	Elevated renin [32]	Impaired lipid metabolism [52]
Feeding difficulties [60]	Hepatic dysfunction [61]	Increased sympathetic nerve activity [33]	Increased haemopoiesis [33]
Vocal cord palsy [62–64]	Dysregulated microbiome [65]		Pyrexia [33] Wound healing [51]

The dietitian's role during this intervening period is to monitor nutritional status and where possible to try to correct nutritional deficits [74–76]. Nevertheless, one study showed delayed or no referral to dietetics services in a fifth of CHD patients with faltering growth prior to their surgery [8]. A consensus-based pathway providing a structured approach to the nutritional care of infants with CHD awaiting surgical palliation or repair may help to achieve timely referral to the dietitian [77]. Patients are categorised into three nutritional risk groups according to cardiac diagnosis, weight gain, feed intake and tolerance parameters [77]. High risk patients require weekly, and medium risk fortnightly follow-up by the tertiary team, with low risk patients requiring follow-up by their local hospital (Figure 14.6). Figure 14.7 summarises a proposed nutritional and feeding care plan/intervention based on the nutritional risk of these infants. In some medium and high risk cases, follow-up may be deferred to a local team with cardiac expertise who are in regular contact with the tertiary centre. An initial study considering the implementation of the consensus-based pre-surgical nutrition pathway (Figure 14.7) demonstrated that growth of infants with CHD was significantly improved at 12 months of age, as well as a 10-day reduction in paediatric intensive care unit length of stay [78].

If sufficient energy is provided, adequate growth can be achieved [79–81] even in severe CHD [76]. Studies measuring TEE in infants with CHD indicate that energy intakes of 30 kcal (125 kJ)/kg/day above the EAR should compensate for elevated energy expenditure in most cases [16, 18, 38, 41]. A reasonable starting point for an infant with faltering growth would be 120–130 kcal (500–545 kJ)/kg/day. However, in the most severe cases, some patient's energy intakes may need to be 150+ kcal (630+ kJ)/kg/day to achieve consistent weight gain [37, 79]. Plotting weight on growth charts is essential in monitoring the effectiveness of nutritional interventions.

Table 14.6 Measures of malnutrition in CHD associated with poorer surgical outcome.

Measure of malnutrition	Effect on outcome
Weight for age <−2 SD	Increased infection risk [54, 66] Increased time on ventilator [54, 67] Increased PICU length of stay [54] Longer hospital stay [68] Increased risk of cardiac arrest [54] Increased 30-day mortality [54, 69] Increased mortality at 1 year of age [67]
Height for age <−2 SD	Increased infection risk [54] Increased time on ventilator [54] Increased PICU length of stay [54, 70] Increased risk of cardiac arrest [54] Increased 30-day mortality [54]
Lower triceps skinfold scores	Increased PICU length of stay [71] Longer duration of ionotropic support [71] Increased time on ventilator [71] Elevated levels of serum B-type natriuretic peptide (greater myocardial stress) [71]
Low bioimpedance spectroscopy score	Increased PICU length of stay [72]

PICU, paediatric intensive care unit.

Choice of feed

Breastfeeding, or expressed breastmilk (EBM), is the initial feed of choice for infants with CHD. The mechanics of breastfeeding may cause less cardiorespiratory stress than bottle feeding, resulting in lower oxygen desaturation episodes [82], and has even been attempted following heart transplant [51]. If breastmilk is not available, a suitable infant formula should be provided. However, early fortification or supplementation with a higher energy infant formula in the first few weeks of life may be needed to achieve satisfactory weight gain and prevent growth faltering. These high energy nutrient-dense formulas provide a favourable protein–energy ratio of around 10%. A summary of these feeds and their macronutrient breakdown is shown in Table 1.18.

Some units supplement EBM with up to 6% w/v infant formula, giving an energy content close to 100 kcal (420 kJ)/100 mL while keeping the osmotic load at around 400 mOsmol/kg H_2O (Dr Graeme O'Connor, personal communication). However, even with this level of supplementation, the protein–energy ratio remains at around 8%, and slower growth may have to be an accepted consequence of

Table 14.7 Cardiac defects requiring staged operations for repair.

Cardiac defect	First-stage operation	Second/final stage operation	Third and final stage operation
Atrioventricular septal defect (AVSD)	Pulmonary artery (PA) band	PA band removal and AVSD repair	N/A
Double inlet right ventricle	Repair of coarctation of the aorta and arch reconstruction, PA band, atrial septostomy	PA band removal Damus–Kaye anastomosis of PA with PA plasty	N/A
Double outlet right ventricle	Modified Blalock–Taussig shunt	AVSD and pulmonary valve repair	N/A
Hypoplastic left heart	Norwood stage 1	Norwood stage 2 (Glenn shunt)	Norwood stage 3 (total cavo-pulmonary connection)
Ventricular septal defect (VSD)	Pulmonary artery band	PA band removal and VSD closure	N/A

N/A, not applicable.

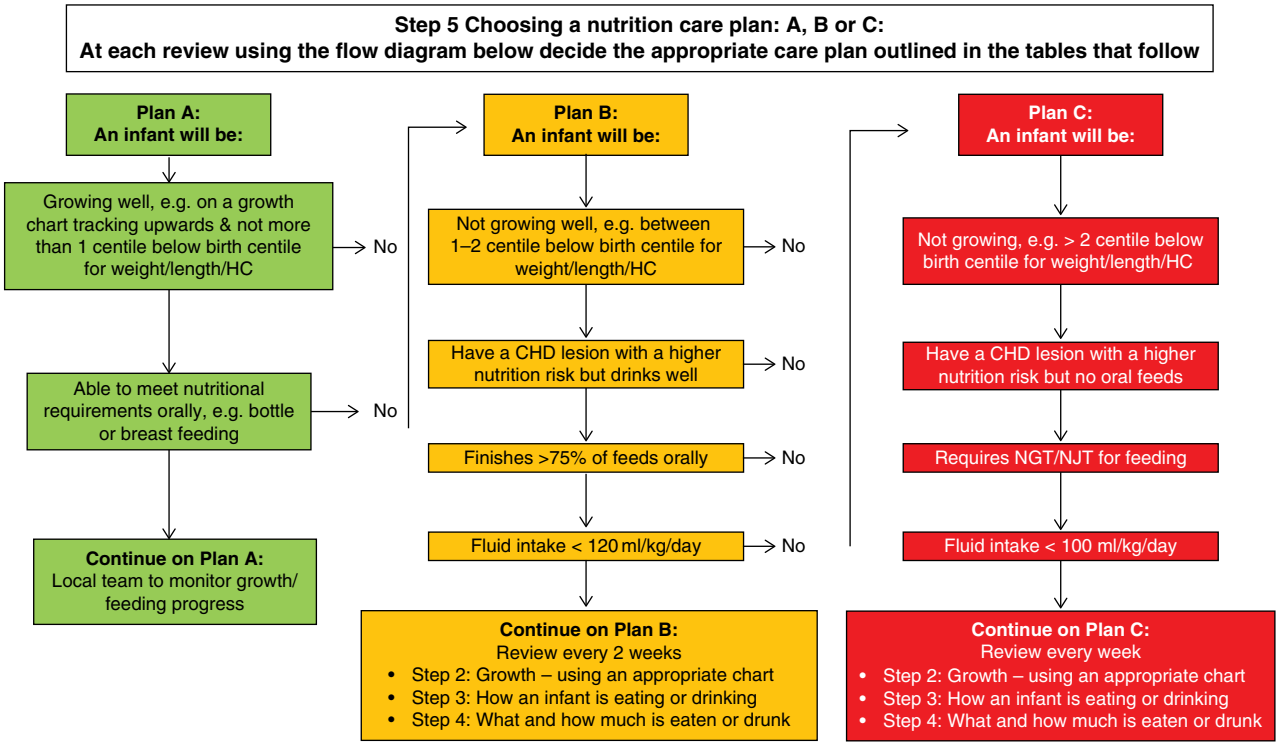


Figure 14.6 Choice of nutritional care plan based on nutritional risk. Source: From Marino *et al*. [77].

this approach. A combination of breastmilk and energy-dense infant formula, adjusting proportions to ensure feed tolerance, is another way of meeting the required energy and protein intakes. If weight gain is unsatisfactory on a 1 kcal (4.2 kJ)/mL feed and feed volumes cannot be increased further, energy density may be increased by adding a fat and carbohydrate supplement or infant formula powder in 1% w/v daily increments up to a maximum of 4%. At this level of fortification, a protein–energy ratio between 9% and 10% is maintained with an energy density of about 1.2 kcal (5 kJ)/mL. As these infants are often at risk of GOR [49, 57], a fine balance must be made between giving a feed of sufficient energy density to achieve adequate growth while limiting vomiting and malabsorption. A hydrolysed protein formula, such as Infatrini Peptisorb, may be useful where there is a degree of malabsorption (Table 8.15). If weight gain continues to be poor, a detailed nutrition review is required to ensure infants are consuming adequate macro- and micronutrients. A nasogastric (NG) tube and micronutrient supplementation may be required to support adequate intake and growth.

Tube feeding

Children with complex congenital heart lesions have been shown to achieve greater energy intakes and weight gain when fed continuously via a feeding tube compared with oral feeding using the same feed [83]. It has been suggested that continuous feeding of high energy formulas may be the only way in which target intakes more than 140 kcal (585 kJ)/kg/day can be met [84]. Improved weight SDS has been demonstrated in patients with percutaneous endoscopic gastrostomies (PEG) [85] and should be considered in patients requiring long-term tube feeding; gastrostomy feeding may be less of an impediment to the development of oral feeding skills than NG feeding. Laparoscopic gastro-jejunal feeding tubes have been successfully placed in infants with severe cardiac anomalies and GOR disease weighing as little as 2.7 kg and may circumvent protracted vomiting [86].

However, one study has shown that children with single ventricle anatomy who have a gastrostomy with or without laparoscopic fundoplication have a mortality risk 2.3 times that of those fed orally or via NG tube [87]. The authors postulated that having a gastrostomy with or without fundoplication might be a marker for more severe disease with evidence of higher risk of complications (GOR, aspiration, faltering growth), but nevertheless found the increased mortality disconcerting.

The timing of weaning off tube feeds to allow for the development of independent feeding skills should be addressed for each individual child. Shine *et al*. have reviewed mainly NG tube-fed patients and identified longer duration of tube feeding, older age and classification of being orally averse as factors increasing transition time to full oral feeding [88]. Dietetic interventions aiding transition included switching from nutrient-dense to standard infant formula, increasing time between feeds and reducing feed volumes while ensuring adequate hydration [88].

Common issues identified by parents such as growth before surgery and how to feed your baby have been described in the literature including information on the

Care Plan	Nutritional and feeding care plan
A	• Normal energy and protein requirements* 90–100 kcal/kg, protein 1.5/kg (e.g. 2 g protein per 150 ml) • Normal fluid allowance, e.g. 150 ml/kg or above • Breastfeeding or standard infant formula on demand • Complementary food from 17 to 26 weeks if ready – 3 small meals/day. Starches should form the basis of all meals, including veg/fruit. Offer protein containing meals (chicken/fish/meat/eggs/pulses) at lunch/supper. • Vitamins supplement to provide up to 10 µg vitamin D • Review by local team – refer to specialist centre with any concerns
B	• Approximately 10% extra energy* 100–110 kcal/kg (protein contributing 9%–12% energy) • Approximately 30%–50% extra protein* (around 2.5 g/kg protein) • Breastmilk or standard infant formula in addition to 30%–80% of nutrition requirements from nutrient-dense infant formula per day • Complementary food from 17 to 26 weeks of age if ready – 3 small meals/day. Starches should form the basis of all meals, including veg/fruit. Offer protein containing meals (chicken/fish/meat/eggs/pulses) at lunch/supper. Around 6 months of age add ½–1 teaspoon of a nut butter or finely ground nuts to both main meals • Vitamin supplement daily to provide up to 10 µg vitamin D • If there are any feeding issues refer to SLT • Paediatric dietetic review growth in 2 weeks – if poor weight gain review earlier and move to plan C
C	• May be fluid restricted • Approximately 10%–20% extra energy* 120–150 kcal/kg (protein contributing 10%–15% energy) • Approximately 50%–100% extra protein (up to 4 g/kg protein – check renal function) • Breastmilk or standard infant formula in addition to a minimum of 50% and up to 100% of nutrition requirements as energy/nutrient-dense infant formula or as overnight or nasogastric feeds • Complementary food from 17–26 weeks of age ready – 3 small meals/day. Starches should form the basis of all meals, including veg/ fruit. Offer protein containing meals (chicken/fish/meat/eggs/pulses) at lunch/supper. Around 6 months of age add 1–2 teaspoon of a nut butter or finely ground nuts to all meals • Vitamin supplement daily to provide up to 10 µg vitamin D • If there are any feeding issues refer to SLT • Paediatric dietetic review of growth in 1 week

STEP 6: Exit criteria for dietetic and SLT support

Dietetics	• Post-operatively it may take 12 weeks or more for sufficient catch-up growth to occur • Nutrition rehabilitation will have been achieved when there is catch-up growth to 1 centile below birth weight
SLT	• Eating and drinking skills are following appropriate stages for infant's presentation • Child is able to feed safely and independently and is growing appropriately • Feeding is an enjoyable experience for child and caregiver • All intervention advice and programmes are in place. Caregivers are skilled in carrying out recommended advice at which point infant should be discharged with support and re-referral options in place

*Based on actual weight rather than expected weight

Figure 14.7 Nutrition and feeding care plan based on nutritional risk in infants with congenital heart disease. Source: From Marino *et al.* [77]. Licensed under CC BY 4.0.

introduction of age-appropriate complementary feeding advice. Parents often feel the introduction of weaning foods is forgotten by health care professionals, in addition to a lack of information on enriching them to make foods more nutrient and energy dense. Parents report recommendations such as cream, oil, and butter often made their infants sick and that the use of nut butters was an acceptable alternative. Parental feeding information has been developed as well as a recipe book, which can be adapted locally [89]

- Feeding advice for infants with congenital heart disease
- Recipe book – for babies who need to make the most of every mouthful

Learning points: improving outcomes in CHD

- *Cardiac lesions requiring a staged repair carry the highest risk of faltering growth*
- *High energy infant formula +/– breastmilk or fortified breastmilk may be required to achieve adequate growth*
- *Care plans based on nutritional risk may help to identify a targeted approach to delivering optimal nutritional support*
- *Nasogastric or gastrostomy feeding should be considered in patients who fail to meet growth targets*

The patient in the paediatric intensive care unit

Surgical procedures for children with CHD vary in their complexity, morbidity and mortality risk. A variety of scoring systems are used to classify surgical risk, one of which is the Risk Adjusted Cardiac Heart Score (RACHS), where surgery for simple lesions such as a patent ductus arteriosus closure is category 1 and the Norwood procedure is category 6 [90]. Some surgical procedures require the use of CPB, involving aortic cross-clamp and circulatory arrest. Children who undergo bypass usually develop capillary leak, which is considered to occur because of the release of inflammatory mediators acting to disrupt intercellular junctions of capillary endothelial cells. As a result C-reactive protein is usually elevated post-cardiac bypass surgery [91].

Post-operative energy expenditure

As during the acute phase of critical illness, only resting energy expenditure should be calculated following cardiac surgery [39, 92] (Table 6.7). Indirect calorimetry has shown energy expenditure in infants and young children in the paediatric intensive care unit (PICU) to be between 60 and 70 kcal (250–290 kJ)/kg/day [45, 93]. There is little difference between metabolic rate of acyanotic and cyanotic patients on PICU, 62 kcal (259 kJ) and 59 kcal (247 kJ)/kg/day [45, 93]. Infants with HLHS in the immediate 3 days following their first complex Norwood stage 1 operation have been shown to have even lower energy expenditure, 39–43 kcal (163–180 kJ)/kg/day [44]. Having CPB does, however, appear to elevate energy expenditure to around 75 kcal (315 kJ)/kg/day [37], although further research is required to confirm this as the phenomenon could be temporary.

Although many predictive energy expenditure equations have been found to be inadequate in estimating resting energy expenditure [45, 94, 95], the use of Schofield (weight) equation has been recommended by all of the major European and American societies in estimating resting energy expenditure during the acute phase [39], stable and rehabilitative phases of critical illness [92]. Recommendations for the first few days post-operatively are to meet two thirds of resting energy expenditure as calculated using Schofield equation [39] (see Chapter 6). Increased periods of sleep, and sedation, use of paralysing agents and mechanical ventilation, suppression of thyroid hormones and surgical stress curtailing growth might all contribute towards conservation of energy expenditure [19]. The general reductions in observed energy expenditure go some way ameliorating the energy deficits inevitably imposed by the fluid restrictions that limit post-operative feed volumes. If the stay on PICU becomes extended, the experience of one of the authors is that energy intakes as low as 70 kcal (230 kJ)/kg/day may be necessary to prevent excessive weight gain in some stable long-term ventilated infants.

Fluid restrictions and feed delivery

Early enteral nutrition via the NG route is recommended in cardiac infants following surgery and can be safely started within 6–24 hours, once haemodynamic stability is achieved. The use of umbilical arterial or venous catheters, prostaglandins or extracorporeal life support (ECLS) does not preclude enteral feeding [96].

In the first 12–24 hours following cardiac surgery, patients are usually fluid restricted to 2 mL/kg/hour (48 mL/kg/day) to manage the post-cardiopulmonary bypass-associated fluid overload. This is usually liberalised to 3 and then 4 mL/kg/hour (72–96 mL/kg/day) on consecutive post-operative days depending upon circulatory status and cumulative fluid balance [97]. Drug infusions are included in the daily fluid allowance; it is possible for some drug infusions to be made up to double or quadruple the usual strength, enabling more of the fluid allowance to be provided as feed. Fluid flushes for intravascular arterial and venous pressure monitoring lines and intravenous drugs are also included in the total fluid allowance; the remaining volume is for feeds.

A number of paediatric/cardiac intensive care units express fluid allowances as a percentage. This is based on 100% equating to 4 mL/kg/hour for the first 10 kg body weight, 2 mL/kg/hour for the second 10 kg and 1 mL/kg/hour for every kilogram thereafter. Once the 100% fluid allowance has been calculated, this is multiplied by a proportion of the allowance depending on whether the patient has had CPB or not. Table 14.8 illustrates changes in fluid allowances following cardiac surgery.

Worked example: Infant weighing 3.5 kg

100% fluid allowance provides 4 mL/kg/hour = 4 × 3.5 = 14 mL/hour or 336 mL/day. A 50% fluid allowance gives 14 mL/hour × 0.5 = 7 mL/hour total fluid allowance from which hourly volumes of intravenous drugs and flushes are subtracted to leave the volume for feeds.

Enteral feeds are increased gradually every 6–12 hours depending on fluid allowance and clinical observation [98]. Most are fed via NG tube for the first few days following cardiac surgery, either as continuous or bolus feeds; there is no evidence to support one method over the other [39].

Breastmilk is again the feed of choice for all infants. However, less than a third of children undergoing cardiac surgery achieve their estimated energy requirement while on PICU, contributing to further declines in weight during

Table 14.8 Fluid allowance during admission to the paediatric intensive care unit after cardiac surgery.

Day post-surgery	Cardiopulmonary bypass	Non-cardiopulmonary bypass
1	50%	80%
2	60%	90%–100%
3	70%	120%
4	80%	Free fluids
5	90%	
6	100%	
7	120%–135%	
8	150%	

inpatient stay [70]. The use of energy-dense infant feeds early in the post-operative PICU stay may reduce this proportion [99, 100] although a small number of patients may show signs of feed intolerance [100]. These feeds are also associated with increased production of nitric oxide and do not require a graded approach to introduction [99, 101].

Learning points: the patient in PICU

- *Indirect calorimetry, if available, and the Schofield equation are the current options for calculating energy requirements*
- *Patients on PICU following cardiac surgery usually have lower energy requirements than prior to surgery*
- *Fluid restrictions often limit adequate delivery of nutrition in the post-operative period*

Most infants and children are discharged from PICU on day 1 or 2 post-cardiac surgery. If the patient's clinical condition results in ongoing fluid restrictions, their nutritional intake will need close monitoring. Even with active dietetic involvement on PICU energy and protein intakes at the end of the first post-surgical week may only be 70% of requirements, with young infants being the most vulnerable [70]. The dietitian's role is to ameliorate the effect of any necessary ongoing fluid restrictions affecting feed delivery by seeking to liberalise fluid allowances when clinically appropriate [102, 103].

Nutrition on transfer from PICU to the cardiac ward

Fluid allowances often increase on discharge from PICU to the ward, providing opportunity to increase feed volumes. The type of residual lesion affecting cardiopulmonary function determines the extent to which energy expenditure is elevated and the requirements for catch-up growth. Where catch-up growth is required, the FAO/WHO recommendations for energy and protein intake should be followed, in addition to the provision of enough micronutrients to replete pre- and post-operative losses.

If not done so already, attempts should be made to establish oral feeds. However, some infants may initially fail to complete feeds by mouth due to fatigue brought on by the effort of sucking, anorexia or early satiety. Others may require short-term tube feeding to ensure requirements are met. Poorer oral feeding capability is associated with long post-operative ventilation, poor weight at surgery and vocal cord injury [104]. A screening tool may help with early identification of those at risk of dysphagia or swallowing difficulties [105], enabling early involvement of a speech and language therapist to address oral feeding issues.

If an infant is regularly failing to complete feeds, one of the following strategies should be employed:

- offer smaller, more frequent oral feeds
- incomplete feeds to be topped up via a NG tube
- small frequent NG tube bolus feeds
- continuous feeds via an enteral feeding pump with some time off to allow gastric pH to return to normal. This must be supervised if via a NG tube

Changes in energy expenditure and nutritional status following repair of CHD

TEE, which more accurately reflects energy requirements in non-ventilated patients, is marginally elevated, but not significantly so at 3 and 12 months' post-surgery [106]. A further study measuring resting energy expenditure showed no difference at 3 months of age post-first-stage palliation for univentricular physiology or correction of biventricular defect compared with healthy infants [107]. These infants had significantly poorer growth and lower percentage body fat compared with healthy infants, implying that lower dietary intakes were the contributory factor, but difficulties encountered in measuring energy intakes could not confirm this.

Weight loss may occur in the immediate period between surgical repair and discharge home, with this attributed to poor post-operative intake [108]. Nevertheless, most infants and children demonstrate catch-up growth following repair of their primary cardiac defect, with improvements in weight for age, weight for height and height for age SDS scores, most of this occurring in the first year following corrective surgery [109–112]. However some infants may continue to exhibit growth failure even after haemodynamic correction [43], and catch-up growth may be limited if malnutrition prior to surgery is marked and prolonged [109, 111].

Learning points: patient transfer from PICU to ward and discharge home

- *Immediate post-operative fluid restrictions are usually liberalised on transfer to the ward*
- *Various strategies may need to be employed to help transition to oral feeding*
- *If growth has been impaired pre-operatively, it should continue to be monitored after correction of the cardiac defect until adequate catch-up growth has been achieved*

Other nutritional issues

Gastro-oesophageal reflux and vomiting

If GOR develops, positioning and feed thickeners may be used as a first-line treatment (p. 133). Although H_2 antagonists and proton pump inhibitors may not prevent GOR, the reduction in acid enables the infant to feel more comfortable and more likely to continue oral feeding, and there are no contraindications to their use in CHD. Other causes of vomiting, such as cow's milk protein allergy, should also be considered [113]. However, although feeding tolerance for some may improve on a milk-free formula, growth among infants

with CHD and cow's milk protein allergy is significantly worse compared with non-allergic CHD infants [113]. This may be associated with a decline in phosphate levels, particularly among infants who are also on anti-reflux medication. The impact of medications on absorption and bioavailability of micronutrients and minerals on growth, as well as the choice of infant formula, needs to be considered in these patients [114].

Electrolyte supplementation of infant feeds

Where infants with CHD fail to gain weight despite energy intakes above 140 kcal (585 kJ)/kg, it is important to consider whether nutrients such as sodium, potassium, zinc, magnesium, phosphorus or iron may be insufficient in the diet to support adequate growth [115]. Loop diuretics are commonly used on PICU following surgery to prevent fluid overload, but by nature increase sodium and potassium excretion. Chronic electrolyte depletion may become a growth limiting factor. Table 14.9 lists commonly used drugs affecting electrolytes. Use of hypertonic solutions after bypass surgery has been shown to improve cardiac function and reduce the need for inotropic support [116]. Patients with cyanotic lesions have higher fractional excretion of sodium compared with healthy individuals and those with acyanotic lesions and may be at higher risk of depletion [117]. In children who have undergone the total cavo-pulmonary connection (TCPC) operation, diuretic use correlates with low levels of serum sodium, resulting in increased risk of rehospitalisation [118]. The gold standard method to establish sodium intake of individuals is to collect 24 hour urine. If growth is poor, this may be due to low sodium intake and/or low total body sodium [119]. It is however not practical to collect 24 hour urine in infants as they are usually not catheterised, and as such a spot urine sodium should be done to establish urinary sodium levels [120]. There is no consensus regarding defined cut-offs for sodium depletion, but levels <30 mmol/L have been associated with poor growth [120].

An infant feeding 150 mL/kg of a standard infant formula receives 1.0–1.3 mmol Na/kg, depending on the formula, compared with the reference nutrient intake (RNI) for sodium for an infant aged 0–3 months of 1.5 mmol/kg. Infants feeding 150 mL/kg of one of the commercially available energy-dense formulas will receive 1.4–1.65 mmol Na/kg. Sodium supplementation of 2–3 mmol/kg may be appropriate in some depleted individuals.

Potassium supplementation associated with diuretic use is common on PICU. Supplementation providing up to 3–4 mmol/kg may be required to keep serum levels within the normal range. Enteral and intravenous supplementation has been shown to be equally effective in increasing serum levels [121, 122] although a small number of patients may vomit supplements given enterally [122]. If additional potassium is needed on an ongoing basis and the serum level is stable, it may be added into the infant's feed. This has the benefit of spreading out the supplementation over 24 hours. Some units may prefer to split the dose and add it to each individual feed.

Iron deficiency

In developing countries where diagnosis of CHD may be delayed, parents may commence early weaning with solid foods either in recognition that breast or formula feeding is insufficient to promote adequate growth or that the infant tires easily on sucking. If weaning foods are nutritionally inadequate, there is an increased risk of iron deficiency anaemia, particularly in those with acyanotic lesions where wasting predominates [11]. Children with cyanotic lesions need to have optimal oxygen delivery to the tissues. Ensuring an adequate haemoglobin concentration is vital to help with tissue saturation [123], and maintaining adequate iron status is important.

Table 14.9 Medication and impact on electrolyte status.

Role	Drug	Electrolyte affected	Effect on serum level
Diuretic	Spironolactone	Sodium	Reduces
Loop diuretic	Furosemide	Potassium	Reduces ++
Thiazide diuretic	Metolazone	Potassium	Reduces ++
	Bendroflumethiazide	Potassium	Reduces +
Antihypertensive	Captopril*	Potassium	Increases
Antihypertensive	Propranolol*	Potassium	Increases
Arterial dilatation, increases blood flow to heart	Milrinone	Potassium	Occasionally reduces
Increases force of cardiac contraction	Digoxin	Potassium	May be toxic if serum potassium is elevated
Anti-reflux medication	Proton pump inhibitor	Phosphate	Reduces +

*Angiotensin converting enzyme (ACE) inhibitor.

Zinc deficiency

Increased pulmonary blood flow resulting in pulmonary hypertension puts children with CHD at increased risk of bronchopneumonia. Low serum zinc levels have been recorded in children with CHD who develop pneumonia [124]. Slicker *et al*. recommend initial intravenous zinc supplementation between 250 and 400 μg/kg/day for patients with HLHS due to chest drain losses [96]. Oral zinc supplementation can be provided in doses of 2 mg/kg/day for up to 6 months (although more commonly 1–2 months) [115, 125].

Thiamin deficiency

Thiamin deficiency has been documented pre- and post-operatively in a small group of infants with VSD and tetralogy of Fallot before and after surgery, with up to a quarter affected despite adequate dietary intakes [126]. Further work may be needed to identify a cause and the level of supplementation needed.

Vitamin and mineral supplementation

Supplementation with a vitamin D containing multivitamin from birth should be considered in all infants with CHD. Low vitamin D levels have been reported in infants with CHD and are associated with greater post-operative cardiovascular dysfunction, increased post-operative fluid requirements and longer duration of mechanical ventilation [127, 128]. Additional micronutrients and trace elements may be worth considering, particularly if growth is suboptimal [115, 129].

Anticoagulation and the vitamin K content of feeds

Children undergoing Blalock–Taussig (BT) and Glenn shunts, TCPC (or Fontan) operation, pulmonary artery reconstruction and some operations requiring tissue homograft or mechanical valves are given either aspirin or warfarin post-operatively for anticoagulation. Vitamin K has an antagonistic effect on some of the anticoagulation drugs and may be given in some instances to counter excessive anticoagulation. Vitamin K doses of 150–250 μg/day have been found to affect anticoagulation in adults [130, 131].

If the child has a history of vomiting around feed or mealtimes, giving the warfarin dose away from these times may help to achieve more stable anticoagulation. Severe vomiting has been associated with excessively elevated international normalised ratio (INR) in adults [132]. The level of vitamin K in some leafy vegetables may have an antagonistic effect on anticoagulation, but the bioavailability of various forms of vitamin K is uncertain [133]. Curly kale, broccoli, spinach, Brussels sprouts and endive have a high vitamin K content. If these foods appear to exert an effect, then temporary or permanent withdrawal may be needed to achieve a satisfactory INR. However, unnecessary manipulation of the normal weaning diet is inappropriate.

Learning points: other nutritional issues

- *Treatment of GOR is essential in ensuring adequate nutrition in CHD, but an awareness of treatment options impacting on long-term mineral status needs to be considered*
- *Dietitians should be aware of how various drugs used in CHD may affect electrolyte status*
- *Sodium, potassium, iron and zinc status may all be affected in CHD*
- *Vomiting and a few foods high in vitamin K may affect clotting in anticoagulated patients, but the diet should not be altered unnecessarily*

Complications of congenital heart disease affecting nutritional status

Chylothorax

Normal transport of chyle

After digestion in the intestinal lumen, dietary fats are absorbed into the mucosal cells as glycerol and fatty acids. Long chain fatty acids of 12 or more carbon atoms are re-esterified to triglycerides and pass into the thoracic lymph duct as chyle. Sixty to seventy per cent of absorbed dietary fat passes through the lymphatic system at a concentration of between 5 and 30 g/L. Flow increases markedly after ingestion of a high fat meal with lesser, but definite increases after mixed meals of protein, carbohydrate and fat [134]. The principal function of the thoracic lymph duct is to transport chyle to where it enters the venous system near the junction of the left internal jugular and subclavian veins [135], and these vessels then drain into the superior vena cava. Figure 14.8 shows the anatomy of the thoracic lymph duct.

Chylothorax is caused by a fistula between the thoracic lymph duct and the pleural cavity resulting in the accumulation of chyle in the pleural cavity itself. Chyle contains lymphocytes, immunoglobulin, enzymes, triglycerides, cholesterol and fat-soluble vitamins, the loss of which, if unchecked, would invariably lead to serious metabolic deficit.

Fistulas

There are three types of fistula:

- *Traumatic fistula*: the thoracic duct drains into the vessels close to where some cardiac surgical procedures are carried out. As the thoracic duct is difficult to see, there is an increased risk of disruption and damage to the duct during surgery, resulting in a traumatic fistula.
- *Obstructive fistula*: results from increased pressure in the thoracic lymph duct itself, which causes its walls to become leaky. This may be secondary to increased venous pressure due to sluggish blood flow or clots in the veins distal to where the thoracic duct empties. Patients with right-sided obstructive cardiac lesions

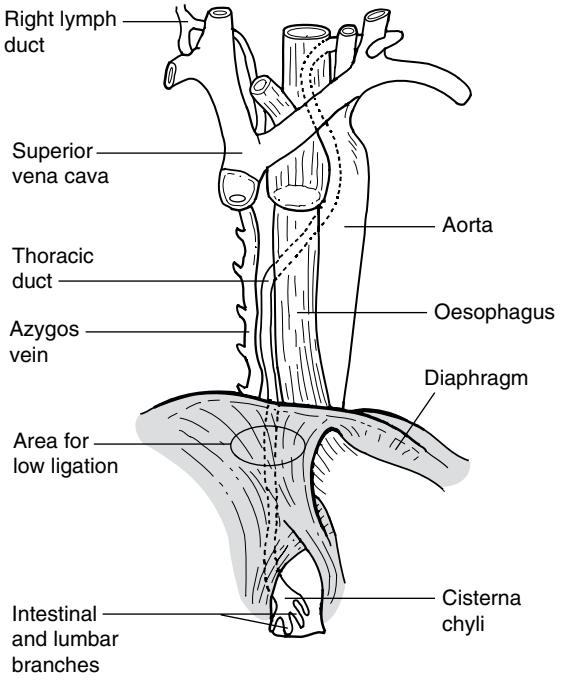


Figure 14.8 Anatomy of the thoracic duct. Source: Merrigan *et al*. [136]. Reproduced with permission from John Wiley & Sons.

require venous to pulmonary artery shunt operations to achieve longer-term oxygenation. Examples of these shunts are the Glenn or the TCPC operation (see Figure 14.12) where the venous return is plumbed directly into the pulmonary vasculature. Under these circumstances the blood flow in the lungs is increased, resulting in 'back pressure' into the pulmonary arteries and the newly connected systemic veins. As a result, the lymph does not drain well into the veins, and the lymphatic vessels themselves become engorged and leaky, with chyle passing into the thoracic cavity. However, it appears that the increased risk of developing chylothorax only occurs with the larger TCPC shunt [137]. An exacerbating factor may be the development of either a chest infection or a post-operative pleural effusion, and chylothorax may occur some days after operation. A list of cardiac defects that may require these operations is shown in Table 14.10.

- *Congenital fistula*: some children may develop congenital chylothorax [138], children with Noonan syndrome being at higher risk.

Diagnosis

As chyle contains fat from the intestinal lacteal system, it has a characteristically milky appearance that often raises suspicion when it appears in post-surgical pleural chest drains. A chest drain sample with a triglyceride content of >1.1 mmol/L, a total cell count >1000/μL with a predominance of lymphocytes, or the presence of chylomicrons has been used to confirm diagnosis [137, 139] although others use a combination of these [140]. As the concentration of triglycerides in chyle is higher than that of plasma, this has also been used to differentiate chylous pleural effusions from those of other origin [136].

Table 14.10 Conditions requiring Glenn and/or total cavo-pulmonary connection (TCPC) shunt operations.

Heart defect	Operation
Ebstein's anomaly	TCPC*
Pulmonary atresia with/without intact ventricular septum	Glenn shunt and TCPC
Tricuspid atresia	TCPC
Single ventricle physiology	Glenn shunt and TCPC
Hypoplastic left heart	Norwood stage 2 and 3†

* TCPC is one of a number of surgical options in Ebstein's anomaly.
† The second stage of the Norwood procedure may be similar to a Glenn shunt or TCPC, and the third stage may be a TCPC operation.

Incidence and duration

The incidence of chylothorax is between 1.34% and 9.2% following cardiac surgery for CHD [137, 139, 141]. Low body weight, longer CPB time and secondary chest closures are all associated with increased risk of developing chylothorax [141]. A higher incidence of chylothorax has been noted in patients undergoing repair of tetralogy of Fallot [139], the TCPC procedure and heart transplantation [137].

A duration of 9–15 days is expected before chest drain output ceases [137, 141], although up to a quarter of cases have continued outputs beyond 30 days [137]. The amount of chylous drainage varies between 2 and 40 mL/kg in most cases [139, 141, 142] with high outputs >100 mL/kg/day indicating that dietary treatment is likely to be unsuccessful [141].

Treatment options

There is a lack of consensus regarding the optimal management of chylothorax, with no evidence arising from a randomised controlled trial [135]. A recent international survey showed there was considerable variation in practice with regards to the management of chylothorax [143]. As a result, variation of practice is considerable, which may result in many infants and children having dietary fat restriction for longer than is necessary, affecting weight gain and growth [144].

Historically chylothorax has been treated conservatively using a minimal long chain triglyceride (LCT) diet [137, 139, 141, 145] or total parenteral nutrition (TPN) [139]. However, some suspected cases of chylothorax may be self-limiting with a median resolution time of 1 week following presentation [140]. As a result, it has been proposed that any intervention be delayed following diagnosis, with an expectation that the chyle drainage will resolve within 7 days [73] and the role of limiting dietary LCT has been questioned. Depending on the cardiac unit, practice is currently to either commence a minimal LCT feed/diet or wait for symptom resolution while continuing to provide a normal feed or diet.

A survey of US centres showed the majority using TPN as the main treatment mode [59].

If after 7 days there is no resolution, a period of parenteral nutrition (PN) for 10–14 days or a 2- to 4-week period of minimal LCT diet may be required to reduce the lymph flow and so allow the fistula to heal [135]. Dietary fat is mainly composed of LCT. Normally medium chain triglycerides (MCT), with 6–10 carbon atoms in the fatty acid chain, do not constitute more than a minor proportion of dietary fats. However, as they are absorbed directly into the portal vein as 'free fatty acids' bound to albumin, they constitute a useful additional source of energy in a diet that may otherwise be low in energy. As diets high in MCT are used to promote weight loss in adults, growth monitoring during the treatment period is important [146].

There have been individual case reports of the hormone, somatostatin or an analogue, octreotide (both of which have antisecretory and antidiarrhoeal properties) being used in isolation or as an adjunct to a minimal LCT diet or PN to treat refractory chylothorax. A dose of 1–4 μg/kg/hour is recommended [147, 148], although benefit has been noted on smaller doses [149]. Despite some promising case reports [147–150], results are inconsistent [139, 140]. Surgical ligation of the thoracic lymph duct is usually reserved for patients who do not respond to 3–4 weeks of conservative management [139, 151].

Prognosis

The conservative dietary approach has a success rate of between 70% and 80% [137, 144, 145]. A useful algorithm for the management of chylothorax has been produced by Cormack *et al*. [145]. Development of chylothorax may almost triple hospital length of stay [137].

Dietary treatment

The publication describing treatment of chylothorax with a minimal LCT diet is now rather old (*Diets for Sick Children*, 4th edition, 1987, Dorothy Francis) and recommends giving no more than 1 g LCT per year of life up to a maximum of 4–5 g LCT/day. The efficacy for this practice has not since been studied in a randomised controlled trial, and it is often breached [144], particularly in older infants and younger children where 1–2 g LCT/day is very difficult to manage. Achieving this without compromising nutritional intake is challenging and supplementary PN should be considered [97]. The use of feeds with a high MCT content is also associated with significant weight loss compared with the use of a fat-free enteral feed with peripheral lipid or TPN, both of which have been shown to significantly reduce chyle drain output in cases refractory to conventional low LCT feeds [144]. If the chylous leak is responsive to a low LCT diet, pleural losses should be reduced to <10 mL/kg/day by day 7 and cease by the end of the second week of treatment. However, if the drain output remains unchanged or output increases after the first week, the low LCT diet should be discontinued and PN should be commenced and is usually required for 14 days. Once the pleural drainage has decreased to <5 mL/kg/day, PN can be replaced by the infant's usual milk if tolerated, or a continuation of a low LCT diet for a further 2–4 weeks [135]. Surgery should be considered for patients who fail these initial steps or in whom complications such as electrolyte and fluid imbalance, malnutrition or immunodeficiency persist [152].

Monogen

Monogen is a whey protein-based infant formula with low LCT content that has been used as the treatment of choice in infants with chylothorax. The fat sources are fractionated coconut and walnut oil. Monogen contains 0.35 g of LCT/100 mL formula at standard dilution (17.5%) (Table 14.11).

If the infant has previously been tolerating normal or concentrated feeds prior to the development of chylothorax, it should be possible to introduce Monogen at full strength despite its relatively high carbohydrate content (12%) and high content of MCT. If the baby has had limited enteral nutrition, then, as a precaution, Monogen may be introduced at half strength, i.e. 9% dilution in the first 12–24 hours. Standard dilution provides 74 kcal (310 kJ)/100 mL. In cases of severe fluid restriction, it has previously been advocated to gradually increase the concentration of the feed to meet requirements. However, the current formulation has a higher LCT content than previously, so it might be prudent to increase energy density using either glucose polymer (in 1% daily increments) or MCT emulsion (in 1%–2% daily increments) up to an energy density of 90 kcal (375 kJ)/100 mL. This allows an increase in energy density while maintaining a protein–energy ratio close to 10%. However, this is often poorly tolerated, particularly in younger infants, and a period of PN may be required. Monogen is a complete infant formula so supplementation with essential fatty acids (EFA) should not be needed. However, falls in EFA status have been noted following commencement on Monogen feeds (Luise Marino, personal communication).

To achieve adequate energy intake to facilitate growth, the total LCT intake may be greater than the 1 g/year of life recommendation. If chest drain output is unaffected, then a higher LCT intake should be allowed to continue. If chest drains are not *in situ*, then clinical signs such as increased respiratory effort can be used to monitor tolerance to

Table 14.11 Nutritional content of standard Monogen per 100 mL.

Energy	74 kcal/310 kJ
Protein	2.2 g
Carbohydrate	12 g
Fat	1.9 g
MCT	1.52 g
LCT	0.35 g
Energy from C18:2 (%)	1.1
Energy from C18:3 (%)	0.17

MCT, medium chain triglycerides; LCT, long chain triglycerides.

increasing amounts of LCT. A chest X-ray may confirm reaccumulation of chyle in the pleural cavity. The 'clock' for the duration of the diet should be started when it is initiated and not when the pleural drains are removed.

Essential fatty acids

EFA in phospholipids are important for maintaining the function and integrity of cellular and subcellular membranes. They also participate in the regulation of cholesterol metabolism, being involved in its transport, breakdown and ultimate excretion. Long chain polyunsaturated fatty acids (LCP) are important in the growth and development of term infants, and their addition to the diet in appropriate quantities is safe [153]. A deficiency state arising from an inadequate intake of linoleic acid has been demonstrated in children [154]. Although a specific deficiency state arising from inadequate dietary α-linolenic acid has not been demonstrated in healthy humans, it is regarded as a dietary essential [154]. It has been recommended that the neonate requires at least 1% of energy intake from linoleic acid (C18:2) and at least 0.2% of energy from α-linolenic acid (C18:3) [155]. The current formulation of Monogen has slightly over the required percentage energy from linoleic acid while having slightly less α-linolenic acid.

EFA supplementation of feeds

If EFA need to be added to a feed, this may be done using walnut oil; the fatty acid content provides linoleic and α-linolenic acids in an acceptable quantity and ratio. Walnut oil contains 55 g linoleic and 12 g α-linolenic acids per 100 mL (Table 30.4). As the energy content of the feed is increased, it will be necessary to increase the EFA supplementation proportionately.

Minimal LCT weaning diet

The following foods contain minimal LCT and can be introduced as weaning solids:

- puréed vegetables, e.g. potato, carrots, swede, green beans
- puréed fruit, e.g. pears, apples, banana, peaches
- puréed boiled rice mixed with minimal fat milk
- baby rice reconstituted with minimal fat milk
- tins and jars of baby foods containing less than 0.2 g LCT per 100 g may be included in the diet (mainly the fruit-based tins and jars). Other commercial baby foods may contain too much LCT and need to be avoided

Even when solids are introduced into the diet of the infant, a minimal LCT formula will continue to form a major part of the nutritional intake providing energy, protein, vitamins and minerals and is an essential part of the diet up to 1 year of age. A sample day's menu for the toddler on a minimal LCT diet is given in Table 14.12.

Table 14.12 Sample day's menu for a toddler on a minimal LCT diet.

Minimal fat milk (MFM)	
60 g skimmed milk powder	Provides 500 kcal (2090 kJ)
35 mL Liquigen	22 g protein
30 g glucose polymer	0.8 g LCT
8 g Paediatric Seravit + water to 600 mL	
Use throughout the day for drinks and mixed with appropriate foods	
Breakfast	10 g Rice Krispies + 60 mL MFM
	Glass MFM (100 mL)
Mid-morning	Glass MFM (100 mL) + 2 MCT biscuits
Lunch	80 g baked beans + 50 g MCT chips
	50 g very low fat fromage frais
	Glass fruit squash + glucose polymer
Mid afternoon	Glass MFM (100 mL)
	Meringue or Rice Krispie cake
Supper	40 g white fish steak fried in MCT oil
	Fat-free mashed potatoes + 2 teaspoons Liquigen
	40 g carrots
	50 g very low fat ice cream
	Jelly
Bedtime	Glass MFM (100 mL)
Total LCT intake for the day = 2 g	

LCT, long chain triglycerides.

A minimal fat milk may replace the minimal LCT formula from 1 year if nutritional intake is not compromised by doing so. This minimal fat milk can be flavoured with Nesquik powder, fruit Crusha syrups or low fat chocolate flavour topping. It can also be used on breakfast cereals, to make custard or in cereal-based puddings. The quantities of the ingredients may be varied to taste if needed, to provide 70–90 kcal (230–375 kJ)/100 mL. Extra energy can be added to the diet by increasing the concentration of glucose polymer in the milk or by using a 10%–15% solution of glucose polymer to make up fruit squash. Increased energy intake can be achieved by the addition of Liquigen (MCT emulsion) to suitable foods such as mashed potatoes or other root vegetables.

Feeding the older child and adolescent with chylothorax

There are no randomised controlled trials regarding the optimal intake of LCT fat in children with chylothorax as the overly restrictive low LCT diet may negatively impact on nutritional quality, particularly as foods that are higher in LCT are also usually protein rich. Based on results from a worldwide survey, a pragmatic approach may be more suitable, allowing a higher LCT intake of around 20–30 g day; this may ensure better compliance, in addition to providing a more individualised approach (Marino *et al*., personal communication).

MCT can be used in the diet in the form of MCT oil or MCT emulsion. MCT oil allows fried foods to be included, such as fried fish, chips and crisps. Both MCT oil and MCT emulsion can be used in baking, cakes, biscuits and pastry; all these foods are valuable sources of energy and can greatly enhance the palatability of the diet to the patient. MCT should be gradually introduced over a period of 7–10 days to avoid abdominal discomfort. Table 14.13 lists foods containing minimal LCT, which can be used freely in the diet.

The weights and fat contents of foods that can be used to construct a day's meals containing minimal fat for the child or adolescent with chylothorax are given in Table 14.14. A review of some suitable low fat foods indicates that there may be up to a threefold variation in fat content of some meat and fish products depending on the brand. To make the diet more manageable, the family can be taught to calculate minimal LCT exchanges as follows:

$$0.2\,\text{g fat exchange} = \frac{0.2}{\text{grams of fat/100 g of food}} \times 100\,\text{g}$$

$$0.5\,\text{g fat exchange} = \frac{0.5}{\text{grams of fat/100 g of food}} \times 100\,\text{g}$$

Vitamin and mineral supplementation

Since a wide range of foods must either be excluded from the diet or taken in reduced quantities, it is essential to check the vitamin and mineral content of the diet, giving supplements if needed.

Length of treatment period

Results from a worldwide survey suggest there is considerable variation in practice regarding treatment duration with a minimal LCT diet: 21% of centres recommend 1–2 weeks, 25% 4 weeks, and 40% 6 weeks (Marino *et al*., personal communication). Research is urgently required to determine duration of treatment and degree of fat restriction. Cormack *et al*. [145] have suggested a return to normal diet 4 weeks after removal of a pleural drain that has not resulted in recurrence of chylothorax, while others suggest 2–4 weeks' continued treatment following chest drain removal [135]. One further study suggested that patients could be transitioned onto normal infant formula within 1 week with limited risk of relapse following use of a 'long chain fatty acid-free' formula with only 1%–2% MCT content [141]. For infants, the risk of limiting the supply of EFA during a critical point in brain and retinal development should be balanced against achieving faster resolution of chylothorax. Following reintroduction of a normal diet, clinical signs usually confirm whether chylothorax has recurred or not, but a chest X-ray may help clarify.

Table 14.13 Free foods for minimal LCT diet.

All fruits fresh, tinned or frozen (except olives and avocado pear)
All vegetables, fresh, tinned or frozen
Sugar, honey, golden syrup, treacle, jam, marmalade
Jelly and jellied sweets such as Jelly Tots, Jelly Babies, wine gums or fruit pastilles
Boiled sweets, mints (not butter mints)
Fruit sorbets, water ices, ice lollies
Meringue, egg white, Rite-Diet egg replacer
Spices and essences
Salt, pepper, vinegar, herbs, tomato ketchup, most chutney, Marmite, Oxo, Bovril
Fruit juices, fruit squashes, Crusha fruit flavouring syrups, Nesquik fruit flavouring powder, chocolate flavour topping, bottled fruit sauces
Fizzy drinks, lemonade, cola, Lucozade

LCT, long chain triglycerides.

Learning points: chylothorax

- *The incidence of chylothorax in CHD is highest in right-sided obstructive lesions that require pulmonary artery shunt operations*
- *Current opinion regarding length of treatment period with a minimal long chain fat diet varies from 2 to 6 weeks*
- *Chylothorax increases the risk of patients incurring nutritional deficits, and the diet treatment needs to be carefully tailored to ensure overall adequacy*

If an older child with chylothorax requires tube feeding, a 'juice' style oral nutritional supplement, e.g. Ensure Plus Juce, Fortijuce, Fresubin Jucy or PaediaSure Plus Juce, may be used as the feed base as they do not contain any fat. These supplements may require additional electrolytes and EFA from walnut oil to make them nutritionally complete. They may be diluted if necessary, should a 1.25–1.5 kcal (5–6 kJ)/mL feed not be tolerated.

Necrotising enterocolitis

The overall incidence of necrotising enterocolitis (NEC) in infants with congenital heart defects is around 10 times that found in healthy term infants. Development of NEC markedly increases PICU length of stay and may double hospital length of stay in patients with HLHS [62]. A review of cases of NEC in a large cohort of term and preterm infants with CHD (n = 643) demonstrated an incidence of 21 cases (3.3%); 7 had a gestational age <36 weeks; 6 term infants had developed an episode of poor systemic perfusion or shock [156]. Of the eight remaining term infants who developed NEC all had lesions that put them at risk of low blood flow in the systemic circulation. HLHS and truncus arteriosus/aortopulmonary window were identified as defects that increased the risk of the infant developing NEC [156] with up to a quarter of HLHS patients affected in one study [62].

Table 14.14 LCT content of foods suitable for use in minimal LCT diet.

Food	LCT (per 100 g)	Average portion size (g)	LCT per portion (g)
Breakfast cereals			
Branflakes	2.0	35	0.7
Cornflakes	0.9	25	0.2
Frosties	0.6	20	0.1
Sugar Puffs	1.6	25	0.4
Special K	1.0	20	0.2
Coco Pops	2.0	20	0.4
Just Right	2.5	40	1.0
Rice Krispies	1.0	25	0.25
Ricicles	0.7	20	0.1
Weetabix	1.9	37.5 (2 biscuits)	0.7
Puffed Wheat	2.5	15	0.4
Frosted Shreddies	1.4	35	0.5
Weetaflakes	1.6	30	0.5
Bread			
White, large thin slice	1.6	35	0.4
Granary	1.7	35	0.6
Matzos	1.0	20	0.2
Crumpets (toasted)	1.0	45 (1 crumpet)	0.45
Dairy foods			
Reduced fat cottage cheese	1.4	50	0.7
Very low fat fromage frais	0.1	100	0.1
Condensed milk, skimmed sweetened	0.2–1.0	50	0.1–0.5
Very low fat yoghurt (Muller Light)	0.1	200	0.2
Very low fat ice cream	0.4	50	0.2
Fish			
White cod fillet, raw	0.1–0.7	100	0.7
White cod steak, raw	0.6	100	0.6
Grilled white haddock fillet	0.6	100	0.6
Steamed whiting	0.9	100	0.9
Steamed smoked haddock	0.9	100	0.9
Fish finger	7.2	25 (1 fish finger)	1.8
Tuna	0.2–0.6	100	0.2–0.6
Shell fish			
Prawns (peeled)	0.5–1.7	80	0.4–1.4
Crabsticks	0.1	50	Neg
Crab (canned)	0.9	50	0.4
Crab (white meat only)	0.1	100	0.1
Shrimps (canned)	1.2	50	0.6
Cockles (boiled)	0.3–3	50	0.1–1.5
Mussels	2–3	50	1.0–1.5
Meat, poultry and alternatives			
Roast turkey, light meat	1.4	70	1.0
Roast chicken, light meat	4.0	25	1.0
Roast lamb, lean	8.0	25	2.0
Roast beef topside, lean only	4.0	45	1.8
Roast beef silverside, lean only	4.9	40	2.0
Thin sliced packet beef cooked with added water	2.6	30	0.8
Ham	2.3–7.0	40	1.2–2.8
Quorn mince	2.0	50	1.0
Legumes, pasta, rice			
Baked beans in tomato sauce	0.5	200	1.0
Tinned spaghetti in tomato sauce	0.1	200	0.2
White rice (boiled)	0.3	150	0.4
White pasta (boiled)	0.8	130	1.0

LCT, long chain triglycerides.

Reversal of blood flow in the mesenteric arteries during diastole was strongly linked with development of NEC irrespective of type of CHD in a further study [157]. However, in a separate smaller study involving neonates with HLHS, none developed NEC despite proven reduced mesenteric artery blood flow [158].

In addition, lesions requiring high doses of prostaglandin (>0.05 μg/kg/minute), to keep the ductus arteriosus open to ensure adequate blood flow to the lungs, may also place the patient at increased risk of NEC. The use of prostaglandin introduces a theoretical risk of blood being 'stolen' from the systemic circulation to the lungs, resulting in reduced mesenteric blood flow and perfusion of the associated gut tissue. Disturbed mesenteric artery blood flow in infants with such systemic to pulmonary circulatory shunts has been demonstrated [159].

Cases of NEC have also been reported in patients with cyanotic lesions, TGA and pulmonary atresia following cardiac catheterisation [160]. The aetiology of NEC in this group of patients remains unclear; possibly hypoxia, resulting in splanchnic vasoconstriction along with catecholamine release due to the stress of cardiac catheterisation, might result in reduced blood flow to the gut. As a precaution it is suggested that feeds might be introduced more cautiously in these patients following catheterisation.

Coarctation of the aorta has not been identified as a predisposing factor for NEC despite the reduced systemic blood flow, which theoretically could reduce mesenteric blood flow and intestinal tissue perfusion. These infants may be admitted with a history of taking feeds at near normal volumes with no signs of intolerance. However, if they are admitted in clinical shock with an acidotic picture, feeds might then be withheld temporarily until the infant is more clinically stable.

It is common practice for infants with HLHS to have feeds withheld in the first few days after birth before the first staged repair (Norwood stage 1 or Sano procedure) with PN providing pre-operative nutritional support. However, del Castillo *et al*. reported that up to one third of their patients are fed pre-operatively with no apparent increase in NEC, although details on quantities and type of feed are lacking [161].

Post-operative feeding protocols and algorithms provide guidance on the introduction of feeds to try to reduce the incidence of NEC in patients with HLHS [161, 162]. Introduction of feeds at around seven days post-operatively using either breastmilk or a hydrolysed protein feed, with a slower increase in volumes, achieving full feeds after a further 7 days has been proposed [161]. Braudis *et al*. have suggested that an adequate cardiac output is required with low requirement for inotropes and good peripheral perfusion before considering commencing enteral feeds [162]. However, once initiated, they propose a rapid increase in feeds, initially at 1 mL/kg/hour, but then increasing by 2 mL/kg/hour every four hours until target volumes are met, and report no incidence of NEC. Breastmilk, with its known benefits in preventing NEC in premature infants [163], should remain the feed of choice in cardiac infants at high risk of NEC [161].

Protein-losing enteropathy

Children with a cardiac anatomy that gives them a single functional ventricle undergo a series of operations in which the venous return is eventually plumbed directly into the arteries of the lungs (TCPC procedure), which has the benefit of improving oxygenation and reducing the load on the ventricle. Protein-losing enteropathy occurs in CHF [45], and there is a growing body of evidence that it occurs in 10%–25% of patients who have undergone a TCPC procedure [164, 165]. Diagnosis is confirmed by positive stool α-1-antitrypsin [53]. The condition may resolve as cardiac function improves following surgery or heart transplant [63]. Localised lesions have been treated by partial bowel resection [164]. There is limited evidence for the dietary treatment of protein losing enteropathy, but a useful starting point would be to follow that for intestinal lymphangiectasia (p. 118). The diet should provide 5–10 g fat per day and be high in protein using MCT to improve energy intake. High protein intakes of up to 3 g/kg/day have been suggested with additional supplementation of fat-soluble vitamins [53].

Hepatic dysfunction

The TCPC operation is known to cause 'back pressure' on the liver, predisposing patients to hepatic dysfunction. Some go on to develop moderate to severe liver disease [61]. Prothrombin time becomes progressively deranged from the time of operation, and it has been proposed that this, along with the ability to eliminate galactose, is used as a test of liver dysfunction in this population [61]. Dietary treatment will depend on the degree of liver failure and its progression.

Vocal cord palsy and feeding difficulties

Vocal cord palsy (VCP) is a well-documented complication of congenital heart surgery with an incidence of between 2% and 8% [64, 104, 166, 167]. Any surgery close to the aortic arch (where the left recurrent laryngeal nerve branches off the vagus nerve), along with the pulmonary arteries, carries an increased risk. Surgery to ligate a PDA has an increased probability of development of VCP due to nerve damage. Smaller infants are particularly at risk with up to two thirds of extremely low birthweight infants developing VCP after PDA ligation [167]. Up to a third of infants with HLHS may be affected [62], but a recent modification in surgical technique connecting the right ventricle directly to the lung circulation (Sano shunt) has resulted in fewer cases [62].

The extent of feeding difficulty varies depending on cardiac lesion. Infants with HLHS have a far higher incidence of feeding difficulties than patients with TGA (48% vs. 4%), take twice as long to achieve a target energy intake of 100 kcal (420 kJ)/kg/day and weigh significantly less at 1 month, 6 months and 12 months of age [60].

Increased breathlessness and fatigue may cause some infants with CHD to feed repeatedly for short periods of

time. Early satiety, vomiting and anorexia, all of which may be interlinked, lead to low energy intake. Up to half of infants admitted for cardiac surgery may have feeding difficulties when assessed by a speech and language therapist [8]. Having CPB and prolonged ventilatory support are associated with delays in achieving post-operative energy intake targets and oral feeding, particularly in those with cyanotic lesions [58]. Feeding difficulties associated with CHD may become entrenched, affecting intake into early childhood. Up to a fifth of patients may continue to show signs of feeding difficulties at 2 years of age [168]. Having repeated operations is associated with a sixfold increase, and those with pre-existing feeding difficulties at operation a 20-fold increase, in feeding difficulties at 2 years of age [168]. Identifying these infants for early intervention and support may help to reduce ongoing problems. In developing countries early weaning may indicate breastfeeding difficulties associated with heart failure [11].

Learning points: other complications of CHD affecting nutritional status

- *There is increased risk of NEC in CHD, but feeding can be cautiously commenced in high risk infants once haemodynamically stable; feeding should stop immediately if signs of NEC develop*
- *Vocal cord palsy occurs in up to 8% of infants with CHD and may take time to resolve; early involvement of a speech and language therapist may help overcome feeding difficulties*
- *Protein-losing enteropathy and hepatic dysfunction are late complications in CHD and may occur in later childhood*

Patients with VCP have abnormal swallowing patterns and are less able to protect their airways resulting in greater risk of aspiration [169]. Low birthweight infants with VCP following PDA ligation need longer ventilatory support, have longer hospital stays and may require long-term tube feeding [167]. In one series, 63% of infants required long-term gastrostomy feeding to meet their nutritional requirements [166]. Infants with hypoplastic left heart who are unable to tolerate oral feeds on discharge may take between 6 and 10 weeks to recover oral feeding, but some may take considerably longer [62].

Factors associated with increased risk of readmission

Readmission to hospital following surgery is not uncommon with rates of around 10% within 30 days of discharge [170]. However, children with single ventricle physiology and those with NG tubes may account for up to 50% of these admissions [170]. It has been suggested that focusing post-operative care on those with four high risk factors may be helpful in reducing readmission (Table 14.15).

Table 14.15 Factors associated with increased risk of readmission [170].

Factor	Odds ratio for readmission
Single ventricle physiology	2.39
Pre-operative arrhythmia	2.59
Long post-operative hospital stay	2.2
Nasogastric tube on discharge	2.2

Source: Reproduced with permission from Elsevier.

Treatment and outcome of patients with specific cardiac lesions

Advances in surgical expertise in recent years has meant that increasing numbers of infants with severe cardiac lesions are surviving and being discharged into the community. The nutritional status of infants and children with CHD depends on both the type of lesion and the number of operations that they require. The more complex the lesion and the greater the number of planned operations, the greater the nutritional risk to the patient.

Atrial septal defects

Because blood flow into and out of the atria is at a considerably lower pressure than that in the ventricles, the effect of a septal defect between the two chambers on energy expenditure and subsequent growth should be negligible. As a result, growth should not be impaired, and closure of the ASD at the correct time, between 2 and 4 years of age, is unlikely to have any bearing on subsequent growth. Although haemodynamic parameters markedly improve in all patients following surgery, those referred specifically because of poor growth demonstrate no significant catch-up growth [13, 171]. However, children left longer before ASD closure may show signs of faltering growth, which improves following repair [172].

Hypoplastic left heart syndrome

HLHS is a condition in which the left ventricle fails to develop fully *in utero* (Figure 14.9). The patient undergoes a series of palliative operations resulting in the right ventricle taking over the role of pumping blood to both the pulmonary and systemic circulations. The first-stage operation, known as a Norwood stage 1 operation, at around 5 days of age involves connecting the pulmonary artery with the aorta to create one large arterial vessel. Traditionally, a smaller head and neck artery is then used to connect to the pulmonary arteries via a Gore-Tex tube, allowing the blood to be oxygenated, a BT shunt (Figure 14.10). A more recent modification (Sano-modification) is to connect the right ventricle directly to the right pulmonary artery using an artificial Gore-Tex conduit. A second-stage operation, known as a Glenn shunt (Figure 14.11), is carried out

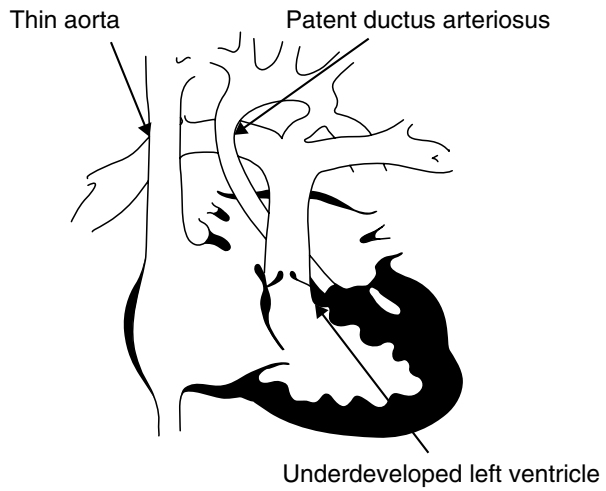


Figure 14.9 Hypoplastic left heart syndrome.

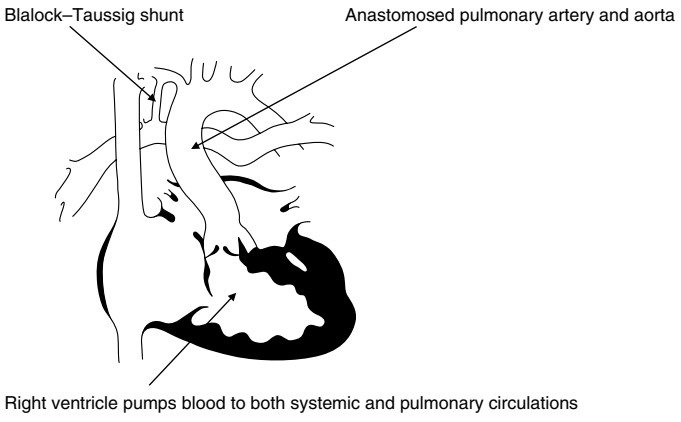


Figure 14.10 Stage 1 Norwood procedure: anastomosis of pulmonary artery and aorta with Blalock–Taussig shunt enabling blood flow to lungs.

between 4 and 5 months [74], connecting the superior vena cava directly to the pulmonary circulation, allowing the venous return from the head to be oxygenated; the initial shunt is taken down. Inter-stage mortality is between 8% and 10% [87, 173], but may be reduced with intensive monitoring [74, 174]. The final palliative operation, TCPC or Fontan (Figure 14.12), is carried out at around 4–8 years and involves connecting the inferior vena cava to the pulmonary vasculature. Having good pre-operative nutritional status is important, and patients are at risk until their second-stage operation.

Feeding and growth from birth to Norwood stage 1 operation

Infants with HLHS have a higher risk of NEC [85] with reduced superior mesenteric [86] and coeliac artery [175] blood flow. However, evidence on giving or withholding enteral feeds before the first Norwood stage 1 operation on incidence of NEC is limited [96]. Having a prostaglandin infusion or an umbilical arterial catheter should not be valid reasons for withholding feeds [96, 176]. In Europe it is more common to give infants with HLHS enteral feeds pre-operatively than in the USA [50, 176]. If available, breastmilk with its benefits in aiding gut maturation and its protective effects from NEC [177] may be the most suitable feed once the patient is haemodynamically stable, but close monitoring for feed intolerance is needed [96]. However, in the absence of breastmilk, it is also possible to use energy-dense feeds, particularly if there is a fluid restriction. One retrospective cohort study has shown pre-operative feeding of 20–30 mL/kg results in shorter post-operative ventilator duration, better perioperative fluid dynamics and earlier full oral feeding than in those remaining nil by mouth [178].

Infants with HLHS tend to be small at birth and continue to lose weight postnatally [7]. The first critical period, where these patients are most vulnerable to growth retardation, is

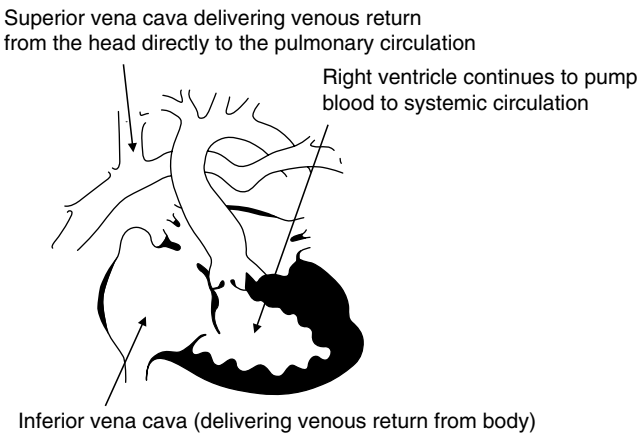


Figure 14.11 Stage 2 Norwood procedure: connection of superior vena cava to left and right branches of pulmonary artery.

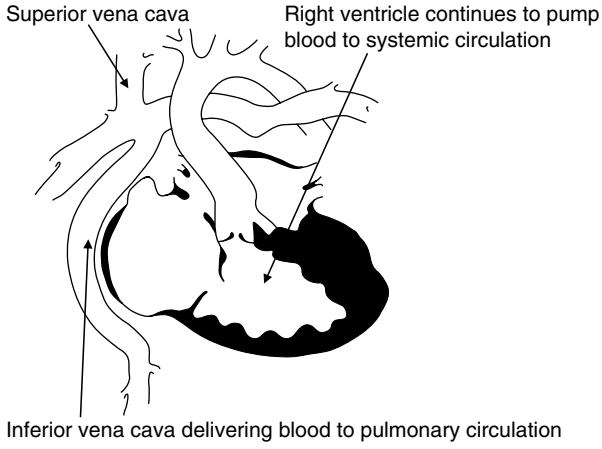


Figure 14.12 Stage 3 Norwood procedure: total cavo-pulmonary connection (TCPC or Fontan).

between birth and discharge from their stage 1 palliative operation at around a month of age. Over 90% of patients suffer a weight loss >−0.5 SDS with over a third experiencing a fall of >−2 SD [7]. Other studies showed median weight remaining static for the duration of admission [9] and 60% of patients do not regain their birthweight by discharge [179]. Male gender, longer post-operative mechanical ventilation, longer hospital stays and, interestingly, greater birth weight are all predictors of falls in post-operative weight SDS [7].

Feeding and growth following Norwood stage 1 operation

Risk of NEC is unaffected by the type of initial shunt [175], but does increase with increasing shunt size that affects blood flow into the descending aorta and mesenteric artery [180]. However, as up to a third of patients may not meet normal energy requirements during their stage 1 admission [179], feeding should commence once they are clinically stable. A post-operative enteral feeding algorithm has shown that feeds may be increased quite rapidly towards target intakes without risk of NEC [162]. Bolus and continuous feeding are equally as effective in achieving satisfactory weight gain in this group of patients if adequate energy intake is achieved [181].

Poor post-operative oral feeding is common following the first-stage operation with one study showing less than 40% achieving full oral feeding on discharge home [62]. Increased risk factors for poor oral feeding are pre-operative inability to feed orally and pre-operative mechanical ventilation, with recovery of normal oral function taking between 2 and 5 months [62]. Issues with poor oral feeding ability or tolerance may only become apparent once the infant is at home. In these cases, the support of a local paediatric dietitian, children's community nursing team, health visitor and speech and language therapist with the capacity to identify and address feeding issues may help to re-establish oral feeding. Although oral feeding may be a marker for less severe disease, those managing oral feeds on discharge do have better inter-operative growth compared with those with tube or oral/tube feeding [174, 182]. Nevertheless, weight gain slows earlier in orally fed infants [183], and ongoing monitoring is required to ensure initial gains do not falter.

Options for ongoing nutrition support include NG, nasoduodenal, nasojejunal and gastrostomy feeding. The option of a gastrostomy should be considered in any child still fed via NG tube after 6 months. The benefits of having less interference in the oral cavity may be quite marked, allowing for rapid improvement in oromotor skills and language development (David Hopkins, personal communication).

The benefits of one mode of tube feeding over another in this group of patients are contentious. One study showed gastrostomy feeding having no significant effect on improving growth [184]. Both NG/nasojejunal [173] and gastrostomy [87] tube feeding have been associated with increased mortality. One study has shown no difference in inter-stage mortality between infants fed orally and those fed via NG tube, but a 2.4-fold increase in those fed via gastrostomy +/− Nissen fundoplication [87]. However, a further study demonstrated an almost threefold increase in inter-operative mortality in patients being fed via NG or nasojejunal tube compared with those either fed orally or via gastrostomy [173]. Infants who require NG tube feeding have a greater burden of medication [182], and the need for tube feeding *per se* may be an indicator of more severe disease.

Overall outcomes on inter-operative growth are variable. One study showed growth stabilisation between the first (Norwood) and second (Glenn shunt) operations [7], but other studies report weight for age falling by up to 1 SDS [68, 184], with admission weights at second operation as low as −2 SD [9]. However, a programme of close cardiovascular monitoring, feed fortification and, where necessary, tube feeding with target intakes of ≥110 kcal (460 kJ)/kg/day demonstrates that catch-up growth is possible, with average weight gains of 26 g/day [174] (Tables 14.16 and 14.17). Nevertheless, infants with HLHS can be expected to remain small with an average weight for age of −1 SD by the time of their second operation.

Growth following stage 2 operation (Glenn shunt)

The best time for catch-up growth to occur is after the stage 2 operation (Glenn shunt) has been carried out. Between this operation and 14 months of age, mean weight gain is of the order of +1 SDS [7]. However, care must be taken to ensure that weight gain does not occur without improvements in length, which would indicate laying down of excess fat (Table 14.18 case study).

Table 14.16 Factors associated with poor weight gain during admission for and after first palliative operation for HLHS [9].

During inpatient stay	Following discharge home
Longer hospital stay	Lower feed energy on discharge
Longer PICU stay	Worse right ventricular function
Shorter course of TPN	More frequent readmissions
High diuretic usage	Higher oxygen saturation at discharge

HLHS, hypoplastic left heart syndrome; PICU, paediatric intensive care unit; TPN, total parenteral nutrition.
Source: Reproduced with permission from John Wiley & Sons.

Table 14.17 Nutritional targets for discharge in HLHS and criteria for contacting monitoring team [174].

Prior to discharge	Alerts for home monitoring team
Intake above 110 kcal (460 kJ)/kg/day	1. Intake < 100 mL/kg/day 2. Weight loss > 30 g in a day 3. Failure to gain 20 g weight in 3 days

HLHS, hypoplastic left heart syndrome.
Source: Reproduced with permission from Springer Nature.

Table 14.18 Case study: treatment progression and dietetic management of an infant with hypoplastic left heart.

Baby boy born at term. Birth weight = 3.42 kg (25–50th centile), length = 51 cm (50th centile). The first child of parents who speak limited English.

The case study illustrates:

- Mix of breastmilk and energy-dense formula required to ensure adequate growth.
- Good nutritional status with tube feeding from tertiary centre enabled local team to transition to oral feeding while ensuring adequate nutritional status.
- The involvement of a local paediatric dietitian with knowledge of paediatric cardiology carrying out home visits enabled treatment options to be discussed and implemented despite language barriers.
- Involvement of multidisciplinary working with speech and language therapist providing support and reassurance in transition from nasogastric to oral feeding.

Chronology	Medical history/investigations	Dietetic interventions
1–4 months old	Early surgical intervention with stage 1 procedure: Norwood and subsequent Stage 2 Glenn procedure	To promote growth along birth centiles for length and weight (50th centile) a mix of 50:50 EBM and Infatrini was provided. During periods of fluid restriction 80%–100% Infatrini was provided
4½ months old	Transition to district general hospital prior to going home. Local dietitian at district general hospital contacted by tertiary centre dietitian for handover of care post-op Norwood stage 1 and 2 operations. History of right diaphragmatic palsy on PICU – plicated diaphragm. Current drugs: omeprazole, ranitidine, aspirin, spirinolactone, furosemide 0.6 mL Abidec	Wt = 7.26 kg (50th centile) Length = 64.5 cm (25–50th centile) BO 1× day. Vomits 1× day, retches 5–6× day Feeding 100 mL/kg using a combination of Infatrini and EBM: 115 mL × 4 hourly × 6 feeds via NG tube (1 feed of EBM and 5 feeds of Infatrini). Current feed gives 95 mL/kg/day, 90 kcal (375 kJ)/kg/day Consultant advises no oral feeding pending SLT review Mum had tried purée weaning solids in tertiary hospital but infant retched Prior to stage 2 operation mum reports that he had been managing 150 mL feed volumes orally with no problems Reviewed on ward every 1–2 days: mum not able to provide enough EBM so alternative standard infant formula given as top up. Vomiting more on Infatrini Home enteral feeding set up prior to discharge
Day 3 post-discharge	Home visit by local dietitian and CCN	Wt = 7.66 kg (↑260 g in 8 days) BO 3× day. Vomits 1× day mostly associated with moving or changing nappy Mum reports him as getting upset/inconsolable after some feeds Feeding: 100 mL Infatrini + 20 mL EBM/infant formula × 6 feeds per day via NG tube Advised on upright positioning if possible following feeds
Day 4 post-discharge	SLT review	SLT reports patient as becoming hot, sweaty and upset before the end of each feed. Ruminating towards the end of feeds (indicating possible GOR). On advice from SLT mum has started him on some purée sweet potato. Managed 3–4 teaspoons
5 months old	CCN review. Oxygen saturations in air: 84%–86%	Wt = 8.04 kg (>50th centile) Continues feeding 100 mL Infatrini + 20 mL EBM/infant formula via NG tube Reports managing only 1 teaspoon solids per day Ongoing weekly telephone calls with local dietitian. Patient continues to vomit in the early morning on waking
6 months old	Telephone discussions with tertiary centre Nutrition Team	No concerns with current weight. Plan to progress with increasing intake of weaning solids while continuing on NG feeds Change in NG tube reported to be better tolerated. Feed regimen altered to give 60 mL in the morning when he is more likely to vomit, larger volumes of 120 mL later in the day. Intake: 77 mL/kg/day, 73 kcal (305 kJ)/kg/day
6½ months old	Further home visit with CCN	Wt = 8.66 kg (50–75th centile). Continues to vomit 2× day associated with opening bowels. Flexible approach to NG feed volumes discussed, feeding 100–130 mL Infatrini + 20–30 mL infant formula via NG tube. Appears to have entrenched food aversion requiring oral desensitisation Further SLT assessment: unable to manage a few millilitres of infant formula and recommends thickened feeds. Plan for gentle approach, applying thickened feeds and purée food to lips regularly each day. Mum feels he is getting hungry
7½ months old	Professionals meeting with SLT, Consultant paediatrician with interest in paediatric cardiology, parents, CCN and local dietitian	Wt = 8.9 kg (50–75th centile). Mum now trained in passing NG tube Combination of 100–110 mL Infatrini + 20 mL infant formula feeds × 5 per day gives 75 mL/kg/day, 71 kcal (295 kJ)/kg/day. Starting to replace Infatrini with some formula feeds to try to improve appetite SLT: starting 'messy play' allowing patient to suck puree food off a variety of soft utensils. Therapy support workers involved

(contiued to overleaf)

Table 14.18 *(continued)*

Chronology	Medical history/investigations	Dietetic interventions
8 months old	Outpatient clinic review with local dietitian	Wt = 8.98 kg (50–75th centile) Length = 69.2 cm (25th centile) No longer vomiting in the morning. Mum concerned about weight, but food intake has improved from 2 weeks ago, now managing 1 dessert spoon solids at some meals. Trying some water from a syringe. Plan: offer water from spouted beaker and offer from a syringe if this does not work, increase to 3 meals per day
9½ months old	Telephone call to mother	Fewer vomits. Now managing 3 dessertspoons of solids at each meal. Using meat, potatoes and vegetables as basis of main meals. NG feeds: 130 mL standard infant formula three times a day and 2 feeds of 95 mL Infatrini mixed with 35 mL standard formula. Trying small amounts of feed orally
10 months old	Outpatient clinic review with local dietitian. Ongoing fortnightly telephone reviews	Wt = 9.22 kg (50–75th centile) Length = 68.9 cm (9th centile) No gagging or vomits reported Now managing 2 small baby bowls of cereal and meat with vegetables. Has started to drink milk again 2 × 30 mL/day, but majority of feeds are still via NG tube. Having a mix of about ½ Infatrini and ½ standard formula Plan: All feeds as standard infant formula. Increase volume of feeds gradually from 140 × 5 to 170 mL × 4 feeds per day and progress with weaning to 3 meals per day including main and dessert items
11½ months old	Dietetic outpatient and SLT review	Weight = 9.44 kg (50th centile) Length = 72 cm (9th centile) SLT review shows good progress with both solids and fluid intake. However, becoming constipated Aiming for 500–600 mL standard infant formula in a total fluid allowance of 800 mL per day. Formula feeds to be given after meals to encourage food intake. Encouraging to drink more from a cup. Discussed removing NG tube, but some medications still needing to be given via tube
1 year old	Telephone review	CCN visit. Wt = 9.46 kg (<50th centile) Length = 72 cm (2nd–9th centile). NG tube removed. Managing all food and fluids orally. Encouraging more lumpy solids

EBM, expressed breastmilk; NG, nasogastric; SLT, speech and language therapist; CCN, children's community nurse; BO, bowels open; GOR, gastro-oesophageal reflux.

Tetralogy of Fallot

This complex cyanotic defect has four separate aspects: a VSD, an 'overriding aorta' in which the aorta straddles the two ventricles, obstruction of pulmonary blood flow from the right ventricle (sub-pulmonary stenosis) and right ventricular hypertrophy (Figure 14.5). The presence of a VSD would usually result in excessive pulmonary blood flow, the development of pulmonary hypertension and subsequent faltering growth. However, the pulmonary stenosis protects the lungs from excessive lung blood flow preventing the development of pulmonary hypertension but increases the workload of the right ventricle causing hypertrophy. Patients who have very little outflow tract obstruction may develop high pulmonary blood flow and require nutritional support.

Rarely, if blood flow to the lungs is very restricted and the patient is very cyanosed, a BT shunt operation is initially performed (Figure 14.10) early in life to try to normalise pulmonary blood flow. Infants who have undergone the BT shunt operation may however develop excessive pulmonary blood flow, increasing respiratory effort that requires additional nutritional support. Once stabilised or after recovery from the shunt operation, the infant can be discharged home. As this is a cyanotic lesion, breathlessness may affect feeding, and growth may slow prior to having the lesion repaired, usually at about 4–6 months of age. The primary defects are repaired with closure of the VSD, repair of the pulmonary outflow tract and, if it has been necessary, removal of the BT shunt. Improvements in feeding ability may then become apparent with full catch-up growth occurring within 2 years of repair [185].

Transposition of the great arteries

With TGA the two main arteries exit from the opposite ventricles from which they would normally, the aorta from the right ventricle and the pulmonary artery from the left. The patient survives because blood mixes through a patent foramen ovale (PFO) and a PDA. Prostaglandin is almost always given to keep the PDA open. In about 25% of

patients, the PFO is enlarged, using a cardiac catheter in a procedure called a balloon atrial septostomy, to allow for better mixing of blood. The patient can recover before a further operation is carried out at about one week of age in which the arteries are switched over to their correct position, the hole between the atria repaired and the PDA closed. These patients tend to have normal birthweights [34, 43] although the reason for this is uncertain. Repairing this complex defect within the first few weeks of life enables patients to be discharged, feeding normally, usually without dietetic intervention, with good prospects for normal long-term growth [12].

Ventricular septal defect

In VSD a hole exists between the two ventricles. There are several types. The most common is a peri-membranous defect in which the hole is located at the 'top' of the ventricle near to where blood exits. A muscular VSD is located near the 'bottom' or apex of the ventricle. In most cases the VSD tends to close or become so small as to have an insignificant effect on cardiac function as the child grows. However, a moderate to large VSD causes increased blood flow into the lungs, resulting in breathlessness, elevated metabolic rate and the child to feed in short bursts. These defects require closure as they invariably result in faltering growth (Figure 14.2). The child may undergo an initial pulmonary artery band operation that reduces the blood flow to the lungs, protecting them from the development of pulmonary hypertension. The infant needs to grow to a size (approximately 5 kg) that enables surgical closure to be carried out more easily. This requires a careful balance between increasing the energy content of the feed to promote growth and trying to limit the almost inevitable GOR and vomiting. However, there has been a tendency towards early closure of clinically significant VSD easing the pressure on the nutritional aspects of treatment. Late diagnosis of a large VSD is associated with marked faltering growth with an imperative to operate as soon as possible [186]. Following surgery most infants demonstrate good catch-up growth [110] although the same authors expressed concern that rapid growth following a period of growth faltering might lead to insulin resistance, obesity and adult cardiovascular disease later in life [110].

Case studies

Case studies illustrating aspects of nutritional management of CHD are given in Tables 14.18 and 14.19.

Future research and unanswered questions

Many studies into the benefits of nutritional support in CHD are retrospective and observational so may be subject to selection bias, resulting in patients with better prognosis being fed earlier and more aggressively [53]. Prospective studies without the risk of selection bias may help to clarify the timing and type of feeding that is most beneficial.

Several studies have now identified energy requirements of patients in intensive care who have undergone specific operations. Further evaluation of post-operative energy requirements in specific patient groups may enable better targeting of nutritional support. Clarification of energy provision of optimum mix of carbohydrate and fat in different cardiac conditions is needed, with evidence of improving cardiac function.

A suitable means of improving breastmilk fortification without raising the osmotic load such that there is increased risk of developing NEC is needed. Evidence of improved vitamin and mineral status from an appropriate supplement is lacking in this group of patients.

There continues to be uncertainty as to whether chylothorax is a self-limiting condition and, therefore, whether a minimal LCT diet is required for treatment; evidence-based outcome data is limited. The use of either TPN or a fat-free feed with peripheral lipid in either speeding recovery or treating cases who initially fail to respond may need further evaluation. There is uncertainty as to whether treatment failures are due to the current level of LCT in feeds (0.35 g/100 mL) not being low enough.

The issue of pre-operative enteral feeding of patients with HLHS differs in Europe and the USA and has not been fully resolved. The conflicting outcomes from varying modes of nutritional support in these patients demonstrate the need for further multicentre studies.

Glossary

Anomalous origin of left coronary artery from pulmonary artery (ALCAPA) ALCAPA is a rare condition in which the left coronary artery arises from the pulmonary artery rather than the aorta. As a result, deoxygenated blood is provided to the coronary artery, resulting in myocardial ischaemia. Cases usually arise in the first few months of life with about half presenting with faltering growth [187]. However, following repair of the primary defect, weight can be expected to be regained.

Aortopulmonary window A hole, or 'window', is present between the aorta and the pulmonary artery. This results in higher pulmonary blood pressure with more blood than usual going to the lungs and less to the systemic circulation.

Atrial septal defect (ASD) A hole between the right and left atria. There is malformation of the septum between the two chambers. The defect may have anomalous pulmonary drainage associated with it, in which some of the venous return from the lungs enters the right atrium rather than the left.

Blalock–Taussig (BT) shunt A procedure in which the subclavian artery is connected to the pulmonary artery in order to provide adequate blood flow to the lungs. Used when the defect results in no direct connection between the right ventricle and the pulmonary circulation, e.g. pulmonary atresia. A modified version of this procedure is to use a

Table 14.19 Case study: treatment of an infant who developed chylothorax and vocal cord palsy following arterial switch operation for transposition of the great arteries.

Baby boy born at term. Birth weight = 3.75 kg (75th centile). Length obtained at 2½ weeks: 53 cm (75th centile) with weight = 4.07 kg (50th centile).

The case study illustrates:
- Limiting the treatment period for chylothorax
- Need for regular follow-up in the initial stages following discharge as the reasons for feeding difficulties may become clearer following discharge home
- Interaction between local and tertiary centre. Monitoring and observations made by the local team on feeding behaviour informed feeding decisions made by tertiary team
- Gradual transition from tube to oral feeding as vocal cord palsy resolved

Chronology	Medical history/investigations	Dietetic interventions
3 weeks old	Transferred from tertiary centre to home following repair of TGA. Post-op development of chylothorax	Feed: Monogen (4-week treatment period). 75 mL × 3 hourly × 8 feeds via NG tube, 150 mL/kg/day Discharged, reported to be feeding well orally pre-operatively but currently taking minimal volumes by mouth Handover reported that he throws his head back and screams when attempts are made to feed orally. Some consideration given to possibility of cow's milk protein allergy, but omeprazole has eased symptoms Local dietitian contacted to arrange home enteral feeding Drugs: spironolactone, furosemide, propranolol
4 weeks old	Local CCN reports Wt = 4.15 kg (25th centile), increase of 80 g since discharge Length = 53.5 cm (25th centile) Patient continuing to cough and vomit feeds	Current feed volumes: 67 mL × 3 hourly × 8, 130 mL/kg/day, advised by tertiary centre dietitian due to issues with vomiting Mum keen to stop NG feeding and revert to bottle feeds. Local dietitian suggests Gaviscon Infant to try to resolve vomiting
4½ weeks old	Tertiary centre commence patient on omeprazole for GOR. Patient coughing but coping better with feeds	Now on 2 hourly feeds of Monogen: 45 mL × 12 feeds to reduce vomiting Local dietitian advises change to 55 mL × 2–3 hourly × 10 feeds if tolerating
5 weeks old	Wt = 4.4 kg (25–50th centile), increase of 250 g/week	Telephone call to mother as she would like information about alternatives to Monogen when treatment stops
6½ weeks old	Request from tertiary centre for NG tube to remain *in situ* to ensure adequate weight gain	Feeds changed from Monogen to standard infant formula
7 weeks old	Home visit by CCN and local dietitian Weight = 4.68 kg (25th centile) Local dietitian contacts tertiary centre to advise of suspicion of vocal cord palsy	Infant is now managing up to 30 mL orally with remaining 65 mL via NG tube. Feeding 95 mL × 3 hourly × 7 feeds with 6 hour break during night Still struggling with oral feeds, only managing half the volume. Has wheeze on feeding and does not appear to like oral feeding Local dietitian suspects vocal cord palsy and advises continued NG feeding to augment oral intake. Advises increase to 100 mL × 7 feeds per day, 150 mL/kg/day mostly via NG tube
8 weeks old	Telephone review by local dietitian	Infant is now managing half of feed volume orally with remainder via NG tube
8–12 weeks old	Ongoing home visits by CCN and telephone reviews by local dietitian Weight = 5.6 kg (9–25th centile) Length = 60.5 cm (25th centile)	Gradual transition to full oral feeding of 150 mL/kg/day of standard infant formula. ENT review scheduled at tertiary centre in 3 months' time
4½ months old	CCN handover to health visitor for ongoing weight monitoring	Dietitian discusses weaning with mum for when baby shows interest in solids. Provided with open appointment with local dietitian

TGA, transposition of the great arteries; NG, nasogastric; CCN, children's community nurse; GOR, gastro-oesophageal reflux; ENT, ear, nose and throat.

Gore-Tex graft between the subclavian and pulmonary arteries (modified BT shunt).

Coarctation of the aorta A narrowing of the aortic arch near to where the ductus arteriosus connects in the foetal circulation. One of the signs is reduced or absent femoral pulses. Surgical repair is either with an end-to-end anastomosis, with the narrowed section being cut out, or by using a flap of subclavian artery.

Cor triatriatum A membrane divides the inside of the left atrium interfering with blood flow into the left ventricle.

DiGeorge syndrome (22Q11 microdeletion) Cardiac defects that affect the pulmonary artery and aorta are associated with this syndrome. Parathyroid hormone is absent, and infants often need calcium supplementation post-operatively. The thymus is also affected, resulting in poor immune function and the need for irradiated blood products to be given if transfusion is required.

Double outlet right ventricle (DORV) Both aorta and pulmonary arteries exit from the right ventricle. A VSD is present, allowing blood to exit from the left ventricle.

Ductus arteriosus This is a connecting vessel between the pulmonary artery and the aorta. Its function is to allow blood to bypass the lungs in the foetal circulation. If it remains open once the infant is born, it is known as a 'patent ductus arteriosus'. This causes excess blood flow to the lungs.

Ebstein's anomaly A deformed tricuspid valve, with missing leaflets, arises lower than normal from the wall of the right ventricle. This results in a small functional right ventricle with the pulmonary artery exiting from above the tricuspid valve. Poor pulmonary blood flow results.

Glenn shunt A procedure in which the superior vena cava is disconnected from where it enters the right atrium and is attached to the right pulmonary artery. The venous return from the upper part of the body therefore flows directly into the pulmonary arteries. This is used as a means of oxygenating blood when there is a non-functioning right ventricle usually due to stenosis of the pulmonary valve or atresia of either the tricuspid valve or pulmonary artery.

Hypoplastic left heart syndrome (HLHS) Due to embryological defects the size of the left ventricle is severely reduced. The aortic and mitral valves are also defective or absent, and the aorta is reduced in size.

Interrupted aortic arch The aorta exits from the left ventricle but fails to continue round to form the usual arch. The descending part of the aortic arch remains connected to the pulmonary circulation via the ductus arteriosus.

Partial anomalous pulmonary venous drainage (PAPVD) As for TAPVD, but fewer pulmonary veins are misdirected.

Patent ductus arteriosus (PDA) The hole that exists between the pulmonary artery and aorta in foetal circulation persists postnatally. Some cardiac lesions require this hole to remain open in order to get blood to the lungs and so be compatible with life. Prostaglandin E1 is used to keep the duct patent.

Patent/persisting foramen ovale (PFO) The hole between the two atria that is normally present in the foetal circulation persists postnatally.

Pulmonary atresia The outflow from the pulmonary artery is completely restricted either at the site of the pulmonary valve or the artery itself. A VSD may or may not be present, and this will affect the surgical course.

Pulmonary stenosis The valve of the pulmonary artery is not formed correctly, resulting in reduced blood flow to the lungs. There are three types with areas of tissue above or below the valve or the valve itself being affected.

Shunt The redirection of blood flow from one area of the circulation to another via a 'short circuit'. This may be due to a physiological defect as in the movement of blood from the left to right ventricle across a VSD or due to an operation such as a BT shunt in which blood is redirected from the systemic to pulmonary circulation (see Blalock–Taussig shunt above).

Tetralogy of Fallot (Figure 14.3) There are four aspects to this defect: a ventricular septal defect, pulmonary stenosis, right ventricular hypertrophy and an overriding aorta in which the aorta straddles the two ventricles.

Total anomalous pulmonary venous drainage (TAPVD) The four pulmonary veins usually return blood to the left atrium. In TAPVD all of these veins empty into a variety of other locations: the superior vena cava, the inferior vena cava, the hepatic vein, hepatic portal vein or the right atrium.

Total cavo-pulmonary connection (TCPC) An operation in which the inferior vena cava is connected directly to the right pulmonary artery. This operation follows on from a Glenn shunt and occurs when a child is older. These operations are used where there are right-sided obstructive cardiac lesions resulting in deoxygenated blood flowing from the body directly into the pulmonary circulation without going through the right side of the heart.

Transposition of the great arteries (TGA) The aorta exits from the right ventricle and the pulmonary artery exits from the left ventricle. Blood is able to mix due to a patent foramen ovale and patent ductus arteriosus. Initially the PFO is enlarged, using a cardiac catheter in a procedure called a balloon atrial septostomy, to allow for better mixing of blood. Surgical repair in which the arteries are cut and switched over is carried out at about 2 weeks of age.

Tricuspid atresia The tricuspid valve between the right atrium and right ventricle fails to from. A PFO or ASD along with a VSD ensures that this lesion is compatible with life.

Truncus arteriosus A single large vessel exits from above the two ventricles due to the pulmonary artery and the aorta failing to divide in the embryo. There is only one single valve to this large vessel, having 3–6 leaflets. A VSD is also present just beneath where the vessel leaves the heart. Truncus arteriosus is classified into four types depending on where the right and left pulmonary arteries arise.

Acknowledgements

Dr Alison Hayes, Consultant Paediatric Cardiologist, Bristol Royal Hospital for Children for providing Figures 14.3–14.5 and 14.9–14.12. Ms Angela Drayton, Mr Tom Wellham and Ms Katie Peck, Yeovil District Hospital Library for help with database searches and sourcing references. Dr Graeme O'Connor, Specialist Paediatric Dietitian, Great Ormond Street Hospital for Children for reviewing the chapter text. Mrs Pamela Wright, Paediatric Pharmacist, Yeovil

District Hospital for checking drugs used in CHD. Dr Kevin Roman, Consultant Paediatric Cardiologist, Southampton Children's Hospital for reviewing medical aspects of the text.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

15 Food Hypersensitivity

Rosan Meyer and Carina Venter

Introduction

Many symptoms are correctly or incorrectly attributed to food hypersensitivity and as a result can lead to confusion when it comes to diagnosis and management. In an effort to improve diagnosis, treatment and general understanding of allergic reactions the Nomenclature Review Committee of the World Allergy Organization issued a report proposing revised nomenclature [1, 2]. This report states that any reaction to food that causes objectively reproducible symptoms or signs, even when the food is eaten unknowingly (blind), should be described as food hypersensitivity. If immunologic mechanisms can be demonstrated, then the reaction can be described as a food allergy. If immunoglobulin E (IgE) is involved in the reaction, then the term IgE mediated food allergy should be used and the term non-IgE mediated food allergic reactions used for immune-mediated reactions that are not mediated by IgE. All other reactions should be described as non-allergic food hypersensitivity, as there is no immunological mechanism involved (Figure 15.1).

Important factors concerning food hypersensitivity reactions

- A food hypersensitivity reaction is known as a food allergy where the immune system is involved. These reactions may involve the immunoglobulin IgE or may involve other immune mechanisms (non-IgE mediated food allergy) (Figure 15.1, A and B).
- Some food hypersensitivity occurs as a result of enzyme deficiency such as lactase deficiency or disorders of amino acid or intermediary metabolism, e.g. phenylketonuria. These reactions are non-allergic hypersensitivities, are well documented and are discussed elsewhere in this book (Figure 15.1, C).
- Some foods may cause unpleasant symptoms, e.g. caffeine in coffee and cola, vasoactive amines in cheese and wine and phenylethylamine in chocolate. These effects are pharmacological and are non-allergic (Figure 15.1, D).
- Some food-induced reactions are non-immune mediated and of unknown origin. These may include a variety of gastrointestinal symptoms related to different foods, e.g. abdominal cramping with garlic or wheat fibre (Figure 15.1, E).

Over recent years a significant amount of research has been undertaken in this area. This chapter can only provide an introduction to food hypersensitivity, and further reading is recommended as new research is constantly produced. Dietetic principles have been concentrated on, but it is essential to understand some of the immunological mechanisms involved to ensure dietetic management is optimal.

IgE mediated allergy

IgE is an immunoglobulin normally present at very low levels in the plasma of non-allergic individuals, but levels are raised in patients suffering from allergic conditions such as asthma, atopic dermatitis, allergic rhinitis and food allergy. When atopic individuals are exposed to a food protein (antigen) via the skin, gastrointestinal tract or lung mucosa, the antigen is taken up and transported to local lymph nodes by specialist processing cells called antigen-presenting cells. These cells break down and present the antigen to T and B cells within specific areas of the lymph node. The type of T cell involved in this encounter is important in determining whether IgE (as opposed to other antibody isotypes, IgA or IgG) is produced. T-helper 2 (Th2) cells play an important role in determining IgE production by B cells. These surround the antigen and present the antigen to T-helper 2 (Th2) cells. This stimulates B cells to produce IgE-specific

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

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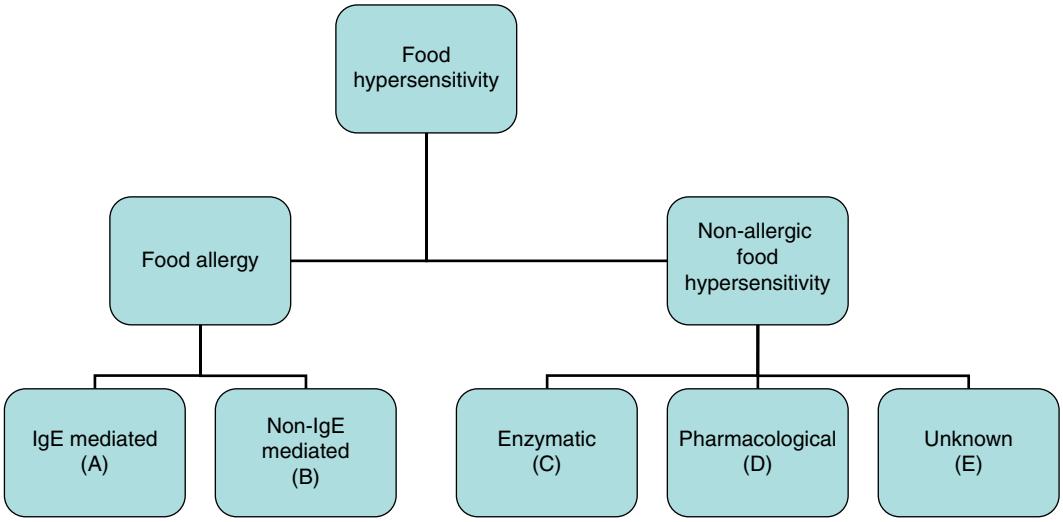

Figure 15.1 Classification of food hypersensitivity [1]. Source: Reproduced with permission of Elsevier.

antibodies, which then bind to mast cells or basophils via high affinity receptors. This cascade of immune reactions then leads to the symptoms associated with an immediate food allergy (Figure 15.2). A variety of cytokines are released, which may induce the IgE mediated late response. Neutrophils and eosinophils invade the site of response and infiltrated cells are activated. These then release a variety of mediators including platelet-activating factor, peroxidase, eosinophil major basic protein and eosinophil cationic protein, leading to a second phase allergic response that is often more severe than the initial response. In the subsequent 24–48 hours, lymphocytes and monocytes infiltrate the area and establish a more chronic inflammatory picture [3].

Clinical manifestation of IgE mediated food allergy

Symptoms generally appear within 0–2 hours after a small amount of food has been consumed. Immediate symptoms may affect the gut, the skin and/or the lungs, and common symptoms are summarised (Table 15.1) [4].

Symptoms of upper airway (laryngeal oedema) and lower airway obstruction (bronchoconstriction), hypotension, cardiac arrhythmias and even cardiac failure constitute the most severe and sometimes life-threatening reactions. The latter is known as anaphylactic shock (which is rare), and although more people are being admitted with this in UK hospitals, food-related fatalities have remained stable at 0.01

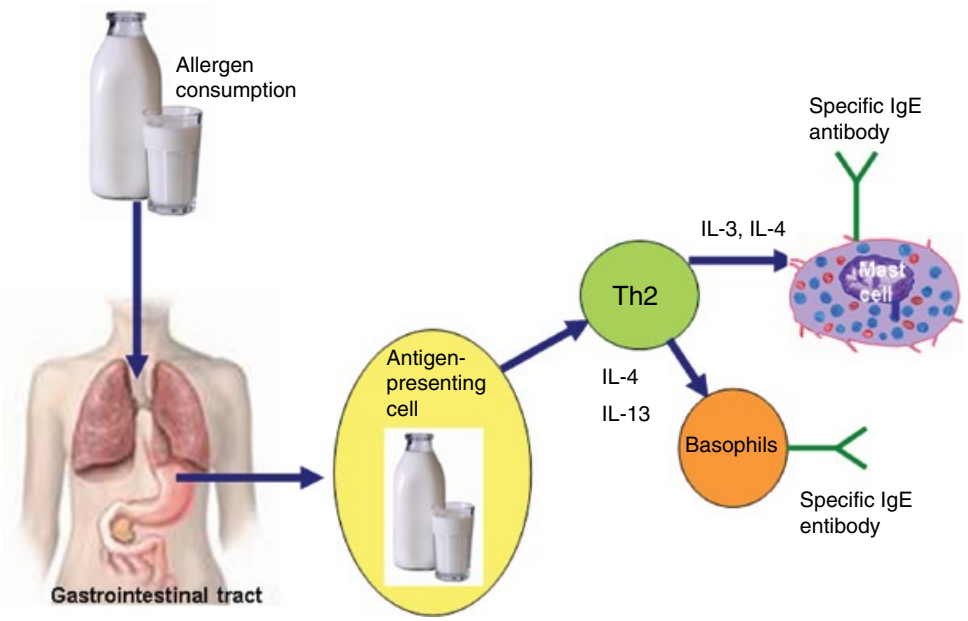

Figure 15.2 Immunological basis for food allergy using cow's milk as an example (exposure through the gastrointestinal tract) [3]. Source: Reproduced with permission of Elsevier.

Table 15.1 Summary of symptom presentation of IgE and non-IgE mediated food allergy.

	IgE mediated (immediate onset)	Non-IgE mediated (delayed onset)
Gastrointestinal	Angioedema of the lips, tongue and palate Oral pruritus Nausea Vomiting Diarrhoea	Gastro-oesophageal reflux Abdominal pain, bloating Vomiting Loose frequent stools Colicky abdominal pain Blood and/or mucus stool Infantile colitis Food refusal/aversion Constipation Perianal redness Pallor and tiredness Faltering growth and one or more of the gastrointestinal symptoms above (with or without serious atopic eczema)
Cutaneous	Acute urticaria Acute angioedema Erythema Pruritus Atopic dermatitis	Atopic dermatitis
Respiratory	Upper respiratory tract symptoms (nasal itching, sneezing, rhinorrhoea) Lower respiratory tract symptoms (cough, chest tightness, wheezing, or shortness of breath)	
Systemic	Anaphylaxis	

cases per 100 000 population per annum [5–7]. The presentation of anaphylaxis is varied, but the major causes of death are obstruction to the upper airway or shock, hypotension and cardiac arrhythmia [7, 8]. The results of double-blind placebo-controlled food challenges (DBPCFC) from several studies in the USA and the UK have shown that the most common foods to provoke immediate reactions are peanuts, tree nuts, milk, egg, soy and wheat, fish and shellfish. Seeds (e.g. sesame) may also cause this type of reaction [6].

Non-IgE mediated food allergy

These reactions are immune-mediated delayed hypersensitivity reactions with symptoms usually appearing more than 2–48 hours after antigen exposure. Although the mechanism of this reaction is not yet fully understood, it is thought that it involves sensitised T cells reacting with the antigen to produce cytokines, which mobilise non-sensitised cells to fight the antigen. This causes inflammation, tissue damage and the formation of epithelioid and giant cells [9].

Clinical manifestation of non-IgE mediated food allergy

These reactions to foods may develop slowly after an hour (e.g. food protein-induced enterocolitis syndrome [FPIES]) [10] or days (e.g. food protein-induced proctocolitis [FPIP] and eosinophilic oesophagitis [EoE]) [11], and the exposure dose evoking a reaction varies from small to larger amounts [12]. As with immediate symptoms, adverse reactions mainly affect the skin and gastrointestinal tract. Symptoms include chronic diarrhoea, chronic or acute vomiting that in severe cases may lead to hypovolaemic shock (e.g. FPIES) [10], diarrhoea, abdominal pain, faltering growth, irritability, colic-like pain, constipation and eczema [13, 14]. Gastrointestinal symptoms are further discussed in Chapter 8.

Mixed IgE and non-IgE food allergy

It is now recognised that patients can present with a mixed picture including both the immediate-type IgE mediated and the delayed-type non-IgE mediated reactions. An example of this overlap is atopic dermatitis and, in some cases EoE, when patients also exhibit IgE sensitisation to pollen [15–17]. The same child may show signs of both IgE mediated allergy, e.g. to egg, and non-IgE mediated allergy, e.g. to milk.

Symptoms often associated with both IgE and non-IgE mediated food allergy

It is important to recognise additional features that are often present in children with food allergies, and these may have implications in the nutritional management. These include faltering growth; vitamin D, calcium and iron deficiency; and feeding difficulties [18].

Non-allergic food hypersensitivity

The most well-known non-allergic food hypersensitivity is lactose intolerance (p. 117). Symptoms arise due to the osmotic effects of lactose and fermentation thereof by

intestinal bacteria. This may cause excessive flatus, explosive diarrhoea, perianal excoriation, abdominal distension and pain [19]. The overlap in symptoms with non-IgE mediated gastrointestinal food allergies often causes confusion with the diagnosis, but is distinctly different due to the absence of an immunological mechanism [20].

More controversial problems that may be related to non-allergic food hypersensitivity are migraine, rheumatoid arthritis, migraine with epilepsy, enuresis, autism and attention deficit hyperactivity disorder (ADHD). Dietary manipulation (elimination and challenge) is the mainstay for diagnosis and treatment of these conditions [2, 21]. It is important to consider nutritional adequacy when such a diet is considered (p. 328).

Diagnosis of food hypersensitivity

IgE mediated allergy

Skin prick tests

The skin prick test (SPT) indicates the presence of allergen specific IgE. It can be performed in a medical setting equipped to deal with anaphylaxis and yields an immediate result, which is very useful for clinicians and parents. Drops of food extract, positive (histamine) control and negative (saline) control are applied using lancets. In the past a cut-off of 3 mm or larger was considered positive; however, with the publication of the LEAP (Learning Early About Peanut Allergy) and EAT (Enquiring About Tolerance) studies, this cut-off has been questioned, and interpretation of SPT should be led by an allergy-focused history [22]. It is important to note that the positive predictive accuracy of SPTs is less than 50% when compared with results from DBPCFC. Negative predictive accuracy is 95% [23, 24]. This means that negative SPT responses are a worthwhile means of excluding IgE mediated allergies, but positive SPT responses only indicate an atopic individual with a tendency to react to this food. Exclusion diets should not be based on these results alone [4].

Specific IgE test

Specific IgE is an *in vitro* assay for identifying food-specific IgE antibodies from serum. It is more expensive than SPT, and the results are not available to the clinician immediately, possibly delaying diagnosis. This test may be preferred when patients have dermatographism, severe skin disease or limited surface area for testing (e.g. in severe atopic dermatitis); where patients have difficulty discontinuing antihistamines; or where patients have exquisite sensitivity to certain foods [23]. Interpretation of results is as difficult as with SPTs as there are no universally accepted cut-offs for each allergen, and interpretation needs to also occur in conjunction with an allergy-focused history. SPTs and specific IgE tests provide useful contributory information towards a diagnosis when added to the clinical history and should be interpreted by clinicians with appropriate competencies [23].

More recently, component-resolved diagnostics (CRD) have been used in food allergy, giving information about which particular allergen or allergens are involved in triggering allergic symptoms. CRD has become extremely useful as it has enabled identification of specific clinical phenotypes, prediction of severity of reactions and identification of cross-reactive specific components to other similar allergens from different pollen species or foods (Table 15.2) [25, 26]. CRD is, however, mainly available only in specialist centres, and its use is limited to cases where it makes a difference in the diagnosis or management.

Table 15.2 High risk components (more likely to lead to anaphylaxis) versus low risk components [25].

Food allergens	High risk	Low risk
Peanut	Ara 1,1,3,9	Ara h 8, profilin
Hazelnut	Cor 1,8,9,14	Profilin
Walnut	Jug r 1,2,3	Profilin
Soya	Gly m 5,6 (4)	Profilin
Rosacea fruit	Pru p 3, Mal d 3	Pru p 1, Mal d 1, profilin
Wheat	Tria 14, Tria 19	Profilin
Shrimp	Pen a 1	N/A

N/A, not applicable.
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Intradermal test

Intradermal tests for food allergy are not recommended in either UK [27] or US guidelines [28]. Unacceptably high false positive rates as well as safety concerns, such as systemic reactions (including fatal anaphylactic responses), are associated with this allergy skin test [29].

Basophil activation test

Studies are emerging on basophil activation test (BAT) as a new diagnostic tool for food allergy. This test is based on a three-step approach: cell stimulation, cell staining and flow cytometry. The expression of activation markers is then measured on the surface of basophils following stimulation with the allergen and has shown high specificity [30]. It has been described as an oral food challenge (OFC) in a test tube and has already been applied to cow's milk, egg and peanut. However, BAT requires a specialist laboratory setting and at this stage is mainly limited to research [4].

Other diagnostic tests

To date there are no additional diagnostic procedures to those described above that can be recommended as useful tests in the diagnosis of IgE and non-IgE mediated food allergy. IgG testing has received a significant amount of attention in the lay press for assisting in the 'diagnosis' of non-IgE mediated reactions or food intolerances. The European Academy of Allergy and Clinical Immunology (EAACI) [31, 32], the American Academy of Allergy, Asthma and Immunology (AAAAI) [33] and the UK National Institute for Health and Care Excellence (NICE) [13] advise against the use of this 'test' for diagnosing any type of food

allergy or intolerance due poor association with actual allergies and the concern that misinterpretation may lead to nutritionally incomplete diets. Other tests that have also been shown to be of no benefit in the diagnosis of food hypersensitivity include vega testing, hair analysis, cytotoxic test, kinesiology, iridology, electrodermal testing and sublingual provocative food testing [34].

Non-IgE mediated allergy

There are currently no validated *in vitro* or *in vivo* tests that can identify foods responsible for non-IgE mediated food allergies [4, 12]. It has been suggested that atopy patch testing could be used to aid the diagnosis of non-IgE mediated food allergy; however, studies have not found the test to be sufficiently accurate, and, therefore, all current guidelines do not recommend this test to be used for diagnostic purposes in delayed food allergy [4, 35, 36]. Currently, the symptomatic improvement on an allergen exclusion diet [37] followed by a return of symptoms on allergen reintroduction or a food challenge remains the gold standard for diagnosing this food allergic condition [4, 14, 38]. Therefore, without the reintroduction of the allergen, the diagnostic process is not complete.

Non-allergic food hypersensitivity

As for food allergy, there is no proven test (outside of those for disaccharide malabsorption) for the diagnosis of non-allergic food hypersensitivity. Advertised diagnostic methods such as applied kinesiology, hair tests or electrodermal tests were evaluated in a Consumer Association report [39]. The verdict was that known allergies in individuals were not picked up, the services exaggerated the number of allergies, and this could result in unnecessarily restricted and inadequate diets. The report suggests that people should not waste their money on these tests. Vega testing has also been assessed in a double-blind study and was shown to be unable to accurately diagnose food hypersensitivity of any mechanism [40].

Elimination diets for diagnosis of IgE and non-IgE mediated food allergies

An allergy-focused history is the cornerstone for making a diagnosis of food allergy and guiding food eliminations. This includes taking a symptom history to assist in the decision whether the reaction may be IgE or non-IgE mediated [41]. Taking a full diet history is mandatory before embarking on an elimination diet as this may indicate provoking foods and also gives an indication of dietary adequacy. The accuracy of the diet history needs to be taken into account, as it is not uncommon for parents to be mistaken as to which foods affect their child and problems with staple foods eaten several times a day, such as milk and wheat, often go unnoticed [41]. Both the clinical and diet history then provide guidance on which diagnostic test may be required to guide the elimination diet and, in the case of non-IgE mediated allergy, to embark on a diagnostic elimination diet [42].

For IgE mediated allergies the elimination diet is implemented to manage symptoms, and reintroduction of these foods into the diet will only occur when there is an indication that the allergy may have been outgrown. However, in some cases (particularly for non-IgE mediated allergy and non-allergic food hypersensitivity), it may not be clear if particular foods are involved, and, therefore, a diagnostic elimination diet is recommended. Before this is embarked upon, it is essential to consider whether the child/parent is sufficiently motivated and able to adhere to the diet. The length of time required on an elimination diet to confirm/refute a non-IgE mediated allergy is around 4 weeks [37], but may vary between 2 and 6 weeks depending on the following:

- type of suspected food allergy (more severe symptoms may take longer to resolve)
- frequency of symptoms
- degree of restriction of diet (i.e. one food versus many foods)
- nutritional status of the child

For non-allergic food hypersensitivity, the elimination time is also poorly defined, but published data indicates an elimination period of also between 2 and 6 weeks being sufficient [21].

Any improvement of symptoms has to be followed up by reintroduction or a challenge with the offending foods, resulting in reproducible deterioration and then recovery on re-elimination in order to confirm the presence of a food allergy. The NICE guidelines recommend that challenges for IgE mediated allergy should be performed in a clinical setting; food reintroduction for delayed symptoms can be performed at home, apart from FPIES that needs to occur in a hospital setting [13, 43].

Keeping a food symptom diary before starting a diet may provide a baseline, but seldom adds any useful information about suspect foods that has not been revealed by diet history; keeping a food diary may increase the burden for families. The initial diet may exclude one food (e.g. cow's milk) or a number of foods (e.g. cow's milk, soya and eggs). The choice of diet is a matter of clinical judgement taking into account age, severity and type of symptoms and whether other elimination diets have already been tried [44]. There are three levels of dietary restriction: an empirical diet, a few foods diet or an elemental diet (Figure 15.3).

Empirical diet

An empirical diet is used where food hypersensitivity is suspected and causative foods are not known. One or several of the most commonly provoking foods are avoided. Cow's milk, hen's egg, wheat, soy, peanut, tree nut, sesame and kiwi are responsible for the majority of IgE mediated food-induced allergic reactions in young children [44]. Fin fish, shellfish, tree nuts and peanut are more common food allergens in older children [44]. In children with atopic dermatitis (mixed IgE and non-IgE mediated), the offending foods are similar to those in IgE mediated allergies; however, studies of common allergens in delayed reactions yield

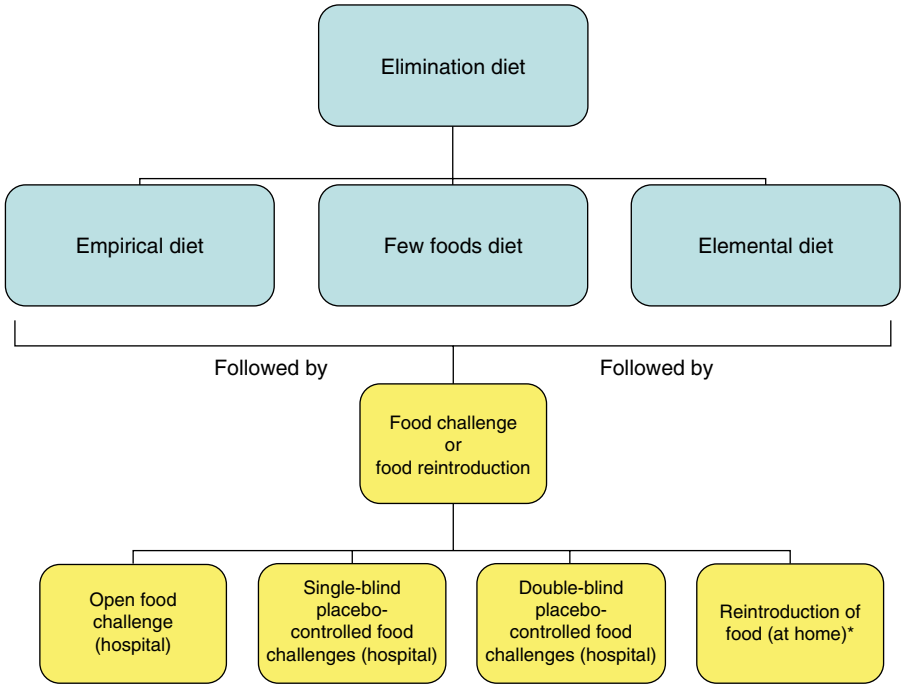

Figure 15.3 Using elimination diets and food challenges/reintroduction to aid diagnosis. *Only if there is no risk of an immediate severe reaction.

anecdotal results. The most common food allergens in the whole spectrum of non-IgE mediated gastrointestinal food allergies are cow's milk, soy, egg and wheat [4, 12, 45]. However, it is important to recognise that there are variations in common allergens, for example, in FPIES foods like rice, oats and also vegetables such as sweet potato may cause reactions [46, 47].

Milk-free, soya-free and milk, egg, wheat and soya-free diets are given in Tables 8.17–8.19.

Outside of non-IgE mediated allergies, parents may also report allergic-type symptoms related to fruit and occasionally to vegetables. It is important to elicit the type of reaction and also the time of year these occur. Pollen food syndrome (PFS) (otherwise known as oral allergy syndrome [OAS]) in children may need to be ruled out as new data generated from the UK indicates that this can occur as young as 1.4 years of age (average 4.5 years) [48]. In infants and young children, citrus and tomato are often blamed for exacerbation of atopic dermatitis. Flare-up of eczema may occur around the mouth/face due to the pH of the fruit and its histamine content, but specific research supporting this is absent. Fruit and vegetables contribute important micronutrients to the diet; it is, therefore, important not eliminate these foods from a diagnostic exclusion diet without ensuring dietary adequacy. Practical advice is to cover the area around the mouth with petroleum jelly (e.g. Vaseline) prior to eating these fruits and vegetables.

Problems can occur with empirical diets when excluded foods are inadvertently replaced by others that can cause adverse reactions, e.g. a child on a milk-free diet may drink soy milk or orange juice instead, and it is possible to be equally reactive to these foods. Failure to respond to an empirical diet does not always, therefore, rule out the possibility of food hypersensitivity.

Few foods diet

A few foods diet consists of a small number of hypoallergenic foods. This diet may be useful if there is a perception that most foods cause an allergic-type reaction. Although it is often suggested as a dietetic option for establishing food-induced hypersensitivity reactions, its use has only been extensively studied in patients with atopic eczema [49–51].

Diets using one meat, one carbohydrate source, one fruit and one type of vegetable have been used in the past [52]. Examples of such diets are given in Table 15.3. If no improvement occurs with the first diet, a second diet containing a different set of foods can be used. Nutritional adequacy should be monitored carefully [18, 44, 53]. In extreme circumstances, more rarely eaten foods such as rabbit, venison and sweet potatoes could be included [53]. As these diets are nutritionally demanding, it is suggested that they should not be followed for more than 4 weeks.

Since the above diets are extremely rigorous, less restricted diets have been used to improve adherence (Table 15.4) [53]. It is much more difficult to find a completely different set of foods for a second attempt if the first is not helpful. However, it is possible to monitor progress closely and adjust or further restrict the diet during the third or fourth week in an attempt to achieve eventual success.

The acceptability of the few foods diet depends greatly on the dietitian's advice regarding planning menus, giving ideas for meals and providing recipes for cooking with the allowed foods. Ideas for packed lunches should be given as school canteens cannot be expected to cope with such a restricted diet. For vegetarians a larger range of vegetables, including pulses, would be allowed. The dietitian should keep in regular contact with the family to ensure adherence

Table 15.3 Two examples of few foods diets.

A	B
Turkey	Lamb
Cabbage, sprouts, broccoli, cauliflower	Carrots, parsnips
Potato, potato flour	Rice, rice flour
Banana	Pear
Soya oil	Sunflower oil
Calcium and vitamins (Table 15.4)	Calcium and vitamins (Table 15.4)
Tap water	Tap water
Hypoallergenic formula (<2 years)	Hypoallergenic formula (<2 years)

Possible additions: milk-free margarine, sugar for baking.
Possible variations: bottled water; rabbit instead of above meats; peaches and apricots, melon or pineapple instead of above fruits.

Table 15.4 Less restricted few foods diet.

This diet should be used for no more than 4 weeks. Children under 2 years require a nutritionally adequate substitute for milk

Choose two foods from each food group

Meat	Lamb, rabbit, turkey, pork
Starchy food	Rice, potato, sweet potato
Vegetables	Broccoli, cauliflower, cabbage, sprouts (brassicas) Carrots, parsnips, celery Cucumber, marrow, courgettes, melon Leeks, onions, asparagus
Fruit	Pears, bananas, peaches and apricots, pineapple
Also included:	Sunflower oil, whey-free margarine Plain potato crisps Small amount of sugar for baking Tap or bottled water Juice and jam from allowed fruits Salt, pepper and herbs in cooking

It is important to achieve daily requirements for vitamins and minerals appropriate for the child's age and diagnosis. On a few foods diet, if insufficient breastmilk or suitable formula for the management of food allergy is consumed, then vitamin and mineral supplementation is required.

and nutritional adequacy of the diet. The cost of the diet may be a problem and should be discussed with the family.

The few foods diet is most difficult to carry out in the toddler age group, as they may still be very reliant on milk or formula for their nutrition. Ideally, they should take a suitable hypoallergenic formula, but it may be refused due to its taste, and in this case an over-the-counter plant-based milk may be considered, but it is important to note that energy, protein and vitamins are much lower than in formulas. The diet can be altered to suit the individual child and, in some circumstances, can be made less restricted by including a larger range of meats, fruits and vegetables.

Few foods diets are usually carried out in the home environment. It is important that the child's lifestyle is not altered; otherwise changes in symptoms could be attributed to factors other than change in diet. Regular medication should not be changed before or during the diet trial for the same reason. Children on regular medication such as anticonvulsants should remain on these, but be switched to a colour/preservative-free version if possible. Attention should be paid to non-food items that may be consumed by small children such as toothpaste (a white toothpaste should be used), chalks and play dough [53]. It is critical that after a maximum of 4 weeks on this diet, the reintroduction of foods occurs. There is very little guidance on the reintroduction of foods following a few foods diet or elemental diet, and practice varies between allergy centres, depending on the:

- type of food allergy and symptoms
- most likely offending foods (which are introduced at the end)
- nutritional status of the child and nutritional adequacy of the existing diet
- foods the child misses most

Foods should be reintroduced singly in order to try and identify trigger foods. Each new food may be tried in a small test quantity, then given in normal amounts every day for a week and then incorporated into the diet as desired. A guide to reintroduction of foods is given in Table 15.5.

Elemental diet

Elemental diets based on amino acid formulas (AAF) (Table 15.6) can occasionally be justified where there has been no response to a restricted diet. AAF (elemental diet) are also indicated for children with EoE, and data indicates that remission is >90% when used as a sole source of nutrition [54, 64]. The use of an elemental diet alone should be carefully considered: for nutritional adequacy; how to maintain oral motor skills, in particular in the young; and whether the feed will be accepted as sole source of nutrition in the long run. In particular older children may find the feed unpalatable, and tube feeding may be necessary to achieve adequate nutrition. The insertion of a feeding tube will involve a hospital admission.

Learning points: elimination diets

- *An individualised elimination diet is essential for the management of known food allergies*
- *For non-IgE mediated allergies and non-immune-mediated food hypersensitivities, an empirical elimination of common culprits may be required to establish a food hypersensitivity reaction*
- *A few foods diet should only be implemented in those patients where an empirical elimination has not lead to symptom improvement and food is still suspected as the cause of the reactions*
- *An elemental feed can be used as either the sole source of nutrition (e.g. in EoE) or the main formula/feed in a restricted diet*
- *Dietary elimination needs to be carefully considered and reintroduction/food challenge should always occur after a trial of few foods diet and to confirm a diagnosis of a non-IgE mediated allergy or a non-immune-mediated food hypersensitivity*

Table 15.5 Open reintroduction of foods.

Each food should be given in normal quantities daily for 4–7 days before being allowed freely in the diet. Smaller doses on the first day of introduction may be recommended initially [44]. The order of reintroduction depends on the child's preference and on which foods were avoided initially	
Oats	Porridge oats, Scottish oatcakes, home-made flapjacks (if sugar is already allowed)
Corn	Sweetcorn, home-made popcorn, cornflour, maize flour, cornflakes if malt is tolerated
Meats	Try meats (including offal) singly, e.g. chicken, beef, pork
Wheat	Wholemeal or unbleached white flour for baking, egg-free pasta, Shredded Wheat, puffed wheat, Weetabix
Yeast	Pitta bread; ordinary bread (this usually also contains soya)
Rye	Worth trying if wheat is not tolerated; pure rye crispbread; pumpernickel
Cow's milk	Fresh cow's milk, cream, butter, plain yoghurt, milk containing foods with tolerated ingredients, e.g. rice pudding Try cheese separately later
Cow's milk substitute	If cow's milk is not tolerated, try substitutes one by one Infant soya formula (if >6 months) or infant hydrolysate formula Sheep milk, goat milk for >1 year olds (boiled or pasteurised) Supermarket liquid soya milk (>2 year olds), supermarket rice milk (>4½ year olds) with additional calcium
Egg	Use one whole fresh egg per day for test period It may be preferred to begin with small amounts of egg in baking
Fish	Fresh or frozen (not smoked, battered, etc.), e.g. cod, herring If one type is not tolerated, others may be. Try shellfish separately later
Tomatoes	Fresh tomatoes, canned and puréed tomatoes, ketchup
Peas/beans	These include peas, green beans, kidney beans, lentils, and baked beans in tomato sauce if tomato is tolerated
Orange	Pure orange juice, oranges, satsumas. If oranges are tolerated, all citrus fruit probably are too
Sugar	Use ordinary sugar on cereal, in drinks and baking Some parents comment that small amounts are tolerated, whereas larger amounts are not
Chocolate	Try only if sugar is tolerated If diet is milk-free, use milk-free chocolate Cocoa powder in drinks and cooking
Carob	Carob confectionery can be tried if chocolate is not tolerated Check other ingredients – it may contain milk or soya
Tea/coffee	Add milk if this is already in the diet
Peanuts	Plain or salted peanuts* Peanut butter
Other nuts	Try singly or mixed*
Malt	Malt/malt flavouring is present in most breakfast cereals Try Rice Krispies if rice is tolerated
Nitrite/nitrate	Corned beef if beef is tolerated; ham and bacon if pork is tolerated
Sodium benzoate	Supermarket lemonade provided other ingredients are tolerated
Sodium glutamate	Stock cubes, gravy mixes, flavoured crisps, provided the other ingredients are tolerated
Sodium metabisulphite	Some squashes, sausages provided the other ingredients are tolerated, dried fruit
Vitamins/minerals	These may be given if needed to enhance nutritional adequacy and introduced singly to test tolerance

Other foods, e.g. fruit and vegetables, can be introduced gradually as desired. Manufactured foods such as ice cream and biscuits can be introduced taking into account known sensitivities. Many additives, e.g. colours and flavours, will be introduced as mixtures in manufactured foods such as sweets and canned/bottled drinks. For children with multiple cereal intolerances, flours such as buckwheat, soya, gram (chickpea) and wheat starch may be tried. Some of the special dietary products for gluten-free and low protein diets may be suitable, but other ingredients must be checked (they may not be prescribed for food hypersensitivity).

*Children under 5 years old must not be given whole nuts as they are a choking hazard.

Table 15.6 Formulas suitable for the management of food allergy [14, 54–56].

Formula	Protein source	Tested for hypoallergenicity*	Osmolality (mOsm/kgH_2O)	Additional information
Nutramigen LGG 1, 2 and 3 (Mead Johnson)	EHF casein	Yes [57]	1 = 290 2 = 420 3 = 300	Clinically insignificant lactose content Nutramigen LGG 1 is suitable form birth Nutramigen LGG 2 is suitable from 6 months of age Nutramigen LGG 3 from 1 year of age Contains LCP and *Lactobacillus rhamnosus GG* probiotic
Pregestimil Lipil (Mead Johnson)	EHF casein	No[§], but same peptide mixture as Nutramigen LGG	280	Contains 55% fat as MCT Clinically insignificant lactose content For allergy and/or fat malabsorption/maldigestion Suitable from birth to 12 months**
Similac Alimentum (Abbott)	EHF casein	Yes [58]	374	Clinically lactose-free Suitable from birth to 12 months**
Aptamil Pepti-Junior (Nutricia)	EHF whey	No, but similar peptide mixture to Aptamil Pepti	275	Contains 50% of fat as MCT Clinically insignificant lactose content For allergy and/or malabsorption/maldigestion Suitable from birth to 12 months**
Aptamil Pepti 1 and 2 (Nutricia)	EHF whey	Yes [59]	1 = 280 2 = 290	Contains prebiotics Pepti 1 contains 41% CHO as lactose and Pepti 2 36% CHO as lactose Pepti 1 is suitable from birth Pepti 2 is suitable from 6 to 12 months of age**
Althera (SMA Nutrition)	EHF whey	Yes [60]	335	Contains 53% CHO as lactose Suitable from birth to 12 months of age**
MCT Pepdite (Nutricia)	EHF pork collagen and soya	No	290	Contains 75% fat as MCT Not suitable for patients requiring Halal or Kosher diet Rarely used for CMPA Suitable from birth to 12 months of age**
MCT Peptide 1+ (Nutricia)	EHF pork collagen and soya	No	460 at 91 kcal (380 kJ)/100 mL 580 at 100 kcal (420 kJ)/100 mL	Contains 75% fat as MCT Not suitable for patients requiring Halal or Kosher diet Rarely used for CMPA Suitable >12 months of age
Infatrini Peptisorb (Nutricia)	EHF whey	No	360	Energy-dense infant formula Suitable for children <1 year of age Occasionally used in CMPA <1 year of age, if faltering growth is present
Nutrini Peptisorb (Nutricia)	EHF whey	No	345	Energy-dense formula Suitable for children >1 year of age Rarely used for CMPA

(continued overleaf)

Table 15.6 (*continued*)

Formula	Protein source	Tested for hypoallergenicity*	Osmolality (mOsm/kgH_2O)	Additional information
Neocate LCP (Nutricia)	AAF	Yes [61, 62]	360	Truly hypoallergenic, no CMP ß-Lactoglobulin Lactose-free With LCP Suitable from birth to 12 months of age**
Neocate Syneo (Nutricia)	AAF	Yes [63]	360	Truly hypoallergenic, no CMP β-Lactoglobulin Lactose-free With LCP Suitable from birth to 12 months of age**
PurAmino (Mead Johnson)	AAF	Yes	350	Truly hypoallergenic, no CMP β-Lactoglobulin Lactose-free With LCP Suitable from birth to 12 months of age**
Neocate Junior (Nutricia)	AAF	No	580 (at 21.1% concentration)	Energy-dense formula Truly hypoallergenic, no CMP β-Lactoglobulin Lactose-free With LCP Suitable for children >1 year of age Can be mixed at different concentrations
Elemental 028 (Nutricia)	AAF	No	Unflavoured powder 502 (at 20% concentration) Flavoured = 637–670 depending on flavour	Truly hypoallergenic, no CMP β-Lactoglobulin Lactose-free Available in ready-to-feed (different flavours) and powder Suitable from >1 year of age Can be mixed at different concentrations

LGG, *Lactobacillus rhamnosus GG*; EHF, extensively hydrolysed formula; MCT, medium chain triglyceride; CHO, carbohydrate; LCP, long chain polyunsaturated fatty acids; CMPA, cow's milk protein allergy; AAF, amino acid formula; CMP, cow's milk protein.
*Tolerated by 90% of children with CMPA with a 95% confidence interval (CI).
§Studies have been performed using this formula in CMPA; however, these were not set out to establish hypoallergenicity.
**Occasionally dietitians may use these feeds in children older than 1 year of age, if nutritionally indicated.

Food challenges

Following improvement on the diagnostic diet, the dietitian will need to either perform a food challenge in hospital, in particular for IgE mediated symptoms, or a reintroduction plan/prolonged food challenge at home for the delayed-type reactions.

History taking

Prior to considering any food challenge, it is important to gather all the history relevant to performing the challenge safely. Taking a history will provide important information on:

- the age of the patient to determine how difficult it may be to perform the food challenge and to help in identifying the possible food causing the symptoms
- the type of food or foods causing reported symptoms, e.g. raw egg versus cooked egg
- the age of onset of symptoms as well as the frequency and reproducibility of the reaction
- the time of onset of symptoms in relation to food consumption; the clinical manifestation and duration of the symptoms
- the quantity of food causing symptoms in order to prevent false negative food challenges
- a thorough description of the most recent reaction is also very important in designing challenges; the details of the most recent reaction may be more helpful than those of more distant reactions
- sometimes, more than one food or factor is needed to elicit a positive challenge outcome (e.g. a combination of foods eaten together, exercise-induced anaphylaxis or with concomitant drug intake)
- a list of foods that are well tolerated and that could be used as a placebo or vehicle to mask the challenge food [65]

There are many different reasons for performing food challenges including determining tolerance to the food allergen, clinical reactions to foods without any tests being positive and severity of reactions, determining threshold doses and, more recently, establishing the efficacy of desensitisation protocols [66]. Challenges can be performed as either open food challenges (OFC), single-blind placebo-controlled food challenges (SBPCFC) or DBPCFC (Figure 15.3) [65].

Open food challenges

During OFC both the clinician and patient (or parent) are informed of the food being administered, and these challenges should be sufficient to either confirm or refute most reported food hypersensitivity. However, many children are very reluctant to eat a food that they do not remember having eaten before or that they have previously been told to avoid. Indeed it is not uncommon for children who have had previous severe reactions to foods to exhibit some degree of food avoidance. It is, therefore, often advisable to provide the challenge in a 'single blind' form (culprit food mixed with another food acceptable to the child) simply to ensure that the child consumes it [67, 68].

OFC are mainly used in the clinical setting, particularly to determine tolerance to a food, and are useful for the diagnosis of objective symptoms [66, 68]. Although factors such as starting dose, dose increment and final dose may not be that critical, it is essential that the patient has consumed an adequate amount of food during the challenge to make a diagnosis accurate [69, 70].

Single-blind placebo-controlled food challenges

During the SBPCFC, both active and placebo challenges are given. The health professionals involved know which food is active and which is placebo, but the patient does not. Sufficient masking of the challenge food is very important. SBPCFC are particularly useful when performing food challenges in children who do not want to ingest a specific food.

Double-blind placebo-controlled food challenges

The gold standard for confirming or refuting food allergy is the DBPCFC [70, 71], although in practice open challenges are more common. One of the strengths of the DBPCFC is that neither the patient nor the investigator knows when the active or the placebo challenge is performed, therefore ruling out reporting bias from the clinician and any psychological effect from the patient.

The DBPCFC is mainly used for research purposes and can be time consuming and difficult to manage. DBPCFC still remains the optimal choice to determine clinical reactivity to food, especially where there is a possibility that any observed reaction could be caused by anxiety, or in diagnosing subjective symptoms such as abdominal pain and nausea [68, 70]. DBPCFC are also most commonly used to determine severity of reactions, threshold doses and efficacy of desensitisation protocols [66].

Considerations when performing food challenges

Elimination period

Prior to a food challenge, the identified food should be excluded from the diet as discussed above.

Challenge dose

Guidance on performing food challenges (OFC and DBPCFC) such as the dosages given and foods used is discussed in the PRACTALL consensus guidance [71].The PRACTALL recommendations suggest the following doses for food challenges [71]: 4.334 g of protein divided into 3, 10, 30, 100, 300, 1000 and 3000 mg doses. In terms of amount of food given, this equates to:

- Milk

12.428 g of skimmed milk powder (8.3 mg; 27.8 mg; 83.3 mg; 277.8 mg; 833.3 mg; 2777.8 mg; 8333.3 mg)

- Soya

134.6 mL of soya milk (0.1 mL; 0.3 mL; 0.9 mL; 3.0 mL; 9.1 mL; 30.3 mL; 90.9 mL)

- Egg

9.45 g of egg powder (6.4 mg; 21.3 mg; 63.8 mg; 212.8 mg; 638.3 mg; 2127.7 mg; 6383.0 mg)

34.711 g of egg (23.4 mg; 78.1 mg; 234.4 mg; 781.3 mg; 2343.8 mg; 7812.5 mg; 23 437.5 mg)

- Wheat

5.5538 g of gluten powder (3.8 mg; 12.5 mg; 37.5 mg; 125 mg; 375 mg; 1250 mg; 3750 mg)

- Peanut

8.886 g of peanut flour (6 mg; 20 mg; 60 mg; 200 mg; 600 mg; 2000 mg; 6000 mg)

18.5126 g of peanut butter (12.5 mg; 41.7 mg; 125 mg; 416.7 mg; 1250 mg; 4166.7 mg; 12 500 mg)

This amount of food should, however, still be followed up with an age-appropriate portion of the food at the end of a negative challenge [71]. The interval between doses can be anything between 15 and 60 minutes, but the timing between each dose should be dependent on the patient's history and sufficient to allow symptoms to develop.

There are currently no specific recommendations regarding the dose or design to be used when performing food challenges to diagnose delayed symptoms, e.g. atopic dermatitis or constipation, apart from that the amount normally known to cause a reaction should be used, or a normal portion of the food [70]. This raises practical issues where the patient is a very vague historian. Another difficult issue is that some reactions only occur when the causative food is eaten in sufficient doses on consecutive days and this must be planned for when designing the food challenge. The advantage of these challenges is that the reactions are not life threatening so the whole challenge can be completed at home.

Challenge duration

For immediate symptoms, if no reaction has occurred after all doses have been consumed, the child can go home (after 1–2 hours) with instructions to incorporate that food gradually into the diet. A longer challenge period (1–4 weeks) is recommended when looking for delayed reactions [71–74].

Challenge food used

Dried, cooked or raw food, as indicated by the history, should be used in order to mimic the history as close as possible [75, 76].

Challenge location

It is recommended to perform a food challenge in hospital if there is a history of immediate reactions and/or if the patient is sensitised to the offending food. If there is the slightest concern that the child may experience an immediate or IgE mediated reaction, the challenge should be performed under professional supervision in experienced hospital units; all other challenges can be performed at home [68, 70, 71].

Considerations when performing double blind placebo controlled food challenges

Time between active and placebo challenges

When dealing with immediate symptoms, at least 2 hours, but ideally 3–4 hours, should be allowed between the active and placebo challenge. In practice, it is very difficult to perform two challenges in a child in 1 day. In the case of delayed symptoms, 1 week between the active and placebo challenge should be allowed [65, 69, 77]. The patient's history will play a major role in the final decision.

Masking of the challenge food

The challenge food should be blinded (masked) in terms of smell, flavour and texture. Ideally, the active and placebo challenges should be identical regarding taste, appearance, smell, viscosity, texture, structure and volume; blindness should also be assessed by standard tests [70, 78]. Although this is paramount in performing food challenges for research purposes, it may not be necessary when performing DBPCFC for a clinical diagnosis or when doing DBPCFC in young children.

There are a number of factors that should be taken into account when choosing a challenge vehicle or placebo:

- The fat content of the vehicle can influence the challenge outcome [79]
- The vehicle must also allow for enough challenge food to be used [70]
- Cooking, canning and roasting can have different effects on the allergenicity of different foods [80–82]. The food challenge should always conclude with consumption of a normal portion of the food, prepared according to the history to eliminate this issue [83, 84]

A variety of foods can be used for blinding. It is often helpful to use foods that are readily accepted by children such as ice cream, yoghurt, milkshake, milky puddings, fruit purée, mashed potatoes, soup, chocolate pudding, fruit juice, cocoa/carob and peppermint [75, 76]. Many commercial products such as cakes, biscuits or pastas that are free of egg, milk and wheat can be used as placebo. Finding a suitable and acceptable vehicle/placebo is particularly difficult if children suffer from multiple food hypersensitivity [76].

Capsules are not recommended to be used in DBPCFC as the challenge food bypasses the mouth. The early oral symptoms seen in some food allergic individuals will not occur, which could warn against later serious reactions when the challenge food hits the gut. Also the symptoms of OAS will be missed in older children (p. 336).

Interpretation of food challenges

The final and most important part of the challenge is the interpretation of the symptoms during the challenge [79, 85]. This is not always easy as there are some confounding effects, such as disease patterns for eczema and chronic urticaria. Presence of aeroallergens, particularly during the hay fever season, may also affect the challenge outcome [48, 86, 87].

The outcome of the food challenge should either be documented on a food challenge chart (hospital challenge) or a food and symptom diary (home reintroduction). Any symptoms at home should be verified by the study clinician if possible [2]. The final outcome of the food challenge should

be decided by the supervising doctor and dietitian involved based on the history of the child and the symptoms experienced. There are no clear guidelines regarding the point at which a challenge should be considered positive, but some advice is summarised in the PRACTALL guidance [71]. This is based on clinical expertise rather than substantiated by evidence. In addition, Koplin *et al*. [88] have published guidelines on performing OFC in children suspected of IgE mediated food allergies. Food challenge involved gradually increasing doses on day 1 in the hospital and continued ingestion of the maximum day 1 dose (one teaspoon of peanut butter or tahini paste or one whole raw egg white) on day 2 to day 7. Different criteria have been set for the outcome of food challenges. The LEAP study in the UK set the following criteria for food challenge outcomes [22]:

1. A positive food challenge is defined as:
   - one or more symptoms from the major criteria
   - two or more symptoms from the minor criteria
2. An equivocal food challenge is defined by the presence of one symptom from the minor criteria
3. A negative food challenge is defined by the absence of any symptoms listed under major or minor criteria

In addition, all symptoms should be of new onset and not due to ongoing disease and must present within 2 hours of consuming the last dose.

Major criteria are:

- confluent erythematous pruritic rash
- respiratory signs (at least one of the following): wheezing or inability to speak or stridor or dysphonia or aphonia
- ≥3 urticarial lesions
- ≥1 site of angioedema
- hypotension for age not associated with vasovagal episode
- evidence of severe abdominal pain (such as abnormal stillness or doubling over) that persists for ≥3 minutes

Minor criteria are:

- vomiting
- diarrhoea
- persistent rubbing of nose or eyes that lasts for ≥3 minutes
- persistent rhinorrhoea that lasts for ≥3 minutes
- persistent scratching that lasts for ≥3 minutes

The food challenge result is also considered positive if any of the above reactions occurred within 2 hours of ingestion of the food on days 2–7 of the challenge at home.

Reintroduction of foods for non-IgE mediated allergies, non-allergic food allergic hypersensivities and supervised challenge for FPIES

In the case of suspected non-IgE mediated symptoms or non-allergic food hypersensitivity, an elimination diet should be followed by the reintroduction of offending foods: to confirm the food-related reaction, to expand the variety foods consumed and to avoid unnecessary eliminations. The reintroduction of foods is often a very difficult step for families, especially if significant symptom relief has been experienced.

There is very limited guidance on how reintroduction should occur for non-allergic food hypersensitivity, but a pragmatic approach using the guidance from Table 15.5 may be useful. For non-IgE mediated allergies, apart from FPIES, reintroduction can take place at home. In the UK, the ladder approach (suitable only for non-IgE mediated allergies) has been well received following the publication of the MAP (Milk Allergy in Primary Care) guideline and then the iMAP milk ladder (Figure 15.4) [14, 89]. The principle of the milk ladder is based on the processing and heating of cow's milk that has an impact its allergenicity [90–94]. There is currently no data on its efficacy; however, it is easy to use at home and thought to increase the quality of life for families [92, 95]. Since the publication of the milk ladder, the Food Allergy Specialist Group (FASG) of the British Dietetic Association (BDA) has also published egg, wheat and soya ladders for use in non-IgE mediated allergies (apart from FPIES). These are available online for BDA members (https://www.bda.uk.com/specialist-groups-and-branches/food-allergy-specialist-group/diet-sheets.html).

Due to the severity of symptoms that can be experienced with FPIES, a supervised challenge is recommended for this non-IgE mediated food allergy. Current consensus is to administer the challenge food at a dose of 0.06–0.6 g, usually 0.3 g of the food protein per kilogram of body weight, in three equal doses over 30 minutes. It is recommended not to exceed a total of 3 g of protein or 10 g of total food (100 mL of liquid) for an initial feeding (which aims to approximate a serving size) and observe the patient for 4–6 hours [43].

After food challenge or food reintroduction, the food should continue to be consumed if there is no reaction or avoided (maintenance diet) if there is a reaction to the food. Despite the clear need for food introduction or challenge, some parents/caregivers may refuse to give a particular food if the child has improved a great deal when it has been eliminated. It is important to discuss this with the parents and highlight the need for a clear diagnosis and also the possible risk of deficiencies [18].

Learning points: food challenges

- *Food challenges, in particular the DBPCFC, are the gold standard for diagnosis of food allergies*
- *It is important to take a careful history before embarking on a food challenge*
- *The type of food challenge will depend on the clinical indication for the challenge and also the available clinical facilities*
- *There are different types of challenges, including open, single blind and the gold standard DBPCFC*
- *PRACTALL dosage guidelines should be used to guide dosages for common allergens, but doses are often too large in the case of other foods, e.g. fruit and vegetables*
- *Challenges at home should ideally only happen for non-IgE mediated allergies (apart from FPIES)*
- *It is important that foods are reintroduced to the diet at home, if a challenge is successful*

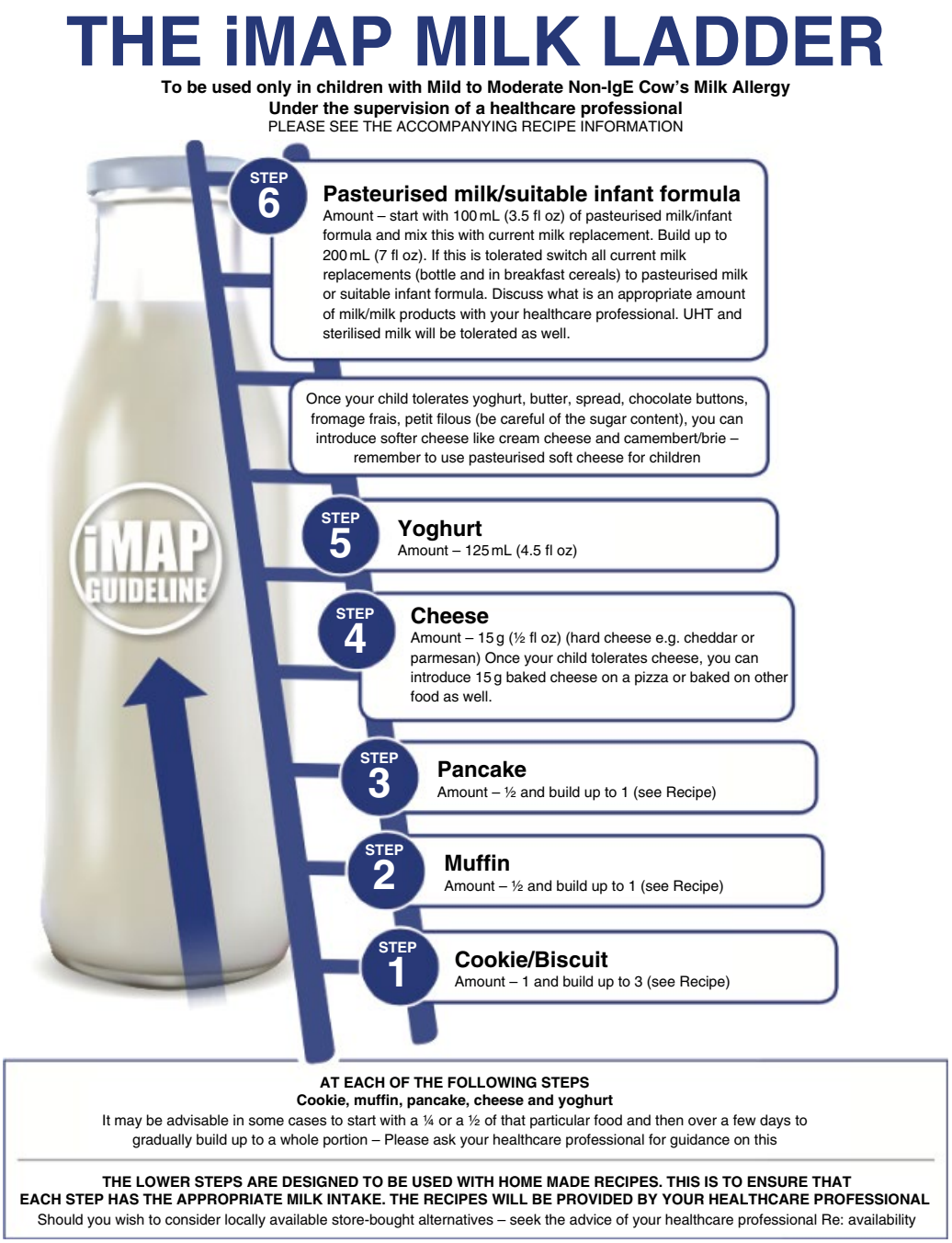

Figure 15.4 Milk ladder for reintroduction of cow's milk at home [14]. Source: Licensed under Creative Commons Attribution 4.0 International License.

Challenges for early introduction of peanut

Following the results from the LEAP study, challenge protocols for introduction of peanut at home or in a supervised setting were published by the AAAAI. Challenge doses vary between 2.0 and 3.9 g of peanut protein, and practical guidance on challenge doses using either peanut puffs, peanut butter powder or peanut butter is given in the publication [96].

Nutritional requirements and dietary management

Currently, the only treatment for any food hypersensitivity is dietary avoidance of the causative allergen. Although symptom improvement is significant with such diets, the nutritional impact must be considered.

Nutritional requirements

Although it is well known that faltering growth and, in particular, poor length/height growth is common in this population, especially in association with eczema, and that there is a higher risk of nutritional deficiencies in children with food allergies [18, 97–99], there is very little research on their requirements. Many factors specific to the allergic child may impact on nutritional requirements, as highlighted in Table 15.7. In the absence of specific guidelines, the prudent approach would be to ensure that the allergic child achieves at least the normal requirements for a child of that age (p. 9) and that any deficiencies should be corrected.

Dietary management

The principles of dietary avoidance in children with food hypersensitivity are:

- which foods need to be avoided
- suitable alternatives to these foods
- practical advice for living on a restricted diet
- dietary adequacy including optimal vitamin and mineral intake
- ensuring that oral motor milestones are achieved with age-appropriate taste and texture exposure

Which foods need to be avoided

Information on foods that may contain 'hidden' allergens, and where these allergens may be found in non-food items, is the mainstay of any advice about dietary avoidance. The European Union (EU) law on food information for consumers (Regulation No 1169/2011) came into full effect in 2016 [101]. This law specifies that pre-packed foods should provide information on the label if any of the following 14 allergens are ingredients in any amounts in the food: cereals containing gluten, such as wheat (including spelt and khorasan wheat), rye, barley and oats; crustaceans, e.g. prawns, crab, lobster and crayfish; eggs; fish; peanuts; soybeans; milk, including lactose; nuts, e.g. almonds, hazelnuts, pistachios, pecans, walnuts, Brazil nuts and macadamia nuts; celery, including celeriac; mustard; sesame seed; sulphur dioxide/sulphites, if there are more than 10 mg/kg or 10 mg/L in the finished product; lupin, including lupin seeds and flour; and molluscs, e.g. mussels, oysters, snails and squid. The information is required to be clearly visible in bold, colour, italics or capital letters.

Loose foods include all items that are not pre-packed. Foods that are wrapped on the same site as they are sold are also known as loose foods [101, 102]. Rules for declaring the 14 allergens in loosely sold foods are the following:

- Information needs to be provided about the allergens used in these foods
- Allergen information should be available in writing or by speaking to staff
- Logos or symbols can be used when accompanied by words and numbers on menus

For loosely sold foods allergen information has to be:

- easily accessible to all consumers
- accurate, consistent and verifiable

If there is a risk of a pre-packed food product being affected by allergen cross-contamination during its manufacture, the label should include one of the following statements: may contain X or not suitable for someone with X allergy. Foods with this precautionary allergen labelling

Table 15.7 Factors that may impact on nutritional requirements [18, 100].

		Possible nutritional deficiencies				
Factors	Explanation	Energy	Protein	Vitamins	Minerals	Trace elements
Elimination diet	Many foods contribute significantly to the child's diet (e.g. cow's milk)	X	X	X	X	X
Severe eczema	Increased itching and possible skin healing may increase energy/protein requirements	X	X			X
Poor sleeping pattern	Disrupted sleep may increase energy requirements	X	X			
Enteropathy/colitis	Diarrhoea and possible malabsorption of nutrients may lead to deficiencies	X	X	X	X	X
Vomiting	Excessive losses	X	X	X	X	X
Irritability/pain	Reduces food intake	X	X	X	X	X
Aversive feeding	Leads to reduced intake	X	X	X	X	X
Medication	Some medication used for treatment has side effects that may impact on nutritional requirements (e.g. corticosteroids)			X	X	

should only be used following a thorough risk assessment. Parent/caregivers should take this warning seriously and the dietitian should discuss the risk with them. The dietitian also needs to address cross-contamination issues [103].

Many manufacturers and supermarkets produce 'free-from' lists for their products. These are very useful in managing food avoidance diets, and families should be encouraged to use these to identify products that can be included in the diet.

It is important for parents/caregivers to be able to identify the sources of allergens in composite foods and to recognise the terminology that may be used for each allergen (Table 15.8). The dietitian needs to consider the nutrients that the offending foods contribute to the diet so that these can be replaced with suitable alternatives.

Suitable alternatives

It is important for dietitians to familiarise themselves with suitable alternatives for foods that must be avoided. Advice should be given on available products (e.g. peanut free confectionery, milk substitutes, egg-free cakes, wheat-free pasta) and where to find them. Products and ingredients change constantly. It is, therefore, essential that dietitians dealing with food allergy continually update themselves with new products and review existing products. This task can be made easier by joining a specialist support group where this information is shared. Dietitians should also be aware of suitable website and phone applications that can help families with the availability of suitable foods.

Food allergies, in particular cow's milk allergy, most commonly occur during the first year of life [56], when breastmilk or infant formula is the sole or main source of nutrition. The young child is particularly vulnerable to nutritional deficiencies and growth failure, so it is important that dietitians can advise parents on suitable alternatives [18].

Human milk

Breastmilk is the ideal source of nutrition and should be encouraged in all infants with food allergy, and the WHO guidelines for breastfeeding should be followed where possible [56, 105]. Occasionally, infants exhibit allergic symptoms while being exclusively breastfed. It is known that allergens, including β-lactoglobulin (a protein unique to cow's milk), egg and soya allergens, consumed by the mother can appear in breastmilk [106, 107] and breastfed infants with multiple food allergies have been described [108, 109]. In these cases, it is not recommended to stop breastfeeding

Table 15.8 Common allergens and their sources and nutrient contribution.

Allergen	Sources	Terminology	Macro- and micronutrients
Milk	Butter and most fat spreads, cheese, cow's milk, sheep and goat milk, evaporated and condensed milk, cream, ghee, yoghurt, ice creams, custard, dairy desserts and manufactured foods using milk or butter in their ingredients	Casein, caseinates, curd, lactoglobulin, lactose, milk solids, whey, buttermilk, milk sugar, whey sugar, whey syrup sweetener	Protein, energy, vitamins A, D and $B_{12,}$ riboflavin, pantothenic acid, calcium, phosphorus
Egg	Egg white and yolk, cakes, biscuits, speciality breads, egg pasta, mayonnaise	Albumin, dried egg, egg powder, egg protein, frozen egg, globulin, lecithin (E322), livetin, ovalbumin, ovomucin, ovovitellin, vitellin, pasteurised egg	Protein, vitamins A, D, E and B_{12}, riboflavin, pantothenic acid, biotin, selenium, iodine, folate
Soy	Soya sauce, soya products, meat substitutes, breads, vegetarian and vegan foods, processed meat	Soya beans, soya flour, soya protein, soya gum, soya starch, texturised (or hydrolysed) vegetable protein, soya flavouring, soya lecithin (E322)	Protein, fibre, thiamin, riboflavin, pyridoxine, folate, calcium, phosphorus, magnesium, iron, zinc
Wheat	Bread, breakfast cereals, pasta, cakes, biscuits, crackers, cold cooked meat, pies, batter, flour, semolina, couscous, bottled sauces and gravies	Bran, cereal filler, farina, starch, wheat, durum wheat, semolina, spelt, kamut, wheat bran, wheat gluten, wheat starch, wheat germ oil, hydrolysed wheat protein, triticale, bulgur wheat	Energy, thiamin, riboflavin, niacin, iron, folate (if fortified)
Nuts	Peanuts/tree nuts, nut oil, nut flour, nut butter, some sprouts, confectionery, frozen desserts, Asian dishes, nut snacks, trail mix, some rice crackers, some cereal bars, some cookies, some brownies, nut toppings on ice cream, vegetarian and vegan foods, satay sauce, some breakfast cereals, some liquors and sauces	Arachis oil and hypogaea (peanut), prunus (almond), juglans (walnut), corylus (hazelnut), peanut protein, groundnut, earth nut, monkey nut	Protein, vitamin E, niacin, magnesium, manganese, chromium; some nuts may contain a significant amount of essential fatty acids
Fish	All types of white and fatty fish, anchovy (Worcester sauce), aspic, caviar, surimi, Caesar salad, Gentleman's Relish, kedgeree, caponata, fish sauce, paella, bouillabaisse, gumbo		Protein, iodine Fish bones: calcium, phosphorus Fatty fish: omega-3 fatty acids, vitamins A and D

Source: Adapted from Venter and Meyer [100, 104].

but to suggest that the mother should avoid all suspected food allergens (p. 317), which appear to upset the infant when she eats it [108]. In very rare cases, if symptoms cannot be controlled by maternal allergen avoidance and harm to either the infant (e.g. faltering growth, rickets or other nutritional deficiencies) or the mother (excessive weight loss or vitamin/mineral deficiencies) is done, as a last resort after careful consideration with the parents, the cessation of breastfeeding may be considered. Breastfeeding mothers on exclusion diets should be reviewed by a dietitian to check the adequacy of their diets as they may need supplements, especially of calcium, vitamin D and iodine [56, 110, 111].

Formulas suitable for the management of children with cow's milk protein allergy

There are currently two definitions widely used in the EU to define products suitable for management of CMPA. The first such definition for labelling infant formulas with reduced allergenicity is arbitrarily based on a content of <1% immunoreactive protein of total nitrogen, which translates into the majority of peptides being <1.5 kDa [112]. However, there is no evidence that this threshold would prevent a clinical reaction. There has, therefore, been a drive by official bodies for hypoallergenic formulas to be tested in clinical trial using another criterion that stipulates that a formula suitable for management CMPA should be tolerated by at least 90% of children with a CMPA with a 95% confidence interval [112]. EAACI [31] is currently reviewing these guidelines, and an updated publication is expected.

Only extensively hydrolysed formulas (EHFs) [113], rice hydrolysates (currently not available in the UK) and AAF fall within either of these definitions, and dietitians should be aware that partial hydrolysates are not suitable for the treatment of CMPA [14, 38, 55, 56, 114]. In the past it was recommended that an EHF should contain a majority of peptides <1.5 kDa; however this is based on old *in vitro* data [115, 116], and studies have shown that the percentage of peptides below this threshold does not predict tolerance, and, therefore, more attention should be given to research proving tolerance as per the current EAACI definition [117, 118].

Extensively hydrolysed infant formulas

An EHF [113] is often the choice for an infant with immediate or delayed adverse reactions to cow's milk (Table 15.6). Casein hydrolysates have been successfully used for over 60 years; whey hydrolysates were introduced in the 1990s, and hydrolysates of pork and soya are also available, but rarely used for CMPA [55, 118]. All EHFs in the UK suitable for CMPA have gone through the necessary testing for growth and also tolerance, as recommended by EAACI. Over the last 5 years, there has been an increase in the use of rice hydrolysates in Europe for CMPA. Many of these formulas have now also gone through the required testing [114, 119], and Meyer *et al*. [120] found very low inorganic arsenic levels in these formulas, comparable with those in standard infant formulas.

Some question the use of hypoallergenic formulas containing lactose in children with non-IgE mediated gastrointestinal food allergies, due to the possibility of brush border damage related to inflammation. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) advises that adverse reactions to lactose in children with CMPA are not reported and states that complete avoidance of lactose may not be needed in the majority of cases [38]. A recent small cohort study has also found that secondary lactose intolerance in a non-IgE mediated population was rare [121]. Formulas suitable for CMPA with lactose may, therefore, be considered for all types of CMPA and may also be of benefit in regard to the gut microbiota [122].

Much of the literature on the use of these formulas relates to IgE mediated allergy. As far as non-IgE mediated gastrointestinal allergies are concerned, both extensively hydrolysed casein and whey formulas have been shown to be satisfactory. However, the incidence of intolerance to EHF seems to be higher (29.7%) in children with this delayed-type food allergy compared with the immediate-type (IgE mediated) cow's milk allergy (around 10%) [45, 54, 123]. Therefore, some infants may react to hydrolysed formulas. Anaphylactic reactions have been described with both casein and whey hydrolysates [54, 58, 124]. However, the majority of cow's milk allergic infants will tolerate any EHF. Luyt *et al*. [56] and Venter *et al*. [14] provide detailed discussion on cow's milk allergy and the formulas available in the UK.

Amino acid-based formulas

AAF (Table 15.6) consist of pure synthetic amino acids and have been shown to be tolerated by infants and children with both IgE and non-IgE mediated food hypersensitivity [125–127]. They are particularly useful for those infants who fail to tolerate an EHF and may be useful in some allergic infants as first-line treatment. In 2007, Hill *et al*. [128] undertook a systematic review of food allergic patients that specifically may benefit from an AAF. This systematic review has recently been updated with a new publication including more recent studies and found that in the following conditions an AAF may be considered preferable in non-breastfed children [54]:

- failure of symptom resolution with an EHF
- faltering growth, in particular if multiple systems are involved, e.g. gastrointestinal tract and skin
- anaphylaxis
- a diagnosis of EoE

The issue about which top-up formula to use for cow's milk allergic breastfed infants, if needed, remains problematic; β-lactoglobulin is detected in EHF made from cow's milk (0.84–14.5 μg/L), a similar level to that in breastmilk, and based on this an AAF would be indicated. However, this is not convincingly supported by studies; in food allergic proctocolitis [129, 130], which most commonly presents in breastfed infants, EHFs have been used with great success. Data also indicates that FPIES in breastfed children is rare and, therefore, most guidelines suggest an EHF as first formula choice.

The choice of formula remains a challenge for dietitians where the clinical need and the cost of the formula have to be weighed up. Table 15.9 summarises the current available

Table 15.9 Summary of first-choice formulas recommended by national and international guidelines.

Clinical presentation	DRACMA (2010) [55]	ESPGHAN (2012) [38]	Australian guidelines (2008) [131]	BSACI (2014) [56]	MAP and iMAP (2017) [14, 89]*
Anaphylaxis	AAF	AAF	AAF	AAF	AAF
Acute urticaria or angioedema	EHF	No specific mention, but EHF in general as first-line treatment	EHF if <6 months of age Soya if >6 months of age	EHF	EHF
Atopic eczema/ dermatitis	EHF	No specific mention, but EHF in general as first-line treatment	EHF if <6 months of age Soya if >6 months of age EHF if >6 months of age if also presenting with faltering growth	EHF, but if symptoms while exclusively breastfed, then use AAF	EHF
EoE	AAF	AAF (for EGID)	AAF	AAF	No recommendation
Gastro-oesophageal reflux disease	EHF	No specific mention but EHF in general as first-line treatment	EHF if <6 months of age Soya if >6 months of age EHF if >6 months of age if also presenting with faltering growth	EHF (unless faltering growth, then use AAF)	EHF
Cow's milk protein-induced enteropathy	EHF	AAF (complicated by growth faltering)	EHF if <6 months of age Soya if >6 months of age EHF if >6 months of age if also presenting with faltering growth	EHF (unless faltering growth then use AAF)	EHF
FPIES	EHF	AAF	EHF	AAF	No recommendation
Proctocolitis	EHF	No specific mention, but EHF in general as first-line treatment	EHF if <6 months of age Soya if >6 months of age EHF if >6 months of age if also presenting with faltering growth	EHF (unless faltering growth then use AAF)	EHF

DRACMA, Diagnosis and Rationale for Action Against Cow's Milk Allergy; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; BSACI, British Society for Allergy and Clinical Immunology; MAP, Milk Allergy in Primary Care; AAF, amino acid formula; EHF, extensively hydrolysed formula; EoE, eosinophilic oesophagitis; FPIES, food protein-induced enterocolitis syndrome; EGID, eosinophilic gastrointestinal diseases.
*iMAP guidelines only cover mild to moderate presentations of non-IgE mediated allergies, therefore excluding guidance on the more severe presentations such as EoE, FPIES and children with faltering growth.

international guidelines on the use of hypoallergenic formulas in the diagnosis and management of CMPA if breastmilk is not available. These guidelines, however, do not replace the clinical expertise of the dietitian. The problem is that there are very few randomised controlled studies directly comparing two different formulas; the studies are relatively poor quality; numbers are small; and clinical profiles of the infants included in the studies are poorly described. Current research indicates that the majority of children with CMPA will improve on an EHF. The guidelines suggest the use of an AAF as a first option only for more severe presentations of CMPA, such as a history of anaphylaxis, Heiner syndrome, EoE, faltering growth, and some of the more severe gastrointestinal and skin presentations.

Formulas based on whole soy protein isolate

Infant formulas based on whole soy protein isolate have been available without prescription for many years. In the past, soy-based formulas were used widely as an alternative to cow's milk formula in those infants with CMPA. However, in 2004 the UK Chief Medical Officer advised against the use of soy formula in infants under the age of 6 months unless there is a specific medical indication due to their high phytoestrogen content [132]. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) is reviewing more recent research in this area.

The prevalence of concomitant soy allergy in infants with CMPA differs between IgE and non-IgE mediated diseases. Klemola *et al*. and Zeiger *et al*. found that 10% and 14% of infants with IgE mediated CMPA, respectively, have concomitant soy allergy, whereas associated soy allergy in non-IgE mediated CMPA is much higher (up to 50%), especially in enterocolitis and enteropathy syndromes [133–135]. This data may, however, vary between countries, which has been shown by a review of 40 worldwide studies on IgE mediated soya allergy, finding a prevalence in allergic children ranging from 0% to 12.9% in different countries [136].

The use of soya formula in the diagnosis and management of CMPA is a highly debated topic, with clear differences between different countries and professional bodies (Table 15.8). Soya formula can be given for the treatment of CMPA in infants over the age of 6 months if it has been shown that they do not have soy allergy and they have failed to take other hypoallergenic formulas due to the taste preferences of the child or if there are strong parental preferences (e.g. following a vegan diet). Soya-containing products such as soya desserts enhance the variety in a cow's milk-free diet and can be given from 6 months of age [56, 137].

Other mammalian milks

The most commonly available other mammalian milks in the UK are sheep and goat milk, which are not suitable for infants with CMPA as their proteins can be as sensitising as cow's milk protein. Dean *et al*. have shown that there is strong cross-reactivity *in vitro* between allergens in all mammalian milks (except human milk) and DRACMA guidelines summarise further cross-reaction [55, 138]. An infant formula, therefore, based on goat milk is not suitable for the treatment of CMPA [55]. Some guidelines also hint towards camel, and donkey milk being suitable, however, there is still >50% cross-reactivity with cow's milk protein. Therefore, the introduction of these milks ideally requires the input of a suitable healthcare professional to advise whether it is safe to do and may require an OFC.

Practical advice

It is important to provide families with practical advice on how to manage their child's food allergy. This starts with how to support breastfeeding. If breastmilk is not available, or a top-up formula suitable for the management of CMPA is needed, the following hints may help with the introduction:

- The formula should be offered when the infant is hungry and thirsty
- It may sometimes be easier if the first bottles are not given by the main caregiver
- Mixing hypoallergenic formula with weaning foods may help the child to get used to the taste of the formula (e.g. in porridge)
- If the child is able to hold a bottle (usually over 6 months of age), then a baby beaker with free flow may also be useful
- Vanilla essence may be helpful to improve the taste, but care must be taken as if too much is added it may make the formula taste more bitter
- Flavourings should be avoided, but if all else fails, a milk and soy-free milkshake powder or syrup can be added (no honey is advised <1 year of age)

Parents also need information on the availability of products to suit their child's exclusion (avoidance) diet. Many supermarkets now stock a range of 'free-from' foods, which may be useful, and there are two apps that are free to download that may help in finding products free from the offending allergens: the Food Maestro App (www.foodmaestro.me/home.html) and the Spoon Guru App (www.spoon.guru/spoon-guru-news). The BDA FASG has produced diet sheets with 'free-from' foods suitable for all types of food allergies, free to be downloaded for BDA members.

Parents find recipes very useful. Some examples include cakes without egg, biscuits and cakes without wheat and gravy and sauces without wheat. A general discussion about menu planning is helpful. Advice may include ideas for weaning foods and packed lunches. Other agencies may need to be contacted, e.g. school caterers. Parents also appreciate tips on how to get a child to take a new food. For example, wheat-free products are often better accepted initially if given with other flavours, e.g. jam on bread and sauce on pasta. A caregiver other than the main caregiver is often able to persuade the child to take the new food. It is also important to discuss the management of food allergies at nursery or school and when the family travels abroad. The FASG diet sheets contain recipes; these can be freely downloaded by BDA members.

Dietary supplements

Whenever a food is removed from the diet, there is the likelihood that the diet will no longer meet nutritional requirements (Table 15.8); the more foods that are eliminated the greater the risk of a deficiency. Infants who consume less than 600–700 mL of hypoallergenic formula, depending on which formula is used, and all infants who are fully breastfed will require a multivitamin preparation containing, in particular, vitamins A and D [139]. In addition, a calcium supplement will be required in children with CMPA who do not consume sufficient formula or calcium-containing foods. Family doctors are generally happy to prescribe supplements, but sometimes an over-the-counter supplement may be more readily accepted, especially in older children. Vitamins and minerals must be free from the offending allergens. Vitamin and mineral supplements are often forgotten in infants less than 6 months of age; if dietary consumption is suboptimal and maternal dietary intake has not been inadequate or there is a known deficiency during pregnancy and lactation, then other vitamins (apart from vitamin D) and minerals may be required. It is also important to consider iron, zinc and iodine status, in particular if gut inflammation is present and cow's milk is avoided; cow's milk is a primary source of iodine in the UK diet [110, 140, 141].

A case study to illustrate the management of a child with food allergy is given in Table 15.10.

Learning points: dietary management of food allergy

- *Breastfeeding should be supported as far as possible in children with CMPA*
- *The elimination of foods increases the risk for both growth faltering and vitamin and mineral deficiencies*
- *The presence of co-morbidities (e.g. eczema) increases the risk in particular for length/height growth failure*
- *Feeding difficulties are common in children with food allergies*
- *For children with CMPA, most will improve on an EHF, but for those with the more severe forms of allergy (including EoE, anaphylaxis, multiple system involvement and faltering growth), an AAF is indicated*
- *None of the mammalian milks are suitable alternatives for children with CMPA*
- *Parents need to have advice on suitable alternatives and, if a formula is required, how to get the child to accept it*

Monitoring

It is essential that children following an exclusion diet are followed up regularly. Children's diets vary enormously as they get older and nutritional requirements also change. It is important to ensure they maintain normal growth. There may also be advances in knowledge that may affect treatment strategies, and it is also important to ensure that as the child gets older, they themselves understand their diet.

The key aspect of monitoring childhood food allergies is establishing when the child has outgrown their allergies or when they have developed tolerance to certain forms of the food, e.g. baked milk/egg [142]. Food challenges or reintroduction of food at home forms an important part of this process.

The dietary management of food hypersensitivity consists primarily of educating patients and their families so they can avoid the causative food while eating tolerated foods and still meeting all nutritional requirements. No dietary manipulation is easy, so it is the role of the dietitian to not only give information on how to avoid the causative food but also how to make the resultant diet as palatable and varied as possible. Before any advice is given, it is essential to consider how strict the diet needs to be. If a child tolerates a food (even with a positive SPT/specific IgE) without any reaction, or if they can tolerated the baked version of the food, it is important not to stop these foods, but to encourage them to keep this food in the diet. On the other hand, when reactions occur when exposed to tiny doses advice on complete avoidance is essential.

Natural progression

Food allergy is most commonly acquired during the first year of life with a peak incidence between 2.2% and 5.5% during the first 2 years of life in the UK [143, 144]. The prevalence falls to 2.3% in teenagers and then plateaus at 1%–2% through adulthood [145]. These figures may be higher in patients seen in tertiary centres [146]. The majority of reactions to foods in infants and young children are to milk, egg, nuts, soy, fish and wheat [147]; however in adulthood the most common food allergens include hazelnut, apple, peach and shrimp [148]. Although the tendency to develop allergies clearly has a genetic component, it is strongly influenced by environment and lifestyle factors. These include air pollution, environmental tobacco smoke exposure, maternal and infant nutrition, environmental allergen exposure, family size, infections and hygiene [149].

It has long been established that most children grow out of their allergies, in particular milk and egg allergy. However, recent studies performed in tertiary centres have shown that some of these allergies are more persistent and children outgrow them later in life than previously thought. Approximately half of egg allergic children will be tolerant by the age of 3 years and 66% by 5 years of age [150]. For milk, about 80%–90% of children may become tolerant according to population-based studies [146, 151]. It is commonly thought that peanut allergy does not resolve although Skolnick *et al*. [152] have shown that it may be outgrown in 21.5% of patients. Tree nut, fish and shellfish allergies tend to develop in older children and are unlikely to be outgrown.

Although many children grow out of their initial food allergies, it is evident that allergic disorders change and progress from eczema and food allergy in early childhood to asthma and rhinitis related to pollen allergy in later

Table 15.10 Case study: management of food allergy in a young child.

Presentation

A 3-month-old baby girl presented with chronic diarrhoea and mild to moderate eczema across her body and face.
Weight = 25th centile, Length = 50th centile
She was fed on normal infant formula from birth.

Family history: Mother has asthma and father has hay fever. Born at full term, normal delivery.

The infant was seen by a paediatrician, an allergy nurse and a paediatric allergy dietitian, who provided advice regarding skin care and changed her formula to an EHF [113], in line with current guidelines. Skin prick tests (SPTs) were not conducted at this stage, based on her current symptoms, which suggested a non-IgE mediated allergy. Written and verbal advice was given on the avoidance of cow's milk and soya, and the introduction of complementary food was advised from around 6 months of age.

Follow-up

Returned to the allergy clinic at age 6 months; her diarrhoea had resolved and her eczema had cleared, with only the occasional flare.
On examination, she was found to be well and thriving, with a normal physical examination.
Weight = 25th centile, Length = 50th centile
Full blood count, clotting profile and liver function were all within the normal range.

Because she was weaning, SPTs were performed to determine which foods could be safely introduced (see table below). The SPT for milk was positive, which suggested that hypersensitivity to cow's milk may have played a role in her eczema flares in the past. Together with her improved symptoms since changing to EHF, this allowed a diagnosis of CMPA to be made. A second, smaller wheal suggested a potential allergy to egg. In consultation with the paediatrician and dietitian, the baby's mother was advised to use milk and egg-free weaning foods, given recipes and website addresses. An egg challenge was planned to assess tolerance. It was also recommended that all other allergenic foods should be introduced one at a time, with the precautionary exclusion of soya, because infants with non-IgE mediated CMPA commonly also have a soy allergy [45]. In addition, the baby's formula was changed to a follow-on EHF, which contains more calcium and is, therefore, suited to babies >6 months of age.

Skin prick tests: results at ages 6 months and 12 months.

Test	Wheal size at 6 months (mm)†	Wheal size at 12 months (mm)†
Milk	3	1
Egg	2	1
Wheat	0	0
Soya	0	0
Peanut	0	0
Positive control	*3*	*4*
Negative control	*0*	*0*

†SPT are considered positive if the wheal is ≥3 mm larger than the negative control; for further information, see Skypala [2].

At age 9 months
Weight = 50th centile, Length = 50th centile
Thriving. Eczema was under control and the diarrhoea had not returned. She was feeding a follow-on EHF and solid foods, excluding milk, egg and soy. An oral challenge with one boiled egg was performed in hospital, with a negative result. Therefore, it was recommended that she should be given a well-cooked scrambled egg at home the next morning, returning to the children's ward if symptoms reappeared.

At age 12 months
Weight = 50th centile, Length = 50th centile
Thriving. Eating a varied diet and consuming 450–500 mL EHF per day with additional supplement of vitamins A and D and consuming calcium-enriched coconut yoghurt. SPT showed negative results for cow's milk and soya, so oral challenges with these foods were given. The soya reintroduction over a period of a week at home was negative. However, the cow's milk challenge, conducted in hospital, resulted in an immediate flare of her eczema, with diarrhoea the following morning. It was recommended that soya yoghurts and puddings could be introduced to increase variety in her diet, but she should continue to avoid all milk products.

2 years

SPT for milk produced a 2 mm wheal. On analysing this toddler's diet, her nutritional intake was found to be adequate. As a result, it was recommended that the milk-free diet was continued and calcium-enriched soy milk could be introduced.

Four months later, this girl accidentally drank a cup of milk at nursery, without an adverse reaction. Consequently, oral challenge was given in hospital, which continued at home for a week. As she showed no allergic symptoms, the mother was advised that milk products could be gradually reintroduced. Subsequently, she occasionally experienced eczematous symptoms, which were treated with emollients, antihistamines and a little hydrocortisone.

3 years

SPTs were negative for all allergens tested and she was tolerating all foods.

childhood. This phenomenon is referred to as the 'allergic march' [153, 154]. The 'allergic march' has been well established for IgE mediated allergy, but it is only recently that a non-IgE mediated 'march' has been hypothesised. Also starting with eczema and food allergies and migrating to the same atopic diseases with age, there is an increased risk of developing functional gastrointestinal disorders and extra-intestinal manifestations when getting older in the non-IgE mediated 'march' [16].

Pollen food syndrome (oral allergy syndrome)

OAS describes any oral symptoms following oral exposure to an allergen, while PFS (also known as pollen food syndrome) is the clinical entity where symptoms, predominantly OAS, occur following exposure to plant foods (fruit and vegetables) that contain allergens similar to pollen such as grass and trees. These reactions are occasionally triggered also by foods cross-reacting with latex [155]. Such cross-reactivity does not always indicate that avoidance of all these foods is necessary, with clinical history being indicative of the requirement to avoid certain foods. These mucosal reactions are normally to raw fruit, so advice regarding cooking/microwaving the food or trying tinned varieties can often result in the child being able to eat the food. This advice is important in helping the child maintain their fruit/vegetable intake. In the UK, Ludman *et al*. recently reported a point prevalence for physician diagnosed PFS of 48% in a selected cohort of 54 children with seasonal allergic rhinitis attending a specialist allergy clinic, the prevalence increasing with age [48].

Transition to adult care

Although many children will outgrow their allergies, some will continue to have their allergies into adulthood, and some may develop new food hypersensitivities. The transitional stage, starting during teenage years, is the time when children will have to take responsibility of their own management. It is important to realise that teenagers with food allergies want to eat the same foods as their peers, often leading to risk-taking behaviour [156].A recent study by Monks *et al*. [157] found that the majority of teenagers reported eating foods labelled 'may contain' an allergen as they perceive that the foods are actually very unlikely to contain an allergen. Many of the teenagers only carried their self-injectable adrenaline (required for anaphylactic patients who accidentally consume an offending allergen) when they thought they were particularly at risk of a reaction; some did not know how to treat themselves if a reaction should occur. A recent systematic review looking into strategies that improve transition between paediatric and adult care in children with chronic illness found four broad categories that improved transition: patient-directed intervention (educational programmes, skills training), staff intervention (named transition coordinators), joint clinics run by paediatric and adult physicians and changes to service delivery (separate young adult clinics, out of hours phone support, enhanced follow-up). All these interventions have been shown to improve care [158].

Problems with dietary management in food hypersensitivity

The avoidance of any foods/food groups in a child's diet can increase the risk of nutritional deficiencies [18]. It is, therefore, important to avoid unnecessary food eliminations. However, there may be parents who feel that diet plays a role in their child's illness, and they should have the opportunity to discuss in an unbiased fashion the possibilities of dietary treatment and, where appropriate, have the opportunity to trial an exclusion diet. A lack of sympathetic approach may lead to self-imposed diets (likely to be inadequate) or self-referral to an unqualified practitioner. Whatever the prejudices of the professionals involved, the question of diet must be discussed as the child may be on an inadequate and inappropriate diet [18]. Although some children may be on unhelpful diets, others benefit dramatically from the correct exclusion diet. The role of the dietitian is to assist in maintaining helpful diets and broaden the diet as much as possible. It is equally important to encourage people to abandon exclusion diets where they confer no benefit. An open-minded approach is necessary. Occasionally, parents will not take advice, and in exceptional cases, the dietary restrictions imposed by the parent on the child may be regarded as a form of child abuse.

Controversial elimination diets

Migraine and epilepsy

Cheese, chocolate and red wine sometimes provoke migraine, allegedly owing to the presence of a pharmacologically active ingredient, tyramine. Children with severe migraine who have failed to benefit from avoidance of cheese and chocolate have been shown to respond to a few foods diet, and the most common provoking foods on food reintroduction were those that are implicated in food hypersensitivity in general [159, 160]. When migraine attacks are less than one per week, it is difficult to use a diet approach. If symptoms are infrequent, 3 weeks of a few foods diet would not be long enough to assess change in rate of attacks, and the reintroduction phase would be very muddled. However, for children with severe frequent migraine who have not responded to medication, a diet trial is a worthwhile procedure. Sometimes children with severe migraine have other symptoms and epilepsy may be one of these. A minority of children with epilepsy who also have migraine respond to dietary elimination, whereas children with epilepsy alone do not [161]. As with migraine, the diet approach cannot be tried unless seizures are frequent. A trial of diet for

such children who have not responded to conventional treatment is worth considering.

Attention deficit hyperactivity disorder

The question of diet and ADHD is very controversial. In 1975 Feingold, an American allergist, claimed that hyperactive children would benefit from avoiding foods containing salicylates together with artificial flavours and colours. Later, food preservatives were also excluded. The results of studies aimed at testing Feingold's hypothesis indicated that only a few hyperactive children responded to the elimination of food additives from their diets. Problems with methodology and interpretation of these studies have been discussed by Taylor [162]. Five studies have looked at the relationship between food (not just additives) and behaviour [163]. More recently, McCann *et al*. [164] performed a double-blind randomised controlled study using two additive mixtures and found that artificial colours or a sodium benzoate preservative (or both) in the diet resulted in increased hyperactivity in 3-year-old and 8- to 9-year-old children in the general population. At the time of publishing this study, the exact mechanism of worsening ADHD through food additives was not known. Since then, the same group has discussed how food additives can exacerbate ADHD symptoms and cause non-IgE dependent histamine release from circulating basophils. The fact that some children reacted worse than others was found to be related to specific genes influencing the action of histamine, which may explain the inconsistency between previous studies [165].

From a practical dietetic point of view, food colourings and sodium benzoate are found in processed foods, often with high sugar and salt content. Parents of a child with ADHD should in the first instance be advised to ensure a healthy balanced dietary intake. For children with severe ADHD whose parents wish to explore the dietary approach (free from colourings and sodium benzoate), they should be given the opportunity to do so with the support of a dietitian; otherwise they will be tempted to experiment with a diet unsupervised, which may lead to nutritional deficiencies. Other treatments such as behaviour modification or stimulant medication may be more effective than dietary management, although some children may end up on a combination of these treatments.

Vasoactive amines and intolerance reactions

Skypala *et al*. discussed the role of food chemicals in possible adverse reactions and concluded that there is limited and mostly outdated evidence for the removal of food chemicals (either added or natural) in the management of suspected adverse reactions to foods, e.g. migraine or chronic urticaria. Foods should only be excluded for a limited period of time, followed by reintroduction to confirm that these foods/chemicals are triggering any reactions. If foods are being eliminated for a longer period of time, a dietitian should be involved to ensure that the diet is nutritionally adequate and take the individual's eating habits into account [21].

Future research needs and unanswered questions

Management of food allergies

With an increase of our understanding of how nutrition impacts on the immune system and tolerance development, questions increasingly arise regarding manipulation of the gut microbiome; the role of particular nutrients, e.g. omega-3 fatty acids; food components such as advanced glycation end products; and diet diversity to increase tolerance development. There is currently no particularly evidence-based advice that can be given to patients, but these are certainly areas of nutrition that provide hope for resolution of food allergies [100].

Food allergy treatment

The use of oral immunotherapy, sublingual immunotherapy, epicutaneous immunotherapy and biologics to induce tolerance to food allergens are currently investigated. However, even though increased threshold levels are seen, sustained unresponsiveness is not guaranteed with any of these treatment modalities, and a number of side effects (including anaphylaxis) are often seen. Allergists may, however, implement these in the allergy clinic based on their level of expertise and confidence in a particular treatment regimen [166].

Prevention of food allergies

Prevention strategies for food allergy are discussed in Chapter 16.

The gut microbiome and probiotics

The microbial diversity and species abundance in children with food allergies have received significant attention in the last 5 years. Studies have shown there to be a difference between children sensitised to food allergens [167], those with clinical CMPA [168], those who remain allergic, and those who develop tolerance [169]. However, we are far from being able to define what optimal gut microbial diversity means and identifying which bacterial strains are of particular importance in reducing symptom severity and induce tolerance [169].

A probiotic is defined as "an oral supplement or a food product that contains a sufficient number of viable microorganisms to alter the microflora of the host and has the

potential for beneficial health effects" [170]. Two publications [171, 172] indicated that a probiotic *Lactobacillus rhamnosus GG* added to a casein-based EHF increased the development of tolerance in children with IgE mediated CMPA at 1 and 2 years of age. Follow-up of this population has indicated also a reduction of allergic manifestations (eczema and asthma) [173]. Three studies, including the strains *L. rhamnosus GG*, *L. casei CRL431* and *Bifidobacterium lactis Bb-12*, have similar findings to the studies on IgE mediated allergies, with increased cow's milk tolerance acquisition in non-IgE mediated CMPA [172, 174, 175].

In terms of other CMPA-related symptoms, one study showed that *L. rhamnosus GG* added to casein-based EHF reduced the occurrence of severe urticaria and any CMPA-related symptoms, but not asthma [172]. Three studies reported severity of eczema measured with a SCORAD (SCORing Atopic Dermatitis) scale. The differences between groups were on average small (1–4 points) and are unlikely to be clinically important [174–176].

Prebiotics

'Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon, and thus attempt to improve host health' [177]. There is currently no data regarding the use of prebiotics for the treatment of food allergies.

Synbiotics

'Combining the rationale of pro- and prebiotics, the concept of synbiotics is proposed to characterise some foods with interesting nutritional properties that make these compounds candidates for classification as health-enhancing functional food ingredients' [178].

Studies have been published using a specific synbiotic blend of fructo-oligosaccharides and *Bifidobacterium breve M-16V* in an AAF. Burks *et al*. [63] found that this formula was well tolerated and reduced allergic manifestations in the same way as the control AAF and there were no statistically significant differences in adverse effects between groups. This was followed by a study on the microbiota in children with non-IgE mediated CMPA by Candy *et al*. [125], which found no statistically significant differences in symptom improvement between the children on the synbiotic AAF and the standard AAF, but the synbiotic group had statistically higher counts of bifidobacteria and lower counts of *Clostridium coccoides* and *Eubacterium rectale*. Data regarding tolerance development has not been published.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

16 Prevention of Food Allergy

Kate Grimshaw

Introduction

Allergic diseases, such as asthma, rhinitis, eczema and food allergies, are rising globally [1–4]. Within this increased prevalence, incidents of food-related anaphylaxis are also increasing, adding to the overall public health burden related to food allergy, particularly in urbanised countries [5]. Food allergy, let alone other manifestations of allergy, has significant individual, household and societal costs [6, 7]. In the UK, allergic disease accounts for 6% of general practice consultations and 10% of the prescribing budget [8]. Add to this the impact allergic disease has on quality of life of both sufferers and caregivers [9–11] and that there is currently no cure, it is natural that attention turns to interventions targeting disease prevention.

Allergic disorders change over time, progressing from eczema and food allergy in infancy and early childhood to asthma, rhinitis and inhalant allergy in older childhood, adolescence and adulthood. This is referred to as the 'allergic march' (or atopic march) [12] and usually starts with the development of atopic dermatitis, which peaks in prevalence within the first 2 years of life [12]. Of the children who develop atopic dermatitis, many, if not most, develop the disease within the first 6 months of life [12–14]. The age at which food allergies present varies depending upon the allergen; allergies to hen's egg and cow's milk generally develop within the first year of life, whereas allergies to wheat, soy and peanut tend to develop later in childhood [15]. Within the allergic march, eczema and food allergy may be outgrown or can persist, resulting in individuals who 'collect' allergic conditions as they age.

It is well established that early life factors influence the development of all atopic disease, including food allergy [16], with research showing that events taking place during pregnancy and foetal development play a key role in determining whether an infant will develop allergic disease [17–21]. The infant's immune system first meets food allergens *in utero* [17] and continues to be exposed after birth via breastmilk [22] and then again when solids are introduced into the diet. It is unclear which, if not all, of these exposure time points are important in initiating the allergic march. This is why prevention strategies tend to focus on pregnancy and the first year of life [18].

Allergen avoidance

As knowledge in the field of immunology has developed, it has become clear that exposure to food allergens early in an infant's immunological development is important in food allergy initiation and that this exposure could be *in utero* or during breastfeeding, as well as directly from the infant's diet. Consequently, maternal allergen avoidance during pregnancy and lactation (alongside delayed allergen introduction into the child's diet) became the primary strategy for allergy prevention in the 1980s and 1990s. A number of randomised controlled trials (RCTs) to investigate this hypothesis were carried out [23–26], accompanied by national and regional guidelines supporting the concept [27, 28].

Early this century, research suggested that acquiring tolerance to foreign (food) proteins was an active rather than a passive process [29, 30]. Therefore, delaying the introduction of allergenic foods into the diet may not protect against sensitisation or allergic disease [31–33]. This meant that avoidance as an allergy prevention strategy was questioned. Additionally, newer publications from observational birth cohort studies [34–37] and a subsequent systematic review [38] suggested evidence for recommending avoidance strategies in pregnancy and lactation was lacking and delaying the introduction of solid foods did not

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

appear to protect against food allergy. Consequently, the latest recommendation for allergy prevention by the European Academy of Allergy and Clinical Immunology (EAACI) does not support avoidance as an allergy prevention strategy during pregnancy, lactation or complementary feeding [18]. The American Academy of Pediatrics (AAP) [39], the Australasian Society of Clinical Immunology and Allergy (ASCIA) [40] and other national bodies [41, 42] have similar views.

Breastfeeding and the development of allergic disease

Breastmilk is thought to play an important role in the development of oral tolerance as there are a number of components in breastmilk that are important in protecting the infant from microbial/antigen attack [43]. Some of these factors initiate the innate immune response, but some are closely involved in the development of the infant's adaptive immune system (p. 315). Immunological factors in breastmilk consist of maternal immunoglobulins, oligosaccharides, cytokines, glycoproteins, long chain polyunsaturated fatty acids (LCPUFAs), lysozyme, nucleotides and complement. Many of these are thought to have a role in the development of oral tolerance, in particular transforming growth factor beta (TGF-β) [44, 45], interleukin-12 (IL-12) [46, 47] and soluble cluster of differentiation 14 (CD14) [48]. Additionally, secretory IgA in breastmilk is thought to shield the breastfed infant's gut-associated lymphoid tissue from dietary allergens, thereby reducing local immune stimulation and contributing to the establishment of oral tolerance [22].

However, the role of breastmilk in allergy development remains unclear with studies showing protection, no effect and even increased risk. This has been explained by the fact that the levels of nutritive and bioactive factors in breastmilk vary according to the nutritional and atopic status of the mother [43, 48, 49]. When levels of cytokines in the milk are taken into account, then a relationship is seen [50]. Due to these findings and the fact that a number of RCTs in high risk infants investigating the effect of different dietary allergy prevention programmes during breastfeeding [51, 52] or pregnancy and breastfeeding [26, 53, 54] found no real benefit, maternal dietary intervention during lactation to reduce allergy risk is no longer recommended [18, 39, 55].

Another explanation for the apparently conflicting findings of the role of breastmilk on allergy development is that the immunomodulatory effect of breastmilk is only apparent when the infant's immune system is exposed to a food at the same time as breastmilk [56–58]. This supports the WHO recommendation that introduction of solid foods should ideally take place alongside continued breastfeeding [59].

Despite these conflicting findings, breastfeeding is recommended for all infants due to its nutritional, immunological and psychological benefits, and it should ideally be continued while allergenic solids are introduced to the infant's diet [18, 40, 58].

Formula feeding

It has long been agreed that feeding with a whole protein infant formula compared with breastfeeding increases the risk of the child developing allergic disease [60]. This is because in newborns, the mucosal barrier is immature and large quantities of macromolecules cross the epithelium into the systemic circulation to be encountered by the immune system.

Hydrolysed protein infant formulas

There have been a number of studies examining the merits of hydrolysed protein infant formulas as a primary prevention for allergic disease. Intervention studies in high risk infants who are not breastfed have compared both partially and extensively hydrolysed cow's milk formulas with formulas based on intact (whole) cow's milk protein. In two studies, a protective effect of hydrolysed infant formulas was found [61, 62], while in three other studies no difference was seen [63–65]. The German Infant Nutritional Intervention (GINI) study examined three different hydrolysed infant formulas and standard infant formula, comparing different allergy outcomes between the groups. Both the extensively hydrolysed casein formula and partially hydrolysed whey formula were shown to have a preventative effect on both physician diagnosis of allergic manifestation and atopic dermatitis. Inexplicably, this was not found for the extensively hydrolysed whey formula [66, 67]. Consequently, there is debate as to which is the best formula for allergy prevention, as reflected by differing national and professional body recommendations [18, 38–42] and individual clinicians' opinions [68, 69].

However, a recent systematic review and meta-analysis, using a rigorous approach, failed to find a beneficial effect of hypoallergenic (HA) infant formulas on food allergy [70]. The authors highlighted that many studies were at uncertain or high risk of bias; they also found evidence of publication bias. Since it appears preventive efficacy is highly dependent on the specific formula studied, the EAACI guidelines group recommended the use of HA formulas with a *documented* preventive effect for high risk children in the first 4 months of life only [18]. No studies show a preventive effect in low risk children. Soya formula should not be used for the prevention of food allergy [18, 39, 71].

Early introduction of allergenic foods

In 2001 WHO advised exclusive breastfeeding for at least 26 weeks of age [72] and this recommendation was supported by the UK Department of Health in 2003 [73]; prior to this the advice was for solids to be introduced between 4 and 6 months (but not before 17 weeks) [74]. The necessity for exclusive breastfeeding for 26 weeks has been questioned [75].

The first studies in this field in the 1980s were observational. Fergusson *et al*. looked at both the timing and rate of introduction of solids into an infant diet with the later development of eczema at 2 years of age [76] and found that solid food introduction before 4 months of age and the number of foods introduced were associated with an increased

incidence of physician-reported eczema. This association persisted to 10 years of age [77]. Kajosaari and Saarinen compared the early introduction of allergenic foods with introduction after 6 months of age and showed no differences in the prevalence of food allergy, either in the first year of life [78] or at age 5 years [79]. A number of similar studies followed, and a systematic review looking at complementary feeding before 4 months of age found few data linking early solid feeding and allergic conditions other than an association with early solids introduction and persistent eczema [80]. However, a recent study using data collected from prospective food diaries has shown solids introduction before 17 weeks of age to be associated with an increased risk of food allergy development [58].

This century, infant feeding data collected as part of birth cohort studies have been analysed to investigate the relationship between solid food introduction and the later development of atopy [34–37]. No study found any benefit on allergic outcome by delaying the introduction of solids, and two found an association between the delayed introduction of milk [37] and egg [81] and increased incidence of eczema and atopic sensitisation. More recently it has been suggested that children exposed to cereal grains before 6 months of age (as opposed to after 6 months of age) are protected from the development of wheat-specific immunoglobulin E (IgE) [35]. All these studies retrospectively collected feeding data, which makes the findings vulnerable to both recall bias and reverse causality, and they only demonstrate an association, not causality. Large scale RCTs are required to determine causality, and a number have reported their findings over the past few years, providing important data to the evidence base.

The first of these studies to report was the STAR (Starting Time for Allergy Reduction) study looking at the introduction of egg powder into the diet of 86 high risk infants aged 4–6 months with moderate/severe eczema [82]. Of the infants randomised to receive egg powder, 31% had an allergic reaction to the egg powder, leading to the study stopping prematurely. At 12 months of age, there was a trend towards fewer infants randomised to the egg ingestion group being diagnosed with IgE mediated food allergy (33% vs. 51%, $p = 0.11$). The next study to report was the LEAP (Learning Early About Peanut Allergy) study, which enrolled 530 high risk infants with moderate/severe eczema and/or egg allergy aged 4–11 months [83]. They demonstrated that in infants randomised to open-label peanut consumption, 1.9% had peanut allergy determined by double-blind placebo-controlled challenge at age 5 years compared with 13.7% in the control group who avoided peanuts ($p < 0.001$). Mean age of peanut introduction was 7.9 months. A follow-up to the LEAP study ('LEAP-On' Study) suggested that early introduction of peanut into the diet may induce long-term tolerance [84].

The EAT (Enquiring About Tolerance) study focused on the early introduction of 6 common food allergens into the diet of 1303 breastfed 3-month-old infants recruited from a general (not high risk) population [85]. In an intention-to-treat analysis, 7.1% of the standard introduction group and 5.6% of the early introduction group developed food allergy to one or more of the six intervention foods (peanut, egg, cow's milk, sesame, white fish and wheat) up to 3 years of age ($p = 0.32$). However, when the analysis was adjusted for adherence to early introduction, there was a statistically significant reduction in food allergy in the early introduction group (6.4% vs. 2.4%, $p = 0.03$), suggesting that introduction of sufficient amounts of allergenic foods into the infant diet from 3 to 6 months alongside continued breastfeeding may be effective in food allergy prevention. However, the poor adherence to study protocol emphasises the challenges around introducing solids into the diets of infants under 6 months of age.

Since the STAR study, further trials into the relationship of egg introduction and allergy development have reported. The Hen's Egg Allergy Prevention (HEAP) study [86] examined 383 infants aged 4–6 months randomised to receive freeze-dried egg white or placebo three times a week until 1 year of age. At 12 months, egg allergy was found in 2.1% in the active group and 0.6% in the placebo group ($p = 0.35$). Overall, this study failed to find evidence that early egg intake prevents food allergy. Comparable results emerged from the Australian Starting Time of Egg Protein (STEP) trial [87] that recruited 820 high risk infants who had no allergic symptoms and had not previously ingested egg. Infants were daily fed 0.9 g pasteurised raw egg (½ egg per week) or placebo from 4–6 to 10 months of age. No difference in egg allergy prevalence was found between the groups (7% active vs. 10.3% placebo, $p = 0.20$). Likewise, the Beating Egg Allergy Trial (BEAT) [88] found no difference in egg allergy prevalence between the active group and the placebo group (10.5% vs. 6.2%) of pasteurised egg introduction from 4 to 8 months of age in high risk infants. Overall, these findings suggest that other factors including genetic features, epigenetic modifications, nutrient intake and alterations of intestinal flora may play a pathogenic role in the development of food allergy.

Further RCTs are under way, but those that have reported have already led to changes in recommendations for the introduction of solids made by expert groups. In their report on feeding in the first year of life, the Scientific Advisory Committee on Nutrition (SACN) has advised that foods containing peanut and hen's egg can be introduced from around 6 months of age and need not be differentiated from other solid foods [89]. It adds that families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods. A joint statement from the British Society of Allergy and Clinical Immunology (BSACI) and the British Dietetic Association (BDA) builds on this advice, addressing the numerous issues associated with making feeding recommendations for allergy prevention [90]. Ideally, the statement should be read in its entirety for full understanding of all the relevant issues. However, its main recommendations are that infants in the general population should be exclusively breastfed for around the first 6 months of life with complementary foods (including allergenic foods) introduced in an age-appropriate manner from around 6 months, alongside continued breastfeeding. For high risk infants with eczema (particularly early-onset or moderate/severe eczema), egg and peanut can be introduced from 4 months, but the decision on whether this should be done under the care of the local allergy service and/or after allergy testing needs to be made on an individual basis, considering the local allergy resources available.

Dietary micronutrients

A different explanation for the observed relationship between delaying the introduction of allergenic foods and allergy development is that delayed introduction may lead to a nutrient difference in the infant diet that has an effect on allergy development. For example, two papers have reported an association between the delayed introduction of egg into an infant's diet and increased allergy risk [81, 91]. This association may not be due to the timing of egg into the diet *per se*, but the fact that delaying the introduction of egg may lead to a diet with lower levels of immunologically active nutrients, namely, vitamins A and D, zinc and selenium. Additionally, there have been reports of an association between fish introduction into an infant's diet and allergy outcome, with early introduction reducing the risk of allergic disease [92–94]. Again, this association may not be due to delaying the introduction of the allergenic food (fish) into the diet, but to a reduced intake of LCPUFAs, selenium, zinc and vitamin D, all of which have a potential role in the aetiology of food allergy [95–98].

Polyunsaturated fatty acids

Health concerns regarding the consumption of saturated fats [99] in the latter part of the twentieth century led to an increase in LCPUFA consumption (particularly n-6 LCPUFAs), and this increase has been causally linked to the increase in allergic diseases [100, 101]. This is backed by epidemiological observations [102–105] and is mechanistically explained by the fact that LCPUFAs are precursors for eicosanoid inflammatory factors including prostaglandins (PG) and leukotrienes (LT). Prostaglandins and leukotrienes such as PGE_2 and LTB_4, derived from n-6 LCPUFA (e.g. sunflower oil) via arachidonic acid (AA), strongly promote inflammatory responses and play a role in allergic sensitisation. Conversely, n-3 LCPUFAs oppose the actions of n-6 LCPUFAs, particularly with regard to eicosanoid synthesis, leading to the production of the less biologically active prostaglandins and leukotrienes such as PGE_3 and LTB_5 via eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [106]. Thus, n-3 PUFAs may protect against allergic sensitisation and allergic manifestations.

There have been a number of studies looking at maternal fish oil supplementation and food allergy/eczema-related outcomes that showed differing results, perhaps due to differing doses and types of n-3 LCPUFA given [106]. Additionally, an intervention study of salmon supplementation during pregnancy showed no significant difference between the two groups for eczema prevalence or severity, in skin prick test positivity or in various allergic manifestations [107]. While a meta-analysis of n-3 LCPUFA intake during pregnancy identified that maternal fish oil supplementation had positive outcomes for eczema and sensitisation up to 12 months in the offspring, it concluded that the effect of maternal n-3 LCPUFA intake on childhood allergies 'could not be unequivocally confirmed or rejected'. Additionally, a Cochrane review looked at eight RCTs of n-3 PUFA supplementation during pregnancy (5 trials), lactation (2 trials) or both (1 trial). The authors concluded 'there is limited evidence to support maternal n-3 LCPUFA supplementation during pregnancy and/or lactation for reducing allergic disease in children' [108]. Further intervention studies are required to identify protective effects and their persistence, but in the meantime encouraging mothers to eat the recommended two portions of oily fish a week [109] appears sensible.

Vitamins and minerals

A number of vitamins and minerals are thought to have a role in the development of allergic disease. The role of vitamin D in the development of allergy was first proposed in 1999 [110]. Since then its role has been strongly debated, and while the first papers advocated that increased vitamin D supplementation was the cause of rising allergy prevalence [111–113], others have since argued the protective effect of vitamin D [114–118]. The VITALITY trial (NCT02112734) is currently looking at the impact of infant vitamin D supplementation on food allergy prevalence at 1 year.

Vitamins C and E have also been suggested to have a role in allergy prevention. A recent review stated that although the studies that had found a positive relationship between these vitamins and allergy outcome were methodologically weak, the possible relationships warranted further investigation [95]. There are studies looking at the relationship between folate and allergic disease. Two studies have shown a positive relationship between increased folate intake and subsequent allergic disease [96, 119]. A third study looked at serum folate and total IgE levels and demonstrated an inverse association [120]. Since folate supplementation is widely advocated for pregnant women to protect against neural tube defects, further research studies have been urgently called for to investigate the relationship between maternal folate intake and allergy development [121].

'Healthy' diet

A change in diet to one that could be viewed as less healthy has been hypothesised as a reason for the observed increase in the prevalence of asthma and allergic disease since the 1970s [99, 122]. Therefore, looking at the whole diet may be a more effective way of establishing relationships between dietary intake and allergic disease. Concerning the maternal diet and allergy outcome, a meta-analysis [95] concluded that there was a (weak) protective effect of fruit and vegetable intake in the development of asthma and allergy and a weak protective effect of a 'Mediterranean' diet for asthma outcome. Additional evidence pointing to the importance of a 'full' maternal diet in allergy prevention is emerging [123, 124]. Consequently, recommending a healthy balanced maternal diet with sufficient portions of fruit, vegetable and n-3 fatty acids with no avoidance of any foods seems the sensible way forward. The benefits of a 'healthy' diet are also applicable for the infant diet. Evidence suggests that an infant diet consisting of high levels of fruits, vegetables and home-made foods is associated with less food allergy by the

age of 2 years [125]. This inverse association with processed foods has been observed elsewhere [126] and may be due to the higher microbial load of home-prepared foods compared to commercially processed foods [127] or that home-prepared fruits and vegetables are good sources of naturally occurring prebiotics. Both are thought to modify immune function [128].

Prebiotics and probiotics

Intestinal microbiota play an important role in the development of the mucosal and systemic immune system [129]. Observational studies show both quantitative and qualitative differences in gut microbiota composition between atopic and non-atopic infants, with decreased populations of beneficial bacteria (bifidobacteria, bacteroides, lactobacilli) and higher numbers of coliforms and *Staphylococcus aureus* [130] in atopic infants; since these differences already exist in the first few weeks of life, a causal relationship is suggested [131–133]. Lower consumption of prebiotics (fibre/indigestible dietary components) are suggested to lead to less favourable colonisation patterns, which may be implicated in the loss or inability to develop oral tolerance. Neonatal prebiotic supplementation trials have failed to show any effect of prebiotics on food allergy development, but have shown favourable results on other allergic outcomes such as eczema [134]. Consequently, manipulating the intestinal microflora of atopic children, using pre- and probiotics, towards a more 'non-atopic flora' could be a way to prevent allergic diseases.

There have been a number of trials to investigate the ability of probiotics to prevent allergic disease in high risk infants, but these studies have mainly focused on atopic dermatitis and not on food allergy and have conflicting results [135–139]. These findings need to be repeated in similar studies using more readily available probiotics before mothers are advised to take probiotics during pregnancy. The most up-to-date Cochrane review on the subject states that further research is needed before probiotic use can be recommended for allergy prevention [140]. However, a World Allergy Organization (WAO) systematic review has suggested using probiotics in infants at high risk of allergy due to the 'likely net benefit' from the prevention of eczema seen with their use [141]. The guideline panel did, however, acknowledge that their recommendation was supported by very low quality evidence, demonstrating a need for high quality intervention trials. There are a number of these ongoing that may provide further insight in the future. These studies will also provide information on which strains may be the most effective for allergy prevention and what dose is required as these are important factors to consider and about which there is currently very little information.

Recommendations

Although more research is needed in order to offer definitive allergy prevention advice, a number of recommendations can be made from the existing evidence base. The following recommendations are from the joint BSACI and BDA guidance for infant feeding and allergy prevention guidance for parents [90].

For all infants:

- Mothers should eat a healthy balanced diet with plenty of fruit and vegetables during pregnancy and lactation. Do not avoid any particular foods, e.g. peanuts
- Omega-3 fatty acids taken during pregnancy and lactation may help reduce the risk of eczema and allergic sensitisation. (Do not eat more than two portions of oily fish a week)
- Ideally, breastfeeding should be the sole source of nutrition until around the age of 6 months
- Standard cow's milk formula should not be given for the first 4–6 months unless the child has other forms of cow's milk in their diet
- Other infant formulas should not be given unless prescribed by your GP. They have not consistently shown to reduce the risk of allergy development
- Weaning should never commence before the age of 17 weeks and ideally not before 6 months of age. Once weaning has become established with traditional weaning foods, then the introduction of high allergenic foods can begin
- Weaning foods should ideally be introduced while an infant is still being breastfed
- All babies (including those exclusively breastfed) should receive a vitamin D supplement containing 8.5–10 μg of vitamin D
- By the age of 12 months, all the major allergenic foods, which would normally be suitable for a child of this age, should have been introduced into the diet
- Delayed weaning, beyond 6 months, could adversely affect the normal dietary and developmental milestones essential to establishing a good varied diet and may increase the risk of allergy development

Additionally for babies with moderate to severe eczema:

- It may be beneficial to introduce peanut and/or egg into the infant's diet before 6 months. Individual advice should be sought from a healthcare professional
- When allergenic foods such as wheat, egg and milk are introduced into the diet, each food category* should be introduced singly, starting with a small amount, e.g. ½ teaspoon (2.5 mL). No more than one new allergenic food group should be introduced at a time

* Food category: for example, introduce wheat as one category by giving pasta, bread and other suitable wheat-based products over a 2- to 3-day period [90].

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

17 Ketogenic Diets

Julia Ackrill, Vanessa Appleyard and Victoria Whiteley

Introduction

The ketogenic diet (KD) is a high fat low carbohydrate diet, with adequate protein content, which has been used for the treatment of severe medically refractory epilepsy since the 1920s [1].

It was designed to mimic the metabolic effects of starvation, with ketone bodies (acetoacetate and beta-hydroxybutyrate) becoming the main fuel source for the brain, following reports of the successful treatment of severe epilepsy by fasting. The diet was widely used during the 1930s but fell out of favour during the 1940s and 1950s when new anti-epileptic drugs (AEDs) became available as the diet was then thought to be too rigid and difficult compared with medication. However, over the past 15–20 years, the use of the KD has expanded considerably worldwide [2] with the increase in clinical evidence of its effectiveness.

Approximately 600 000 people in the UK have a diagnosis of epilepsy with the incidence in children being approximately 1 in 240 [3]. Around 60% will be controlled on monotherapy, usually with the first or second AED chosen, with the remaining 30%–40% being difficult to control [4]. Brodie found only 11% of patients with inadequate control on the first AED later became seizure-free. Therefore, with approximately a third of cases not responding to anti-epileptic medication [5], alternative treatments are required. The 2012 National Institute for Health and Care Excellence guidelines [6] state that children and young people with epilepsy whose seizures have not responded to appropriate AEDs should be referred to a tertiary paediatric epilepsy specialist to be considered for ketogenic diet therapy (KDT). Since then the number of patients in the UK treated with KDT for epilepsy has increased considerably. In 2010 there were 28 centres in the UK offering KDT, treating 152 patients. This increased to 39 centres, treating 754 patients in 2017, with 267 patients on waiting lists to start KDT [7].

Disorders of brain energy metabolism

KDT is recommended as the first choice of treatment for two disorders of brain energy metabolism: glucose transporter 1 deficiency syndrome (GLUT1DS) and pyruvate dehydrogenase deficiency (PDHD) [8]. The KD produces ketone bodies to bypass the metabolic defect, and they provide an alternative energy source for the brain.

Glucose transporter 1 deficiency syndrome

Glucose transporter 1 (GLUT1) is a glycoprotein that facilitates transport of glucose across the blood–brain barrier to the brain. In GLUT1DS this process is impaired, resulting in insufficient glucose supply to the brain [9]. The classic phenotype presents in infancy as early onset seizures and is often associated with a complex movement disorder and developmental delay [10]. However, GLUT1DS is now recognised as showing wide phenotypic diversity ranging from mild impairment to severe disability, with or without epilepsy [10, 11]. As the condition was only described as recently as 1991 [9], the disease course remains unclear. Epilepsy appears to diminish, but paroxysmal exertional dyskinesia (PED), which responds to KDT, has been described in adolescence and adulthood [12, 13].

It is recommended that KDT should be started early [9, 14–16] as GLUT1DS is a treatable disorder with the majority of patients treated with KDT showing a significant reduction in seizures (67% achieving seizure freedom) and reducing severity of movement disorder [11, 15], and it is further recommended that the diet should be continued until at least adolescence to meet the increasing energy demands of the developing brain [10]. It remains to be seen whether there is benefit in following the diet lifelong. It may be prudent to

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

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avoid caffeine in those affected by GLUT1DS, as it is known to down regulate GLUT1 *in vitro* [17].

Triheptanoin (C7) is an artificial ester that has been theorised as a treatment for GLUT1DS, but it is currently only being used in clinical research [18, 19]. Triheptanoin has an odd number of fatty acids, so it can provide ketone bodies that cross the blood–brain barrier and also replenish the tricarboxylic acid (TCA) cycle by providing the intermediate substrate pyruvate (a process known as anapleurosis).

Pyruvate dehydrogenase deficiency

In PDHD pyruvate cannot be metabolised into acetyl-CoA, resulting in a mitochondrial disorder with lactic acidosis, seizures and severe encephalopathy. Ketones bypass the enzyme defect providing an alternative source of acetyl-CoA and thus normalising blood lactate levels. KDT has been shown to be effective at prolonging life in PDHD and may improve neurodevelopment, especially if initiated early [20, 21]. However, as PDHD is a degenerative disorder, it is difficult to monitor effectiveness of KDT, particularly if seizures are absent. Some families may decline KDT, as in this condition KDT may be considered 'life-extending, but not improving quality of life'. The International Ketogenic Diet Study Group supports any parents making this decision for their child [8]. Weber [22] suggests it may be more appropriate to avoid excessive carbohydrate (CHO) intake in this condition, rather than following a true KD.

The principles of introducing and monitoring KDT in both GLUT1DS and PDHD are the same as in the population being treated for epilepsy, but consideration as to the type of KDT in these conditions may be different and is discussed later in this chapter.

Learning points: disorders of brain energy metabolism

- *KDT is first-line treatment for both GLUT1DS and PDHD – the ketone bodies produced act as an alternative energy source by bypassing the metabolic defect*
- *GLUT1DS shows wide phenotypic diversity – seizure control and improvement in PED have been demonstrated on KDT*
- *PDHD is a degenerative disorder and the benefit of KDT is not always measurable*

Mode of action of the ketogenic diet

Research into the mechanism of the KD has greatly increased; however despite this, the anti-epileptic mechanism of KDT remains an 'enigma' [23]. A few hypotheses are outlined below.

The anti-seizure effect of ketone bodies was first demonstrated by Keith in the 1930s. Acetoacetate was shown to protect against thujone-induced seizures in rabbits [24]. This was followed decades later by two studies showing *in vivo* anti-seizure effects of ketone bodies [25, 26]. However, whether ketone bodies themselves have a direct effect on seizure control or whether they are merely a marker of a shift in metabolism remains unclear.

One of the more popular hypotheses for KD action involves γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the mammalian brain. Yudkoff *et al*. proposed that ketosis induces major shifts in brain amino acid handling, favouring the production of GABA, which in turn dampens hyperexcitability throughout the brain [27]. Several studies support this possibility [28, 29].

Failure to meet energy needs may also contribute to initiation and spread of epileptic activity. Another key feature of the KD is a relative reduction in glycolysis and an increase in non-glucose sources of fuel through the oxidation of fatty acids and ketone bodies, which ultimately feed through the TCA cycle through a process known as anapleurosis. Glycolytic restriction is thought to be an important mechanism mediating the anti-seizure properties of the KD [30].

It would seem that multiple mechanisms including the production of ketone bodies, decrease of glucose and reactive oxygen species and increase in adenosine triphosphate, creatinine and GABA levels may contribute to the anti-convulsive effect of the KD [31]. Further studies on the mechanisms of action are needed and could help determine which specific seizure types or syndromes respond better to KDT [32].

Learning points: mode of action

- *The mechanism of the KD remains unknown*
- *It would seem multiple mechanisms exist that contribute to anti-convulsive effect of KDT*
- *More research is needed in this area*

Types of ketogenic diet

Several different forms of the diet have been developed. There are four specific diet protocols: the traditional classical ketogenic diet (CKD), the medium chain triglyceride (MCT) diet; the low glycaemic index treatment (LGIT) and the modified Atkins diet (MAD). Increasingly in the UK, modified versions of the KD are being used, but protocols are individual to the KD centres.

The CKD is the traditional form of the diet and is largely unchanged from the original described by Wilder in 1921 [1]. It is based on a ratio of fat to protein and CHO, usually in the range of 2:1 to 4:1, i.e. 2–4 g fat to every 1 g of protein and CHO combined. Fat is provided as long chain triglycerides (LCTs), protein is adequate for growth and CHO is minimal. Each meal needs to be carefully weighed and calculated.

The MCT diet was developed by Huttenlocher *et al*. in 1971 [33]. As MCT fat produces more ketones per gram than LCT, this allows for a more generous allowance of CHO and protein in the diet. The MCT diet has been shown to be equally effective as the CKD [34].

The LGIT was developed by Pfeifer and Thiele in 2005 [35] following observations that children on the CKD have stable blood glucose levels and that this may in part relate to the mechanism of the diet. The LGIT allows approximately 40–60 g CHO per day but regulates the type to those with a glycaemic index <50. The LGIT has been shown to be efficacious both as a first dietary treatment and as a way of liberalising the KD [36]. It is not widely used in the UK.

The MAD was originally designed and investigated at Johns Hopkins Hospital and has been shown to be similar in efficacy to the CKD [2]. It was first formally referred to as MAD in 2006 to distinguish it from the Atkins diet used for weight loss [37]. While CHO must be measured, fat, protein, calories and fluids are allowed freely, thus making meal planning easier and, therefore, more tolerable.

In the UK a broad spectrum of modified ketogenic diets (MKD) are increasingly being used in clinical practice, which lie somewhere between the CKD and the MAD [38].

Learning points: types of ketogenic diet

- *There are four specific KDT protocols: CKD, MCT, LGIT and MAD*
- *Modified ketogenic diets are increasingly being used in the UK; protocols are individualised*

Efficacy of the ketogenic diet

There is a large clinical database of evidence on the efficacy of the KD. A 2018 Cochrane review looked at the evidence for the efficacy of the KD from 11 randomised control trials (RCTs) [32]. All studies examined the efficacy of the KD in children apart from one [39], which looked at efficacy of the MAD KD in adults.

Seizure reduction rates (>50% reduction) ranged from 38% in children following the CKD and MCT KD in one study [34], up to 60% in children following MAD [40] and 85% in children following classical KD in a further study [41]. Interestingly, one study [42] found no overall difference in seizure reduction rates between those following classical KD and those following MAD.

Seizure freedom rates were found to be as high as 25% in a study of efficacy of MAD in children [42] and as high as 55% in a classical 4:1 KD study [41]. The review highlighted the paucity of evidence for the use of KDT in adults and infants and recommended that further studies are needed in these groups [32].

Indications

NICE recommends that the KD should be considered in children with complex epilepsy that has not responded to two anti-epileptic medications [6]. The 2018 International Ketogenic Diet Study Group recommendations [8] suggest that the diet should be used early in the course of treatment, in particular for conditions where at least a 20% improvement in efficacy above the norm has been consistently demonstrated, i.e. 60%–70% responder rates (Table 17.1).

Table 17.1 Conditions for which ketogenic diet has been reported to have 20% above the norm* efficacy rates [8].

Angelman syndrome
Complex 1 mitochondrial disorders
Dravet syndrome
Doose syndrome
Glucose transporter 1 deficiency syndrome (GLUT1DS)
Febrile infection-related epilepsy syndrome (FIRES)
Solely formula-fed children or infants
Infantile spasms
Ohtahara syndrome
Pyruvate dehydrogenase deficiency (PDHD)
Super-refractory status epilepticus
Tuberous sclerosis complex

*Norm being 40%–50% chance of 50% reduction in seizures.

Table 17.2 Conditions for which ketogenic diet has been reported to be effective, but with no more than 40%–50% responder rates [8].

Adenylosuccinate lyase deficiency (LSD)
CDKL5 encephalopathy
Childhood absence epilepsy
Cortical malformations
Epilepsy of infancy with migrating focal seizures
Epileptic encephalopathy with continuous spike and wave during sleep
Glycogenosis type V
Juvenile myoclonic epilepsy
Lafora body disease
Landau–Kleffner syndrome
Lennox–Gastaut syndrome
Phosphofructokinase deficiency
Rett syndrome
Subacute sclerosing panencephalitis (SSPE)

The KD is first-line treatment for two metabolic disorders: GLUT1DS and PDHD (p. 344). Other conditions for which the International Ketogenic Diet Study Group reports KD as being effective in, but with no more than 40%–50% responder rates, are shown in Table 17.2.

Learning points: indications

- *The KD should be considered in children with complex epilepsy that has not responded to two anti-epileptic medications*
- *The KD is first-line treatment for two metabolic disorders: GLUT1DS and PDHD*

Contraindications and pre-diet screening

A pre-diet clinic assessment with a consultant neurologist is essential to establish that a diagnosis of epilepsy has been made and if it has been optimally treated to date, including

Table 17.3 Disorders where ketogenic diet is contraindicated [8].

Carnitine deficiency (primary)
Carnitine palmitoyltransferase (CPT) or II deficiency
Carnitine translocase deficiency
Beta-oxidation defects
Medium chain acyl dehydrogenase deficiency (MCAD)
Long chain acyl dehydrogenase deficiency (LCAD)
Short chain acyl dehydrogenase deficiency (SCAD)
Long chain 3-hydroxyacyl-CoA deficiency
Pyruvate carboxylase deficiency
Porphyria

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Table 17.4 Baseline laboratory investigations [8].

Complete blood count with platelets
Electrolytes including serum bicarbonate, total protein and calcium
Serum liver and kidney tests including albumin, urea and creatinine
Fasting lipid profile
Serum acyl carnitine profile
Vitamin D
Urine organic acids (if diagnosis unclear)
Serum amino acids (if diagnosis unclear)

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consideration of other treatments such as epilepsy surgery or vagal nerve stimulation.

The KD is contraindicated in several specific disorders (Table 17.3). KDT uses fat as the primary fuel source rather than CHO. Therefore, if a child with a disorder of fat metabolism is placed on a KD or fasted, it could result in a devastating metabolic crisis. As such, it is essential that these conditions are screened for prior to starting KDT.

It is important not only to rule out these metabolic conditions but also to screen for other complicating factors, which may require closer monitoring or consideration. These include liver disease, severe gastro-oesophageal reflux (GOR), familial hyperlipidaemia, review of medications (e.g. diuretics or medications that increase the risk of acidosis), constipation, cardiomyopathy, kidney stones and poor nutritional status. It is also important to optimise clinical management prior to commencing KDT. For example, constipation and GOR are common side effects of KDT; therefore, reviewing management prior to commencing KDT will help to minimise these adverse effects and, thus, optimise KDT. It is particularly important to maintain a regular bowel habit as constipation can cause seizure activity to increase [43].

A list of pre-diet screening investigations is listed in Table 17.4.

The International Ketogenic Study Group recommends that blood tests should be done every 3 months during the first year on KD and then every 6–12 months thereafter and should include at least full blood count with platelets, liver and renal profiles, fasting lipid profile and serum calcium, vitamin D and magnesium levels. Other tests often carried out include serum selenium and carnitine profiles and urinary calcium and creatinine.

Learning point: contraindications

- *Pre-diet screening, including baseline bloods, is essential to rule out pre-existing metabolic conditions and to uncover potential complicating factors*

Nutritional assessment and considerations

A detailed nutritional assessment is essential prior to commencing KDT to assess suitability, nutritional status and requirements and also to assess which type of KDT is most appropriate. Table 17.5 shows the factors to consider in pre-diet dietetic assessment.

Energy requirements

A detailed food diary together with growth history is necessary to estimate energy requirements, particularly for those on CKD, which may differ from those recommended for healthy children of the same age. Energy requirements for children with neurological disabilities are disease specific and vary with the severity of their disability as well as their mobility, the presence of feeding difficulties and the degree of altered metabolism.

Calories have historically been restricted to 80%–90% of the daily recommendations for age; however, this has not been proven to be beneficial, and most centres do not routinely calorie restrict [8]. The prescription should be regularly monitored and adjusted based on evaluation of growth, changes in level of activity, ketosis and seizure control, e.g. if seizure activity decreases mobility may increase and, therefore, energy requirements may increase.

Protein requirements

Adequate provision of dietary protein, vitamins and minerals is mandatory when dietary intake is modified to obtain the desired growth rate [44]. Providing a minimum protein intake

Table 17.5 Factors to consider in pre-diet dietetic assessment.

3–4 day food diary/enteral feeding regimen if tube fed
Weight, height, BMI and growth history
Head circumference in infants
Mobility
Food allergy/intolerance
Food preferences
Behavioural feeding difficulties
Swallowing difficulties/texture of diet
Fluid intake/thickened fluids – consider carbohydrate content of thickeners and swap to suitable alternative where possible
History of GOR
Constipation

BMI, body mass index; GOR, gastro-oesophageal reflux.

of 1 g per kg body weight on KD has been shown to maintain nitrogen equilibrium and allow for growth [45]. However, rapidly growing younger children may require higher amounts, whereas older children may not need as much. Protein requirements should be based on safe levels for growth. WHO/FAO/UNU has published minimal safe levels of protein intake [46] (Table 28.48).

Fluid

Historically fluid has been restricted; however, this is no longer deemed to be necessary [47]. Normal fluid requirements should be encouraged, and if intakes are low on pre-diet assessment, intake should be increased to help minimise the risk of renal stones developing [47] and also help in the prevention and management of constipation.

Food allergy and restrictions

In the case of food allergy, it is first important to ensure the correct diagnosis has been made and that the food does indeed need to be excluded. The KD can be adjusted to accommodate dietary restrictions and allergies; however, it needs to be assessed case by case as further dietary restriction on top of an already restricted diet may make the KD impractical.

Feeding difficulties

Behavioural feeding problems such as food refusal, selective eating and physical feeding difficulties including difficulties chewing and swallowing, increased aspiration risk and prolonged feeding times are commonly found in children with neurological disability. In the authors' experience, it is important these issues are identified and the appropriate treatment/referral made before the KD is initiated; if enteral feeding is required, this should be established before KDT is commenced.

Learning points: nutritional considerations

- *A nutritional assessment is essential prior to commencing KDT*
- *Feeding difficulties should be identified, and appropriate treatment/referral made before initiating KDT*
- *Calorie and fluid restriction is not necessary*
- *Protein requirements should be based on safe levels for growth*
- *The KD prescription should be regularly reviewed*

Parental expectations and follow-up

Parental expectation should be discussed in advance regarding not only seizure reduction but also possible medication reduction and cognitive improvement [48]. It is important to assess parents' and caregivers' commitment to the diet and that they are aware from the outset what is involved in terms of providing the diet, monitoring, side effects, length of trial and follow-up. It is recommended that children should be reviewed after 1 month on KD and that the diet should be followed for at least a 3-month period before considering whether it is efficacious or whether the diet should be discontinued [8]. If deemed efficacious at the end of the 3 month trial, there should be regular review of benefit, tolerability and side effects at clinic appointments. At the authors' centres, patients are reviewed every 3 months in alternate joint neurologist/dietitian and nurse/dietitian clinics. Consideration of weaning off the diet should be given after 2 years on the diet. There are some conditions where this period may be increased, e.g. GLUT1DS and PDHD, or shortened, e.g. infantile spasms. Discontinuation of diet is described on p. 369.

Learning points: parental expectations and follow-up

- *Parental expectations should be discussed in advance*
- *KDT should be followed for at least a 3-month period before considering whether the diet is efficacious or discontinuing the diet*
- *Consideration of weaning off the diet should be given after 2 years on the diet; there are some conditions where this period may be increased or shortened*

Setting for initiation of ketogenic diet

The traditional method of initiating the KD involved a period of fasting (12–24 hours), which required hospital admission for monitoring. However, it is now widely accepted that this is no longer necessary [2] and that a gradual initiation has been found to result in better tolerance and fewer adverse effects while maintaining the efficacy of the diet [49]. This means KDT can be initiated at home with the proper support of a dedicated team [2]. Fasting may lead to a quicker onset of seizure reduction and, therefore, may be advantageous when a more immediate response is desired, e.g. in refractory status epilepticus [8]. It is recommended that infants less than 12 months of age should be hospitalised to initiate KDT using a non-fasting protocol [50].

Learning points: setting for initiation of diet

- *Fasting is no longer essential, so KDT can be safely initiated at home with the proper support of a dedicated team*
- *Infants less than 12 months of age should be hospitalised to initiate KDT*

Classical ketogenic diet

CKD is the traditional form of the diet with approximately 90% calories coming from fat. It is calculated based on a ratio of fat to protein and CHO based on a method first described more than 90 years ago [45, 51]. Typically, ratios range from 2:1 to 4:1, the higher the ratio indicating increased intensity of diet, e.g. 4:1 = 4 g fat to every 1 g of protein and CHO combined. The amounts prescribed are based on individual energy requirements. Fat, CHO and protein are carefully calculated for each meal, and it is important that the whole prescription is consumed to optimise effectiveness of the diet. All meals and snacks must be in the same diet ratio, so the relative proportions of fat, CHO and protein remain the same.

Dietary units

A worked example of calculating the diet using the method of dietary units as described by Kossoff *et al*. [52] is shown in Table 17.6. A dietary unit is calculated based on the calorie content of fat being 9 kcal/g and protein and CHO being 4 kcal/g each in the chosen ratio, i.e. a dietary unit on 4:1 ratio = (4 × 9 kcal) + (1 × 4 kcal) = 40 kcal.

The diet is usually started at a lower ratio, e.g. 2:1, and then gradually increased if needed to a 3:1 or 4:1 ratio depending on tolerance, level of ketosis and seizure control. It is not always necessary to increase to 4:1 ratio if good seizure control can be achieved on a lower ratio.

Meal planning

Once the diet prescription has been calculated, some centres in the UK use food choice lists for fat, protein and CHO based on UK food composition tables [54] in order to prepare meal plans. However, these are not standardised, but are individual to each centre. Once families have been given training using this method, it has the advantage of giving them greater flexibility and control over meal planning rather than relying on their dietitian to calculate menu changes. There are also a number of meal planning websites available (see Companion website, Useful addresses).

An example meal plan using a 4:1 ratio is shown in Table 17.7.

Free foods

Some centres provide families with a list of 'free foods' containing minimal amounts of CHO, which can be incorporated into the diet without being included in the CKD prescription. They can help to make meal planning easier and improve tolerability of the diet. However, this is not standard practice and is individual to KD centre. In addition, the following foods may be allowed freely:

- water, tea and coffee (without milk); at the authors' centres, sugar-free squash is allowed providing it contains <0.7 g CHO per 100 mL undiluted, and fizzy drinks/flavoured waters providing they contain <0.3 g CHO per 100 mL

Table 17.6 Worked example of classical ketogenic diet using dietary units.

8-year-old boy in mainstream school, active and enjoys sports. A food diary estimates his intake = 1750 kcal/day. Weight = 25 kg. He has 3 main meals, a snack after school and supper	
Daily requirements	Calories = 1750 kcal Protein RNI = 28 g/day (minimum 1 g/kg/day = 25 g) [46]
Ratio	4:1
Dietary unit – based on ratio of 4:1	(9 kcal × 4) + (4 kcal × 1) = 40 kcal per dietary unit
Divide calorie requirements by number of calories in dietary unit	1750 ÷ 40 = 44 units daily
Fat = number of units × ratio	44 × 4 = 176 g
Protein and carbohydrate = number of units × ratio	44 × 1 = 44 g
Protein = RNI or minimum 1 g/kg	28 g
CHO = number of units minus grams of protein	44 – 28 = 16 g
Daily prescription	176 g fat 28 g protein 16 g CHO = 4:1 ratio
Divide into 3 meals, 1 snack and supper	Breakfast, lunch, evening meal =45 g fat per meal, 6 g protein and 5 g CHO (4:1) Snack =16 g fat, 3 g protein, 1 g CHO (4:1) Supper =24 g fat, 5 g protein and 1 g CHO (4:1) Total = 175 g fat, 26 g protein, 17 g CHO = 4:1 ratio 1747 kcal/day

RNI, reference nutrient intake [53]; CHO, carbohydrate.

Table 17.7 Example meal plan using a 4:1 ratio.

	Fat (to nearest g)	CHO (to nearest 0.5 g)	Protein (to nearest g)
Breakfast – onion and tomato omelette			
1 egg	5 g	–	6 g
12 g butter	10 g	–	–
30 g double cream	16 g	0.5 g	–
80 g raw tomatoes	–	2.5 g	–
25 g raw onion	–	2 g	–
14 mL oil	14 g	–	–
Total	45 g	5 g	6 g
Lunch – tuna mayo salad			
20 g tuna canned in oil, drained	1 g	–	5 g
30 g mayonnaise	22 g	0.5 g	–
30 g cucumber	–	0.5 g	–
32 g raw tomato	–	1 g	–
Pudding – strawberries and cream			
40 g strawberries	–	2.5 g	–
41 g double cream	22 g	0.5 g	1 g
Total	45 g	5 g	6 g
Snack – cheese with cucumber sticks and mayo dip			
60 g cucumber	–	1 g	–
16 g mayonnaise	12 g	–	–
12 g cheddar cheese	4 g	–	3 g
Total	16 g	1 g	3 g
Evening meal – minced beef and courgettes			
25 g raw minced beef	4 g	–	5 g
41 g oil	41 g	–	–
56 g raw courgette (cut into thin strips then fried)	–	1 g	1 g
26 g canned tomatoes	–	1 g	–
Pudding			
70 g cantaloupe melon	–	3 g	–
Total	45 g	5 g	6 g
Supper – cheese and apple with sugar-free jelly and Calogen			
12 g cheddar cheese	4 g	–	3 g
8 g apple	–	1 g	–
Sugar-free jelly sachet	–	–	2 g
40 mL Calogen	20 g	–	–
Total	24 g	1 g	5 g

- salt, pepper, herbs and spices may be used to flavour meals
- some artificial sweeteners contain CHO and, therefore, may be unsuitable, such as most sugar alcohols (e.g. maltitol, polyglycitol) or those containing maltodextrin
- suitable sweeteners include aspartame, saccharine, sucralose, stevia, acesulfame K and erythritol

Learning points: classical ketogenic diet

- *It is based on a ratio of fat to protein and CHO, typically 2:1 to 4:1*
- *All meals and snacks must be in the same diet ratio*
- *The diet is usually started at a lower ratio and then gradually increased if needed*

MCT ketogenic diet

The medium chain triglyceride ketogenic diet (MCT KD) is an alternative to the classical KD and uses another source of fat, MCT, in place of a proportion of LCT. MCT metabolism produces more ketones per gram than LCT, due to several factors: MCTs enter liver mitochondria faster [55, 56], are metabolised preferentially rather than stored in adipose tissue and are promptly and efficiently oxidated to acetyl-CoA via β-oxidation [57]. MCTs are converted to ketone bodies within 30 minutes of ingestion, and blood levels remain elevated for up to 4 hours [58, 59], which make them a useful addition to KDT. These properties mean that less total fat is required to achieve ketosis and a larger proportion of protein and CHO can be included; this could improve compliance and palatability [33, 60].

Dietary prescription

The original MCT KD provides 60% of total calories from MCT [33], which in practice can lead to poor tolerance and gastrointestinal problems. A modified MCT diet was developed, using 30% of energy from MCT, with an additional 30% from LCT [61], but poor ketosis was noted. In the 2009 RCT by Neal *et al*. [34], MCT KD was seen to be as effective as the CKD, using levels of 40%–45% of total calories from MCT. This is now a common starting point, and MCT can be increased further if ketosis is suboptimal and tolerance is good during the fine-tuning stage. The dietary prescription for the MCT KD is:

- 40%–45% calories from MCT
- 10% calories from protein (ensuring this meets WHO lowest safe protein intake [46] (Table 28.48))
- 10%–15% calories from CHO
- 30%–40% calories from LCT

The energy content of MCT is uncertain. European Union (EU) labelling guidance requires that the value of 9 kcal/g is used on product information, but studies state energy content to be between 7 and 9 kcal/g [62]. Multiple literature sources suggest a value of 8.3 kcal/g, which is the value used in common UK practice.

Once the dietary prescription has been calculated for the day, this can be divided into meals and snacks to suit the child's daily routine. Exchange or choice lists of fat (LCT) (Table 17.8), CHO (Table 17.9) and protein (Table 17.10) [54] foods are often used, and education is provided around the MCT products available on prescription that need to be

included at each meal and snack through the day. Prescribable products are given in Table 17.17. A worked example of the MCT KD is shown in Table 17.11.

Initiating the MCT KD

MCT is known to cause gastrointestinal symptoms including abdominal cramping and discomfort, loose stools and diarrhoea, nausea and vomiting [63]. These symptoms can be reduced if the MCT is increased slowly over a period of 7–10 days to the goal intake. MCT should be included in all meals and snacks, and a supper time drink or snack containing MCT will help to maintain ketosis overnight. All foods should be weighed, and parents should be educated in reading labels as they will likely want to include foods not on the choice lists that contain both protein and CHO, e.g. yoghurt and baked beans. There are several standard recipes provided by the feed manufacturers who supply specialist food and drink products; the charity, Matthew's Friends, is also a source for recipes. Families should be educated on how to adjust these to meet their dietary targets. Full vitamin and mineral supplementation should be advised to meet age-related requirements.

Fine-tuning of the diet is likely to be required as with any KDT and could involve reducing CHO, increasing LCT or MCT depending on tolerance and ketosis. Some centres have adapted MCT KDT VW further and do not prescribe an amount of protein, but advise modest intake, and have found this works well and report improved compliance, although efficacy of these modified KDT has not been researched.

Table 17.8 Fat (LCT) choices.

5 g fat choices
6 g butter
5 g oil
6 g mayonnaise
10 g double cream

Table 17.9 Carbohydrate choices.

1 g carbohydrate choices	
8 g apple, eating, raw	31 g broccoli, raw
7 g blueberries, raw	23 g cauliflower, raw
13 g peaches, raw	43 g celeriac, raw
22 g raspberries, raw	56 g courgette, raw
16 g strawberries, raw	6 g garlic, raw
32 g tomatoes, raw	13 g onion, raw
26 g tomatoes, tinned	8 g tomato puree
5 g carbohydrate choices	
14 g white rice, boiled	
23 g spaghetti, boiled	
29 g potatoes, old, boiled	
8 g Ready Brek, raw	
12 g wholemeal bread	

Learning points: MCT KD

- *MCT is included to provide 40%–45% of total daily energy*
- *As MCT is more ketogenic, it allows for more CHO in the diet, which may make the diet more palatable for school-aged children*
- *MCT can cause intestinal discomfort, including diarrhoea and vomiting, so it needs to be introduced slowly*
- *MCT KD has comparable efficacy to CKD*

Modified Atkins diet

In 2003 the Johns Hopkins Hospital published a small case series of six children and adults with complex epilepsy who were treated with a KD which was less restrictive than the CKD as it allowed free protein and calories [64]. This new version of a KD was based on the well-known 'Atkins diet,'

Table 17.10 Protein choices (fat adjusted).

Each choice provides 6 g of protein and has been adjusted to ensure each contains 3 g of fat [54].

Food	Amount to give 6 g protein	Added fat required
White fish (cod, coley, haddock, plaice)	33 g raw or 29 g cooked (baked, poached, grilled or steamed)	3 g oil or 4 g butter or mayonnaise
Salmon	30 g raw or 29 g cooked (grilled or steamed)	
Tuna, canned in oil	22 g	
Ham	33 g	2 g oil or 3 g butter or mayonnaise
Bacon rashers, back	37 g raw or 26 g grilled	
Cheddar cheese	24 g	
Minced beef, lean meat	27 g raw weight or 20 g cooked	
Chicken, light meat	25 g	3 g oil or 3 g butter or mayonnaise
Eggs	1 medium (approx. 50 g)	

Table 17.11 Worked example for MCT ketogenic diet.

8-year-old boy in mainstream school, who enjoys sports, and parents report he is very active. His most recent weight is 25 kg. A food diary estimates intake at 1750 kcal/day. He has three main meals per day, an after-school snack and a supper. He enjoys toast and cereal

Dietary calculation

	Proportion	Amount	Translation to dietary choices	
MCT	45%	95 g		
Protein	10%	44 g	7½ choices including 22.5 g fat	
CHO	15%	65 g	65 g	
LCT	30%	58 g	35 g (minus fat in protein) 7 × 5 g choices	
	MCT	Protein	CHO	LCT
Breakfast	25 g		15 g	10 g
Lunch	25 g	3 choices	20 g	5 g
Snack	10 g	1 choice	5 g	5 g
Evening meal	25 g	3 choices	20 g	5 g
Supper	10 g	½ choice	5 g	10 g
Total	**95 g**	7½ choices **45 g protein** and 22.5 g fat	65 g	35 + 22.5 g from protein choices **57.5 g**
Menu				
Breakfast – cereal	MCT	Protein	CHO	LCT
24 g Ready Brek			15 g	
125 mL Betaquik	25 g			
21 g double cream				10 g
Truvia sweetener			–	
Lunch – sandwich	MCT	Protein	CHO	LCT
48 g wholemeal bread			20 g	
66 g ham with 6 g butter		2 choices		6 g
24 g Cheddar cheese		1 choice		3 g
6 g mayonnaise				5 g
50 mL Liquigen in sugar-free jelly	50 g			
Snack – cheese and fruit	MCT	Protein	CHO	LCT
24 g Cheddar cheese		1 choice		
40 g apple slices			5 g	
Milkshake with				
50 mL Betaquik	10 g			
10 g double cream				5 g
Sugar-free Da Vinci syrup				
Evening meal – pasta and sauce	MCT	Protein	CHO	LCT
25 mL MCT oil	25 g			
13 g onion			1 g	
3 g garlic			½ g	
4 g tomato puree			½ g	
62 g minced beef		2 choices		6 g
68 g tomatoes, tinned			3 g	
32 g boiled pasta			10 g	
24 g Cheddar cheese, grated		1 choice		3 g
80 g strawberries			5 g	
10 g double cream				5 g
Supper – milky drink	MCT	Protein	CHO	LCT
50 mL Betaquik	10 g			
100 mL semi-skimmed milk		½ choice	5 g	1.5 g
21 g double cream				10 g
Chocolate Da Vinci syrup				

MCT, medium chain triglyceride; CHO, carbohydrate; LCT, long chain triglyceride.

devised by Robert Atkins as a weight reduction programme [65]. The Johns Hopkins' MAD differs from the original Atkins diet in several ways, primarily because seizure control, not weight loss, is the goal. In addition, the induction phase (during which CHO is restricted) is continued indefinitely, and fat is encouraged (as opposed to just being allowed). This diet was first referred to as 'modified Atkins diet' in a prospective trial, which showed that 65% children had >50% seizure reduction [37]. A subsequent RCT supports the effectiveness and tolerability of MAD but reinforces that although less restrictive, it does still have side effects and close medical supervision is required [5].

The Johns Hopkins modified Atkins KD protocol restricts CHO to 10 g/day in children aged 2–12 years and 15 g in adolescents (but this can be increased to an adult intake of 20 g daily if adherence is difficult). CHO can be given throughout the day or at one meal. Fibre is not counted in the CHO allowance, but sugar alcohols are. A high fat intake is mandatory, but unlike the CKD, fat is not counted and protein is free. A ketogenic ratio is not calculated and may, therefore, change from day to day. Examination of food diaries estimates an approximate ratio of fat to CHO + protein of 0.9:1 with 65% of calories provided by fat, in comparison with 90% in the CKD [40]. Calories are not restricted, and there is no initial fasting period, which at the time was often typical on the CKD, and so it became possible to initiate the KD in an outpatient setting. The diet induces ketosis, although studies are contradictory as to whether the level of ketosis correlates to the degree of effectiveness [37, 66, 67].

A strict CHO limit is important during the first 3 months, but a study by Kossoff *et al*. [40] suggests that it is possible to later 'relax' the CHO intake from an initial 10 g to 20 g while still maintaining seizure control. A ketogenic 'shake' drink given in the first month may also improve outcome [68].

A sample menu plan for a modified Atkins diet is shown in Table 17.12.

Learning points: modified Atkins ketogenic diet

- *Modified Atkins diet is a protocol that specifies CHO intake (10–20 g/day depending on age) while freely allowing protein, and it does not specify fat intake*
- *It has been shown to be effective at reducing seizures in all age groups*

Table 17.12 Sample menu plan for modified Atkins diet.

Menu plan for an 8-year-old boy (10 g CHO per day) [54]

	Protein	g CHO (excluding fibre)	Fat
Breakfast – scrambled egg			
2 eggs scrambled with butter	Not counted	0	Not counted
40 g mushrooms (fried in oil)	Not counted	Trace	–
Total	Not counted	Trace	Not counted
Lunch – sandwich			
2 slices low carbohydrate bread (3 g CHO per slice)	Not counted	6	Not counted
Ham and Cheddar cheese with butter	Not counted	0	Not counted
Sugar-free jelly with 50 mL Calogen	Not counted	0	Not counted
Total	Not counted	6	Not counted
Snack – cheese and celery			
Cheddar cheese	Not counted	0	Not counted
Celery (¼ stick)	–	Trace	–
Total	Not counted	0	Not counted
Evening meal – minced beef and courgette			
Oil	–	0	Not counted
13 g onion	Not counted	1	Not counted
Garlic	–	–	Not counted
Minced beef	Not counted	–	Not counted
26 g tomatoes (canned)	–	1	–
56 g courgette (cut into thin strips and boiled/fried)	Not counted	1	Not counted
Cheddar cheese, grated	Not counted	–	Not counted
16 g strawberries	Not counted	1	–
Total	Not counted	4	Not counted
Daily total	Not counted	10	Not counted

CHO, carbohydrate.
Source: Courtesy of Royal Society of Chemistry.

Modified ketogenic diets

In UK practice, a broader spectrum of 'modified ketogenic diets' (MKD) has been described that refers to a KD, which does not use diet ratios (i.e. not CKD), but neither does it follow the MAD protocol. A survey of UK ketogenic practice in 2011 reported the use of 'an adapted version of the MAD' in seven of eight centres [69]. More recently, 40% of centres in the UK report using an MKD with no single definitive protocol [38]. Published studies are at present limited, but there is growing interest in research using MKD. A single-centre study of 100 paediatric patients on MKD found 40% of children had a >50% reduction in seizures with 16% showing a >90% reduction in seizures after 3 months on diet [70]. This MKD protocol did not prescribe calories and counted total CHO (with individual CHO allowance being determined by ketone levels) while fat and protein were freely allowed. A study of an MKD in adults with epilepsy showed MKD to be tolerated and feasible with ketosis achieved, but it did not examine effectiveness on seizure control [71]. This MKD protocol encouraged a fat intake of up to 70% of total energy and limited CHO to 20 g/day. Protein was not restricted. Another small study in adults has demonstrated effectiveness of an MKD on seizure control using 15–50 g net CHO/day [72]. The authors' personal experience and feedback from other UK centres confirms the effectiveness of MKD and their increasing use in clinical practice.

Learning points: modified ketogenic diets

- *There is no set modified ketogenic diet protocol – the term refers to any ketogenic diet, which produces ketosis, but does not follow the protocols of either the classical ketogenic diet, MCT diet or modified Atkins diet*
- *Modified ketogenic diets are used effectively in clinical practice in many ketogenic centres in the UK*

Low glycaemic index treatment

The LGIT was developed at Massachusetts General Hospital in 2002 [35] as an alternative to the CKD. The authors theorised that as it has been noted that blood glucose levels are stable in those following a KD and that there can be increased seizure activity associated with high CHO loads in this group, then a more liberalised diet increasing CHO content, but ensuring that it is all sourced from low glycaemic index (LGI) foods, may have a similar effect to KDT.

Several studies have documented that LGIT is associated with reduced seizure frequency [35, 36, 73–75]. It has been successful in both focal and generalised seizure types, and the retrospective study in 2005 demonstrated that 73% of patients had at least 50% improvement in seizures, with a third becoming seizure-free [35]. More recent studies [73, 74] found similar efficacy with 66% and 53% of patients having at least 50% improvement in seizures.

The use of LGIT in some genetic disorders has also showed efficacy. Thibert noted in a prospective study of six children with Angelman's syndrome that five tolerated the diet well and reported over 90% reduction in seizures, which is a potentially higher degree of efficacy than in the general epilepsy population, despite the small study size [74]. In 15 patients with tuberous sclerosis complex, a prospective study found 47% of patients had a 50% improvement in seizures [75], and multiple studies highlight that stabilised blood glucose, rather than ketosis, correlates with the improvement in seizures [73]. Ketone bodies may be measured on LGIT, but they are not a goal of LGIT; blood glucose is monitored to ensure stability within the normal range.

Dietary prescription

The dietary prescription for LGIT is:

- 10% energy from low glycaemic index CHO (GI < 50–55), equating to 40–60 g/day
- 60% energy from fat
- 30% energy from protein

Foods are measured using household measures, and only general estimates for quantities of fat and protein are given to families. Food choice lists can be adapted from those used in other dietary therapies, e.g. 10 g fat choices, which may help to give a guide to families on how much fat is required. It should be advised that fat should always be included in a meal or snack containing CHO, e.g. fruit and cream, to further reduce the GI and aim to avoid peaks in blood glucose level. Education on CHO sources should be given with reference to label reading, considering low CHO products that may be sourced over the internet, perhaps from the USA.

Full vitamin and mineral supplementation is still required as with other KDT, and regular follow-up, including blood and urine monitoring and anthropometry, must be provided. As with other KDs, fine-tuning may be necessary, and this could include reduction in CHO or reduction in protein to allow for a higher fat intake.

LGIT is used more in the USA and India, with only a few centres offering this KD therapy in the UK. From experience, the authors have found that a further restriction on the type of CHO, not just the quantity, has discouraged its use with families.

An example meal calculation is given in Table 17.13.

Learning points: LGIT

- *Carbohydrate from low GI sources (<50–55)*
- *10% energy from LGI carbohydrates*
- *Use household measures and encourage fat intake*
- *Ketosis is not a goal of LGIT*

Which ketogenic diet to use?

There are four KDTs, which have been described by a protocol specifying the quantities of specific macronutrients; these are summarised in Table 17.14. The MKD is not a

Table 17.13 Example meal calculation for low glycaemic index treatment [54].

8-year-old boy with estimated calorie requirements of 1725 kcal/day, following assessment of 3-day food diary and growth history
10% of energy from CHO = 40–50 g low GI foods
60% energy from fat = 115 g (not routinely measured, but encouraged liberally)
30% energy from protein = 130 g (not routinely measured)
Breakfast
Omelette – 2 eggs, 2 tablespoons of double cream, 1 teaspoon of butter and grated cheese
2 rashers of bacon fried in oil
1 slice of low CHO bread (10 g CHO) with butter
Lunch
Low CHO wrap (6 g CHO) with grilled chicken breast, 1 tablespoon of mayonnaise, grated cheese and lettuce
5 strawberries (5 g CHO) with mascarpone
Evening meal
Fried steak with mushroom and cream sauce served with 4 tablespoons of green beans (2.5 g CHO) and 3 tablespoons of carrots (2.5 g CHO)
Chopped peach (10 g CHO) with 2 tablespoons of double cream
Supper
Hot chocolate made with 100 mL semi-skimmed milk (5 g CHO) and cocoa powder, sweetened with liquid Hermesetas sweetener and topped with double cream
Total intake CHO = 41 g

CHO, carbohydrate; GI glycaemic index.

single protocol, but rather a spectrum of KDs. There are few studies that directly compare the effectiveness of these various diets. Variations in diet protocols make it difficult to accurately compare outcomes between studies, with different ratios or CHO allowances being used, with or without calorie restriction or an initial fasting period [42, 76]. The efficacy of CKD and MAD when the diet is eaten (rather than being delivered by tube feed) seems to be very similar [77–80]. A randomised study by Kim *et al*. [42] found no significant difference in outcome between groups randomised to CKD or (a calorie restricted) MAD, although MAD was better tolerated with less side effects. The CKD and MAD have been described as 'complementary and not competing' [81].

A lower (2.5:1) ketogenic ratio may be just as effective as a higher (4:1 ratio) in the CKD [82]. A randomised trial by Neal *et al*. [34] showed CKD and MCT KDs to be comparable. The CKD delivered in liquid form appears to be more effective than oral CKD or MAD, which may be expected as there is less risk of diet miscalculation or indiscretion [67, 83]. There are no studies directly comparing LGIT or modified versions of the KD with the other KDTs.

The International Ketogenic Diet Study Group concluded that 'the specific ketogenic diet therapy chosen should be individualized based on the family and child situation, rather than perceived efficacy, together with the expertise of the ketogenic diet center' [8]. In UK practice, dietitians are evolving the KD to suit their patients' individual needs and allow flexibility, with modified versions of the KD being widely used [38].

The CKD is, by default, used when liquid tube feeding is required and is generally the first-line method of feeding in status epilepticus where rapid seizure control is required and a 4:1 starting ratio is often used [84–86]. The MAD has been successfully used in a case report of status epilepticus [87]. The CKD is recommended in international guidelines for infants under 2 years of age [8, 50]. The MAD has successfully been used in this age group [88–90]; however, Kim *et al*. [42] found the CKD more effective in a group of patients less than 2 years of age with 53% showing a significant response on the CKD compared with 20% on the MAD.

The MAD is considered less restrictive and so may be preferred in adolescents and adults in whom it has shown to be effective [91, 92]. It has also been suggested that MAD may have a role in developing countries with fewer dietetic resources [93] and remote treatment in adults [94]. For patients who require longer-term use of KDT (i.e. disorders of brain energy metabolism and in those who are either reluctant or unable to wean off the diet after 2 years of treatment), a switch to MAD may be considered if adherence becomes an issue. It is also hypothesised that MAD may have milder side effects, but this has not been proven [78].

Switching from the MAD to the more prescriptive CKD may improve seizure control in one third of patients who have already responded to the MAD (especially for those children with myoclonic atonic epilepsy). However, if the child has not responded to the MAD, then there appears to be no benefit in swapping to the CKD [95]. As calories are controlled with CKD, it may be preferred for those patients where weight gain or loss is a concern.

Studies have shown it is possible to transition from the CKD or MCT diet to a less restrictive MAD without an increase in seizures [77, 76, 96].

In GLUT1DS ketones provide fuel for the developing brain. Cerebral glucose utilisation has been shown to increase linearly after birth, with the brain of a 4-year-old metabolising twice as much glucose as an adult; glucose consumption gradually decreases in adolescence [97]. It is recommended that in infants and preschool children, the CKD should be the first choice of diet, and, if tolerated, it should be maintained as long as possible [50, 98]. The MCT diet has also been reported as successful in a GLUT1DS case study [76]. A survey by Kass *et al*. [16] found that a similar percentage of children with GLUT1DS were seizure-free on CKD/MCT compared with MAD/LGIT (74% vs. 63%), and it has also been shown that seizures can be well controlled with a low (2:1) ratio CKD [82]. A clinical benefit has been seen even with only mild ketosis in the GLUT1DS population [12, 76]. However, the long-term effects of GLUT1DS are as yet unclear, and it may be that seizure control is not the only marker of disease course, with the relationship between ketosis and neurodevelopment still to be established. A less restrictive KD has also been reported successful in a case study with PDHD [99]. The LGIT is not recommended for treatment of disorders of brain metabolism as it does not provide ketones [98].

Table 17.14 Comparison of four specific ketogenic diet therapy protocols.

	Classical ketogenic diet	MCT diet	Modified Atkins diet	Low glycaemic index treatment	Modified ketogenic diet
Date first described	1921 [1]	1971 [33]	2003 [64]	2005 [35]	2012 [69]
Ketogenic ratio	2:1 to 4:1	No set ratio (approx. 1.2 to 1.6:1)	No set ratio (approx. 1:1)	No	No
Fats prescribed	Yes Depends on ratio 4:1 approx. 90% total calories	Yes 40%–45% total calories from MCT and 30%–40% from LCT	No	No	Maybe Depends on individual centre's practice
Carbohydrates prescribed	Yes Depends on ratio and protein requirements	Yes 10%–15% total calories	Yes 10–20 g/day depending on age	Yes 40–60 g/day	Yes
Protein prescription	Yes Depends on age requirements approx. 1–1.5 g/kg	Yes Approx. 10% total calories	No	No	Maybe Depends on individual centre's practice
Ketosis goal	Yes	Yes	Yes	No	Yes
Type of carbohydrates specified	No	No	No	Yes GI < 50–55	No
Initiation setting	Historically inpatient	Historically inpatient	Outpatient	Outpatient	Outpatient
Multivitamin/mineral prescribed	Yes	Yes	Yes	Yes	Yes
Age range	All Preferred choice in infants <2 years of age	All May be helpful in adolescents/adults as it allows increased carbohydrate intake	All May allow more flexibility in adolescents/adults	All May be helpful in adolescents/adults as it allows increased carbohydrate intake	All
Use recommended in GLUT1DS/PDHD?	Yes	Yes	Yes	No	Yes

MCT, medium chain triglyceride; LCT, long chain triglyceride; GI, glycaemic index; GLUT1DS, glucose transporter 1 deficiency syndrome; PDHD, pyruvate dehydrogenase deficiency.

Learning points: which KDT to choose?

- *All four main KDT protocols have been shown to be effective in studies, and choice of diet should consider the individual patient and experience of the ketogenic centre*
- *There is currently limited published research into other modified versions of the ketogenic diet; however, their success in clinical practice in the UK is undisputed*
- *LGIT is not recommended for disorders of brain metabolism as it does not produce ketones, which are essential to act as alternative fuel in these disorders*

Management of the diet

Measuring ketones

It is controversial whether ketone bodies themselves have a direct effect on seizure control or are merely a marker of a shift in metabolism, and clinical evidence is contradictory [100–104]. However, ketone monitoring allows fine-tuning of the diet to ensure a 'therapeutic' level of ketosis while avoiding hyperketosis. Traditionally, urine ketones have been used to monitor the KD as they are generally thought to be a less invasive method of testing (although urine collection is not always without difficulty and urine concentration can be affected by hydration and does not reflect current ketosis [105]). The International Ketogenic Diet Study Group [8] recommends home monitoring of urine ketones several times per week, preferably at different times of the day as ketone levels have been shown to be lowest in the morning [106]. Ketone bodies can be monitored in the blood in the form of β-hydroxybutyrate (BHB), using home blood glucose meters (as provided to people with diabetes mellitus), and in the urine as acetoacetic acid or acetoacetate. The International Ketogenic Diet Study Group [8] also suggests that checking BHB at routine clinic visits may be beneficial as there is evidence to suggest that blood levels correspond more closely with seizure control than do urine ketones [100, 101]. High urine ketone levels (3–4+ or 8–16 mmol/L) have been shown to correspond to blood ketones of 2 mmol/L, while blood ketones of greater than 3 or even greater than 4 mmol/L may be most effective at seizure reduction [100, 101]. Blood BHB monitoring is recommended in infants on KDT [50]. It is practice at the authors' centre to measure blood ketones twice daily (morning and evening) during the 3 month trial (or if dietary changes are being made), reducing to three or four times per week (at different times of day) once established and stable on KDT. If on the LGIT then ketosis is not a goal and so ketones do not need to be measured.

There is no agreed definition of hyperketosis on KTD; van der Louw [50] recommends an ideal ketone range of 2–5 mmol/L in infants, but ketones up to 6 mmol/L may be considered acceptable in children [107]. Hyperketosis should not be confused with the life-threatening condition diabetic ketoacidosis (where ketone production is uncontrolled due to lack of insulin and hyperglycaemia). Symptoms of hyperketosis include facial flushing, rapid breathing and increased heart rate, nausea and vomiting, lethargy and irritability. Many of these symptoms are not specific, and hyperketosis may not always be clearly identifiable as a cause without capillary monitoring, especially in children who have non-verbal communication. Urine ketone testing is not sensitive enough to accurately identify hyperketosis [105] and cannot identify hypoglycaemia. Treatment is with a measured amount of CHO sufficient to prevent any symptoms of hyperketosis while avoiding complete loss of ketosis, with potential risk of seizure recurrence. There is no research to support the correct amount of CHO to be given in this instance. The Matthew's Friends Medical Board [107] advises 5 g CHO (given as glucose polymer solution or a high CHO drink such as milk or fruit juice), but practice at ketogenic centres varies with 5–10 g CHO being given.

As the KD is extremely low in CHO, hypoglycaemia is a risk, especially during initiation of the diet or during illness. There are reports of hypoglycaemia in infants [85, 108–110]. The Matthew's Friends Medical Board [107] recommends treating blood glucose <2 mmol/L (or symptomatic hypoglycaemia) with 5 g rapidly absorbed CHO in children <5 years of age and 10 g CHO in older children. This treatment should be repeated if blood levels have not improved within 15 minutes. Ketogenic centres may have different thresholds for when to treat hypoglycaemia (the authors' centre uses 5 g CHO <1 year of age and 10 g CHO >1 year when blood glucose is ≤2.5 mmol/L), and van der Louw [50] recommends treatment with 2–4 g CHO (as breastmilk, normal infant formula or 10% glucose solution) if blood glucose levels drop below 2.0–2.5 mmol/L in infants.

Supplements

Vitamins and minerals

The KD lacks vitamins, trace minerals and electrolytes and needs to be properly supplemented [111]. Osteoporosis is increasingly recognised in patients with epilepsy, and the causes are likely multifactorial. Children with intractable epilepsy are exposed to many factors that can increase the risk of poor bone health including falls, which increase the risk for fractures, and also anti-epileptic medications, which may negatively affect nutrient metabolism and bone health [112]. The restricted intakes of foods on KDT and the acidosis associated with the diet may further increase the risk. It is, therefore, recommended that a CHO-free multivitamin and mineral supplement that provides the recommended daily allowance of vitamin D and calcium should be prescribed [8], e.g. FruitiVits and Phlexy-Vits (p. 362).

Serum levels of vitamins A and E have been found to be high on KDT due to its high fat content [113, 114]. Vitamin E toxicity is rare [115]; however, excessive vitamin A has been associated with adverse effects such as skeletal and intracranial abnormalities [116]. At the authors' centre, levels of vitamin A and E are monitored routinely.

Selenium deficiency has been reported in children on KDT [117], which has been linked with impaired myocardial function [118]. A recent study found selenium levels declined after 6 and 12 months on a KD and suggested that patients on KDT need close monitoring of this trace element [119]. However, it remains unclear if additional selenium above that provided in a standard multivitamin is required [8].

Carnitine

Carnitine has an essential role in fat metabolism, facilitating the transfer of long chain fatty acids into the mitochondria for oxidation. The high fat content of the KD means there is an increased need for carnitine, potentially increasing the risk of depletion of body stores. In addition, carnitine deficiency has also been linked with long-term use of the AED, valproate [120]. Carnitine deficiency can compromise ketosis due to impaired ketone synthesis. Tiredness and muscle weakness can be symptoms of deficiency. However, carnitine supplementation remains controversial. The International Ketogenic Diet Study Group found the majority of KD centres only supplement carnitine if levels are low or the patient is symptomatic [8]. A starting dose of 10 mg/kg is frequently used and gradually increased as required to avoid potential risk of increased seizures, diarrhoea and poor absorption associated with starting with higher dose supplementation. Most children do not require more than 50 mg/kg/day [111].

Essential fatty acids

Due to the restrictive nature of the KD, it is important to ensure adequate essential fatty acid (EFA) intake. This is of particular importance for children following MCT KD, where a large percentage of their energy requirements come from MCTs. It may be necessary to supplement the diet with a small amount (2–3 mL) of omega-3 oil, e.g. walnut or flaxseed oil [121]. If EFA supplements are advised, levels of vitamins A and E should be monitored regularly due to the high levels of fat-soluble vitamins in EFA oils.

Other supplements

There is growing interest in the potential link between gut microbiota, KD and epilepsy and also the potential use of exogenous ketone supplements. However, there are no recommendations for the empiric use of probiotics or ketone esters currently [8].

Learning points: supplements

- *KDT needs to be properly supplemented*
- *A carbohydrate-free multivitamin and mineral should be prescribed that provides recommended daily allowance of vitamin D and calcium*

Medications

Medications should be reviewed by a neurologist before commencing KDT. Carbohydrate content should be assessed, and alternative low CHO formulations prescribed where possible; or the amount of CHO must be included in the KD calculations [122]. Often, sugar-free medications contain sugar alcohols, such as sorbitol, which contribute some CHO to the diet, and, therefore, alternatives should be recommended where possible. Suppositories or tablets are generally preferred to liquid medications as they tend to have lower CHO content. It is important to liaise with pharmacy colleagues for guidance on the most appropriate formulation. Some centres in the UK have a pharmacist as a member of the KD team.

Learning points: management of the diet

- *Measurement of ketone levels allows fine-tuning of the diet to optimise clinical outcome and also to reduce the risk of side effects secondary to hyperketosis and hypoglycaemia*
- *Training in ketone monitoring and identification of abnormal levels and appropriate action to take is an essential part of education for KDT*
- *Blood or urine monitoring can be used; however, blood levels appear to be more accurate and are also more helpful in identifying hyperketosis and hypoglycaemia*
- *All medications should be as low in CHO as possible; advice from a pharmacist regarding the most appropriate formulations is essential*

Ketogenic diet in infants

Historically, the KD has been avoided during infancy, with Freeman *et al*. [123] cautioning that 'The ketogenic diet is not normally advised for children under one year old'. Reluctance to use the KD in this age group was multifactorial but included concerns about the risk of hypoglycaemia and the potential impact of a severely restricted diet on neurodevelopment, growth and feeding behaviour at this key life stage. The absence of a ketogenic infant formula made delivery of the diet difficult until Ketocal 3:1 became commercially available in the UK in 2012. Prior to this, the only way to provide a ketogenic feed for an infant was either to modify Ketocal 4:1, a formula designed for children over 1 year of age, or to use a modular feed. There are concerns in using Ketocal 4:1 in infants due to its high sodium and potassium content, high calorie density (1.5 kcal/mL) and low calcium/phosphate ratio.

A paucity of clinical research also contributed to the lack of confidence in using a KD in infants, and an RCT by Neal *et al*. [124] excluded children less than 2 years of age. More recently, however, there have been several studies demonstrating efficacy and safety in this age group [108, 110, 125–128], including case reports of the KD being used successfully

in neonates [109]. The Ketogenic Diet in Infants with Epilepsy (KIWE) trial is an RCT multicentre UK study currently underway assessing outcomes of the KD in comparison with anti-epileptic medication in infants aged 3 months to 2 years [129].

International guidelines for the use of the KD in infancy were published in 2016 [50], which recommend that infants under the age of 1 year start the diet as an inpatient as they have been shown to be at increased risk of hypoglycaemia and acidosis. Good growth has been shown to be achievable in infants on a KD [108, 130], although it has been proposed that shorter diet duration shows better growth outcomes with no detrimental effect on seizure recurrence [131].

Feeding the infant

The KD for infants prior to being weaned onto solid foods is, by default, a liquid CKD. Ketocal 3:1 ketogenic formula provides a 3:1 ratio and at standard dilution provides 66 kcal/100 mL. It has been demonstrated that it is possible to provide an infant a KD while still receiving some breastmilk, either from breastfeeds or expressed breastmilk (EBM), with ketogenic formula top-ups [132]. However, in order to achieve optimal ketosis, the amount of breastmilk received may need to be limited since it contains approximately 7 g lactose per 100 mL [133]. If an infant is breastfed and the mother wishes to continue, then a measured volume of Ketocal 3:1 should be given before each breastfeed (Table 17.15). This principle assumes that the infant will consume expected volumes for age and, therefore, the ketogenic infant formula will reduce appetite for breastmilk and so limit CHO intake. Depending on ketone levels, the amount of Ketocal 3:1 given can be either increased (thus reducing breastmilk intake if higher ketones are desired) or decreased (to increase breastmilk intake and consequently, increasing CHO intake if hyperketosis is a concern).

For exclusively formula-fed infants, if ketones are routinely too high, then some feeds of normal infant formula can be included, or, alternatively, glucose polymer can be added to the Ketocal 3:1 feed to lower the ratio. If optimal ketosis is not achieved on a 3:1 infant formula, then small volumes of fat emulsion may be added to the feed to increase the ratio. MCT emulsion may be preferred as MCT is more efficient at producing ketones [134]. If extra fat is added, then tolerance and weight gain will need to be closely monitored.

Table 17.15 Relative proportions of EBM and ketogenic infant formula and ratio provided.

Percentage EBM	Percentage Ketocal 3:1	Ketogenic ratio
0	100	3:1
5	95	2.5:1
15	85	2:1
25	75	1.5:1

EBM, expressed breast milk.

The principles of weaning onto solids are the same as for the normal population, i.e. appropriate age, developmental stage, food textures and advice about any potential allergies. A speech and language therapist assessment may be indicated if there are concerns that neurological impairment has affected the ability to swallow. When first introducing weaning foods, the CHO content may not be significant due to the small volume consumed. However, it is prudent to still avoid high CHO foods, particularly sweet foods, to avoid the infant developing a preference for these foods at the expense of lower CHO choices. As the amount increases, then solid meals will need to be calculated in the diet prescription.

An example of feeding regimen for an infant starting a KD at a 2:1 ratio is given in Table 17.16.

Learning points: KDT in infants

- *KDT can be used safely and effectively in infants*
- *Breastfeeding (or expressed breastmilk in the case of tube feeding) on a ketogenic diet is possible; however, the high CHO content of breastmilk may make it difficult to achieve optimal ketosis in some infants*

Use of the ketogenic diet in emergency situations

KTD is being used increasingly in an intensive care setting in the management of super-refractory status epilepticus (SRSE) and febrile infection-related epilepsy syndrome (FIRES). SRSE is defined as refractory epilepsy that continues 24 hours after initiation of general anaesthesia or reappears after the discontinuation of general anaesthesia [135]. Prior reports demonstrate that outcomes in SRSE and FIRES are poor, with hospital mortality ranging from 30% to 40% and about 75% of patients experiencing a poor functional outcome at discharge [136, 137], so an effective intervention is essential. Both these conditions have been highlighted as conditions in which KDT should be used early, showing a higher than average efficacy [8, 138]. There is limited research into the use of KDT as the published papers are often case reports which could have selection bias.

It is likely that in the above scenarios, KDT will be administered via an enteral feeding tube (although parenteral nutrition may also be considered), and a CKD ratio should be selected. Due to the nature of the setting in intensive care, a rapid introduction of the diet can be used over 24–48 hours as closer monitoring is available for blood glucose and blood ketone management. With a rapid induction, blood glucose levels may be more likely to drop, so levels should be checked more frequently. Energy requirements should reflect clinical status, considering the reason for admission; pyrexia should be considered, particularly if FIRES is the cause of status epilepticus. All drugs, including intravenous (IV) medications and fluids, should be reviewed with the ward pharmacist to ensure that they are the lowest CHO formulations [139] and nursing and

Table 17.16 Example of feeding regimen for a 6-month-old infant starting ketogenic diet at 2:1 ratio.

A male infant, weight = 8 kg, is receiving all his nutrition as 5 oral feeds per day. He is not yet taking solid foods. Mum is keen to continue to provide some breastfeeds

Calculation of intake of formula:

Assuming an age appropriate intake of 120 mL/kg/day, expected intake = 120 × 8 = 960 mL/day

Total expected volume per feed = 960/5 = 192 mL

To provide a feed with 2:1 ratio, the feed should contain 15% breastmilk and 85% Ketocal 3:1 (Table 17.15)

85% × 192 mL = 163 mL formula per feed. Top-up feed given as breastmilk = either 192 – 163 = 29 mL EBM or fed to appetite from breast

Feeding regimen = 163 mL × 5 feeds Ketocal 3:1 per day, with a top-up feed of breastmilk

The infant is tolerating the feeding regimen, but ketones are <2 mmol/L with no reduction in seizures.

The ratio of the feed can be adjusted to improve ketosis:

The volume of ketogenic infant formula should be increased (from 173 mL × 5 to 180 mL × 5 per day would be a sensible adjustment), and it would be expected that the volume of breastmilk taken by the infant would spontaneously reduce to correspond to appetite, thus increasing the overall ratio of the diet.

Feed contains 94% Ketocal 3:1 (180/192 mL) and 6% breastmilk (12/192 mL) providing approximately 2.5:1 ratio (Table 17.15).

Ketones are now in the therapeutic range 2–5 mmol/L, and the infant is gaining weight appropriately. A speech and language therapist has advised that weaning solids can be introduced.

Calculation of 2.5:1 ketogenic meal prescription:

Calorie intake divided over three meals and 2 bottles per day, continuing the current volume of 180 mL Ketocal 3:1 per bottle with a breastfeed top-up to be given afterwards (estimated total intake per feed = 192 mL, including assumed 12 mL from the breastfeed, as per previous calculation)

	100 mL Ketocal 3:1 provides	192 mL feed provides	Dietary exchanges (rounded to nearest 0.5 g)
Fat (g)	6.4	12.1	2.5 × 5 g exchanges
CHO (g)	0.68	2.1	2 × 1 g exchanges
Protein (g)	1.5	2.8	3 × 1 g exchanges

Sample 2.5:1 meal plan
Provides: 12.5 g fat, 3 g protein and 1.5 g CHO per meal [54]

Breakfast – scrambled egg and fruit	Fat (rounded to nearest 0.5 g)	Protein (to nearest g)	CHO (rounded to nearest 0.5 g)
½ egg	2.5	3	–
15 mL Calogen	7.5	–	–
3 g butter	2.5	–	–
13 g apple (stewed)	–	–	2.0
Total (2.5:1)	12.5	3	2.0

Lunch – Cheesy celeriac mash	Fat (to nearest 0.5 g)	Protein (to nearest g)	CHO (rounded to nearest 0.5 g)
12 g Cheddar cheese (grated)	4	3	–
50 g boiled celeriac (mashed)	–	–	1
15 ml gravy	–	–	0.5
17 g double cream	8.5	–	0.5
Total (2.5:1)	11.5	3	2.0

Evening meal – salmon in creamy sauce with broccoli	Fat (to nearest 0.5 g)	Protein (to nearest g)	CHO (rounded to nearest 0.5 g)
12 g steamed salmon	2	3	–
20 g double cream	10.5	–	0.5
43 g broccoli (steamed)	–	–	1.5
Total (2.5:1)	12.5	3	2.0

medical staff should be made aware that IV fluids and medications should not contain CHO.

The length of time that KDT is used in the above conditions is unclear, and recent research has supported successful use in shorter time periods compared with the usual 2 years [140, 141]. It may be that if the patient responds to KDT and is extubated and ultimately discharged back to the ward, they can be weaned off KDT as they are re-established onto oral feeding, without deterioration of seizure control. This may be an opportune time to wean back to a normal diet as it can be challenging to wean from enteral to oral KD in these scenarios.

Prescribable items

There is an increasing, but limited, range of prescribable products available for use in KDT. It should be noted that, with the exception of Ketocal 3:1, the prescribable items in the UK are not approved by Advisory Committee on Borderline Substances (ACBS) for children below 3 years of age for use in the community, e.g. Ketocare breakfast cereals, Keyo and FruitiVits. This is due to EU legislation prohibiting sweetener use in foods for infants and young children [142]. Items available on prescription are given in Table 17.17.

Enteral feeding

The KD can be provided as an enteral feed via nasogastric, gastrostomy or jejunostomy feeding tubes. Efficacy in this group has been shown to be high. A study by Kossoff [83] found 59% of children exclusively tube fed to have >90% seizure control at 12 months. Compliance in this group has also been found to be high [143]. This may be due to the relative ease of delivery of this form of the diet and reduced room for error compared with an oral diet.

Ketocal is a specially designed nutritionally complete ketogenic formula available in the UK. It comes in various ratios and formulations, which are suitable as a sole source of nutrition in specific populations (Table 17.17).

Enteral feeds should be calculated based on the child's current feeding regimen and growth history (p. 349) and calculated in a similar way to an oral CKD. Where possible feeds can be administered in a similar way to the child's usual regimen.

Feeds are usually introduced slowly starting at a low ketogenic ratio of 1:1 or 2:1 and then gradually increased according to ketosis/seizure control. The ratio of the feed can be altered by adding/subtracting CHO/protein modules (Tables 1.19 and 1.21). Macronutrient and micronutrient levels should be checked and supplemented where necessary to meet requirements [111], e.g. children with particularly low energy requirements, and, hence, low volumes of feed may require extra supplementation of protein and electrolytes. As MCT fat is more efficient at producing ketones [134], addition of MCT fat may also be useful, particularly in this group, in order to optimise ketone levels when protein requirements do not allow for further increase in the diet ratio.

An example calculation of a ketogenic tube feed is given in Table 17.18.

Modular feeds

The Ketocal range of products contains cow's milk protein. A modular feed is, therefore, necessary in the case of a child with cow's milk protein allergy or whole protein intolerance. It is important to consider the CHO content of protein modules used in the feed, e.g. Complete Amino Acid Mix may be required due to the CHO content of hydrolysed protein modules such as Prosource TF and Hydrolysed Whey Protein/Maltodextrin Powder (Table 17.17). Consideration must also be given to ensuring electrolyte, vitamin and mineral requirements are also met. Further information on modular feeds can be found in Chapter 8.

Learning points: enteral feeding

- *The KD can be provided as an enteral feed*
- *Enteral feeds should be calculated based on the current feeding regimen and growth history*
- *Feeds are usually introduced slowly starting at a low ketogenic ratio of 1:1 or 2:1 and then gradually increased as needed*
- *Macronutrient and micronutrient levels should be checked and supplemented where necessary to meet requirements*
- *A modular feed may be necessary for children with cow's milk protein allergy or an intolerance to whole protein feeds*

Parenteral nutrition

Indications

Parenteral nutrition is indicated in KDT when enteral intake is impaired (inability to absorb nutrients through the gastrointestinal tract), and bowel rest is required [144], and ketosis for seizure control must be maintained. It may also be needed when KDT is indicated, but enteral application is temporarily impossible [145]. In UK practice, ketogenic parenteral nutrition (kPN) is not used at dietary initiation, and there are only a few case reports supporting the use of kPN in the literature, which are summarised in Table 17.19.

Calculation and provision of prescription

The flow chart in Figure 17.1 shows the steps to calculate the prescription for kPN. Standard bags are not available for kPN, so a multidisciplinary approach is key to successful implementation. There needs to be close working with an experienced pharmacist to calculate the kPN script, ensuring its stability and suitable osmolality. It will also be necessary to work with the nursing and medical team to ensure all IV medications, fluids and solutions are CHO-free to support

Table 17.17 Items available on prescription for ketogenic diet therapy.

Product	Company	Description	Indications
Nutritionally complete			
Ketocal 4:1 powder	Nutricia Advanced Medical Nutrition	Powdered feed enriched with fibre and LCPs available in vanilla and unflavoured varieties. The standard feed concentration is 14.3%	Suitable as a sole source of nutrition, or as a supplementary feed, in children over 1 year. For sip and tube feeding
Ketocal 4:1 LQ	Nutricia Advanced Medical Nutrition	Ready to use fibre enriched liquid feed available in vanilla and unflavoured varieties	Suitable as a sole source of nutrition in children aged 1–10 years or as a supplement for those over 10 years and adults
Ketocal 3:1 powder	Nutricia Advanced Medical Nutrition	Powdered feed, fibre-free, enriched with LCPs, unflavoured. The standard feed concentration is 9.5%	Suitable as a sole source of nutrition in infants from birth to 6 years or as a supplement in those over 6 years
Ketocal 2.5:1 LQ	Nutricia Advanced Medical Nutrition	Ready to use fibre-enriched liquid feed available in vanilla flavour	Suitable as a sole source of nutrition in children aged 8 years to adults or as a supplement
Keyo	Vitaflo International Ltd.	Ready to eat semi-solid food	Suitable from 3 years of age onwards. Suitable as a sole source of nutrition up to 10 years of age
Fat modules			
Liquigen	Nutricia Advanced Medical Nutrition	50% MCT emulsion	Suitable from birth
MCT oil	Nutricia Advanced Medical Nutrition	Liquid containing only a mixture of MCT	Suitable from birth
Calogen	Nutricia Advanced Medical Nutrition	50% LCT fat emulsion	Suitable from birth
Carbzero	Vitaflo International Ltd.	Ready to use 20% emulsion of LCT	Suitable from 3 years of age
Betaquik	Vitaflo International Ltd.	Ready to use 20% emulsion of MCT	Suitable from 3 years of age
Protein modules			
Protifar	Nutricia Advanced Medical Nutrition	Powdered, unflavoured, high protein supplement	Suitable from birth
Hydrolysed Whey Protein/Maltodextrin Powder	Nutricia Advanced Medical Nutrition	Powdered, whey protein hydrolysate	Suitable from birth
Prosource TF	Nutrinovo Ltd.	Liquid high protein milk-free (beef collagen derivative) supplement for tube feeding	Suitable from 3 years of age
MCTprocal	Vitaflo International Ltd.	Neutral tasting protein powder supplement high in MCT	Suitable from 3 years of age
Complete Amino Acid Mix	Nutricia Advanced Medical Nutrition	Powdered mix of essential and non-essential amino acids	Suitable from birth
Carbohydrate modules			
Super Soluble Maxijul	Nutricia Advanced Medical Nutrition	Powdered unflavoured CHO supplement	Suitable from birth
Polycal Powder	Nutricia Advanced Medical Nutrition	Powdered unflavoured CHO supplement	Suitable from 1 year of age
Vitajoule	Vitaflo International Ltd.	Powdered unflavoured CHO supplement	Suitable from birth
Vitamin and mineral supplements			
Phlexy-Vits sachets	Nutricia Advanced Medical Nutrition	Concentrated powdered vitamin, mineral and trace element preparation	Suitable for children over the age of 11 years and adults
Phlexy-Vits tablets	Nutricia Advanced Medical Nutrition	Tablets containing vitamins, trace elements, calcium, phosphorous and magnesium	Suitable for children over the age of 8 years and adults

(continued overleaf)

Table 17.17 *(continued)*

Product	Company	Description	Indications
FruitiVits	Vitaflo International Ltd.	Orange flavour vitamin, mineral and trace element supplement	Suitable from 3 to 10 years of age
Food products			
Ketoclassic bar	Ketocare	3:1 ratio, high fibre bar	Suitable from 3 years of age
Ketoclassic savoury	Ketocare	3:1 ratio, high fibre solid meal	Suitable from 3 years of age
Ketoclassic chicken	Ketocare	3:1 ratio ready meal	Suitable from 3 years of age
Ketoclassic bolognese	Ketocare	3:1 ratio ready meal	Suitable from 3 years of age
Ketoclassic porridge	Ketocare	3:1 ratio, high fibre ready-prepared breakfast meal	Suitable from 3 years of age
Ketoclassic muesli	Ketocare	3:1 ratio, high fibre ready-prepared breakfast meal	Suitable from 3 years of age

LCP, long chain polyunsaturated fatty acids; MCT, medium chain triglycerides; LCT, long chain triglycerides

Table 17.18 Example calculation of a ketogenic tube feed.

A 3-year-old girl who is completely tube fed
Wt = 14 kg, following appropriate centiles for weight and height
Current feeding regimen is 700 mL/day of 1.5 kcal/mL nutritionally complete whole protein feed:
100 mL bolus × 3 in the day
40 mL/hour × 10 hours overnight
Water flushes of 40 mL are given pre- and post-feeds, plus extra 180 mL water/24 hours as flushes with medications
The feed provides: 1050 kcal, 28.7 g protein. Total fluid = 1200 mL
Plan: to base ketogenic feed on current feed regimen
Initiate at 2:1 ratio using the dietary unit method (p. 349)
Prescription = 96 g fat; minimum 1 g/kg protein = 14 g (RNI = 14.5 g); 33.5 g CHO
100 mL Ketocal 4:1 LQ = 14.8 g fat, 0.61 g CHO, 3.09 g protein
Fat required from Ketocal 4:1 LQ = 96 g fat ÷ 14.8 = 650 mL Ketocal 4:1 LQ
650 mL Ketocal 4:1 LQ provides 3.09 × 6.5 = 20 g protein
0.61 × 6.5 = 4 g CHO
Add in 24 g Maxijul glucose polymer to reduce ratio to 2:1
Provides: 96 g fat, 20 g protein, 28 g CHO, 1056 kcal/day
The feed meets full nutritional requirements in the desired ratio; there is no need to restrict protein to minimum requirements
The ratio can then be gradually increased if required by decreasing the amount of Maxijul depending on ketosis and seizure control

RNI, reference nutrient intake.

ketosis. It is not always possible to provide full calorie requirements with kPN due to the limited capacity for lipid per day and the infusion rate. This also means that the ketogenic ratio can be limited, so it is particularly important to eliminate additional CHO sources where possible. kPN can be built up over 1–2 days, either building up the fat content from 3 to 4 g/kg/day or providing half a bag on day 1 and a full bag on day 2. An example calculation for an adolescent on kPN is given in Table 17.20.

Monitoring

Daily monitoring of kPN should follow the schedule as outlined in Chapter 5. If the patient is new to KDT, then they should have had standard baseline monitoring as per the International Ketogenic Diet Study Group consensus statement [8]. In addition to standard PN monitoring, twice daily bedside blood glucose and blood ketone measurements should be taken to assess effectiveness of the kPN at

Table 17.19 Summary of literature for ketogenic parenteral nutrition.

Reference	Sample size	Reason for kPN	Duration of kPN (days)	Established KD prior to kPN	Ketosis achieved (defined as BHB > 2 mmol/L)	Efficacious	Adverse effects	Remained on KD after kPN discontinued	Conclusions
Kang *et al*. [146]	10	Bowel rest	4.1 (±1.5 days)	Yes	Yes	Yes	↑ ALT ($n = 1$) ↑ amylase and lipase ($n = 1$) ↑ triglycerides ($n = 1$)	9 continued	kPN is a safe short-term method of continuing KDT to maintain seizure control
Strzelczyk *et al*. [147]	1	Significant reflux and SRSE	9.5	No	Yes	Refractory seizures resolved	Non-reported	Yes	kPN is safe and feasible
Chiusolo *et al*.[148]	1	Ileus and refractory status epilepticus	3	No	Yes	NA	Non-reported	No, weaned onto enteral KDT but stopped after 8 days due to non-response	kPN is a temporary bridge for KDT for those with partial or total intestinal failure who need to start KDT
Zupec-Kania *et al*. [139]	1	Not identified	1	No	No	Yes, once transitioned to enteral KDT	Non-reported	Weaned after 2 months due to poor compliance	Poor ketosis due to carbohydrate content of phenobarbitone infusion and glycerol content of lipid infusion, which had not been accounted for
Lin *et al*. [149]	1	GI bleed	8	No	Yes	Yes	↑ triglycerides and cholesterol	Yes	Early intravenous initiation of a KD in SRSE is an effective and safe alternative treatment
Rosenthal *et al*. [150]	1	Bowel rest for intractable diarrhoea	140	Yes	Yes	Yes	Abnormal LFT Iron deficiency anaemia ↑ triglycerides and cholesterol	Died	Relatively safe, effective short-term treatment
Roan *et al*. [151]	1	Intestinal failure	448	Yes	On day 3 of initiation	Yes	Mild ↑ in triglycerides, cholesterol and LFT	Remain on kPN long term with minimal enteral input	Well tolerated and safe with close and careful monitoring
Dressler *et al*. [145]	17	Non-functioning GI tract ± status epilepticus	1–41 days	Yes – 13 No – 4	Yes – 10 No – 7	Those previously on KDT maintained efficacy. Of the 7 remaining, only 2 responded to the diet	Transient ↑ in triglycerides ($n = 3$), cholesterol ($n = 5$), HDL ($n = 6$), LDL ($n = 4$) and LFT ($n = 4$) All resolved after stopping kPN	12 continued KDT	Ketosis can be maintained successfully, and relevant adverse effects were not noted in short- or long-term application (41 days)

kPN, ketogenic parenteral nutrition; KD, ketogenic diet; BHB, β-hydroxybutyrate; ALT, alanine transaminase; SRSE, super-refractory status epilepticus; KDT, ketogenic diet therapy; NA, not applicable; GI, gastrointestinal; LFT, liver function tests; HDL, high density lipoproteins; LDL, low density lipoproteins.

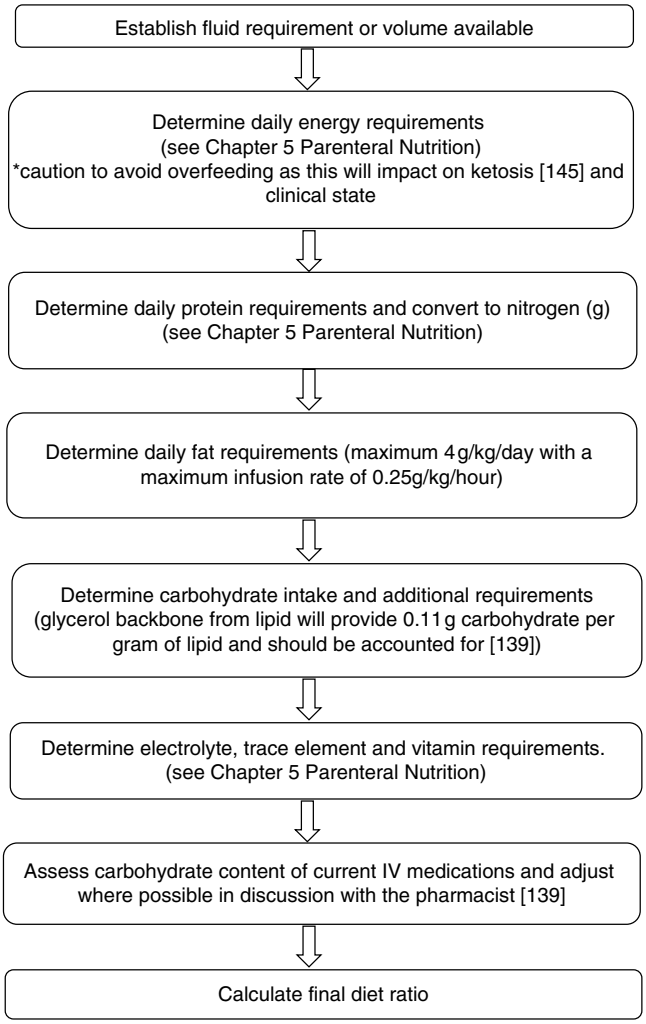

Figure 17.1 Calculation of prescription for ketogenic parenteral nutrition.

achieving ketosis. The kPN may need adjustment as a result of these monitoring tests, so working closely with the pharmacist and ward staff is essential.

Adverse effects

As noted in the cases in Table 17.19, short-term use of kPN is not associated with significant adverse effects, with transient increases in lipids being the most commonly seen response. With close monitoring, short-term kPN can be safe and effective for those patients already established on KDT who require bowel rest or have a non-functioning gastrointestinal tract. Enteral nutrition should be re-established as soon as possible as there is little research into long-term use of kPN.

Learning points: ketogenic parenteral nutrition

- *kPN can be used for those established on KDT, for short periods of time, if the enteral route cannot be used and ketosis needs to be maintained*
- *Nutritional intake is often impaired due to the limited lipid infusion rate and volume*
- *All IV medications and fluids need to be carbohydrate-free to support ketosis*

Fine-tuning the ketogenic diet

Fine-tuning is necessary to ensure therapeutic levels of ketones and as a result, hopefully, to improve seizure control. Fine-tuning is often associated with the initial trial period but can occur at any stage. Selter *et al*. [152] showed that fine-tuning lead to an improvement in seizure control in 18% of patients who had already responded to the KD and

Table 17.20 Example calculation for an adolescent on ketogenic parenteral nutrition.

A 14-year-old male is established on a modified ketogenic diet (oral and by nasogastric tube) following super-refractory status epilepticus at 12 years of age and is maintaining good ketosis He is admitted to the paediatric intensive care unit following emergency laparotomy: 25 cm necrotic bowel is resected following obstruction secondary to adhesions. Bowel rest and parenteral nutrition is advised	
Weight = 65.6 kg (91st centile)	Height = 179.5 cm (75th–91st centile)
Usual ketogenic diet	
Energy	1973 kcal
Protein	65.6 kg = 10.5 g nitrogen/day (lowest safe intake protein = 58.4 g/day)
Fat	228 g (129 g LCT and 99 g MCT) per day
kPN prescription	
Fat	3 g/kg/day = 197 g fat per day = 0.13 g/kg/hour, given over 18 hours to avoid overfeeding = 0.17 g/kg/hour
CHO	21.67 g CHO from glycerol (0.11 g per g lipid); all medication given IV and CHO-free
Micronutrients	Standard supplementation meets requirements
Final bag	197 g fat, 10.5 g nitrogen, 21.67 g CHO = 2.25:1 ratio providing 2035 kcal
Ketosis was maintained once kPN was established and the patient was weaned back onto enteral KDT after 7 days	

LCT, long chain triglycerides; MCT, medium chain triglycerides; kPN, ketogenic parenteral nutrition; CHO, carbohydrate; IV, intravenous; KDT, ketogenic diet therapy.

3% achieved seizure freedom. Fine-tuning is also important to help manage side effects and to optimise weight gain and growth. Fine-tuning may also improve palatability and thus adherence to diet. Common fine-tuning strategies are summarised in Table 17.21.

If there is a sudden reduction in ketosis, with subsequent increase in seizures, then thorough investigation is necessary to find the cause. There may have been accidental ingestion of excess CHO. A food diary can be helpful to check that the diet is being administered correctly. Common errors include miscalculation of meals and incorrect interpretation of food labels, product changes and the use of sugar polyols as sweeteners in foods and medications. Non-adherence or 'cheating' by the child is always a possibility and can sometimes be facilitated by a misguided relative or teacher who believes that the 'occasional treat won't hurt'. Intercurrent infection is a common cause of low ketones, and levels should improve post-illness. If the level of ketones has lowered with no obvious increase in seizures, then there may be no need to alter the diet, so avoiding unnecessary further restriction.

Table 17.21 Fine-tuning the ketogenic diet.

Problem	Action
Difficulty establishing ketosis or a sudden loss of ketones	If ketones lower than usual, but child still in ketosis and no associated increase in seizures: no immediate action necessary, but be vigilant for possible cause of decreased ketones
	If seizures increased: check for consumption of extra CHO (e.g. cheating, miscalculation of meals or misinterpretation of labels); a detailed food diary may be helpful
	If intercurrent illness: temporary reduction in CHO may help, but ketosis should improve as child recovers
	If no obvious cause for loss ketosis: reduce CHO allowance (MAD) or increase diet ratio (CKD); consider addition MCT emulsion to diet in small volumes
	If still struggling to regain ketosis: consider checking carnitine levels and supplementing if low
Hyperketosis	If occasional and/or only associated with illness: treat with 5–10 g liquid CHO
	If repeated episodes: first check all the CHO allowance is being consumed; if not consider using higher CHO foods
	If all CHO allowance is being consumed: increase the CHO by 1–2 g (MAD) or reduce the ratio by 0.5:1 (CKD)
	If using MCT emulsion: consider reducing or discontinuing, but generally the preference is to increase CHO allowance and thus improve palatability/variety diet
Concern that excessive weight gain or loss	If on CKD: recalculate diet using amended calorie requirements
	If on MAD: adjust fat intake; if issue is ongoing consider changing to CKD to enable calorie prescription

CHO, carbohydrate; MAD, modified Atkins diet; CKD, classical ketogenic diet; MCT, medium chain triglycerides.

If the diet is being given correctly with no obvious indiscretions, then to optimise ketosis it may be necessary to increase the ratio of the classical diet (in 0.5:1 increments) or to decrease the CHO (in 1–2 g decrements) if the child is on MAD. If there is consistent hyperketosis, then the converse would apply. Calorie control has not been shown to be effective in improving seizure control on KDT [152, 153]. Carnitine supplementation may be of benefit [152, 154] although the International Ketogenic Diet Study Group recommends that supplementation should only be given if levels are low [8]. The use of MCT as a supplement to the CKD or MAD, rather than giving MCT as the full MCT KD, can be a fine-tuning tool [155]. The authors have found the addition of small measured amounts (15 g MCT given three times a day) of an MCT emulsion, e.g. Betaquik or Liquigen, to the diet can boost ketosis and so prevent the need for further reduction in CHO allowance, but only when mild to moderate ketosis has already been established. If ketones are minimal (<1.5 mmol/L), then the addition of MCT to the diet does not appear to have an effect. A small pilot study [156] investigated if intermittent fasting improved outcome in children already established on a KD, whereby the child was fasted for two meals on 2 non-consecutive days per week. Although there was some seizure improvement, it was not sustained, and adherence to this regimen was found to be difficult.

It is suggested that during the initial 3 months on a KD, it may be beneficial to follow a stricter diet but that it may be possible to 'liberalise' the KD subsequently with no deterioration in seizure control. Both a randomised crossover comparison of either 10 g or 20 g CHO on MAD [40] and a crossover 3:1 or 4:1 CKD [41] showed improved seizure control for the groups on the stricter protocol (i.e. either 10 g CHO or 4:1) at the end of trial period, but outcome was maintained, and tolerability was improved when crossed over to the less strict protocol (20 g CHO or 3:1).

Learning points: fine-tuning the ketogenic diet

- *Fine-tuning can help to optimise ketosis, growth and adherence and reduce risk of hyperketosis and hypoglycaemia and can happen at any stage of KDT*
- *It has been suggested that it may be possible to liberalise the diet after the initial 3 month trial period while still maintaining effectiveness*

Management of illness

During episodes of intercurrent illness, dietary adjustment may be required to maintain ketosis and prevent seizure recurrence. Closer monitoring is also advisable to identify hyperketosis or hypoglycaemia as the risk is higher during illness.

As with all children who are unwell, medical advice should be sought if there are concerns or if the illness is ongoing to ensure correct treatment is received. Where possible, medications should be low CHO formulations, but medication should not be withheld as the illness needs to be treated. Further information about medications and KTD is given on p. 358.

Ketones and blood sugars should be checked every 4 hours if oral intake is significantly reduced, if the child is vomiting or if recent levels have required treatment. Hyperketosis should be treated in the first instance, and if there are repeated episodes, then it may be necessary to temporarily increase the CHO allowance of the diet. Further information about measuring ketones is given on p. 357.

If ketones are low then, if possible, the CHO allowance can be temporarily reduced in the diet to compensate. If the CHO allowance is already at a minimum, then the addition of MCT emulsion, e.g. Betaquik or Liquigen, to the diet may help to optimise ketone levels, although if vomiting or abdominal discomfort is associated with the illness, then starting MCT simultaneously is not ideal.

If the child has a poor appetite, then higher CHO foods, e.g. juice or glucose polymer, fruits and potato, may be helpful to ensure the CHO allowance is consumed (although it is preferable to still avoid those foods that are not usually permitted on the diet, such as chocolate or normal bread, to avoid confusion for the child upon return to their usual KD allowance after illness has resolved). If meals are not eaten, then a meal replacement 'shake' drink may be used temporarily (Ketocal LQ 4:1 or 2.5:1 with additional glucose polymer if necessary to provide the correct classical ratio or CHO allowance). Sugar-free fluids should be given to ensure adequate hydration. Oral rehydration solutions may be used, but the CHO content should be taken into consideration, e.g. Dioralyte provides 1.8 g glucose per 100 mL. If vomiting or diarrhoea is present, then it may be necessary to temporarily reduce fat intake, especially MCT.

If nil by mouth for a surgical procedure, then ketones and blood sugars should be checked 4 hourly, and diet reintroduced as soon as is feasible after the procedure. If IV fluids are required, then saline or Plasmalyte is preferred to dextrose (unless treating hyperketosis or hypoglycaemia). Valencia *et al*. [157] showed that serum glucose remained stable in children on KD who underwent general anaesthesia on CHO-free IV solutions. However, metabolic acidosis was observed in several patients, so it is recommended that serum pH or bicarbonate levels are monitored if undergoing prolonged surgical procedures.

Learning points: management of illness

- *Close monitoring is advisable during illness to maintain therapeutic ketone levels and also to reduce the risk of hyperketosis and hypoglycaemia*
- *Temporary modification of the diet may be needed to compensate for abnormal ketone levels, poor intake or feed intolerance; a 'shake' drink can be used as a meal replacement*

Adverse effects of the ketogenic diet

The most commonly seen side effects of KDT are gastrointestinal symptoms, hypercholesterolaemia, kidney stones and slower linear growth. Other potentially more serious side effects are rare but support the requirement for monitoring on KDT and regular follow-up by an experienced team. A review by Kang *et al*. [158] looked at 129 patients following a KD for a mean duration of 12 months (±10.1); early-onset symptoms occurred within the first 4 weeks (Table 17.22). Of the 46.5% that experienced dehydration, 52 were fasted prior to starting the KD and maintained on 75% of fluid requirements as part of the initiation protocol, which is not common practice in the UK. Bergqvist *et al*. [49] highlighted that fasting is not necessary to achieve ketosis; it is commonly associated with the adverse effects of hypoglycaemia, acidosis and dehydration.

In practice the most commonly seen side effects in the short term are constipation and GOR. In the longer term there can be impacts on growth, raised cholesterol levels and renal calculi. The diet is generally well tolerated, and nutritional deficiencies are not commonly seen if the diet is adequately supplemented with vitamins and minerals (p. 357).

Constipation

As the CHO content of the diet is limited, fibre-containing foods are also limited. Families should be encouraged to regularly include high fibre CHO sources and to optimise fluid intake; CHO-free laxatives, e.g. macrogol (Movicol Paediatric Plain), may be required [159]. Constipation is not only more common with the CKD than the MCT diet [8] but is also seen with MAD or MKD. It may be a concern for those children with swallowing difficulties or learning difficulties where their fluid intake may already be compromised. Sugar-free jellies or sugar-free ice pops can be important sources of fluid to supplement intake.

Table 17.22 Complications experienced on the ketogenic diet [158].

Early-onset complications		Continuing or late-onset complications	
Dehydration	46.5%*	Gastrointestinal effects	27.9%
Gastrointestinal effects	38.7%	Hypercholesterolaemia	19.4%
Hypercholesterolaemia	14.7%	Hepatitis	5.4%
Raised urate	26.4%	Osteopenia	14.7%
Hypoglycaemia	7%	Renal stones	3.1%
Hypomagnesemia	4.7%	Hydronephrosis	0.8%
Hyponatraemia	4.7%	Iron deficiency	1.6%
Hepatitis	2.3%	Carnitine deficiency	1.6%
Acute pancreatitis	0.8%	Cardiomyopathy	0.8%
Metabolic acidosis	0.8%	Raised urate	10%
		Hypomagnesemia	14%

* Fluid is no longer routinely restricted on dietary introduction.

Gastro-oesophageal reflux or vomiting

GOR is common in this patient group, particularly if tube feeding is necessary. The incidence of epilepsy in cerebral palsy (CP) is estimated to be between 15% and 62% [160]. GOR is predicted to affect 50% of patients with CP [161]; in this patient group their GOR is likely exacerbated by the high fat content of KDT and will need careful management, considering proton pump inhibitors [8] and feeding methods, e.g. pump-assisted feeds or jejunal feeding. Input from the gastroenterology team can help to fully investigate GOR and advise regarding optimisation of treatment prior to dietary initiation.

Vomiting is most commonly associated with MCT [34] in children feeding orally, but this side effect can be avoided by gradual introduction of MCT over a number of days to improve tolerance. If vomiting persists, a reduction in the MCT prescription may be required.

Growth and bone density

Numerous studies have reported impacts on linear growth with KDT, both with short-term and long-term use [162–166] and that this impact may be greater in younger children [163]. This does not seem to be related to nutritional content of the diet as those with a larger protein intake, following MCT KD, for example, still experienced reduced growth velocity [165], although a study looking at 35 patients noted that poor linear growth was only seen when protein intake was <1.4 g/100 kcal [167]. Growth needs to be monitored regularly, paying particular attention to height and considering alternative measures for non-ambulatory patients if necessary. Following discontinuation of the diet, significant catch-up growth has been noted in both height and weight after a year [168], despite the similar calorie content of the diets. This suggests that the impact on growth could be related to acidosis, which can be managed if poor growth is identified, but there may also be an effect on insulin-like growth factor by KDT [169]; further research is required.

In long-term use of the diet, a higher risk of bone fractures [170] has been reported. Many children considered for KDT are already at risk for poor bone health due to long-term use of AEDs and potential non-ambulatory status (particularly in CP) [8]. The acidosis associated with KDT may increase this risk further. It is essential that calcium and vitamin D intakes are supplemented to meet requirements; some centres over-supplement, but there is no evidence base to support this practice. Some centres routinely monitor with dual-energy X-ray absorptiometry (DEXA) scans after 2 years on diet, but this is not a consensus, and there are limitations in the use of DEXA dependent on age and practicalities. The International Ketogenic Diet Study Group recommendations [8] include this as an optional test during follow-up and reported that less than half of centres (12/25) advocate using DEXA scans in children to evaluate for osteopenia.

Renal stones

Risk of renal stones may be higher for those children on the diet for longer periods and for those that are concurrently using carbonic anhydrase inhibitors, such as topiramate and zonisamide [171]. The use of oral citrates (potassium citrate or Effercitrate) appears to be helpful, but there is no consensus on whether these should be used empirically [8]. Often, common practice is to introduce them if urine calcium/creatinine ratio is raised, and it may be prudent to introduce early if they are taking topiramate or zonisamide. Good fluid intake of at least 100% of calculated fluid requirements is essential, with some specialists advising up to 120% of requirements if patients are deemed at higher risk of renal stones. This can be particularly challenging in children with GOR or with swallowing difficulties and needs to be considered. Renal ultrasound scans are not advised as a routine baseline investigation unless there is a perceived risk, e.g. family history [8], but they can be useful for monitoring in high risk patients.

Abnormal lipid profiles

Hyperlipidaemia has been reported in a number of KDT studies in children [163, 172–176], but whether this is associated with atherosclerotic and inflammatory risk is not clear. Cardiovascular risk can be better assessed by looking at lipoprotein fractions: LDL and HDL levels. Raised total cholesterol and LDL cholesterol is not an indication to stop the diet, but will require continued monitoring, and dietary manipulation could improve levels. This could include alternative fat sources, e.g. choosing polyunsaturated fats and considering the use of some MCT in place of LCT. There may also be a place for giving omega-3 fatty acids to normalise lipid levels [176].

It has been reported in some studies that despite initial hypercholesterolaemia, lipid levels can normalise after 12 months [163, 172] on diet, which could suggest some metabolic adaption, but the long-term impacts of KDT and hypercholesterolaemia on cardiovascular health are unknown. Studies have shown in the short term, up to 12 months, that carotid intima media thickness did not alter [177], but other studies have shown local and systemic arterial stiffness associated with KDT and raised cholesterol and triglyceride levels [178, 179]; the impact of this is not clear.

Learning points: adverse effects

- *Common early onset side effects include constipation and vomiting, which can be managed easily*
- *Long-term side effects can include renal stones, dyslipidaemia, reduced bone density and poor growth, and the risk and presence of these needs to be monitored closely*

Discontinuing the ketogenic diet

Reasons for discontinuing KDT are individual, and the decision to withdraw KDT should always be made after a joint discussion between parents, the child if they have the capacity, dietitian and neurologist. KDT is a medical treatment with risk of side effects and should not be continued if it has, unfortunately, been unsuccessful in reducing seizures in a child. The International Ketogenic Diet Study Group [8] recommends that KD should be discontinued after 3 months if unsuccessful. It has been shown that 75% of children who responded to the diet will respond within 14 days, but some can take over 2 months to respond [180]. If a trial of KD has shown no benefit, then it can be discontinued safely over days [181].

Occasionally, even if seizure control has improved on KDT, the decision may be taken to stop the diet if the child and/or family find it so restrictive or unpalatable that it is affecting adherence to diet and/or quality of life. If significant adverse effects have been experienced that have not responded to diet manipulation or medical treatment (p. 367), then it may also become necessary to stop diet. Less commonly, KDT may be discontinued after epilepsy surgery has treated a focal cause for seizures, so the diet is no longer required. In some cases it necessary to withdraw the diet when there is no access to a ketogenic service when transitioning from paediatric to adult healthcare.

The KD is not intended to be a lifelong treatment for epilepsy, and the International Ketogenic Diet Study Group advises that risks and benefits should be reviewed at every clinic appointment, and discontinuation should be considered at 2 years' duration of diet [8]. The Group also states that 'Shorter durations may be appropriate for infantile spasms and status epilepticus, but longer diet durations are likely necessary for Glut1DS and PDHD and may also be appropriate based on individual responses for other forms of intractable epilepsy'. It also recommends that there is no maximum diet duration and indeed KDT has been continued safely for more than 20 years [182].

Seizure recurrence is a potential risk of KDT discontinuation in responders, and the recurrence rate has been estimated as 14%–25% [181, 183, 184]. Factors that have been associated with increased recurrence risk include focal abnormality on magnetic resonance imaging (MRI), abnormal electroencephalogram (EEG) on discontinuation and the genetic condition tuberous sclerosis [181, 183, 184]. It is accepted practice that the diet should be gradually discontinued (a process known as 'weaning' from the KD), rather than stopped abruptly, as would be the case with any anti-epileptic medication. Stopping the diet, rather than weaning, is only relevant in rare situations where the KDT is a major risk to health, e.g. severe hypertriglyceridemia on kPN. The reverse method to introducing the diet is followed, i.e. a stepwise reduction of ratio on the CKD and increasing CHO on the MAD. Kossoff *et al*. [8] suggest reducing the ratio by 1:1 each month on CKD, e.g. 4:1 to 3:1 to 2:1, until ketosis is lost.

A faster speed of weaning off the diet has been shown not to be associated with an increased risk of seizure recurrence, and Worden *et al*. conclude that 'weeks rather than months appeared to be safe' [181]. A study by Kang *et al*. [131] suggests that in infantile spasms KDT can be discontinued after just 8 months, with no increase in seizure recurrence and improved growth compared with the more typical 2-year diet duration.

The rate of diet discontinuation should be decided in discussion with the child and parent/caregiver, as it will depend on the reason for discontinuation. If the presence of side effects or the diet being too challenging or unpalatable is the reason, then a quicker 'wean' may be preferred; in other circumstances families may be more anxious and prefer to adjust the diet more slowly.

Learning points: discontinuing KDT

- *The KD can be discontinued over days if the diet has been ineffective after a trial period (usually 3 months)*
- *If KDT has been successful, then consideration should be given to discontinuing the diet after 2 years; the majority of children can safely discontinue KDT without an increase in seizure recurrence after 2 years on diet*
- *The risk of recurrence is not associated with speed of 'weaning' the diet, although (in the absence of significant side effects) it is prudent to discontinue the diet gradually over weeks (as would be done with any anti-epileptic medication that was discontinued)*
- *When to discontinue the diet and how quickly will depend on the individual circumstances and preference and should be discussed with the patient and parent/caregiver*
- *There is no maximum diet duration, and for disorders of brain metabolism, it is generally recommended that the diet should be followed into adolescence, although the benefits of a lifelong diet are not clear*

Transition

Guidance from NICE [6] supports the use of KDT in children and young people. Unfortunately, this guidance does not recommend use in adults, as there is limited evidence and an RCT has not been undertaken in this age group. In contrast to earlier guidance, it does recommend further research into the potential applications for KDT in adults, which is ongoing within the UK [71].

Despite this there are some adult ketogenic centres in the UK, but they are limited with only 7 out of 39 centres treating adults [7]. The consequence is that over 80% of paediatric centres in the UK do not have access to transition services to adult care for KDT; children who are reaching transition age may need to be weaned off KDT. A study at Johns Hopkins Hospital [185] found that those with seizure reduction on KD experienced recurrence or worsening of seizures with attempts to wean off diet for this purpose, concluding that transition plans need to be in place for adolescents to support continued KDT in adult care. It has also been seen that

referrals for older children (over 14 years of age) are avoided to prevent this challenge when they reach transition age [186].

NICE guidance advises that service providers and commissioners [187] ensure there are systems in place for young people with epilepsy to have an agreed transition period during which their continuing epilepsy care is reviewed jointly by paediatric and adult services. Unfortunately, this is not the case within KDT services, and more work is needed nationally to improve service provision for this older age group.

Extended use of ketogenic diet therapy in paediatric dietetics

Historically, the KDT has been used exclusively in treatment of epilepsy. There is 'evidence to suggest that low-carb diets are safe and effective in the short term for improvements in glycaemic control, weight loss and cardiovascular risk in people with Type 2 diabetes', but KDT is discouraged in children with type 2 diabetes due to concern about growth [188].

There is also increasing attention on the role of KDT in a diverse range of adult neurological conditions, including Alzheimer's disease, schizophrenia and Parkinson's disease [189–191].

There is interest in KDT as a potential treatment in adult malignant gliomas by stopping glucose supply to tumour cells and as a consequence inhibiting tumour growth [192]. Extended use of KDT in oncology is not, at present, mainstream clinical practice, and a systematic review concluded that 'high-quality evidence on the effects of KDs is currently lacking in oncology patients' [193] with evidence so far limited to animal models, early phase trials and case study reports, although RCTs are in development [194].

The diet has also been associated with increased energy supply to skeletal and cardiac muscles in glycogen storage disease type III with KDT improving cardiomyopathy in case studies [195].

Learning points: extended use of ketogenic diet therapy

- *KDT is recommended by NICE for the treatment for epilepsy in paediatrics, and its effectiveness has been proven in randomised controlled trials*
- *KDT in adults for weight management and treatment of type 2 diabetes is gaining acceptance, but its use for these conditions in children is not currently recommended*
- *There is growing interest in KDT in other adult neurological conditions and as a potential treatment for gliomas, but more evidence is needed before being used as a mainstream treatment for these conditions*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

18 Childhood Cancers and Immunodeficiency Syndromes

Evelyn Ward and James Evans

Childhood Cancers

Evelyn Ward

Introduction

With advances in the treatment of childhood cancers achieving an overall survival of around 82% in developed countries [1, 2], the role of nutrition has become essential in terms of treatment, supportive care and treatment-related morbidity. Childhood cancers are rare. Currently in the UK 1 in 500 children under the age of 15 years develops a cancer, equating to approximately 1600 newly diagnosed children each year [1]. Childhood cancers generally refer up to the age of 15 years. These cancers are different from cancers affecting adults in terms of appearance, location and response to treatment. There are 21 Children's Cancer and Leukaemia Group (CCLG) principal treatment centres (PTC) in the UK with many having dedicated Teenage Cancer Trust Units where adolescents and young adults are treated. Many of the 21 PTCs have shared care facilities with local district general hospital paediatric departments known as paediatric oncology shared care units (POSCU).

The use of refined multimodal therapy and combination chemotherapy, as well as new immunotherapies, continues to result in an ever increasing number of children and young people being treated and surviving childhood cancers. New second and third line treatments for relapsed disease have also led to an increase in the numbers susceptible to the nutritional problems associated with their disease, treatment and survivorship. The need for optimal nutritional status to deal with the rigours of the disease and treatments as well as to maintain healthy growth and development throughout treatment, which can often span several months if not years, is paramount.

Implications relating to nutritional status

During cancer treatment poor nutritional status is linked to adverse outcomes. Both undernutrition and overnutrition can lead to clinical complications, higher relapse rates, reduced well-being and quality of life [3–9]. Malnutrition contributes to a reduced tolerance to therapy, altered drug metabolism, delayed wound healing and decreased immune function leading to increased risk of infection and longer hospital stay [10–16]. However, the existence of malnutrition at diagnosis or during treatment on overall survival is controversial and may depend on the disease and its extent [14, 17].

Learning points: implications of nutritional status

- *The provision of appropriate and effective nutritional support and advice for the child undergoing treatment for cancer is well recognised as an important part of supportive care in order to:*
  - *reverse any malnutrition seen at diagnosis*
  - *prevent malnutrition associated with treatment*
  - *enhance therapy and improve tolerance to treatment*

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

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  - *promote growth and development*
  - *improve immunological status*
  - *improve general quality of life*
- *Overnutrition and undernutrition are both recognised as major nutritional concerns in both the short- and long-term [18]*
- *Both can lead to adverse outcomes such as more complications, higher relapse rates, reduced well-being and quality of life*

Types of cancers seen in childhood

The types of cancers seen in children can be divided into three main groups:

- leukaemias
- lymphomas
- solid tumours

Table 18.1 gives information on diagnostic tests, treatment and 5-year survival rates [1, 2].

Leukaemias

Leukaemia is the most common malignant disease in infancy and childhood and accounts for 31% of all childhood cancers. Acute lymphoblastic leukaemia (ALL) is the most common form of the disease. Approximately 80% of ALL in children is of precursor B-cell origin, about 15% is T cell, and 5% is more mature B-cell derived [19]. Acute myeloid leukaemia (AML) is the second most common leukaemia accounting for 10%–15% of leukaemias, with 15%–20% of the cases occurring in patients with predisposing conditions that include certain congenital syndromes such as Down's syndrome, Li-Fraumeni syndrome or DNA instability syndromes such as Fanconi anaemia [20]. Although rare, accounting for 15% of leukaemias, chronic myeloid leukaemia (CML) can occur in older children. It should be noted that prognosis in infants with ALL is poor.

The leukaemias are fatal unless treated and clinical features at presentation include bone marrow failure, anaemia, neutropenia (fever, malaise), thrombocytopenia (bruising, purpura, bleeding gums, nose bleeds) and organ infiltration, tender bones, lymphadenopathy, splenomegaly and hepatomegaly.

Current treatment for ALL includes initial induction chemotherapy aimed at achieving remission. The protocol is graded as regimen A for those children with standard risk disease, regimen B for those children with intermediate risk disease and regimen C for those children with high risk disease who have not responded to initial treatment or those with poor cytogenetics: Philadelphia chromosome t (9;22), near haploidy (<44 chromosomes), iAMP21 t (17;19) and MLL gene arrangement. All of these are rare.

Following induction the next phase of treatment is consolidation, and central nervous system (CNS) treatment aimed to prevent or treat CNS disease. There are one to two intensification treatment blocks in children depending on the presence of any minimal residual disease (MRD) detected after induction chemotherapy.

Maintenance chemotherapy is then given for up to 2 years in girls and up to 3 years in boys.

Intensive chemotherapy is primarily the treatment for AML, generally given as four blocks of chemotherapy, 3 weeks apart, but is dependent on neutrophil-count recovery.

Lymphomas

Lymphomas account for approximately 10% of all childhood cancers and can be divided into two main groups:

- Non-Hodgkin's lymphomas (NHL) account for 60% of lymphomas and are a large group of lymphoid tumours. Those most commonly seen in children include B-cell NHL and T-cell NHL. The majority of patients present with asymmetric enlargement of lymph nodes in one or more peripheral lymph node regions. Those with diffuse bone marrow disease present with anaemia, neutropenia or thrombocytopenia.
- Hodgkin's lymphoma accounts for 40% of lymphomas. Presenting symptoms are usually painless cervical and/or mediastinal adenopathy. Symptoms also usually include fever, night sweats, weight loss, fatigue and anorexia.

Solid tumours

Solid tumours account for approximately 45% of all malignant disease in children. The most common solid tumours are as follows:

- *Brain tumours*. Brain and spinal CNS tumours are the most common solid tumours with medulloblastoma the most common CNS tumour. Signs and symptoms of CNS tumours are generally caused by increased intracranial pressure including headaches, vomiting, drowsiness, irritability, fits and diplopia. Other symptoms may include weakness or unsteadiness on walking.
- *Neuroblastoma* accounts for 8% of all childhood cancers. It arises from the neural crest tissue in the adrenal medulla and elsewhere in the sympathetic nervous system; therefore, it most frequently occurs in one of the adrenal glands but can also occur alongside the spinal cord in the neck, chest, abdomen or pelvis. Most children present with an abdominal mass, loss of appetite, lethargy and bone pain. At presentation the tumour mass can often be large and complex. The presence of the biological marker MYCN, (known as MYCN amplification) suggests more aggressive disease, and treatment is more intensive. Treatment and survival depends on the stage of the disease.
- *Wilms' tumour* is a congenital malignant kidney tumour, which can be bilateral. The majority present with a large abdominal mass. Other symptoms may include poor weight gain and loss of appetite, blood in the urine and

Table 18.1 Common age of occurrence, diagnostic tests, treatment and 5-year survival rates for some childhood cancers.

Diagnosis	Common age range	Diagnostic tests	Treatment					5-year survival rate
			Chemotherapy	Surgery	Radiotherapy	HSCT	Other	
ALL	3–7 years	Blood tests Bone marrow aspirate Lumber puncture	Yes		May be needed if CNS or testicular disease at diagnosis	Yes – if likely to recur or relapsed disease	Steroids	87%
AML	3–7 years	Blood tests Bone marrow aspirate Lumber puncture	Yes		May be needed if CNS disease at diagnosis	Yes – if likely to recur or relapsed disease		67%
NHL	Any age	Blood tests Biopsy, bone marrow aspirate x-ray, USS, CT, MRI scans	Yes			Yes – if relapsed disease	Steroids Rituximab	85%
Hodgkin's lymphoma	Adolescents	Blood tests x-ray, CT, MRI, PET scans	Yes		Yes – if extended disease or poor response to chemotherapy	Yes – if relapsed disease	Steroids	95%
Medulloblastoma	Any age	Biopsy CT, MRI scan Biological markers	Yes	Yes	Yes – if over 3 years of age		Steroids to reduce swelling around the brain	80% standard risk disease 60% high risk disease
Neuroblastoma	≤5 years	Blood tests, x-ray MIBG, CT, MRI scans Urinary catecholamine Biopsy Biological markers – to check if MYCN amplification Bone marrow aspirate	Yes – unless stage 1 and complete surgical resection	Yes	Yes – high risk disease	Yes – high risk disease	High risk disease 1-*cis*-retinoic acid Dinutuximab (ant-GD2) +/– interleukin–2	67%
Wilms' tumour	≤5 years	Blood tests USS, CT, MRI scans Biopsy	Yes – unless stage 1 disease	Yes	Yes – if poor histology			90%
Rhabdomyosarcoma	≤10 years	Blood tests CT, MRI scans Biopsy	Yes	Yes	Yes – depending on histology			67%
Ewing's sarcoma/ pPNET	Adolescents and older children	Blood test CT, MRI scans Biopsy	Yes	Yes	Yes – if incomplete surgical resection	Yes – if poor response		66%
Osteosarcoma	Adolescents and older children	Blood tests CT, MRI scans Biospy	Yes	Yes	Yes – if poor response		Mifamurtide	60%
Retinoblastoma	≤5 years	Eye examination Blood test for RB gene	Yes	In some cases – enucleation			Cryotherapy, laser therapy, brachytherapy	95%

ALL, acute lymphoblastic leukaemia; CNS, central nervous system; AML, acute myeloid leukaemia; NHL, non-Hodgkin's lymphoma; USS ultrasound scan; CT/MRI, computerised tomography/magnetic resonance imaging; PET, positron emission tomography; MIBG, iodine-123 meta-iodobenzylguanidine; pPNET, peripheral primitive neuroectodermal tumour.
Source: Adapted from [1, 2].

high blood pressure. Children with the WT1 gene or WT1 syndromes have an increased risk of developing a Wilms' tumour.

- *Rhabdomyosarcoma* is the most common type of soft tissue sarcoma in children that develops from muscle or fibrous tissue. There are two main subgroups: embryonal (80%) and alveolar (20%). Rhabdomyosarcoma occurs at a wide variety of primary sites but is most common around the head and neck. Other sites include genito-urinary and occasionally limb, chest or abdominal wall.
- *Ewing's sarcoma and peripheral primitive neuroectodermal tumour (pPNET)*. Ewing's sarcoma is a type of bone tumour. Any bone can be affected, but it is more common in the pelvis, femur or shin bone. Persistent localised bone pain is a characteristic symptom that usually precedes the detection of a mass. pPNET is a soft tissue sarcoma of neuroepithelial origin, which can be thought of as being similar to a Ewing's sarcoma.
- *Osteosarcoma* is a high grade bone tumour. It often occurs at the end of bones where new bone tissue is forming, predominantly in the arms or legs, particularly around the knee. Pain and swelling around the affected bone are the most common symptoms.
- *Retinoblastoma* is the commonest malignant eye tumour in children, accounting for around 3% of childhood cancers. All bilateral tumours are thought to be hereditary due to the RB1 gene in 40% of cases, as are 15% of unilateral cases. Children of affected families are screened from birth.
- Additional information on rarer tumours, e.g. hepatoblastoma and germ cell tumours, can be obtained from the Children's Cancer and Leukaemia Group (CCLG) website [1].

Aetiology of malnutrition in children with cancer

The incidence of malnutrition in children at diagnosis differs partly due to variation in the studies conducted in different types of paediatric malignancies and variation in the nutritional assessment parameters used [14]. A review of studies concluded an estimated prevalence in developed countries to be [21]:

- 5%–10% at diagnosis and around 0%–5% during treatment for leukaemia
- 50% at diagnosis and 20%–50% during treatment for neuroblastoma
- 0%–30% at diagnosis and during treatment for other solid tumour patients

Consensus is that the risk of nutritional morbidity is higher in children with advanced disease, metastatic solid tumours and higher treatment intensity. The initial nutritional problems resulting from the tumour are soon compounded by iatrogenic nutritional abnormalities, the consequence of the treatment and its complications. Metabolic and psychological factors also have a role [22–25].

Metabolic factors

Cancer cachexia is complex and multifactorial involving involuntary progressive weight loss as a result of skeletal muscle mass depletion with or without adipose tissue depletion. It is characterised by systematic inflammation and metabolic changes resulting in a negative protein and energy balance leading to progressive functional impairment. Additional factors to consider in a diagnosis of cancer cachexia are chronic inflammation, anaemia, protein depletion, anorexia and fatigue [26]. Although studies in the 1990s demonstrated changes in the metabolism of fat, carbohydrate and protein in the child with cancer [10, 27, 28], a recent review paper suggested that the presence of cachexia in children could not be confirmed [21]. More robust studies are required to determine the presence of the inflammatory process in childhood cancer patients and its impact on nutritional status [21, 23]. Other factors can affect the metabolic turnover of a child with cancer such as age, gender, nutritional status, body composition, hormones, physical activity, energy intake, anti-cancer treatment, surgical stress and infections [23].

Complications of the disease and treatment

In childhood cancer, malnutrition is generally due to an insufficient intake and absorption of nutrients caused by gastrointestinal (GI) side effects of treatment [22]. Anorexia, stomatitis, mucositis, constipation, vomiting, diarrhoea and dysgeusia are important contributory factors to the weight loss seen in children undergoing treatment for cancer [29]. Table 18.2 shows the side effects relating to drugs commonly used in treatment of paediatric malignancies.

Psychological factors

Learned food aversions, nausea and vomiting associated with foods consumed close to chemotherapy administration, have been demonstrated in children with cancer along with the phenomenon of anticipatory vomiting [30]. Food is one area of treatment that both the child and parent can try to control resulting in increased tension and anxiety around food, which can lead to negative feeding behaviour and eating becoming an unpleasant experience for both the child and their family.

Identification of nutritional risk and assessment

Assessment of nutritional status is a vital component of supportive care and is essential for monitoring the need for nutritional intervention. Nutritional status indices may be useful prognostic markers of response to therapy or toxicity [31]. Despite height and weight measurements being the mainstay of nutritional assessment in children with cancer [32], the reliability of weight-related indices is reduced in children with solid tumours, as outlined in Table 18.3. Assessment at

Table 18.2 Side effects relating to treatment seen in paediatric oncology patients.

Side effect	Causative drug
Infection	Both chemotherapy and radiotherapy are known immune depressants
Diarrhoea	Actinomycin, doxorubicin, methotrexate, cytosine, interleukin-2, irinotcan
Nausea and vomiting	Actinomycin, carboplatin, cisplatin, cyclophosphamide, doxorubicin, ifosfamide, cytosine, etoposide, methotrexate, procarbazine, thioguanine, interleukin-2
Stomatitis mucositis	Actinomycin, adriamycin, daunorubicin, doxorubicin, epirubicin, bleomycin, melphalan, methotrexate
Renal damage and nutrient loss	Cisplatin, cyclophophamide, ifosfamide
Constipation	Vincristine
Weight gain and raised blood glucose levels	Dexamethasone, prednisolone
Hypoalbuminaemia	L-Asparaginase, dinutuximab
Pancreatitis	L-Asparaginase
Weight loss	α-Interferon
Bone morbidity	Dexamethasone, prednisolone, methotrexate, ifosfamide Vincristine (due to reduced physical activity) L-Asparaginase associated with osteonecrosis

Table 18.3 Anthropometric assessment.

Anthropometric assessment	Potential limitations
• Weight	• Can be unreliable due to solid tumour mass/ascites/hyper-hydration given with chemotherapy
• Height	• Some lack of growth in height is observed in children undergoing treatment for cancer
• Growth charts	• A decrease in current centiles for weight (or height) of two major centiles – indication for nutritional support
• Percentage weight:height	• Percentage weight:height ≤90% – can be indication for nutritional support
• BMI	• Weight change can be distorted by large solid tumours therefore not reliable and doesn't correlate to changes in fat free mass
• Total weight loss ≥5% relative to pre-illness weight	• Check – some weight loss may be due to solid tumour shrinkage or post-surgical resection
• Mid upper arm circumference (MUAC)	• Useful measurement to do in children with solid tumours as independent of tumour shrinkage
• Triceps skinfold thickness (TST)	• Not routinely used in clinical practice

diagnosis may not be the best indicator of overall nutritional status, indicating the need for ongoing nutritional assessment and intervention throughout treatment [33].

It is well documented that the nutritional risk of the child with cancer is associated with the diagnosis of certain tumours and stages of the disease, either as a result of the underlying disease and/or as a result of the anticipated toxicity from the current treatment protocol (Table 18.4) [23, 33, 34]. Studies highlight that there is no simple method to accurately identify poor nutritional status in children treated for malignancy, and there is also inconsistency between treatment centres [35, 36]. The UK Royal College of Nursing (RCN) in their guideline *Nutrition in children and young people with cancer* includes a condition specific assessment tool based on STAMP (screening tool for the assessment of malnutrition in paediatrics) [37] and the disease criteria in Table 18.4 [38]. However it has not been audited or validated. SCAN (nutrition screening tool for childhood cancer) has been assessed for children and young people with cancer. It is designed to identify those who are at risk of malnutrition by asking six questions [39]:

- Do they have a high risk cancer?
- Are they currently undergoing intensive treatment?
- Do they have any GI tract symptoms?
- Have they had a poor intake over the past week?
- Any weight loss over the past month?
- Do they show any signs of under nutrition?

In practice assessment tends to be a combination of nutritional risk based on diagnosis (Table 18.4), anthropometrics and questions similar to the SCAN screening tool.

Learning points: nutritional risk and assessment

- *In children with cancer body weight can be influenced by tumour mass and hydration given alongside chemotherapy*
- *This can mask loss of fat and skeletal muscle*
- *There are no simple measures that accurately identify poor nutritional status in children with cancer*
- *In practice nutritional risk is associated with the diagnosis and stage of the disease, age of the child and intensity of the treatment*

Nutritional requirements and feeding

- Non-catabolic, low nutritional risk: aim for estimated average requirement (EAR) for energy and the reference nutrient intake (RNI) for protein, vitamins and minerals [40, 41]
- Catabolic children, undernourished children or children with increased losses due to the GI losses or renal tubular losses: an estimation of the protein and energy requirements for sick children is given in Table 1.13
- Consideration of requirements and method of nutritional support must take into account the child's age, weight and clinical condition

Table 18.4 Types of childhood cancers associated with high or low nutritional risk and high risk of fat accumulation [23, 33, 34].

High nutritional risk	Low nutritional risk	High risk of fat accumulation
Advanced disease during initial intense treatment	ALL regimen A patients	ALL patients on corticosteriods
High risk neuroblastoma	Non metastatic solid tumours	Craniopharyngioma
Stage III and IV Wilms' tumour	Retinoblastoma	Other malignancies with large or prolonged does of corticosteroids
High risk rabdomyosarcoma	Hodgkin's disease	Total body or cranial irradiation
Ewing's sarcoma/pPNET	Germ cell tumours	
Osteosarcoma	Advanced disease in remission during maintenance treatment	
Medulloblastoma/CNS PNET		
Diencephalic tumour		
Nasopharyngeal tumour		
B-cell NHL		
AML Some ALL Infants and teenagers Regimen B and C Patients relapsed ALL		
Bone marrow-transplant patients Allogeneic Autologous		

pPNETnet, peripheral primitive neuroectodermal tumour; CNS PNET, central nervous system primitive neuroectodermal tumour; NHL, non-Hodgkin's lymphoma; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia.

- Energy intake should be regularly reviewed, particularly in children at high risk of fat accumulation (Table 18.4)

With changes in body composition now well documented and highlighting an increase in fat mass and risk of overnutrition in children treated for cancer, requirements for energy in particular should be regularly reviewed throughout the child's treatment [22, 42]. Although there is an increased awareness to try to improve the physical activity of children undergoing treatment for cancer, for the non-catabolic child who is inactive energy requirements should be adjusted accordingly for low physical activity [43].

Oral feeding

Advice should be given routinely about:

- the impact of cancer and its treatment on nutritional status
- eating problems related to the side effects of treatment [44]
- food safety [44]
- use of high energy foods, food fortification and small frequent meals and snacks [44]

Oral nutritional supplements

Oral feeding is the best method of nutrition support in patients with a low nutritional risk if they are able to consume enough food. However, some will require oral nutritional supplements. In clinical practice their consumption can be limited mainly due to treatment-related taste alterations and compliance. The following should be considered:

- Advice on how to modify sip feeds, e.g. adding to normal commercial milkshakes or juice; trying as ice lollies; using neutral flavoured supplements to add to milk to drink, milk for breakfast cereals, soups, puddings
- Fresh milk-based supplements are more acceptable [45]
- Low volume energy supplements can be more acceptable either taken on their own like a 'medicine' or added to food and drinks
- Nutritionally complete 'compact' supplements should be considered as less volume needs to be consumed

The aim should be to provide the right food at the right time by taking a flexible approach tailored to the individual needs of the child [46]. With this is mind some treatment centres have the facility for meals and/or snacks to be prepared at ward level to achieve this more flexible approach to eating.

Enteral nutrition

Children at higher nutritional risk due to their disease and/or treatment should be identified early in treatment

and enteral nutrition (tube feeding) instigated. Early intervention can prevent nutritional decline during treatment [47]. It is well documented [48–50] that enteral nutrition is successful in:

- reversing any malnutrition seen at diagnosis
- improving nutritional status and maintaining an adequate nutritional status
- improving energy intake and well-being
- offering an alternative route for fluid and medication. Children on treatment frequently require additional electrolyte supplementation such as potassium, phosphate; an enteral tube *in situ* can help with their administration and subsequently improve compliance
- helping to reduce both parental and child anxiety related to trying to achieve an adequate oral intake

Enteral nutrition has advantages over parenteral nutrition (PN) [34, 49, 50]. While nasogastric feeding is effective, when there is a need for long-term nutrition support or there are problems such as vomiting, thrombocytopenia, mucositis or dysphagia, a gastrostomy tube is more beneficial. Gastrostomy feeding is safe, effective and only associated with minor complications [51–54]. Table 18.5 gives criteria for gastrostomy tube placement in children with cancer. Jejunal feeding should be considered in children with prolonged vomiting or gastric dysmotility associated with treatment in whom antiemetics and prokinetics have had a limited effect. A gastrostomy/jejunostomy feeding tube has proved useful in children with brain tumours who have an unsafe swallow post operatively and vomit large bolus gastrostomy feeds.

The choice of enteral feed depends on the child's age, GI function and, to some degree, their treatment protocol. A wide variety of feeds and formulas are used in paediatric oncology:

- Generally an age-appropriate standard enteral feed is tolerated in children with normal GI function
- A fibre-containing feed should be used in children at risk of constipation due to treatment with vincristine, e.g. ALL, brain/spinal CNS tumours
- A hydrolysed protein feed is recommended if there is impaired GI function due to malabsorption, lower gut mucositis, radiation enteritis, graft versus host disease (GvHD) or when weaning off PN
- An amino acid-based formula may be required if a hydrolysed protein feed is not tolerated, e.g. with severe lower gut mucositis, grade III GvHD
- A higher energy feed should be used if there are increased energy requirements or to maximise intake over a shorter period of time
- A higher energy feed is beneficial if there is a fluid restriction due to, e.g. veno-occlusive disease (VOD) or fluid overload
- A higher energy feed is also used where, due to abdominal disease, large feed volumes are not tolerated, e.g. neuroblastoma, hepatoblastoma, Wilms' tumour
- A trial of a lactose-free feed may be necessary if diarrhoea does not settle post-chemotherapy, or the child has had rotavirus or norovirus infections
- A minimal long-chain triglyceride (LCT) formula is indicated if there is post-operative chylothorax, e.g. neuroblastoma

Table 18.5 Indications for gastrostomy placement.

Indications for gastrostomy placement
Patients treated on intensive protocols with high emetogenicity or risk of mucositis
Patients requiring long-term nutritional support ≥3 months
Patients unwilling to accept or tolerate a nasogastric tube
Adolescent patients should routinely be offered the choice of a gastrostomy
Nasopharyngeal carcinoma or any other tumour in head and neck area requiring radiotherapy treatment
Brain or CNS tumour with post-operative swallowing dysfunction
Contraindications for gastrostomy placement
Poor anaesthetic risk
Short-term feeding <3 months
Abdominal disease present (individual assessment)

CNS, central nervous system.

The volume and delivery of the feed regimen should be determined according to the child's normal daily routine and can be provided as a continuous infusion, intermittent bolus feeds or a combination of both:

- Continuous feed regimens are usually better tolerated than intermittent bolus feeding due to the GI side effects of treatment such as nausea and vomiting
- During periods of intensive treatment or admissions for febrile neutropenia, it may be necessary to feed continuously 20–24 hours in order to achieve tolerance and maximum nutrient intake
- Children prone to vomiting and those with large abdominal masses tolerate continuous feeding with frequent breaks by feeding in cycles of say 5 hours with 1 hour rest
- In between treatments and when at home, most children are able to tolerate bolus feeds or combination of continuous and bolus feeding

Frequent monitoring is essential to provide effective nutrition support as feed tolerance and oral intake can vary due to treatment and its side effects. The majority of children will require enteral feeding throughout their intensive treatment protocol, but once treatment is completed or they go onto maintenance treatment, an effort should be made to wean off enteral feeding. Maintaining some oral intake while being tube fed can make this process a lot easier and quicker. Input from a psychologist is helpful for those with feeding behaviour problems struggling to get off enteral feeding.

Infants treated for cancer can be more challenging due to the length of treatment, problems with gut toxicity and stomatitis. Starting complementary feeding around 17 weeks of age may be considered to establish some oral feeding skills

in between periods of severe oral mucositis; otherwise feeding development is delayed making it harder for the infant to develop normal feeding skills [55]. Input from a speech and language therapist should be considered.

Learning points: enteral nutrition

Adequate enteral feeding support can be provided even in children at risk of mucositis by:

- *identifying those at risk early in treatment*
- *early tube placement*
- *type of feed – consider hydrolysed protein feed if there is lower gut toxicity*

Parenteral nutrition

A Cochrane review highlighted there is limited evidence from individual trials to suggest that PN is more effective than enteral nutrition in well-nourished children and young people with cancer undergoing chemotherapy [56]. PN is generally indicated in children with:

- neutropenic enterocolitis
- ileus or bowel obstruction
- typhlitis
- severe mucositis
- severe GvHD of the gut following haemopoietic stem cell transplant (HSCT)
- chylous ascites post-surgery when there is no response to a minimal LCT diet

Careful consideration should be given before commencement of PN; it is of limited nutritional benefit if given for less than 1 week [57]. Metabolic complications of PN are described [58] and are not significantly different between children with malignancies and other children requiring PN. The child's clinical condition may also limit the effectiveness of PN. The majority of children with cancer will have central venous access. Table 18.6 highlights potential problems and solutions in using PN in children treated for cancer and post-HSCT.

Nutrition and the child with cancer undergoing haemopoietic stem cell transplant

HSCT is widely used in children with malignancies. Allogeneic transplant is indicated for patients with high risk leukaemia or patients with leukaemia who have disease recurrence. Some children with solid tumours, e.g. high risk neuroblastoma and Ewing's sarcoma may undergo autologous stem cell transplantation.

The priming chemotherapy causes severe nausea, vomiting, mucositis, diarrhoea and protein-losing enteropathy. Transient intestinal failure is common. Nutrition support is provided to minimise the morbidity of both the conditioning regimens and complications resulting from the procedure such as GvHD or VOD of the liver.

VOD can be life-threatening and is typically characterised by hyperbilirubinaemia, hepatomegaly, hypoalbuminaemia, increased platelet consumption, rapid weight gain and ascites [59]. Incidence rates of 60% have been reported, however few studies report an incidence above 40% [60].

PN continues to have a role in children who develop severe GI toxicity or GvHD. Table 18.6 highlights some of the

Table 18.6 Challenges and solutions in the use of parenteral nutrition in children with cancer and post-HSCT.

PN challenges	Potential solution
Fluid restriction due to VOD, fluid overload, drug and blood product volumes	Check child has central venous access Use more concentrated solutions to maximise protein and energy intake
Ascites related to VOD	Keep sodium addition to a minimum
Large diarrhoeal losses due to mucositis or GvHD	Close monitoring of electrolytes and if safe may require additions above normal recommended amounts [58]
Renal tubular losses post-cisplatin or ifosfamide chemotherapy	Close monitoring of electrolytes and if safe may require additions above normal recommended amounts [58]
Hypokalaemia due to antifungal amphotericin	If safe increase potassium in PN Consider use of potassium sparing diuretics – amiloride, spironolactone, potassium canrenoate Monitor blood potassium levels
Risk of iron overload	Parenteral iron is not given routinely due to the majority of patients receiving frequent blood transfusions
Low blood zinc and selenium levels	Routinely monitor trace element levels if on PN for >2 weeks
Hyperglycaemia due to steroids for management of GvHD	Consider insulin infusion if a reduction in glucose in PN would compromise nutritional intake
VOD – hyperbilirubinaemia/abnormal LFTs	Consider ω3PUFA and MCT lipid solution, e.g. SMOFlipid

HSCT, haemopoietic stem cell transplant; PN, parenteral nutrition; VOD, veno-occlusive disease; GvHD, graft vs. host disease; LFT, liver function test; PUFA, polyunsaturated fatty acid; MCT, medium chain triglyceride.

potential challenges and solutions to using PN in children following HSCT.

Adequate nutrition support can be provided enterally [61, 62], and during periods of gut toxicity, a hydrolysed protein-based feed is recommended or an amino acid-based formula if this is not tolerated. Some centres use a graded dietary guideline for children with GvHD consisting of different phases relating to the grade of GvHD. An example is given below:

- phase 1 – gut rest and supported with PN (Grade IV GvHD)
- phase 2 – clear liquid diet and amino acid-based enteral feed (Grade III GvHD)
- phase 3 – low fat, low fibre, low acid, low irritant, lactose-free diet (Grade III–II GvHD)
- phase 4 – continuation of low fat, low fibre, low acid, low irritant, lactose-free diet (Grade II GvHD)
- phase 5 – lactose-free diet (Grade II–I GvHD) [63, 64]

Children who receive a cord blood stem cell transplant may have prolonged diarrhoea that is distinct from GvHD, and if all other causes have been excluded, cord colitis syndrome may be considered [65, 66]. Treatment involves a 10- to 14-day course of metronidazole alone or in combination with a fluoroquinolone.

In addition patients undergoing bone marrow transplant (BMT) are severely neutropenic and need to have a 'neutropenic' diet to prevent GI infection from food-borne pathogens. The provision of a neutropenic diet is described elsewhere (p. 49).

Learning points: monitoring and follow-up

- *Children on nutritional support need frequent monitoring and review throughout treatment*
- *It is often necessary to change the method of nutritional support, type of enteral feed and route of delivery depending on treatment, nutritional status and tolerance*
- *Once on maintenance treatment or completed treatment follow-up continues until weaned off enteral tube feeding or if still tube feed dependent, care may be transferred to local dietetic services:*
  - *advice on the importance of following a healthy diet and exercise should routinely be given at the end of treatment review with the medical team*
  - *medical follow-up, repeat scans and blood tests continue at regular intervals, although they reduce in frequency until 5 years off treatment when care will transfer to annual review at the late effects clinic*

Steroid-induced diabetes

Children treated for ALL regularly receive the corticosteroid dexamethasone as part of their treatment. Dexamethasone has potent lymphocytotoxic activity causing lymphoblast lysis. Side effects include an increased appetite and raised blood glucose levels. Hyperglycaemia is usually only transient while the child is receiving the dexamethasone; however, in some cases it may be permanent. Children who appear more susceptible to hyperglycaemia include those with a family history of diabetes, those overweight at diagnosis and older children and adolescents.

Sliding scale intravenous insulin is given until blood sugar levels are controlled. Subsequently an alteration in diet may be all that is necessary to control blood sugar levels; however, a twice daily injection of premixed analogue and isophane insulin may be advised, or a basal bolus regimen. Using basal and rapid-acting analogue insulins allows greater flexibility with regard to mealtimes as there is no need to adhere to rigid meals and snacks as a bolus of insulin is injected prior to food. Children treated for ALL can have variable appetites and food intakes, and hence a basal bolus regimen allows for this variation.

Dietary advice should be simple: the avoidance of rapidly absorbed carbohydrate with suitable alternatives and snack suggestions. Restriction of high fat foods and increased fibre intake may not be appropriate in children who have poor appetites and who would be unable to achieve an adequate energy intake.

Late effects of treatment

The development of curative therapy for the majority of paediatric cancers has resulted in a growing population of childhood cancer survivors who are at an increased risk of various health problems [67, 68].

Bone morbidity

Bone morbidity in children with cancer both during and after completion of treatment is increasingly recognised as both a short-term and long-term problem [69, 70]. This is especially the case in children who receive large cumulative doses of glucocorticosteroids and methotrexate for treatment, such as ALL. Risk factors, particularly for children treated for ALL, are highlighted in Figure 18.1. Other patients at risk include those treated for Ewing's sarcoma and osteosarcoma who have received methotrexate and ifosfamide [67, 74].

During treatment the majority of PTCs routinely check vitamin D status at diagnosis and at regular intervals during treatment. Vitamin D supplementation during treatment is advised in line with current national guidelines [75] (Table 18.7). As a precaution, some centres are not supplementing vitamin D during induction chemotherapy for ALL due to the potential risk of hyperphosphataemia based on one small study [76]. Children and young people who are 5 years off treatment and attend long-term follow-up clinics annually will routinely have vitamin D levels measured.

Osteonecrosis is a debilitating complication seen both during and after treatment for ALL and is an iatrogenic complication attributed to the risk factors highlighted in Figure 18.1.

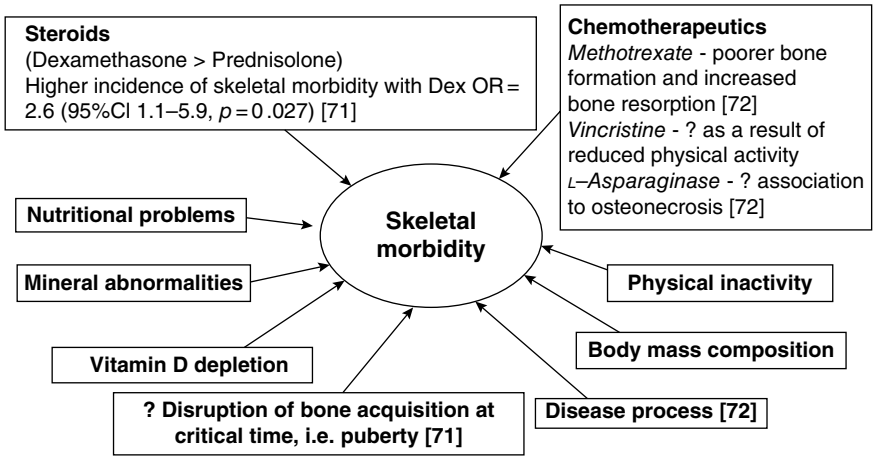

Figure 18.1 Factors that contribute to skeletal morbidity in patients with ALL. ALL, acute lymphoblastic anaemia; ? = other potential factors.

Table 18.7 Serum 25-hydroxyvitamin D concentrations, health and disease [75].

Serum 25(OH)D (nmol/L)	Vitamin D status	Manifestations	Management
<25	Deficient	Rickets Osteomalacia	Treat with high dose calciferol
25–50	Insufficient	Associated with disease	Vitamin D supplementation: 400 IU (10 µg)
50–75	Adequate	Healthy	Lifestyle advice
>75	Optimal	Healthy	None

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The prevalence is around 5.5% with 38% of patients requiring some form of surgery [77].

Correction of bone mineral loss may be possible by correcting dietary deficiencies including those of calcium and vitamin D; however, in some cases bisphosphonates such as pamidronate or alendronate are given. Advice on improving diet and physical activity should be recognised as a strategy for amelioration and prevention [74].

Obesity

Another well-reported effect in childhood cancer survivors is the prevalence of obesity, particularly in children treated for ALL and brain tumours [11, 78, 79]. The majority of studies have looked at ALL survivors where, as well as obesity, there is a high prevalence of endocrine and metabolic disorders such as growth hormone deficiency, hypothyroidism, insulin resistance, hyperlipidaemia and increased cardiovascular risk [80, 81].

The mechanism for the onset of obesity following treatment for ALL may be partly due to a sustained imbalance between energy expenditure and energy intake. Lack of physical activity, high energy intake and metabolic changes following prolonged courses of chemotherapy and steroids may all play a part in altering body composition in ALL survivors [81–84].

Attention is also focusing on the increased risk of obesity during treatment (Table 18.4), with a prevalence ranging from 25% to 40% [85]. Studies have identified that significant weight gain can occur in ALL patients between diagnosis and the end of treatment [83–86]. As well as affecting emotional and social health-related quality of life [8], studies suggest it may influence survival rates [4, 7, 87]. The mechanisms for weight-influencing event-free survival are unclear. Some possibilities include pharmokinetic variations on chemotherapy, direct influence on adipose tissue on leukaemia resistance, differences in protein synthesis and haematopoietic reserves causing reduced target dose delivery or other yet unidentified causes [4]. Studies vary as to when the risk of obesity is highest during treatment for ALL [4, 7, 86] so routinely giving advice on 'healthy eating' and exercise throughout the different stages of treatment should be considered, with monitoring of weight and BMI to guard against overweight and obesity.

Learning points: nutrition related late effects of treatment

These include:

- *overweight and obesity*
- *endocrine and metabolic problems*
- *growth hormone deficiency*
- *hypothyroidism*
- *insulin resistance*
- *hyperlipidaemia*
- *bone morbidity*

As weight gain and obesity are identified as risk factors during treatment for ALL, advice on healthy eating and exercise should be given during treatment and reiterated at the end of treatment.

Complementary and alternative diets

Some families will seek out alternative treatments on the internet including the role of alternative or complementary nutritional therapies. They seek information on food choices, dietary supplements and complementary nutritional therapies in a bid to improve quality of life and increase chances of survival [88]. The majority of such diets are made up of components that claim to have three major functions: detoxification, strengthening of the immune system and specific therapies to attack the cancer cell [83].

Apart from a lack of robust evidence for their use, these diets are not recommended for children being treated for cancer [89, 90] as they:

- usually advocate a strict vegetarian or vegan regimen, restrict animal products, refined carbohydrates and only allow small quantities of fat
- can be high fibre, high fruit/fruit juice/juicing and vegetable-based diets
- can involve fasting and use of laxatives and enemas
- advise addition of supplements that can be toxic in high doses

This can result in early satiety and diarrhoea leading to weight loss [90]. The low energy density and low protein content can lead to malnutrition, which in turn can result in a reduced immune function, increased toxicity from conventional treatment and, therefore, a poorer response [89].

High doses of vitamins and minerals may be harmful to children and there being a risk of interaction with conventional treatment. It is essential that any parent contemplating the use of an alternative diet seeks appropriate advice from their child's physician or dietitian. Frenkel *et al*. provide useful information on 10 supplements that have the best suggestions for benefit, highlighting the safety and interactions of the supplements [91]. Best practice is to discuss any potential supplements parents may want to give their child with the hospital pharmacist involved in their care. They will be aware of potential interactions with all medications the child is taking. A useful information book for families is *Complementary and natural therapies for your child* available from the CCLG website [92].

Areas requiring further research

Vitamin supplementation/antioxidants

Certain chemotherapy agents' mode of action involves the generation of free radical oxidants to cause cellular damage and necrosis/apoptosis of malignant cells. The formation of free radicals, leading to oxidative stress, is one of the main pathogenic mechanisms for toxicity with toxicity being a dose limiting factor for treatment. However, there is concern that the formation of reactive oxygen species by antioxidants during treatment may impair the action of some chemotherapy drugs [93, 94]. A small study has shown an inadequate antioxidant intake, especially in children not on any form of dietary supplementation [95].

Currently there are very few good quality studies looking at changes in antioxidant status and oxidative stress in children undergoing treatment for cancer. It is clear that further research is required, and until then the UK Paediatric Oncology Dietitians' Group advises the following for children with cancer:

- Generally children on supplementary enteral feeds or nutritionally complete oral nutritional supplements should not need additional vitamin and mineral supplements
- Megadoses of a single vitamin or combination of vitamins should be advised against (with the exception of prescribed vitamin D)
- Children not receiving nutritional support who have a limited fruit and vegetable intake may benefit from a general multivitamin supplement
- Advice on how to incorporate more fruit and vegetables into the diet should be given
- Due to frequent blood transfusion, it is advisable that they take a supplement that does not contain any iron, or only a small amount (maximum of 15% RNI)

Glutamine

Many chemotherapy drugs cause structural and functional injuries to the GI tract resulting in mucositis. It is well documented that glutamine is a major fuel and important nitrogen source for enterocytes and plays a key role in maintaining mucosal cell integrity and gut barrier function [96]. An oral dose of up to 0.65 g/kg has been shown to be safe and acceptable to use in paediatric oncology patients [97]. A significant reduction in the severity and duration of stomatitis using a smaller dose of oral glutamine in children has been demonstrated [98]. Although no significant difference in oral mucositis was observed, significant reductions in the number of children requiring PN and duration of PN have been demonstrated in other studies using oral glutamine [99, 100],

perhaps reflecting the role of glutamine in improving lower gut mucositis.

Evidence for the use of glutamine in PN given to children with cancer remains weak. One randomised study in children following stem cell transplantation found no significant difference in the incidence of mucositis [101].

Although oral glutamine has been shown to be safe to use in paediatric oncology, studies to date are not statistically significantly in terms of mucositis, infection rates and length of stay [56]. It is not widely used.

Eicosapentaenoic acid

Eicosapentaenoic acid (EPA) derived from fish oil has been studied in adult cancer patients with cachexia. EPA may modulate aspects of the inflammatory responses implicated in the metabolic changes associated with weight loss and muscular atrophy. EPA may downregulate production of pro-inflammatory cytokines and attenuate progression of the acute phase protein response. A Cochrane review looking at EPA supplements in adult studies highlighted insufficient data to define the optimal dose and insufficient evidence that it improved symptoms associated with cancer cachexia [102].

There is only one poor quality study in children with cancer [103, 104]. While some paediatric enteral feeds have EPA added, there is still insufficient information to determine the ideal amount of EPA that would be effective in children [105]. There are lipid PN emulsions containing fish oils, e.g. SMOFlipid, Omegaven, and further studies are required to determine their safety and benefits for the child with cancer. Despite concerns regarding interaction of EPA with ciclosporin and platelet function in HSCT and cancer patients, there is no strong evidence of this in studies involving other patient groups [106, 107]. PTCs are using fish oil-containing lipids if the clinical need arises, e.g. where there are increasing conjugated bilirubin levels or increasing abnormal liver function tests, with no adverse issues being highlighted.

Probiotics

Current UK dietary advice is for neutropenic cancer patients to avoid products containing probiotics [108]. It is important to investigate the safety of probiotic use in immunocompromised cancer patients, as case reports have identified *Lactobacillus* strain use in probiotic therapy to be involved with sepsis [109]. Two systematic reviews have highlighted that the use of probiotics in people with cancer may reduce the severity and frequency of diarrhoea [110, 111]. Both highlighted five case reports of probiotic related bacteraemia/fungaemia/positive blood cultures. A third systematic review, looking specifically in children with cancer, highlighted evidence of gut dysbiosis, which potentially may be improved using prebiotic and probiotic supplements [112]. As well as treatment related diarrhoea, other potential interest in the use of probiotics in cancer patients includes reducing the incidence and severity of mucositis [113] and prevention and treatment of GvHD [114]. A recent feasibility study in children and adolescents undergoing stem cell transplantation reported no cases of bacteraemia or unexpected adverse events related to the probiotics [115]. Currently there are insufficient studies to assess the effects of probiotics in children with cancer, but there is an increasing interest for studies to be undertaken.

Ketogenic diet

Ketogenic diets have gained popularity amongst patients and researchers, although the efficacy and benefits are still controversial in oncology [116, 117]. The aim of the ketogenic diet for cancer patients is to reduce energy production of the cancer cells and therefore decrease tumour cell proliferation [116].

The theory and science behind this notion is due to the resurgence of the Warburg effect. Warburg described how cancer cells consume glucose and produce lactic acid under aerobic conditions, and this glycolysis induces carcinogenesis [118]. However, the discovery of oncogenes and tumour suppressor genes, leading to theories that activated oncogenes or the inhibition of tumour suppressor resulted in tumourigensis, meant that the Warburg effect fell out of favour [119].

Recently the cancer metabolism debate and the Warburg effect have provoked new interest as it is now thought oncogenes and tumour suppressors are linked to altered metabolism that in turn affects the cancer epigenome [118–120]. Part of the debate is which is the cause and which is the effect? Some propose that tumours switch to aerobic glycolysis through activation of oncogenes or loss of tumour suppressors and that this oncogene driven metabolic reprogramming is needed to support the cancer cell survival and proliferation [120]. Others propose that increased glycolytic activation can result in upregulating oncogenic signalling leading to tumour development and growth or that damage to cell respiration precedes the genomic instability that results in tumour development [118, 121].

It is known that many of the well-established oncogenes and tumour suppressors, such as HIF, AKT, MYC, RAS and p53 have a direct effect on metabolism, particularly on glucose uptake and glycolysis and have been implicated in the Warburg effect [122]. The insulin pathway, including insulin, insulin like growth factor (IGF-1) and the IGF-receptor IGF-R1 are involved in cell growth, proliferation and inhibition of programmed cell death by activating the AKT signal pathway [123]. This pathway is upregulated by carbohydrates:

Higher glucose levels stimulate insulin secretion

↓

Drives glucose into the cells to produce energy

↓

Synthesis and high rate of cell proliferation

Hence the minimisation of carbohydrates in general or by a ketogenic diet is one potential way to reduce the energy production for cancer cells and decrease tumour proliferation [116]. This is the main reason why families ask 'Does sugar feed my child's cancer?'

The majority of studies investigating the use of a ketogenic diet have focussed on brain tumours, particularly malignant high grade glioma/glioblastoma, where recurrence rate is high resulting in decreased survival. Ketone bodies can be used as an energy source by neurons, glia and other cells; however cancer cells are unable to metabolise them.

Currently there are very few clinical studies, with the majority being small samples and in adult patients. Improved clinical studies to provide stronger evidence are needed [116, 117]. The ketogenic diet is complex and not without side effects and requires close monitoring and guidance. Due to the lack of good clinical trials in children, the ketogenic diet is currently not recommended by CCLG centres. However, it is imperative that any family contemplating a ketogenic has a fully informed choice including taking into account the child's quality of life, especially if their disease is palliative. If they do embark on a ketogenic diet, it must be properly monitored to prevent nutritional deficiencies.

Immunodeficiency Syndromes

James Evans

Introduction

The immune system is composed of a variety of organs, cells and proteins, which collaborate to protect the body from disease. Each component has its own unique function in recognising and reacting against foreign material, and the spread of each component throughout the body enables a rapid response to infection. This response is typically divided into two broad categories: the innate and adaptive immune systems.

The innate, or 'first line', immune response occurs rapidly after the invasion of a pathogen and involves phagocytic cells ready to engulf the pathogen through phagocytosis. These cells do not require previous antigen exposure making innate immunity crucial to survival in early infancy. Innate immunity is important in containing an infection and includes complement cascade reactions and phagocytic cytokine release that induce inflammation. However, it is non-specific and does not produce antibodies nor confer lifelong immunity to a repeated infection. This initial response alerts and triggers the adaptive immune system that can take several days to fully activate.

The adaptive, or 'second line', immune response is more specific enabling the body to recognise and remember pathogens and amount a stronger immune response during subsequent exposures. This response involves B cells (B lymphocytes), T cells (T lymphocytes) and natural killer (NK) cells, some of which produce antibodies that can be targeted at specific pathogens during future exposures [124]. The adaptive response undergoes rapid maturation during early life as children become exposed to a variety of infections [125]. An overview of the structure of the immune system, including cell components, is shown in Figure 18.2.

There are four main types of pathogens that should illicit an immune response:

- fungi, e.g. *Aspergillus fumigatus*
- protozoa (free-living or parasitic), e.g. *Plasmodium falciparum*
- bacteria (extracellular or intracellular), e.g. *Streptococcus pneumonia*
- viruses, e.g. cytomegalovirus (CMV)

Defects or failures in any part of the immune system may lead to immune-pathological reactions and disease, often because of not being able to mount an immune response against an antigen, thus allowing it to successfully infiltrate and cause harm. Immunodeficiency disorders are categorised as either:

- primary – the deficiency is caused by defects in the immune system itself, which can be hereditary or due to genetic defects
- secondary – the deficiency is caused by other conditions such as chemotherapy or immune suppression therapy

Organs of the immune system

The immune system is made up of numerous organs known collectively as lymphoid organs. These can be primary or secondary depending on the stage of lymphocyte development and maturation the organ is involved in.

Lymphocytes are formed and mature in primary lymphoid organs including the bone marrow and thymus. All cells of the immune system are created from haematopoietic stem cells in the bone marrow. Some lymphocytes mature in the bone marrow forming B cells, whereas others migrate to the thymus and mature into T cells.

Secondary lymphoid organs are where the defence cells do their work and include the spleen and lymph nodes. The spleen removes old or damaged erythrocytes and stores and releases various defence cells when needed. Lymph nodes produce and store different defence cells that trap pathogens and activate the production of antibodies.

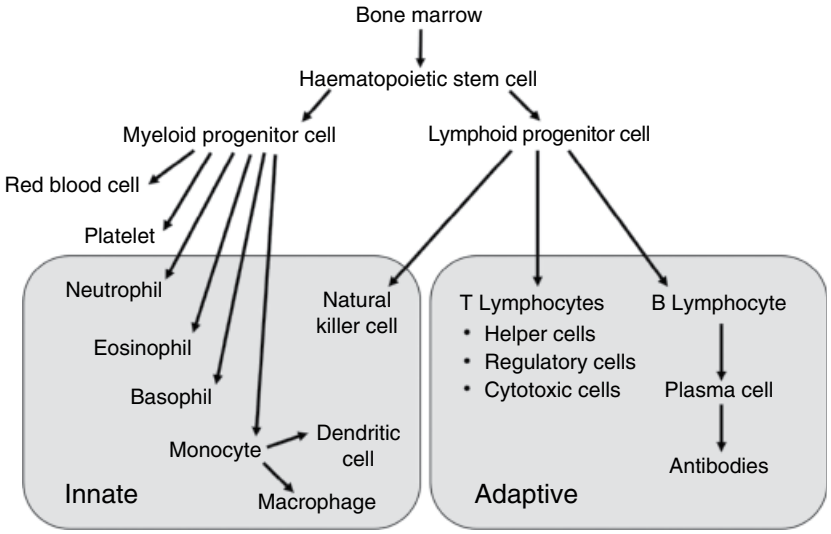

Figure 18.2 Overview of the immune system. Source: adapted with permission from [126].

Cells of the immune system

B cells make up the humoral (antibody mediated) immune response, and their main function is to produce antibodies (immunoglobulins), namely IgA, IgD, IgE, IgG and IgM [127]. The humoral response protects the extracellular spaces from pathogens, particularly bacteria. There are two types of B cells:

- B_1 cells – are polyspecific with low affinity for many antigens
- B_2 cells – are constantly renewed in the bone marrow

B_2 cells then progress through a further maturation process, which results in more specific B-cell subsets [127]:

- plasma B cells (effector B cells) – already exposed to antigens, subsequently producing and secreting antibodies
- memory B cells – made from activated B cells specific to a previous antigen; they are secreted quickly on encounter with the same antigen for the second time
- marginal zone B cells – resident in the spleen
- follicular B cells – resident in lymphoid tissues

T cells undergo positive/negative selection during maturation in the thymus. This ensures the resulting T cells will not over- or under-recognise host 'self' antigens. T cells illicit a cell mediated, intracellular immune response; therefore, they can help to fight off intracellular pathogens such as viruses. There are three main categories of T cells [127]:

- naïve T cells
- memory T cells
- effector T cells

NK cells are important in the defence against viruses. The name 'natural killer' comes from the fact these cells do not require the same maturation as T cells.

Phagocytes are the cells of the immune system that provide innate immunity. They include eosinophils, basophils, monocytes, macrophages and neutrophils, the latter being the most abundant of all white blood cells. Their main role is to ingest and destroy bacteria and fungi.

Learning points: immune system

- *Innate immunity involves a rapid response to an invading pathogen but does not produce antibodies nor long-lasting immunity*
- *Adaptive immunity produces antibodies and creates immunological memory after an initial response to a specific pathogen*
- *B cells mature in the bone marrow and form the humoral response that involves antibody production*
- *T cells mature in the thymus and illicit a cell-mediated response involving phagocyte activation*
- *Primary immunodeficiency disorders arise from inherited or genetic defects leading to a dysfunctional immune system*

Primary immunodeficiency diseases (PIDs)

PIDs are a large and growing group of conditions with more than 350 recognised by the World Health Organization [128]. The lives of patients with PIDs are profoundly impacted by their condition that, if not treated, can be chronic, serious or

even fatal [129]. Most are inherited in one of three different ways [130]:

- X-linked recessive
- autosomal recessive
- autosomal dominant

Some PIDs affect a single part of the immune system, while others can affect multiple components. The defective immune system increases susceptibility to infections and, if poorly regulated, may also start to attack tissues leading to autoimmunity and inflammation [131].

Diagnosis

Early diagnosis allows prompt initiation of supportive treatments including prophylactic antibiotics and immunoglobulin replacement therapy, as required by the specific disorder. Early searches can also begin for matched donors for those requiring definitive treatment with haematopoietic stem cell transplant (HSCT). These factors mean infants will be more protected from infection and transplanted earlier in a better clinical condition, thus improving the chance of survival [129].

Laboratory and genetic investigations are necessary to determine the presence of PIDs. Clues from the patient's medical history, which typically include recurrent and/or chronic infections, and physical examination direct the appropriate choice of investigations. Diagnostic protocols are available to optimise the speed of diagnosis and referral for treatment [132].

Classification

The International Union of Immunological Societies (IUIS) currently classifies PIDs into numerous groups depending on the part(s) of the immune system affected [128]. These can be broadly differentiated into disorders of:

- B cell maturation and/or their ability to produce antibodies
- T cell defects
- combined T and B cell defects
- phagocyte defects
- complement deficiencies

Over 50% of affected patients have antibody deficiencies and treatment consists of replacing the missing antibodies [133]. Cellular lymphocyte defects are more severe requiring stem cell replacement through HSCT [134]. Common PIDs and their possible dietetic considerations are listed in Table 18.8.

B cell defects

B cell defects can range in type and severity. They may encompass:

- absent B cells – severe reduction in all antibodies such as X-linked agammaglobulinemia (XLA)
- low B cell count but deficient B cell subclass, resulting in a variable degree deficiency such as low IgA/IgG
- normal B cell count but with light-chain deficiency/isotype selective IgA deficiency

Table 18.8 Common primary immunodeficiency diseases and possible dietetic considerations.

PID	Possible dietetic considerations
B cell defects	
IgA deficiency	Malabsorption, coeliac disease [135], gastrointestinal infection
IgG subclass deficiency	Malabsorption, possible food allergy/colitis [136, 137]
Common variable immunodeficiency	Abdominal pain, diarrhoea
T-cell defects	
Autoimmune enteropathy	Protracted diarrhoea of infancy, severe faltering growth, often failure of normal nutritional interventions [138], hypoallergenic diet may be required
Class II MHC deficiency	Chronic diarrhoea, severe infections
Combined T and B cell defects	
SCID (including X-SCID, adenosine deaminase deficiency SCID and Omenn syndrome)	Diarrhoea, malabsorption, vomiting, gastro-oesophageal reflux, infectious diarrhoea, faltering growth, increased nutritional requirements [139], skin losses, possible fluid/electrolyte imbalance, hydrolysed protein formulas often required
Wiskott–Aldrich syndrome	Malabsorption, bloody diarrhoea [127]
Phagocyte defects	
Chronic granulomatous disease	Diarrhoea, protein-losing enteropathy, pancolitis, frequent infections, intolerance of high feed volume, increased nutritional requirements requiring nutrient dense enteral feeds [140]
Leucocyte adhesion deficiency	Mucosal infection and inflammation

PID, primary immunodeficiency disease; IgA, immunoglobulin A; IgG, immunoglobulin G; MHC, major histocompatability complex; SCID, severe combined immunodeficiency.

Selective IgA deficiency (SIgAD)

SIgAD is the most common of the primary antibody deficiencies affecting approximately 1 in 875 people in England [141]. Patients may have a deficiency or total absence of IgA, but usually have normal levels of other immunoglobulins. Patients may be asymptomatic with 'silent IgA deficiency' or may require immunoglobulin treatment. IgA acts to protect mucosal surfaces; deficiency, therefore, leads to recurrent or chronic infections such as sinusitis, pneumonia, bronchitis and gastrointestinal infections. There is no specific treatment for patients with symptomatic SIgAD, although prophylactic antibiotic therapy along with immunoglobulin replacement could be helpful for patients with a severe phenotype [142].

The prevalence of coeliac disease is up to 30% higher in patients with SIgAD than the general population [135]. This IgA deficiency persists when following a gluten-free diet despite the return of normal mucosa [143]. IgA antibodies against both tissue transglutaminase (tTG) and endomysial antibodies (EMA) are relied upon for serum screening of coeliac disease; therefore, patients with IgA deficiency will not have a reliable tTG/EMA serum level and should have IgG, tTG and EMA testing when available [144]. IgA plays a vital role in mucosal integrity and so is also associated with the onset of food allergy [142].

IgG and IgG subclass deficiency

Children may have deficiencies in one or more of the IgG subclass (IgG1–4). Clinical presentation depends on the severity and combination of the deficiency, with some individuals being asymptomatic. Most commonly children may present with recurrent infections, usually of the upper airways, food allergy or food allergic colitis [136]. However, food allergy testing involving IgG is not recommended [137].

The outlook for patients with selective IgG subclass deficiency is generally good with low IgG subclass levels in children very likely to improve with age and return to normal by around 10–12 years of age [145]. If necessary treatment requires only occasional use of antibiotics to clear infections as they occur. For patients with a persistent deficiency and significant documented infections, immunoglobulin replacement therapy may be used to prevent serious infections and complications.

T cell defects

T cell defects range in type and severity, for example:

- complete insufficiency of T cell/T cell function, with/without concurrent B cell defect such as severe combined immunodeficiency syndrome (SCID), including Omenn syndrome and major histocompatability complex (MHC) class II deficiency
- partial or complete insufficiency of T cell function such as DiGeorge syndrome (often associated with absent thymus) or Wiskott-Aldridge syndrome
- T cell dysregulation, i.e. autoimmune enteropathy

Autoimmune enteropathy (AIE)

AIE is a rare disease resulting in immune mediated damage to the intestinal mucosa. The immune dysfunction may vary in nature including activation of mucosal T cells causing persistent damage to the gut mucosa or by autoantibodies present on the gut mucosa [146]. This condition most commonly affects infants in the first 6 months of life who commonly present with intractable diarrhoea, malabsorption and anorexia leading to severe weight loss [147]. Severe inflammation, villous atrophy with crypt hyperplasia, and increased mitosis may be seen on small intestinal biopsy. These changes in the small intestinal mucosa may resemble those found in coeliac disease [138]. However, patients do not respond to dietary modification, including a gluten-free diet [146]. Medical therapy commonly uses corticosteroids, but some patients are refractory to this, and immunosuppression may be required to control the disease. If these conventional therapies fail, HSCT can be a successful treatment [148].

Intense nutritional management is a crucial component of care as poor nutritional status can worsen mucosal integrity. A trial of oral nutritional supplementation may be successful [147] though for many patients parenteral nutrition (PN) is required [147, 149]. Nutritional management of patients undergoing HSCT for AIE is similar to that in graft versus host disease (GvHD) in that post-transplant, patients are usually maintained on a milk, egg, wheat and soya-free diet for up to 2 years. Extreme caution should be applied when challenging with new feeds or foods.

DiGeorge syndrome (DGS)

DGS is caused by abnormal migration and development of certain cells and tissues during foetal development. As part of the developmental defect, the thymus gland may be affected consequently impairing T cell production, which results in low T cell numbers and frequent infections. DGS with athymia, known as complete DGS (cDGS), occurs in around 1.5% of children with DGS [150].

Two approaches have been used to correct cDGS. The first is HSCT, but because of the absence of the thymus, this approach can only achieve engraftment of post-thymic T cells, and the quality of immune reconstitution achieved is poor [151]. The alternative approach is to use thymus transplantation that aims for a more complete reconstitution. A recent study on 12 children undergoing thymus transplant for cDGS concluded this should be the corrective treatment of choice [152]. It offers the possibility of immune reconstitution that will produce a quality of life not limited by infection susceptibility, and, despite the significant risk of autoimmune complications for survivors, these can often be managed.

Phagocyte defects

Phagocytic cells are important in host defence against pyogenic bacteria and other intracellular organisms. These cells leave the bone marrow and migrate to peripheral tissues, particularly to sites of infection or inflammation. Phagocytes ingest pathogens and degrade them. Therefore, phagocyte defects can lead to severe infections and as a result may be fatal [4]. Some patients may present with gastrointestinal complications similar to those of inflammatory bowel disease [140].

Chronic granulomatous disease (CGD)

In CGD phagocytes are unable to produce microbial oxygen metabolites so cannot degrade pathogens after ingestion. This leads to recurrent, often life-threatening, bacterial and

fungal infections that are difficult to cure. These frequent infections increase nutritional requirements and decrease the appetite for food and tolerance of adequate volumes of oral feeds. It is, therefore, often necessary to initiate enteral feeding as soon as an acute episode begins to prevent excessive weight loss. Diarrhoea is usually common due to intensive antibiotic therapy, but despite this, children are often able to tolerate a whole protein, energy-dense feed. Recent HSCT outcomes have produced excellent results suggesting all children should undergo HSCT if a matched donor is available [153].

Leucocyte adhesion deficiency (LAD)

LAD is characterised by impaired migration of neutrophils from the intravascular space to the site of infection. It usually presents in early infancy with deep tissue infections, impaired pus formation and delayed wound healing.

Haemophagocytic lymphohistiocytosis (HLH)

HLH is characterised by the early onset of fever and hepatosplenomegaly associated with pancytopenia, hypertriglyceridaemia and haemophagocytosis in the bone marrow. The pathogenesis has been associated with uncontrolled T cell activation leading to increased inflammatory cytokine levels. The condition is fatal if not treated with HSCT, which gives an overall 3-year survival of 64% [153]. Veno-occlusive disease (VOD) is the major toxicity associated with HSCT in HLH and reduced intensity conditioning may be a preferential option.

Combined immunodeficiencies

Wiskott–Aldrich syndrome (WAS)

WAS is an X-linked disorder characterised by thrombocytopenia with small platelets, early infantile eczema and progressive immunodeficiency leading to numerous chronic infections. These children often bleed easily, including bloody diarrhoea, and many are given amino acid-based feeds from diagnosis. Without HSCT children with WAS have a poor prognosis with the main causes of death being infection, bleeding and lymphoproliferative disease [153]. Outcomes for WAS patients undergoing HSCT between 1980 and 2009 have shown overall survival of 84% [154].

Severe combined immunodeficiency (SCID)

SCID arises from a variety of genetic defects that lead to an absence of lymphocyte development and function. Most forms of SCID have absent T cells but are further divided by the presence or absence of B and NK cells leading to various immunophenotypes including X-SCID, recombinase-activating gene (RAG) deficiency and adenosine deaminase (ADA) deficiency. The latter is the most common form and results from a deficiency of the ADA enzyme causing accumulation of metabolic substrate precursors that are toxic to lymphocytes [155].

Data from newborn screening programmes in the USA estimate the incidence of SCID to be approximately 1 in 58 000 live births [156]. Infants with SCID are unable to fight infections until they have restored immune function. Siblings diagnosed at birth, following testing due to a positive family history, have an overall survival rate above 90% compared with 40% in the first presenting family member [157]. Otherwise most infants present between 3 and 6 months of age with recurrent infections after the protective effects of maternal immunoglobulins have worn off [158]. When diagnosis is delayed, the onset of infections leads to end-organ damage, meaning a significant number of infants die in the first year of life before definitive treatment with HSCT can be undertaken [158]. Even those who make it to HSCT with ongoing infections or organ damage have a poorer outcome [159]. The key to improving the outcome for SCID is early diagnosis and treatment so that severe infections can be prevented [157].

Newborn screening

Newborn screening for SCID can now be performed by detecting biomarkers of healthy T cell development: T cell receptor excision circle (TREC) in DNA extracted from blood spot on routine Guthrie cards in the first days of life [160]. Results from recently established screening programmes in the USA have demonstrated improved outcomes [156]. Despite this, screening for SCID is not currently available in the UK. However, in December 2017 the UK National Screening Committee recommended that screening for SCID should be trialled in the National Health Service (NHS).

Dietetic management of infants with SCID

Infants diagnosed with SCID often face a nutritional challenge. They may suffer from persistent diarrhoea, malabsorption, oral thrush, recurrent or opportunistic infections [158], vomiting and gastro-oesophageal reflux [161] and/or faltering growth, despite a seemingly adequate oral intake. One study has shown infants with SCID have increased nutritional requirements due to hypermetabolism; 100% of the infants presenting with diarrhoea, independent of pneumonia, were at risk of hypermetabolism and subsequent faltering growth [139]. Infants diagnosed between 3 and 12 months of age were at greatest risk.

Due to the increased risk of cytomegalovirus (CMV) transmission through breastmilk, breastfeeding is discouraged until the mother's and infant's CMV status is known [162]. If breastfeeding is commenced, an energy-dense formula, e.g. 0.9 kcal (3.8 kJ)/mL or 1 kcal (4 kJ)/mL, may need to be given in addition. Hydrolysed protein feeds are generally better tolerated, particularly in Omenn syndrome with marked gut inflammation, as they are better absorbed [158]. Feeds can be given either orally and/or via a nasogastric tube, as commonly indicated, to optimise nutritional intake. A nasojejunal

tube can be considered in infants where ongoing gastro-oesophageal reflux or delayed gastric emptying is preventing the establishment of oral or nasogastric feeding.

Parenteral hydration and nutrition may be necessary where an infant requires stabilisation pre- or post-diagnosis. Some infants with very high requirements may need PN alongside enteral and/or oral feeds. It may not be possible to meet full requirements with PN alone. Sodium status (urinary and serum) can be a useful tool to ensure adequate sodium levels for growth [163]. In practice, a urinary sodium level <20 mmol/L may indicate poor sodium status (despite normal serum sodium), and sodium supplements may be necessary or the sodium content of PN increased in increments of 1 mmol/kg/day. Urinary sodium levels should then be monitored weekly or biweekly until a level >20 mmol/L is maintained. There is limited evidence for this practice, but clinically this can be effective, especially for infants with chronic diarrhoea who may have high sodium losses. Where full PN is given (except at times of complete gut rest), trophic feeds should be given to help maintain the integrity of the gut mucosa.

Reintroduction of feeds following period of gut rest

At all times reintroduction of enteral feeds should be considered a priority and started as soon as the infant is medically stable. Oral rehydration solution may be given first. If this is tolerated, then a suitable formula can be introduced. Reintroduction of feeds should be done slowly. Continuous feeding over 20–24 hours is recommended to begin with, often starting at slow rates of 5 mL/hour and increasing in 5–10 mL/hour increments daily, as tolerated. Rather than whole protein feeds, extensively hydrolysed protein or amino acid-based formulas are likely to be better tolerated. These formulas have a higher osmolality than standard formulas; therefore, it may be beneficial to start with half standard concentration, building up gradually in 1%–2% increments per day, as tolerated. Once standard concentration is achieved and tolerated, it is often necessary to increase the concentration further to achieve higher energy and nutrient density. This should be done with caution, increasing by 1% at a time, usually not exceeding a concentration of 1 kcal/mL (4 kJ/mL). It is often possible to offer the infant a proportion of their feed (however small) orally. This will help to promote oromotor skills, avoid oral sensitisation and can also be a valuable input to the infant's care by the parent(s).

In older children or infants of weaning age, food can be introduced as early as tolerated. Initially the diet may be milk, egg, wheat and soya free. This is usually necessary following HSCT for autoimmune enteropathy and in patients who have developed gut GvHD post-transplant. In addition, foods may be kept 'bland' with the introduction of one new food at a time. Once immune function has stabilised following transplant, and in the absence of gastrointestinal symptoms, restricted foods can be added in one by one.

Treatment for SCID

Conservative management is centred on reducing infection and associated end-organ damage prior to definitive treatment with HSCT. Most infants remain in hospital between diagnosis and HSCT and during this time will be isolated in individual high-efficiency particulate air (HEPA) filtered rooms to reduce exposure to pathogens. Conservative management will involve replacement immunoglobulins given 2–3 times weekly and regular surveillance for viruses, respiratory and stool organisms.

Enzyme replacement in the form of polyethylene glycol-adenosine deaminase (PEG-ADA) is used in the treatment of ADA deficiency SCID. This is administered 1–2 times weekly by intramuscular injection causing cellular immune reconstitution, which reduces the toxic accumulation of metabolites. However, the extent of immune recovery is variable, and over time patients show a decline in T cell numbers, loss of thymic function and remain lymphopenic [164].

Possibly the greatest advance over recent decades in the treatment of PIDs has been the development of gene therapy. This uses autologous gene-corrected HSCT and has become a novel treatment option for patients with ADA deficiency SCID and X-SCID. The use of autologous cells precludes the risk of GvHD, there is no requirement for immunosuppressive prophylaxis, and much lower doses of conditioning agents can be used than in those regimens used for allogenic HSCT; thus there is a reduction in organ toxicity [165]. So far over 50 patients worldwide with ADA deficiency SCID have been treated by gene therapy. Encouraging results have been shown suggesting this may offer a viable treatment option for patients where there is no well-matched donor for HSCT [158].

Learning points: SCID

- *SCID is characterised by absent T cells combined with the presence or absence of B and NK cells*
- *Early diagnosis optimises survival through avoiding severe infections and allowing prompt work up for HSCT*
- *Gene therapy is an emerging treatment option for ADA deficiency and X-SCID*
- *Newborn screening is now being trialled in the NHS*
- *Diarrhoea, infections, vomiting, gastro-oesophageal reflux and faltering growth pose dietetic challenges*
- *Many require nasogastric tube feeding with extensively hydrolysed protein feeds*
- *Some may need PN in place of, or alongside, enteral feeds*
- *Reintroduction of feeds following gut rest should be done cautiously, often starting with continuous half strength feeds*

Haematopoietic stem cell transplant

HSCT remains the primary treatment for SCID, as well as many other PIDs. The procedure begins with the child

receiving various conditioning chemotherapy regimens for 7–10 days prior to transplant. The purpose of conditioning is to destroy the existing bone marrow and make space for donor stem cells to engraft and undergo normal haematopoiesis. Such regimens are typically categorised as highly toxic myeloablative conditioning (MAC), or less toxic reduced intensity conditioning (RIC). MAC generally leads to the highest levels of donor engraftment, but at the risk of significant morbidity. RIC results in less chemotherapy-induced organ damage allowing more unwell children, who would previously have been deemed not fit for chemotherapy, to undergo transplant [158].

After conditioning the child receives their transplant, commonly referred to as 'day 0' (the preceding days referred to as day −1, −2 etc. and proceeding days as day +1, +2 etc.). Sources of donor stem cells include bone marrow and peripheral blood from related or unrelated donors, or umbilical cord blood from unrelated newborns. The donor type is a major factor influencing outcome. European data from children undergoing HSCT for SCID over the past 30 years have shown over 90% survival with a matched sibling donor, 69% with an unrelated donor and 66% with a mismatched relative [166].

Complications post-HSCT leading to impaired nutritional status

After conditioning the child enters an extremely vulnerable period where their existing bone marrow is destroyed, and the donor stem cells have not yet engrafted and started to produce healthy, functioning blood cells. They are, therefore, extremely susceptible to infection and will be prescribed a plethora of prophylactic medications and remaining isolated in HEPA filtered rooms.

Oral mucositis occurs in most patients treated with chemotherapy for HSCT. It is characterised by mucosal damage ranging from mild inflammation to extensive ulceration and may affect the oral cavity and other parts of the digestive tract mucosa. This makes eating or passing a nasogastric tube painful. The potential breakdown of mucosal barriers increases the risk of systemic infection and, coupled with mucositis associated pain, causes significant morbidity and mortality [167]. Mucositis usually occurs between day +6 and +12 with resolution coinciding with engraftment. If a child develops severe mucositis, most will require pain management, gut rest and PN [168].

Once engraftment has taken place, the child is at risk of GvHD – reactions between the donor stem cells (graft) and the host's own tissues. If GvHD occurs soon after engraftment, it may affect one, or all, of the skin, liver and gut. Prophylaxis typically involves ciclosporin and mycophenolate mofetil; if severe GvHD develops, it may be treated with steroids. Gut GvHD results in profuse watery diarrhoea, exacerbated by feed/food, with a concurrent rapid decline in oral intake and nutritional status [169]. Gut rest and PN are recommended if gut GvHD develops [168].

Continuous low volume enteral formulas can be initiated once stool frequency has decreased. Again extensively hydrolysed protein or amino acid, rather than whole protein, formulas are usually better tolerated from observations in clinical practice, despite a lack of published evidence. In severe cases it may be necessary to start with half-strength feeds to reduce osmotic load. Some patients tolerate feed or food better than others, with no known explanation. The first foods offered should be low in fat and fibre [170], and some patients may tolerate a simple 'few foods' diet very well, e.g. plain chicken with potato or rice. For those suffering from more severe gut GvHD, a milk, egg, wheat and soya-free diet may be required, with reintroduction of these foods sequentially once the child is medically stable.

VOD is a condition where the tiny blood veins in the liver become blocked due to chemotherapy given during conditioning, particularly busulfan, high dose melphalan and/or total body irradiation. If VOD is suspected, fluid restriction is indicated and lipid-free PN may be necessary. The evidence base for this practice is lacking. It will be difficult to meet energy requirements in this situation, and it is important to monitor and restart lipids as soon as possible. Supplementation with walnut oil (p. 649) to meet essential fatty acid requirements should be considered early on, particularly if lipid-free PN is used for prolonged periods, or if the patient is a young infant.

Dietetic management of children undergoing HSCT

Regardless of diagnosis prior to transplant, maintaining nutritional status pre-, peri- and post-transplant is essential as there are negative associations between malnutrition and survival, transplant-related mortality and relapse risk [171].

Energy requirements calculated using Schofield equations to predict basal metabolic rate (BMR) have been shown to closely resemble resting energy expenditure (REE) pre-HSCT [172]. However, REE has been shown to reduce to 79% of predicted BMR in the early weeks post-transplant putting children at risk of being overfed [173]. Patients are typically less active post-transplant, being kept in isolation, and receive sedatives for pain relief, both possibly contributing to reduced REE. Estimates of BMR using equations developed from healthy children are also likely a poor reflection of the energy expended during recovery following HSCT. Children are likely to require somewhere between 80% and 100% requirements predicted using Schofield throughout admission for HSCT.

Almost all children going through HSCT will require nutritional support beyond oral supplementation. It is recognised from European guidelines [168] and a Cochrane systematic review [174] that enteral nutrition should be provided as first line nutrition support over PN. A proactive approach to enteral tube placement should be encouraged, and timing of nasogastric tube placement is crucial. If nasogastric tubes are placed during conditioning (approximately days −7 to −2) there is a chance the tube will be dislodged multiple times through vomiting. If placed too late

(approximately after day +7), the procedure may be traumatic or contraindicated if mucositis is severe, or the child is thrombocytopenic. Placing nasogastric tubes between day −1 and +1 seems to be a good compromise and has been shown to be well tolerated and acceptable [175]. Some families may even opt for prophylactic gastrostomy placement prior to admission. Although this has potential benefits of avoiding dislodgement due to vomiting and irritation to the throat when mucositis develops, there is a paucity of studies investigating the benefits of this feeding route in HSCT.

Dietetic management of HSCT is similar to that described for SCID patients. Hydrolysed protein formulas are usually better tolerated post-transplant than whole protein formulas. Patients may initially require a continuous feeding regimen, building up to an overnight feed, daytime boluses and oral diet. Infection remains life-threatening to children having HSCT, and a 'neutropenic' diet (p. 49) is required. Meals may be provided by a designated ward or diet kitchen, or main hospital menus adapted following food safety precautions to reduce the risk of infection from food borne microorganisms. Oral and enteral feeds may be pasteurised as an additional precaution. A diet including cow's milk protein can be given during this time in the absence of gut GvHD and is usually tolerated. Some centres may allow commercial bottled water to be taken orally. However, common practice is to only allow water that has been boiled, whether tap or bottled water. Pharmacy grade sterile water can be used, but is often unpalatable. Food safety precautions usually continue for 3–6 months post-transplant depending on immune reconstitution. Oral intake is often slow to recover to achieve full nutritional requirements. Therefore, many children often require enteral feeds for several months post-discharge.

Learning points: HSCT

- *HSCT remains the primary treatment for PIDs*
- *Conditioning leads to numerous dietetic challenges including nausea, vomiting, diarrhoea, anorexia, mucositis, VOD and cytopenia with infection risk*
- *Following engraftment there is a risk of GvHD of the skin, liver and/or gut*
- *Gut GvHD will require a period of gut rest and PN*
- *Reintroduction of feeds following gut rest is similar to SCID*
- *Food reintroduction in gut GvHD will require restriction of milk, egg, wheat and soya, alongside food safety precautions*

Follow-up and monitoring

Frequency of patient reviews post-discharge for HSCT will vary between centres, but generally children will be monitored closely by the transplant team, a minimum once to twice monthly for the first year. Following this care will be shared between the child's local hospital supported by 6 monthly visits to the transplant centre [176]. After 5 years the transplant team will review annually. Reviews will monitor immune reconstitution (from which duration and intensity of antimicrobial prophylaxis can be adjusted), chimerism (proportion of the child's lymphocytes which are native or donor), GvHD and need for immunoglobulin replacement. It is also becoming increasingly recognised that effects on mental health, well-being and quality of life of both the child and family should be monitored, with counselling offered as required [158].

Growth and development will also need to be monitored closely, and the dietitian has a key role in this. Many patients will require enteral nutrition support at home following discharge, and advice will be needed regarding weaning off enteral feeds according to improvements in oral diet, and reintroducing any restricted foods to normalise intake. This will help ease parental anxiety. Close team working and communication between the dietitians within the transplant centre and the child's local hospital, as well as the medical teams within each site, will be crucial to facilitating appropriate growth.

A case study showing the dietetic management of a child with SCID undergoing HSCT is given in Table 18.9.

Future research needs and unanswered questions

There is a paucity of literature investigating the effectiveness of nutrition support specifically in PIDs, with most studies combining those having HSCT for PIDs with those having the same procedure for haematological malignancies and other disorders. Most of the current paediatric literature comprises low to moderate quality cohort studies investigating the feasibility and benefits of early enteral nutrition, with some making comparisons to the provision of upfront PN, during HSCT.

There is, therefore, a need for more well-designed trials assessing the effectiveness and safety of nutritional support in children with PIDs during the early stages of diagnosis and throughout HSCT. The main research recommendations from the literature regarding nutrition support during HSCT include:

- an urgent need for randomised controlled trials investigating the benefits of enteral versus PN
- further research investigating the effectiveness and safety of enteral nutrition interventions including both the route of nutrition, e.g. comparisons between nasogastric, gastrostomy and jejunal feeding, and the type of formula used
- the effect of enteral and parenteral glutamine on mucositis, diarrhoea, infections, GvHD and malignancy relapse rates

From the existing literature a diverse range of clinical outcomes have been reported making it difficult to compare trials. For such future studies listed above, consideration should be given to the adoption of standard multicentre clinical outcomes. Families should be involved in the setting of outcomes that are important to them and could include factors such as anthropometry, cost of interventions, complications and quality of life to improve the nutritional and immune status of transplanted patients.

Table 18.9 Case study: treatment progression and dietetic management of a child with SCID.

Summary

Anthropometry: Baby boy born at term weighing 2.75 kg (9th centile). Over the first 6 months of life (up to admission for HSCT), weight decline to 0.4th centile. Over the first month of HSCT, weight continued to decline to <0.4th centile. By discharge the child, now 8 months old, had increased weight to 0.4–2nd centile. At 1 year of age, he was on the 2nd centile with further increase in weight centile.

Biochemistry: At 4 months old the child was found to have low T and B cells following investigations for an ear infection. Following conditioning, immune cell counts flattened between day +1 to +7 post-HSCT. Counts began to reconstitute between day +8 to +20, and had recovered by day +30.

Clinical: Following an ear infection revealing an opportunistic bacterial pathogen, the child was referred to an immunology team and diagnosed with RAG1 deficient SCID. He was admitted for a RIC conditioned, matched family donor, HSCT.

Dietary: Following admission a nasogastric tube was placed due to weight loss and reducing oral intake. The child was changed from a standard to a high energy formula and, shortly after, to an extensively hydrolysed protein and later amino acid-based formula to aid absorption as mucositis developed. Despite this, diarrhoea and weight loss persisted and the child was placed on PN. Following engraftment an extensively hydrolysed formula was gradually reintroduced and titrated against PN until this was eventually stopped. At discharge, the child was beginning to take small amounts of feed and puréed foods orally, but required ongoing nutrition support as four pump-assisted day boluses of a high energy formula.

Environment: The baby was a first child of healthy parents. During admission he was isolated in a high-efficiency particulate air-filtered room as standard infection prophylaxis.

Focus: The dietetic aims were to prevent further weight loss following admission, maintain weight during the period of mucositis after conditioning and, following engraftment, gradual weight gain towards that on admission. To achieve this the aim was to provide 80%–100% requirements via oral, enteral and/or parenteral nutrition.

Chronology	Medical history/investigations	Dietetic interventions
1–3 months old	Multiple visits to GP with recurrent ear infections requiring antibiotic treatment. The infant also suffered three bouts of diarrhoea each lasting 3–5 days. Weight initially plateaued and later fell to 0.4th centile.	Infant not seen by dietitian, but after initially being breastfed had been changed to a standard infant formula.
4 months old	Taken to GP with further ear infection, but this time cultures grew *Pseudomonas aeruginosa* (a bacteria not typically found in infant ear infections). Full blood count showed low levels of T and B cells. Referred to tertiary centre for further management under an immunology team.	NA
5 months old	Admitted to tertiary centre and following genetic tests a diagnosis of RAG1 deficient SCID was made. Infant to remain an inpatient in preparation for HSCT with father agreeing to be the donor.	Nasogastric tube inserted due to weight loss since birth (currently weight on 0.4th centile), and minimal oral intake. Feed changed to high energy 1 kcal/mL (4 kJ/mL) whole protein-based formula to facilitate weight gain. Feeds offered orally with nasogastric gravity bolus top-ups as needed, given 3–4 hours to meet full nutritional requirements. Once feed plan established no further weight loss occurred, and weight began to increase gradually.
6 months old	Care transferred to HSCT team.	Infant stopped feeding orally, so full nutritional requirements met entirely via nasogastric feeds. Occasional vomiting with feeds so delivered via pump assisted boluses, each feed given over one hour. Gradual weight gain continued.
Day −7 to −1 pre-HSCT	RIC conditioning. Infant suffered from frequent vomiting and diarrhoea.	Nasogastric tube displaced twice, promptly replaced each time without difficulty. Commenced continuous feeding, given over 20 hours, and changed to extensively hydrolysed protein formula to facilitate tolerance and absorption.
Day 0	Infusion of peripheral blood stem cells from matched family donor.	NA
Day +1 to +7 post-HSCT	Immune cell counts flatten. Severe mucositis develops with associated pain, irritation and worsening of diarrhoea.	Feed changed to amino acid-based formula to facilitate tolerance and absorption in light of severe mucositis. Volume of feed allowance reduced to 90 mL/kg as infant required occasional blood products and plentiful IV medications. Feed concentrated to 1 kcal/mL (4 kJ/mL) to continue to meet 80%–100% requirements.

(continued overleaf)

Table 18.9 *(continued)*

Chronology	Medical history/investigations	Dietetic interventions
Day +8 to +20	Immune cell counts remain low, but starting to reconstitute. Mucositis and diarrhoea persist.	Due to weight loss following day 0 (weight now <0.4th centile) and persistent diarrhoea, PN started and child placed on gut rest without enteral nutrition.
Day +21 to +30	Immune cell counts recovered. Mucositis and stool output improved so enteral feeds reintroduced. Mild skin GvHD treated with topical steroids. No evidence of gut GvHD, VOD or infections.	While PN continued to provide full nutritional requirements, an extensively hydrolysed protein formula was reintroduced at 5 mL/hour × 20 hours continuously via nasogastric tube. Feeds increased by 5 mL/hour/day until approximately 50% of nutritional requirements were met enterally. After this PN was gradually reduced over three days, while nasogastric feeds continued to increase towards providing full requirements. Oral intake remained minimal during this time. Weight returned to 0.4th centile.
Day +31 to +40	Medicines converted from IV to oral in preparation for discharge.	PN stopped. Regimen gradually transitioned from continuous to small volume 2-hourly boluses; subsequently 3- then 4-hourly boluses of increasing volume. Boluses given via pump due to semi-frequent vomiting. Feed gradually transitioned back to 1 kcal/mL (4 kJ/mL) whole protein infant formula. Infant started to take small amounts of feed and pureed foods orally. Pump training and home enteral feeding arrangements made.
Day +41	NA	Infant discharged on four pump assisted day time boluses via nasogastric tube of 1 kcal/ml (4 kJ/mL) formula providing 80% requirements. Oral intake of both feeds and pureed foods slowly increased. Weight slowly increased to 0.4th-2nd centile. Handover to local dietitian for follow-up.
9–12 months old	Ongoing monitoring of immune reconstitution, GvHD and infection status. Nil concerns.	Oral intake and weaning continued to progress well. Bolus feeds gradually reduced and stopped with nasogastric tube removed at 1 year of age. Weight on 2nd centile and increasing.

SCID, severe combined immunodeficiency; HSCT, haematopoietic stem cell transplant; RAG1 recombinase-activating gene 1; RIC reduced intensity conditioning; PN, parenteral nutrition; GP, general practitioner; NA, not applicable; IV intravenous; GvHD, graft versus host disease; VOD, veno-occlusive disease.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

19 Eating Disorders

Graeme O'Connor and Dasha Nicholls

Introduction

Eating disorders are a range of mental disorders characterised by abnormal or disturbed eating habits associated with significant impairment of function or distress. They occur across the spectrum of body weight. The three main diagnoses of eating disorders are anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED). Atypical variants of these are also specified in diagnostic manuals (other specified feeding and eating disorders [OSFED]), e.g. atypical AN, which has all the features of AN except for extreme low weight and purging disorder (PD), in which the patient purges but does not binge eat. Avoidant restrictive food intake disorder (ARFID), which has replaced the diagnosis of feeding disorder of infancy and early childhood, is included in the broad category of feeding and eating disorders but is not normally classified as an eating disorder. Obesity is not classified as an eating disorder, although a subgroup of those who are overweight will have significant eating disorder psychopathology [1].

Among the eating disorders, AN carries the highest risk [1] and is most likely to require nutritional as well as psychological intervention. AN is defined as maintaining a weight below a healthy range by restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory and physical health. Additionally AN is commonly linked with other comorbid psychological conditions including depressive disorders, anxiety disorders, obsessive–compulsive disorder and personality disorders [2]. However, there is a significant morbidity and mortality associated with all eating disorders regardless of weight status [1], in particular PD [3].

The peak onset for AN diagnosis in females in the UK is between 15 and 19 years of age with an incidence rate of 0.2% of the population [4]. This timing of the peak onset during adolescence is problematic in that it is also the time when energy requirements, which are essential for pubertal growth spurt, are at their highest. The combination of high energy requirements, nutritional restriction and excessive exercising lends itself to a rapid deterioration in health particularly during vulnerable periods of brain development and physical growth, resulting in potentially permanent physical and psychological consequences [5]. For BN onset is typically a little later. Data on BED in young people is sparse, with significant variation between studies. However among overweight or obese adolescents, binge eating or loss of control eating is found in around a quarter of adolescents [6].

Nutritional intervention is an important component of the treatment of eating disorders, and the dietitian is an essential member of the multidisciplinary team, especially when the eating disorder occurs in the presence of other co-morbidities such as coeliac disease, food allergies and type 1 diabetes mellitus. Dietitians should not treat patients with eating disorders as sole practitioners and must work within a multidisciplinary team [7].

Screening and diagnosis

Paediatricians and general practitioners often refer young people with a history of weight loss to the dietitian. It is therefore not unusual for dietitians to be the first health professionals to identify or question a possible eating disorder.

Anorexia nervosa: clinical features

AN predominately affects females, although at least 1 in 10 patients will be male (more in the younger age group). AN varies in severity, with extreme nutritional restriction accompanied by other associated behaviours such as binge eating, self-induced vomiting, purging, over-exercising and

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

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self-harm [8]. The cognitive distortion associated with AN results in dieting behaviour and an intense fear of weight gain and fatness. Generally, there is no loss of appetite; satisfaction in feeling 'empty' and hungry overrides the need to eat, and weight loss is viewed as an achievement. Thus, sufferers have limited desire to change [9].

Identifying an eating disorder in the early stages is difficult due to the deceptive nature of the disease, especially when presentation is atypical. Such a lack of awareness that AN can occur in younger children and boys may lead to a delay in referral, diagnosis and treatment [10], although this may be changing. Clinical signs of AN include:

- *weight loss* – leading to significantly low body weight in the context of what is minimally expected for age, sex, developmental trajectory and physical health. The World Health Organization (WHO) definition of underweight is a percentage body mass index (%BMI) below 85% (where %BMI is BMI/median BMI for age and sex). Cole *et al*. provide cut-offs for degrees of malnutrition based on international BMI data [11]. For the majority of the population, a healthy %BMI will fall between 95% and 105% [12, 13]. A consequence of low weight is that pubertal development is halted, resulting in either a delay in reaching menarche or secondary amenorrhoea, which can have implications on bone health. Physical signs of poor nutrition and low weight include: sunken cheeks, temporal lobes and eyes; dull and thinning hair; lanugo hair; cold extremities and feeling cold; and delayed puberty [14].
- *avoidance of food* – this can occur gradually over time, with subtle restriction of nutritional intake including eliminating snacks, reducing portion sizes, hiding food and missing meals. Furthermore avoidance of food can transfer into the social setting; the young person will avoid eating out perhaps due to a lack of control over food preparation, or it may interrupt rigid exercise routines or other 'rules'. Conversely the young person can be overly involved with food shopping, meal preparation and baking but will avoid eating themselves. Young people with eating disorders will often have an extensive knowledge about the calorie content of food, but this is often the limit of their understanding about food and nutrition. It is a common misconception that young people with AN have a good comprehension of nutrition, but they are often unable to understand information or interpret it correctly, hence the importance of nutrition education [15].
- *morbid preoccupation with weight and/or shape* – energy-dense foods are avoided through fear of gaining weight or a change in body shape that may accompany it. Girls perceive their stomach and thighs as particularly fat, whereas boys may be more concerned about musculature and are more likely to exercise excessively.
- *poor self-esteem* – feelings of ineffectiveness are extremely common and often married with depressive and anxiety features, impaired concentration and obsessional symptoms. Social interests decline as young people with eating disorders lose weight, and most become socially withdrawn. Many of these features reverse with weight gain [14]. Perfectionism is a trait that can converge with poor self-esteem, resulting in extreme competiveness, asceticism and the need to please; subsequently, young people with AN tend to be high achievers and can be perceived by peers and family as flourishing.

Bulimia nervosa: clinical features

In BN a persistent preoccupation with eating is present, with craving and consequent binges, usually with a feeling of loss of control. Weight is usually maintained within the normal range by compensatory exercise, vomiting or purging. A preoccupation with weight leads to attempts at weight control with characteristic cyclical pattern of missing meals, which is not sustained as hunger reinforces a propensity to binge eat, often followed by compensatory behaviours and guilt.

There are well-validated treatments that are effective in over 60% of patients; however, BN is less obvious than AN to recognise and may only come to light through suspicion of a family member or friend. Clinical signs of BN include:

- irregular menses
- Russell's sign – callouses on the knuckles of forefingers due to abrasions from self-induced vomiting
- dental erosion from damage to teeth enamel from stomach acid
- swollen parotid glands
- depression/low mood

Binge eating disorder

In BED the patient has binge episodes, a sense of loss of control over food intake and a preoccupation of weight and/or shape but does not utilise compensatory behaviours following a binge episode.

Purging disorder

In PD, weight is in the normal range, and the patient purges but does not binge, in order to maintain their weight. Purging includes a variety of methods including, but not limited to, self-induced vomiting, laxative or diuretic misuse, or the omission of insulin in those with type 1 diabetes mellitus. PD is classified as an OSFED.

Learning points: anorexia nervosa

- *Among the eating disorders, AN carries the highest risk and is most likely to require dietetic input*
- *The peak onset for AN is between 15 and 19 years of age but can present as young as 7 years old, affecting boys and girls*
- *AN is linked with low self-esteem, anxiety and perfectionism*
- *AN is characterised by extreme nutritional restriction accompanied by other associated behaviours such as binge eating, self-induced vomiting, purging, over-exercising and self-harm*
- *AN can be focused on weight or shape or both weight and shape*

Assessment of eating disorders

The mainstay of diagnosis is a clinical interview. For young people this would typically include parents or the whole family in the first instance, although it is important to interview the young person on their own too, bearing in mind that all young people have a right to confidentiality, and this needs to be balanced against the parents' right to parent, i.e. to have the necessary information to make decisions in their child's best interest, particularly before the child is assumed to have the capacity to do this for themselves at the age of 16 years.

Areas to explore in an assessment include how everyone feels about coming to the appointment; the history of the concern including who is most worried (often justifiably); ideas the family have about triggers for onset of the eating disorder (providing an opportunity to explain that families do not cause eating disorders and that triggers are not the same as cause or blame); previous experience of eating disorders or other mental health problems within the young person or the family; specific questioning about eating disorder behaviours, including direct questions about vomiting, exercise, binge eating; other areas of risk (eating disorder behaviours, self-harm and suicidal ideation, anger towards others, risk of abuse and neglect) and then looking at what the family or young person has tried, what resources they have accessed, what resources and strengths they have as a family and what ideas they have about treatment. Thoughts and feelings about eating, anxiety and mood are best elicited with young people on their own, while families often given the clearest narratives about the development of the eating disorder and factors that may be important in maintaining it.

Medical

Although medical investigations may be necessary to rule out organic aetiology responsible for weight loss or food avoidance, eating disorders are much more common than most possible differential diagnoses for weight loss: hyperthyroidism, type 1 diabetes, inflammatory bowel disease (IBD), coeliac disease or neoplastic disease (tumour). Amenorrhoea may result from ovarian or pituitary disease or following use of the contraceptive pill. Clinical assessment should focus on determining the severity of malnutrition as well as possible causes and should include hydration status, temperature, muscle wasting and cardiovascular status with particular attention to heart rate and orthostatic blood pressure. The sit up, squat, stand (SUSS) test is a useful clinical sign to monitor the clinical status of malnourished patients [16].

Anthropometric

The simple use of weight or BMI has limited use in young people, owing to the normal changes in weight, height and BMI in childhood and through puberty. Weight and BMI can be used to track changes in an individual, but any comparison of weight against population norms needs to take account of height, sex and age. It is perfectly correct to use BMI centile charts and to report BMI centile in young people. However, for patients below the 0.4th BMI centile, there is a need to quantify the degree of underweight. Using %BMI (BMI/median BMI for age and sex) instantly provides information about a patient's nutritional status without the need to refer to a chart. Furthermore, young people and parents understand the concept of %BMI.

Mid-upper arm circumference (MUAC) is a simple and effective additional anthropometric measure; its use can eliminate some of the methods employed by young people with eating disorders to mislead practitioners about their true weight, such as water-loading and attaching weights to various parts of the body [17].

Nutritional

Acquiring an accurate diet history from young people with an eating disorder has the added barrier of intentional over- and underestimation of intake. Therefore, it is essential to have input from families along with a 4-day food record. Nutritional assessment should expand on the history of food restriction and other self-imposed nutritional 'rules' such as exclusion of a food group (fats and/or carbohydrates), vegetarianism/veganism, daily calorie limits, ritualistic behaviours or even a limit to the number of spoonsful of food the young person will allow themselves to eat each day. Additionally, when reviewing young people with binge eating tendencies, the dietitian will need to ascertain if there is a specific binge food/food group, specific binge time, cyclical pattern to binges and which meals are missed.

Exercise routines should form part of the nutritional assessment and be taken into account when estimating nutritional requirements. An in-depth nutritional assessment also allows the dietitian to gauge the extent of the young person's nutritional knowledge.

Biochemical

The initial consultation should include a detailed laboratory assessment to rule out any organic cause of weight loss and to obtain baseline biochemistry. Additional markers that should be monitored include vitamin B_{12}, folate, zinc, fat-soluble vitamins A, D and E, and ferritin [16, 18]. Biochemical monitoring for patients at risk of refeeding syndrome is given at the end of this chapter.

Learning points: assessment process

- *A detailed multidisciplinary assessment is warranted to elicit the nature of the disordered eating*
- *All family members who have regular contact with the young person should be part of the assessment*
- *A thorough medical and biochemical assessment should be performed to exclude any organic cause of disordered eating*
- *An in-depth diet history can provide valuable information about eating habits and rules*

Management: family-based treatment

Although inpatient and day patient treatments are generally effective for weight restoration of patients with AN, they are disruptive to family, social and educational life. Therefore, intensive outpatient treatment using an evidence-based treatment approach should be sought by preference if the risks are manageable. Family-based treatment (FBT) can be summarised as an intensive outpatient treatment where parents play an active and positive role in promoting recovery in their adolescent child with AN or BN and has the strongest evidence base of available therapies. Parents are seen as a resource and play an active role in treatment, using their own methods to restore their malnourished adolescent's weight. Families are encouraged to explore how the eating disorder and the interactional patterns in the family have become entangled and how this entanglement has made it difficult for the family to get back on track with their normal developmental course. However, in some cases, outpatient treatment is just not an option: presence of overt systemic issues (the young person is at risk in the family environment, e.g. parents unable to provide the necessary level of care); or AN cognitions and behaviours are too strong or risky. In most cases, the treatment comprises three phases consisting of 15–20 treatment sessions over 6–12 months. The phases of treatment in FBT for AN, highlighting the potential role of the dietitian at each phase, are described below. In FBT for BN, the first phase focuses on cessation of binge and purge episodes rather than weight gain. An in-depth manual, *Clinical guidelines for dietitians treating young people with anorexia nervosa: family focused approach,* has been published by Great Ormond Street Hospital; it is endorsed by the British Dietetic Association (BDA) and is available to BDA members at https://www.bda.uk.com/uploads/assets/257c0404-894c-4c69-b909af56b1da9b70/Clinical-Guidelines-for-Treating-Young-People-with-Anorexia-Nervosa.pdf.

Dietetic management within an FBT framework

Phase 1: help restore their child's weight to a healthy range

Accurately calculate energy requirements

Energy requirements vary considerably throughout the course/treatment of AN due to normal increments associated with age/height, changes in percentage body fat and varying activity levels. Healthy adolescents have very high energy requirements because of the demands of pubertal growth phase. However, low-weight adolescents with AN have reduced energy requirements because their depleted body fat stores have led to an increase in cardiac vagal tone, causing bradycardia and hypotension, all of which aid conservation of energy [8, 9].

This altered metabolic state observed in low-weight adolescents with AN supports the need for a graded incremental meal plan, outlined in Table 19.1. Initially, the aim is to stop weight loss and build a relationship with the family by devising a realistic achievable meal plan, which encourages the young person to engage with treatment. Once weight loss has slowed and the patient has been able to adhere to the meal plan, then energy intake can be increased to achieve a weight-gaining meal plan.

Table 19.1 Graded-up meal plan for a 15-year-old female accounting for hypometabolic state of low weight.

Estimated energy intake on assessment	900 kcal/day (3760 kJ/day)	
Estimated average requirements (EAR) for height age	2400 kcal/day (10.80 MJ/day)	
Estimated energy requirements: hypometabolic (BMR)	1400 kcal/day (5850 kJ/day)	
Meal plan: 1	1500 kcal/day (6270 kJ/day)	Day 1–3: halt weight losing trajectory
Meal plan: 2	1800 kcal/day (7520 kJ/day)	Day 3–7: weight gaining
Meal plan: 3	2000 kcal/day (8460 kJ/day)	Week 2+: continual weight gain
Meal plan: 4	2500 kcal/day (10.45 MJ/day)	Week 7+: established energy requirements for age and height
Energy requirements are driven by % body fat and total body weights; therefore, as weight increases, so will energy requirements. If weight stabilises, it may be due to this as opposed to compensatory behaviours.		

EAR, estimated average requirements [19]; BMR, basal metabolic rate (Schofield equation [20]).
Source: Data from [20].

Refeeding syndrome

It is essential to ascertain whether the patient is at risk of the refeeding syndrome prior to commencing this graded meal plan. A detailed assessment and nutritional intervention schedule for refeeding high risk patients is given at the end of the chapter (p. 400).

Physical implications of malnutrition and low weight

Outlining the physical complications of malnutrition and low weight to the young person is an important part of the treatment, and these should be reiterated regularly throughout the three phases of therapy.

Bone health

Chronic fasting, malnutrition and low weight, along with compensatory behaviours, have profound effects on all of the body's physiological systems [21]. However, bone health is of particular importance in adolescents as it is a time when linear growth and mineralisation is rapid and when bone formation should normally exceed bone reabsorption in order for peak bone mass to be acquired [22]. Impaired linear

growth and possible permanent short stature are significant medical problems in adolescents with AN [23]. Invariably, short stature in AN is due to delayed growth, the result of delayed puberty as a consequence of having a low weight [24]. With a few exceptions patients with AN ultimately reach their expected height [25]. Furthermore, low levels of insulin-like growth factor-1 (IGF-1), as seen in adolescents with AN, have been linked with low bone mineral density (BMD) [26]. Other factors associated with the uncoupling of bone turnover in AN include: low levels of oestrogen (amenorrhoea), testosterone, dehydroepiandrosterone and leptin; and high levels of cortisol, ghrelin and peptide YY. All contribute to low BMD and susceptibility to the development of osteopenia, osteoporosis and increased fracture incidence [27]. Emphasis should also be placed on:

- cardiovascular adaptations – hypotension, bradycardia and QTc prolongation
- growth and final height (stunting)
- cognitive functioning
- primary secondary amenorrhoea
- anaemia
- constipation

Meal planning

The overarching aim of FBT is to empower the parents and build their confidence in feeding their child. Therefore, how confident parents feel will determine how prescriptive the weight-gain meal plan needs to be. The majority of families may only require guidance on portion sizes of main meals and the importance of incorporating snacks and fluids. However, some parents may feel disempowered and require a prescriptive meal plan, which minimises the opportunity for manipulation. Table 19.2 outlines an example of a prescriptive meal plan. Typically meal plans do not include specific calories if they are to be shared with the young person.

A recent food diary should give guidance when devising a new meal plan, which should:

- be clear, concise and comprehensive
- be initially devoid of 'fear foods' – these will be challenged later

Table 19.2 Example prescriptive meal plan.

Meal	Food	Portion (household measures)	Energy kcal (kJ)
Breakfast 7.30–8.15	Cereal – Shreddies Semi-skimmed milk (SSM)	80 g (3 teacups) 100 mL (half glass)	150 (630) 50 (210)
	Fruit Fruit juice – fresh/concentrate	1 medium-sized piece 200 mL (full glass)	75 (315) 100 (420)
			Breakfast total 375 (1575)
Mid-morning snack 10.30–11.00	Cereal bar Fruit juice/SSM	45–50 g (large size) 200 mL (full glass)	250 (1050) 100 (420)
			Snack total 350 (1470)
Lunch 12.30–13.45	Large bagel or 2 slices bread (butter optional) Meat/egg	10 cm diameter 50–60 g	250 (1050) 100 (420)
	Popcorn/rice cakes Low fat yoghurt Water	3 cups/3 servings 150 g (1 pot) 200 mL (full glass)	100 (420) 100 (420) 0
			Lunch total 550 (2310)
Mid-afternoon snack 16.00–16.30	Fruit Fruit juice/SSM	1 medium-sized piece 200 mL (full glass)	75 (315) 100 (420)
			Snack total 175 (735)
Dinner 18.45–19.30	Chicken breast Steamed broccoli Rice	150 g 1 cup 1 cup	200 (835) 50 (210) 200 (835)
	Low fat yoghurt Water	150 g (1 pot) 200 mL (full glass)	100 (420) 0
			Dinner total 550 (2300)
Bedtime snack 21.30–22.00	SSM	200 mL (full glass)	100 (420)
			Day total 2100 (8810)

- avoid 'anorexic language' – discussion of calories and grams
- transparent – build trust: calories should not be secretly added to a meal plan

As the weeks progress the parents would be expected to lead on changes to the meal plan with the guidance of the dietitian and therapist, in the context of the family meeting and guided by weekly weight measurements.

Meal supervision

Meals and snacks should be provided under supervision, ideally by someone who can demonstrate empathy and understanding while setting firm boundaries about what is expected, e.g. how much is to be consumed in a set period of time [28]. It is essential that appropriate observations are in place at mealtimes, i.e. consideration is given to who is present at each snack and mealtime and who has the responsibility for observation of the food and fluid consumed and the time limits set for snacks and meals. Time limits for eating, e.g. 15 minutes per snack and 30 minutes per meal, all need to be agreed. Support and supervision is recommended for 1 hour after each meal and has been shown to reduce the need for nasogastric (NG) feeding [28]. Additionally, meal supervision is a good opportunity to explore and discuss normal hunger and feelings of satiety.

Any actions to be taken if a meal is not completed need to be agreed and documented in advance, e.g. volume of sip feed to be given instead of the incomplete meal. Individual circumstances will help to dictate the exact needs of the young person and any help that may be needed with respect to helping them eat the required amount of food.

Sip feeds

High energy sip feeds (e.g. Fortini Compact Multi Fibre, Fortisip Compact, Nutrini Energy, Fortisip 2kcal, Pro-Cal shot) can be invaluable supplements for the young person who is struggling to consume the large quantity of food that they need for growth. A top-up supplement can provide a nutrient-rich addition, used as an adjunct to the meal plan, given after meals or snacks.

Expected weight gain

Weighing in the same way and at the same time each week will help to minimise fluctuations in weight from non-nutritional reasons, e.g. the patient should be weighed on the same scales in the morning before breakfast and after emptying their bladder, in underclothes only (bearing in mind that items can be hidden in these). Access to the ward or family weighing scales may need to be restricted to decrease the likelihood of frequent weighing by the individual.

Consideration needs to be given to water-loading by the patient in order to effect a gain in weight. This may necessitate restricted access to fluids, and the team needs to be aware that other patients' drinks may be consumed. Water may be drunk from taps, toilets and showers; access to these facilities may need to be restricted. If water-loading is suspected, then unplanned/spot weighing may be warranted.

Assuming the patient is medically stable, weight restoration at a rate of 0.8–1.0 kg per week for inpatients and 0.3–0.5 kg in an outpatient setting [7, 16, 18] is safe. Initially, weight restoration can usually be achieved by meeting the estimated average requirements (EAR) for energy for height age. However, sometimes this is not adequate, and daily increments of 200–300 kcal (840–1255 kJ) are required until sufficient weight gain is achieved.

It is not uncommon for a member of the psychiatric team to request that the dietitian put a hold on weight gain once the young person is out of the high risk category (once their %BMI is >85%) to allow for directed therapy around anxiety, which has resulted from the weight gain.

If the young person is still expected to grow, then the use of target weights should be avoided as a marker of health, but instead, a target %BMI is better used as it accounts for expected changes in height.

Learning points: phase 1

- *Accurate calculation of energy requirements is necessary, taking into consideration the hypometabolic state of the young person and risk of refeeding syndrome*
- *Energy requirements should be regularly recalculated to account for normal growth and development, along with an increase in percentage body fat and subsequent increase in resting energy expenditure*
- *Meal plan prescriptiveness should be devised based on the level of parental empowerment*
- *A prescriptive meal plan should be concise and clear to avoid any confusion and possibility of manipulation once at home*
- *Weight gain is an expectation of outpatient treatment*

Phase 2: returning control over eating to the adolescent

This phase of treatment focuses on encouraging parents to help their child to take more control over eating again in an age-appropriate manner.

Dietetic goals

During this second phase it is important to expand on the importance of a balanced diet with particular focus on bone health. This needs to be age-appropriate, with caution around giving too much nutritional information to younger patients. Furthermore, it should be ascertained whether the family and young person understand their nutritional needs to optimise catch-up growth and healthy development.

Table 19.3 Example of a young person's 'eating and feeling diary'.

	Amount served	What was suggested addition?	What addition was managed?
Sunday			
Breakfast	Good portion	nil	
Lunch	Good portion	nil	
Dinner	Not enough	2 more roast potatoes	1 roast potato
Monday			
Breakfast	Good portion		
Lunch	Not enough	1 pot of yoghurt	1 pot of yoghurt
Dinner	Not enough	Finish food on plate	Left rice: 3 tablespoons
Tuesday			
Breakfast	Not enough	Half cup more of Rice Krispies	Half a banana (an appropriate negotiation)
Lunch	Good portion	nil	
Dinner	Good portion	nil	

Positive signs that eating is becoming easier include eating to appetite, serving larger portions and having additional snacks not included on the meal plan. Once parents and the therapy team agree that there is a significant shift in attitude towards eating, then a 'food and feeling diary' can be trialled. Table 19.3 gives an example of how to promote the return of eating to the young person. In the example, at breakfast the parents documented that a sufficient amount of food was served by the young person, and therefore, no suggestion or addition was needed. However, at dinner time the parents felt that an insufficient amount of food was served and therefore suggested another two roast potatoes; what was actually managed was one roast potato. The point here is that, if there are consistent shortfalls in expected intake and regular battles, it may be that the young person does not have a grasp of what is expected or is not ready/capable of taking control of their condition. A 'feeling section' can be added to the diary, which can be kept private or discussed with family or individual therapist.

Challenging feared/forgotten foods

It is during this second phase of FBT that challenging the young person's 'feared foods' can start. This can be performed in a number of ways including the reintroduction of foods that were most recently excluded, in a sequential manner, gradually increasing the number of foods eaten. Alternatively, a list of feared foods can be formulated, which is usually completed with the parents in conjunction with the young person as it is a difficult task for the young person; it is essential to have trust between all parties.

Starting with the least feared food, there is discussion how it can be incorporated into a family meal or simply just touching or tasting the food. It is important to continue with regular exposure to feared foods to help with reducing anxiety. There must be observance that there is no increase in compensatory behaviour, i.e. exercise, to counteract the addition of feared foods, and if there is, it must be ensured that it is time limited.

Activity level

Exercise and activity levels are a contentious issue in young people with AN who have previously used exercise to control weight or shape. It is important to remember that healthy exercising has many benefits; one of note is its cathartic value, as well as its antidepressant qualities. Therefore, once the team has deemed exercise to be safe, based on cardiovascular health, BMD and percentage BMI >85%, low level activity can be introduced. This may include walking to and from school (20 minutes per day) or partaking in physical education lessons at school. Table 19.4 outlines expected energy expenditure from a variety of different activities with worked examples of how to calculate energy requirements.

Once the young person has demonstrated that they can continue to gain weight while performing low level activity and manage additional snacks to account for the increased energy level, then it is viable to consider starting out of school clubs. However, it is important to avoid solitary sports such as running and swimming, which inadvertently promote rigidity (counting lengths/laps), or activities that emphasise body shape, e.g. gymnastics, dance and ballet. Team sports, which have a social component, like hockey, football and netball, should be encouraged.

Suitable snacks for episodes of 20–30 minute exercise (200 kcal, 840 kJ per portion) are:

- cereal bar – nut based
- banana toasted sandwich with butter or honey
- 75 g dried fruit
- 50 g mixed nuts
- blueberry muffin

Table 19.4 Exercise energy requirements.

Exercise/activity	Duration/intensity	EER = EAR × (PAL × time spent)
Seated jiggling/swinging legs	4 hours/day	EAR × (1.4 × 4/24)
Walking/jogging	2 hours/day	EAR × (1.8 × 2/24)
Competitive training (gymnastics/dance/swimming)	High intensity 2 hours/day	EAR × (2.4 × 2/24)

Worked examples:
A 10-year-old girl spends 5 hours seated jiggling per day. EER = 1935 kcal (8090 kJ) × (1.4 × 5/24) = 564 kcal (2360 kJ)
Total daily energy requirements = 1935 kcal (8090 kJ) (EAR) + 564 kcal (2360 kJ) (EER) = 2500 kcal (10.45 MJ)

A 7-year-old boy spends 2 hours jogging per day. EER = 1650 kcal (6895 kJ) × (1.8 × 2/24) = 250 kcal (1035 kJ)
Total daily energy requirements = 1650 kcal (6895 kJ) (EAR) + 250 kcal (1045 kJ) (EER) = 1900 kcal (7940 kJ)

A 14-year-old girl spends 2 hours swimming per day and 1 hour jogging. EER = 2340 kcal (9780 kJ) × ([2.4 × 2/24] + 2340 kcal (9780 kJ) × ([1.8 × 1/24]) = 545 kcal (2275 kJ)
Total daily energy requirements = 2340 kcal (9780 kJ) (EAR) + 545 kcal (2275 kJ) = 2885 kcal (12.10 MJ)

Source: Adapted from [29].
EER, exercise energy requirement; EAR, estimated energy requirement for energy; PAL, physical activity level.

These snack portion sizes take into account the raised energy expenditure that occurs after exercise.

Learning points: phase 2

- *There is a focus on a balanced diet with bone health at the forefront of discussion and rationale for maintaining a healthy weight*
- *The most appropriate time to commence exercise should be decided as a team and considers medical and psychological state*
- *If exercise is to commence, then so must appropriate snacking*
- *Team sports with a social aspect are encouraged rather than solitary/rigid-focused sports*

Phase 3: establishing healthy adolescent identity

This phase can be initiated once the adolescent is able to maintain a healthy weight (three regular menses or if premenarche/male >95% BMI) and focused on establishing a healthy age-appropriate relationship with parents.

Dietetic goals

This can be the most rewarding phase for the young person, their clinicians and family as it is a time when control of their AN becomes noticeable, and they should be encouraged and challenged in a guided manner. It is important not to push too hard even if the young person wants to move faster.

During this phase rigid calorie counting can be challenged by recommending eating out at new restaurants without calling ahead and checking the menu or advising the young person to buy new products and brands without first checking their calorie content.

There is a focus on untangling normal adolescent behaviour and development and their AN. Discussions may need to be around abuse of alcohol and recreational drugs in relation to low self-esteem. This can be facilitated within a group session along with other mental health professionals.

Refeeding Syndrome: Young People with Anorexia Nervosa

Introduction

Although infrequent and rarely critical, refeeding syndrome is a serious potential complication of commencing feeding in children and young people who have experienced starvation and should be considered and monitored for in such patients [30, 31]. As starvation and malnutrition can occur for a large number of reasons in childhood and adolescence, it should be considered in all children irrespective of underlying condition or specialty.

Refeeding syndrome is a physiological phenomenon driven by insulin, resulting in deranged biochemistry, which leads to cardiovascular abnormalities. During starvation, insulin concentrations decrease, and glucagon levels rise in response to depleted glucose levels. Glucagon breaks down glycogen, forming glucose, which rapidly depletes muscle and liver glycogen stores [32]. As glycogen stores are depleted, gluconeogenesis is activated, utilising lipids and proteins as metabolic substrates to form glucose. However, gluconeogenesis has a limited capacity to support the body's energy requirements. Therefore, during this period of low serum insulin, hormone-sensitive lipase is activated, which breaks down adipose tissue to form fatty acids and glycerol; the fatty acids are transported to the liver to be converted to ketones. Ketones now replace glucose as the body's major energy source during acute starvation [33, 34].

Complications manifest with the introduction of carbohydrates (from diet or intravenous [IV] fluids), triggering a metabolic sequence of events due to a switch from ketone to glucose metabolism. The subsequent insulin surge that occurs in response to rising serum glucose levels causes a rapid intracellular movement of glucose, fluid and electrolytes [35, 36].

For most children and young people, the most significant finding will be a fall in serum phosphate levels. When undernourished patients are fed, there is an increased requirement for phosphate as the body switches back to carbohydrate metabolism, which can be potentiated by a background of relative phosphate depletion in starvation. Phosphate levels in the blood begin to fall, and cardiovascular and neurological sequelae may follow [37].

On the initiation of feeding after a period of starvation, it is of the utmost importance to anticipate and remain vigilant for the biochemical and clinical features of refeeding syndrome, especially in the first 48 hours, and then the first 5 days after commencement of feeding. Low phosphate levels will usually correct when treated with oral phosphate supplements or given intravenously if the enteral supplement is not tolerated.

Refeeding syndrome may occur up to 2 weeks after initiating feeding. While it is important to be vigilant and refeed safely, 'underfeeding syndrome', i.e. weight loss or inadequate weight gain, should also be avoided.

Management of refeeding syndrome

At risk groups

Those most at risk of refeeding syndrome are children and young people who have:

- very low body weight (in particular those <70%–80% weight for height/median BMI) [38]
- acute starvation with rapid weight loss prior to commencement of nutrition
- prolonged IV fluid therapy devoid of glucose; prolonged fasting; prolonged periods of nil by mouth
- previous history of refeeding syndrome
- electrolyte abnormalities prior to starting feeds
- low white blood cell count [38]

Important considerations prior to commencing feeding

The following should be undertaken before any feed is given:

- Baseline blood samples should be taken (see Biochemical monitoring)
- Electrolyte disturbances must be corrected as feeding commences and prophylactic phosphate supplementation considered for those who are known to have had refeeding syndrome before
- An electrocardiogram (ECG) according to the individual, especially where there is pre-existing cardiac arrhythmia (particularly prolonged QTc), should be considered
- Strict monitoring of fluid balance should be put in place

Commencing nutrition

The refeeding of malnourished patients needs to be gradual and closely monitored and must increase in controlled phases in order to avoid further weight loss (underfeeding syndrome).

Note that although initial feed rates provided below are for safe initiation of feeding, children and young people may well have additional requirements, e.g. for increased losses or catch-up growth, which should be considered and incorporated into feeding plans after the safe commencement of nutrition, as per the protocols below.

Adolescents are at particular risk as their high energy requirements coupled with restricted nutritional intake lend itself to a rapid deterioration in health. Table 19.5 outlines the refeeding phases that can be adopted to promote appropriate weight gain in a timely and safe manner. A worked example of a phased refeeding regimen is given in Table 19.6.

Table 19.5 Refeeding phases for adolescents at high risk of refeeding syndrome [38].

Refeeding phase	Target energy requirements and weight gain
Primary Day 1–2	• Commence at 30–40 kcal (125–165 kJ)/kg/day • Increase by 200 kcal (840 kJ)/day until secondary refeeding phase reached • Correct deranged electrolytes; do not stop refeeding • Weight loss/maintenance likely during this primary refeeding phase • Consider oral thiamine 100–200 mg twice a day, continue for 10 days
Secondary Day 2–4	• Basal metabolic rate (BMR) + physical activity level (PAL) • Maintain secondary refeeding phase if adequate weight gain (0.5–1.0 kg/week) • Once weight gain reduces, increase by 200–300 kcal (840–1255 kJ)/day until tertiary refeeding phase reached
Tertiary Day 7–14	• Estimated average requirement (EAR) energy for height age • Maintain tertiary phase if adequate weight gain (0.5–1.0 kg/week)
Progression	• If sufficient weight gain not achieved with EAR, continue to increase energy intake by 200–300 kcal (840–1255 kJ) every 4 days until weight increase of 0.5–1 kg/week
Maintenance	• Once weight is >85% median BMI, weight gain can be slowed or maintained depending upon the therapeutic plan as discussed with the multidisciplinary team

BMI, body mass index.
Source: Reproduced with permission of John Wiley & Sons.

Table 19.6 Worked example of a phased refeeding regimen.

14-year-old girl with anorexia nervosa, weight = 30 kg. She is restricted to limited activity on the ward giving her a physical activity level (PAL) = 1.2. Her basal metabolic rate (BMR)* = 1223 kcal (5112 kJ).	
Day (refeeding phase)	Target energy requirements and weight gain
Day 1 and 2 (primary phase)	It has not been possible to elicit an accurate reliable diet history **Start a meal plan:** at 40 kcal/(165 kJ)/kg = 1200 kcal (4950 kJ)/day **Now, calculate the secondary phase energy intake target:** BMR × 1.2 PAL (restricted to ward) [(17.686 × 30 kg) + 692.6] × 1.2 PAL = 1468 kcal (6140 kJ)/day
Day 3 and 4 (secondary phase energy intake target)	Increase meal plan by 200 kcal (820 kJ)/day until secondary phase requirements met = 1468 kcal (6140 kJ)/day Weight should increase as a result of hydration and glycogen store replenishment **Now calculate the tertiary phase energy intake target:** EAR for energy = 2342 kcal (9836 kJ) [19]
Day 7 (tertiary phase energy intake target)	Increase meal plan by 200 kcal (820 kJ)/day until tertiary phase energy requirements met Halt energy increments and monitor weight gain From this point weight gain target: 0.6–1.0 kg/week (0.1 kg/day) If weight gain is <0.6 kg/week, increase meal plan by 300 kcal (1255 kJ) = 2650 kcal (11.07 MJ)/day
Progression	If sufficient weight gain is not achieved, continue to increase energy intake by 300 kcal (1255 kJ) every 4 days until weight gain target of 0.6–1.0 kg/week (0.1 kg/day) is achieved Be mindful of compensatory behaviours (secret exercising/purging) if exceeding 3000 kcal (12.54 MJ)/day while bed/ward bound

EAR, estimated average requirement for energy.
*Schofield equation for calculating BMR can be found in Table 19.7.

Table 19.7 Schofield equations to calculate basal metabolic rate (kcal) for children at risk of refeeding syndrome [20].

Age (years)	Male	Female
<3	(59.5 × Wt[kg]) − 30.4	(58.3 × Wt[kg]) − 31.1
3–10	(22.7 × Wt[kg]) + 504.3	(22.7 × Wt[kg]) + 485.9

Furthermore, Tables 19.7 and 19.8 provide guidance for target energy requirements, which takes into account the reduced activity along with the hypometabolic state associated related with malnutrition.

Other considerations when starting nutrition:

- Rehydration should ideally be done as part of the feeding regimen or corrected before to avoid fluid overload associated with refeeding

Table 19.8 Estimated energy requirements per day based on low physical activity.

Age (years)	Energy males (kcal)	Energy females (kcal)
1	80 per kg	80 per kg
2	65 per kg	65 per kg
3	65 per kg	60 per kg
4	60 per kg	60 per kg
5	60 per kg	55 per kg
6	1150	1050
7	1200	1100
8	1250	1200
9	1350	1250
10	1500	1400
11	1600	1500
12	1650	1550
13	1800	1650
14	1950	1700
15	2100	1750
16	2200	1800
17	2300	1850
18	2400	1850

Source: Adapted from [19]. Licensed under Open Government License.

- NG tube insertion should be considered if daily energy requirement is not met orally with food and/or nutritional supplements
- Bolus NG feeds are preferable to continuous as they closely mimic normal physiology and reduce the individual's preoccupation with energy. However, continuous feeds may be considered in those with hypoglycaemia, upper gastrointestinal symptoms or malabsorption

Monitoring refeeding syndrome

The characteristic and most common finding in refeeding syndrome is hypophosphataemia, which, if untreated, can lead to cardiovascular and neurological sequelae. Other electrolytes can also be affected including potassium, magnesium and sodium.

Monitoring for clinical features is also important and must be responded to, especially fluid balance. Important clinical features to look for include an unexplained resting tachycardia, oedema, confusion or conscious level.

Daily clinical and biochemical monitoring is required until full calories are achieved, and the patient is stable.

Nutritional monitoring

- Monitoring the amount of calories/intake that is actually being received, as well as changes in weight/BMI, is an essential part of the management of refeeding syndrome

Table 19.9 Normal ranges for electrolytes according to age.

Age	4–9 years	9–15 years	>15 years
Magnesium (mmol/L)	0.66–1.0	0.7–0.95	0.7–1.0
Age	4–9 years	1–15 years	>15 years
Potassium (mmol/L)	3.5–5.5	3.5–5.5	3.6–5.0
Age	4–9 years	10–15 years	>15 years
Phosphate (mmol/L)	1.2–1.8	1.1–1.75	0.8–1.45

to ensure that appropriate nutrition is being given, and supplementation can take place
- Urinary sodium may be useful measure to determine sodium depletion
- Early weight gain may be secondary to fluid retention

Clinical monitoring

- The presence of oedema or confusion should be monitored frequently throughout the day
- In particular, identification and reporting of tachycardia to members of the medical team is important as this can be an early sign that refeeding syndrome is developing

Biochemical monitoring

- Urea, creatinine, sodium, potassium, phosphate, calcium, albumin and magnesium levels should be measured daily for 5 days (Table 19.9 shows electrolyte levels where normal ranges are age-dependent)
- As refeeding syndrome can occur for up to 2 weeks after commencing feeds, electrolyte levels should be repeated at days 10 and 14
- Abnormalities usually occur within the first 72 hours after commencing nutrition
- Blood sugar levels should be measured if a patient is symptomatically hypoglycaemic
- Measuring urine for osmolality, electrolytes, pH, glucose and protein in the first 5–10 days should be considered in those patients with blood or clinical signs of refeeding syndrome; this should be discussed and considered with the senior medical team responsible for this patient

Treatment of refeeding hypophosphataemia

The following practice points are advised for the treatment of the hypophosphataemia seen in refeeding syndrome:

- no increase in the feed regimen until phosphate levels are corrected and normalised
- check vitamin D and parathyroid hormone (PTH) levels to optimise phosphate homeostasis
- daily monitoring of urea, creatinine, sodium, potassium, phosphate, calcium, magnesium and albumin levels until phosphate is normal
- consider oral phosphate supplements for mildly low levels or IV phosphate supplements for significantly low levels of serum phosphate (e.g. <0.5 mmol/L), poor clinical status or where oral supplementation is not possible/tolerable
- involvement and discussion between all relevant staff: medical consultant, senior nurse, ward nurses, dietitian and pharmacist
- ensure there is peripheral IV access if no central IV access, particularly in those considered most at risk and those with other medical co-morbidities. Some children with mild hypophosphataemia who are otherwise clinically stable may not automatically need IV, but the decision should be based on likely risk and other medical problems and should be decided by the medical team
- repeat ECG if there is evidence of refeeding syndrome – monitor for QT interval prolongation
- phosphate level <0.3 mmol/L is considered severe, and HDU/PICU support may be needed – this should be discussed with consultant, senior nurse and PICU leads for the shift

Treatment of clinical features refeeding syndrome

The clinical features of refeeding syndrome include resting tachycardia, peripheral oedema and confusion/altered conscious level. If these features are evident, it is recommended to:

- reduce the energy intake to starting dosage with no increase in energy until serum phosphate levels are normal, and the patient is clinically stable
- check full blood count (FBC), urea, creatinine, sodium, potassium, phosphate, magnesium, calcium, liver function tests (LFT), gas-correct any electrolyte and acid–base abnormalities
- check blood sugar levels
- start cardiac monitoring
- observations must include full physical examination, lying/standing blood pressure and neuro-observations

Carbohydrates and refeeding syndrome

Despite low energy intakes in the secondary phase of refeeding, weight gain is often achieved due to the rapid replenishment of glycogen stores. However, refeeding syndrome is driven by insulin, and therefore, the carbohydrate intake should not exceed the recommended amount of 60% of dietary energy [39]. Most oral nutritional supplements and enteral feeds contain 42%–46% energy from carbohydrates, regardless of whether they are standard or high energy formulas. However, the total energy load from high energy formulas is higher than that from standard formulas, which may have an overall deleterious effect [40].

Learning points: refeeding syndrome

- *Refeeding hypophosphataemia is the commonest symptom of refeeding syndrome, a result of phosphate's essential role and utilisation in glucose metabolism*
- *High risk group includes acute onset with rapid weight loss, significantly affecting %BMI and white blood cell count*
- *Initial meal plans should be based on 30–40 kcal (125–165 kJ)/kg/day and increased by 200 kcal (840 kJ)/day*
- *EAR should be achieved within 14 days*

Overview

FBT is the evidence-based model for young people with AN and BN. Therefore, dietitians should be focusing their treatment programs to align with FBT. Treatment should be personalised to the needs of each specific young person. It is important to appreciate the changeable energy requirements and therefore the importance of regularly calculating energy requirements throughout the treatment period. A concise well-structured meal plan can provide parents with the confidence needed to engage with FBT, opening the opportunity to promote weight gain and avoid hospitalisation. Working in conjunction with the therapy team will guide the dietetic treatment, ensuring appropriate challenging of AN and optimising nutritional intake, while minimising the long-term physical complications associated with AN.

Dietitians working in eating disorders must have an understanding of the underlying dynamics [41] and be aware of their professional boundaries when treating these complex patients. It is important to highlight the synergy between psychological and nutritional factors; without psychological understanding and support, nutritional rehabilitation is likely to be ineffective. Conversely, malnutrition will impact cognitive function and behaviour, including increasing preoccupation with food and eating in a way that mirrors the eating disorder itself.

Future directions

The recommendations in this chapter are largely drawn from accumulated consensus opinion and some limited research evidence. There have been few clinical trials to date in the areas of refeeding or dietetic involvement in the care of children and young people with eating disorders. Furthermore, research evidence is needed to support the reintroduction of carbohydrates into the diet and the safest refeeding procedure to ensure adequate weight gain without the complications associated with refeeding syndrome.

Trials, which evaluate the effectiveness of structured nutritional sessions in conjunction with psychological input, would help elucidate the most effective method of working with young people with eating disorders from a nutritional perspective.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

20 Autism

Zoe Connor

Introduction

Autism is a common developmental condition that affects communication and behaviour. It is reported to be the costliest condition in the UK, and autistic adults have high early mortality rates, which may be partly attributed to nutrition. Typical autism characteristics of rigid thinking, resistance to change and sensory processing difficulties (SPDs) make feeding problems common. Traditional approaches to dietary behaviour change are often inadequate. At least 1% of children and young people (CYP) in the UK and worldwide are autistic [1–3]. There are no significant differences in prevalence by geographic region or ethnic/cultural or socioeconomic factors [3]. Diagnosis in males is four times that of females, partly due to a difficulty in recognition in females who are more able to mask their differences [4].

Diagnosis, terminology and common investigations

Signs of autism can be apparent from the first months of life, and diagnosis typically occurs between 2 and 5 years old, but sometimes later, even into adulthood [5]. Parental or other caregiver concerns around social interaction or delayed speech typically lead to an initial screening by a general practitioner or health visitor using a tool such as the validated M-CHAT (Modified Checklist for Autism in Toddlers) [6]. UK national guidelines for recognition, screening and diagnosis are the National Institute for Health and Care Excellence (NICE) clinical guideline 128 in England, Wales and Northern Ireland [7] and the Scottish Intercollegiate Guidelines Network (SIGN) clinical guideline 145 [8]. Diagnosis involves in-depth expert observations and assessments against criteria in either of the most current editions of the American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [9] or the World Health Organization (WHO) International Classification of Diseases (ICD-11) [10]. Medical investigations are not necessary for the diagnosis of autism; however, genetic testing is recommended if the child has learning disabilities or congenital anomalies, and electroencephalography if there is suspicion of epilepsy [7].

Previous diagnoses of Asperger's, classic autism and others have been replaced by the single term autism spectrum disorder (ASD) in the most recent diagnostic manual editions, with the use of various specifiers. Current and previous WHO and APA ASD classifications and criteria are summarised in Table 20.1. The umbrella term ASC is sometimes preferred to ASD to highlight its existence as part of a normal continuum of neurodiversity rather than as a 'disorder' [11] and to be inclusive of those diagnoses prior to the current diagnostic term of ASD [5].

Causes

Up to 15% of autistic people have 1 of more than 60 identified genetic causes such as fragile X syndrome, tuberous sclerosis and Timothy syndrome [12]. For the remainder the cause is unknown and is likely to be varied and multifactorial. Twin and family studies have shown that autism is strongly heritable, from 50% to 95% [13–15]. Genetic studies have failed to find any single 'autism gene'; however, multiple gene families have been identified that link to autism and other neurodevelopmental and psychiatric disorders [16–18]. Methylenetetrahydrofolate reductase (MTHFR) gene variants have been found more commonly in autistic CYP [19–22].

Neuroimaging has shown brain differences in autistic CYP: accelerated brain development and higher brain volume

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 20.1 Comparison of the criteria and classifications for autism spectrum disorder in WHO IDCD-11 and APA DSM-5.

	DSM-5 (2013) [9]	ICD-11 (2018) [10]
ASD diagnostic criteria	A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested *by all of the following:* 1. Deficits in social-emotional reciprocity 2. Deficits in nonverbal communicative behaviours used for social interaction 3. Deficits in developing, maintaining and understanding relationships B. Restricted, repetitive patterns of behaviour, interests or activities, as manifested by **at least two** of the following: 1. Stereotyped or repetitive motor movements, use of objects or speech 2. Insistence on sameness, inflexible adherence to routines or ritualised patterns or nonverbal behaviour 3. Highly restricted, fixated interests that are abnormal in intensity or focus 4. Hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment C. Symptoms must be present in the early developmental period D. Symptoms cause clinically significant impairment in social, occupational or other critical areas of current functioning E. These disturbances are not better explained by intellectual disability or global developmental delay	'Autism spectrum disorder is characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour and interests. The onset of the disorder occurs during the developmental period, typically in early childhood, but symptoms may not become fully manifest until later when social demands exceed limited capacities. Deficits are sufficiently severe to cause impairment in personal, family, social, educational, occupational or other important areas of functioning and are usually a pervasive feature of the individual's functioning observable in all settings, although they may vary according to social, educational, or another context. Individuals along the spectrum exhibit a full range of intellectual functioning and language abilities'
ASD specifiers	Severity based on social communication impairments and restricted, repetitive patterns of behaviour: Level 3 'Requiring very substantial support' Level 2 'Requiring substantial support' Level 1 'Requiring support' With or without accompanying intellectual impairment	Autism spectrum disorder With/without disorder of intellectual development and with mild or no impairment functional language/ with impaired functional language/with the absence of functional language
New diagnoses related to ASD	Social (pragmatic) communication disorder	Developmental language disorder
Terms used for ASD in previous manuals that are no longer included	Pervasive developmental disorders, autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, pervasive developmental disorder not otherwise specified (PDD-NOS)	Autistic disorder, pervasive developmental delay

(but not head circumference) in infancy and early childhood compared with typically developing children [23]. These changes are associated with altered connectivity both throughout the brain and in specific regions [24–27]. The underlying cellular mechanisms are poorly understood.

More than 20 environmental factors linked to increased risk of autism have been identified, many of which focus on maternal exposure before and during pregnancy and include both maternal and paternal increasing age, pregnancy spacing and use of some medications [28–32]. Taking folic acid before and after conception is associated with more than a 40% reduction in risk for having an autistic child, with greater reductions in risk when mothers or children carried the gene variant MTHFR 677 C>T [22, 33–36]. However, other studies do not support these associations [37, 38]. Other maternal dietary factors that have been linked to increased risk of autism are low iron intakes in pregnancy [39], high polyunsaturated fatty acid (PUFA) intake [40] and low vitamin D levels [41–44].

Outcomes and public health impact

Autism is seen as a lifelong condition; however, 4%–40% of children lose their diagnosis as they get older [45–47]. Loss of diagnosis is more common for those more 'mildly' affected or without other coexisting conditions. Whether these changes are due to 'recovery' or just a shifting of how much underlying autistic traits impede 'normal' life is not known [48].

Autistic people have an increased risk of many preventable nutrition-related conditions including vitamin and mineral deficiencies, dyslipidaemia, hypertension and type 2 diabetes and die on average 18 years younger than the general population (30 years younger for autistic people with intellectual/learning disabilities) [49, 50]. Autism costs the UK £32 billion per year in treatment, lost parental earnings, care and support – more than heart disease, cancer and stroke combined [51, 52]. The government has highlighted the need to reduce the health gap between autistic people and the general population and increase UK research spend from the

current £4 million per year (£6 per year per autistic person compared with £220 spent per person with cancer) [53–56].

Co-morbidities

Over 95% of autistic CYP have at least one coexisting medical, psychiatric or behavioural condition [57]. Autistic CYP have an increased prevalence of gastrointestinal (GI) conditions and feeding problems. These conditions further impair social and psychological functioning and increase the need for medical and dietetic input. Prevalence of a selection of conditions are listed in Table 20.2. Assessment for coexisting conditions, including feeding and nutrition problems, and referrals to appropriate professionals (including dietitians) on diagnosis are recommended in UK guidance [7, 8].

Sensory processing difficulties

Impairment in the perception of sensory stimuli is reported in over 90% of autistic people [79, 80] and has been incorporated into the DSM ASD criteria for the first time in the current 5th edition: 'Hyper- or hypo-reactivity to sensory

Table 20.2 Prevalence of coexisting conditions in autism.

Coexisting condition	Prevalence
Learning and behavioural problems	
Intellectual/learning disability [58, 59] (IQ < 70)	USA: 38% of 3820 aged 8 UK: 55% of 156 aged 9–14
Speech and language delay [48, 60]	USA: 87% of 87 aged 3
Sleeping problems [57, 61]	USA: 25%–40%, 10 times more insomnia than controls in 3800 aged 7–13; 27% of 783 aged 4; 37% of 1091 aged 8
Attention deficit hyperactivity disorder (ADHD) [57, 62]	UK: 28.2% of 112 aged 10–14 USA: 5.5% of 783 aged 4; 26.1% of 1091 aged 8
Pica (eating inedible substances) [63]	UK: 60% of 70 autistic adults with learning disabilities vs. 4% of adults with Down's syndrome and learning disabilities
Mental health problems	
Anxiety disorder [50, 57, 62, 64]	USA: 29.1% of 1507 adults vs. 9.1% of 15 070 controls UK: 29.2% of 112 aged 10–14 USA: 4.8% of 783 aged 4; 11.2% of 1091 aged 8
Depression [65]	USA: 25.8% of 109 adults, 2.9 times higher than 56 controls (9.9%)
Mood disorder [57]	USA: 56% of 783 aged 4; 75% of 1091 aged 8
Bipolar disorder [50]	USA: 10.6% of 1507 adults vs. 1.7% of 15 070 controls
Obsessive–compulsive disorder (OCD) [50]	USA: 7.6% of 1507 adults vs. 0.5% of 15 070 controls
Schizophrenic disorders [50]	USA: 7.8% of 1507 adults, 22 times higher than in 15 070 controls (0.4%)
Medical problems	
Autoimmune disease [50]	USA: 13.9% of 1507 adults vs. 10.8% of 15 070 controls
Food allergy [66, 67]	USA: 0.9% of 5565 children vs. 0.5% of 27 825 controls (diagnosed); 11.25% of 1868 children vs. 4.25% of 199 520 controls (reported)
Motor coordination problems [68, 69]	UK: 79%–89% of 97 children aged 10–14, 1.2 times more prevalent in a meta-analysis
Epilepsy [50, 70]	USA: 8.6% vs. 1.2% of 85 248 aged 2–17; 11.9% in 1507 adults vs. 0.73% in 15 070 controls
Mitochondrial disease [71]	5.0% vs. 0.01%, meta-analysis of 11 studies of 112 autistic children
Gastrointestinal problems	
Gastrointestinal symptoms [50, 72–74]	Four times more prevalent in autistic CYP than non-autistic CYP (9% to >70%), meta-analysis of 2215 autistic CYP, 15 studies USA: 34.7% of 1507 adults vs. 27.5% of 15 070 controls
Diarrhoea [73]	3.6 times more prevalent in autistic CYP than non-autistic CYP meta-analysis of 2215 autistic CYP, 15 studies
Constipation [73, 75]	3.9 times more prevalent in autistic CYP than non-autistic CYP (12 times more prevalent in nonverbal CYP), meta-analysis of 2215 autistic CYP, 15 studies 85% of autistic CYP in a clinically validated sample of 121 CYP
Coeliac disease [76–78]	Sweden: in 36 714 CYP same prevalence in autistic and non-autistic CYP Italy: 3.3% of 150 screened CYP three times higher than in non-autistic CYP

Table 20.3 Examples of how sensory processing difficulties could affect food preferences and mealtime behaviour.

Sense	Hyper-reactivity	Hypo-reactivity
Taste (gustatory)	Strong preference for bland tasting foods Aversion to spicy foods/many foods Ability to detect tastes that others may not, e.g. attempts to hide foods or supplements in preferred foods	Preference for strong tasting spicy foods Licking objects Pica
Smell (olfactory)	Distracted or disturbed by food smells Ability to detect odours that others may not, e.g. in protein-rich foods	Preference for strong scents
Sight (visual)	Distracted by lighting, movement or colours at mealtimes Distracted by 'specks' in food Preference for bland-coloured foods Preference for different foods to be presented separately Disturbed by foods not displayed in the usual way Aversion to certain coloured foods	Difficulty making out foods on a plate Preference for contrasting foods and plates
Sound (auditory)	Dislike of the sound of self or others eating, particularly crunchy or noisy foods Distracted or disturbed by background sounds, some of which may not be obvious, e.g. fluorescent light tubes	Preference for foods that make sounds when eaten, e.g. crunchy ones
Touch (tactile)	Dislike of mixed textures in the mouth Dislike of hot or cold foods and drinks Dislike of some cutlery in mouth Dislike of tooth brushing Dislike of busy eating places in case someone bumps against them Dislike of getting messy	Preference for lumpy or crunchy foods May not notice when face gets messy when eating Preference for very hot or very cold foods and drinks (possibility of burning self as hyposensitive to pain) A tendency to frequently put foods and other objects to the mouth Pica
Proprioception	Alterations can contribute to clumsiness in eating or drinking or being distracted by arm movements during eating	
Vestibular attention	Changes can cause a child to be distracted by moving or not moving self or by body position during a meal	
Interoception	Alterations may create a lack of or excessive experience of hunger and thirst and might affect the ability to know when to defaecate and urinate or indeed a dislike of these sensations	

input or unusual interests in sensory aspects of the environment' [9]. The reasons for these sensory processing difficulties are not understood.

SPDs can fluctuate between hyper- and hypo-reactivity in each sense and can have marked negative impacts on a child's functioning in daily activities including eating [81]. SPDs not only relate to sight, sound, smell, touch and taste but also to proprioception, sensations from muscles and joints that give a sense of where the body is in space; vestibular, sense of head movement in space that relates to balance; and interoception, the sensations associated with the physiological and physical condition of the body such as the sense of thirst, hunger and body temperature.

SPDs impact on a child in many ways. Firstly, they may directly impact the way they experience the world around them, impairing (or sometimes enhancing) their understanding of objects and experiences, including food and mealtimes. Secondly, they can affect their alertness: hypo-responders may be understimulated and not alert enough to take part in a learning activity, for example, or too busy self-stimulating ('stimming') to concentrate; hyper-responders may be overstimulated by a learning activity and overwhelmed. Thirdly, coping behaviours may be directly related to sensory processing difficulties: common behaviours such as fidgeting, spinning, rocking or hand flapping are often forms of self-stimulation when hypo-reactive to external stimulation; aversions to touch, light, smell, taste, sound or certain movements may be due to hyper-reactivity. Table 20.3 gives examples of sensory issues that could affect food intake and mealtimes.

Learning points: features of autism

- *Autism is a complex, common and costly condition*
- *It is characterised by a range of social difficulties with unpredictable outcomes and trajectories*
- *Causation is likely a complex interplay between multiple genes and mostly unavoidable environmental stressors*
- *Vitamin D and folate supplements peri-conception may play a role in development of autism*
- *Autistic people often have numerous coexisting conditions that can impair quality of life and affect mealtimes and eating*
- *Sensory processing difficulties are often a major contributor to eating problems*
- *High premature mortality rates are of great concern and are an increasing public health priority*

Future research needs/unanswered questions

- *the role of maternal nutrition*
- *the role of nutrition in the prevention of premature mortality in adults*
- *the role of nutrition in the treatment and prevention of coexisting conditions*

Management of autism

The challenges (and talents) of autistic CYP vary widely. Management should be individualised, with the aim of managing comorbidities, and maximising their skills and their quality of life. Some individuals who were very challenged as children can, with the right support, have a great quality of life, find work, have a family and live independently, whereas many still need much support in adulthood [48].

Medical management

Pharmaceutical interventions are limited to treating coexisting conditions, for example, risperidone or aripiprazole for irritability and agitation (with common side effects of weight gain) and methylphenidate, atomoxetine and guanfacine for ADHD (with common side effects of appetite suppression) [82]. Other coexisting conditions are generally treated as they would be for autistic CYP.

Management of social communication and social interaction issues

There are many education and behaviour interventions to teach CYP (or to help parents to teach their child) effective communication and appropriate responses to social situations. These include approaches such as PECS (Picture Exchange Communication System), TEACCH (Treatment of Autistic and Communication Handicapped Children), ABA (Applied Behavioural Analysis), social stories and speech and language therapy. Physical activity is proven to help not only with general fitness and motor skills, but social functioning too [83].

Pathological demand avoidance

Pathological demand avoidance (PDA) is accepted by some as incorporated within the spectrum of ASC [84, 85]. CYP with PDA become very anxious when feeling that they are losing control when others put demands on them; this can result in extreme behaviours including being very withdrawn or volatile. CYP with PDA often have good levels of social interaction and communication, and their behaviour can be very challenging for parents, carers and professionals. Strategies for communication and behaviour change need to be modified with CYP with high demand avoidance, e.g. avoiding rewards and use of more tentative language [86].

Management of sensory processing problems

Help for sensory processing problems may include changes to the environment to avoid stimuli that are upsetting where possible, e.g. reducing bright lighting and noise, wearing ear defenders or coloured lenses or increasing the stimulation when someone seems hypo-responsive, e.g. by having spicier food or brighter lighting. To manage alertness and arousal levels throughout the day and maximise learning, a 'sensory diet' may be used, which incorporates lots of sensory activities that are either calming or arousing for the individual. Activities that involve high proprioceptive input (massage, squeezing, heavy lifting) are generally calming, and vestibular activities such as swinging and spinning may have a calming or arousing effect depending on the intensity. Vestibular and proprioceptive input can also dampen down sensory information from other senses so that environments that are usually overwhelming can sometimes be better tolerated. Specialist assessment and advice are available from sensory integration trained occupational therapists, speech and language therapists and music therapists, although access to these varies. Practical and straightforward help like wearing specially designed weighted clothing, having a discrete object to fiddle with, changing lighting or reducing noise can sometimes have very significant effects on concentration and reduction in undesirable behaviours.

Management of stress and anxiety

The world can be a very stressful place for autistic individuals. The cumulative effects of sensory difficulties, communication barriers and a dislike of the unpredictable can lead to high anxiety levels day to day. Anxiety can heighten or supress appetite and make it difficult for autistic CYP to feel in a relaxed enough state to tackle difficult situations like exploring new foods. The following may help to reduce anxiety:

- effective management of sensory processing difficulties and other coexisting conditions
- a 'sensory diet'
- establishing daily routines to give predictability that allows the individual to make sense of the world around them and forewarning of any changes
- using visual timetables and visual prompts to aid understanding of situations
- help with challenging social interaction, e.g. allowing to sit alone sometimes and social stories to explain how to deal with tricky situations
- help to express, e.g. using stress scales, phone apps or coloured wristbands that enable them to let someone know if he or she is very stressed and unable to verbalise it
- relaxation and mindfulness
- sleep and exercise
- time spent engaging in preferred special interests

Transition to adult care

The NICE [87] and SIGN [8] guidelines have recommendations on the transition to adult services. Preparation for

transition should include all the family and be considered as early as possible, being particularly mindful that autistic young people may find change incredibly hard.

Learning points: management

- *Autistic CYP often need tailored education and behavioural support*
- *Pharmacological treatment is primarily for coexisting conditions*
- *Management of stress, anxiety and sensory processing difficulties can help with overall functioning and eating problems*

Dietary and nutritional issues

Prevalence

Feeding problems such as extremely fussy eating are up to five times more common in autistic CYP than in non-autistic CYP, affecting up to 90% of children [88–91], and were recognised even in the earliest descriptions of autism by Leo Kanner in 1943 [92]. Mealtimes for parents of autistic CYP and feeding problems can be 'one of the most stressful times of the day', absent of enjoyment, horrible and even 'hell on earth' [93]. A lack of support from professionals is commonly reported [94–96].

Compared with typically developing controls, autistic children have more severe eating problems that include not staying seated, not eating with their families, 'food jags' (persistently wanting the same foods), narrower food repertoires, restrictions by food category, texture and the way they are presented [88, 97–99]. Eating habits can be extremely rigid, e.g. only eating two or three foods, preference for food that is only 'dry' or 'wet', a particular colour or shape or from a specific brand packaging [89]. Feeding problems are not associated with the autism 'severity' [99–102]. Many autistic CYP with eating problems may meet the criteria for the new DSM-5 feeding and eating disorder diagnosis of avoidant and restrictive food intake disorder (ARFID), but prevalence is yet to be studied [103]. Pica, packing or pocketing food in their cheeks, rumination and regurgitation and other abnormal feeding practices are also common, particularly in those with intellectual/learning disability [63, 104–106].

The prevalence of autism in adults and young people with anorexia nervosa (AN) is estimated to be 23% (4%–53%), although accurate ascertainment of levels is problematic due to individuals acutely ill with AN displaying high levels of symptoms characteristic of autism [107–110]. Screening for autism in AN has been recommended as autistic CYP may require significant treatment adaptations [108].

Food hypersensitivities, GI problems, constipation, diarrhoea and abdominal pain, disordered gut microbiota and increased intestinal gut permeability are more common than controls (see Table 20.2) [67, 68, 74, 111–120]. Coeliac disease (CD) can present as autism, and a prospective study found CD to be three times more common in autistic CYP and, therefore, recommended routine screening for CD in autistic CYP however, a large Swedish study of biopsy registers did not find a higher prevalence in autism, but instead found a strong link between autism and CD serology in the absence of histologically normal intestinal mucosa [76–78].

An expert US multidisciplinary group consensus statement recommends that 'individuals with autism who present with gastrointestinal symptoms warrant a thorough evaluation, as would be undertaken for individuals without autism who have the same symptoms or signs' [120]. Markers of abdominal pain or discomfort include irritability, agitation, aggression, constant eating, pica, unusual posturing and unexplained repetitive behaviours, aggression and sensitivity.

Autistic CYP are significantly more likely to be at risk for developing nutrient deficiencies [121, 122] and have a significantly lower consumption of calcium, protein and vitamins B_{12} and D [121–123], and a third have intakes below the lower reference nutrient intake (LRNI) for iron, zinc, calcium and vitamins A, B_2 and B_{12} [89]. Bone mineral density of young autistic children has been found to be significantly lower than the reference for their age [124–131]. Serum 25-hydroxy-vitamin D levels are significantly lower than in peers [132]; rates of iron deficiency range from 8% to 24% [133–137]; and biochemical markers of biotin, folate and vitamins B_5, B_{12} and E are lower than in controls [138]. There are many published case reports of severe nutritional deficiencies including scurvy presenting as rash and/or muscle atrophy [139–152], concurrent vitamin A and D deficiency presenting as a limp and periorbital swelling [153], vitamin B_{12} deficiency presenting as partially reversible optic neuropathy [154], vitamin A deficiency presenting as vision loss [155–160] and other multiple deficiencies leading to severe malnutrition [161–166].

It is unclear whether rates of underweight, overweight and obesity in autistic CYP are higher than or comparable to rates in the general population [167–176].

Assessment and management of dietary and nutritional issues

There is no evidence that autistic CYP have different nutrient requirements to the general population. In the main, dietary and nutritional management of coexisting conditions, GI conditions and nutritional problems should be as per the general population, taking an individualised approach to each child.

Having a good understanding of the core and coexisting challenges facing autistic CYP and their families is essential in providing assessment and treatment that is accessible and appropriate. 74% of respondents in a large survey of parents of autistic CYP and professionals felt that autistic people receive 'worse' or 'much worse' healthcare than non-autistic people [177]. In another survey, the lowest satisfaction with the National Health Service (NHS) was with those related to feeding, nutrition and diet with 24% unable to access support; 77% of those who did have support did not find it helpful [178].

Reasonable adjustments

The UK 2010 Equality Act and the 2008 Health and Social Care Act require that all health providers make 'reasonable adjustments' to ensure their services are accessible and effective to all, including autistic people [179, 180]. Suggested adjustments that may be appropriate are given in Table 20.4. The National Autistic Society has further guidance for health professionalsathttp://www.autism.org.uk/guidance-health-professionals.

Table 20.5 summarises some possible underlying causes to consider for eating problems in autism.

When assessing and treating autistic CYP, the author proposes the use of the following framework in addition to the usual dietetic aspects, adapted from the author's work (Table 20.6) [184].

Feeding therapy

For some autistic CYP, dietary change will be no more difficult than for other CYP. However, most have some element of rigidity around their diets, and so to achieve any change, additional support will need feeding therapy. Dietitians are uniquely qualified to assess and treat the nutritional aspects of feeding problems but also may lead or contribute to feeding therapy.

There is no clear consensus on the effective management of feeding problems in autism due to a lack of quality evidence [185]. SIGN guidance is to refer to a dietitian [8]; however, NICE gives no advice as to whom should be involved in the treatment of feeding problems [87]. Various techniques and terminology used in feeding therapy are described in Table 20.7. Pilots of parent education strategies for feeding problems in autistic and non-autistic CYP have been encouraging for parent reported factors [90, 186–188].

Much of the published evidence of treatment of feeding problems (usually food refusal or extreme fussy eating) are case studies using applied behavioural analysis (ABA) techniques [189–192]. ABA in autistic CYP is controversial; it has been associated with post-traumatic stress disorder (PTSD) in individuals [193]. The most 'effective' ABA techniques for increased acceptance of foods typically involve escape extinction, which is described in a book instructing on and advocating its use as 'a difficult and emotionally upsetting intervention … imagine if someone put something you truly hate directly in your face and they would not move it. Non-removal of the spoon is probably among the most intrusive ABA interventions that are still considered appropriate … it is no surprise that the procedure often evokes challenging behavior' [194].

Table 20.4 Reasonable adjustments for autism.

Area	Possible adjustments
Consultation location	Consider alternatives to clinic appointments if attendance is stressful: phone, email, video, home visits Consider lighting and noise levels in consultation location and waiting rooms, provide a quiet area if needed Consider if the autistic CYP needs to attend the consultation, especially if needing to discuss things that may be upsetting to them
Consultation timing duration	Allow double time for processing of information Be punctual and warn if this is unlikely to be possible. Consider giving the first appointment or last appointment of the clinic, or scheduling appointments outside busy times
Consultation preparation	Ask in advance what adjustments are needed Provide visual information to prepare for appointment, e.g. photos of the building entrance, room, dietitian Provide easy-read appointment letters
Verbal communication	Simplify, slow down, avoid idioms that could be taken literally (e.g. 'I'll be back in a second', 'Eating that will put hairs on your chest'), use positive commands rather than negative (e.g. 'Sit down there' rather than 'Don't stand over there') Don't assume that CYP who cannot communicate verbally cannot understand verbal communication or that those who can speak well can comprehend easily
Visual supports	Use visual supports to complement any verbal instructions, e.g. written information, signing, the use of objects or pictures Provide easy-read information leaflets and advice summaries
Training	Training in autism awareness is mandatory for all ancillary staff who work in public services, and more in-depth training is mandatory for all dietitians. Essential skills and knowledge for dietitians and ancillary staff are set out in the Skills for Health Learning Disabilities Core Skills Education and Training Framework and Autism Skills and Knowledge Checklists [181, 182]
Assessment	Ask direct questions. Allow written answers in advance Autistic CYP may have symptoms (e.g. constipation, abdominal pain, symptoms of food hypersensitivities) that they are not able to communicate verbally or distinguish well due to sensory processing difficulties, but may be indicated by different behaviours, e.g. unusual irritability, food refusal, behavioural outbursts, unusual posturing See Table 20.5 for possible underlying causes for eating problems in autism
Giving advice	Simplify for some, provide detailed science-backed information for others Bear in mind that individuals with high IQ may struggle with executive functioning that may make following recipes and food preparation difficult without simplified directions Avoid unnecessary dietary rules that may be followed rigidly Ensure advice is consistent and unambiguous from all that are involved

Table 20.5 Possible underlying reasons for dietary issues in children and young people with autism.

Dietary problem	Possible underlying reasons
Pica	• Understanding: not understanding the substance is not food • Pain: eating inedible objects may ease gut pain or gum pain (or cause it in a sensory seeking way) • Sensory: may be seeking some sensory input and stimulation from the substance • Attention: the child or young person may enjoy the response they get from their caregivers when eating the substance • Anxiety: high anxiety levels may increase sensory seeking behaviour • Mineral deficiencies: often cited as a reason for pica, but it is not clear if this is a true contributing factor
Restricted diet/'fussy' eating	• Behavioural rigidity and understanding: may need food presented in a certain way to be comfortable to eat it; may need a predictable routine to be comfortable to eat; may not recognise food or may be upset by foods mixing because they do not recognise the mix as food, may have self-imposed rigid dietary rules • Anxiety: high anxiety levels may adversely affect appetite and increase reliance on only foods seen as 'safe' • Sensory: aversion to certain textures, tastes and smells or strong preference for others • Obsessive–compulsive disorder (OCD): the need for rigidity around food presentation and routines around food may become compulsive; may fear contamination or dislike perceived contamination of foods with other foods or from germs, smells or tastes • Skills: delayed oromotor or motor skills affecting the ability to eat or prepare food, impaired executive functioning making planning of intake and food preparation challenging (in young people)
Overeating/voracious appetite	• Sensory: a strong preference for certain textures, tastes, smells, the feel of being full, etc. (sensory seeking behaviour); may not know when full or when to stop eating • Pain: interpretation of gut pain as hunger; eating for comfort in the presence of pain, e.g. dental, gastrointestinal, headaches • Anxiety: anxiety can promote hunger or increase reliance on 'safe' foods – which may be high calorie • Understanding: general desire to eat/enjoyment and lack of understanding that eating cannot happen constantly; lack of understanding about when to eat and when not to eat (e.g. when inadequate structure to the day, constant access to food), impaired executive functioning making planning of intake and food preparation challenging (in young people) • Skills: delayed oromotor or motor skills affecting the ability to eat or prepare food, resulting on reliance of easier to eat foods, which may be higher calorie • Medications: that promote hunger such as risperidone
Undereating/low appetite	• Anxiety: high anxiety levels may adversely affect appetite and increase reliance on only foods seen as 'safe' • Pain: suppressing hunger or causing pain when eating (which could be dental, gastrointestinal, headaches or anywhere else) • Constipation: suppresses hunger • Sensory: may be averse to foods on offer • Understanding: may not understand the need to eat and drink to feel well; may not understand the sensations that occur in the body on eating and so may avoid eating to avoid them, impaired executive functioning making planning of intake and food preparation challenging (in young people), may have self-imposed rigid dietary rules • Medications: that suppress hunger such as methylphenidate • Skills: delayed oromotor or motor skills affecting the ability to eat or prepare foods

Inspired by an Autism West Midlands family information sheet [183].

The author's suggested best practice approach is to carry out feeding therapy as part of a multidisciplinary team (MDT), involving as many of the following as possible: parents, teachers, speech therapists, sensory integration trained occupational therapists, paediatricians, clinical psychologists, play therapist and portage. Table 20.8 details a pragmatic stepwise approach to feeding therapy that could include group or one-to-one sessions with parents and/or parents and the child or young person.

Two case studies are described in Tables 20.9 and 20.10, suggesting approaches to two of the most common issues parents of autistic CYP seek dietetic help for: firstly extremely fussy eating and secondly overeating.

Learning points: dietary issues

- *Feeding, dietary and GI problems are widespread*
- *All dietitians should be trained in working with autistic CYP and ensure their practice is autism-friendly*
- *Reasonable adjustments include allowing extra time for consultations, care with communication and consideration of consultation location*
- *An in-depth understanding of autism is vital in taking a full history and designing support and interventions*
- *There is little consensus in the best way to manage feeding problems, but there are a number of options and MDT working is ideal*

Table 20.6 The autism 6Ss.

The autism 6Ss	Assessment considerations	Treatment considerations
1. Self-esteem	Don't undermine	Don't undermine
2. Sensory	Look for patterns in current diet preferences	Consider the need for 'sensory diet' Work with sensory preferences not against
3. Structure	Is there currently a structured: (a) daily routine and (b) food time routine	Advise on a more structured: (a) daily routine and (b) food time routine
4. Supports	What are in place? What helps with other issues, e.g. visual timetables, social stories	Advise on putting these in place, e.g. visual timetables, social stories Ensure any dietary information is given consistently and unambiguously with appropriate visual supports
5. Special (intense) interests	What are they? Many autistic CYP have a very intense interest in a particular subject, e.g. commonly Thomas the Tank Engine, or a game. Sometimes it is their diet, e.g. veganism	Can they be used to help with dietary change?
6. Stress	What coping strategies are in place?	Advise on coping strategies, e.g. sleep, exercise, relaxation and mindfulness

Source: Adapted from Connor and Mealey [184].

Table 20.7 Components of feeding therapy approaches.

Feeding therapy component	Examples/explanation
Satter's division of responsibility in feeding	Trust that if a parent provides the what, where and how of offering food, the child will decide whether to and how much to eat, a 'no pressure' approach to feeding all children (and discourages all the other components in the table as they involve pressure)
Positive reinforcement	Praise, compliments, rewards (food or non-food), distraction
Negative reinforcement	Warning, punishing, withholding preferred food until child eats non-preferred food, selective attention (looking away when she/he does not eat, paying attention when she/he does), stopping a video if the child does not eat
Differential reinforcement of alternative behaviour	An example of negative reinforcement – the child is allowed access to a preferred item or activity, e.g. a toy only after eating a non-preferred food
Escape extinction	Non-removal of the spoon (spoon held in front of the child's mouth until she/he gives in and takes a bite), physical guidance (physically opening the child's mouth and putting in the food)
Systematic approximation	Eating-related activities, such as chewing on a washcloth, sitting in the chair at the table, offering food and encouraging interacting with it, then touching it, then smelling it, then licking it, etc.
Food chaining/spreading the sets	Widening variety of foods eaten by starting with favourite and then offering closely related foods that are a bit more challenging

Source: Adapted from www.ellynsatterinstitute.org.

Future research needs/unanswered questions

- *Which interventions are best in managing feeding problems while avoiding harm?*
- *Do feeding problems improve with time and age without interventions?*
- *What is the prevalence of nutrient deficiencies?*
- *How can we best screen and test for nutrient deficiencies in children and young people who are averse to blood tests?*
- *How can we aid compliance in taking supplements?*
- *How can we promote general healthy eating and physical activity?*
- *What role does childhood diet and nutrition play in the high early mortality rates in autistic adults?*

Popular therapeutic diets and supplements

Dietary changes could plausibly improve functioning in autism. Individual nutrients or diet patterns could directly affect brain cell structure (e.g. omega-3 fats), neurotransmitter activity (e.g. B vitamins) or brain cell metabolism (e.g. ketogenic diets). Indirectly, nutrient deficiencies, reactions to foods or microbiota imbalance could all affect functioning, the ability to concentrate and learn and behaviours by causing pain. Sound evidence to support recommending dietary changes are, however, lacking. There are many barriers to carrying out high quality dietary intervention studies in autism: diverse subject groups due to autism being a probable group of conditions with differing aetiologies [204], a lack of consensus of autism-specific target outcomes or tools [205, 206] and the complex challenges of clinical nutrition research [207–209].

Table 20.8 Suggested stepwise approach to feeding therapy in autistic children and young people.

Step	Detail
1	**Do nothing:** This is an option if there are few nutritional concerns and it is not a priority for parents. Often one of the key things parents seek from a dietetic consultation is reassurance that their child is growing well and that their problem is not unique
2	**Standard fussy eating management:** Changes to the environment and feeding relationship in line with the trust model of feeding and Satter's division of responsibility in feeding (sDOR) [195–199]. sDOR is reported by proponents to 'work' even in severe feeding issues in ASC, but there is no empirical evidence for this
3	**Autism-specific fussy eating management:** Step 2 plus additional strategies for autism (but no pressure to try any new foods in line with sDOR as above), which may include: • Visual timetables detailing when and where they will eat and what will be eaten • Visual schedules with written or picture symbol schedules detailing behaviour expected at mealtimes or foods to be tried at a mealtime • Very structured routines day to day and before and after meals • Social stories or social articles (specially written stories or articles explaining how and why to do something) [200] • Relaxation exercises before meals, e.g. progressive muscle relaxation • Stress-reducing strategies during meals, e.g. playing favourite music/video clips • 'Sensory diet' specific to mealtimes, e.g. incorporating calming or alerting activities before a mealtime such as blowing bubbles, washing hands and face to 'wake them up', heavy lifting or swinging before meals, sitting on a large ball during eating, using a weighted lap tray, adjusted cutlery
4	**Home-based food introduction:** Step 3 plus slow desensitisation to new foods via food play outside mealtimes (if tolerated) and/or food chaining/spreading the sets [201]. Useful motivators to engaging in food exploration include: • 'Eat it up' books. A written list or picture symbol list of foods liked, foods parents want the child to try and the foods the child is going to try next. Foods can be moved gradually up the lists • Using 'special interests' to motivate. Autistic CYP often have intense interests, e.g. watching the same part of a popular children's DVD story. Reserving access to special interest to 'reward' times may be an effective motivator • Modifying a favourite game to include activities to taste new foods, e.g. snakes and ladders – trying a new food to prevent going down a snake. An example of a clinical use of a specially devised board game is described by Gillis [202]
5	**Professional food introduction:** Professional intervention working directly with the child on developmentally appropriate food desensitisation systematic approximation, e.g. the SOS (Sequential Oral Sensory) Approach [203] is an MDT approach to intensive feeding therapy using a developmentally informed food school or food scientist approach in groups of CYP, alongside parental training to continue the approach at home
6	**More invasive options:** Enteral feeding may be necessary to improve nutritional status in the short to medium term while feeding therapy is provided. There may be a role for ABA approaches if enteral feeding is contraindicated or rejected (e.g. gastrostomy tube pulled out) and improved nutritional status is urgently needed

NICE guidance advises against using any therapeutic diets or supplements for core autism 'symptoms' [87]; SIGN guidance found insufficient evidence to draw firm conclusions and recommended further research [8].

There are many organisations and complementary and alternative medicine (CAM) practitioners (and some mainstream practitioners) who recommend various diets and supplements for autism, and many companies sell tailored supplements, parent training and books [210–215]. Many anecdotes on the Internet describe autistic CYP (and adults) who have benefitted from one or more dietary changes, sometimes dramatically so. Unsurprisingly then, around a third of parents in England have tried exclusion diets for their child, and over a half have tried micronutrient supplements [216].

Dietary approaches and supplements for autism range in plausibility, evidence base and safety [217]. A report by the Westminster Commission on Autism highlighted particularly dangerous options, e.g. the 'supplement' Miracle Mineral Solution (MMS), a 28% sodium chlorite solution equivalent to industrial strength bleach, and found that ingestion as 'recommended' could be lethal [218].

Systematic reviews have found inadequate evidence to recommend gluten and casein/milk exclusion [219–221], supplementation with omega-3 fatty acids [219], vitamin B_{12} [219], levocarnitine [219], digestive enzymes [219], vitamin B_6 and magnesium [222] or camel milk [219]. There is some pilot evidence for supplementation with iron [223], sulphoraphane (from broccoli sprout extract) [224], ubiquinol [225], folic acid [38, 226], high dose vitamin C [227], vitamin A [228], probiotics (*Lactobacillus plantarum* WCFS1) [229], prebiotics [230] and a multiple dietary and supplement intervention [231]. Dimethylglycine (DMG) [232] and *N*-acetylcysteine (NAC) [233] supplementation showed no significant effects compared with controls. Randomised controlled trials (RCTs) of vitamin D supplementation have given conflicting results [234, 235]. A double-blind RCT of a multivitamin and mineral supplement in adults (containing high doses of B vitamins, no iron and a subclinical dose of lithium) showed promising results in improved functioning [236].

A ketogenic diet has shown promise in mouse models of autism [237] and in pilots in autistic CYP [238]. Popular dietary approaches that have no published evidence include the exclusion of phenolic compounds and salicylates, the Specific Carbohydrate Diet (SCD) and the Gut and Psychology Syndrome Diet (GAPS). SCD has a history of more than 50 years; it eliminates grains, sucrose and lactose with the theory that this modifies intestinal bacteria growth

Table 20.9 Case study: Gina, an autistic 5-year-old who has a very selective diet.

Assessment

- Anthropometry: no concerns – tracking the 50th centiles
- Biochemistry: none available – aversive to having blood tests
- Clinical/physical: diagnosed with ASD at 3 years of age, bowels open regularly, good energy levels, no other diagnosis
- Dietary: severely limited diet – eats 4–6 times a day, banana sandwiches, in total six slices white bread with four bananas and 600 mL full-fat milk to drink plus water. Dietary analysis shows that despite the lack of variety, the RNI is met for most nutrients and the EAR is achieved for all micronutrients except for vitamin D
- Environmental/behavioural/social: attends mainstream primary school, limited verbal communication, learning to use PECS but not yet proficient
- Focused on parents' concerns in order of priority: (1) worry about nutritional adequacy and (2) how to widen food range

Plan

Focus 1: Worry about nutritional adequacy

1. Reassure parents of Gina's growth and relative dietary adequacy
2. Address vitamin D shortfall:
   a. Recommend a vitamin D test due to likely low historic intake and high levels of deficiencies in autistic CYP. A finger prick test may be better accepted
   b. Recommend a standard vitamin D supplement until vitamin D levels established
   c. Advise on acceptance of supplement:
      i. Hiding it in a preferred food is likely to backfire with autistic CYP who often have very sensitive taste detection
      ii. Advise it is usually better to introduce it as a medicine and to use social stories, visual supports and explanations that it is a medicine and is essential
      iii. It can be mixed with something of a preferred taste to reduce its likelihood to elicit a disgust response or paired with a spoonful of a preferred food directly after
      iv. Find out from parents how they have managed to accept medicines previously; often they never have
      v. Help from teachers, speech therapists, play therapists, etc. can be utilised to make acceptance of the supplement in the short term the absolute priority

Focus 2: How to widen food range

1. Establish if this falls under remit of the dietetic service or that of other members of the MDT. If the dietetic service has scope and training and knowledge to provide feeding therapy, continue as below
2. Explore underlying issues:
   a. No apparent underlying oromotor or medical issues
   b. Feeding problems have been apparent since introduction of solids at 5 months; no identified traumatic experience associated with it starting (e.g. choking, silent reflux, tube feeding, illness)
   c. 6Ss
      i. Self-esteem – No issues identified
      ii. Sensory – Gina has help with various sensory integration issues – messy play has helped accepting getting her hands dirty; massage and body brushing has helped to calm her down when anxious and the parents and school already have a sensory diet plan that they follow
      iii. Structure – Gina has a relatively well-structured day and mealtimes are very structured to her preferences: the same cutlery, place setting, sat at a table, etc.
      iv. Supports – At school they use visual timetables, PECS and a choice board at mealtimes. Gina is still getting used to these
      v. Special (intense) interests – Gina loves kittens; using books with kittens has been used effectively with toilet training
      vi. Stress – Change in Gina's routine cause anxiety. Changes to the presentation or any aspect of her food causes extreme anxiety and often food refusal. Introduction of new foods in her proximity provokes a fear response
3. Explore management options (from steps shown in Table 20.8):
   a. **Step 1: Do nothing:** Give parents permission to do this as there is little evidence whether feeding therapy is effective in autism; incidental exposure to foods via family mealtimes, school activities and sensory activities may help her to vary her diet with time. If parents opt for this, they can be advised to seek further help immediately if Gina's diet reduces in range as she would then need a multivitamin and mineral supplement to ensure nutritional adequacy
   b. **Step 2: Standard fussy eating management:** Parents have consistently applied this and it hasn't helped
   c. **Step 3: ASC-specific fussy eating management:** Gina's parents have a good understanding of autism and its management. Discussion of why feeding problems may be more common in autism helps them to see the problem through Gina's eyes, e.g. sensory issues, behavioural rigidity and social demands at mealtimes. As Gina becomes more used to visual supports used at school, these may help with mealtimes at home and with slow introduction of new foods
   d. **Step 4: Home-based food introduction:** If Gina's parents want to try to push her on with food acceptance, they could try food chaining at home making small changes to her preferred foods, e.g. adding a bit of food colouring or changing the way it looks on the plate. The worry with this with such a restricted range is that she might then reject a core food and they have reported that changing her foods invokes stress. Parents and school staff may be able to come up with creative ways to motivate her to interact with new foods in a non-threatening way outside mealtimes, e.g. using her special interest of kittens; could they play with feeding foods to a toy kitten supported by a home-made book about kittens eating different foods?
   e. **Step 5: Professional food introduction:** Gina may be a suitable candidate for group food play sessions aiming for systematic approximation as in the SOS Approach

RNI, reference nutrient intake; EAR, estimated average requirement; PECS, Picture Exchange Communication System.

Table 20.10 Case study: Rajesh, a 14-year-old autistic boy who overeats.

Assessment

- Anthropometry: height tracking 50th centile, weight >99.6th centile and moving further upwards, BMI >99.6th centile and moving further upwards
- Biochemistry: none available
- Clinical/physical: diagnosed with autism at 3 years of age; chronic constipation, no other diagnoses
- Dietary: eats three meals a day, snacks a lot in the evenings, demands food when he wants it. Meal choices not excessive in fat and sugar and portion sizes, but evening snacks consist of crisps, chocolate, biscuits and sugary drinks and make up at least a third of his energy intake
- Environmental/behavioural/social: attends a special educational needs school, teachers find his behaviour around food challenging – demanding food off others' plates, etc. Rajesh has limited verbal communication but makes his desires known via behaviour and PECS. Rajesh does little physical activity
- Focused on parents' priorities, unable to ascertain from Rajesh due to communication barriers; parent priorities: (1) reduce behaviours that challenge around demanding food and (2) reduce the risk of diseases associated with obesity

Plan

Focus 1: Reduce behaviours that challenge around demanding food

1. Establish if this falls under remit of the dietetic service or that of other members of the MDT. If the dietetic service has scope and training and knowledge to provide support in changing behaviours that challenge, continue as below
2. Explore underlying issues:
   a. No apparent oromotor or medical issues apart from constipation
   b. Discuss better medical management of constipation and ruling out potential underlying causes such as coeliac disease
   c. 6Ss
      i. Self-esteem – Rajesh is very sensitive about having his weight and eating discussed. After an initial brief consultation meeting Rajesh and establishing with parents and school staff, further advice and assessment is given without Rajesh present. School staff can monitor his weight prior to each follow-up appointment to avoid him needing to be involved further unnecessarily
      ii. Sensory – Rajesh hasn't had sensory issues considered previously. He seems to love the crunch of snack foods in the evening – could this be 'sensory seeking' behaviour? If so could other sensory activities help to replace this, e.g. munching on raw vegetables or wearing an age-appropriate chew ring
      iii. Structure – Rajesh has a structured day at school but free access to food in the evenings. A very set routine around eating and rules about when and where food can be eaten can be very effective, especially when backed up by social stories, visual supports and even locked kitchen doors
      iv. Supports – At school Rajesh uses visual timetables, PECS and a choice board at mealtimes. At home little is used. Introducing these around foods and food times is advisable. Visual supports around home food rules will help parents to say 'no' consistently to Rajesh's demands. Teaching about hunger and satiety levels using a visual hunger scale, supported by social stories to explain this, can sometimes be effective in helping autistic CYP manage their desires to eat
      v. Special (intense) interests – Rajesh loves dinosaurs. Could activities about dinosaurs and what they eat be used to help to learn about healthier eating and being more active?
      vi. Stress – Could Rajesh's appetite in the evenings be driven by his stress levels? He does very little exercise – could regular evening exercise serve the double purpose of reducing stress and reducing the time he is able to access snack foods? Could mindfulness and relaxation help?

Focus 2: Reduce the risk of diseases associated with obesity

1. Dietary management
   a. Help parents consider keeping tempting foods out of the house or locked away
   b. Avoid giving any hard and fast dietary rules or advice that could cause harm if followed rigidly, e.g. 'avoid fat', 'avoid fatty foods', etc. If giving prescriptive dietary advice, ensure that it is clear that it is ok to have some days when they don't follow them, e.g. at celebrations or religious feast days
   c. Ensure verbal advice given directly to Rajesh is accompanied with clear and unambiguous written information that is developmentally appropriate. Could appropriate materials be given to the parents to discuss with Rajesh at home?
2. Advise on physical activity levels
   This is not primarily for weight management, but for overall health and well-being, lowering of anxiety and possibly a way to keep him busy in the evenings and away from food. Sensory issues are sometimes a barrier to engaging in some activities, e.g. aversion to the noise in the gym, and social communication can sometimes make team sports challenging to participate in. Could going to the gym with a parent in the evenings be an option, or getting a treadmill or exercise bike at home, or going for long walks, runs, bike rides or swims? Could the family get a trampoline for their garden?

PECS, Picture Exchange Communication System.

and treats various digestive disorders [239]. GAPS is a more recent modification of SCD, with multiple supplements, and its author claims it is effective in many different disorders, including autism [240]. Both GAPS and SCD have extensive (differing) lists of foods to be avoided with limited rationale. GAPS has aspects that risk malnutrition, e.g. the advice to follow the first stage – a limited range of broths and fermented foods – for as long as it takes for diarrhoea to settle and 'the gut to heal', over a year if necessary [241].

A pragmatic approach to therapeutic diets and supplementation

Parents of autistic CYP often do not readily disclose their use of complementary health approaches, including dietary approaches and supplements, to professionals and may wish to pursue them despite their weak evidence base [217, 242, 243]. Left unsupported, parents are at risk of putting their child on more and more restricted and imbalanced diets,

accompanied by expensive and often excessive supplements. Dietitians and other professionals should inquire in a non-judgemental manner about all interventions families are using and considering [217]. A 'shared decision-making' model is recommended to avoid a paternalistic approach that may alienate parents [242, 244, 245].

Dietitians should not interpret lack of RCT evidence of efficacy as evidence of inefficacy and should recommend standard dietetic approaches including a healthy lifestyle, vitamin and mineral supplementation and trials of exclusion diets when indicated. Table 20.11 compares the ease, supporting evidence and potential risk to health when using therapeutic diets in autistic CYP. Families should ideally be advised to introduce one intervention at a time to monitor effectiveness and side effects [246].

Table 20.12 adapts the classification of approaches that clinicians can recommend, monitor, tolerate or avoid, based on their evidence and safety from a review of integrative approaches in autism [247]. Vitamin and mineral supplementation in the absence of a clear biochemical or dietary need, and exclusion diets in the absence of visible effects after a trial, should not be recommended, but are relatively safe when monitored so can be accepted/tolerated. Overly restrictive diets such as SCD and GAPS should be recommended against due to their lack of sound rationale, evidence, nutrition risk, cost and inconvenience. However, if parents are determined to continue, careful dietetic monitoring can help to reduce these risks, although this may fall outside the scope of stretched NHS dietetic service provision. Advice on vitamin and mineral supplementation to meet the reference nutrient intake (RNI) when dietary intake is insufficient is appropriate. Pharmaceutical doses for corrections of deficiencies usually fall under medical rather than dietetic scope, and appropriate referrals and requests when deficiencies are suspected should be made.

Table 20.11 Qualitative comparison of therapeutic diets used in autism.

Intervention	Difficulty in following the intervention	Supporting evidence	Negative impact on nutrition/health
Exclusion of gluten and/or milk	Moderate*	Some	Insufficient calcium, iodine, fibre and energy intake possible, but minimised with dietetic support
Other exclusion diets	Moderate*	None	Possible dietary deficiencies, but minimised with dietetic support
Ketogenic diet	High*	Some	High risk of dietary deficiencies and growth faltering, but minimised with dietetic support
Individual vitamin and mineral supplementation	Low*	None/some for vitamin B_6	Possible side effects at high doses, e.g. neuropathy in high dose vitamin B_6; a possible antagonistic effect for other vitamins and minerals
Multivitamin and mineral supplement (standard levels)	Low*	None (some for supplements with high doses of some nutrients)	Unlikely (possible side effects of high doses)
Fish oil supplements	Low*	Some	Unlikely
Probiotics	Low*	Some	Unlikely
Digestive enzymes	Low*	Very little	Unlikely

Improvement when on dietary modifications may mask underlying disorders (e.g. coeliac disease, metabolic disorders, epilepsy); therefore continued communication with the patient's doctor is vital.
*Ease of intervention is significantly decreased if the child is resistant to changes in diet/resistant to taking supplements.

Table 20.12 When to recommend, monitor, tolerate or avoid a dietary therapy for autism.

		Safe	
		Yes	No
Effective	Yes (generally accepted dietetic practice or evidence from two RCTs)	**Recommend:** Healthy eating, supplementation to meet dietary deficits (including omega-3 fatty acids) or correct deficiencies, probiotics, physical activity and general healthy lifestyle	**Monitor:** Exclusion diets – recommend a time-limited trial when hypersensitivities suspected, e.g. gastrointestinal, skin or behavioural symptoms
	No or not established in two or more RCTs	**Tolerate and monitor:** Single or multivitamin and mineral supplementation, digestive enzymes, amino acid supplementation Exclusion diets in the absence of evidence of them resolving food hypersensitivities or gastrointestinal disturbances	**Avoid:** SCD and GAPS diet, high dose vitamin A supplementation, dangerous 'supplements' such as MMS, self-directed ketogenic diet

RCT, randomised controlled trial; SCD, Specific Carbohydrate Diet; GAPS, Gut and Psychology Syndrome Diet; MMS, Miracle Mineral Solution.
Source: Adapted from Klein and Kemper [247]. Reproduced with permission of Elsevier.

Learning points: therapeutic diets

- *Therapeutic diets and nutritional supplements are popular with parents of autistic CYP but lack a quality evidence base*
- *Dietitians should directly ask parents about interventions they are using or considering as spontaneous disclosure is not usual*
- *Care is needed to guide parents away from harmful interventions*
- *Support in following interventions that are low risk should be offered to reduce any risk of harm*

Future research needs/unanswered questions

- *Are there subsets of autistic CYP who would benefit from different therapeutic diets or supplements?*
- *What role does an individualised approach to testing and correcting metabolic differences in autistic CYP play, and what role can dietitians take in this?*

Summary

Autism is complex, costly and under-researched. Dietary issues are common and further study into effective management is needed. Research into the role of diet and nutrition in reducing comorbidities in autistic CYP continues to emerge, but the quality remains weak partly due to inherent barriers to quality research in this area. All dietitians must ensure they are adequately trained to best support autistic CYP and address poor satisfaction with existing care. Dietitians should ensure that commissioners and service managers are aware of the additional resources needed to provide a service with the reasonable adjustments that are essential to ensure optimal care.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

21 Feeding Children with Neurodisabilities

Jennifer Douglas

Introduction

Neurodisability is a term used to describe conditions affecting the brain and central nervous system (CNS) and includes muscular, developmental, motor, sensory, learning and neuropsychiatric disorders. CNS damage can be due to disease, genetics, oxygen deprivation or acquired brain injury and can occur at any stage in a child's life. The majority of research is on children with motor disorders and cerebral palsy (CP), which are the two most common causes of neurodisability [1]. These children often have neurological involvement of other body systems as part of their condition [2]. In the past 10 years, there has been a steady increase in the number of children with severe disability due to increased survival of preterm infants and better survival outcomes for children with brain injury. In 2016 there were 54 143 infants born before 37 weeks' gestation in England and Wales [3]. Survival rates have improved dramatically in the UK, but neurological impairment is seen in 45% infants born at 22–23 weeks, 30% at 24 weeks, 25% at 25 weeks and 20% infants born at 26 weeks' gestation [4].

Many children with neurodisability have difficulties with eating and drinking, and they are likely to have nutritional concerns that need to be addressed [1, 5]. Oromotor dysfunction is associated with poor health and nutritional outcomes, affecting up to 98% of children with moderate to severe CP [6]. Those with motor, physical or sensory impairments are more likely to struggle, and the more severe the disability, the more likely the child is to be at nutritional risk [1, 7]. The ability of infants, children and adolescents to achieve their potential for growth and development depends on the intervention provided at critical time periods. Many children with neurological impairment would benefit from individual nutritional assessment and management as part of their overall care [8]. It has been accepted in the past that children with neurodisability, especially those with CP, are small as part of their condition. With the evolution of enteral feeding, it has become evident that children with neurodisability have the potential to grow if adequate nutrition is provided [9].

Cerebral palsy

CP is defined as 'a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain'. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and by secondary musculoskeletal problems [10]. There is currently no test before birth to identify CP. The incidence in the UK is currently 1 in 400 children and 2.1 per 1000 live births [11].

CP is a condition where there may be abnormal brain development or brain injury during development. This can occur before, during or after birth, and even during early childhood. It is not unusual for children to be diagnosed at a later stage when the child's motor development is almost complete. Even before diagnosis is established, children may already be experiencing oromotor problems.

Causes of CP may be complex with no obvious single cause. However, there are certain risk factors that may contribute: premature birth, placental abnormalities, birth defects, low birthweight, meconium aspiration, instrumental/emergency caesarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia and neonatal infections [12].

There are four main types of CP, which correspond to injuries to different parts of the brain [13]. Children may have:

- spastic CP – the most common form of CP causing hypertonia, or increased muscle tone, giving movements that

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

are stiff or jerky. This form is caused by damage to the motor cortex either during or after birth
- dyskinetic CP – involves involuntary movements causing slow twisting or repetitive movements or abnormal sustained postures. This form is caused by damage to the basal ganglia
- ataxic CP – the least common form of CP causing shaky movements, clumsiness, imprecision or instability when walking or picking up objects. This form is caused by damage to the cerebellum
- mixed-type CP – a mixture of two or more of the above

The Gross Motor Function Classification System (GMFCS) can be used to classify a child according to their current level of function and gives an idea of what equipment and mobility aids may be needed in the future. The GMFCS defines five grades for children between 6 and 12 years of age [13]:

- level I: can walk, run, jump at home, school or in the community, but speed, balance and coordination is limited
- level II: can walk in most settings, but may find long distances and uneven terrain challenging without mobility aids. They have minimal ability to run or jump
- level III: can walk indoors with a handheld mobility aid. They need a wheeled mobility aid for longer distances and can self-propel their wheelchair
- level IV: uses mobility aids that require physical assistance or powered mobility. They may walk for short distances at home with physical assistance or use powered mobility or a body support walker when positioned
- level V: is transported in a manual wheelchair in all settings

Improved nutritional status in children with CP is associated with improvements in general health, such as decreased irritability and spasticity, improved healing of pressure sores and improved circulation [1]. In contrast, undernutrition is significantly associated with poor functional status, poor motor function, reduced communication ability and increased dependence on the caregiver for feeding [14]. The level of feeding dysfunction can be directly related to the degree of undernutrition, and even those who have mild feeding dysfunction may have poor growth and limited fat stores [5, 8]. Therefore, a child requiring any modified consistency of food and fluids can be at risk of nutritional compromise. It has been documented that 89% of children with CP need help with feeding and 56% regularly choke during mealtimes [1]. Poor growth and nutritional status is common in children with CP and is more prevalent in those with higher GMFCS grading. Prevalence of poor growth in children with CP can range from around 20% to 51% depending on which growth chart has been used [15]. CP specific growth charts were first developed by Krick [16] and further developed by Day [17]; they show similar growth in children with lower GMFCS grade to that in normal children, but substantially different growth in children with moderate to severe disability. These growth charts may be a poor predictor of nutritional status and should be used alongside the WHO standard growth charts and other anthropometric measurements of nutritional status [5].

Low micronutrient intake and low micronutrient serum concentrations are common in children with CP and can also occur in those who are tube fed [18, 19]. Nutritional status should be assessed frequently to ensure that micronutrient requirements are met [5]. Tube feeding and the use of nutritional supplements are associated with higher micronutrient concentrations [19]. It is important to take into account the type of CP the child is diagnosed with (including other comorbidities) as this has significant implications on the chosen nutritional management plan. Children with spastic quadriplegic CP, hypotonic patients and those having seizures often have significant feeding difficulties [20].

The following factors should be taken into consideration when assessing a child with CP:

- type of CP and limb involvement
- mobility: including information about locomotion such as the use of wheelchair or a walker
- gastrointestinal problems: gastro-oesophageal reflux (GOR) and chronic constipation are common in children with CP [21]
- dependence on feeding: ability to self-feed, dependent or partially dependent on assistance from caregivers
- feeding dysfunction: detailed information regarding how the child manages food textures such as puréed, mashed or chopped foods [5, 22]
- feeding skills: should be assessed at regular intervals in order to identify children at nutritional risk. Parents/caregivers should be asked about the presence of tongue thrust, drooling/dribbling causing fluid loss, lack of hand to mouth coordination, poor lip seal causing food or fluid loss, inability to communicate hunger, prolonged feeding times and dysphagia [5, 14]
- environment: environmental factors can have an impact on growth and nutrition, e.g. the child's living situation, mealtime environment, lifestyle, involvement in therapy groups, school and respite care arrangements [23]. Information about the family and the child's experience with oral feeding should be sought as this may affect decisions about future oral or non-oral feeding methods
- other medical conditions and respiratory health: these children are vulnerable to respiratory morbidity for several reasons, so it is important to find out about frequency of chest infections and other respiratory problems that may have an effect on energy requirements [24]
- bone health: there is a higher risk of low bone mineral density, osteopenia and osteoporosis due to reduced weight-bearing activity or being bed bound, lack of nutrition, medication limiting vitamin D metabolism and limited sun exposure. DEXA scans may be useful to determine bone mineral density [5]
- anthropometry: there is no universally accepted method for measuring children with CP. Alternatives to measuring height are available and are discussed later (p. 423)

Down's syndrome

Down's syndrome (also called trisomy 21) is the most common genetic cause of learning disabilities. The incidence of Down's syndrome in England is estimated at approximately 1 in 990 live births [25]. There were 1698 cases in England of Down's syndrome in 2014 with 64% diagnosed prenatally by cytogenetic diagnosis, and only 574 resulting in a live birth [25]. Median life expectancy for those with Down's syndrome is 58 years, and average life expectancy is 50.1 years [26].

Many children with Down's syndrome will have other complications such as congenital heart defect (43%), gastrointestinal problems (10%), coeliac disease (5%), recurrent respiratory infections, joint problems, endocrine dysfunction particularly hypothyroidism, constipation, haematological cancers and GOR [27, 28]. Regular screening is recommended for children with Down's syndrome to enable early identification of the common comorbidities.

Down's syndrome is associated with anatomical facial abnormalities, which can have significant effects on feeding. Feeding skills should be assessed at regular intervals [5]. Dysfunction occurs due to poor neuromotor control, dental anomalies, orofacial dysmorphology and hypotonia particularly of the tongue and lips. Children with Down's syndrome are frequently mouth breathers due to narrowing of the nasal cavity and chronic inflammation of the tonsils as a result of an increased incidence of upper respiratory infections. The palate is often short and narrow, and this underdevelopment of the maxilla may alter the position of the muscles used for chewing. Infants with Down's syndrome may have difficulty in initiating a suck and have a weak lip seal, poor coordination of the suck/swallow/breathing sequence with early fatigue and jaw instability [29]. Breastfeeding is possible for infants with Down's syndrome, but for many it will be more difficult to establish due to the associated oromotor difficulties. Adequate support is needed to achieve successful breastfeeding [30]. Down's syndrome is associated with impaired immune function and higher incidence of obesity. Therefore, breastfeeding may confer long-term benefits. Comorbidities such as congenital heart disease and gastrointestinal dysmotility may further compromise feeding [31].

Parental surveys suggest that due to oromotor difficulties, children may also have increased choking and vomiting with feeding [32]. With adequate feeding support children are likely to become independent feeders by early childhood.

Anthropometric assessment of children with Down's syndrome is complicated because of the associated abnormalities related to growth such as short stature, decreased head circumference and altered growth patterns. Cronk suggests that while height in people with Down's syndrome is significantly lower than the norm, the period in which most significant growth failure occurs is during the first 5 years of life [33, 34]. Specific growth charts have been developed for children with Down's syndrome, and they describe typical growth, not necessarily ideal growth [33].

Despite an energy intake below the normal requirement, there is a high prevalence of obesity in children and adults with Down's syndrome [35, 36]. Causes of obesity in those with Down's syndrome may be related to increased leptin levels, decreased resting energy expenditure, comorbidities, undesirable food intake and low activity levels [36]. As obesity is prevalent in adolescence and adulthood, it is recommended that growth charts are used in conjunction with body mass index (BMI), using the same cut-offs for obesity as are applied to the general paediatric population. With appropriate support around nutrition and exercise, obesity can be managed successfully [37].

The general consensus is that the majority of children with Down syndrome can meet vitamin and mineral requirements if they are eating a normal diet, but monitoring may be needed for those who are unable to eat a healthy balanced diet or those requiring tube feeding [5, 38].

Neuromuscular and progressive neurological disorders

There are approximately 60 different types of muscular dystrophy and related neuromuscular conditions. Congenital neuromuscular disorders in children include spinal muscular atrophy and muscle disorders such as Duchenne muscular dystrophy and congenital muscular dystrophies. These conditions are characterised by the loss of muscle strength as progressive muscle wasting or nerve deterioration occurs.

Progressive neurological disorders are extremely rare conditions where deterioration advances over time. There are a large number of different diagnoses, e.g. Batten's disease, leukodystrophies, Cockayne syndrome and Rett syndrome. In some conditions there is a steady rate of deterioration; in others it occurs in phases.

Due to the vast number of different neuromuscular and progressive neurological disorders, it is essential to conduct a literature search at the time of patient review for the most up-to-date information. Table 21.1 shows some of the more common disorders referred to the dietitian and some of the nutritional considerations associated with each disorder.

Nutritional requirements for children with neurodisability

Energy

Children with disabilities often have lower energy needs than healthy children due to reduced activity and lower muscle tone. Prediction equations and dietary reference values therefore tend to overestimate requirements [5]. This has been shown by the Oxford Feeding Study research team, where children with disabilities tended to lay down stores of fat rather than muscle when gastrostomy fed beyond their needs [8, 24]. There is currently no universally accepted

Table 21.1 Neuromuscular and progressive neurological disorders and nutritional considerations.

Common conditions	Nutritional considerations	Useful websites
Lysosomal storage disease (Tay–Sachs, Fabry, Pompe, metachromatic leukodystrophy, Krabbe, Canavan, Zellweger)	Commonly have short stature, skeletal deformities, muscle weakness or lack of control (e.g. ataxia, seizures), neurological failure/decline and/or loss of gained development. Poor swallow may require tube feeding or texture-modified diet. Can have both undernutrition and overnutrition. Frequent dietetic monitoring required due to progressive nature of the disease (Chapter 27)	www.ninds.nih.gov www.sanofigenzyme.com www.rarediseases.org www.ulf.org www.hideandseek.org
Adrenoleukodystrophy	Lorenzo's oil can be used in children who are asymptomatic, and this may delay onset of symptoms. Symptom control is needed for all other children [39] (Chapter 27)	www.ninds.nih.gov www.rarediseases.org www.ulf.org
Rett syndrome	Growth failure, oromotor dysfunction, gastro-oesophageal reflux, constipation and low bone density are common. Often need assistance with feeding. May need gastrostomy feeding to improve growth [40]	www.ninds.nih.gov www.rettuk.org www.reverserett.org.uk www.rarediseases.org
Duchenne muscular dystrophy	Predominantly affects males. High prevalence of obesity related to lower resting energy expenditure, steroid use and reduced physical activity. Muscle wasting, poor feeding and poor swallow coordination can lead to malnutrition as they get older. Assistance is often needed with oral feeding and texture modification may improve intakes. Tube feeding may be required. Will need supplementary calcium and vitamin D if they are on steroids as they have high risk of osteoporosis. Regular dietetic monitoring required [41]	www.ninds.nih.gov www.rarediseases.org www.muscular-dystrophy.org www.dfsg.org.uk
Spinal muscular atrophy	Muscle weakness and bulbar dysfunction lead to swallowing difficulties. Respiratory problems are common including aspiration pneumonia. Undernutrition and overnutrition can occur and regular dietetic monitoring is essential. Gastro-oesophageal reflux and constipation are common [42]	www.ninds.nih.gov www.jtsma.org.uk www.smafoundation.org www.actsma.co.uk www.rarediseases.org
Prader–Willi syndrome	At birth the infant typically has low birth weight for gestation, poor muscle tone ('floppy'), difficulty sucking and may require tube feeding to prevent faltering growth. Feeding difficulties resolve over time and at 2–5 years of age hyperphagia sets in and lasts throughout the lifetime, leading to obesity if not correctly managed (Chapter 25)	www.pwsa.co.uk www.geneticdiseasefoundation.org www.fpwr.ca www.pwsausa.org www.fpwr.org
Cockayne syndrome	Premature ageing and short stature. Growth failure and likely to have feeding problems especially as an infant. Will need tube feeding to treat faltering growth and/or manage poor swallow coordination. Likely to have developmental delay and increased tone/spasticity. Regular dietetic monitoring needed due to progressive nature of the disease [43]	www.ncbi.nlm.nih.gov www.amyandfriends.org www.cockayne-syndrome.net
Batten's disease	A neurodegenerative disease. Feeding becomes more difficult with resulting poor weight gain and frequent symptoms of aspiration or difficulty coordinating swallowing (due to progressing lack of coordination and progressive poor muscle tone). Most children will eventually need tube feeding. If they manage to feed orally, they are likely to need assistance due to abnormal limb movement and poor muscle strength. Frequent dietetic monitoring is required to support child at various stages of disease progression [44]	www.ninds.nih.gov www.bdfa-uk.org.uk www.bdsra.org www.nathansbattle.com www.hideandseek.org www.brainfoundation.org.au

formula for predicting energy requirements in children with neurodisability; however, the Schofield equation may be a good starting point to estimate energy requirements [5]. Requirements need to be based on individual clinical assessment, degree of mobility, fat stores and muscle mass. Regular reassessment, with any necessary alterations to the estimated energy requirement, should be carried out and intake adjusted accordingly.

Children with neurodisability are often smaller than an average healthy child, and until further research becomes available, dietetic consensus opinion is to use height age (a crude estimation of bone age) as a basis to estimate nutritional requirements [45]. This should then be adjusted depending on whether weight loss or weight gain is needed. A child entering their pubertal growth spurt will require more energy than one who is not. In practice energy requirements are often no more than 75% of the estimated average requirement (EAR) for height age and are often considerably less; a child receiving as little as 20–30 kcal/kg/day (85–125 kJ/kg/day) can still gain weight. The exceptions to this are those children with mixed CP that includes an athetoid component; excessive involuntary movements make their energy requirements higher and closer to the EAR for chronological age.

Protein

Protein requirements for those with neurodisability are likely to be similar to those of the healthy paediatric population (p. 9). When energy requirements are low, it may be hard to meet protein requirements, and the use of a high protein formula or a protein supplement may be necessary [5].

Micronutrients

Micronutrient deficiencies (calcium, iron, zinc, vitamins C, D, E and selenium) can occur in those with neurodisability, especially when oral intake is poor or tube feeding volumes are low [5]. There are no studies showing requirements for micronutrients differ from those of healthy children. However, when feed volumes are low due to low energy requirements, micronutrient intake may also be low; aiming to provide the lower reference nutrient intake (LRNI) for age, rather than the RNI for micronutrients, may be sufficient.

Fluid

Actual body weight is used to calculate fluid requirements and can be based on general recommendations (p. 12). However, it is interesting to note that many children appear well hydrated on fluid intakes that are lower than those derived by calculation, and 75% of estimated fluid requirements may be adequate to maintain hydration. A fluid balance chart may be useful to measure hydration status.

Fibre

The Scientific Advisory Committee on Nutrition (SACN) recommends daily fibre intake for age should be [46]:

- 2–5 years: 15 g
- 5–11 years: 20 g
- 11–16 years: 25 g
- 16–18 years: 30 g

For those with oromotor dysfunction requiring a texture-modified diet, it may be hard to meet these recommendations as intakes of wholegrains, vegetables and fruit may be limited, and an additional source of fibre (e.g. Benefiber, Resource OptiFibre) may be indicated. For those needing to be tube fed, a fibre-containing feed should be the preferred choice.

Nutritional assessment

Anthropometry

Children with neurological disorders should not have their nutritional status assessed based solely on weight and height, but all aspects of their health should be considered [5]. There should be discussion with the multidisciplinary team (MDT) involved in their care: paediatrician, dietitian, speech and language therapist (SLT), occupational therapist (OT) and psychologist. The use of knee height (KH) or tibial length (TL) should be used regularly to assess linear growth when height cannot be measured.

Weight

Weight should be measured routinely on the most appropriate weighing equipment for the individual child. These include standing scales, hoist scales, wheelchair scales and sitting scales for the child, as well as the caregiver holding the child on the scales and then their weight being subtracted. The chosen method should be recorded and used when subsequently weighed. Personal equipment such as splints should be removed before weighing. Weight measures should be plotted on growth charts, the frequency depending on local practice and the child's individual circumstances, but should be a minimum of every 6 months for older children and young adults but more frequently for children under the age of 2 years [5].

Height

Accurate height measurements are often difficult to obtain in children with disabilities and young people, due to scoliosis or kyphosis caused by a twisted posture or contractures of the spine. A standing height using a stadiometer is preferable, but where this is not possible, a supine length can be used if they can lie straight. It is important to note, however, that a supine length will measure longer than a standing height and serial measurements should not be confused.

Where a length or height is not possible, there are three suggested alternatives; upper arm length (UAL), TL and KH all of which have been found to correlate with actual height and are repeatable [5]. The frequency of measurements will depend on local practice and individual circumstances. Height should be taken a minimum of every 6 months for an older child or young adult, with more frequent measurements for children under 2 years. Measurements should be plotted on a growth chart for each measurement.

Upper arm length

UAL is measured from the acromion to the head of the radius (Figure 21.1). It should be measured on the right or the least affected side. Two measurements are taken and then averaged. Research suggests it can only be taken accurately using an anthropometer. The measurement can be converted into a height measure using the following formula [47]:

$$\text{Estimated stature}\,(\text{cm}) = (4.35 \times \text{UAL}) + 21.8$$

The technical error is ± 1.7 cm

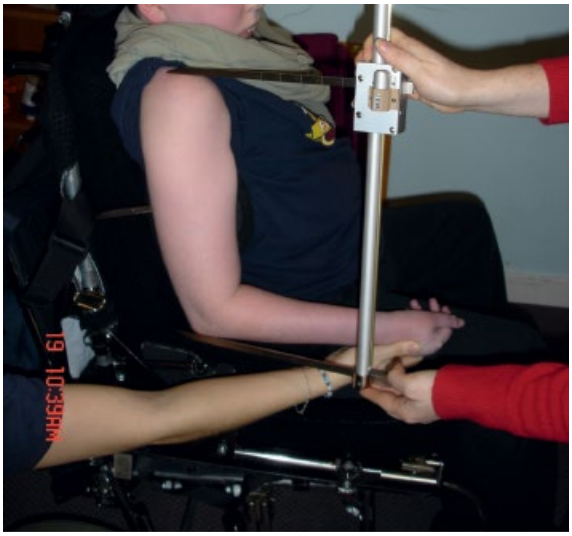

Figure 21.1 Upper arm length.

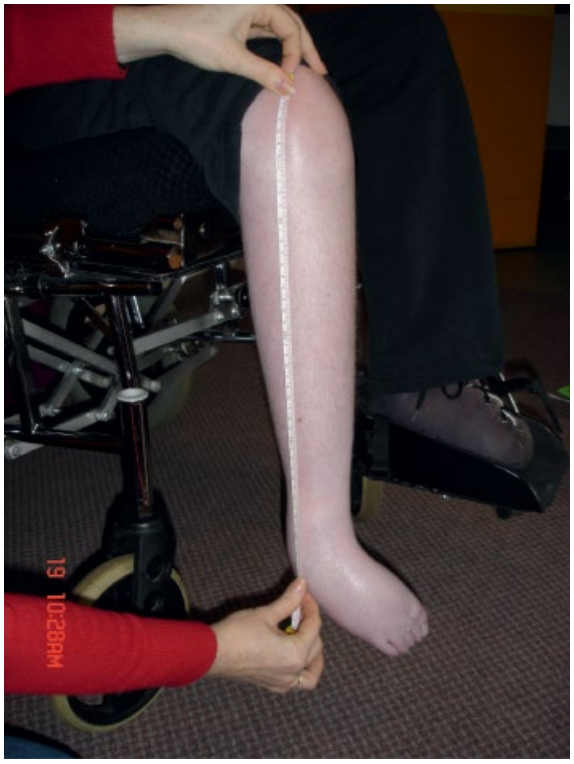

Figure 21.2 Tibial length or lower leg length.

Tibial length

The TL is measured from the tibia to the sphyrion. It requires the child to be sitting and is taken on the right side or the least affected side. This measurement can be taken accurately with an anthropometer or steel tape measure (Figure 21.2). Two measurements should be taken and averaged. The measurement can be converted into a height measure using the following formula [47]:

$$\text{Estimated stature}\,(\text{cm}) = (3.26 \times \text{TL}) + 30.8$$

$$\text{The technical error is} \pm 1.4\,\text{cm}$$

Knee height

The KH is measured with the child sitting down and the knee and ankle bent to 90°. Using a sliding caliper the distance from the heel to the superior surface of the knee over the femoral condyle is measured on the left side or least affected side (Figure 21.3). Two measurements should be taken and averaged. The measurement can be converted into a height measurement using the following formula [47]:

$$\text{Estimated stature}\,(\text{cm}) = (2.69 \times \text{KH}) + 24.2$$

$$\text{The technical error is} \pm 1.1\,\text{cm}$$

When an alternative length measurement is taken, note of the limb from which the measurement was taken should be made, and this should be consistently used for all subsequent measurements. Estimated height measurements should be plotted on standard growth charts.

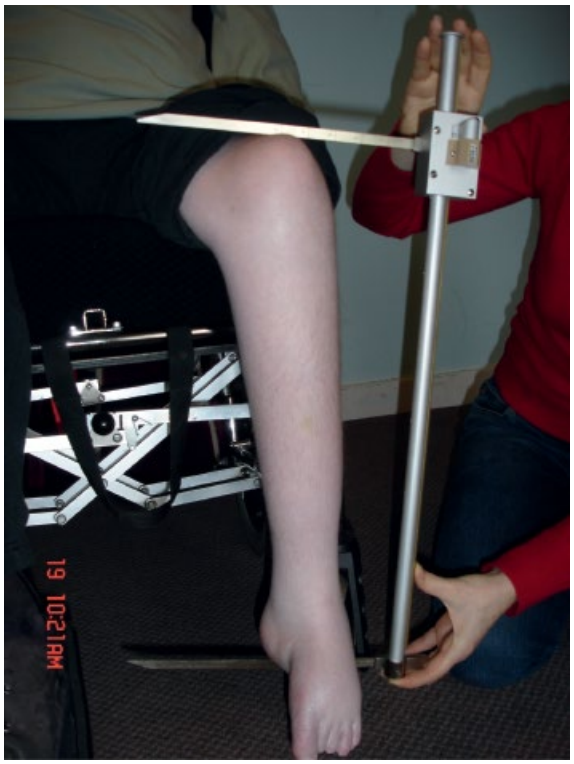

Figure 21.3 Knee height.

Body composition

Whole-body dual-energy X-ray absorptiometry (DEXA) is an accurate method for measuring body composition, but it is unavailable to most centres. There is some research into the use of bioelectrical impedance analysis (BIA), and this has been found to be effective in estimation of body composition in children with CP [5]. There is good evidence that body composition of children with disabilities can be ascertained by measuring skinfold thickness with mid-arm circumference (MAC) and this should be done routinely [5]. Triceps and subscapular skinfold thicknesses in particular correlate highly with true fat and fat-free mass. However, in routine practice, it can be difficult to take accurate skinfold thickness measurements, e.g. subscapular skinfold thickness measurement may be impractical due to the need to remove clothing or spinal jackets. In practical terms annual serial measurements of MAC and triceps skinfold thickness (TSFT) can be a useful monitoring tool and can be used to estimate mid-arm muscle circumference (MAMC) [48]:

$$\mathrm{MAMC}\,(\mathrm{cm}) = \mathrm{MAC}\,(\mathrm{cm}) - 0.314 \times \mathrm{TSF}\,(\mathrm{cm})$$

Skinfold thicknesses and MAC can be compared with the WHO arm circumference and skinfold thickness charts and tables [48, 49] or Addo and Himes charts [50]. Measurements should be taken a minimum of every 12 months. Where possible other anthropometric measurements, such as subscapular skinfold thickness, should be taken. Children with CP can have higher levels of central adiposity, and so waist circumference may be a useful measurement to do routinely.

Subjective global nutritional assessment

Subjective global assessment is a method of assessing nutritional status based on clinical judgement, and this method can be useful for children with neurodisability [51, 52]. Subjective global nutritional assessment (SGNA) is a questionnaire relating to nutrition history and physical examination, signs of fat, functional ability, muscle wasting and oedema, while objective assessments of weight, height and TSFT measurements can also be collected [52].

Growth charts

The standard UK-WHO growth chart 0–4 years and UK growth chart 2–18 years should be used for monitoring weight and height centiles for the majority of children with disabilities [53]. There are specific charts for children with Down's syndrome [54], reviewed in 2011, that can be used instead of the standard UK charts compiled in 2009. Growth charts are available for children with CP aged 2–20 years, classifying children into groups according to the severity of their CP. The charts show observed growth patterns in these groups but may not indicate optimal growth [17]. The charts show that children with moderate to severe CP lack a significant pubertal growth spurt. These charts should not be used exclusively, but rather in combination with clinical assessment, UK-WHO growth charts and anthropometric measurements.

Biochemistry

Serum albumin and prealbumin levels do not reflect nutritional status in children with neurodisability. Albumin and prealbumin levels are very rarely below normal reference values and do not correlate with anthropometric measurements or general health [17]. Regular blood monitoring may be useful for children who are at risk of nutritional deficiencies, such as those on texture-modified diets due to dysphagia, or those with faltering growth due to poor oral intake. The 2017 guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) suggest that children with neurodisability should have annual blood monitoring of electrolytes, urea, creatinine, glucose, full blood count, haemoglobin, ferritin, iron, calcium, magnesium, phosphate, albumin, liver enzymes, vitamins A, B_{12}, D, E and folic acid, parathyroid hormone (PTH) and zinc [5]. A study conducted by Gonzalez Ballesteros *et al*. highlighted hypophosphataemia in those fed exclusively on an amino acid (AA)-based formula, and therefore serum phosphorus, calcium and alkaline phosphatase may need regular monitoring if using these formulas [55].

Clinical

Clinical assessment requires knowledge of the type of neurodisability, level of disability and stage of disease (for progressive disorders). The following indices are useful to make an overall assessment of nutritional needs: neurological function (including seizure activity), respiratory function, cardiac function, muscle tone (including limb function), skin integrity, sensory difficulties, gastrointestinal function, urinary and/or faecal incontinence.

Dietary assessment

There are three common methods of assessment: food diaries, dietary recall and food frequency questionnaires. Evidence to support one method over another for assessing food intake is poor, and no method gives absolute accurate information on food intake. Over-reporting is the main problem and can be as high as 54% more than the child's actual intake [56].

Dietary feeding assessments are useful for assessing meal patterns and the types of food offered and eaten, in relation to the food groups. Observation of a child at a mealtime may be useful and can highlight other factors that affect dietary intake such as the child's posture and the mealtime environment [45].

Social context

Children with disabilities are more vulnerable to both physical and emotional abuse, and child protection is a high priority. It is important that services work together to ensure there is a focus on safeguarding children [57, 58]. It is important that agencies work together to identify children who need help early as laid out in the 2018 guide *Working Together to Safeguard Children* [58]. Specific standards for the health and social care of children with disabilities are described in the National Service Framework for Children, Young People and Maternity Services: *Disabled Children and Young People and those with Complex Health Needs* [59].

The social issues affecting a child with disabilities are far reaching, and the pressure on parents/caregivers to provide for their child is immense as they cope with difficulties in all areas of life: housing, transport, finances, education, family dynamics and managing medical interventions. Consideration of all aspects of the child's life is important when giving recommendations for nutrition intervention. Ideally the dietitian should work within an MDT to get an understanding of any social factors that could affect the child's ability to achieve nutritional goals.

Multidisciplinary assessment

Multidisciplinary and multi-agency working is vital in supporting and safeguarding children with complex needs. Children with disabilities are classified as in need in the Children's Act (2004), and as such it is the duty of care of every local authority to provide a range of services at the level appropriate to these children's needs [57]. Strong links within the professional team and effective communication are essential to ensure each child's potential is met and maintained [59]. Having an overview of all sources of information is important to ensure a holistic assessment and allows for practical interventions to optimise the child's potential. Often these children, with very complex health and social needs, have a large number of professionals and services involved (Figure 21.4). If managed well, this can be a huge benefit to those involved and the families themselves.

A multidisciplinary approach to nutritional assessment for children with neurodisabilities is essential to achieve feeding and lifestyle goals [45, 60, 61], drawing together the skills and expertise of caregiver and a range of healthcare professionals. In the absence of a validated nutrition screening tool, nutrition and feeding problems are identified by

Figure 21.4 Professionals and services involved in the care of the disabled child. GP, general practitioner; OT, occupational therapist.

measuring children, observing mealtimes and questioning caregivers, other MDT members and nursing staff.

Speech and language therapist

A feeding assessment by an SLT should always be included in the nutritional assessment of a child with neurodisability [62]. Assessment of feeding competence provides important information for identifying children at risk of poor nutritional status. Feeding dysfunction is related to nutritional risk, and it has been shown that even those who have mild dysfunction are still lighter and shorter than their peers [7, 63]. The assessment will also highlight any problems with drooling or excess salivation, which will need to be factored into calculation of fluid requirements.

Occupational therapist

The OT takes a particular interest in the child's position for eating and drinking, their level of independence and any special equipment that may aid the child. A child will need to have a secure base and symmetrical position to obtain optimum trunk, limb, head and oral control. The position may be either on the caregiver's lap for infants and small children or in adapted seating. The assessment should also involve the caregiver's needs, so they adopt a position that is comfortable and safe for their back and facilitates the techniques necessary to help the child. Sometimes this will require the caregivers experimenting with different positions until they have the best arrangement for them both.

The child's position during mealtimes can affect their ability to swallow safely. Young babies are usually fed in a reclined position. Children should eat and drink in an upright position to ensure a safe swallow. If a degree of tilt is required on their seating system, a reassessment of their ability to swallow safely should be carried out.

There is a wide range of specialised equipment available to assist with eating and drinking for children with special needs. A joint assessment between the child's OT and SLT (and perhaps also a physiotherapist) is required to ensure the correct equipment is selected.

Clinical psychologist

The input of a clinical psychologist may be necessary for a full feeding assessment. A child's early feeding experiences may impact on how they currently feed, particularly those children who have experienced distress because of early feeding practices. This can sometimes result in learned aversive behaviour often mistaken for a dislike of food or a poor appetite, which can only be resolved with adequate psychological support. The psychologist will consider factors influencing feeding including:

- the environment where the child usually eats
- parents' eating history and attitude to food
- early attachment difficulties, especially with an ill child
- marital/family stress, life events, social support, family networks
- general parenting skills
- parent–child relationship and interaction
- past and present parental mental health
- parental level of anxiety and obsessions

Nutritional intervention

Nutritional management of children with neurodisabilities can be challenging, and there is little supportive research. Nutritional care is determined by the individual child's needs and is often based on observations rather than set guidelines. Nutrition aims should focus not only on linear growth but also on functional and physiological improvements [5].

Oral nutrition

Food fortification

This should be based on the same principles as for other children whose growth is faltering. The energy content of food should be increased by using energy-dense foods and monitoring the outcome. Energy-dense foods need to be of the correct consistency for the child's oromotor skills. Caregivers familiar with prevailing healthy eating messages are often concerned about the use of high fat foods for their child, and their re-education is important. Children with neurodisabilities often can only eat small portions, and, therefore, adding fat/sugar to foods can increase energy density without appreciably increasing volume. Caregivers should choose high fat dairy products, such as whole milk, butter, cream and full fat yoghurt as additions to meals/snacks. Adding oil to foods can also increase energy density. Foods that can quickly be added to instant mashed potato, e.g. grated cheese, cream cheese, mashed tinned fish, corned beef, cooked lentils and avocado, all provide variety without too much preparation time. Protein foods, e.g. eggs, lentils, meat, nuts and cheese, can be added to meals to increase nutritional value as can skimmed milk powder added to foods or milkshakes. Adding sugar and cream to puddings and milkshakes will increase the energy content.

Fluids

Inadequate consumption or excessive fluid loss is a feature common to many children with feeding difficulties. Advice should be based on assessment of why the child is not able to consume adequate fluids. Children with poor lip seal, and who thus lose fluid from the mouth, will need to be offered drinks more frequently. The OT and SLT can identify the best drinking method, allowing the child to drink enough fluid safely.

For some children thickened fluids can enable more successful drinking. Commercial pre-thickened drinks are

available (Table 21.2). Other fluids can be thickened using foods such as thick yoghurts, ice cream, instant powdered desserts, instant sauce granules and smooth puréed fruit. A range of proprietary thickening agents is also available on prescription (Table 21.2). Many caregivers have fears about offering thick drinks as they perceive these as not as thirst quenching, and their use should be fully discussed.

For children who manage food better than fluids offering foods with a high water content between meals, e.g. puréed fruit, thick yoghurts, fromage frais, ice cream and ice lollies, will increase their fluid intake. Jelly can be useful, but it dissolves immediately on entering the mouth, resulting in the same problems as thin fluids.

The following can be noted to monitor an increase in fluid intake: whether there have been more wet nappies, fewer urinary tract infections, softer or more regular bowel movements. Despite all efforts some children still find it extremely difficult to achieve an acceptable fluid intake orally and may require tube feeding to meet fluid requirements.

Increasing fibre

Children with neurodisability are at risk of constipation, which is very common. Poor fibre intake increases the risk and arises from the use of low fibre foods for puréed or mashed meals, enteral feeds with no added fibre and poor fluid intakes. Therefore, increasing dietary fibre and fluid intake alongside the use of medications is important [64]. Puréed fruit can be added to breakfast foods, and extra vegetables can be incorporated in gravy, mashed potato, casseroles and thick soups. Wholegrain cereals and breads or high fibre white/wheatmeal breads, given with plenty of fluids, are also useful. Other foods high in fibre, such as linseed, psyllium husk, ground seeds and nuts, can be added to smoothies, porridge or gravies.

If the child is tube fed, it is advisable to change to a fibre-containing formula. The use of prescribed soluble fibre supplements, e.g. Resource OptiFibre or Benefiber, may be useful where it is difficult to increase dietary fibre or when there is no alternative fibre-containing tube feed. These supplements are of benefit for both constipation and diarrhoea.

Oral nutritional supplements

Prescribed oral nutritional supplements, e.g. PaediaSure, Frebini Energy, Fortini (Table 12.3), may be appropriate for some children. The child's current nutritional intake should be assessed first to ensure that the supplement with the desired composition is selected. The use of supplements should be reviewed regularly. Supplements can be thickened as recommended by the SLT by a powdered thickener or can also be supplied as a ready thickened drink (Table 21.2). Energy modules based on fat and/or carbohydrate, e.g. Duocal, Calogen, Vitajoule, can be used to improve energy intakes, and these can be added to food or enteral feeds. A protein supplement, e.g. Protifar, can be added to foods and drinks to increase protein intake.

Presentation of food and drink

Mealtimes need to be enjoyable for the child to eat and drink to their best ability. When the child is alert and healthy, they

Table 21.2 Prescribable thickeners and pre-thickened drinks.

	Manufacturer	Product	Suitable for*
Powdered thickeners	Cow & Gate	Instant Carobel	Infants and small children
	Aptamil	Feed Thickener	Infants and small children
	Abbott	Multi-thick	Over 1 year
	Sutherland	Thixo-D original	Over 1 year
	Vitaflo	Vitaquick	Over 1 year
	Nestle	Resource ThickenUp Clear	Over 3 years
	Fresenius Kabi	Thick and Easy	Over 3 years
	Fresenius Kabi	Thick and Easy Clear	Over 3 years
	Nutricia	Nutilis Powder	Over 3 years
	Nutricia	Nutilis Clear	Over 3 years
	Slo Drinks	Slo Drinks Powder	Over 3 years
Thickened drinks	Nestle	Resource Thickened Drinks	Over 1 year
	Fresenius Kabi	Fresubin Thickened Stage 1	Over 3 years
	Fresenius Kabi	Fresubin Thickened Stage 2	Over 3 years
	Nutricia	Nutilis Complete Stage 1	Over 3 years
	Hormel	Thick and Easy	Over 3 years
	Thick-It	AquaCare H_2O	Over 3 years
Semi-solid desserts	Nutricia	Nutilis Fruit Stage 3	Over 3 years
	Nutricia	Forticreme Complete	Over 3 years
	Fresenius Kabi	Fresubin 2 kcal Creme	Over 3 years
	Abbott	Ensure Plus Creme	Over 3 years

*Indicated by manufacturer.

will manage a more challenging consistency of food than if they are tired or unwell. The child's caregiver needs to be sensitive to their needs on each eating/drinking occasion. To reduce the risk of aspiration and improve swallow coordination, a child should be offered a reasonable choice of food with a texture they can manage. If the child can feed assisted, this should be encouraged as the hand to mouth action will help with anticipation of receiving food into the mouth.

The way food is presented to the child is important for success. Food should be given slowly and rhythmically, allowing time to finish each mouthful and anticipate the next one. Small mouthfuls are more likely to be successful. For some children the food needs to be heaped towards the tip of the spoon to provide sensory cues for the lips. The spoon should normally be presented horizontally from the front, and, depending on the techniques being practised at the time, it could be centrally or towards the side of the mouth when encouraging chewing. Scraping food off the spoon with the top teeth should be avoided. The SLT or OT can suggest other methods to help the child to learn to take food from the bowl of the spoon and achieve lip closure.

Communication

A child or young person with a severe neurodisability may not be able to verbalise or signal their wish for food. This inability to make their request leads to an increased risk of insufficient nutrition, as they are unable to make the same demands as a healthy child. As a child grows older or their condition progresses, oromotor abilities may also change, which can result in new difficulties with managing food and drinks. Children with unrecognised feeding difficulties may be incorrectly interpreted at mealtimes. Often rejection of certain textures or consistencies can be mistaken for the child being fussy, lazy or badly behaved, or disliking the food. They may even display self-injurious behaviour or pica as a sign of distress. When a child is reported to be fussy or badly behaved at mealtimes, thorough investigation of exactly what is happening is needed, as the possibilities of misinterpreting intentions are very great. An SLT and OT can help with these issues. Special communication aids, also known as augmentative and alternative communication (AAC), may be used such as communication boards, charts, books or electronic communication aids with voice output to help the child communicate their needs.

Prompts

If the child is unable to feed themselves, then the caregiver will need to use appropriate prompts to ensure the child is aware that food is coming and what they are eating. Prompts can be:

- visual, e.g. an environment with other people eating; mirrors; seeing, smelling and hearing the food being prepared or arriving at the table
- physical, such as the smell of food; stroking the lower lip with the spoon; giving very small amounts so allowing time for the child to experience the taste, texture and temperature of the food
- verbal, to promote the awareness of the concepts of eating; asking the child how they would like to be fed; telling the child what is going to happen next; explaining what is being done as it occurs. Repetitive phrases throughout the meal help the child know what they are doing, e.g. 'bite', 'chew' and 'swallow'
- object recognition, such as a spoon being placed in the child's hand prior to each meal, helps the child to understand and anticipate that a food is on its way

Assessment will inform which combination the child will prefer; however, consistency by all helpers is important.

Assistance with feeding

All people who could possibly be involved with feeding the child should be identified. Total reliance on one main caregiver should be discouraged as this can make the child dependent on one person's feeding technique and makes changing caregivers very difficult. Other members of the family, friends, respite caregivers, social service family support, students and volunteers can all give support at mealtimes. The caregiver should be encouraged to let another person help with at least one meal a week. Training and support should be offered to the helpers, and they should be involved in the assessment and review process. Clear details of the programme such as a 'mealtime guidance sheet' must be accessible to all involved with feeding. A model of how the task of feeding is best carried out provides caregiver a clear picture of what is expected. Also, this can increase the empathy of the demonstrator by briefly experiencing the difficulties experienced by the feeder at every meal.

Special feeding aids and equipment

Positioning of the child is important to ensure they can feed safely as even a slight change in the angle of the child's head or body can affect their ability to feed safely [65]. Children may need their seating adapted to ensure they are in the correct posture and an OT can help with this.

Special feeding aids and equipment are tailored to improve eating and drinking and promote independence. Examples of these are:

- eating systems
- special bowls and plate guards
- cutlery such as spoons with textured, contoured or curved handles, e.g. angled spoons and good grip spoons
- drinking equipment: cups, mugs and bottles with special features such as two handles, one-way valves, weighted bases to reduce tipping, cup holders and straws. Specific special cups are the Doidy cup (slanted towards the child for easier drinking); the anyway drinking cup (designed to reduce spillage); special needs Medela teats, bottles, cups; Easyflow cups
- bibs and aprons to help keep children clean during mealtimes
- slip-resistant tableware such as placemats

Eating with other people

Eating with other people is important for children with feeding difficulties. However, limitations may prevent this from happening, for instance, the special chair may not fit under the family table. Such problems should be identified in an MDT mealtime assessment. In some cases the caregiver may find it easier to give the child their meal before everyone else. Practical ways in which the child can join in with family mealtimes need to be identified. A tube-fed child can have their tube feed at the same time as the rest of the family have their meal to promote associations between feeling full and seeing/smelling foods. This may help a child progress to oral feeding if this is possible in the future. Eating out may be a problem, and familiarisation with popular commercial menus will provide ideas for the caregiver, e.g. many venues serve thick shakes which, if transferred to the appropriate cup, can provide a perfect consistency for some children requiring thickened drinks.

Enteral nutrition

Children with disabilities form the largest group of children requiring long-term home enteral tube feeding (HETF) in the UK [66]. A British Artificial Nutrition Survey (BANS) report found that 31% of children registered for HETF in 2010 had a diagnosis relating to the CNS or mental health [67].

The decision to initiate enteral feeding is an emotive one, which can have many ethical considerations. The decision must be in the best interests of the child, from a medical point of view, for quality of life and ensuring dignity is maintained. Parents are often reluctant to consent to placement of a gastrostomy tube for feeding, as it can be perceived as a failure or start of degeneration of their child's health condition. Gastrostomy feeding may present another loss of normality and be a sign of disability for some parents [68]. Parents should be given all the information they need to reach an informed decision about the benefits and risks of gastrostomy placement and the process should not be rushed [69–73]. An MDT approach to these conversations is beneficial. It is important to talk through this process with families explaining that often oral feeding can continue with advice from the SLT.

Enteral nutrition should be considered in children with:

- malnutrition, or where they are unable to achieve catch-up growth with oral nutrition alone
- unsafe swallow
- severe oral aversion
- significant stress during mealtimes
- inadequate hydration
- inability to take medications orally

The choice of nasogastric (NG) versus gastrostomy feeding has to be carefully assessed for the child with feeding difficulties. NG feeding can be used as a short-term (approximately 6 weeks) method of feeding; however, this can cause oral/facial aversion if used for extended periods of time. Gastrostomy feeding is a longer-term (more than 6 weeks), safe and useful method to allow adequate nutritional intake and prevention of dystrophy in children with neurodisability and dysphagia [69, 74]. Gastrostomy placement carries a surgical risk. Tube feeding does not prevent aspiration of oral secretions or of gastric contents unless the tube is placed in the jejunum. Enteral feeding in children with neurodisabilities is well tolerated and can improve energy and protein intake, weight gain and nutritional status in addition to improving the parent's/caregiver's perceptions of their child's health and quality of life [69, 75, 76].

Feeds

Children with neurodisability often have relatively low energy expenditure and high body fat content, and, therefore, caution should be taken not to overfeed patients [77]. Many children appear to grow adequately on very low energy intakes, and it may not be possible to meet their macronutrient and micronutrient requirements (based on the child's height age) if standard 1 kcal/mL (4 kJ/mL) enteral feed volumes are simply reduced to provide less energy. In this case a low energy paediatric feed, such as Nutrini Low Energy Multi Fibre (0.75 kcal/mL, 3 kJ/mL), may be the best choice (Table 4.2). A vitamin and mineral supplement may be needed to complement any low energy feed, e.g. Paediatric Seravit or Phlexy-Vits; additional sodium and potassium supplementation may be given from an oral rehydration solution, e.g. Dioralyte; a protein module may be added to the feed if required, e.g. Protifar. Feeds designed for older children or adults, including feeds that are complete in 1000–1200 mL (such as Fresubin 1000 Complete, Nutrison 800 or 1000 Complete Multi Fibre), are worth considering in smaller volumes for children. However, the micronutrient levels must be checked and kept within safe intakes. Constipation is often an issue; therefore a feed containing fibre should be the preferred choice.

Many families choose to give blended foods down the enteral feeding tube, and the associated risks, such as blocking the tube and bacterial contamination, will need to be discussed with the family. ESPGHAN advises against the practice of giving liquidised food via feeding tubes [78]. If families decide to change to a fully blended diet, then it should only be given down a gastrostomy tube feeding into the stomach and not down an NG tube or fed into jejunum. The nutritional content of the diet, using appropriate dietary analysis software, will need to be determined. It is likely that additional nutritional supplements will be required alongside blended foods. The British Dietetic Association (BDA) toolkit on liquidised food via gastrostomy tube [79] is expected to be updated in 2020 (p. 62).

Enteral feed choices include:

- breastmilk or standard infant formula
- energy-dense infant formula (Table 1.18)
- standard paediatric feed with or without fibre (Table 4.3)

- high energy paediatric feed with or without fibre (Table 4.3)
- low energy paediatric feed with fibre (Table 4.3)
- adult feeds for older children/adolescents with energy density 1–2 kcal/mL (4–8 kJ/mL) with varying protein content (Table 4.3)
- adult feeds nutritionally complete in 1000–1200 mL volume (Table 4.3)
- specialised paediatric/adult feeds based on AAs, peptides or soya (Tables 8.14–8.16 and 8.20)

A case study to illustrate enteral tube feeding in a child with neurodisability is given in Table 21.3.

Feeding regimens

The feeding regimen should be discussed with the child, their family and caregivers.

Common choices are:

- continuous
- bolus via syringe or gravity set
- bolus via pump

The choice of regimen will be affected by whether the child is still allowed to eat and drink (whether or not they have a safe swallow). The feed may be used merely as a top-up after meals, or it may replace all oral intake. Commonly, children who are at risk of aspiration may still be allowed to take small tastes of food for pleasure (as directed by the SLT), and this should be taken into account when calculating energy requirements.

If the enteral feed is to be the sole or major source of nutrition, it is common to give a small feed via bolus or pump at each mealtime to mimic the psychological and physiological effects of a meal. Overnight feeding can accompany this type of regimen if a larger volume is required, but this should be used with caution if the child has an NG tube due to the risk of displacement and aspiration, particularly as children with disabilities often have irregular postures when lying down. Overnight gastrostomy feeding can only be offered if the child can maintain a safe sleeping position, propped up to at least 30°. The use of a sleep system can help with safe positioning. The choice of feeding regimen may depend on the child's tolerance, particularly if GOR is present, and activity during the day.

Overweight

Gastrostomy feeding is beneficial for children with neurodisabilities who have oral or motor dysfunction and clinical signs of undernutrition. It aids weight gain; however, caution should be taken not to overfeed as it has been shown that children with CP have significantly higher body fat content and lower lean body mass than the healthy population [77]. Sometimes children become very overweight when enteral feeds have not been carefully monitored or higher volumes (and hence higher energy) have been given to ensure an adequate supply of protein and micronutrients. This can be a very difficult problem to rectify and has led to the precaution of underestimating energy requirements rather than overestimating these when feeds are initially started. A low energy paediatric feed or a reduced volume of an adult feed can be useful.

Monitoring and follow-up

Monitoring and follow-up will depend on the type of neurodisability, stage of progressive disorder and symptom control as it arises. Therefore, it is difficult to give guidance on frequency or method. There are often limited resources for regular review of these patients, and dietitians may rely on other healthcare professionals, parents, or caregivers to highlight problems and monitor nutritional parameters for these children. Many of the children may be lost to follow-up due to non-attendance at reviews. To minimise non-attendance it is important to choose locations that are convenient for the child and their parents and caregivers, e.g. home and special school.

Weight gain is a crude guide to assessing whether the right amount of nutrition has been prescribed. Often the subjective opinion of the parent or caregivers on how well nourished their child appears is sought as a guide. However, these children tend to put on weight as fat rather than muscle and often do not grow taller no matter how much additional nutrition is provided [80]. Measuring body composition by taking skin fold thickness and mid-arm circumference measurements can help clarify this quandary. The rate of growth and weight gain can be tracked using the child's growth chart. It is usual for many of these children to be tracking below the 0.4th centile for both height and weight and this is acceptable providing they are following the shape of the growth curve.

Children receiving tube feeds should be reviewed every 2–6 months once stable, depending on their age, to monitor weight and height, assess clinical indices and alter feeds as necessary. These guidelines may be used for children feeding orally who are at risk of nutritional deficiencies or problems with growth. Monitoring nutritional parameters in blood tests for high risk children or those on tube feeds should be carried out every 6–12 months [5, 56].

Complications

Faltering growth

Faltering growth, or low weight for height, has been well documented in children with neurodisabilities [1, 5, 81, 82]. Nutrition intervention for children with CP has been shown to produce improvements in growth and nutritional status [83, 84]. There are beliefs that it is 'normal' for children with severe disabilities, particularly children with CP, to have poor stature and low weights, which has been ascribed to their underlying cerebral deficit or physical inactivity rather than to chronic malnutrition [16, 81]. Normal parameters for identifying faltering growth may not be appropriate in this

Table 21.3 Case study to illustrate enteral tube feeding in a child with neurodisability.

A 2-year-old boy with quadriplegic cerebral palsy

Insertion of a gastrostomy tube and Nissen fundoplication procedure done simultaneously at the age of 18 months due to feeding difficulties, poor weight gain, constipation and severe GOR
Weight prior to gastrostomy placement 8 kg at the age of 17 months (0.4th centile)
Length measurement (using alternative measure) 77 cm (2nd centile)

He was established on full gastrostomy feeds of 800 mL PaediaSure, 1 kcal/mL (4 kJ/mL) given as:
130 mL × 4 boluses through the day (intermittent with feeding pump)
35 mL/hour over 8 hours continuously overnight (via feeding pump)
He was allowed tastes of puréed food 1–2 times per day as recommended by the SLT

He was not reviewed for 6 months post-gastrostomy placement. The dietitian visited at home at age 2 years, and on assessment his weight gain had been rapid: weight = 11 kg (9th–25th centile)

Clinically he appeared overweight, well hydrated with regular bowel movements, adequate absorption of feeds with no feed loss due to vomiting
Alternative length measurement was taken: tibial length = 15.4 cm
Height estimated at 81 cm using tibial length (2nd centile)

Plan at 2 years of age: Feed changed to 800 mL Nutrini Low Energy Multi Fibre, 0.75 kcal/mL (3 kJ/mL) = 600 kcal (2510 kJ)/day
Although fluid requirement for 11 kg child was 1050 mL/day, he was well hydrated on 800 mL total fluid volume (assessment of bowel movements, urine output and concentration, alertness and skin turgor)

Follow up at 2 years 3 months of age: Further dietetic assessment undertaken
Weight 11.9 kg (>25th centile for age)
Rate of weight gain had slowed down; however, still too rapid when plotted on UK-WHO growth chart and CP growth charts. He is not mobile; therefore, his requirements are much lower than originally estimated. He continued to gain weight on a low energy feed

Plan at 2 years 3 months of age: Volume of Nutrini Low Energy Multi Fibre further reduced to 500 mL providing 375 kcal (1570 kJ)/day: 30% of EAR energy for actual age, equivalent to 32 kcal (135 kJ)/kg

Additional water flushes of 300 mL to be given to meet his fluid requirement of 800 mL/day. The reduced feed volume does not meet RNI for micronutrients. Consider the addition of Paediatric Seravit and Dioralyte to improve the nutritional profile:

Nutrient	RNI (1–3 years boy)	Daily requirements based on 10.9 kg (using height age)	500 mL Nutrini Low Energy Multi Fibre	Addition of 5 g Paediatric Seravit	Addition of $^1/_2$ sachet Dioralyte (dissolved in 100 mL water)	500 mL Nutrini Low Energy MF + 5 g Paediatric Seravit + $^1/_2$ sachet Dioralyte
Energy	95 kcal (400 kJ)/kg/day (EAR)	1036 kcal (4330 kJ)	375 kcal (1570 kJ)	14 kcal (58 kJ)	–	389 kcal (1625 kJ) 36 kcal (150 kJ)/kg
Protein	1.1 g/kg/day	12 g	10.5 g	–	–	10.5 g (1 g/kg/day)
Sodium	1.7 mmol/kg/day	15.5 mmol	13 mmol	0.05 mmol	10.2 mmol	23.25 mmol (2.1 mmol/kg)
Potassium	1.6 mmol/kg/day	17.4 mmol	17 mmol	0.04 mmol	3.85 mmol	20.9 mmol (1.9 mmol/kg)
Calcium	350 mg/day	350 mg	300 mg	129 mg	–	429 mg
Iron	6.9 mg/day	6.9 mg	5 mg	3.50 mg	–	8.5 mg
Vitamin A	300 µg/day	300 µg/day	205 µg	210 µg	–	415 µg
Vitamin D	7 µg/day	7 µg/day	5 µg	2.80 µg	–	7.8 µg
Vitamin E	3.2 mg/day	3.2 mg/day	6.5 mg	1.10 mg	–	7.6 mg
Thiamin	0.36 mg/day	0.36 mg/day	0.75 mg	0.16 mg	–	0.91 mg
Riboflavin	0.5 mg/day	0.5 mg/day	0.8 mg	0.22 mg	–	1.02 mg
Vitamin B_6	0.7 mg/day	0.7 mg/day	0.6 mg	0.17 mg	–	0.77 mg

The addition of $^1/_2$ sachet of Dioralyte in 100 mL water and 5 g of Paediatric Seravit makes up the requirements for vitamins and minerals. The GP and paediatrician were notified of the patient's feed plan, and a request was made to monitor his bloods annually to ensure nutritional adequacy of the feed with electrolyte supplementation.
GOR, gastro-oesophageal reflux; EAR, estimated average requirement; RNI, reference nutrient intake; GP, general practitioner.

population, and a variety of methods may be needed to assess nutritional status [5]. Many patients with neurodisabilities have malnutrition and growth failure as the result of inadequate energy intake [85]. There is evidence that the severity of feeding problems in children with neurodisability is directly related to the degree of faltering growth [7]. Resulting malnutrition is linked to poorer health status and reduced ability to participate in normal daily activities [7].

Gastro-oesophageal reflux disease

GOR is the passage of stomach contents into the oesophagus. Gastro-oesophageal reflux disease (GORD) is GOR with secondary complications such as feeding difficulties, respiratory problems, faltering growth, abdominal pain and excessive regurgitation [86]. GORD is common in children with neurodisability and can affect up to 70% of children [5, 87]. The most important mechanism of GOR is the prolonged relaxation of the lower oesophageal sphincter. Other mechanisms are reflux and strain-induced reflux, when abdominal pressure exceeds the pressure of the lower oesophageal sphincter [87]. GOR differs from vomiting, the emetic reflex following ingested toxins, which acts as a protective mechanism.

Diagnosing GORD involves taking a thorough history and physical examination, alongside any changes in lifestyle, diet and medications. Endoscopy may identify oesophagitis, eosinophilic oesophagitis, coeliac disease or erosions [88]. Oesophageal pH studies may be used to diagnose GOR and involves insertion of a microelectrode probe into the lower oesophagus for 24 hours and measuring the duration and number of reflux episodes. Oesophageal pH studies will not show non-acid reflux [88]. A barium swallow may be used to detect anatomical abnormalities.

Treatment for GORD depends on the age of the child and the severity of GORD. Offering smaller more frequent meals and/or feeds with thickener may help manage symptoms in those with mild symptoms [5]. In older children diet modification, weight loss (if overweight) and other lifestyle changes may help to improve reflux. Elevating the cot or bedhead when a child is sleeping may help. For those with severe GORD, a 2- to 4-week trial of a hydrolysed protein or AA-based formula, or elimination of cow's milk from the maternal diet in a breastfed infant, should be considered before the use of medications [88]. A referral to a paediatric gastroenterologist may be helpful to identify underlying causes. There are various drug therapies used to treat GORD. Acid suppression medications are most widely used [88]. Proton pump inhibitors (PPI), e.g. omeprazole and lansoprazole, are effective acid suppressants and should be first-line medication treatment for children with GORD and neurodisability [5]. H2 receptor antagonists, e.g. ranitidine, are rarely used as PPI are more effective. Prokinetics agents, e.g. domperidone, may help to accelerate gastric emptying, but there is limited evidence for their use [5, 88].

Where drug therapy fails, the child may be offered anti-reflux surgery as either a complete fundoplication or partial wrap [88]. Often a gastrostomy tube is placed at the same time. Complications such as dumping syndrome, gas bloating and retching can occur (p. 155). If underlying oesophageal dysmotility still remains and if retching or attempted vomiting are not controlled by continuing drug therapy, slippage or unwrapping of the fundoplication can occur [88]. An alternative to fundoplication for children on tube feeds is for a change to transpyloric feeding via nasojejunal (NJ) tube, percutaneous endoscopic jejunostomy (PEJ) or percutaneous endoscopic gastrostomy with jejunal tube (PEG-J). The latter two procedures have been shown to improve quality of life and to show decreases in aspiration pneumonia in children with neurological impairment, with similar rates of mortality [89–91]. However, small amounts of reflux may still occur with transpyloric feeding [92].

Constipation

Constipation is a common problem for children with neurodevelopmental disabilities with an estimated prevalence of 26%–70% depending on the definition [60, 93, 94]. There is often a delay in recognising and treating the problem either because of the inability of the child to communicate effectively or because constipation is accepted as inevitable or because higher priority has been given to other aspects of the child's medical management [64]. There are multiple factors predisposing to constipation, both neurological and lifestyle. Colonic transit times may be prolonged, and some children have problems with coordination in anal sphincter and pelvic floor muscles [64]. It is generally felt that constipation is related to poor ambulatory function with CNS damage being suggested as an important risk factor [64]. Constipation has also been linked with medications, particularly those known to slow intestinal motility [94].

Dietary fibre and fluid intakes in these children are often poor and can be exacerbated with drooling and poor oromotor function [5]. Dietary intake is often high in fat, moderate in protein and low in carbohydrates, all of which contributes to a lower fibre intake [85]. Additional fluid and fibre may help for long-term management of constipation, but initial management involves disimpaction and laxative use [5, 64].

National Institute for Health and Care Excellence (NICE) guidelines recommend a clear treatment for constipation, starting with disimpaction and then maintenance of regular and painless defaecation. Laxatives are recommended as first-line treatment, starting with polyethylene glycol, e.g. Movicol, and then moving on to stimulant or osmotic laxatives as necessary [95]. There is no set treatment regimen for children with neurodisabilities with constipation, but a consistent approach with clear instructions for caregivers on how and when to adjust medications is recommended [5, 94]. A bowel habit diary can be useful in assessing response to treatment.

Dietetic assessment and treatment is necessary in order to avoid further nutritional compromise, and supplementation with dietary fibre from food, enteral feeds or commercial preparations may help to normalise bowel function [5, 96].

However, often simply increasing the child's fluid intake can have the most success.

Micronutrient deficiency

Micronutrient deficiencies are common in children with neurodisability due to lower overall food intake and variety, poor enteral feed tolerance, vitamin losses through liquidising foods or long cooking methods and other factors affecting oral or enteral intakes [85]. Studies have shown lower intakes of iron, vitamin D, selenium, folate and calcium [85]. Nutrient deficiencies can cause neurological changes, which may be hard to distinguish from the underlying medical condition and could be considered a progression of the disease rather than initiating an investigation into deficiency [85]. Sodium and potassium intakes can be low; however, current opinion is that a level between the RNI and LRNI for height age is acceptable provided urine and blood biochemical parameters are within normal ranges [19].

Osteopenia

Children with neurodisabilities are more susceptible to osteopenia (poor bone density) and increased risk of fractures because they are often non-weight-bearing and have limited exposure to sunlight. Many studies have found deficiencies in vitamin D status [5, 18, 85]. Long-term use of anticonvulsant therapy has been associated with alterations in vitamin D and calcium metabolism [5]. NICE guidelines suggest that children should be supplemented with vitamin D if they are under 4 years old and/or spend significant periods of time indoors [97]. It is advisable that vitamin D and calcium intakes meet the reference nutrient intakes (RNI) for age. The requirement for vitamin D for those older than 4 years to prevent deficiency is 10 µg (400 IU) daily [98]. It is also important to ensure that there is an adequate calcium intake to build and maintain bone strength, and a preparation with calcium and vitamin D may be indicated. Regular blood monitoring every 6–12 months for bone indices should be done and supplementation given as indicated. The use of DEXA scans to measure bone mineral density is a useful part of nutritional monitoring for children with neurodisability if this is available in their area [5].

Dental caries

There is a higher incidence of oral/dental problems in these children [5] and are caused by a number of factors:

- poor dental hygiene due to hypersensitivity to teeth cleaning
- inability to clean teeth oneself and dependent on caregivers for support
- difficulty accessing oral cavity for children who have behavioural, structural or muscular conditions
- cariogenic effect of some medications due to sugar content or decreasing saliva production
- inability to clear the mouth of food after eating
- GORD
- frequent consumption of energy-dense meals and drinks
- children may be unable to communicate to caregivers that they have dental pain and therefore caries are not investigated promptly

There are some strategies to help prevent dental caries:

- teeth should be brushed twice daily with a small amount (a smear for children <2 years and a pea-sized amount for children >2 years) of fluoride toothpaste (1000 ppm ± 10%). If the child is nil by mouth, a cloth or suction catheter should be used to wipe away excess toothpaste
- chlorhexidine mouthwash can be wiped over the teeth and gums using a pink sponge
- teeth should be flossed daily
- children should be seen by their local dentist biannually; they may advise topical fluoride application as a preventative measure
- children who cannot be treated by their local dentist should be referred to a specialist community or hospital dental team; they may also be able to arrange dental cleaning at hospital with sedation
- a dry mouth or decreased saliva production increases the risk of dental caries; Luborant artificial saliva sprays can be used for these children
- care should be taken when advising on diet and nutritional supplements for possible cariogenic effect on the teeth
- bottle feeding for prolonged periods of time should be avoided where possible and alternatives should be advised

Oral dysfunction and dysphagia

Oral dysfunction may result from either structural abnormalities such as high roof of the mouth, cleft, enlarged tongue, abnormal dentition or motor difficulties such as those seen in CP. Children with neurological impairment commonly have oromotor difficulties, and around 89% need assistance with feeding, 56% choke with food and 28% have prolonged feeding times [1].

There are four stages of swallowing, all of which need to be functioning correctly for the safe and efficient passage of fluid or solids to the stomach (Table 21.4).

From infancy to childhood, as the CNS matures, certain reflexes usually disappear. Children with physical disabilities may keep some of these, and, when coupled with abnormal movement patterns, they can make it difficult to coordinate the passage of food and fluids to the mouth. Table 21.5 summarises the effect of abnormal movement on eating.

Texture modification

In order to ensure a safe swallow and to allow for different structural, behavioural or reflexive movements, the SLT may alter food and fluid consistencies to reduce the risk of

Table 21.4 Stages of swallowing.

Stage of swallow	What is happening	Difficulties that can occur at this stage
Pre-oral (anticipatory)	The process of thinking about food, smelling food, seeing food, touching food and bringing food to mouth	Lack of coordination to touch food or bring food to mouth Blindness Unable to smell/see food if inside packaging, e.g. pouch food
Oral preparatory	The process consists of head and jaw movements including voluntary opening of the mouth, lip closure around the utensil or biting food, transferring the food around the mouth including chewing, sorting and mixing to form a bolus and holding onto this bolus ready for swallowing	Inability to open the mouth voluntarily Inadequate lip closure Overbite or tonic biting (biting down hard) Tongue thrust Oral hypersensitivity indicated by food refusal
Oral	This relates to the initiation of the swallow and involves elevation of the front of the tongue to seal the mouth, propulsion of the bolus by the tongue to the back of the mouth and raising the soft palate to provide a nasopharyngeal seal	Lack of coordination of tongue movement Incomplete nasopharyngeal seal
Pharyngeal	This is an involuntary stage triggered by the movement of food to the lower part of the pharynx. The nasal passage and airway are closed as the food passes from the pharynx into the oesophagus. The bolus of food is transported through the oesophagus by peristalsis. Closure of the vocal fold prevents aspiration	Ineffective function of peristalsis Problems with pharyngeal anatomy
Oesophageal	This depends on the peristaltic action of oesophageal muscles to propel the bolus of food into the stomach and the contraction of the cricopharyngeus muscle to prevent reflux	Oesophageal obstruction Gastro-oesophageal reflux

Table compiled from information in Matsuo and Palmer [99].
Source: Reproduced with permission of Elsevier.

Table 21.5 Abnormal movements and reflexes affecting eating and drinking.

Name	Description	Effect on mealtimes
Asymmetrical tonic neck reflex	Caused by turning the head and triggers extension of the limbs on the side which the head is rotated and an increased flexion of the opposite side	Posture: The child can be difficult to position Feeding: The child may be unable to look at their hand and bring their hand to mouth Swallow: Head turned severely to one side may prevent an effective swallow
Extensor thrust	Voluntary or involuntary strong push back of head and trunk	Posture: The child can be difficult to position Swallow: Chin thrust inhibits effective swallow, may cause choking Oral: Jaw thrust prevents mouth closure and can obstruct suckling and chewing
Startle reflex	Sudden extension of arms and opening of hands, stimulated by sudden noise or unexpected movements	Posture: The child can be difficult to position for self- or assisted feeding Feeding: The sudden loss of posture may rouse feelings of insecurity Swallow: Associated with a fast intake of breath, which may cause choking
Rooting reflex	When cheek is touched, the head turns to that side	Oral: When head is out of midline, the configuration of the mouth changes including the jaw and lip positioning
Bite reflex	When mouth touched there is a sudden jaw closure	Oral: Cannot coordinate jaw movement in order to introduce or withdraw utensil
Tongue thrust	Tongue moves in direction when touched	Oral: Difficult to introduce food, retain food and deal with it in the mouth

aspiration and improve swallow. The International Dysphagia Diet Standardisation Initiative (IDDSI) has developed descriptors for both food and fluid [100]:

7 – regular food
6 – soft bite-sized food
5 – minced and moist
4 – puréed food, or extremely thick drink
3 – liquidised food, or moderately thick drink
2 – mildly thick drink
1 – slightly thick drink
0 – thin drink

This sequence and overlap of textures is shown in Figure 21.5.

The required texture should be described to the caregiver, giving plenty of examples of ways of achieving the desired

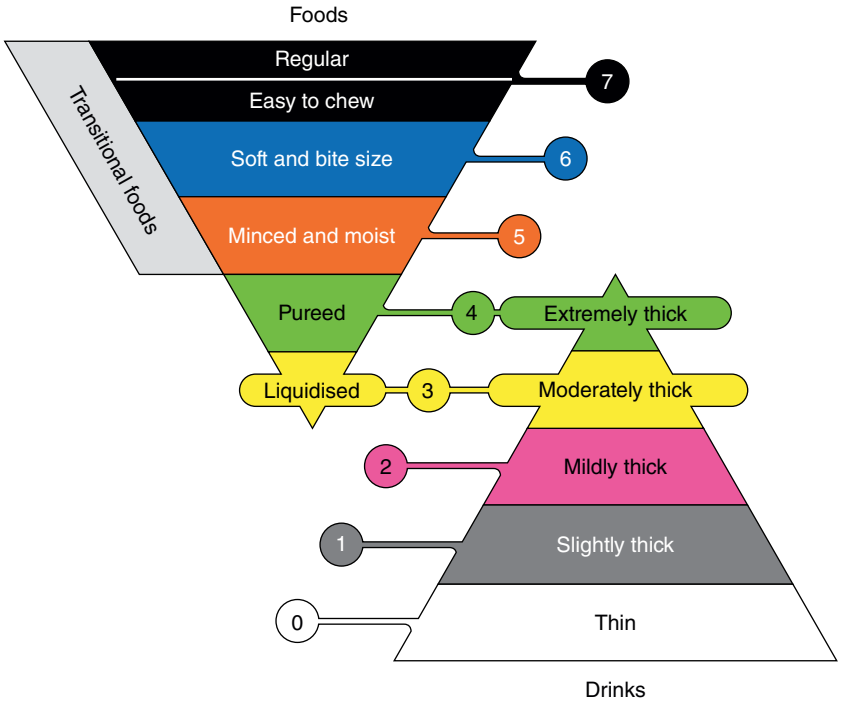

Figure 21.5 Descriptors for foods and drinks. IDDSI framework. https://iddsi.org.

texture. The effect that cooling or warming the food may have on texture, the effect of stirring the food repeatedly and how saliva from the spoon will thin the consistency during a prolonged meal need to be discussed.

Cleft lip and palate

Children with neurodisability may also have a cleft lip and/or palate. They are at risk of poor growth and nutrition because they may not be able to get an effective suck. Feeding adaptation may involve using different techniques when breastfeeding, different shaped teats with enlarged or different positioned holes, soft squeezy bottles that may help the flow of milk and temporary maxillary plates, or if the child is unable to safely meet nutritional needs orally, then they may be tube fed [101]. Surgical repair of the lip and palate can occur any time from 4 to 12 months of age. Normal feeding can often resume if the cleft has been completely repaired [101].

Drug and nutrient interactions

Medications can have an impact on nutritional status by causing changes in taste, appetite, weight, alertness and/or gastrointestinal upset. This can be a problem when a new drug is being introduced and adjusted. Anti-epileptic drugs (AED) may have impact on bone health and are associated with an increased risk of bone fractures and reduced bone mineralisation relating to lower availability of vitamin D. Supplementation with calcium and vitamin D may reduce the rate of bone loss for patients on AED [5, 102]. Children on AED may also have reduced levels of vitamin B_{12}, folate and vitamin B_6, and these nutrients may need monitoring and supplementation given [103, 104].

Muscle relaxants, such as baclofen, are commonly used for children with CP and other neurological conditions. If the dose is correct, posture for eating can be improved in children with spasticity. However, if the dose is too high, then muscle weakness can lead to feeding difficulties.

Food can affect absorption of some medications making them more or less effective, e.g. phenytoin, which should be given 2 hours before or after a meal/feed. Medications, especially antibiotics, can also alter the gut microbiota of a child, and this may increase risk of gastrointestinal upset, e.g. diarrhoea [105].

Transition to adult care

The transition of children to adult care normally takes place when the child leaves full-time education, and this could be up to 19 years of age. Children are often very carefully monitored within a paediatric MDT, and care should be taken to ensure that all relevant information is handed over to all the adult team such as dietitian, general practitioner, hospital consultant, allied healthcare team and district nurses (where appropriate). There is often a transition period where a child will start getting used to day-care units, and the MDT needs to support this transition. Parents and caregivers will need support as often adult services offer different facilities to children's services, and they may find the change quite stressful.

Future research needs and unanswered questions

The following issues need to be addressed in children with neurodisability:

- long-term use of adult enteral feeds and the effects of high micronutrient intakes over prolonged periods of time and gut microbiota
- the need for routine supplementation of vitamin D and calcium with modern AED
- changes to gut microbiota with medications for children with disability
- prevalence of food allergy or intolerance in children with disabilities
- energy and protein requirements and whether the use of height age is a good estimator of requirements

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

22 Epidermolysis Bullosa and Rare Skin Disorders

Natalie Yerlett

Epidermolysis Bullosa

Introduction

Epidermolysis bullosa (EB) comprises of a group of rare genetically determined skin blistering disorders characterised by extreme fragility of the skin and internal mucous membranes.

Types of epidermolysis bullosa

The most recent classification [1] separates EB into four main types (Table 22.1), which are further divided into major subtypes, of which there are many further subtypes not listed here. The first three types are illustrated in Figure 22.1.

The classification of each EB type and subtype is based on mode of transmission and phenotypic, ultrastructural, immune-histochemical and molecular findings [1]. All types result from genetic mutations, which cause a defect in, or a partial or full absence of a structural protein in the dermal–epidermal basement membrane zone; or, in the case of suprabasal EB simplex (EBS), between adjacent keratinocytes. The resultant defective adhesion means that minor knocks or friction can cause the skin to blister. The depth of these blisters and how they heal differs depending on the EB subtype. DNA blood tests of the patient (or the parent if they have the same phenotype of EB) are taken in infancy to ascertain subtype. Classification of EB subtypes has changed and been updated many times, and many more genes are yet to be identified. Occasionally, the EB subtype is classified by clinical presentation alone if genetic testing fails to identify the genetic defect; often the gene has yet to be identified. The consequences of different EB types vary greatly in their impact ranging from infantile mortality to minor blistering on extremities. Some patients presenting with the same subtype of EB may manifest a wide range of symptom severity. The intellectual development of these children is normal.

Mode of inheritance

EB is usually inherited either dominantly or recessively; it may also result from a spontaneous genetic mutation with no previous family history [2]. In dominant inheritance, the affected parent (who has EB) passes on the affected gene to their child. There is a one in two chance with each pregnancy that a child will inherit the affected gene. The more severe forms, where each parent carries the affected gene (but does not have EB), are generally recessively inherited. In each pregnancy with two carrier parents, there is a one in four chance of an affected child being conceived.

Diagnosis

In some cases EB may be suspected at birth. Occasionally, the severity of skin damage at birth does not correlate with the severity of the diagnostic subtype; due to this, great care is taken to deliver the diagnosis as quickly as possible while trying to avoid a presumed diagnosis. Parental anxiety is often very high while awaiting such results as they have likely found out that some forms of EB are fatal. In milder cases EB may be diagnosed much later on. To make a diagnosis, the 'onion skin' approach is recommended [1]:

- a full personal and family history and physical examination is undertaken with presence or absence of cutaneous

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 22.1 Classification of epidermolysis bullosa.

Level of skin cleavage	EB type	Major subtypes	Main group of targeted proteins
Intraepidermal	EB Simplex (EBS)	**Suprabasal** Skin fragility syndromes such as desmoplakin deficiency	Transglutaminase 5, plakophilin 1, desmoplakin, plakoglobin
		Basal EBS localised (previously called Weber-Cockayne) EBS generalised severe (previously called Dowling-Meara)	Keratin 5 and 14, plectin, exophilin 5, BP23, KLHL24, kindlin-1
Intralamina lucida	Junctional EB (JEB)	JEB generalised severe (previously called Herlitz) JEB generalised intermediate (previously called non-Herlitz) JEB with pyloric atresia JEB LOC syndrome	Lamini-332, collagen XVII, α6β4 and α3 integrin
		JEB localised	Collagen XV11, laminin-332, α6β4 integrin
Sub-lamina densa	Dystrophic EB (DEB)	Dominant (DDEB) Including bullous dermolysis of the newborn	Collagen VII
		Recessive (RDEB) RDEB generalised severe RDEB localised RDEB generalised intermediate	Collagen VII
Mixed	Kindler	–	Fermitin family homolog 1 (kindlin 1)

or extra-cutaneous symptoms; the EB major subtype could be elucidated from this
- following this, localised or generalised diagnosis may be elucidated with further symptomology and later from information related to the mode of transmission
- this may be followed up with a skin biopsy, undergoing microscopy with immunohistochemical techniques (immunofluorescence antigen mapping [IFM] with EB-specific monoclonal antibodies)
- finally, a genetic mutation analysis [1, 3, 4].

Prevalence

The exact prevalence of EB is difficult to assess as very mild cases may go undiagnosed, while the severely affected may die before diagnosis. In the UK, it is currently estimated that there are approximately 5000 people living with all subtypes of EB. Prevalence of all types of EB and all ages in late 2010 was estimated at 15 : 1 000 000 [5]. EB affects the sexes equally and is prevalent in all ethnicities.

Management

Severe types of EB can be extremely physically disabling coupled with constant severe pain. Many patients will have chronically compromised nutritional status as outlined in Table 22.2. These include those diagnosed with RDEB, JEB and the EBS generalised severe patients, all of whom are likely to require nutritional intervention from birth. Despite worldwide research investment and many advances in treatment, there is currently no cure for any type of EB. Treatment with exclusion diets combined with topical and systemic treatments (the Kozak regimen) was disproved in an open evaluation [6]. Multidisciplinary management is focused on symptom control, wound dressing, therapeutic input, treatment and prevention of infection, monitoring, pain management, surgery, gastrointestinal (GI) review and optimisation of nutritional status [7].

Worldwide research efforts are under way to find new therapies that provide longer lasting improvement in patients' conditions and, ultimately, a cure. These include [8]:

- therapies such as gene therapy, protein therapy, drug therapy, molecular and cell therapy
- local therapies that target healing such as grafting with genetically corrected skin or subcutaneous injections of collagen or fibroblasts
- systemic therapies aimed at whole body healing using intravenous (IV) injections of bone marrow stem cells from a donor, mesenchymal stem cells or, in the future, induced pluripotent stem cells

While some interventions aim for temporary improvement (collagen or fibroblast therapy), others aim for a permanent cure (grafting with genetically corrected skin or bone marrow transplant).

Nutrition support

Current practice relies on retrospective studies of small numbers of children, expert clinical experience and extrapolation from other conditions affecting the skin such as burns and pressure ulcers. Early proactive intervention has the best chance of optimising nutritional status, well-being and wound healing in the longer term [9–12].

Breastfeeding should always be encouraged; however, rooting at the breast may cause or exacerbate facial lesions, and suckling may lead to blistering of the mouth, tongue and

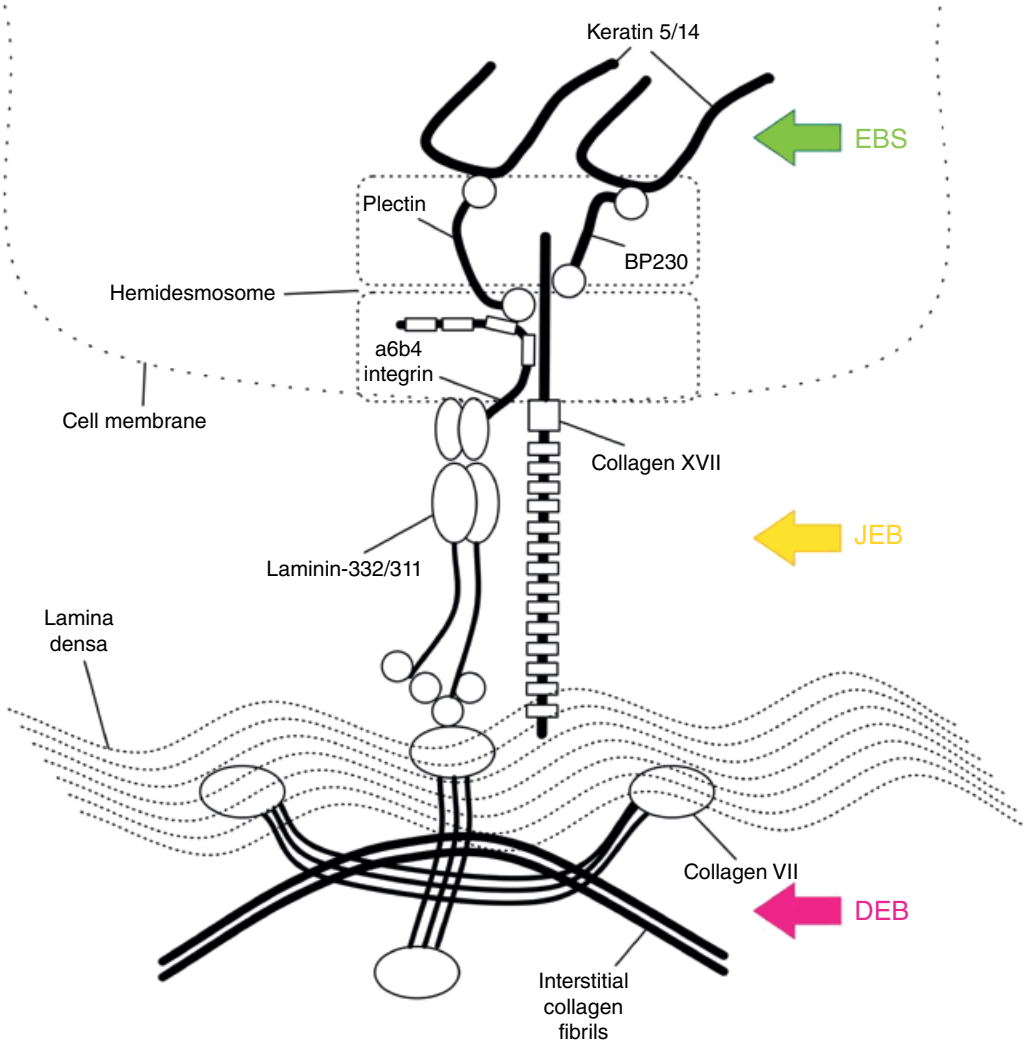

Figure 22.1 Schematic representation of the dermal-epidermal basement membrane zone. This shows the position of specific structural proteins relevant to EB. Source: Image reproduced with permission from Medscape Drugs & Diseases (https://emedicine.medscape.com), Epidermolysis Bullosa, 2018, available at: https://emedicine.medscape.com/article/1062939-overview

gums. This can be eased by applying petroleum jelly to the lips and to the nipple to reduce friction. In severe cases breastmilk may need to be supplemented to meet high nutritional requirements. Breastmilk can be supplemented with standard infant formula or hydrolysed protein infant formula if indicated. These can be either mixed with expressed breast milk (EBM) (p. 13) or given in addition to direct breastfeeding. In some cases, topping up with one or two feeds of a high energy, high protein formula may be useful. If fully formula fed, a concentrated infant formula or a commercial energy and protein-dense formula can be used (Table 1.18).

Soft silicone teats are generally better tolerated. If needed, teats can be moistened with cooled, boiled water before feeding to avoid the teat sticking to the lips and causing damage when it is removed. In addition, petroleum jelly or teething gel can be applied if needed to the teat itself before feeding. Occasionally a slightly larger teat hole may be beneficial as more milk is delivered without as much sucking effort – grading up through the size of teat hole is helpful to avoid giving too fast a flow. If feeding is very difficult due to pain and inability to form a vacuum, a 'Special Needs Feeder' (www.medela.com) may be useful as no vacuum is needed, and the carer can learn to gently squeeze the shaft of the feeder to deliver a steady flow of milk.

Weaning foods can be offered at the usual time of around 6 months (always after 4 months) of age using a shallow soft plastic spoon with rounded edges. Carers may need reassurance if progression to solids is slow and babies with an extremely fragile mouth may feed more confidently from the carer's fingertip initially. It is common to make good progress then have a short period of painful oral blistering that may stop progress all together. Carers can be reassured that this is common in EB and that, once the blister has healed, steady progress can resume. Reluctance to try new foods maybe exacerbated by gastro-oesophageal reflux (GOR) [13], a very painful mouth or nasogastric (NG) tube feeding. Scarring and tongue tethering can cause an uncoordinated swallow with the risk of aspiration [14].

There is often early aversion to food composed of mixed textures (such as the soft lumps within a more liquid matrix found in many commercial baby foods), whereas uniform

Table 22.2 Main complications influencing nutritional status and suggested interventions in some of the main types of EB.

EB type	Complications	Suggested nutritional intervention
RDEB generalised severe	Recurrent severe generalised blistering that heals poorly with scarring and contractures (causing digits to fuse). Severe growth faltering. Dystrophic or absent nails. Internal mucosal membrane scarring and contractures cause microstomia, dysphagia and oesophageal strictures. Other complications include osteoporosis/osteopenia, refractory anaemia, anal fissures, ocular issues, constipation, bowel inflammation/colitis and pubertal delay. Dental caries often requiring extractions	Significantly increased requirements for energy and protein Supplementation of certain micronutrients may be indicated including vitamins C and D, zinc, calcium and iron Gastrostomy tube feeding often indicated Specialised formula feeds and exclusion diets may be considered for severe GI symptoms Fibre and laxative management is often required
RDEB generalised intermediate	Recurrent mild–moderate generalised blistering that heals poorly with scarring and contractures (causing digits to fuse). May have a degree of growth faltering. Dystrophic or absent nails. Internal mucosal membrane scarring and contractures may cause microstomia, dysphagia and oesophageal strictures. Other complications may include mild anaemia, anal fissures, mild ocular issues and constipation	Slightly increased requirements for energy and protein Supplementation of certain micronutrients may be indicated including vitamins C and D, zinc, calcium and iron Fibre and laxative management is often required
DDEB	Mild–moderate lesions with minimal scarring. Growth may be normal. Anal fissures may cause painful and reluctant defaecation. Constipation is common. Oesophageal strictures may be problematic	Intervention is not generally indicated other than advice on healthy eating and age-appropriate increases in fibre and fluid intakes if defaecation painful Iron levels should be checked periodically
JEB generalised intermediate	Recurrent moderate to severe blisters that heal without scarring, but often very slowly. May be genito-urinary involvement. May have airway narrowing requiring MLB. Other complications may include anaemia, ocular issues, enamel hyperplasia and dental caries requiring extractions, scalp abnormalities affecting hair growth, dystrophic/absent nails	Moderately increased requirements for energy and protein Supplementation of certain micronutrients may be indicated including vitamins C and D, zinc, calcium and iron Gastrostomy tube feeding may be indicated Specialised formula feeds and exclusion diets may be considered for severe GI symptoms Fibre and laxative management may be required
JEB generalised severe	Fatal usually within 1–2 years of age. Recurrent moderate to severe and widespread lesions. Dental pain due to abnormal tooth composition. Laryngeal and respiratory complications. Initial weight gain usually followed by profound, intractable growth failure, possible protein-losing enteropathy and diarrhoea. Tissue granulation occurs, may effect nostrils	Maintain hydration, feed to appetite, address deficiencies within terminal care framework Gastrostomy placement not usually recommended as laryngeal/respiratory issues greatly complicate general anaesthesia and healing around stoma may be poor NG feeding can be discussed with the family as an option High energy, hydrolysed protein, MCT feeds may be an appropriate choice of formula Weighing can be undertaken to determine best regimen for pain relief Emphasis to be placed on quality of life Advice for weaning onto solids may be needed if appropriate
JEB with pyloric atresia	Recurrent severe blisters. May have large areas of absent skin. Complex genito-urinary involvement. May have anal, duodenal or pyloric atresia. Other complications may include renal complications, rudimentary ears, anaemia, ocular issues, enamel hyperplasia and dental caries requiring extractions, dystrophic/absent nails. High risk of infant mortality in severe cases despite early atresia repair. In milder cases who survive infancy, blistering can improve with age	Depends on severity of phenotype. Early repair of atresia. Significantly increased requirements for energy and protein (and fluid if large areas of skin missing). Supplementation of certain micronutrients likely needed including sodium, vitamins C and D, zinc, calcium and iron Enteral feeding can be considered if appropriate Specialised formula feeds and exclusion diets may be considered for severe GI symptoms Fibre and laxative management may be required in later years
EBS generalised severe	Severity of skin involvement at birth also dictates level of feeding and growth difficulties in infancy. In severe cases gastro-oesophageal reflux, malabsorption and oropharyngeal blistering may be significant and difficult to manage. Nutritional replacement of sodium, micronutrients and protein may be needed if large areas of skin are absent. Problems may lessen in late infancy/early childhood. Catch-up growth often occurs around adolescence. Painful hands and feet may reduce ability to take part in activities/physical education at school and this may lead to becoming overweight in teenage years. Anal fissures frequently cause painful defaecation often with constipation	As for RDEB generalised severe in early years, but gastrostomy placement is rarely necessary In severe cases, NG feeding is often needed initially and may lead to oral aversion Sodium, protein, fibre, iron, zinc and vitamin supplementation may be indicated Advice on healthy eating and weight maintenance/reduction may be indicated later on

(continued overleaf)

Table 22.2 *(continued)*

EB type	Complications	Suggested nutritional intervention
EBS localised	Lesions usually confined to hands and feet, especially in hot weather, often severely limiting mobility. Frequently painful defaecation with/without constipation	Intervention is generally not indicated other than advice on healthy eating and age-appropriate increases in fibre and fluid intakes if defaecation painful Due to compromised mobility, advice on weight maintenance/reduction may be indicated
Kindler syndrome	Photosensitivity. Thin papery skin with variable tendency to develop moderate to severe blisters that predominantly affect limbs and fingers (which may fuse). Other complications may include oesophageal, laryngeal, urethral and anal mucosa involvement, colitis, gingival fragility and inflammation with poor dentition. May develop anaemia. Growth faltering not common. Blistering tendency may lessen around adolescence	Intervention not generally indicated unless growth falters and/or GI complications necessitate relevant management Nutritional blood samples should be monitored at least annually

EB, epidermolysis bullosa; RDEB, recessive dystrophic EB; DDEB, dominant dystrophic EB; JEB, junctional EB; MLB, microlaryngoscopy and bronchoscopy; NG, nasogastric; MCT, medium chain triglycerides; GI, gastrointestinal; EBS, EB simplex.

textures tend to be accepted with more confidence. Hard or sharp foods such as toast, crisps or baked rusks are unsuitable as they can damage the fragile mucosa of the mouth and gums in some babies. Some bite-dissolve weaning snacks may need vigilance, so they do not get stuck to the lips, which can then cause a blister – moistening them a little first can help.

Practical information for carers and community personnel can be found in the booklets *Nutrition for Babies with Epidermolysis Bullosa* and *Nutrition in Epidermolysis Bullosa for Children over 1 Year of Age* published by the Dystrophic Epidermolysis Bullosa Research Association (DEBRA) and downloadable from www.debra.org.uk/publications. DEBRA's nutritional guidelines for the management of EB are currently being revised and will be a valuable resource once published.

The complications of RDEB in particular begin in infancy and, except in mild cases, progressively increase as the child gets older [11, 15]. The causes and effects of severe generalised RDEB on nutritional intake are shown in Figure 22.2. Factors such as painful defaecation (with or without constipation), extensive non-healing lesions, chronic infections, general skin and bone pain, anaemia, malaise and refusal of oral medications and supplements contribute significantly to the potential for profound nutritional compromise.

Nasogastric tube feeding

NG feeding maybe required in early infancy in severe cases and occasionally in some older children. The majority of older children who are considered for gastrostomy (G) placement will have one placed without a period of previous NG feeding. Internal nasal and oesophageal damage may be caused by placing the NG tube and securing the tube on the cheek should be done in consultation with an EB clinical nurse specialist. Advice can be sought on non-adhesive dressings and silicone tapes to minimise trauma

Circumstances in which NG feeding may be indicated as a temporary measure include:

- a baby's mouth becomes excessively traumatised by suckling
- not meeting nutritional or fluid requirements
- gastrostomy placement is considered appropriate, but evidence of the effects of improved nutrition are needed before surgery can be agreed

Gastrostomy tube feeding

G-tube placement is often a vital and highly beneficial method of improving the nutritional intakes of children and young adults with EB. Particular benefits are increased fluid intake, increased energy and protein intake, and increased adherence to medications, particularly laxatives and micronutrient supplements. Discussion about G-tube placement is often greeted with great concern by families as they may be worried that it is an extra burden of work and may be complicated by poor skin healing and/or become a source of potential infection. Great care and consideration of these emotive issues is needed, and multidisciplinary team (MDT) work with expert communication skills are required for sometimes long periods to talk with the patient and the family to ensure the best outcome. Ideally the idea of a G-tube should be discussed early for patients suffering with severe types of EB, as preventing a severe decline in nutritional status may benefit all symptoms and help to establish a positive balance between oral intake and intake via gastrostomy.

Dietetic review is essential to ensure the right balance of nutrition is provided by feeds, oral foods are encouraged when able, and weight gain is proportionate to good linear growth and not just creating central obesity.

In practice, patients and parents are happy with the decision to have a G-tube placed as it often improves weight gain, reduces the burden of oral medications, improves bowel function and maintains nutritional status and hydration during periods of oesophageal stricturing. A recent systematic review concluded that G-tube placement, although not risk free, is safe and effective for improving nutritional status and quality of life (QoL) in children with EB [16].

While G-tube placement has been associated with minimal complications and improved growth and bowel function, it has also been previously linked to pain, intractable leakage,

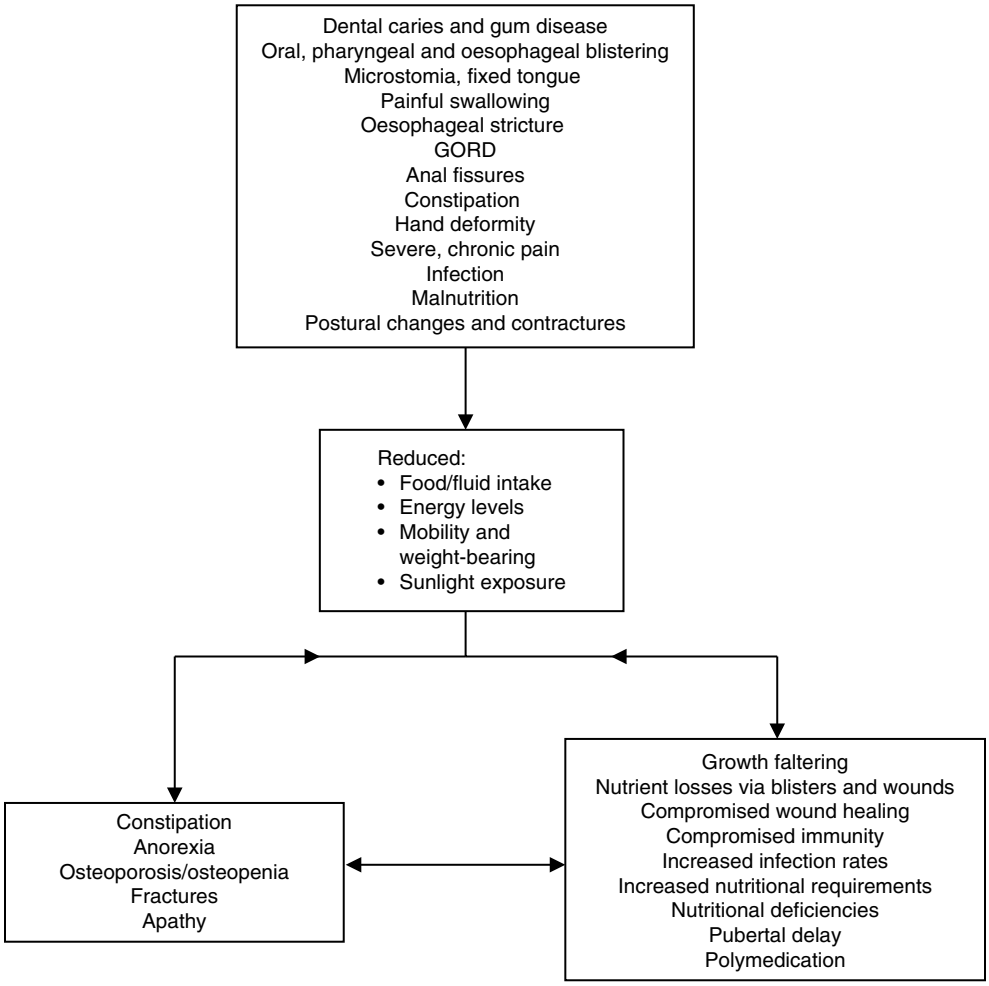

Figure 22.2 Causes and effects of nutritional problems in severe generalised recessive dystrophic epidermolysis bullosa.

infection and excoriation around the G-tube insertion site, bloating, colitis, gastro-oesophageal reflux disease (GORD) and central obesity [16–23]. Improvements in G-tube placement techniques, aftercare, proactive placement of a G-tube prior to decline to a severe malnourished state and management of constipation are all factors that may improve outcomes of G-tube placement. Pro-inflammatory cytokines are thought to play a critical role in GI complications and the central obesity, increased fat mass and poor linear growth seen in some G-tube fed children with EB [22].

Different methods are preferred for G-tube placement at the EB centres around the world. A team with experience in EB should ideally create the gastrostomy. Techniques that avoid endoscopy and risk of trauma to the oesophagus are preferred and may include open surgical gastrostomy, laparoscopically assisted endoscopy, modified laparoscopic gastrostomy and non-endoscopic percutaneous gastrostomy [22, 23]. The G-tube should have soft silicone securing material where possible. The type of tube placed and local policy will dictate if it should be rotated and how often. Some G-tubes may not need to be rotated, but just pushed gently in and out to ensure it does not become buried in the stomach wall. The tube may be replaced by a low-profile device 10–12 weeks postoperatively if the patient wishes to change it [23].

Regular review of the gastrostomy site is essential to make sure the fit is right, and over time the position of the G-tube may need to be changed to ensure it is anatomically in the most beneficial place. G-tube feeds are generally begun within 4–6 hours of surgery, initially using sterile water, to ensure absence of leakage; discharge from hospital is usually within 48–72 hours depending on progress and local policy. Parents/carers may need to be trained on feed pump use and feeding regimens, especially as often a prior period of NG feeding has not taken place.

In rare cases it may be necessary to place a gastrostomy with a jejunal extension if GOR or aspiration is severe. As with any other child, this has implications for the rate at which feeds can be given, their volume and composition (Table 4.4).

Parenteral nutrition

The use of parenteral nutrition (PN) in EB babies and children is rare but can be used for profound malnutrition when enteral feeding has failed repeatedly. Intravenous lines pose a risk of septicaemia, so PN should be considered as a last resort [18, 24].

Nutritional assessment

Measurements of weight and height velocity are the most practical means of assessing growth in EB. Weight and height (length), if able, should be measured regularly. Downward deviation from the birthweight centile in the first year is common in infants born with extensive skin loss despite intensive nutritional interventions.

Weight measurements should ideally be performed directly after or during a dressing change as wound exudates in the dressings could lead to overestimation. Although nude weight is ideal, the skin damage incurred during handling usually precludes this.

Due to pain and contractures around joints, height measurements are impractical in severely affected children. A supine stadiometer or measuring mat may provide greater accuracy. If neither of these is possible, other anthropometric measurements may be attempted if safe to do so, such as ulna length.

Despite proactive nutritional intervention, growth retardation can occur early in the course of severe EB [20, 21]. Standard growth charts should be always used with the aim that the disparity between weight and height should aim to be no greater than 2 centiles. If high requirements are met, normal growth can be achieved even in the severe subtypes of EB. Although body mass index (BMI) does not differentiate between lean and fat tissue, data from a centre with good outcomes following G-tube placement suggests it is a reliable means to monitor growth and can predict optimal timing for placement [25].

Regular nutritional assessment is important not only to address ongoing problems but also to try to prevent their severity. The proforma in Table 22.3 can be used to record relevant information.

A tool to help identify nutritional compromise (THINC) (currently not validated) has been developed as a comprehensive method of assessing the risk of actual or potential nutritional compromise in children with EB under and over

Table 22.3 Suggested proforma for recording nutritional intake and other relevant information.

Name		**DOB**	**Hospital number**		**Date**
Weight	kg	centile	**Height**	cm	centile
Consistency of food		Normal	Soft	Purée	Fluid
Reason(s)	Oral blistering		Microstomia	Fixed tongue	
	Dental caries		Dysphagia	Oesophageal stricture	
	Regurgitation of mucus/pooled secretions			Gastro-oesophageal reflux	
Typical bowel habit		BO	× day	× week	
		Pain	Bleeding per rectum	Stool consistency	
Laxative(s), prebiotic(s), probiotic(s) etc.					
Lactulose		Movicol	Sodium picosulphate	Other*	
Fibre supplement		Other prebiotic*	Probiotic*		
Typical	Breakfast				
	Snack				
Meal	Lunch				
	Snack				
Pattern	Evening				
	Bedtime				
Time taken over an average meal:		minutes	Finishes amount offered?		
Feeding tube *in situ?*		Type (including make, shaft length)			
Nutrient dense/energy dense supplement(s)/gastrostomy feeds					
Record name(s), dose, frequency					
Other supplement(s)		Record name(s), dose, frequency			
Iron	Zinc	Fluoride	Calcium	Vitamin D_3	
Other vitamins		Selenium	Other		
Approx. daily intake		Protein	g (/kg)	Normal DRV = g (/kg)	
		Energy	kcal (/kg)	Normal DRV = kcal (/kg)	
Comments/action					

DRV, dietary reference value for age and sex matched healthy child.
*Record name(s), dose, frequency

18 months of age and forms part of nutrition clinical practice guidelines written for EB, currently being updated [26]. It has been developed to aid, not replace, clinical judgement and its scoring charts rate the three key aspects of the child's state: weight and height, gastroenterology and feeding; dermatology. The higher the score, the greater is the likelihood of nutritional compromise. According to the total nutritional compromise score, algorithms suggest varying courses of action.

Biochemistry and haematology

Interpretation of laboratory results in EB children is difficult because of the inflammatory nature of the condition. Table 22.4 [27] lists investigations that should be carried out with suggested sampling intervals. Frequency may vary depending on disease severity.

Nutritional requirements

Every patient with EB has different nutritional requirements that may fluctuate. Some milder cases of EB may have close to normal requirements for energy and protein, whereas more severe cases of EB may likely have much greater requirements for energy, protein, fluid and micronutrients.

The main factors potentially compromising nutritional status in EB are:

- open skin lesions will likely lose blood, serous fluid, protein, fluids, electrolytes and heat. The body constantly attempting to heal these wounds can result in a chronic hyper-catabolic state. In addition, the risk of infection is high with such wounds that can increase requirements further
- the degree to which oral, oropharyngeal, oesophageal and GI complications limit intake
- the diversity of disease severity of patients even with the same EB type
- the variability over time of individual patients' requirements
- varying mobility levels over time and even within the same type of EB
- the difficulties associated with estimating desirable weight gain when height growth is compromised
- the presence of infection that complicates the interpretation of laboratory results
- the chronic inflammatory nature of EB characterised by continued expression of pro-inflammatory cytokines [19]

Energy

Energy requirements can be estimated using the following formula [15]:

$$\text{weight (kg)} \times (\text{kcal/kg for height age}) \times [1 + (\text{sum of 3 additional factors})]$$

Additional factors:

1. Ratio of blisters to body surface area (BSA): 20% BSA = 0.19, 40% BSA = 0.5, 100% BSA = 0.95
2. Sepsis: mild = 0.2, moderate = 0.4, severe = 0.8
3. Catch-up growth: 0.1–0.2

An example calculation using this formula is given in Table 22.5. Although this method provides a working figure, the scoring of skin involvement is subjective, and the

Table 22.4 Laboratory investigations.

Investigation	Suggested sampling intervals
Urea and electrolytes: Sodium, potassium, urea, creatinine	6 monthly unless abnormal
Urinary sodium	Every 2–3 weeks initially in severely affected newborns until corrected above 50 mmol/L, then less frequently. Older infants and children with exudate loss should have this checked approximately 6 monthly
Liver function tests Total bilirubin, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase	6 monthly
Bone profile Calcium, phosphate, alkaline phosphatase, vitamin D (total)	6 monthly
Trace elements Zinc, selenium, copper, vitamin B_{12}, vitamin A, vitamin E, vitamin C, folic acid/folate, vitamin K	Annually – unless previous deficiency
Iron studies: Haemoglobin Total iron binding capacity Serum iron Ferritin % transferrin saturation	6 monthly – may be needed more frequently depending on degree of anaemia
Full blood count (FBC)	6 monthly – may be needed more frequently depending on degree of anaemia

Table 22.5 Case study: high energy and protein requirements in a boy with EB.

A 6-year-old boy with RDEB generalised severe
Weight = 13 kg (<0.4th centile), Height = 107 cm (2nd centile), Height age = 4.7 years
He has liquid iron supplements twice a day and suffers from constipation. He has 20% body surface area (BSA) blistered, with mild sepsis. He has microstomia and after two oesophageal dilatations within a year a gastrostomy was placed. He continues to manage small amounts of food orally.
Daily requirements
Fluid requirement based on actual weight 1150 mL
Energy requirement calculated by applying the formula (p. 445): 13 × 90 × [1 + (0.19 + 0.2 + 0.2)] = 1860 kcal (7.8 MJ) or 143 kcal (595 kJ)/kg
Energy requirement based on 130–180 kcal/kg = 1690–2340 kcal (7.1–9.8 MJ)
Protein requirement based on 2.5–4.0 g protein/kg = 33–52 g
Fibre requirement = 20 g
Gastrostomy feeds
1000 mL high energy paediatric fibre containing formula, e.g. PaediaSure Plus Fibre: 152 kcal (635 kJ), 4.2 g protein and 1.1 g fibre per 100 mL
Energy = 1520 kcal (6.4 MJ) Protein = 42 g Fibre = 11 g
Feeding plan
Building up gradually to 100 mL/hour × 10 hours continuously overnight (or 2 × 200 mL boluses morning and late evening with 60 mL/hour × 10 hours overnight) depending on tolerance and family's preference
Continue to offer oral intake of foods with the textures altered accordingly. Soft foods orally with high fibre, protein and energy content should be encouraged.
Follow-up
Initially 2–4 weekly to assess feed tolerance and weight gain and then every 3 months

formula is complex. It may be that the skin involvement is not always directly observed by the dietitian at hospital review, which makes this value harder to estimate. A simpler method is to use 115%–150% of the average energy requirement for the normal population [28] in order to provide sufficient energy to promote weight gain and wound healing: 130–180 kcal (545–750 kJ)/kg actual body weight per day. Requirements may be as high as 225 kcal (940 kJ)/kg if the skin is septic or growth failure is profound.

Protein

Protein plays a most important role throughout the entire wound healing process. Collagen is the protein that is produced mainly in the healing wound of normal skin; therefore, a lack of protein decreases the synthesis of collagen and the production of fibroblasts [29]. Protein requirements in EB are estimated to be approximately 10%–15% of energy intake, extrapolated from the recommendation of 9% energy intake for catch-up growth in children with normal skin [30]. Children with extensive lesions will require an intake at the higher end of the range, especially where there is associated sepsis. Protein requirements tend to be 2.5–4.0 g/kg, 115%–200% of the reference nutrient intake [31], based on chronological age.

Micronutrients

Micronutrients are known to play essential roles in metabolism, wound healing, cellular immunity and antioxidant activity. Research in burns and pressure ulcers suggests that it may be beneficial to supplement certain micronutrients in EB [32] since deficiencies of specific micronutrients including iron, selenium, zinc and vitamins A, B_6, B_{12}, C and D have been identified [15, 17, 33]. However, the role of increased intakes of single or multiple micronutrients is unclear even in individuals with normal skin, and more work is required to identify both the clinical conditions and the doses of individual micronutrients that actively promote or accelerate healing [34, 35]. Although understanding of drug-nutrient interactions are limited, especially when body composition is altered [36], care should be taken to advise families on the timings of supplementation to maximise bioavailability of the nutrient absorption.

Vitamins

It is likely that severely affected children need increased amounts of all vitamins [33]. Babies and older children who successfully take concentrated or nutrient-dense feeds receive correspondingly increased amounts of all vitamins. In some instances additional iron and other micronutrients may still be required so serum monitoring is highly recommended (Table 22.4).

Children relying on oral diet alone are likely to require an age-appropriate multivitamin and mineral supplement. Supplements available over the counter that provide a wide range of nutrients, including iron and zinc, are preferable.

Vitamin C enhances iron absorption and promotes collagen synthesis [37]. It also plays a role in the immune response [29] through its antioxidant properties where it limits tissue

damage and prolonged inflammation [38]. Children with EB may avoid the more astringent food sources of vitamin C due to their tendency to irritate the mouth and pharynx; however, in practice many patients enjoy foods such as cauliflower or broccoli cheese bake, sweet or white potatoes, avocado, mango, berries and the less acidic fruit juices given with a meal (such as apple or mango juice). Fruit puree mixed with yoghurt or ice cream can also be enjoyed.

Where dietary intake is markedly low in fruit and vegetable content, it would be beneficial to ensure an age-appropriate multivitamin and mineral supplement is given daily, most of which will contain vitamin C.

Zinc

Zinc is an essential trace element in the human body as it serves as a cofactor in numerous transcription factors and enzyme systems including zinc-dependent matrix metalloproteinases that augment auto-debridement and keratinocyte migration during wound repair [39]. Zinc confers antioxidant activity including resistance to epithelial apoptosis, protecting membrane stability, and is important in immune function [39, 40]. Zinc deficiency of hereditary or dietary cause can lead to pathological changes, poor growth and delayed wound healing. In addition, zinc may be involved in anti-inflammatory responses with chronic zinc deficiency causing an increase in the production of pro-inflammatory cytokines [40, 41].

Most patients with severe types of EB will likely need long-term zinc supplementation due to their higher requirements for chronic wound healing. However, the degree of desirable supplementation is unclear. Generally, evidence has shown supplementation of zinc is safe and non-toxic; however, if high levels are given, it is prudent to monitor both serum zinc and copper levels to ensure the dose is not too high as excessive zinc may increase copper levels [42]. In practice, if serum zinc is very low, dosing procedure is followed as per local protocol for deficiency and levels monitored routinely. Soluble zinc tablets available on prescription can be taken orally (or via gastrostomy); it is often necessary to ensure the dose is split and taken with food or feed to reduce nausea or gastric irritation and aid absorption.

Interpretation of serum zinc results can be difficult in EB as the levels are affected by the acute phase response during periods of infection or inflammation, both of which are common in EB. In addition, a low serum albumin will also effect the serum zinc level. All of these findings will reduce the serum level of zinc [43]. Supplementing with excess zinc at this time may result in it just being excreted as the cells are saturated with zinc.

Iron and zinc have the potential to interact, leading to potentially reduced absorption of both [29]. Timings of supplements should be planned carefully to minimise these micronutrient interactions, but not increase the daily burden of poly-medication.

Immune-enhanced formulas

'Immune-enhanced' formulas containing nutrients such as arginine, glutamine and essential fatty acids are marketed for adults as promoting healing, optimising immune status and exerting a beneficial effect on inflammatory conditions [38, 44]. It has been shown in critically ill burns patients that supplementation with glutamine has reduced gram positive bacteraemia and mortality as the requirements for glutamine increase significantly during this time [44]. More studies need to be completed specifically in EB patients who have chronic wounds looking into the effectiveness of supplementing with these nutrients.

Calcium and vitamin D: osteopenia and osteoporosis

A number of mechanisms are thought to contribute to the observed low bone mineral density (BMD) for chronological age seen in children with RDEB and JEB [24, 45–47]. These include reduced mobility, poor nutritional intake, reduced sunlight exposure (from restricted outdoor activities and extensive bandaging), chronic inflammation (pro-inflammatory cytokines increase osteoclastic activity) and pubertal delay. In addition, GI complications may affect absorption of relevant nutrients [11].

Annual monitoring of all children with RDEB and JEB from 5 years of age is recommended. Lateral X-rays of the lumbar and thoracic spine and ankles are suggested to detect clinically significant osteoporosis and fractures, respectively. Dual energy X-ray absorptiometry (DEXA) scan was previously routinely undertaken; however, current practice may move away from such frequent DEXA scanning unless clinically indicated, such as to monitor impact of bisphosphonate treatment. Annual bone age assessment for adolescents with pubertal delay can also be undertaken [48].

Intravenous pamidronate and oral risedronate have been used to address bone pain associated with osteopenia, osteoporosis and fractures. However, information on their effects on BMD in this group of patients is lacking. If osteoporosis, fractures and/or low serum levels are detected, calcium and vitamin D should be supplemented and the serum bone profile monitored (p. 445).

Iron and anaemia

Children with severe EB are at high risk of chronic and severe iron deficiency anaemia through reduced dietary intake, high requirements from chronic wound healing, blood loss and possible reduced GI iron absorption. Patients often have chronic inflammation, and iron homeostasis is changed significantly during the acute phase response; iron may accumulate in the hepatocytes instead of being available for use [49]. Although iron's participation as a cofactor for antioxidants and collagen synthesis has been demonstrated, causal links between iron supplementation and improved wound healing have not been identified [38].

Haemoglobin (Hb) levels correlate very poorly with measures or markers of iron status in EB. Hepatic mechanisms respond to inflammation by decreasing intestinal uptake and release of iron into plasma. In addition, transferrin levels decrease in response to inflammation, and ferritin levels can increase. Interpretation of iron status is multifaceted, and correction of deficiency is done with care and experience.

Prescribable sodium feredetate syrup is widely used, although compliance is often poor as this can directly cause constipation, which is usually already an issue for most patients with EB. Iron ionic water supplements, iron liquid preparation and iron spray supplements are all available over the counter and can sometimes be much better tolerated and more palatable than sodium feredetate, with less GI side effects; however, these are not always available on prescription. IV iron supplementation may be necessary in children with severe chronic deficiency who are refractory to, or unable to tolerate, oral supplements. IV iron must be administered carefully under constant clinical supervision due to the risks of anaphylaxis and other potential side effects. It is often a short infusion, so this one-on-one nursing can be arranged before admission. An Hb level of <80 g/L or symptoms such as shortness of breath and extreme fatigue are taken as a signal to intervene with an IV blood transfusion. This only provides temporary benefit, and some patients may need to have a few transfusions per year to maintain a safe level of circulating Hb. Care needs to be taken when administering any IV treatment for iron deficiency anaemia so that iron overload is avoided [19].

The limited data on the use of erythropoietin (EPO) or an analogue in EB, either alone or in conjunction with IV iron, indicate that such treatments result in improvement in Hb levels and general well-being. However, the need for regular injections of EPO and its high cost limits its usefulness in routine practice for children with EB [19].

Selenium and carnitine: dilated cardiomyopathy

No clear cause of dilated cardiomyopathy (DC) in children with EB has yet been identified [50], but poor global nutritional status, chronic iron overload from repeated transfusions [51], low carnitine and selenium levels [51], concomitant viral illness, chronic anaemia, coexistent renal failure and medications (amitriptyline and cisapride) [52] have been proposed as possible contributors to its development. Most reported cases have been fatal, and to date there is no evidence that the underlying genetic mutations in RDEB have a role in the pathogenesis of DC. Annual cardiac assessment (echocardiogram and electrocardiogram and referral to a cardiologist if either of these is abnormal) should be performed in all children with severe RDEB and JEB to identify early changes leading to DC.

Serum selenium levels are difficult to interpret due to potential effects of chronic inflammation as this will falsely reduce the serum level of selenium. Fifty-five percent of children with EB-related DC did have selenium deficiency; therefore, it is important to monitor closely and supplement when appropriate [51]. Selenium supplementation reverses cardiomyopathy if started early in the disease process [51]. A liquid formulation of selenium is available on prescription, e.g. Selenase oral solution, and provides 500 µg/10 mL.

When total plasma carnitine is normal, any decrease in free carnitine should not be considered as a real deficiency and does not represent a risk for the development of DC [17]. Carnitine supplementation does not reverse cardiomyopathy, but it can prevent its progression. Carnitine deficiency should be addressed by giving 50–100 mg/kg/day Carnitor Paediatric Solution.

Painful defaecation and constipation

GI complications are present in all types of EB with up to 58% of patients presenting with some form of GI complication [53]. Painful defaecation, with or without constipation, is one of the most common of these GI problems and is seen in all major subtypes, especially RDEB. Constipation results from straining to defaecate leading to painful perianal blistering and fissures, or faecal retention due to pain or fear of defaecation. Restricted food intake or a soft blended diet, due to oral lesions, dental problems and dysphagia, may be lower in total fibre content and, therefore, may worsen constipation. This situation is exacerbated by reduced physical activity [18].

Measures to normalise bowel habit include increasing intake of fluid and fibre in the form of age-appropriate fibre-rich foods and fibre-containing feeds, and pure fibre supplements such as Optifibre or HyFibre. Stool softeners such as polyethylene glycol sachets, e.g. Movicol, Laxido, are very commonly used [54] and show very good success in most patients. To treat constipation it is optimal to give a regular dose of a smaller amount of stool softener than to give large doses and then none; getting the right dose is trial and error as every patient will require a varying amount. In young patients with mild constipation, a starting dose of ¼ sachet is appropriate once a day, building up to twice a day, then increasing the amount given gradually at these two doses. UK guidance on the fibre requirements for children now recommends between 15 and 30 g for 2–18 year olds (with no specific guidance for <2 years) [55].

Fragility of the anal mucosa means that suppositories and enemas should never be given. If clearance of faecal impaction or preoperative bowel preparation is required, an osmotic agent, given orally or via feeding tube, is preferred [24]. In the older child, overflow incontinence can be mistaken for diarrhoea, and carers often reduce or stop the prescribed laxative therapy, inadvertently exacerbating the situation. Children with faecal impaction demonstrable on abdominal radiograph must have their bowel evacuated before the introduction of a further fibre source. If such preparations are introduced while the child remains faecally loaded, abdominal pain, GOR and vomiting will ensue, and compliance will be jeopardised [11].

Constipation is very common in all types of EB patients. Occasionally, if constipation is severe and a thorough history reveals a suspicion of non-IgE mediated food allergy, then it would be worth considering a trial period of an elimination diet for 8 weeks to rule this out as a cause for the constipation.

Prebiotics and probiotics

Food groups that are natural prebiotics and prebiotic formulas and powders are generally considered a safe addition to any

child's diet and may act to potentially improve bowel function by improving overall diversity of the individual's microbiome.

Probiotics, such as probiotic yoghurt drinks, natural yoghurt or fermented yoghurt such as kefir, are popular additions to many EB family's diets. To date the author has no experience of a negative impact on the use of such products; currently there is not enough evidence to routinely advise giving probiotics to treat constipation [56]. Studies have shown probiotics to be potentially beneficial in other areas of health, such as enhancing immune function, improving colonic integrity and reducing incidence and duration of intestinal infections, post-antibiotic use and improvement in digestion and defaecation – all of which would be very desirable for children with EB. However, they have also been associated with adverse effects such as bacteraemia, sepsis and endocarditis [11]. It would be prudent to advise probiotics only in selected and carefully monitored EB children.

Sodium

In very severe cases of EB where, at birth, a high percentage of skin loss has occurred, the infant may need a period of admission in the neonatal intensive care unit (NICU). Growth can be difficult to achieve at these times, and often additional iron, zinc and other micronutrients may be necessary. Urinary sodium concentration should be measured, and if <20 mmol/L the infant should be supplemented with NaCl at 1 mmol/kg/day until the urinary sodium is maintained around 50 mmol/L. Low sodium status may have a direct impact on the ability to gain weight and should be monitored carefully. If the dose of required NaCl is very high, it is better to split it throughout the 24 hours to reduce the impact of nausea and potential vomiting.

Other issues

Bowel inflammation (colitis)

The precise mechanisms responsible for the colitis seen in EB are not yet understood, but absence of type VII collagen that is normally expressed in the colonic mucosa has been implicated. There have been reports of children with RDEB presenting with explosive diarrhoea with their histological features ranging from absence of abnormality to moderately severe inflammatory changes. The mechanism underlying these changes is uncertain, but the defective cell adhesion may result in altered epithelial cell turnover and abnormal mucosal permeability stimulating an inflammatory response [53, 57]. Children with suspected or proven inflammatory bowel disease are often treated with steroids and, if appropriate, an amino acid-based feed.

Suspicions that colitis is exacerbated by food antigens have led to regimens excluding milk, egg, wheat and soya [53] (Table 8.19). In two RDEB patients (one adult and one child), exclusion of gluten with concomitant low dose cortisone is reported to have reversed compromised renal function and proteinuria, with a reduction in skin blistering, pain, itch and improved mobility [58]. A coeliac screen is appropriate in all EB patients when displaying symptoms of anaemia, constipation and diarrhoea. More research is needed into dietary restrictions in EB with outcomes and improved QoL weighed against the difficulties of following a restricted diet and the subsequent impact on nutritional status.

Protein-losing enteropathy

Protein-losing enteropathy (PLE) and diarrhoea have been described in JEB [53], mostly in those with pyloric atresia. α-6-β-4 deficiency has been shown in an infant with total GI mucosal separation and intractable diarrhoea [59]. Hydrolysed protein feeds containing mainly medium-chain triglycerides (MCT) as the fat source have been used empirically. As in the treatment of intestinal lymphangiectasia (p. 118), the use of a predominantly MCT source of fat decreases lymphatic flow, and its use has been suggested to improve hypoalbuminaemia and to reduce levels of stool α-1-antitrypsin in JEB [53].

Gastro-oesophageal reflux disease

GORD is very common in many types of EB [53]. GORD may start early in infancy and may remain throughout childhood. Recurrent oesophageal scarring by acidic gastric contents may cause shortening of the oesophagus, which may predispose to GORD and to stiffening of the lower oesophageal sphincter, fixing it in an open position and so worsening the reflux [59]. GORD may be exacerbated by oesophageal dilatation that allows reflux of stomach contents into the oesophagus, or by the introduction of gastrostomy feeding [24, 60]

When vomiting and poor weight gain are observed, GORD should be investigated and managed in accordance with age and symptoms as in the child without EB (p. 125). Nissen fundoplication (p. 152) has been used for refractory GORD in children with EB, but there was only a temporary (<1 year) reduction of symptoms [53]. The surgery is believed to have failed owing to abnormal structure and fragility of the gastric mucosa.

Oesophageal strictures

Oesophageal strictures and dysphagia are common in patients with severe types of EB and may also be seen in patients with DDEB. Every patient's incidence of stricturing is different, even within the same type of EB. Lower oesophageal strictures are likely to be precipitated or exacerbated by GORD, whereas upper strictures probably arise from blistering related to ingestion of food. The latter tend to impose ever greater restrictions on the textures of foods that the child is able to swallow, showing dysphagia with hard or bulky foods initially, then with softer foods and eventually with liquids [24].

When an oesophageal blister or stricture is suspected, food consistency should be modified to tolerance with

nutritional supplementation. Moist foods of soft consistency are often preferred, but, if swallowing problems are more severe, foods should be puréed [15]. Sips of water between mouthfuls are helpful. Reliance on oral nutritional supplements (ONS) and milky drinks is paramount at this time to prevent an acute deterioration in nutritional status. Drinking while food is still in the mouth risks gagging and aspiration. Oral dexamethasone can be prescribed initially, which can sometimes be enough to alleviate symptoms and for the potential blister to heal. If these measures are insufficient to ensure adequate nutritional intake, oesophageal dilatation (OD) should be considered as soon as possible.

Balloon dilatation (which applies mainly radial forces), either endoscopically or fluoroscopically, has been used very successfully and can often be undertaken as a day case. An experienced team with knowledge of EB should undertake the dilatation. Endoscopic dilatation techniques all carry the inherent risk of oropharyngeal and oesophageal trauma, potentially resulting in strictures that worsen over time. Fluoroscopic-guided balloon dilatation uses larger balloons that can achieve a greater dilatation diameter. Once children are awake and alert post-procedure, they can drink. When they are comfortably able to swallow (usually within 2–4 hours), a soft diet can be given with most resuming a normal diet within 24 hours of the procedure. One potential disadvantage of this procedure lies in the repeated exposure to radiation. This is particularly significant for children with RDEB who are known to be predisposed to aggressive squamous cell carcinoma of the skin in late teenage or adulthood [61].

When oesophageal strictures are too tight to allow antegrade passage of a guide wire, or if oral contractures severely limit mouth opening, a retrograde approach through a gastrostomy may be successful. If OD is unavailable or strictures have not responded satisfactorily to this procedure, surgical interventions including colonic interposition and the resection of localised oesophageal strictures with end-to-end anastomosis (oesophago-colonoplasty) have been very rarely used. However, these procedures involve highly complex surgery and have high rates of morbidity and mortality [24]. They, therefore, remain the last resort for those whose nutritional status cannot be maintained by any other means.

Oral manifestations

Oral manifestations in children with EB vary markedly depending on the specific EB type. Features include microstomia (reduced mouth opening), trismus (spasm of the jaw muscles), ankyloglossia (fixation of the tongue to the mouth floor), malocclusion, blistering and scarring; all compromise mouth opening and the normal cleansing action of the tongue. Teeth can be structurally defective, having little or poor quality enamel that erodes easily, rendering them more prone to decay and gum disease [19].

Other factors contributing to increased dental caries include consumption of a diet high in fermentable carbohydrate, slow and frequent eating, ineffective use of a toothbrush due to pain, extreme fragility of the oral mucosa and reduced manual dexterity, side effects of some medications that cause a dry mouth, GORD and carers' capabilities [19, 62].

Dental reviews should be scheduled according to caries risk. Caries prevention is the dentist's approach of choice. This includes [19, 63]:

- dietary changes to modify when high sugar foods and drinks are consumed. These items should ideally be restricted to the end of mealtimes where possible and continuous sipping of sugary drinks outside mealtimes should be discouraged
- mechanical plaque/substrate control by brushing (using appropriate equipment and techniques), flossing, rinsing (with alcohol-free mouth washes)
- adjuvant therapies that include fluoride (in toothpaste or supplement) and chlorhexidine (in mouth washes, swabs, sprays, gels or topical varnish)
- protective covering of teeth using fissure sealants and stainless steel crowns

Exercises for maintaining mouth opening by using 'mouth expanding devices' as well as for the tongue to maintain mobility for adequate swallowing are mentioned in the literature, but the author has not seen this in practice, and the evidence for their effectiveness is lacking [64].

Pubertal delay

Malnutrition can affect the entire hormonal system (involving insulin, thyroid hormones, cortisol and growth hormone [GH] and the hypothalamic–pituitary–gonadal axis) and is a direct cause of pubertal delay [65]. Chronic inflammation mediated by cytokines causes disturbances in the pathway involving GH and insulin-like growth factor 1 (GH/IGF-1) and the hypothalamic–pituitary–gonadal axis [66, 67]. Improving nutrition and growth with the use of G-tube feeding and OD may facilitate attainment of puberty. However, the introduction of such measures after adolescence may mean that catch-up growth is not possible. Attention should be paid to the likely increased requirements in puberty, and oral or G-tube intake may need to be increased to ensure there is no a decline in nutritional status [15]. Radiographs of the left hand and wrist to evaluate bone age can assess skeletal maturation and help to confirm the picture of delay. In girls, a pelvic ultrasound scan may be helpful to assess uterine development and ovarian activity. Induction of puberty with appropriate hormonal intervention is necessary from a psychological point of view as well as to optimise peak BMD. This may prove problematic for boys as intramuscular testosterone injections may be painful and buccal preparations may be difficult to take when microstomia has led to obliteration of the buccal sulci [68]. It is important for young adults to attain puberty at around the same as their peers. Collaboration with an endocrinologist may be necessary to achieve timely puberty.

Reduced mobility

Mobility in severe EB is frequently reduced due to complications such as fixed flexion contractures, bone and skin pain and fatigue secondary to anaemia and poor nutritional status [19, 69]. When longitudinal growth falters, wheelchair dependency is more likely. Consequent lack of weight bearing compounds low BMD, and possible bone pain and fractures leads to further immobility. Maintenance of a balance between mobility, growth and nutritional status is challenging [47]. Assessment for bone fractures should be undertaken periodically or when symptomatic; however, often EB patients have a very high pain threshold and may not report the severity of pain you might expect from, say, a spinal fracture. Regular review by an experienced physiotherapist with knowledge of EB is crucial from a young age to optimise motility.

Psychological and psychosocial issues and QoL

The psychological and psychosocial issues affecting both children with severe EB and their parents can be significant. Building a rapport over time is essential for establishing a relationship where families will accept dietetic advice. Tact and empathy is needed at all times during dietetic consultations due to the significant demands of everyday life for patients with EB. Growth and eating can often be the one thing that families can work to improve, and it is very hard for families to accept that, despite their best efforts, occasionally the demands of EB are so great that extra intervention is needed. This is particularly evident when discussing the need for a gastrostomy or weight management advice in older children with EB simplex. Coping with the everyday regimen of dressing changes, lancing blisters, pain management and medication intake can be overwhelming and can greatly increase family stresses, interpersonal problems and likelihood of depression [70].

Practices, such as rewarding the child for painful procedures with sweet treats or compensating for eating difficulties by allowing a child to drink milk from a bottle for prolonged years, may be detrimental to dental health and appetite. Discussion of issues such as these should always be done carefully and with understanding of the greater priorities the family may have.

Multiple factors affect QoL for those with EB and these greatly depend on severity and age. The family burden has been found to be high independent of EB type or severity [71]. There is a validated tool to assess QoL specifically in adults with EB [72], in addition to the family burden score (EBBoD) that has been developed for families with children with EB [73]. A study has found that children with severe EB express five main areas of distress: continually itchy skin, pain, difficulties in participation with peers, lack of understanding by others and being different [74]. All these can impact on nutritional intake, either directly or indirectly. Early intervention with a psychologist is optimal to help patients and their families develop coping strategies and deal with the changing stresses that growing up with EB can involve.

Transition from paediatric to adult care

For young people with any severe form of chronic illness, transition to adult services is a major life event involving the loss of lifelong trusted professional carers [75]. With EB, increasing age and transition may be perceived as moving a step closer to increasing and worsening of complications, the potential development of terminal metastatic squamous cell carcinoma [76] and death [70], highly sensitive issues that are openly discussed.

Awareness of potential transition-related problems is paramount, and protocols should be in place to minimise them [77]. EB clinical nurse specialists are key in liaising between parents, patients and healthcare professionals in the hospital and community settings, and good communication between all concerned should ease the transition process.

It is important that a comprehensive history is provided by the paediatric dietitian at the time of transition, such as:

- a summary of relevant medical history including oesophageal dilatations, bowel pattern, iron, bone, mobility and dental status
- a growth chart, ideally from birth, details of supplements tried and rejected
- if G-tube fed details of brand of device, dimensions, when placed/changed, ordering procedure, problems encountered, details of current feeds and feeding regimen
- current medication regimen including vitamins and minerals, orally or via gastrostomy
- contact details for general practitioner and any other relevant key professionals
- social details – family dynamics, educational stage, career ambitions and hobbies

Future research needs

There are many specialist EB centres worldwide. Establishment of collaborative studies between them greatly facilitates improved practice in several areas:

- macro- and micronutrient requirements for children with severe EB
- appropriate biochemical and haematological monitoring in order to implement and evaluate nutrition support
- validation of THINC (p. 444)
- minimising the adverse effects of the inflammatory process in EB as chronic inflammation impacts on anaemia, osteoporosis and abnormal body composition
- role of dietary exclusion regimens in the potential reduction of bowel inflammation
- role of pre- and probiotics in promoting gut health and immune status in EB
- techniques to better manage oesophageal disease and stricture prevention

Harlequin Ichthyosis

Introduction

Harlequin ichthyosis (HI) is the most severe subtype of all the autosomal recessive ichthyoses [78]. HI presents with a severely compromised skin barrier. It is caused by mutations in the *ABCA12* gene leading to defective lipid transport [78]. Newborn infants present with ectropion (outwardly turned eyelids) and eclabium (outwardly turned lips), and the skin is formed of dense white scales separated by deep fissures [79]. Families may find it difficult to bond with the infant due to their appearance. HI often goes undetected prenatally [78] as the skin changes are only evident in the second trimester and may only show on a 3D scan undertaken by an experienced sonographer.

Historically, HI diagnosis has had a very poor prognosis, often families being offered just palliation. However, with greater awareness of the condition and good multidisciplinary working, including medical, nursing, dietetic, occupational therapy, physiotherapy, social work and psychology, long-term survival rates have significantly improved [79]. The main medical management consists of treatment with retinoid therapy (acetretin), which is a synthetic form of vitamin A.

The main risks to infant survival are severe hypernatraemic dehydration, sepsis, respiratory failure and malnutrition. Infants with HI need immediate transfer to a level 3 NICU where possible and placed into an incubator with high humidity [79]. Narcotics may be appropriate for pain relief [79]. Twice-daily baths to promote shedding of scales and frequent application of bland emollients (or wet wraps) are essential to stabilise the skin [79]. Antimicrobial technique is essential when applying any product to the skin: application with a clean spoon, dispensing cream into a clean bowl each time, wearing sterile gloves, etc. A central line maybe needed to administer fluids, PN or antibiotics. The risk of line infection is very high, and close monitoring and swabbing are needed with targeted antibiotic treatment as per local policy.

Nutritional requirements and feeding

Trans-epidermal water loss (TEWL), high skin turnover and infection all act to increase nutritional requirements for energy, protein and fluids. The thickened plaques of skin may restrict chest expansion and increase work of breathing too, which in turn can increase energy requirements [79]. Eclabium and restricted jaw movement can lead to poor vacuum suckling/sucking, which can prevent breast or bottle feeding initially and can result in tiring on feeding. Due to this orogastric or NG feeding should be commenced as soon as possible as it may be very difficult to meet nutritional requirements solely with oral feeds for several months. Often the mouth will improve gradually, and oral feeding should be retried at frequent stages to encourage this where possible. Breastfeeding is always encouraged and can help to build a maternal bond [80].

In clinical practice energy requirements appear to be higher than normal; however, there is no data on basal metabolic rate (BMR) or energy requirements in these infants. A range of 130–170 kcal (545–710 kJ)/kg/day in the first 3 months would be an appropriate target.

Infants have very high fluid requirements and may require 180 mL/kg/day on average, and occasionally this might increase to 200–220 mL/kg/day to maintain serum sodium levels within the normal range during particularly difficult times. During episodes of infection or vomiting, dehydration can quickly occur, and a low threshold for IV fluids or NG feeding (if not already established) should be encouraged.

Protein requirements are higher than normal; however, there are no data on the amount needed and will depend on the severity of the disease at presentation; 4.0–4.5 g/kg/day may be needed. Renal function should be monitored and protein intake graded down if indicated.

Nasogastric feeding

Placement and securing of NG tubing can be a difficult challenge. Due to the frequent application of emollients, sometimes 2 hourly, it is difficult to get dressings to stick to the cheeks to secure the tube. In addition, the nostril may be narrow or blocked with skin, and this may present further complications.

Techniques to secure a feeding tube:

- The 'lasso' technique: This involves cutting a 2–3 cm loop band of 'Tubifast' or similar dressing. This is then passed over the head so it is secure, paying attention to the nasal septum and the soft issue of the ear to ensure it is not rubbing. The NG tube is then passed as usual, and the external portion can be spiralled around the lasso over one ear. To keep the tube more secure, a soft hat, with a hole made for the tube, can worn by the infant if needed. Close monitoring is necessary to ensure the tube is in the correct position. This technique should be used with caution in mobile babies or older children.
- The 'dressing sandwich' technique: This involves bathing the cheek as usual, but not using emollients in the area to be dressed. A dressing such as 'Duoderm' is put underneath the tube, then multiple pieces of 'Duoderm' are stuck on over the top of the tube. This dressing will need changing daily if it peels away.

Gastrostomy placement

Due to the difficulties in maintaining the position of a NG tube, coupled with the chronically high nutritional requirements, a

gastrostomy can be considered very early on and has proved highly successful.

Tolerance of feeds

The high volume of feeds required can often be difficult to tolerate. GORD and vomiting is common and can be treated with anti-reflux medications as per local policy. Patients may present initially with steatorrhoea, together with raised faecal calprotectin levels and severe exocrine pancreatic insufficiency requiring administration of pancreatic enzyme therapy. Measurement of faecal calprotectin and faecal elastase could be warranted to rule out malabsorption in early life and rechecked at periods throughout infancy and childhood. Breastfeeding or giving EBM should be encouraged (if tolerated) and made a priority. If no malabsorption is suspected or identified and additional energy and protein is required, fortification of EBM with standard infant formula or the use of energy-dense formula is indicated. If additional energy and protein is required and the infant does have malabsorption, EBM can be fortified with the addition of an extensively hydrolysed protein formula or amino acid-based formula; and/or a liquid high energy, high protein extensively hydrolysed formula can be used. If an amino acid-based formula is required, then the feed concentration will need to be gradually increased to provide a higher energy and protein intake.

Prolonged continuous tube feeding is often needed for the infant to tolerate the high fluid volumes required. Wherever possible oral feeds should be offered in breaks from continuous feeding to enable maintenance of oral feeding skills.

Weaning onto solid foods can be started as per normal guidelines and may often be enjoyed as a positive interaction between the parents and the baby. This may also reduce the volume of feed needed slightly and can help ameliorate symptoms of GORD.

Growth may be delayed due to chronic inflammation and high requirements and careful and ongoing dietetic monitoring can help to optimise growth and nutritional status of patients with HI. Patients can often have their gastrostomies closed as they get older and are able to meet their requirements orally.

Nutritional monitoring

Close attention needs to be paid to monitoring nutritional parameters:

- Serum electrolytes need to be monitored closely in the initial period. Hypernatremia can occur quickly if fluid requirements are not met
- Serum albumin may be chronically low due to protein losses via the skin. Stabilisation of the skin will improve this. The addition of extra protein to feeds may be warranted
- Sodium (Na) losses can occur through the skin and when serum Na levels are stable it may be appropriate to supplement with Na if urinary Na is <20–30 mmol/L as per local policy
- Vitamin D levels can quickly become deficient, and supplementation should be started prophylactically. Levels should be monitored 3 monthly initially, then annually. Vitamin supplements containing vitamin A should be avoided as this can be contraindicated when having retinoid treatment
- Iron levels often need supplementing. Liquid iron supplementation should start as per local policy
- C-reactive protein (CRP) levels will often be high, and this may artificially show a reduction in serum zinc and selenium. Careful monitoring is vital and if levels continue to fall then supplementation is needed

Copper transport in ichthyosis

An autosomal recessive disorder of copper metabolism characterised by mental development delay, enteropathy, deafness, neuropathy, ichthyosis and keratodermia (MEDNIK) has been recently described with patients presenting with significantly low serum copper levels and ichthyosis. A mutation in the affected gene *AP1S1* causes abnormal intracellular copper trafficking, which subsequently affects copper-dependent enzymes leading to the symptoms of MEDNIK syndrome [81]. Copper may accumulate in the liver and brain tissue causing symptoms of copper overload despite clinical serum copper deficiency. Liver function tests, brain MRI and treatment with zinc acetate (to treat copper overload) are suggested starting points for treatment [81, 82]. Treatment with copper supplements should be avoided until a full diagnosis is made, and it can be ensured that additional copper is not going to worsen the symptoms of copper overload.

It would be good practice to check the serum copper levels in all patients with ichthyosis to ensure this condition is not missed.

Netherton Syndrome

Introduction

Netherton syndrome (NS) is a rare autosomal recessive skin disorder, which presents with severe erythroderma, skin inflammation and scaling, hair shaft abnormalities and allergic manifestations [83]. NS is caused by loss of function mutations in *SPINK5* (serine protease inhibitor of Kazal type-5) encoding *LEKTI-1* (lympho-epithelial Kazal type-related inhibitor type-5), which regulates skin barrier and immunity [84].

There is a clinical spectrum of severity in NS. Some infants may be born with severe NS with approximately 75% of skin affected. These infants are at very high risk of hypernatraemic dehydration, and there is often great difficulty with establishing feeding and hence optimising their growth. Historically, the survival rate for severely affected infants was poor, compounded by a lack of recognition of their condition and being misdiagnosed and, hence, not getting adequate treatment. Some infants with NS may present with a milder phenotype, with less than 25% of skin affected. These infants may establish feeding more easily, with a good growth projection. They may not get diagnosed as early as the severe type and may be misdiagnosed with atopic dermatitis.

The main risks to survival are severe hypernatraemic dehydration, hypoalbuminemia, enteropathy, infection, poor body temperature control, sepsis and malnutrition. Nursing or parental care to ensure twice-daily baths and frequent application of bland emollients is essential to stabilise the skin. Antimicrobial technique is vital when applying any product to the skin: application with a clean spoon, dispensing cream into a clean bowl each time, wearing sterile gloves, etc. Due to the reduced integrity of the skin barrier, topical medications are absorbed very readily, so topical steroids may be contraindicated.

Greater awareness of NS and good MDT working has improved survival rates significantly. The main difficulties and risks to survival present in early infancy; after 1 year of age the acute nature of the medical and dietetic intervention may stabilise somewhat, although the condition is lifelong and requires daily dedication to the skin care regimen.

All patients with NS are at high risk of developing IgE (immunoglobulin E)-mediated allergies, which does not appear to correlate with severity of skin affected. A characteristic feature of NS can be an exponentially increasing and very high total serum IgE level [85], although this may not always present early in infancy.

Infants are often born prematurely between 34 and 37 weeks' gestation with their weight between the 2nd and 50th centiles. Almost all patients will display faltering growth within 3 months of birth, with many faltering until at least 1 year of age. Patients with severe disease often have chronic inflammation, which has a negative effect on growth. Patients with the milder phenotype may display good growth within normal parameters.

Early nutritional intervention and monitoring may prevent poorer growth later on. Some late presenting patients, although stable, may present with chronic severe faltering growth and in some cases acute protein-energy malnutrition (PEM) [84]. The number of infections, allergic disease, enteropathy, use of steroids and endocrine abnormalities may all impact on growth projection [86]. More research is needed into the impacts on growth outcomes in NS patients.

Nutritional requirements

TEWL infection and high skin turnover all significantly increase nutritional requirements for fluids, energy and protein. Patients are at greater risk of sepsis, which can also increase requirements and reduce feed tolerance. In severe cases in early infancy, steatorrhoea, diarrhoea and poor feed tolerance with very high fluid requirements can make dietetic management very difficult. Breastfeeding can be established successfully from birth and should be encouraged if tolerated well. Breastfeeding may transfer important immune complexes to the infant. Breastfeeding or giving EBM should be made a priority, and if EBM is used, this can be fortified as described above (p. 440).

Fluid requirements are higher than normal due to TEWL and tend to remain very high throughout life. In infancy, the volume required to maintain sodium in the normal range may be approximately 200–220 mL/kg/day. To achieve and tolerate this high volume, an orogastric or NG tube is often needed. Older patients often display high thirst levels and enjoy drinking of large quantities of water, potentially impacting on appetite and nutritional intake.

During episodes of infection or vomiting at any age, dehydration can quickly occur, and a low threshold for IV fluids or tube feeding (if not already established) should be encouraged. Adolescent patients who have been stable for many years can become unwell with infection and quickly become severely hypernatraemic, requiring hospitalisation.

Energy requirements are higher than normal; however, to date there is no evidence as to exactly what requirements might be. A range of 130–170 kcal (545–710 kJ)/kg/day in the first 3 months would be an appropriate target. In severe cases of NS with extreme faltering growth, supplementary feeding with a high energy, high protein formula is usually indicated. The initial presentation of steatorrhoea, diarrhoea or carbohydrate malabsorption secondary to enteropathy and/or severe exocrine pancreatic insufficiency, seen in severe cases, requires administration of pancreatic enzyme replacement therapy. Tests, such as faecal calprotectin, sugar chromatography and faecal elastase, could be warranted to rule out malabsorption in early life and rechecked at periods throughout infancy and childhood. These GI disorders may improve with time, and therapy can be weaned off. Growth may be severely delayed in such cases, and amino acid-based formulas with a high percentage of MCT are likely to be required. Refeeding syndrome risk may be high when changing formulas so should be managed carefully.

PN may be necessary in some cases; however, risk of line infection is very high. It is often difficult to maintain a sufficient intake due to the increased risk of infection from bacterial presence on the skin.

Protein requirements may be higher than normal due to skin losses, although there is no data on the amount needed, and will depend on the severity and stabilisation at presentation. The protein-energy ratio of the diet needs to be maintained at an appropriate level and a protein intake of 4.0–4.5 g/kg/day has been needed in some patients. Renal function should be monitored and protein intake graded down as necessary. Liquid high energy and high protein extensively hydrolysed formulas can be effective if malabsorption is identified or suspected. If amino acid-based feeds are required, then the concentration will need to be increased to provide a higher energy and protein intake.

GORD and constipation are common from infancy and throughout life. Anti-reflux medications can be used as per local policy. Constipation is likely secondary to difficulty in maintaining a high fluid intake. Increasing fibre intake, using regular stool softeners and increasing fluid intake is often successful in achieving a regular bowel motion. Weaning can be started as per normal guidelines and may often be enjoyed as a positive interaction between the parents and the baby. This may also reduce the volume of feed needed slightly and can help ameliorate symptoms of GORD.

Early gastrostomy placement can be life-saving and essential to maintain good nutritional status. Most patients have been able have the gastrostomy tube removed a few years after placement when intake has stabilised sufficiently. Some patients may benefit from prolonged use of a gastrostomy if helpful for optimising fluid intake.

Nutritional monitoring

Close attention needs to be paid to monitoring nutritional parameters:

- Vitamin D supplementation is essential, and rickets has been observed in older patients with NS. Levels can be monitored 3 monthly initially, then annually throughout childhood
- Iron levels may need supplementing in infancy as per local policy
- Zinc, selenium and copper should be monitored annually. A general multivitamin supplement for children containing iron and zinc may be sufficient to maintain levels in childhood
- Electrolytes need to be monitored closely. Risk of hypernatraemia needs to be balanced with supplementing with sodium chloride (NaCl) if the urinary Na is <20–30 mmol/L (depending on local policy) to ensure adequate growth
- Serum albumin may be chronically low due to protein losses via the skin, particularly in infancy. Stabilisation of the skin and the addition of protein to the diet or feed may be beneficial in severe phenotypes

Allergy

Allergic manifestations can show in approximately 75% of all NS patients due to the diminished skin barrier, with no correlation to severity of skin involvement. These include: eczema, rhinitis, urticaria, pruritis (itch), asthma, angioedema and anaphylaxis [84, 87]. Patients may have a normal total serum IgE level at birth, often increasing significantly on each sequential measure with total serum IgE ranging from 300 to 7000 kU/L. Due to the very high total serum IgE levels, specific IgE levels can be hard to interpret correctly and may often show false positives [88]. Symptom history is very important to ensure foods are not removed from the diet unnecessarily. Skin prick testing is often contraindicated due to damaged skin. Antihistamine medication is often used to reduce itch and patients may have allergies to a wide range of foods, environmental antigens and animal dander. In the author's cohort the most common proven allergenic foods are nuts, eggs and fish, but patients have reported many foods to elicit allergic reactions including milk, wheat, soya, watermelon, coconut, kiwi fruit, berries and cantaloupe melon. In very severe cases where an infant is having breastmilk and has acute faltering growth, dehydration and GI involvement, the removal of allergens from the maternal diet may be indicated to attempt to stabilise the patient's skin and any GI inflammation. There is no literature to support this in NS. More research is needed to identify if allergen avoidance in early infancy or early introduction of allergens would be helpful to reduce later onset of allergic manifestations in NS.

Acknowledgements

The author wishes to thank Dr Anna Martinez for her medical expertise and help guiding the writing of this chapter and to all the remarkable children and young adults living with EB and rare dermatological conditions. Thanks to Rosie Jones and Lynne Hubbard for their ongoing collaboration and shared passion for this area of dietetics. Thanks also to Lesley Haynes and Melanie Sklar for their dedicated work and previous edition of this chapter.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

23 Burns

Helen McCarthy and Jacqueline Lowdon

Introduction

A review of the international Burn Injury Database (iBID) for England and Wales report estimated that between 2003 and 2011 the proportion of children under 16 years of age contributing to admissions for a burn injury increased from 42.8% to 48.2%. The majority of these were a result of contact burns or scalds [1].

Assessment of injury

Thermal injury can be classified in a number of ways but includes contact, flame, electrical and chemical burns as well as scalds [2]. The main causes and types of thermal injury in children and adolescents are listed in Table 23.1. The most common injury reported in children is a scald with contact burns almost as common. Of all admissions for children under the age of 16 years, scalds accounted for 52.9% and 60.2% (males and females, respectively), while contact burns accounted for 21.2% and 19.1% (males and females, respectively) [1].

It is well documented that the size and depth of a thermal injury has a direct impact on morbidity and mortality [3, 4]. Burns are dynamic injuries that are rarely uniform in depth and, therefore, require continual reassessment [2, 5].

Burn depth is generally classified as partial or full thickness. Partial thickness injuries are further subdivided into superficial, where only the epidermis is affected; superficial dermal, where the injury extends through the epidermis into the dermis and blistering is observed; and deep dermal, where the injury extends through the dermis, but does not infiltrate the subcutaneous tissue [5].

Burn size relates to the surface area affected by the injury. There are a number of ways to assess burn size. The simplest method is the 'palmar surface', which is based on the palm of the patient's hand (including fingers) being approximately 0.8% of the total body surface area (TBSA) [5]. This method works well with small injuries, but with increasing wound size becomes less accurate. In adults the Wallace 'rule of nines' is commonly used, and this has been adapted for children (Table 23.2) [5]. The most common method for determining burn size in children is using the Lund and Browder charts, which have been reproduced in many formats since originally proposed in 1944 [5–8].

The severity of an injury combines the depth, size and other factors. In children severe injury can be classified as:

- a major burn, defined as a full thickness injury covering an area of >10% TBSA
- a partial thickness burn injury of >20% TBSA
- burn injuries to the eyes, ears, face, hands or feet or other areas that are likely to result in functional impairment
- burns complicated by another major trauma or inhalation injury [4]

Metabolic response to burn injury

Thermal injury results in a marked change in metabolism that is reported to last up to 12 months or longer depending on the severity of the original injury [9–12]. Initially there is a reduction in metabolic rate that lasts 3–5 days. This is the 'ebb phase'. During this period there is evidence that the requirements of the child fall below the estimated average requirements (EAR) for age [13]. This is then followed by the hypermetabolic 'flow phase' that is associated with physiological, endocrine and immunological changes [9–12, 14, 15]. The exact cause of the hypermetabolic response remains poorly defined; however, catecholamines, corticosteroids and inflammatory cytokines are primary mediators with raised levels being observed for an extended period

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

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post-injury [14]. Hypermetabolism affects glucose, fat and protein metabolism. Burn-induced hyperglycaemia can have significant detrimental effects; elevated triglycerides have been associated with poor organ function, and the up-regulation of protein catabolism with associated muscle weakness prolongs the need for ventilation and can result in prolonged growth delay [16].

Modern medical and nursing management has had the effect of moderating the hypermetabolic response to the burn injury [10, 14]. These include early excision and grafting, increased use of artificial skin and other novel wound coverings, regular analgesia, control of ambient temperature, and nutritional intervention [15, 17, 18]. Nonetheless the metabolic response remains elevated, and evidence clearly links this to the extent of the injury and, in children, their age and sex [19–21].

Table 23.1 Causes and types of burn injury.

Type of burn	Cause of burn
Water	Kettle, teapot, cup, mug, bath, saucepan
Contact	Radiator, iron, oven, hot water bottle, hair straighteners
Flame	House fire, chip pan, electric/coal fire, barbecue
Fat	Chip pan, oven trays
Chemical	Cement, hair dye, cleansing agents, cytotoxic drugs
Electrical	Electrical appliances, overhead and underground cables
Other	Overexposure to radiotherapy, frostbite, animal manure

Aim of nutritional support

The aim of nutritional support in a child with a thermal injury is to provide appropriate intervention in order to moderate the hypermetabolic response, promote optimal wound healing and maintain normal growth. It is well documented that improved nutritional status in the critically ill patient reduces the likelihood of complications (e.g. infection, poor wound healing) and length of stay in hospital [22–24].

Nutritional requirements

Factors influencing the nutritional requirements of a child with a thermal injury are listed in Table 23.3. A full assessment of nutritional requirements should be made taking these and any additional factors, such as surface area used as donor sites for skin grafts, into consideration. As thermal injuries are dynamic, regular reassessment and adjustment of regimens is essential to achieve optimal outcomes for patients.

Energy requirements

Several researchers have investigated energy requirements in children with thermal injuries. Although the gold standard method for estimating energy requirements would be to measure them daily using indirect calorimetry and adjusting all nutritional support to meet these figures, this is often impractical. Calculations have been proposed to estimate energy requirements, and, while these are commonly used in

Table 23.2 Methods of quantifying burn surface area.

	Wallace 'rule of nines'		Lund and Browder					
	Adult	Child	<1 year	1 year	5 years	10 years	15 years	Adult
Head (front and back)	18%	9%	19%	17%	13%	11%	9%	7%
Neck (front and back)			2%	2%	2%	2%	2%	2%
Chest/trunk (front)	18%	18%	13%	13%	13%	13%	13%	13%
Back/trunk (back)	18%	18%	13%	13%	13%	13%	13%	13%
Arm (front and back)	9%	9%						
Upper arm (front and back)			4%	4%	4%	4%	4%	4%
Lower arm (front and back)			3%	3%	3%	3%	3%	3%
Hand (front and back)			3%	3%	3%	3%	3%	3%
Perineum	1%	1%						
Genitalia			1%	1%	1%	1%	1%	1%
Buttocks (both)			5%	5%	5%	5%	5%	5%
Leg (each)	18%	13.5%						
Thigh (front and back)			5.5%	6.5%	8%	9%	9%	9.5%
Lower leg (front and back)			5%	5%	5.5%	6%	6.5%	7%
Foot (top and bottom)			3.5%	3.5%	3.5%	3.5%	3.5%	3.5%

Source: Adapted from Hettiaratchy and Papini [5].

Table 23.3 Factors influencing nutritional requirements.

Age
Sex
Weight
Height/length
Pre-injury nutritional status
Current nutritional status
Percentage burn surface area
Thickness of burn
Grafted area
Extent of healing
Comorbidities

Table 23.4 Formulas for energy requirements.

Hildreth/Galveston equations [28]	
Infants <1 year	2100 kcal (8.8 MJ)/m² TBSA + 1000 kcal (4.2 MJ)/m² BSA
Children <12 years	1800 kcal (7.5 MJ)/m² TBSA + 1300 kcal (5.4 MJ)/m² BSA
Children >12 years	1500 kcal (6.3 MJ)/m² TBSA + 1500 kcal (6.3 MJ)/m² BSA
Curreri Junior equations [29]	
Infants <1 year	RDA + 15 kcal (0.063 MJ)/m² BSA
Children 1–3 years	RDA + 25 kcal (0.105 MJ)/m² BSA
Children 4–15 years	RDA + 40 kcal (0.167 MJ)/m² BSA
Scofield equation [30]	
Girls 3–10 years	(16.97 × wt) + (161.8 × ht) + 371.2
Boys 3–10 years	(19.6 × wt) + (103.3 × ht) + 414.9
Girls 10–18 years	(8.365 × wt) + (465 × ht) + 200
Boys 10–18 years	(16.25 × wt) + (137.2 × ht) + 515.5

TBSA, total body surface area; BSA, burn surface area; RDA, recommended dietary allowance; wt, weight in kg; ht, height in cm.

clinical practice, there is some evidence to suggest their accuracy is limited [25, 26].

Energy requirements in children with burns rarely rise above the EAR in the first 24 hours post-burn injury [13, 27]. Therefore, it may be reasonable to aim for the EAR for age initially for all injuries, particularly those classified as minor or of a small surface area. Commonly used formulas for estimating energy requirements for children are detailed in Table 23.4. These include the Curreri Junior formula and the Galveston or Hildreth formula, which have been recommended for some time [28, 29, 31–33]. There is recognition that these formulas can overestimate energy requirements and provision of excess energy and/or protein has been shown to have detrimental effects on outcomes [34, 35]. Current guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) [35] suggest that the Schofield equation [30] may be the most suitable for children, but acknowledge that this is a fixed equation and will not integrate change over time. With the exception of the Schofield equation, these formulas require an estimate of body surface area and burn surface area. There are a number of equations to aid with this estimation, but the simplest is probably the Mosteller formula [36]:

$$\text{Total body surface area} = \sqrt{\left[\left(\text{weight kg} \times \text{height cm}\right) / 3600\right]}$$

Any formula is only a guideline and provides a starting point for estimating requirements. As already stated, thermal injuries are dynamic and require frequent reassessment and amendment of nutritional requirements.

Protein requirements

Protein requirements for children with burn injuries remain unclear, but it is evident that these will be increased above the recommended nutrient intake (RNI) for age [37]. The hypermetabolic response to the thermal injury results in an up-regulation of protein turnover with both protein catabolism and synthesis being increased. Losses of lean muscle mass and negative nitrogen balance have both been recognised in studies investigating the nutritional needs of this patient group [38, 39]. Cunningham *et al*. suggest that appropriate wound healing is achievable in children receiving 2–3 g protein/kg/day [32]. It has also been suggested that higher protein intakes may have beneficial outcomes in thermally injured children [38, 40]. However, a recent review by Herndon and Tompkins states that protein intakes of 3 g/kg/day may raise urea production without improvement in muscle protein synthesis [10].

Protein synthesis, as well as wound healing, does appear to be improved when relatively higher protein provision is made in combination with anabolic agents such as growth hormone and oxandrolone [14, 15, 41]. Studies have reported improvements in lean muscle mass, wound healing and scarring at 2 years post-injury when recombinant human growth hormone (rhGH) is administered during the hospitalisation, although its use is not without side effects [15, 16]. Oxandrolone has similarly been shown to have beneficial effects on lean muscle mass, muscle strength and bone mineral density [41].

Several amino acids become conditionally essential following trauma, particularly burn injuries, including glutamine, arginine, histidine and cystine [24]. Most of the research into supplementation of specific amino acids has focused on glutamine and arginine [42–44]. Current evidence suggests that while there are benefits to supplementation of major burn-injured patients with glutamine, supplementation with arginine does not appear to provide any benefits despite the role it plays in wound healing [45]. Recommended levels of supplementation for glutamine have not been established for children, although deficiency has been reported and further research is required in this area [46]. Currently a large multicentred trial is being undertaken to establish the role of glutamine supplementation in burn injuries [34].

Moderate hypoalbuminaemia is common in children with thermal injuries, and this can be well tolerated. Increasing protein provision above that recommended in the literature has little impact on this. However, it has been suggested that if the serum albumin level falls to <25 g/L, then albumin infusions should be considered [24, 47].

Vitamin and mineral requirements

Vitamin and mineral requirements at the varying stages of recovery from a thermal injury are still very much under debate and very few studies specifically look at the requirements for vitamins and minerals in children. Animal models and studies in adults suggest that requirements are increased for certain vitamins and minerals due to their role in the metabolic pathways of the body. When assessing the nutritional requirements in burns patients, the following should be considered:

- Deficiency in vitamins A, E and C has been reported [48]. This deficiency would appear to respond well to enteral supplementation. The benefits of routine supplementation over and above meeting the RNI when deficiency is not present has yet to be proven, with the evidence presently equivocal in this area [49].
- B group vitamins are required proportional to energy intake; however, little research has been undertaken so there are no clear recommendations other than ensuring nutritional adequacy.
- Low levels of serum iron in most cases are not diet related and may have a protective effect against infection. Supplementation should be closely monitored in relation to transfusions and status [50].
- Both zinc and copper have been shown to be depleted in serum following thermal injury. Copper supplementation can result in increased urinary losses; similarly, the role of zinc in the up-regulated inflammatory processes suggests that redistribution rather than deficiency may explain low serum levels [50, 51].

In recent years an increased incidence of fractures has been reported in children post- burns injury raising awareness of vitamin D deficiency in this group. It has been suggested that risk factors for vitamin D deficiency include lack of sunlight exposure, reduced intake and poor absorption post-injury, coupled with a pre-injury insufficiency [52, 53]. Current evidence suggests that standard supplementation of vitamin D is not sufficient to correct deficiencies seen in burn-injured children; however, the provision of therapeutic doses routinely has not been proven [54–56].

While it is generally recommended that multivitamin supplementation be given as standard, the enteral route has limitations as the route of administration and doses required are unclear for many of the key micronutrients [34, 35, 57]. Before a vitamin and mineral supplement is considered, it is important to check the nutritional composition and bioavailability of enteral and/or parenteral nutrition (PN) intervention, in conjunction with the biochemical status of the child. Excessive routine supplementation with a multivitamin and mineral preparation may result in a nutritional imbalance and potential toxicity, as well as interference with the utilisation of other nutrients.

Novel substrates

Novel substrates include immune-enhancing nutrients such as antioxidants, omega-3 fatty acids, glutamine, arginine and nucleotides. The limited number of studies has focused on use in adults, and much of the available research has used heterogeneous intensive or critical care unit patient groups, which include a small number of thermal injury patients [58]. As such the current recommendation is that immune nutrition is not used in children [59].

Antioxidant therapy (vitamins A, C, E) has been shown to reduce burn and burn sepsis mortality in adult burns patients [60]. Omega-3 fatty acids may impact on immune response and wound healing, although the anti-inflammatory properties have led to confounding results in some studies [58, 61]. The potential therapeutic benefits of specific amino acids, e.g. glutamine, requires more research to establish appropriate supplementation levels in children [34, 46].

These substrates are usually provided in combination rather than individually, and early studies have suggested some benefits both in terms of the immune-enhancing nutrients included and in the ratio in which they are presented alongside macronutrients [62, 63].

Meeting nutritional goals

Additional factors need to be considered in a child with a thermal injury over and above those for normal healthy children; these are listed in Table 23.5. The size and depth of the injury will have a direct impact on the hypermetabolic inflammatory response and therefore the nutritional requirements of the child. The position and the psychological impact of the injury, including the cause, can have a significant effect on compliance with dietary management strategies.

Table 23.5 Factors influencing the achievement of nutritional requirements.

Percentage burn surface area
Site of injury
Pre-existing clinical conditions
Previous nutritional status
Special dietary needs
Gastrointestinal function
Pain management and sedation
Pyrexia
Periods of fasting
Psychological distress

Minor burns (<10% body surface area)

A 'food first' approach should be taken with minor injuries of <10% surface area (not including the face) and if the child does not have a compromised nutritional status pre-injury. The child should be encouraged to start eating and drinking as early as possible, and every effort should be made to provide familiar foods in order to promote appetite. Nutritious drinks such as milk and milkshakes, in preference to juice or fizzy drinks, should be encouraged.

Daily food and fluid intake should be accurately recorded by nursing staff. If this highlights difficulties in meeting the dietary targets, alternative nutritional intervention may be necessary. A multivitamin supplement or an oral nutritional supplement (ONS) may be beneficial in this group if acceptance of hospital food is limited.

Major burns (>10% body surface area)

In a major thermal injury, an enteral feeding tube should be passed during the resuscitation period, and also where the injury is complicated by smoke inhalation, the injury is extensively to the face or where additional trauma has been incurred. Many studies report that early enteral feeding of burns patients (within the first 6 hours) reduces the incidence of paralytic ileus and may moderate the hypermetabolic response [64–66]. However, a Cochrane review on early versus later initiation of enteral feeding found that the benefits were inconclusive as only three studies met their inclusion criteria [67]. Other benefits of early enteral feeding include maintenance of gut integrity and a reduction in bacterial translocation, as well as improvements in immune status and wound healing [64–66].

Current practice in most UK centres is to commence continuous enteral feeding at a low rate and increase as tolerated, aiming to achieve full requirements within the first 24–48 hours post-injury. This should be done cautiously and be guided by the severity of the thermal injury. While published studies have failed to demonstrate irrefutable evidence of the benefits of early feeding, there are reports of feed-related intestinal necrosis, and thus for more severe injuries just trophic feeding in the early phases may be indicated [68].

Nasogastric feeding is routinely used in many centres, but where this is poorly tolerated, as demonstrated by increased gastric aspirates, transpyloric feeding should be considered [69, 70]. Delayed gastric emptying and gastric aspirates in excess of the hourly feed rate are closely correlated with ileus, infection and sepsis [71]. Diarrhoea occurs frequently in children with burn injuries but appears to be more closely related to the use of broad spectrum antibiotics rather than feed osmolality or volume [72]. It has been suggested that the use of prebiotics and probiotics may have a beneficial effect on gut flora, thus reducing the incidence of diarrhoea; however, the timing and dose, as well as the most effective strain, remains unclear [73].

Optimising nutrient provision via enteral feeding can prove difficult as feeding regimens must take into account fasting periods related to surgical intervention, dressing changes, physiotherapy and medications. Several studies within a critical care environment have demonstrated suboptimal provision of nutrition support; therefore, effective communication and team working are imperative to the nutritional management of children with thermal injuries [74].

PN should only be considered when there is prolonged paralytic ileus or where poor tolerance of enteral feeding prevents nutritional requirements from being met by this route alone. Where possible, trophic enteral feeds should continue to be infused at a very low rate (as little as 2 mL/hour) to maintain the brush border integrity of the gastrointestinal tract [24, 75, 76]. The complications of PN are well recognised, and as infection risks are already high in burns patients, special care must be taken when considering PN. Other issues, such as electrolyte imbalances and hyperglycaemia, also require particularly close monitoring. Further guidance on enteral and PN support in children may be found in Chapters 4 and 5.

Choice of oral and enteral feeds

The choice of feed will vary depending on the age of the child, the calculated requirements, any unrelated medical condition and the clinical course during admission. There is some evidence to suggest that the use of high carbohydrate, high protein, low fat feeds may improve protein synthesis and muscle mass accretion, although such feeds are not routinely used in the UK at the present time [10, 77]. A 2012 Cochrane review concluded that there were limited randomised controlled trials on optimal feed composition and further research is, therefore, required [78].

As the child's condition improves, the move from enteral feeding to oral diet, with or without supplementation, should take place as a managed process. Weaning from enteral feeding is challenging requiring team work and clear communication between the healthcare professionals, the family and the child. Much of the published work on weaning from enteral to oral nutrition is related to children with long-standing feeding aversion and not short-term nutrition support [79]. Enteral feeds should be reduced gradually to encourage oral intake, but nutritional requirements should continue to be met; simply stopping the enteral feed without adequate oral intake being established increases the risk of nutritional deficiency and wound breakdown.

Examples of oral nutritional supplements and enteral feeds are given in Tables 4.3 and 12.5.

Monitoring and outcomes

Objectively assessing the success of nutritional support of a burns patient is difficult, as the endpoint is global and incorporates many variables. Commonly used variables include body weight, nitrogen balance, lean body mass measurements, biochemistry and measurement of serum proteins. Functional measures, such as exercise tolerance, are also possible measurements.

It is important to remember that burn injuries are dynamic and this patient group has constantly changing nutritional needs related to the healing of their wounds. As the percentage burn surface area changes, so the nutritional requirements need to be reassessed. There is no one method that is universally reliable or applicable for the nutritional monitoring of paediatric burns patients. It is important that the overall clinical picture is incorporated into the assessment.

Body weight

Body weight is a common measure of nutritional status as it is easy to obtain and can be related to the general paediatric population; however, it can be very misleading in burns patients. The initial fluid resuscitation after severe burn will increase body weight, and although this will eventually lead to diuresis, the time period is unpredictable [80]. Additional fluid shifts occur with infections, ventilator support and hypoproteinaemia, making body weight a very unreliable gauge of nutrition in this population. Patients can have increased total body water for weeks after the burn injury, masking the loss of lean body mass that will have occurred [81]. Regular weights (without dressings) should be recorded and plotted on appropriate centile charts. These should be compared with pre-admission measurements where available; asking parents and caregivers for these weights can be helpful. Long-term monitoring of trends in weight are valuable, especially during the rehabilitation phase. It is important to remember that oedema and fluid shifts may mask true weight and any loss of lean tissue early in the clinical course. Studies in severely burned children found that increasing energy intake to maintain weight resulted in increased fat mass instead of improved lean body mass [51, 82].

Biochemistry

Routine biochemistry should be monitored. Frequency of monitoring will vary depending on the child's clinical course.

Protein

Adequate protein intake is extremely important after a burn injury. Measurement requires accurate urine collection to determine urine urea nitrogen (UUN) as well as documentation of dietary nitrogen intake [83]. Nitrogen balance for burns patients can be approximated with the following formula although this has been shown to underestimate nitrogen losses [84, 85]:

$$\text{Nitrogen balance} = \text{nitrogen intake in 24 hour} - \left[1.25 \times (\text{UUN} + 4)\right]$$

In practice the collection of UUN is rarely done with the measurement of serum proteins, such as albumin and prealbumin, more commonly used. However, these are not without their limitations. After a burn injury, serum albumin levels are depressed acutely and chronically, despite successful nutrition, making it a poor marker [86]. Prealbumin has a short half-life of 2 days, which should make it more responsive to nutritional changes. However, the level falls quickly after a burn injury and recovers slowly, meaning that it may not correlate well with ongoing nutritional status [87]. Raised serum levels of C-reactive protein (CRP) can act as a predictor of sepsis in children with burns injuries [88].

Vitamin, mineral and trace element status

Vitamin, mineral and trace element status should also be monitored in extensive burns injuries as evidence of deficiency has frequently been reported in the literature [48–54]. Guidelines for monitoring blood parameters in burns patients have been developed by several of the regional burn networks and local policy should reflect these.

Imaging techniques

Although a few imaging techniques are now available for nutritional monitoring, due to availability and cost, they are typically used in research only. Bioelectrical impedance analysis calculates total body water and the body's fat-free cell mass by measuring the body's resistance to the passage of electrical currents. However, it is unknown how the fluid shifts after a burn injury affects this measurement.

Changing clinical condition

The clinical condition of the child is constantly changing and includes aspects such as burn area and healing, temperature, infection and sepsis, ventilation issues and rehabilitation programmes. All of these should be closely monitored and requirements recalculated on the basis of these changing factors.

Feed intake and tolerance

Feed intake and tolerance should be closely monitored. Prescribed versus actual intakes can vary for a number of reasons and under-delivery of nutrition is a commonly recognised problem [74]. Aspirate volumes and bowel motions (frequency and consistency) should be recorded accurately. Adjustments to feeding regimens, including rate, type of feed and route of administration, may be beneficial. As the child moves from enteral to oral nutrition, intakes should be recorded accurately to ensure adequate nutritional intake is being achieved.

Nutrition post-discharge

Monitoring of nutritional intake and overall nutritional status should continue post- discharge. Changes in the medical management of burns patients have resulted in earlier discharge home, with follow-up being provided within the community or at outpatient clinics. The hypermetabolic response has been demonstrated to continue for 12 months or more following a burn injury [9–12, 89], putting these children at risk

of longer-term nutritional deficiencies and growth failure [89–92]. It should also be noted that even with adequate nutritional intake, poor growth often continues to be an issue. In these circumstances, children exhibit increased body fat stores, but no significant increase in lean body mass [12, 92].

Specifically, with major burn injuries, bone health should be reviewed longer term with studies reporting significant increases in long bone fractures post-injury [52]. Paediatric burns patients can suffer significant dysfunction of calcium and vitamin D homeostasis for a number of reasons including increased bone resorption, osteoblast apoptosis (programmed cell death) and urinary calcium wasting. Additionally, burned skin is not able to manufacture normal quantities of vitamin D_3, the main source of vitamin D for the majority of the population. This causes further imbalance in calcium and vitamin D levels. Studies of paediatric burns patients have found that supplementation with a multivitamin containing 400 IU of vitamin D_2 did not correct vitamin D insufficiency. More research is required to determine benefits of supplementation and optimal levels [54, 93, 94]. The use of dual X-ray absorptiometry (DEXA) scanning is another imaging option, which can measure bone density and lean body mass.

Long term follow-up and monitoring of nutritional status and intake should be integral to the dietetic management of burn injuries, particularly those falling into the major burn classification.

A case study of a young girl with a mixed thickness scald is described in Table 23.6.

Table 23.6 Case study: A young girl with a mixed thickness scald.

A girl aged 2 years and 11 months old has sustained a 12% mixed thickness scald (7% full thickness, 5% partial thickness) to the lower legs and feet as a result of being placed in a bath of hot water.

On admission

Weight = 12.85 kg (25th centile). Estimated height = 92 cm (25th centile)

Blood results are within the normal range, and there is no history of iron deficiency anaemia.

She eats three meals plus supper daily and has no noted dislikes or food intolerance. Usual dietary intake is reported to be 'children's food' such as chocolate-based breakfast cereals, ham or cheese sandwiches, chicken nuggets and chips or sausage and mashed potatoes. Reported portion size appears appropriate for age. Drinks are mainly diluted juice or fizzy drinks. No additional vitamin or mineral supplements are taken.

She is receiving pain medication and is currently sedated.

Nutrition assessment

From the information presented, this child had a reasonable intake of food prior to her injury, although the nutritional quality may not have been adequate. Anthropometric measurements and biochemical results are all currently in the normal range. Sedation and pain management is likely to reduce dietary intake in the early stage of management.

Calculating requirements

Total body surface area (TBSA)

$= \sqrt{\left[\left(\text{weight} \times \text{height}\right) / 3600\right]}$

$= \sqrt{\left[\left(12.85 \times 92\right) / 3600\right]} = 0.57\ \text{m}^2$

Burn surface area (BSA)

$= 12\,\% \times 0.57 = 0.068\ \text{m}^2$

Requirements using the Hildreth/Calveston equation:

Energy: 1800 kcal (7.5 MJ)/m^2 TBSA + 1300 kcal (5.4 MJ)/m^2 BSA

= 1114 kcal (4.6MJ)

Protein: 2–3 g protein/kg

= 26–39 g protein

Fluid: 1140 mL

Requirements using the Schofield equation: (kcal/day) in infants from 0–3 years

Female BMR = $16.25 \times \text{Wt} + 1023.2 \times \text{Ht} - 413.5$

$= (16.25 \times 12.85) + (1023.2 \times 0.92) - 413.5$

$= (208.8 + 941.3) - 413.5$

$= 737$ kcal

BMR, basal metabolic rate; Wt, body weight in kilograms; Ht, length/height in metres.

There is a difference of approximately 400 kcal between the two different equations. While ESPEN [35] recommend the Schofield equation [30], it has to be remembered that it may underestimate requirements as it calculates BMR and does not account for energy requirements for activities of daily living or the impact of disease and injury. This, coupled with reduced feeding days due to theatre visits and changes of dressings, could significantly reduce a patient's nutritional intake and ability to meet their requirements.

(continued overleaf)

Table 23.6 *(continued)*

Nutritional diagnosis

Nutritional intake is likely to be inadequate to meet requirements specifically for protein, vitamins and minerals, related to increased nutrient requirements and poor dietary intake post-injury, as evidenced by the extent of injury requiring sedation at present, and dietary history indicating energy dense, nutrient poor dietary intake pre-injury.

Nutritional intervention

Nutritional prescription is for a nutrient dense intake to meet requirements. Initially this will be met via nasogastric feeding and oral intake. In deciding the nutritional prescription, the following points should be considered:

- Site of injury – Lower legs, therefore, not likely to directly compromise oral intake.
- Percentage burn area – This is >10% and is, therefore, a major burn.
- There is no previous medical history of note
- Previous nutritional status – reasonable, possibility of vitamin insufficiency, particularly vitamin D.
- No gastrointestinal problems.
- Pain management – As a result of the injury, the child will be in a great deal of pain and will be commenced on pain relief; this should be considered when planning intervention.
- Pyrexia – none noted yet.
- The child is scared and unsure of what is happening to her.

Method of feeding

An enteral feeding tube should be passed during the resuscitation period. Enteral feeds should commence within 6 hours of admission via this route, until such time as the child is able to feed orally. Enteral feeds should gradually be replaced by oral intake to meet full nutritional requirements. Good oral hygiene should be maintained throughout.

Choice of feed

- A fibre containing 1 kcal (4 kJ)/mL paediatric enteral feed. The advantage of this option is a nutritionally complete feed that should meet all nutritional requirements without modification. A fibre containing feed is recommended from initiation due to the high risk of constipation in patients with burn injuries. This is due to significant fluid shifts and losses as a result of the injury and high doses of sedatives and opioids frequently required for analgesia [35].
- The final feeding regimen should be planned in conjunction with medical and nursing management taking account of times of dressing changes, physiotherapy sessions and other interventions.
- If taking anything orally, or as oral intake begins, encourage nutrient dense foods that are familiar and acceptable to the child. Encourage high protein foods. Avoid diluted juice and fizzy drinks; encourage milk-based drinks or oral nutritional supplements instead.

Nutrition monitoring and evaluation

Review nutritional requirements weekly; this should take account of the following:

- Dressings are changed twice weekly. The child should be weighed and the degree of healing assessed on each of these occasions. Nutritional support should be reassessed according to these factors.
- Nutritional biochemical markers should be requested and monitored weekly in the early stages of recovery and then as necessary to 'fine tune' dietetic intervention and promote a positive outcome.
- A possible side effect of analgesia is constipation; bowel habits should be monitored closely and fibre-enriched feeds considered.
- Increasing oral intake should be monitored through dietary intake records.

At the point of discharge the child should be reassessed and a new nutritional care plan put in place. At this time, she is likely to be eating better, but care needs to be taken in terms of overall energy intake and adequacy of micronutrient intakes, particularly vitamin D. Input should be guided by progress, but at every appointment with the burns team, a weight and height should be recorded, and dietary intake should be considered. Longer-term use of a multivitamin and mineral supplement, particularly if the oral diet is limited, should be recommended.

Learning points: nutrition in burns and thermal injury

- *Early intervention in the form of enteral feeding within 12 hours of injury to maintain gut integrity*
- *Regular reassessment of nutritional requirements to account for healing of burn and graft sites and changing oral intake*
- *Follow-up post-discharge should consider body composition and bone health*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

24 Faltering Weight

Lisa Cooke and Julie Lanigan

Introduction

Growth monitoring is the cornerstone of paediatric care. Faltering weight may be a marker of undernutrition or disease, and early recognition allows prompt intervention to protect short- and long-term health. Therefore, regular monitoring is advised throughout infancy and early childhood [1].

Definitions

Failure to thrive (FTT) is an outdated term previously used to describe infants and young children who failed to reach their expected growth [2]. This definition is still used by some clinicians and researchers. However, 'faltering growth' or 'faltering weight' is now the most widely accepted definition for infants and children with inadequate weight gain.

Growth assessment

Growth charts are used to compare measurements in children of the same age and sex. It is recommended that international growth standards are used, which are based on infants and children growing under optimal conditions in a range of settings, i.e. the WHO Child Growth Standards [3]. The UK-WHO 0–4 years growth charts combine data from the WHO standards with UK term and preterm data. The UK 2–18 years growth charts combine data from the UK 1990 growth reference for 4–18 years with the WHO standards for 2–4 years [4]. Growth is monitored according to progression along centiles [1, 3]. The growth of healthy infants and children will normally follow an established centile from about 2 weeks of age. However, small deviations are common and not always a cause for concern [5].

Defining faltering weight

In infancy and early childhood, faltering weight is identified by downward centile crossing. The degree of centile crossing that would lead to concern depends on birthweight (Table 24.1).

Weight below the 2nd centile on the UK-WHO 0–4 years and UK 2–18 years growth charts indicates faltering regardless of birthweight. Infants and children exhibiting the growth patterning described in Table 24.1 are at risk of growth faltering, and regular monitoring is recommended [6].

Further measurements

Where there is concern about growth faltering, weight should be measured and plotted on the relevant growth chart. Previous measurements should also be plotted to allow a longitudinal assessment of growth. In addition, length (in infants and children under 2 years of age) and height (in older children) should be measured. Where there are concerns regarding a child's length or height, parents' height should be measured, and the mid-parental height centile (MPC) calculated. If the child's length or height is more than two centile spaces below the MPC, this could suggest undernutrition or a growth disorder [7]. Head circumference is also a useful indicator of growth in the first 2 years of life.

Mid-upper arm circumference (MUAC) is a useful anthropometric measure of nutritional status that can be done simply with minimal equipment. Data show that in a well-nourished population, there are very few children aged 6–60 months with a MUAC less than 115 mm. Those with a MUAC less than 115 mm have a highly elevated risk of death compared with those who are above this cut-off [3].

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

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Table 24.1 Centile crossing relative to birthweight.

Birthweight centile	Fall across weight centiles causing concern
<9th centile	One or more centile spaces*
9th–91st centile	Two or more centile spaces
>91st centile	Three or more centile spaces

*A centile space is the distance between two adjacent centile lines.

Growth charts are the most reliable tools for identifying faltering weight. However, the following features are commonly reported in association with weight faltering:

- muscle wasting, poor skinfold thickness
- thin, wispy hair
- visible or prominent bones (e.g. pointed chin in a baby)
- pale complexion (could suggest iron deficiency)
- poor sleep pattern
- developmental delay (particularly in communication skills)
- emotional and behavioural issues (ranging from withdrawn/passive to active/chaotic with poor concentration)

Research has shown that health professionals do not always recognise faltering weight. Batchelor and Kerslake found that one in three children whose weight had fallen substantially were not identified [8]. There were various reasons for non-recognition: lack of awareness of the problem, well-cared-for children with no signs of physical neglect, no reported feeding difficulties, acceptance of children as small and underuse of growth charts.

The prevalence of faltering weight varies between and within populations and is influenced by socio-economic factors. For example, 5% of infants living in deprived inner city areas are affected, but it occurs across a wide social range [9].

Causes

Historically, the focus has been on differentiating faltering in weight as 'organic' (resulting from an underlying medical condition) or 'non-organic' (related to unknown psychosocial factors). It is now clear that only 5% of cases of faltering weight have an underlying medical problem. The two categories are not mutually exclusive, and undernutrition is recognised as the primary cause of poor weight gain in infancy [10].

During infancy and early childhood, relative energy and nutrient requirements are high to support rapid growth. Infants and young children are at risk of nutritional deficiencies due to feeding difficulties and, in a minority of cases, food insecurity. For some children, medical conditions may be the underlying cause of growth faltering (Table 24.2) [11].

Despite an apparently adequate intake, gastrointestinal disorders may lead to faltering weight because of malabsorption, e.g. coeliac disease. Children with congenital cardiac or respiratory defects may show poor growth due to breathing problems, anorexia or increased energy requirements caused by their disease.

Table 24.2 Factors contributing to faltering weight.

- Inability to digest or absorb nutrients
  - Coeliac disease
  - Cystic fibrosis
- Excessive loss of nutrients
  - Vomiting
  - Chronic diarrhoea
  - Protein-losing enteropathy
- Increased nutrient requirements due to underlying disease
  - Chronic cardiac or respiratory failure
  - Chronic infection
- Inability to fully utilise nutrients
  - Metabolic disease
- Reduced intake of nutrients
  - Functional problems
  - Suck–swallow incoordination
  - Oral hypersensitivity

Table 24.3 Factors contributing to inadequate intake.

- Delayed/problematic progression of solids
- Early feeding difficulties, e.g. tube feeding, gastro-oesophageal reflux
- Poor appetite following illness or dental problems
- Parental attitudes to food and feeding, including cultural practices
- Behavioural difficulties, e.g. coercive feeding
- Limited or rigid parenting skills
- Parental ill health, e.g. maternal depression
- Family characteristics, e.g. chaotic household and lack of routine, poor facilities, neglect

Children with neurological dysfunction may have problems with oromotor development, which can affect the ability to suck and swallow. They may also suffer from oral hypersensitivity and therefore refuse to feed. Children with metabolic disorders can present with faltering weight as a result of poor feeding or inability to utilise energy correctly. Faltering weight is common in infants born prematurely; their special nutritional needs and oromotor problems are reviewed separately (p. 96).

For children with poor weight gain and no apparent medical problem, inadequate energy intake is the underlying cause. Many factors contribute to inadequate intake as discussed below (Table 24.3).

Early feeding problems

For many infants, growth begins to falter around the time of complementary feeding. During complementary feeding the diet is expanded to include a wider range of foods aiming to establish a diet that meets nutritional requirements. As the infant's oromotor skills develop, this allows the introduction of new foods with a wider range of tastes and textures. Complementary feeding is a time when infants become accustomed to new foods. If this period of acceptance of new foods, in particular those with more 'lumpy' textures and bitter tastes, is interrupted, progression through the introduction of solid foods can be difficult and may compromise the nutritional adequacy of the diet. Overdependence on

cow's milk and fruit juice is common in infants and toddlers. This may restrict intake of solid foods, leading to insufficient energy intake to support normal growth [12, 13].

As complementary feeding progresses, infants show increasing independence and a desire to self-feed. It is important that infants are given opportunities to develop self-feeding skills.

Infants and young children with faltering weight are reported to experience more feeding problems compared with those growing normally [14]. In a case–control study, infants with faltering growth were introduced to solids and finger foods later than a control group and were described as variable eaters with low appetite and poor feeding skills. While causality could not be defined from this observational study, findings suggest that feeding difficulties may increase the likelihood of faltering weight [15].

Faltering growth is often accompanied by chronic feeding difficulties [14]. For example, one study found that children with faltering weight also had severe feeding difficulties, according to parental reports. Parents described stressful mealtimes, children crying, clamping their lips, turning away, pushing food away, spitting out food and being sick [16].

Behavioural feeding problems, including food refusal, can present at an early age, and there are many contributing factors [17]. One of the earliest forms of infant communication occurs during feeding, with the caregiver and infant responding and reacting to each other. When interactions are appropriate, feeding is termed responsive. However, parental feeding interactions may be affected by worry, anxiety or concern about a child's intake and will influence how a child reacts to food. Feeding cues relayed by the child, e.g. signalling discomfort, might not be appropriately interpreted by the caregiver. For young infants with gastro-oesophageal reflux, food might well be associated with vomiting and pain. Feeding can then be an unpleasant experience, leading to food refusal. There are many reasons for food refusal including extreme temperatures of food, inappropriately sized pieces, insensitive feeding or reluctance of parents to allow the child to feed themselves fearing an inevitable 'mess'. If the child has dental caries, then pain may be a factor. Feeding problems can cause severe distress and disruption to family life and if unchecked can lead to persistent weight faltering.

Family and maternal influences

Some studies have focused on psychosocial characteristics of the family and the environment of the child with faltering weight. Parents' inability to provide emotional nurturing may well contribute to the problem. Family conflict before the age of 7 years has been shown to have a strong and significant association with slow growth [18].

Maternal attitudes towards food and feeding have been shown to have an influence on the eating habits of children. McCann *et al*. reported that mothers of children whose weight faltered showed greater dietary restraint, both concerning what they ate themselves and what they were prepared to offer their children [19]. In another study, infants of mothers who were both depressed and deprived showed poorer weight gain [20].

Poverty

Poverty is not a factor in isolation, and there is little evidence to suggest an increased risk of faltering weight in the poorest families [20]. However, it has been suggested that children from larger families are at increased risk of weight faltering [7].

Neglect and abuse

Two population studies found that between 5% and 10% of children who had faltering weight were registered with social services as having suffered abuse or neglect [15, 21]. It is suggested that children in abusive or neglecting families are at an increased risk of faltering weight, but these families only represent a small proportion of all cases.

Outcomes for children with poor weight gain

Nutrition in the early years of life is a major determinant of growth and development and influences future adult health [22]. Evidence suggests that poor weight gain from birth to 6–8 weeks of life is a stronger predictor of developmental delay than poor weight gain over the remainder of the first year [23]. A meta-analysis found that infants with early onset faltering weight were likely to be shorter and thinner than age-matched peers. Evidence supporting adverse effects of early faltering on later growth and intellectual development was not strong. However, it was acknowledged that poor growth could be an important marker and indicate the need for intervention in children where there is neglect, a medical condition, developmental problems or feeding issues [24]. Early home intervention has been reported as mitigating the effects of faltering weight [25].

Assessment of faltering weight

Health visitors, with appropriate training, are ideally placed to identify children with faltering weight when they undertake routine child health checks. In the UK, babies are weighed at birth, 8, 12 and 16 weeks, 1 year and at school entry. If there is concern, they should be weighed more often (p. 2).

A holistic assessment, preferably undertaken at home, should evaluate a child's intake, feeding behaviour and family circumstances. The health visitor can provide a detailed picture of family life, where it is not possible for this to be completed by a dietitian. The paediatric dietitian can help to clarify any dietary concerns and assess nutritional adequacy. Should the child appear to have affected oromotor skills, assessment by a speech and language therapist (SLT) may be beneficial. If available, joint consultations with the SLT and

dietitian can not only save time but can also offer reassurance and reduce anxiety for the family.

A multidisciplinary team approach has been advocated where the medical and psychosocial aspects are combined into a clear focus on food and feeding [26, 27]. A full paediatric assessment can be undertaken including medical and feeding history, dietary intake and psychosocial and developmental aspects. Potential members of a multidisciplinary feeding team include:

- paediatrician
- paediatric dietitian
- specialist health visitor
- clinical psychologist
- nurse/nursery nurse
- SLT

Joint working enables discussion of individual cases and close cooperation between families and professionals. Clinical investigations only need to be undertaken if there are any suggestions of symptoms in order to exclude organic disease and to reassure anxious parents. The feeding clinic-style approach is resource costly, although offers a really good approach to managing ongoing difficulties. There are very few of these services available, but when in place they offer a 'one-stop shop' with opportunities for positive outcomes.

Dietary assessment

It is important to construct a complete picture of all aspects of and influences on the child's feeding. Early feeding history, together with the start and progression of solids, will help to identify if there were problems in the first year of life. Dietary recall with further information on the variety, textures and frequency of foods offered and eaten, mealtime routines and drinks taken through the day will all help in the assessment of the child's current intake. It is important to understand the family practices and dynamics around food as these are important factors that may influence poor intake in the child. Information on where food is purchased and its preparation within the home will also help in understanding which strategies will best fit the family and their lifestyle. Discussion with the parent/caregiver will identify how long mealtimes last and whether they are stressful. Gathering background information will help to identify any difficulties experienced by the family.

There is little research on the dietary intake of children with faltering weight. One study raised the difficulties in collecting dietary information and suggested that only a minority of children with faltering weight will have dietary histories that are obviously inadequate, but that wider ranging nutritional assessment will be more revealing [28].

A food diary is a useful tool in supporting nutritional assessments and can provide information on the quality of diet and help identify dietary inadequacies [29]. Food diaries that have been validated for use in children are available from Nutritools and can be downloaded from their website [30].

Table 24.4 Poor feeding techniques.

- Infant fed with a bottle in a semi-lying position
- Infant fed with a bottle while asleep ('dream' feeding)
- Anxious parent following the child around with food or forcefully feeding a child
- Excessive cleaning of the child with every mouthful of solids
- Dummy (pacifier) or infant bottle available at any time
- Child discouraged from participating in feeding itself
- Child chastised with threats or punishment for not eating

Observing a child eating is useful to obtain more information about:

- seating of the child and parent positioning
- child's interest in its own food or food of other family members
- quantity, texture and type of food offered and what is eaten
- child's desire or ability to feed or drink by themselves
- child's oromotor function and self-feeding skills
- interaction between the child and parent, including parental response to child's cues
- communication between the child and parent, e.g. verbal encouragement
- atmosphere and emotions at mealtime

If there is a specialist team available, it is possible, with parental agreement, to video mealtimes. This is difficult to do unless home visits for appointments are possible. However, most parents have smart phones and may be able to bring short videos of their child feeding into clinic. Observations of mealtimes can allow parents to see feeding from a different perspective. For example, a parent who viewed a feeding session made the following comment: 'Well I'm not surprised she's not eating. I didn't realise I was so forceful. If someone tried to feed me like that, I wouldn't eat either'. When parents are able to suggest changes and contribute to the management plan, there is a greater chance of success. A mealtime video helps the dietitian to support the parents with positive adjustments to feeding. Feeding observations can also highlight ineffective feeding of an infant or young child (Table 24.4), allowing issues to be sensitively raised with parents.

It is important to listen to parental concerns and their view should be taken into account. It is also useful to know who else is involved in the care and feeding of the child. For some children, with parental agreement, it is useful to observe the child's behaviour around food in a setting other than the home, e.g. nursery, children's centre or school. This can help identify differences in eating and feeding, adding further valuable information to a supportive action plan for the family.

Assessment of oromotor function

For a small number of children who may have neurodevelopmental problems or continue to exhibit food refusal and faltering weight, it is important for a SLT to assess oromotor

function. Such assessments, often in conjunction with videofluoroscopy, will identify those who are unable to coordinate their suck–swallow reflex. These children are likely to aspirate feeds and may require nasogastric or gastrostomy feeding. The SLT will also detect oral hypersensitivity and be able to help with desensitisation programmes. In certain areas, occupational therapists (OT) lead on oral desensitisation programmes. Joint appointments with the dietitian, SLT and OT can help with children who have physical issues with feeding, leading to faltering growth.

Nutritional management

Nutritional requirements

A dietary intake that provides energy and protein requirements for age [31, 32] will usually allow for maintenance of growth along an established centile. Additional protein and energy will be required to allow for rate of weight gain to improve (catch-up growth). Guidelines suggest that the percentage of energy supplied from protein should be between 8.9% and 11.5% to provide optimal improvement of lean and fat mass [33].

A formula for predicting energy requirements to improve weight gain in infants and young children has been suggested [34]:

$$\text{kcal(kJ)/kg} = \frac{120 \times \text{ideal weight for height (kg)}}{\text{actual weight (kg)}}$$

This may mean an intake of 1.5–2.0 times, the normal recommended energy requirements for age. Experience and judgement should be used when advising additional energy density, making sure that fortification of the diet does not displace other foods or is provided at the expense of essential nutrients. Therefore, close monitoring with regular review is essential.

Anaemia is common in children with faltering weight, and in one study one-third of a sample had iron deficiency anaemia [35]. Often young children who falter in growth are high consumers of cow's milk, which is low in dietary iron and may inhibit iron absorption. Excessive intake is also associated with gastrointestinal bleeding and iron depletion in infants and young children. There is also evidence that zinc deficiency affects growth [36]. Requirements for vitamins, minerals and trace elements are increased during periods of rapid growth, and a suitable supplement should be included if the child's intake is thought to be inadequate. No guidelines exist, but intakes should be at least appropriate for the proposed energy intake.

Achieving nutritional requirements

Following a detailed feeding assessment, a strategy for catch-up growth needs to be planned. The main nutritional objectives are:

- to improve protein and energy intake
- to promote weight gain enabling catch-up and allowing optimum growth
- to correct nutritional deficiencies and achieve an adequate nutritional intake

If a child is underweight for height and failing to gain weight at the expected rate, whatever they are consuming is not enough for their needs. Working in partnership with parents and engaging them in any decisions on nutritional intervention is crucial.

In a young breastfed infant where weight is faltering, the maternal diet needs to be assessed, and its quantity and quality improved. It is essential that observation of the mother breastfeeding is carried out to make sure the infant is latched on correctly. Additionally, an understanding of the mother's mental and general health and well-being is needed to identify factors that may affect faltering growth [37]. Supplementation of breastfeeds may be necessary, but this should be done under dietetic supervision and with caution as it may suppress production of breastmilk. The breastfeeding mother will need lots of support around her. A study in formula-fed infants found greater benefits from using a ready-to-feed nutrient-dense formula (Table 1.18) compared with adding energy supplements to standard infant formula [38]. Full-strength high energy formula has been shown to be tolerated well by infants under the age of 12 months with faltering weight, but some may benefit from a gradual introduction to avoid increased bowel frequency [39].

In general, young children have high energy requirements relative to their size. In cases of poor weight gain, when catch-up growth is the aim, requirements are even higher. This is difficult to achieve as many children have small appetites and consume small food portions at any one time. There are various ways of increasing energy intake:

- regular meals
- snacks in between meals
- use of energy-dense foods
- fortification of foods
- supplements
- enteral feeding

Emerging evidence supports that rapid growth in the first year of life can lead to metabolic concerns later in life [40]. Therefore, growth faltering should be managed with energy requirements adjusted on an individual basis to allow for healthy catch-up growth and avoidance of continued rapid growth once the child's previously established centile is reached.

Provision of regular feeding

Children need a routine with regular meals, which include energy- and nutrient-dense foods. It is advisable to start with small quantities and offer realistic portions of everyday family foods, with the opportunity for the child to be given more if they can manage. Emphasis may need to be removed from mealtimes, and the importance of a balanced intake over the day emphasised.

Frequent snacks

Meals alone will usually not enable the child to catch up. One study found that when children with faltering weight were offered a high energy snack, they took more at the next meal compared with a control group where there were no concerns about growth [41]. In clinical practice, small regular snacks as well as meals are advised to encourage interest in food and improve appetite, so increasing overall energy intake. Excess juice and milk consumption encountered in many young children should be discouraged, and solid food should be offered before fluids.

Energy-dense foods

Children need to consume as wide a variety of foods as possible from the four main food groups: bread, other cereals and potatoes; meat, fish and alternatives; full-fat milk and dairy foods; and fruit and vegetables (Table 2.11) with a greater emphasis on energy-dense foods. Foods with a very high fibre content are bulky and may have high phytate levels, compromising both energy intake and the bioavailability of micronutrients, and so should be limited.

Fortification of foods

Energy-dense products, such as butter, margarine and cheese, can be added to popular foods. Dried full-fat milk powder can be used to fortify puddings, soups and milk. If necessary, the iron status of young children can be improved initially by giving iron supplements and, in the longer term, encouraging children to consume iron-containing foods.

Supplements

The use of dietary supplements is not recommended for children with no medical reason for poor weight gain. The use of these products can medicalise the problem and give the impression to parents or caregivers that they do not have a role in helping their child to improve nutritional intake.

However, for children who are unable to take an adequate intake from food alone, dietary supplements may be necessary and can be prescribed. Carbohydrate, fat or protein supplements can be used to enrich foods, or ready-to-feed nutrient- and energy-dense drinks (oral nutritional supplements) may be more suitable (Tables 1.19, 1.21, and 12.5). The principle of frequent feeding, regular meals and snacks, use of energy-dense foods and fortification of solids with extra energy still applies.

A case study of a child with faltering growth is given in Table 24.5.

Enteral feeding

If the child has severe faltering weight and it is not possible to achieve a reasonable intake orally, enteral feeding (nasogastric or gastrostomy) may be required initially. Full follow-up support should be offered to allow for the child and family to continue to move forward with oral feeding where appropriate.

Behavioural management

For the child where there are negative associations with food, parents should be helped in a sensitive way, offering support and constructive advice, with no blame attached and no criticism of their parenting. Behavioural management includes:

- avoidance of force feeding
- positive reinforcement of good feeding behaviour; aberrant behaviour should be ignored, e.g. by turning the face away from the child
- a time limit of 20–30 minutes for mealtimes
- small, frequent meals are a possibility to maximise the opportunity for feeding practice and to reduce the pressure to eat at any one meal

Young children with feeding difficulties often benefit from messy play. In a relaxed and fun way, a child is encouraged to touch, feel, smell and possibly attempt different food tastes and textures. The case study in Table 24.5 illustrates the benefit from play experience, which tackles fears around food, mess and delayed self-feeding skills.

The Paediatric Specialist Group of the British Dietetic Association offers supportive resources that provide advice to families on the management of children who are refusing to eat.

Social care

In some families where there has been no improvement or poor weight gain continues, with evidence of parental inability to address the child's physical, nutritional and emotional needs, a common assessment framework (CAF) may be initiated by a concerned professional. In many cases this is the health visitor, but it can be initiated by any healthcare professional who feels this is necessary. A CAF is a shared assessment and planning framework to identify a child's additional needs and coordinates the services to meet them. If the family still struggles to engage and no progress is made, a referral to social care services, requesting input from a social worker under the category of a 'child in need', is necessary. This will enable a better assessment of the family dynamics and allows support from a wider range of services. Referral to social services is very important whenever there are concerns about a child's care, safety or well-being [42].

Summary

To thrive, children need adequate nutrition, appropriate nurturing and supportive parenting. The routine use and correct interpretation of growth charts help the prompt

Table 24.5 Case study: Dietetic management of a child with faltering growth.

Summary
Anthropometry: Baby boy Arlo born at term weighing 3.62 kg. Breastfed for 6 weeks and then started on a standard infant formula. Lives with mum and has an older sibling aged 5 years. Referred from GP at 2 years of age with faltering growth. Weight = 10.2 kg (9th centile). Height = 85.5 cm (25th centile). *Clinical*: Faltering growth and becoming ill with lots of coughs and colds. Mum reports child is grumpy and not sleeping well, listless and lethargic, crying a lot. Mum is a single parent, exhausted with older child and struggling with Arlo's lack of sleep and behaviour. *Dietary*: Intake inadequate, drinking lots of milk and very little solid food. Diet very low in fruit and vegetables and iron-rich foods. *Environment*: Mum has few cooking skills and relies on processed food. Family lives in a small flat with only a hob, fridge with freezer box and microwave oven. Mum receiving benefits and has very little money. Has a small table in the lounge.

Chronology	Medical history/assessment	Dietetic intervention
1–6 months old	Thriving well. No problems when checked by health visitor	
6 months old	Started solid foods Wt = 8 kg (50th centile) Length = 68 cm (50th centile)	
2 years old	Frequent coughs and colds and regular visits to GP Wt = 10.2 kg (9th centile) Ht = 85.5 cm (25th centile) Two centile drop in weight from 6 months of age so GP referred to dietitian	
2 years and 2 months old	Wt = 10.3 kg (2nd centile) Ht = 86 cm (9th–25th centile) Appointment with dietitian **Diet history:** *8 a.m.:* 200 mL cow's milk *Mid-morning:* banana *Lunch:* 2–3 tsp. scrambled egg/2–3 tsp. beans on ½ slice toast 250 mL cow's milk *Mid-afternoon:* 200 mL cow's milk *Tea:* 2 tsp. cottage pie/fish pie 1 pot fromage frais *Bedtime:* 200 mL cow's milk **Dietary assessment:** Total energy = 760 kcal (3175 kJ) of which 555 kcal (2320 kJ) from 850 mL cow's milk Total protein = 34 g of which 30 g from 850 ml cow's milk EAR for energy = 1000 kcal (4180 kJ/day, 82 kcal (345 kJ/kg/day) RNI for protein = 14.5 g/day, 1.2 g/kg/day	**Advised:** • Eat around the table as a family at set mealtimes • Keep mealtimes to no longer than 20 minutes • Do not offer alternative food, use finger foods, try and all eat the same as a family • Reduce milk feeds to mid-afternoon and bedtime only • Add extra, butter/margarine to foods like mashed potato, vegetables, pasta, rice • Add grated cheese to pasta and potato • Offer 3 meals and snacks at the table • Give a multivitamin • Given written information to back up advice: 'Help my child won't eat' diet sheet* • Written letter to GP for prescription for multivitamin preparation • Review in 4 weeks with a plan to suggest oral nutritional supplements instead of cow's milk if weight not increasing due to inadequate intake of food • Discussed with mum whether she can access a local nursery for Arlo to give her support and some free time

EAR, estimated average requirement; RNI, reference nutrient intake; GP, general practitioner.
*Available from the British Dietetic Association Paediatric Specialist Group. https://www.bda.uk.com/specialist-groups-and-branches/paediatric-specialist-group.html

identification of suboptimal weight gain. Regular surveillance, e.g. by the primary care team, and early intervention are important to help ensure adequate nutritional intake and correct growth faltering.

Many factors contribute to poor weight gain, and interventions will require a multidisciplinary team approach to enable investigation into possible underlying organic causes including medical diagnoses and social factors; assessment of dietary intake, oromotor function and feeding; and identification of behavioural difficulties. It is important that parental concerns are acknowledged and there is avoidance of blame. Parenting strengths and difficulties should be acknowledged, and support offered to encourage responsive feeding practices. A strong working partnership between the care team and the family is essential for the successful management of growth faltering and should be upheld at all times.

Learning points: faltering weight

- *Faltering weight may be a marker of undernutrition or disease*
- *Regular monitoring is advised throughout infancy and early childhood*
- *Prompt referral is recommended to investigate possible underlying medical causes*
- *Timely dietetic intervention is recommended to support catch-up growth and prevent further weight faltering*
- *UK-WHO Growth Charts 0–4 years should be used to assess weight faltering in term infants and young children*
- *UK-WHO Neonatal and Infant Close Monitoring Growth Charts should be used to assess weight faltering in preterm infants*
- *Feeding difficulties are common in infants and young children and increase risk of nutritional deficiencies*
- *There are many other signs of malnutrition, e.g. wasting, dry skin, thin hair and fatigue, that should also be considered (Table 1.5)*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

25 Obesity in Childhood

Laura Stewart and Chris Smith

Obesity

Laura Stewart

Introduction

Obesity is the most common childhood nutritional disorder in the world and is widely acknowledged as being a global epidemic [1, 2]. In the UK the importance of implementing effective strategies for the prevention and treatment of childhood obesity has national significance with the publication of government policy documents [3–5] as well as evidence-based guidelines [6–8]. The role of the specialist paediatric weight management dietitian should now be viewed as an important member of a paediatric or weight management service. Dietitians may work with children living with obesity and their families in primary or secondary care, utilising group or individual sessions [9, 10]. Background information, lifestyle advice and the use of behaviour change tools that a specialist paediatric dietitian will require to manage childhood obesity in any combination of these settings are discussed.

Definition

The definition of childhood overweight and obesity associates excess body fatness with the clinical relevance of such excess body fat. Body mass index (BMI) is generally recognised as the most appropriate proxy measure for body fat to define and diagnose childhood obesity and overweight [2, 6, 11]. BMI in childhood changes with age and differs between the sexes; therefore, it must be plotted correctly on age and sex-specific centile charts (WHO/UK 1990 data). UK BMI 2–20 years centile charts are available from Harlow Printing Ltd (see Useful addresses), and all dietitians working in weight management in the UK with children and adolescents should use these charts [12, 13].

In the UK the debate over the most appropriate BMI centile cut-off points for definition has been long agreed with both the National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guideline Network (SIGN) clinical guidelines recommending ≥98th centile (WHO/UK 1990 data) for obesity and ≥91st centile (WHO/UK 1990 data) for overweight. For epidemiological studies ≥95th centile (WHO/UK 1990 data) defines obesity, and ≥85th centile (UK 1990 data) defines overweight [6, 7].

Data on waist circumference centiles for British children [14] was previously available on the reverse side of the UK BMI centile charts; these have been removed. With no agreement on the relevant clinical cut-off points for the waist circumference centiles, they are not recommended for diagnosis of childhood obesity [2, 7, 11] although they can prove useful in monitoring progress.

Aetiology

Obesity is the accumulation of excess body fat associated with medical consequences. The aetiology of all obesity is both complex and multifactorial [15]. It is well recognised that the development of childhood obesity is an interaction between the modern obesogenic environment

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

and family lifestyle choices [16]. Increases in the amount of energy-dense foods eaten combined with large portion sizes, more time spent watching television, using computers and playing video games (screen time) with a simultaneous decrease in the amount of physical activity undertaken by children have all been mooted as causes of the current epidemic [2, 17, 18].

Genetics

The polygenetic theory of obesity suggests that the most common genetic cause will be found to involve a number of genes that could 'predispose' a person to gaining excess fat, which in turn would lead to obesity if or when that person is then exposed to an environment that encourages the necessary behaviours, i.e. a high energy diet and low levels of activity [19–21]. It has been suggested that by identifying common gene variants that predispose individuals to obesity subgroups of people living with obesity could be targeted for particular interventions such as specific diets, behavioural approaches or drugs [22, 23]. The Human Obesity Gene Map is an interesting resource to look for information in this area [22]. Research into polygenetics and obesity is complex, and it may be some years before any findings can be of use in day-to-day clinical practice [16, 20].

Although described as rare, monogenetic causes of obesity in humans have been found [19, 24, 25] with much of the research being carried out by the Genetics of Obesity Study (GOOS) group. The GOOS project recruited children from across the world who have severe obesity (BMI > 3.0 SD), a strong family history of obesity and from consanguineous families. The GOOS has identified seven monogenetic causes of obesity [21]. Most of these have involved mutations in leptin production, leptin receptors, propeptide pro-opiomelanocortin (POMC) and the melanocortin 4 receptor (MC4R) [19–21].

Mutations in MC4R are believed to be found in approximately 3%–5% of people with a BMI > 40. Mutations in MC4R appear to result in a range of phenotypes ranging from those showing no obesity to individuals with severe obesity (particularly at an early age), hyperphagia, increased lean body mass, increased linear growth and hyperinsulinaemia [24]. Deficiencies in the hormone leptin are reported to produce extreme obesity (usually from a young age), increased appetite, hyperphagia and hypogonadotropic hypogonadism. Injections of leptin in these individuals have been shown to reverse the hyperphagia and extreme obesity [19]. Individuals with POMC mutations are reported as having severe obesity (from an early age), hyperphagia, altered pigmentation, usually red hair and adrenal insufficiency [19, 25].

Inheritable disorders

A number of known inheritable disorders have obesity as a clinical feature of the syndrome. Lobstein *et al*. [2] noted around 30 such inherited disorders; most are associated with learning disabilities and dysmorphic features. The most common inherited disorders associated with childhood obesity seen in routine clinical practice are:

- Down's syndrome
- Prader–Willi syndrome
- Duchenne muscular dystrophy
- Fragile X

Endocrine causes

The endocrine glands produce hormones that are important in the regulation and maintenance of a stable body environment. In childhood they are important in ensuring normal growth and puberty. Dysfunction of these hormones can lead to hypothyroidism, growth hormone insufficiency, hypopituitarism, hypogonadotropic hypogonadism, hypogonadism, excessive corticosteroid administration, pseudohypoparathyroidism and craniopharyngioma; all of which are associated with rare causes of childhood obesity [26, 27].

Many of these endocrine disorders and the inheritable syndromes present with short stature as a clinical feature [26, 28]. There is strong agreement in clinical guidelines and practice that children with obesity who present with short stature for their age and weight should be referred to a paediatric endocrinologist for further investigation of possible underlying medical reasons for their obesity [2, 6].

Consequences

There are a number of consequences of childhood obesity that are seen both in childhood and adolescence, and indeed later life. Clustering of cardiovascular risk factors has been reported in children and adolescents including high blood pressure, dyslipidaemia, abnormalities in left ventricular mass and/or function, abnormalities in endothelial function, hyperinsulinaemia and/or insulin resistance. There is evidence that these cardiovascular risk factors are seen in adults who were living with obesity as children or adolescents [29, 30]. Hyperinsulinaemia, the metabolic syndrome and type 2 diabetes are also seen in adolescents [31, 32]. Psychological problems, particularly in girls, have been reported in relation to low self-esteem and behavioural problems. There are also long-term consequences of social and economic effects, particularly in women achieving a lower income [29, 30].

An important reason why tackling childhood and adolescent obesity is government policy is the evidence that obesity in childhood and adolescence tracks into adulthood. Risk factors for persistence into adulthood include:

- parental obesity (high risk if one parent is living with obesity and higher if both are living with obesity)
- level of obesity (increasing risk with increasing level of obesity)
- obesity in adolescence [29, 30]

Management

The role of the dietitian, either as a sole professional or as part of a multidisciplinary team, is to educate the child and

family on the necessary lifestyle changes while facilitating behavioural change [33]. A dietitian should be positive, non-judgemental and empathetic while developing a rapport with the child and parents [34, 35].

For group sessions it is common practice to include some separate child and parent sessions. Practice shows that parents value the opportunity to discuss situations and solutions with other parents without the child being present. For dietitians working with individual children and their families consideration should also be given to seeing the parents alone, as information is often revealed by parents that would otherwise not be discussed in front of their child [9].

Good practice suggests that different age groups require different engagements:

- for preschool and lower primary school-age children, the intervention, including ownership and responsibility, engagement directly with the parent/carer
- for upper primary-aged children, engagement jointly with the child and parent/carer
- for teenagers engagement directly with the adolescent, with the parent in a supporting role

Assessment

At the first session weight and height should be measured and plotted on child growth centile charts. BMI should be calculated [weight (kg) ÷ height (m)^2] and plotted at the correct age on the appropriate centile chart for sex (WHO/UK 1990 data). Although used regularly in research in clinical practice, arm anthropometry such as triceps skinfold measurement and mid-upper arm circumference is rarely used. Taking the waist measurement can be difficult in children living with obesity but can be a useful tool in monitoring progress in weight management.

The assessment of any child within a weight management service should ensure that a holistic view of the child's health and well-being is taken. An example of a current model in taking a health and well-being holistic viewpoint is the *Getting it right for every child (GIRFEC)* [36] used in Scotland, which has been underpinned in legislation. An important and useful aspect of GIRFEC has been the assessment tool known as SHANARRI:

- Safe
- Healthy
- Achieving
- Nurtured
- Active
- Respected
- Responsible
- Included

These eight aspects are reviewed from the child's point of view and are a useful concept for ensuring a weight concern is not seen in isolation of the child's whole life circumstances and well-being.

Lifestyle changes

Establishing current lifestyle

Asking for a 'typical day' scenario or a lifestyle diary, to be completed after the child's first appointment, is useful for establishing current lifestyle and is more child friendly for developing rapport than an interrogative diet history [34, 35].

Behavioural change tools

Both NICE CG189 and SIGN 115 guidelines concur that behavioural change tools in particular stimulus control, goal setting, self-monitoring, problem solving and use of rewards should be utilised in the management of childhood obesity [6, 7, 35].

Goal setting

Goal setting is used to help the child (and parents) to identify small and reasonable behavioural changes towards the long-term target of positive lifestyle changes. Goal setting allows the child (and parents) to take responsibility and ownership for identifying the lifestyle changes they feel able to make and subsequently keep to these agreed goals [37, 38]. The dietitian should facilitate goal setting by ensuring that the goals are SMART: specific, measurable, achievable, recorded and timed [9, 39]. Typically goals are written down to help with the continuing progress [40].

Rewards for reaching goals

Some programmes use 'rewards' for achieving the agreed lifestyle goal as these can be a positive reinforcement to both the setting and attainment of goals [38, 41, 42]. Rewards should be inexpensive, non-food or screen time items such as a book, football or a family excursion. It should be remembered that praise can be a very powerful reward and should be utilised by the dietitian [40].

Self-monitoring of lifestyle

The recording of specific lifestyle elements by the child and/or parents is a key component of behavioural change tools that enhances motivation to change lifestyle by increasing self-awareness [38, 41, 43]. Monitoring the child's food and drink intake, physical activity levels and screen time in a diary/journal helps raise awareness of current lifestyle, helps to identify potential goals for changes and then monitors progress towards their goals [40].

Problem solving

Problem solving is used to help the child and their parents to identify barriers and then to explore ways to overcome these

barriers [38, 42]. A patient centred approach would recommend that the child and/or parent identifies their own solutions to barriers and difficult situations [37, 40].

It is also used in relapse prevention by identifying 'high risk' situations where keeping to goals could be difficult, e.g. holidays, parties and wet weather, and then exploring strategies to cope with these situations such as participating in an indoor activity during wet weather. Relapse prevention is particularly important at the end of the programme to ensure that the child and family maintain behaviour/lifestyle changes in the long term [40, 42].

Stimulus control

Environmental/stimulus control involves identifying and then changing/removing stimuli or cues that encourage or sustain the 'unhealthy behaviour' and substituting cues that support/promote the new necessary lifestyle changes [42]. Examples include parents reducing the purchase of high sugar/high fat snacks in their shopping or the child avoiding walking home from school past a local sweet shop or a football being left at the front door to encourage physical activity after school [40].

Guidelines also recommend that parents should be encouraged to be the role models for the positive behavioural changes required; i.e. they need to change their eating habits, physical activity and screen time behaviours and let their child see them undertaking these positive activities. Giving affirming, concrete praise to the child when they undertake positive changes is also important to reinforce behavioural change [6, 7].

Implementing lifestyle changes

As discussed, the aetiology of childhood overweight and obesity is multifactorial and management requires both energy in and energy out to be tackled. A Cochrane review of the treatment of childhood obesity showed that the most effective treatments were those that combined diet and lifestyle changes [44]. Therefore, the dietitian must facilitate changes in total energy intake, physical activity levels and screen time (sedentary behaviours) while using the behavioural change tools outlined above.

Dietary advice

A systematic review concluded that no one particular type of dietary manipulation in childhood obesity was more effective than any other [45]. The child (and the whole family) needs to reduce the total energy intake in their diet while balancing essential nutrients. Collins *et al*. found that the traffic light type scheme was the most commonly used [9, 41, 45]. Calorie counting is not normally used with children.

A recent systematic review of the effectiveness of dietary intervention concluded that childhood weight management interventions could be successful in:

- reducing energy-dense but nutrient poor foods
- reducing sugar sweetened drinks
- increasing fruit and vegetable consumption
- decreasing the overall total energy intake

These changes came through programmes that lasted a minimum of 3 months, with less intense follow-up periods of between 3 and 18 months through face-to-face meetings or via phone/texting. Importantly the systematic review noted that if these dietary changes were maintained they led to a long-term decrease in BMI SD scores [46].

Children and their families should be encouraged to reduce the amount of foods and drinks in their diet that are high in sugar and fat and replace them with foods with lower energy content such as fruits and vegetables. Very importantly the dietitian needs to explore that age-appropriate portions are being taken by all the family. This can often be the main area of education for the child and family. There should also be consideration of:

- the number of takeaway meals taken
- the amount and types of snacks the child eats
- the amount of pocket money the child has
- school lunches

It is important to ensure that normal growth occurs when dietary intake is restricted and that age-appropriate quantities of protein, vitamins and minerals are taken. There are some children who dislike certain foods and do not consume a nutritionally adequate diet, and they may require a supplement of vitamins or minerals (particularly iron and calcium). Some children may, therefore, require regular assessment to compare their intake with recommended nutrient requirements [47]. Regular plotting of weight, height and BMI on approved growth and BMI centile charts is important.

Physical activity

NICE and SIGN obesity guidelines recommend that overweight and children with obesity undertake at least 60 minutes of moderate to vigorous activity per day [6, 7]. Physical activity guidelines in the UK recommend that children under 5 years who can walk unaided should take up to 180 minutes of activity each day [48].

Many children living with overweight or obesity dislike team sports and physical education (PE) at school. It is, therefore, important to help the child and family find local activities that they enjoy and are not embarrassed to take part in. In practice this can be done by working in partnership with local leisure/physical activity organisations. Increasing everyday 'lifestyle activities', such as walking and taking the stairs rather than lifts, has been demonstrated to be effective in controlling weight in the long term [41].

Screen time (sedentary behaviours)

NICE and SIGN guidelines recommend that children reduce their screen time (watching television, using computers, playing video/computer games) to no more than 2 hours daily or an

average of 14 hours over a week [6, 7, 49, 50]. Some countries' guidelines, e.g. the USA, Canada and Australia, recommend that children under 2 years should have no screen time [51].

For some children and parents, this is the most difficult change to make and there needs to be a discussion how this reduction can be attained over time.

The management outlined above covers all age groups. A case study to demonstrate weight management in an 11-year-old boy is given in Table 25.1. Infants, preschool children and adolescents may require particular consideration.

Infants and preschool children

It is difficult to overfeed a breastfed infant, but bottle fed infants can be persuaded to consume a greater volume than

Table 25.1 Case study: child weight management.

An 11-year-old boy referred for weight management advice by his family general practitioner

After triaging by the paediatric weight management team, he was accepted into the structured weight management programme SCOTT [9], which involves 10 family sessions over 4–5 months, including 2 parent-only sessions

Anthropometry
Referral weight = 50 kg; height = 1.46 m
BMI = 23.5 (98–99.6th centile) therefore classified as obesity
Assessment weight = 49.6 kg; height = 1.474 m
BMI = 22.9 (98th centile)

Biochemistry
None taken. In clinical practice it is not usual to review biochemistry in childhood weight management unless there is an indication of an underlying medical cause, e.g. short stature; or indication of a comorbidity, e.g. symptoms of type 2 diabetes

Clinical
Obesity due to BMI being above the 98th centile. No medical history to note

Dietary
From a typical day diet assessment, he appeared to eat well-balanced meals; however, these appeared to include excessively large portion sizes and multiple snacking in between meals

Environment
Social history
He lived at home with his mother, father and younger brother. He was in his last year of primary school. There was no involvement of social work or child and adolescent mental health services (CAMHS)

A SHANARRI assessment indicated that he had:
- A supportive family
- Low self-esteem and confidence
- His screen time was excessive with very low activity levels
- Making changes might be difficult for him, and he may not be able to take responsibility to make changes outside the home
- He had few friends and was being bullied at school due to his weight

Focus
He and his mother had attended the GP surgery due to mother's concerns that he had been progressively gaining weight in the preceding 2 years, including having gained 4 kg in the last month. Both were concerned about his weight but did not feel he had an unhealthy dietary intake. He appeared at assessment stage to be very sedentary, with excessive use of screen time

Motivation to change
The boy 8/10
His mother 8/10

PASS statement
Problem – childhood obesity
Aetiology – sedentary lifestyle, excessive hunger with snacking on sweets
Signs and symptoms – BMI above 98th centile, bullying
At his second appointment (appointment 3 in the programme) he set goals:
- 30 minutes of activity four times per week
- To have pudding four times a week instead of current seven times
- To reduce portion size

Over the course of 4 months, he made the following changes to his lifestyle:
- Decreased the portion sizes of food at meal times
- Stopped having crisps as snacks
- Increased his physical activity to 30–90 minutes every day
- Changed from bakery foods in the morning for breakfast to Rice Krispies

End of programme weight = 48.3 kg; height = 1.496 m
BMI = 21.6 (91–98th centile) therefore classified overweight, rather than obesity

they want or require; in addition feeds can be made more concentrated than recommended, or items such as cereal can be added to the bottle [52]. In general there should be no need to restrict an infant's diet, but for those gaining weight too quickly, or those already living with obesity, specific advice on feeding and weaning practices and lifestyle will be necessary. The following advice may be helpful:

- Make sure that parents react appropriately to the infant's crying; often crying is perceived as indicating hunger, when in fact the baby may be bored, tired or uncomfortable
- Avoid any additions to the infant's bottle, e.g. sugar or cereal
- Make certain that the feed dilution is correct and that the volume is appropriate for age
- Solids should not be introduced before the age of 6 months
- Weaning solids should initially have a low energy density, e.g. vegetables and unsweetened fruits
- Reduced fat products can be used in the weaning diet, e.g. low fat yoghurts and reduced fat cheese
- When a greater variety of foods is being consumed, e.g. lean meat, white fish and cereals, then the quantity of milk should be decreased
- Infants should be introduced to a cup or teacher beaker from about 7–8 months of age and bottles omitted by 1 year of age; more milk is generally consumed when feeding from a bottle
- Review if bottles of milk are being given at night particularly to aid getting to sleep or to enable getting back to sleep during the night; discussion with the parents and seeking help for them from early years workers to support good sleep practices is important
- Semi-skimmed and skimmed milk should not generally be used before the ages of 2 and 5 years, respectively; however, these lower fat milks are a useful way of decreasing energy intake in a toddler with overweight; it is important that a supplement of vitamins A and D are given with these milks
- Drinks of water should be offered with and in between meals; if the child is reluctant to drink water, then pure unsweetened fruit juice (well diluted) can be given once or twice daily with meals

Adolescents

Adolescents present dietitians with their greatest challenge. Normal adolescent behaviours and peer pressure for the consumption of snack foods dense in fat and sugar can lead to resistance towards lifestyle changes. The lifestyle advice outlined above should be given, but with careful consideration of how to approach the adolescent to ensure that they feel ownership of goal setting and all stages towards behavioural change.

Slimming foods and medications

'Slimming foods' and drinks as a replacement for a meal are not appropriate as they usually contain insufficient protein, minerals and micronutrients to meet the requirements for this age group.

Drugs for the treatment of obesity are used in adults, although these have not been licensed for use in children or adolescents in the UK. NICE and SIGN guidelines both recommend that they could be used in adolescents with obesity and comorbidities under strict supervision [6, 7].

Written advice

Written information should be provided to support any advice that has been given. It is usual to record goals and rewards (if used). The Caroline Walker Trust has very useful pictorial information on portion sizes. Written information on reading food labelling can be helpful, e.g. that produced by the British Heart Foundation.

Treatment success criteria

Current guidelines agree that the goal of childhood weight management for most children is weight maintenance, with height growth leading to a natural decrease in BMI. For some older children, and particularly those with very severe and extreme obesity, a weight loss of around 0.5–1.0 kg per month is acceptable.

When reporting outcomes on programmes, it is standard practice to report on BMI SD scores, also known as *z*-scores. There is a limited evidence base on the impact of BMI SD scores on reducing cardiovascular disease risk factors. The studies suggest that a reduction of between 0.1 and 0.5 BMI SD score after 1–2 year follow-up is significant enough to show changes in cardiovascular risk factors [53, 54].

Prevention

Promotion of a healthy lifestyle must start in early childhood if the present trend in childhood obesity is to be reversed. Current government initiatives around healthy eating and increasing physical activities at schools may be helpful in the future. Dietitians, particularly those working in the area of public health nutrition, have a key role to play in prevention strategies.

Growth in infancy and the early years is an important period in relation to the risk of obesity later in childhood and adulthood. It appears that infants at the upper end of weight and BMI for their age, and also those who gain weight rapidly as infants, are at a higher risk of excess body fat and obesity later [55]. The Avon Longitudinal Study of Parents and Children (ALSPAC) has noted eight particular risk factors in early childhood that were significantly related to later childhood obesity [55]. These are:

- parental obesity
- very early BMI or adiposity rebound
- more than 8 hours watching television per week at age 3 years
- weight at 8 and 18 months

- catch-up growth
- weight gain in the first year
- birthweight
- short sleeping duration at age 3 years

Prevention programmes that take place in schools and also target parents would appear to be an effective route. Prevention strategies need to focus on the complex issues around childhood obesity involving diet, physical activity, sedentary behaviour, family lifestyle and environment. These interventions must, therefore, engage complex behavioural changes. An example of such an intervention is the school-based Planet Health project, although this appeared to be more effective for girls than boys [56].

Without a doubt the role of tackling the obesogenic environment [4, 5] is now seen to be fundamental in helping with both the prevention of overweight and obesity and with supporting those undertaking weight management. Promoting this role and indeed working with communities to co-produce community-based healthy weight planning [57] is certainly a role that dietitians should be taking up.

Learning points

- *Obesity is the most common childhood nutritional disorder worldwide and is an important area for dietitians*
- *A paediatric weight management dietitian should be seen as an important member of the team*
- *WHO/UK 1990 BMI centile charts should be used to diagnosis overweight and obesity and for monitoring progress*
- *Interventions should be family based, with at least one of the parents involved*
- *Changes in diet, physical activity and screen time should be targeted equally*
- *Dietitians working in paediatric weight management should have training in the use of behavioural change tools and techniques*

Prader–Willi Syndrome

Chris Smith

Introduction

Prader–Willi syndrome (PWS) is a rare genetic disorder in which genes on chromosome 15 are either deleted or unexpressed. The three main molecular mechanisms that result in PWS are the following: paternal deletion, maternal uniparental disomy (UPD) and imprinting defect. The prevalence of PWS is difficult to ascertain, but in Europe it has been reported between 1 in 8000 and 1 in 45000 births [58, 59] making it the most common genetic cause of obesity. PWS occurs equally in males and females and affects all ethnic groups. There is no cure for PWS. However, the prevention of obesity and complications, as well as quality of life, can be significantly improved with an early multidisciplinary approach including diet, growth hormone treatment, activity and behaviour modification [60].

Diagnosis is most commonly made through the presentation of hypotonia in infancy, and it is confirmed with a genetics blood test. The main characteristics of the condition include [61]:

- hypotonia
- hyperphagia
- short stature
- hypogonadism
- varying degrees of developmental delay
- scoliosis
- sleep disturbances
- high pain threshold
- speech apraxia/dyspraxia
- infertility
- poor/immature emotional and social development

The most commonly associated characteristic of the condition, however, is hyperphagia. Children with PWS have an insatiable appetite, leading to gross obesity if not controlled. This is the result of a chronic imbalance between energy intake and energy expenditure due to hyperphagia, decreased physical activity and reduced metabolic rate.

Historically, two distinct phases characterised this syndrome, representing the two extreme ends of nutritional status:

1. Faltering growth in infancy. The presence of hypotonia results in significant feeding difficulties and subsequent faltering growth. Tube feeding is often required during this period [62], which can be from birth to approximately 2 years of age.
2. Excess weight gain in childhood. From around age 5 years onwards weight escalates as a switch from poor

Table 25.2 Nutritional phases in PWS.

Phase	Age	Feeding behaviour	Dietary intervention	Growth pattern
0	Prenatal – birth	N/A	N/A	Lower birth weight than siblings
1a	0–9 months	Weak suck Breastfeeding may be difficult Unlikely to wake or cry for feeds Progress with texture and weaning may be slow	Orogastric/nasogastric feeding* Specialist teats	Growth failure Downward centile crossing common
1b	9–25 months	Improved feeding Vocalises appetite	May no longer require orogastric/nasogastric support	Close monitoring of growth pattern Upward centile improvement
2a	2.1–4.5 years	No obvious increased appetite or excess intake	Energy assessment and restriction Requires consistent and structured approach to food	Weight begins to accelerate Can enter obese phase if unrestricted
2b	4.5–8 years	Obvious increased appetite and preoccupation with food	Energy restriction and limited portion sizes Requires consistent and structured approach to food	Accelerated growth is common Height growth remains slow (improved with GH treatment)
3	8 years – adulthood	Hyperphagia	Possibly more significant energy restriction Requires consistent and structured approach to food	Rapid weight gain possible Comorbidities due to obesity common
4	Adulthood	Appetite may not be insatiable and can fluctuate Many adults may however not enter this phase	Continued energy restriction	Rapid increase in weight possible with increased independence Comorbidities due to obesity common

N/A, not applicable; GH, growth hormone.
* Gastrostomy placement is rarely required as improvements in oral development will happen as the infant develops.
Source: Adapted from [63]. Reproduced with permission of John Wiley and Sons.

feeding to hyperphagia occurs, resulting in the establishment of the second phase of obesity.

More recently, however, a large USA study has proposed a more gradual and complex range of phases. In total seven different nutritional phases are described (five main phases and two sub-phases), each with distinct characteristics (Table 25.2) [63].

Throughout these phases it is recognised that the combination of behavioural and nutritional problems requires a multidisciplinary team approach [64, 65]. It is important that dietary intervention and advice are given before the onset of weight gain, in order that excessive weight gain is curtailed. Consistent dietary advice from all professionals must be given to parents and carers, and the need to adhere to this explained. Gross obesity can occur during adolescence, and behavioural problems encountered during this period can add to the difficulties of care. However, obesity should not be considered inevitable, as weight can be controlled with comprehensive management.

Growth assessment

The inherent growth pattern of children with PWS varies from that of healthy children in that they have early childhood obesity, absent pubertal growth spurt and adolescent short stature. Therefore, sequential plotting on standard growth charts may make growth interpretation difficult. PWS specific charts are recommended for evaluating growth for comparison purposes, monitoring growth patterns, nutritional assessment and recording responses to growth hormone (GH) therapy. Several PWS specific growth charts have been proposed and produced from groups in Japan [66], Germany [67] and the USA [68], although there are no charts from UK data. Most recently, centile charts for non-growth hormone-treated children have been produced by the USA from birth up to 36 months [69], and from 36 months to 18 years [70]. Centile charts for growth hormone-treated children from 0 to 18 years are also now published [71].

There are thought to be no racial differences in growth patterns, but interestingly, on comparison, the data suggests the degree of overweightness is milder in Japanese children compared with Caucasian, with the same pattern reflected in adults [66].

Body composition is also inherently different in people with PWS, with lower lean body mass even in very young infants and toddlers [72]. There is limited reference data, but assessing body composition using valid techniques, where resources and skills allow, can be useful in the long-term monitoring of PWS children. Measurements can highlight good weight gain (lean mass) as a result of GH treatment, or a change in diet or physical activity that may be missed by

one dimensional weight or BMI measurements. In addition, the accuracy of determining energy requirements can be improved by taking into account body composition measurements [73].

Learning points

- *PWS is a rare condition with no cure. However, lives of children with PWS can be improved with a multidisciplinary approach, and paediatric obesity should not be considered inevitable*
- *Inherent growth difference occurs in PWS children and adolescents*

Nutritional requirements

A recent systematic review concluded that absolute total energy expenditure, resting energy expenditure, sleep energy expenditure and activity energy expenditure are all lower in individuals with PWS than in age, sex and body mass index-matched individuals without the syndrome [73]. The causes for these differences are multifactorial, including inherent disturbed body composition [74]. Limited studies have evaluated energy requirements, and calculating specific energy requirements for PWS children is controversial. There is particular uncertainty about energy requirements for small children.

Consensus appears to suggest the energy needs of children with PWS are typically 60%–80% of the recommended daily allowance [61]. There are several proposals for basing energy requirement for preschool- and school-age children on kcal/cm. These are 10–11 kcal/cm height for weight maintenance and 8–9 kcal/cm height for weight loss [75], and more recently 10–12 kcal/cm height for weight maintenance and 6–8 kcal/cm height for weight loss [76].

As with all children, the precise energy intake required will depend on many factors and requires close monitoring of growth as a guide.

Dietary considerations

While a significant difference in energy requirements is required, conversely requirements for micronutrients do not appear to be different from age-matched healthy controls. Therefore, focus on the quality, as well as the quantity, of the diet is paramount. Dietitians must take care to balance the need for provision of sufficient energy and nutrients for growth without excess energy intake leading to unwanted weight gain. Prevention of over-restriction, particularly in the younger more vulnerable infant, is of particular importance.

Surprisingly, for a condition with fundamental links to dietary intake, there are very few studies published on the actual nutritional intake of people with PWS. Only two studies have specifically investigated and reported micronutrient intakes in paediatric PWS patients. These studies were small and took patients from different continents: Europe [77] and the USA [78]. Due to the considerable variation in international eating habits and diets, extrapolation of these results to other populations should be done with caution, and some of the results from these studies were contradictory. Lindmark *et al*. [77] showed iron to be under-consumed in this group; conversely, Rubin *et al.*'s [78] study showed adequate iron consumption in all of the PWS patients. Calcium intake was below the reference nutrient intake (RNI) in 18% of the group in Rubin's study; Lindmark's study found calcium was not a nutrient of concern. Bone health, however, is an important consideration in PWS. Younger PWS children have been shown to have no significant difference in bone mineral density compared with controls, but a decline in adolescence is reported in both females and males [79]. Osteoporosis is common by adulthood [80]; therefore, vitamin D and calcium are of particular importance. A recent Italian study reported vitamin D levels in a group of PWS patients to be similar to a control group with the prevalence of levels <20 ng/mL in 30% of the PWS group [81]. No study to date in this patient group has included the assessment of zinc and selenium intakes. However, these have been shown to be two of the nutrients that were highlighted as very likely to be below the lower RNI (LRNI) in a UK group of patients [82].

In addition to awareness of likely low micronutrient intakes, care must also be taken in ensuring balanced macronutrients and, in particular, fat. Historically, a low fat intake was the diet of choice for management, but several studies have suggested that over-restriction of fat (<20% of total energy intake) can occur [20, 78]. This is associated with poly-unsaturated fatty acid deficiency, increasing the risk of associated negative consequences on development.

Dietary treatments

Evidence-based dietary approaches in children with PWS are scarce. Several dietary modifications have been proposed for treating adults: simple energy restriction (6–7 kcal/cm height per day); the 'red, yellow, green' diet that limits foods with higher energy density, sugar or fat; and general fat restriction [83]. A recent paediatric study proposed the principle of altering the proportion of energy from macronutrients in the diet (30% fat, 45% carbohydrates and 25% protein). When compared with a simple energy restricted diet, encouraging results were shown in both weight and body composition [84]. As yet no one specific strategy can be concluded to work best, as successes have been described with each. This in part supports the notion that, regardless of the approach, the common element of success is the consistency of that approach.

As a low energy diet may be lacking in some nutrients, it is widely recommended that children have a daily vitamin and mineral supplement [85]. Interestingly, in the largest and most recent review of PWS diets published [78], only 40% of patients supplemented their diet with multivitamins (with or without calcium).

The balance of fat sources, ensuring sufficient essential fatty acid intake, is advised. Anecdotally, supplementation

with medium-chain triglycerides (MCT) is increasingly popular. Nutritional supplements such as coenzyme Q10 and carnitine are also, anecdotally, widely used (and recommended in many USA clinics) for their association with energy metabolism. An investigation using serum sampling found no difference in levels in PWS patients compared with obese controls or sibling control groups [86]. Dosing and use for both of these remain controversial.

In addition to specific nutrient advice, several practical restrictive interventions have been proposed, including locking refrigerators and food cupboards, supervising meals and food shopping, and monitoring access to spending money. Maintaining strict control of portion sizes through standardised weights or measurements can also be very useful.

Undoubtedly strict control over dietary intake and access to food is necessary. However, it is worth noting that the preconception that PWS children will eat indiscriminately has been challenged by several studies. Joseph *et al*. conducted a small experiment offering PWS children and a control group of children with obesity the option of a larger quantity of food delivered after a delay (15, 30 or 60 seconds) or a small quantity of food delivered immediately. Individuals with PWS selected the larger food quantity, suggesting perceived differences in food quantity may be an important determinant of food choice [87]. A recent systematic review on food preferences concluded that PWS patients have a preference for sweet-tasting foods but recognises that the food choices and behaviours require substantially more work in order for the mechanisms to be understood [88].

Constipation is common in PWS children, and usual dietary treatments and prevention strategies can be applied.

Regardless of the type of dietary treatment, it is widely agreed that proactively starting on a consistent approach to mealtimes and intake before the child becomes hyperphagic is a key recommendation for the long-term successful management of the PWS child. Communication with other health professionals is essential to ensure a consistent message and, therefore, consistent approach to management. Equally important is the emphasis of communication by the parents to the extended family. This should include family, friends, teachers and other caregivers to prevent them from undermining established and agreed management principles.

Learning points: dietary treatments

- *Energy requirements are likely to be approximately 60% of normal requirements for age*
- *Requirements for macronutrients may require restriction while requirements for micronutrients should be considered to be the same as for healthy children*
- *Assessments of diet quality as well as the quantity is fundamental*
- *Evidence is lacking on the best dietary approach*
- *The principle of a structured and consistent approach from a young age is most likely to yield the best results*

Behaviours

Many behaviours of children with PWS are similar to those seen in autism. Table 25.3 shows the common behaviour characteristics of people with PWS.

An understanding and appreciation of the psychological aspects associated with PWS is important. Several common behaviours, such as the preference for a rigid and structured pattern, can be used to management advantage by establishing clear boundaries surrounding food.

The majority of the data on food behaviours supports the common theme that restricted, but predictable, food availability is an ideal model. Again utilising the inherent behaviours of this group can be to the child's benefit. PWS children are preoccupied with thoughts of food and so ensuring food security (such as the use of visual menus) can help to limit some of the more difficult anger and food-seeking behaviours. Table 25.4 suggests some behaviour strategies and principles to consider.

Food scavenging, ingestion of inappropriate foods (such as from bins) and stealing food can be common. Frozen

Table 25.3 Common behaviour characteristics of people with PWS.

Preference for rigid routine
Difficulty coping with change
Difficulty coping with emotions
Temper tantrums
Stubbornness/oppositional behaviours
Manipulative behaviours
Obsessive–compulsive characteristics
Psychosis (affecting 10%–20% by young adulthood; more frequent in those with UPD) [60]

UPD, uniparental disomy.

Table 25.4 Strategies that may help manage PWS eating behaviours.

Structured daily schedule with activities, including meals, snacks and exercise. Visual schedules placed somewhere consistent may help
Give advanced warning of any changes to the normal routine
Educate the child on healthy eating and appropriate food choices
Single plate rule or concept of 'my plate' and 'your plate'
Consistent strategies for dealing with constant food requests – these can include distraction and visual menus
Consider 'no doubt, no hope, no disappointment' approach [89]
Ensure consistent approach between all caregivers and family members
Avoid trying to reason with the child
Avoid using food as a reward

Source: Adapted from [89, 90].

foods and toiletries that resemble or smell like food can also be eaten. Attempts should be made to check all potential sources of food, e.g. from neighbours or friends, in keeping with a strict controlled intake. Offering food as a reward or withholding food as a punishment is almost always counter-productive and should be avoided.

Growth hormone

Best practice in early intervention management for PWS now includes recommendations for GH therapy, which is supported by the National Institute for Health and Care Excellence (NICE) [91]. A recent systematic review and international guideline for the use of GH in PWS provides good background on this topic [92]. It is widely recognised that GH will aid height growth, promote leaner body composition, increase energy expenditure, improve weight management, increase energy and physical activity, and improve strength, agility endurance and respiratory function [89, 91–95].

A recent 4-year longitudinal randomised controlled trial of 50 PWS children (aged 3.5–14 years) on GH treatment suggested it also prevented deterioration in cognition function, with the most benefit being seen in those with the greater deficit [96].

In another small study GH treatment showed improved body composition to be variable and suggested it increases total energy and fat intakes (although effects appear to vary depending on the developmental status of the child). It should also be noted that in this study the children on GH still had raised BMI, and the authors concluded that the treated children should have been on a tighter calorie controlled intake [97]. Indeed, it should be noted that GH-treated patients do not show complete normalisation of weight or BMI. However, a downward shift of these profiles when compared with non-GH-treated PWS individuals is evident [70]. GH treatment is not without risks, so its initiation and monitoring should be done by a suitable endocrinologist, ideally with experience in PWS [92].

Activity

It is very easy for people with PWS to gain weight. This is due to the combination of the overriding desire to eat coupled with low muscle tone, making exercise difficult and slow and, therefore, of little enjoyment. However, activity is a key element of treatment. Increasing energy expenditure and aiming to increase fat-free mass should be considered a constant goal, and maximising activity can help this [71]. Some activities are physically difficult for the PWS child due to poor muscle strength, but walking and swimming can be accomplished by most and should be encouraged. A small prospective study in prepubertal PWS children from the Netherlands showed daily muscle training increased lean body mass when compared with controls, although it did not normalise lean mass [98].

Learning points: behaviours and activity

- *Common PWS behaviours associated with the condition can be very challenging but can be utilised to promote successful management*
- *Growth hormone and activity are important adjuncts to treatment for weight control*
- *Establishing a pattern of regular activity should be encouraged and supported*

Monitoring

There is no current UK national standard recommending the frequency or specific monitoring or considerations for follow-up in people with PWS. Monitoring guidelines have been published in the USA [99], which suggest evaluating diet (including adequacy of vitamin and mineral intake), growth parameters (height, weight and BMI) and activity:

- every month in infancy
- every 6 months in the first decade of life
- at least annually thereafter

The application of this for UK dietitians would appear sensible. More recently, specific recommendations for endocrine monitoring and screening have been published [100].

PWS patients may be followed up in a variety of settings. There are several PWS specialist multidisciplinary clinics in the UK and the follow-up timeframe varies between these. However, the principle of close monitoring and support is well recognised and consistent.

A case study to show the management of a boy with PWS is given in Table 25.5.

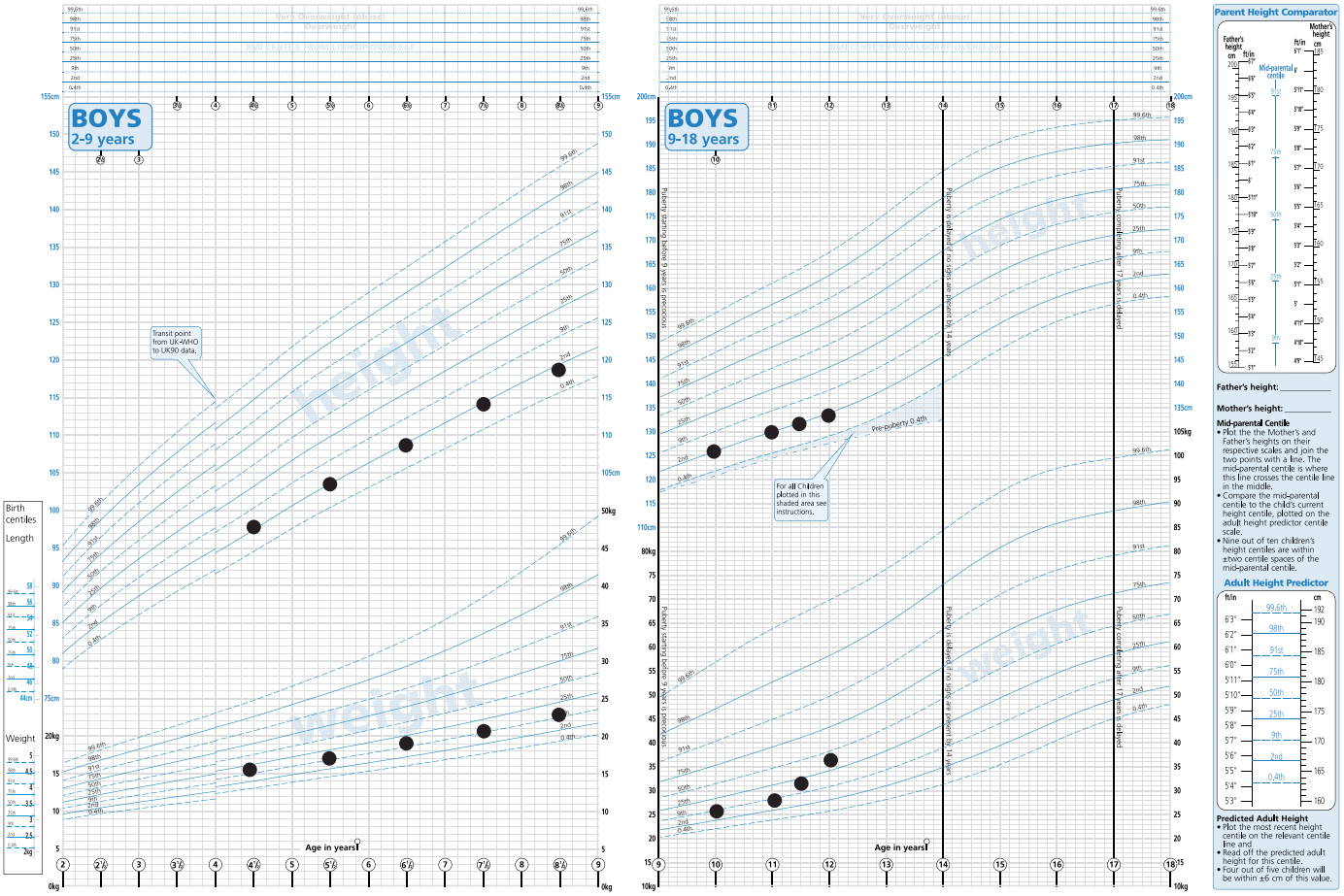
Transition

Ideally a young person with PWS should be transitioned to an adult service with a dietitian who has an interest and experience in PWS. In some areas this may come under the remit of the Learning Disability Dietetic Team. Monitoring in adult patients is as important as in children. As the child approaches transition, education and identification of tools for adult life should be discussed and recommended. There are four options for adult patients with PWS:

- living with parents or other relatives
- group home placement
- supported living services
- specialised residential services

Each may require different levels of nutritional and weight monitoring, depending on the level of support. It is widely acknowledged that adults with PWS probably lack capacity relating to food choices (when and how much), so there is a duty of care to support the individual to manage their food intake appropriately. The issue of mental capacity with respect to PWS patients in the UK is important and discussed

Table 25.5 Case study: management of a boy with Prader–Willi syndrome.



Presentation

A 12-year-old boy with PWS (growth hormone-treated) attends clinic for 6 monthly review. Presents with clear and sustained acceleration of weight gain over the last year. Linear growth is maintained. No signs of puberty. Otherwise well with no new medical issues. Historical strict control and management of diet and steady controlled weight gain (as evidenced from growth chart)

Assessment

a. Anthropometry
   Plots on Boys UK Growth chart 2–18 years reveal accelerated acute weight gain
   BMI calculations and comparison show significant increase in the last 12 months
   Plots on PWS specific growth charts for growth hormone-treated child suggest overall pattern within that expected, but with recent acceleration clear
   Body composition measurements compared with his historical data (as there are no standards to compare with) show a notable increase in % body fat and a reduction in lean body mass
b. Biochemistry and other lab results
   Review of blood tests indicated growth hormone is at appropriate dose
   Review of nutritional bloods including vitamin D, parathyroid hormone, zinc and iron reveal all in range, but with ferritin and zinc borderline
c. Health and disease state
   Scoliosis stable. Behaviour aspects challenging
d. Nutritional and food intake
   Diet recall with family reveals consistent nutritional intake from previous reviews
   No changes to family management strategy
   Detailed 3-day food diary requested from family
   Analysis: intake 65% of estimated average requirement for energy; micronutrient intakes low for many minerals, however achieving reference nutrient intake when vitamin and mineral supplement included
e. Social circumstances
   Recent change to mainstream secondary school, but with education, health and care plan (EHCP) in place
   New teachers, new peers and small increase in independence
   On discussion with patient it becomes obvious access to food much less controlled in the school environment coupled with a lack of understanding of diligence required from teaching assistant (1:1 supervision necessary)

(continued overleaf)

Table 25.5 *(continued)*

Identification of diagnosis

Problem:
Accelerated weight gain. Concern of both long- and short-term consequences of this on the child's health and quality of life if left unaddressed

Aetiology:
Unprepared new environment (school) where previous well established safety mechanisms to prevent access to food no longer in place. Family/home environment proven successful in the past; main area of issue is external

Sign and symptoms:
Accelerated weight gain and BMI
Changes in body composition
Discussions with school and 1:1 supervisors

Implementation
Education for key school supervisors on principles of PWS care
Provision of written support documentation for school
Request for evaluation of patient's access of food/any unsupervised situations in school environment
Diet management and requirement for daily structured activity written into EHCP

Monitor and review
Review situation with school and family
Re-evaluate patient's access to food
Weekly weight recommended until weight stable

Evaluation
Patient's weight gain stabilised

Learning points: case study

- *Identification of changes in growth pattern weight gain is key to identify an issue with management*
- *Changing environments for PWS children require careful planning and evaluation to ensure strategies to control access to food are minimised*
- *Accelerated weight patterns should be addressed with urgency as uncontrolled weight gain and subsequently raised BMI and % body fat can have long-term impacts on the child's health and quality of life*

in detail in a recent guide written in association with the UK PWS Association [101].

Ensuring young people with PWS transition to adult services with an acceptable weight/BMI is a key target for paediatric dietitians. The development of metabolic syndrome and complications in PWS adults is closely associated with obesity status. Type 2 diabetes is estimated to affect 25% of adults with PWS [102]. A useful paper describes the common issues in adult care [103].

Surgical interventions, such as gastric bypass, have been used in adults with PWS, although these are not recommended as treatments [104]. In addition to not addressing the inherent hyperphagia, they are also associated with high complication rates.

Future research

Clinical trials investigating potential treatments for PWS are ongoing. Work is progressing across five main areas:

- genetic therapies
- use of cognitive therapies, e.g. cognitive behavioural therapy (CBT)
- implanted devices, e.g. vagus nerve stimulation
- medications to address hyperphagia
- medications to impact behaviour

Oxytocin has attracted particular interest in recent years in relation to the behaviours of PWS patients. While many of these clinical trials (four of five) showed promising results, a recent review of all of these concluded that due to limitations there is currently no convincing evidence that it improves symptoms [105].

There is much interest currently in the use of ketogenic diets. However, there are currently no robust good quality studies that allow any conclusions to be drawn on this as a viable treatment approach.

Summary

In PWS dietary management presents a tremendous challenge for the child, family, caregivers, and health professionals. Even so, weight control and even weight loss is achievable and is frequently associated with improved behaviour, often due to the establishment of routines and clear rules. In addition, weight control can

importantly be a source of pride and achievement for the individual with PWS.

A good multidisciplinary approach, agreed early interventions and careful appropriate monitoring can improve quality of life greatly for people with PWS and their families. Good quality nutritional support is essential to ensure PWS individuals achieve their full potential.

Parents and dietitians involved in PWS are encouraged to join the UK PWS Association charity for support and information.

Acknowledgements

Jackie Waters (PWSA), Dr Shankar Kanumakala and Dr Anne Livesey.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

26 Eating for Children from Minority Ethnic Groups

Eulalee Green

Introduction

The UK is the home to a multicultural and multi-ethnic society. Immigration during the late 1950s and early 1960s was in response to labour shortages. Since the 1980s conflict in Africa and Europe has led to further immigration, and, together with movement of people from European Union countries, the diversity of the UK has increased. As with the early migrations, ethnic communities have remained near large industrialised cities. These ethnic groups have introduced a wide variety of cultures, including dietary beliefs and practices, which have had to fit into their new lifestyles. Achieving nutritionally adequate diets became a challenge with people finding themselves in an environment very different from their homeland.

The top 25 countries of birth of migrants to the UK from July 2017 to June 2018 are shown in Table 26.1. Table 26.2 shows the percentage of ethnic groups in England and Wales from the latest national census report of 2011.

It is essential that healthcare professionals understand religious and cultural attitudes towards diet when they are initiating any dietary intervention in order to achieve optimal growth and development in these children. Assessment of intake must be accurate, and any advice given must be relevant to dietary custom so that it is both realistic and achievable.

Children are subject to many outside influences and often start to develop Westernised dietary ideas. With time, these ideas are taken home and adopted by other members of the family. The extent of adoption of dietary practices that differ from traditional customs is variable; therefore, all diets must be individually assessed.

Table 26.3 shows the religions practised in the UK, and Table 26.4 gives a guide to religious and cultural influences on the diet.

Vegetarian and vegan diets

Vegetarianism and veganism are common dietary practices among many religious and ethnic groups. In addition, increasing numbers of the indigenous population are restricting their intake of meat and animal products for either humanitarian, ethical or health reasons. Table 26.5 gives a classification of vegetarian and vegan diets. Providing that careful attention is given to ensuring nutritional adequacy, these diets can support normal growth and development [4–6]. In general, the greater the degree of dietary restriction, the greater is the risk of nutritional deficiency [7]. The vegan diet is most restricted. Parents who chose a vegan diet for their children should be supported to ensure that their children have adequate intake. A recent position paper from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) suggests that vegan diets in infancy should only be used under medical or dietetic supervision and that parents should understand the consequences of failing to follow advice regarding supplementation of the diet, such as retarded growth, fat and muscle wasting, slower psychomotor development and an increased risk of irreversible cognitive impairment [8]. Table 26.6 gives dietary sources of the nutrients most at risk in a vegan diet.

Infant feeding

The current recommendation in the UK is for babies to be exclusively breastfed for around the first 6 months of life and for breastfeeding to continue for at least the first year while solid foods are being introduced; most infants should not start solids until around 6 months of age [9]. There is a higher proportion of women from minority ethnic groups who

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Table 26.1 Top 25 countries of birth of all migrants to the UK (excluding living in communal establishment), July 2017 to June 2018.

Ranking	Country of birth	Number of migrants (thousands)	Percentage of population
1	Poland	889	1.4
2	India	862	1.3
3	Pakistan	529	0.8
4	Romania	410	0.6
5	Republic of Ireland	380	0.6
6	Germany	309	0.5
7	Bangladesh	259	0.4
8	Italy	237	0.4
9	South Africa	235	0.4
10	China	210	0.3
11	Nigeria	205	0.3
12	Lithuania	184	0.3
13	France	178	0.3
14	USA	159	0.2
15	Spain	155	0.2
16	Philippines	144	0.2
17	Australia	142	0.2
18	Sri Lanka	135	0.2
19	Portugal	132	0.2
20	Jamaica	124	0.2
21	Kenya	123	0.2
22	Zimbabwe	116	0.2
23	Ghana	113	0.2
24	Somalia	104	0.2
25	Latvia	96	0.1

Source: Office of National Statistics [1]. Licensed under Open Governemnt License.

choose to breastfeed their babies up to 6 months of age [10] (Table 26.7). There is no data about breastfeeding at 6 months and ethnicity after 2010.

All breastfed infants and infants having less than 500 mL of infant formula should be given a vitamin D supplement, which should continue throughout childhood (p. 28) [11]. Suitable vitamin drops include Healthy Start, Abidec and Dalivit (Table 1.22).

If the infant is not breastfed, an infant formula must be given. Table 26.8 shows normal infant formulas, milks and special therapeutic formulas that are suitable for vegetarian and vegan families and for those who require a halal or kosher formula. Some families will accept 'unsuitable' formulas if there is a clinical need and may seek advice and assurance from their religious leader.

Some vegetarian families choose to give their babies goat's milk or ewe's milk in the belief that these confer health benefits and are preferable to cow's milk. These milks are contraindicated because of their nutritional inadequacy, high renal solute load and doubtful microbiological safety [12, 13]. The European Food Safety Authority considers that protein from goat milk can be suitable as a protein source for infant formula provided the formula complies with the compositional criteria laid down in Directive 2006/141/EC [14].

Providing the maternal diet is adequate, breastmilk will be nutritionally adequate for the first 6 months of life for most infants, with a recommended vitamin D supplement. Specific attention must be paid to the mother's vitamin D, calcium and iron intakes. Vegan mothers may require supplementation with additional vitamin B_{12} [15]. Vitamin B_{12} deficiency resulting in neurological damage, irritability, faltering growth, apathy, anorexia and developmental regression has been reported in breastfed infants of vegan mothers [16]. Some algae (e.g. spirulina) and seaweeds (e.g. nori) contain natural compounds that are similar to vitamin B_{12}; however, the human body cannot use these nutrients. Furthermore, because they are so similar to B_{12}, they compete with it and can be the cause of B_{12} deficiency in people who do not eat animal products. Vegetarian sources of iron and vitamin B_{12} are given in Table 26.9.

Weaning

At around 6 months of age, solids should be gradually introduced to the infant's diet, increasing flavours and textures with time. Only a small number of women choose to introduce solids before their child is 4 months old, but only 10% of women wait until their child is 6 months old. Table 26.10 shows the age of introduction of solids by ethnic group.

Pulses must be thoroughly cooked to destroy toxins such as trypsin inhibitors and haemagglutinins, which may cause diarrhoea and vomiting [13]. Breastfeeding or infant formula should be continued until 1 year of age. As the child gets older, they should be encouraged to take 500 mL/day full fat cow's or approved calcium fortified alternative, or the equivalent in cheese or yoghurt, in order to provide enough calcium. Suitable weaning foods for vegetarian and vegan diets are given in Table 26.11.

Children

Vegan diets are typically high in fibre and low in fat, so care must be taken to ensure an adequate energy intake to support growth. A systematic review of vegetarian and vegan diets found that growth in children was similar or slightly less than their non-vegetarian peers [18]. To provide optimal nutrition a vegetarian or vegan diet should be well balanced, containing two or three helpings of protein foods daily plus cereals, vegetables, fruits and fats (Table 26.12). Vegetable and pulse proteins have a lower concentration and range of essential amino acids than protein from animal

Table 26.2 Percentage of ethnic groups in England and Wales, 2011.

		Percentages	
		Total population	Ethnic population
White	White British	80.5	
	Irish	0.9	4.6
	Gypsy or Irish traveller	0.1	0.5
	Other white	4.4	22.5
Mixed/multiple ethnic groups	White and black Caribbean	0.8	4.1
	White and Asian	0.6	3.1
	White and black African	0.3	1.5
	Other mixed	0.5	2.6
Asian/Asian British	Indian	2.5	12.8
	Pakistani	2.0	10.3
	Bangladeshi	0.8	4.1
	Chinese	0.7	3.6
	Other Asian	1.5	7.7
Black/African/Caribbean/black British	African	1.8	9.2
	Caribbean	1.1	5.6
	Other black	0.5	2.6
Other ethnic group	Arab	0.4	2.1
	Any other ethnic group	0.6	3.1

Source: Office of National Statistics [2].

Table 26.3 Percentage of the UK population belonging to a religion, April 2011 to March 2012.

Religion	Population percentage	Number (thousands)
Christian	62.0	37 191
Islam/Muslim	4.6	2 755
Hindu	1.4	860
Sikh	0.6	350
Jewish	0.5	287
Buddhist	0.4	246
None or undeclared	29.9	17 927

Source: Office of National Statistics [2].

or fish sources. Therefore, careful planning of menus with pulse and cereal combinations is necessary to provide sufficient protein of high biological value. The protein and energy content of the diet can be increased by the use of nuts, beans and oils.

The main micronutrients at risk of deficiency in the vegan diet are shown in Table 26.5. In addition, vegan children may require a daily supplement of 1–2 μg vitamin B_{12} [12]. The increased intake of phytate-containing legumes and whole grains may lead to poor bioavailability of zinc [19] and iron [20]. It is important to ensure that a food or drink rich in vitamin C is given alongside iron-containing foods to increase bioavailability. When considering recommendations for dietary fat, a vegan diet is often regarded as 'healthy'. The essential fatty acid, docosahexaenoic acid (DHA) (22: 6*n*–3), has been found to be absent from vegan diets [21]. DHA has an important role in growth, the health of the retina, central nervous system and skin. Vegans should, therefore, use oils with a low linoleic-α-linolenic acid ratio such as walnut, rapeseed, flax and linseed oils (Table 26.13). Sources of vitamin D and calcium in the diet are shown in Tables 26.14 and 26.15.

Fruitarian diets

Fruitarian diets are based on fruit and uncooked fermented cereals and seeds. These diets are nutritionally inadequate for children of any age and can lead to severe protein–energy malnutrition, anaemia and multiple vitamin and mineral deficiencies.

South Asian subcontinent

The communities from the South Asian subcontinent include those from India, Pakistan, Bangladesh and Sri Lanka and those who came to the UK via East Africa. Migrations to the

Table 26.4 A guide to religious and cultural influences on diet.

Food	Buddhist	Christian	Hindu	Jewish	Muslim	Rastafarian	Seventh-Day Adventist	Sikh
Eggs	Acceptable to some	Acceptable	Acceptable to some	No blood spots	Acceptable	Acceptable to some	Acceptable to most	Acceptable
Milk, yoghurt	Acceptable	Acceptable	Acceptable to some	Acceptable	Acceptable to some	Acceptable to some	Acceptable to most	Acceptable
Cheese	Acceptable	Acceptable	Not with rennet	Not with rennet	Not with rennet	Acceptable to some	Acceptable to most	Acceptable to some
Pork	Acceptable to some	Acceptable to most	Rarely acceptable	Not acceptable	Not acceptable	Not acceptable	Not acceptable	Rarely acceptable
Beef	Acceptable to some	Acceptable	Not acceptable	Kosher	Halal	Acceptable to some	Acceptable to some	Not acceptable
Lamb	Acceptable to some	Acceptable	Acceptable to some	Kosher	Halal	Acceptable to some	Acceptable to some	Acceptable
Chicken	Acceptable to some	Acceptable	Acceptable to some	Kosher	Halal	Acceptable to some	Acceptable to some	Acceptable to some
Fish	Acceptable to some	Acceptable – some only fish with fins and scales	Acceptable – with fins and scales	Acceptable – with fins, scales and backbone	Acceptable – with fins and scales	Acceptable – with fins and scales	Acceptable – with fins and scales	Acceptable to some
Shellfish	Not acceptable	Acceptable to most	Acceptable to some	Not acceptable	Acceptable to some	Not acceptable	Not acceptable	Acceptable to some
Animal fats	Acceptable to some	Acceptable	Acceptable to some	Kosher	Halal	Acceptable to some	Not acceptable	Acceptable to some
Alcohol	Not acceptable	Acceptable to most	Not acceptable	Acceptable	Not acceptable	Not usually wine	Not acceptable	Acceptable
Cocoa, coffee, tea	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Not acceptable	Decaffeinated are suitable	Acceptable
Fasting		Good Friday and Ash Wednesday for some	3 days a year or 1–2 days every week	Yom Kippur 1 day of atonement (no food or liquid for 25 hours)	Ramadan 1 month fasting (no food or liquid during daylight)			
Other comments	Most Buddhists are vegetarians or vegans, although some may not be		Certain foods are taken during prayers. Some Hindus may be vegetarians or vegans (Jains)	Kosher (food fit to eat), i.e. meat from animals slaughtered by a kosher butcher. Milk and dairy products are not consumed within 3 hours of each other	Halal, i.e. meat must be from animals that have been bled to death and the phrase 'in the name of God' is said	Processed, preserved or tinned foods may be avoided. Most only eat Ital foods, i.e. in a whole and natural state. No fruits of the vine, e.g. sultanas, grapes, currants	Some are vegetarians	Some may be vegetarians
Black and ethnic minority groups	Chinese, Vietnamese	Afro-Caribbean, Chinese, Greek, Greek Cypriot, Ugandan, Vietnamese, West African (e.g. Nigerian and Ghanaian), Indian	Gujarati, Punjabi, Indian	Jews of all nationalities	Arab, Bangladeshi, Pakistani, Gujarati, Somali, Turkish, Turkish Cypriot, Ugandan, West African (e.g. Nigerian and Ghanaian), Indian	Afro-Caribbean	Afro-Caribbean	Indian

Source: Adapted from British Dietetic Association [3].

Table 26.5 Classification of vegetarian and vegan diets.

	Foods excluded	Animal protein source	Non-animal protein source	Nutrients at risk of deficiency
Partial vegetarian	Red meat Offal	Poultry Fish Eggs Milk Cheese Yoghurt	Beans Lentils Nuts Seeds	Iron Vitamin D
Lacto-ovo-vegetarian	Red meat Offal Poultry Fish Eggs	Milk Cheese Yoghurt	Beans Lentils Nuts Seeds	Iron Vitamin D
Lacto vegetarian	Red meat Offal Poultry Fish Eggs	Milk Cheese Yoghurt	Beans Lentils Nuts Seeds	Iron Vitamin D
Vegan	Red meat Offal Fish Poultry Eggs Milk Cheese Yoghurt		Beans Lentils Nuts Seeds	Protein Energy Omega-3 fatty acids (especially DHA) Vitamin D Iron Vitamin B_2 Vitamin B_{12} Calcium Zinc

DHA, docosahexaenoic acid.

Table 26.6 Sources of nutrients at risk of deficiency in a vegan diet.

Nutrient at risk of deficiency	Suitable dietary alternative sources
Protein	Pulses (soya, tofu, tempeh, beans and lentils), grains (wheat, rice, rye, millet, etc.), seeds, groundnuts*, nuts* and nut spreads*. Meals should have a combination of grains with seeds or grains with pulses to get the right balance of essential amino acids to ensure the best use of the available protein
Energy	Vegetable oils/margarine, groundnuts, nut spreads
Iron	Iron fortified cereals, wholegrain cereals, wholemeal bread, pulses, dried fruit and nuts. Dark leafy green vegetables are not a suitable source of iron for infants and young children as the portion size is so large (120 g for 2 mg iron). Foods rich in vitamin C, such as fruits and vegetables, aid the absorption of non-animal sources of iron
Fat-soluble vitamins	In England, white people will make enough vitamin D for the year from 30 minutes a day of moderate sunlight from April to October. Black and Asian people living in England will not make enough and must rely on dietary sources or supplements: vegetable oils/margarines, fortified soya milk and fortified cereals
Essential fatty acids	Whole grains, nuts, seeds and seed oils
Vitamin B_2	Wheat germ, almonds, green leafy vegetables, yeast extract (e.g. Marmite, Tastex**), avocado, soya beans, fortified soya milk
Vitamin B_{12}	Fortified yeast extract (e.g. Marmite, Tastex**), fortified cereals, fortified soya milk, tofu
Calcium	Fortified soya products (soya milk and yoghurt), seaweed products (kombu, wakame, nori), nuts and seeds. Other sources (bread, leafy green vegetables, pulses) are not suitable sources of calcium for infants and young children as the portion size is so large (>120 g for 100 mg calcium)
Zinc	Some soya products (flour, miso, cheese and tempeh), nuts, seeds, wheat germ, wholemeal bread, fortified breakfast cereals, seaweeds and hard cheeses
Iodine	Whole grains, seaweeds and vegetables

*Whole nuts should not be given to children under 5 years of age as they are a choking hazard. Nut allergy is discussed on p. 319.
**Yeast extracts should be used with care in children under 2 years of age due to the high salt content.

Table 26.7 Prevalence of breastfeeding at ages up to 6 months by mother's ethnicity in Great Britain, 2010.

	Total Great Britain (%)	White (%)	Mixed (%)	Asian or Asian British (%)	Black or black British (%)	Chinese or other ethnic group (%)
Birth	82	79	87	96	95	96
2 days	77	75	81	88	90	94
3 days	75	73	80	86	90	93
4 days	73	71	80	85	90	93
5 days	72	69	79	84	90	93
6 days	71	68	79	83	90	93
1 week	70	67	79	83	90	92
2 weeks	66	63	79	81	89	87
6 weeks	56	52	75	73	85	82
4 months	43	39	60	58	73	76
6 months	35	32	49	49	61	66

Source: Data.Gov.UK. *Infant Feeding Survey – 2010* [10]. Licensed under Open Governement.

Table 26.8 Infant formulas and milks suitable for religious and cultural diets.

Milk-based feeds	Suitable for kosher	Suitable for halal	Suitable for vegetarians
Abbott PaediaSure	√	√	√
Abbott PaediaSure Compact	X	X	√
Abbott PaediaSure Fibre	√	√	√
Abbott PaediaSure Plus	√	√	√
Abbott PaediaSure Plus Fibre	√	√	√
Abbott PaediaSure Plus juce	√	√	√
Abbott Similac High Energy	√	√	√
Cow & Gate Anti-Reflux	X	X	X
Cow & Gate Comfort	X	X	X
Cow & Gate First Infant Milk	X	√ (P)	X
Cow & Gate Follow-on Milk	X	√ (P)	X
Cow & Gate Growing-up 3	X	X	X
Cow & Gate Growing-up 4	X	√ (P)	X
Cow & Gate Hungrier Baby	X	√ (P)	X
Cow & Gate Nutriprem 1	X	√	X
Cow & Gate Nutriprem 2	X	√	X
Cow & Gate Nutriprem Human Milk Fortifier	X	X	X
Cow & Gate Nutriprem Hydrolysed	X	√	X
Mead Johnson Enfamil AR	√	X	X
Mead Johnson Enfamil Human Milk Fortifier	√	√	X
Mead Johnson Enfamil Infant	√	X	X
Mead Johnson Enfamil Premium	√	X	X
Mead Johnson Enfamil Premium Newborn	√	X	X
Mead Johnson Enfamil Premature	√	√	X
Nestle NAN Comfort 1	X	√	X
Nestle NAN Comfort 2	X	√	X
Nestle NAN Comfort 3	X	√	X

(*continued overleaf*)

Table 26.8 *(continued)*

Milk-based feeds	Suitable for kosher	Suitable for halal	Suitable for vegetarians
Nestle NAN Optipro 1	X	X	X
Nestle NAN Optipro 2	X	√	X
Nestle NAN Optipro 3	X	√	X
Nestle NAN Supreme 1	X	X	X
Nestle NAN Supreme 2	X	X	X
Nestle Resource Junior	X	X	X
Nutricia Aptamil Anti-Reflux	X	√	X
Nutricia Aptamil Comfort	X	√	X
Nutricia Aptamil First	X	√	X
Nutricia Aptamil Follow-on Milk	X	√	X
Nutricia Aptamil Growing-up 3	X	√	X
Nutricia Aptamil Growing-up 4	X	√	X
Nutricia Aptamil Hungry Milk	X	X	X
Nutricia Aptamil Lactose Free	X	X	X
Nutricia Infatrini	√	√	X
Nutricia Nutrini	√	√	X
Nutricia Nutrini Energy	√	√	X
Nutricia Nutrini Energy Multifibre	√	√	X
Nutricia Nutrini Low Energy Multifibre	√	√	X
SMA Extra Hungry Infant Milk Powder	X	√	√
SMA First Infant Milk	X	√	X
SMA Follow-on Milk Powder	X	√	X
Peptide-based feeds			
Abbott PaediaSure Peptide	X	√	√
Abbott Similac Alimentum	X	X	√
Mead Johnson Nutramigen	X	X	X
Mead Johnson Pregestimil	X	X	X
Nestle Peptamen Junior Advance	X	X	X
Nestle Peptamen Junior Liquid	X	X	X
Nestle Peptamen Junior Powder	X	X	X
Nestle SMA Althera	X	X	X
Nutricia Aptamil Pepti 1	X	X	X
Nutricia Aptamil Pepti 2	X	X	X
Nutricia Aptamil Pepti-Junior	X	X	X
Nutricia Infatrini Peptisorb	√	√	X
Nutricia Nutrini Peptisorb	√	√	X
Soya feeds			
Mead Johnson Enfamil ProSobee	√	X	X
Nestle SMA Wysoy	X	√	√
Mead Johnson PurAmino	√	√	X

(*continued overleaf*)

Table 26.8 *(continued)*

	Suitable for kosher	Suitable for halal	Suitable for vegetarians
Amino acid-based feeds			
Nestle SMA Alfamino Infant	X	X	X
Nestle SMA Alfamino Junior	X	X	X
Nutricia Neocate Junior	√	√	X
Nutricia Neocate LCP	√	√	X
Nutricia Neocate Syneo	√	√	X

P, powder only.
This information is correct at the time of writing.
Always check with the manufacturer.

Table 26.9 Sources of iron and vitamin B_{12} suitable for vegetarians.

Sources	Iron (mg)	B_{12} (μg)
Infant formula, 200 mL	1.4	0.2
Milk (all types except UHT), 200 mL	0.4	2
Yoghurt full fat (1 medium pot), 150 g	0.3	0.3
Cheddar-type cheese (1 slice), 50 g	0.1	1
Fromage frais (1 medium pot), 100 g	0.1	1.4
Soya cheese (1 slice), 40 g	0.4	0.75
Spinach boiled (3 tbsp), 100 g	4	0
Fenugreek (methi) seeds (1 tbsp), 11 g	4	0
Watercress (1 bunch), 80 g	2	0
Broccoli/peas (2–3 tbsp), 80 g	1	0
Apricots (6), figs (3) dried, 60 g	2	0
Raisins/sultanas (1 tbsp), 30 g	1	0
Bread wholemeal (2 slices), 60 g	2	0.3
Bread white (2 slices), 60 g	1	0
Bran flakes (3 tbsp), 25 g	4	0.5
Fortified breakfast cereals, e.g. Special K, Cheerios (3 tbsp), 25 g Weetabix (2 biscuits), 40 g	3	0.5
Lentils (dhal) green/brown boiled (½ cup),100 g	3	0
Black-eyed beans/kidney beans, chickpeas boiled (4 tbsp), 100 g	2	0
Baked beans (1 small can), 200 g	3	0
Hummus (2 tbsp), 50 g	1	0
Tofu fried (1 average serving), 50 g	2	0
Vegeburger soya mince, fortified with B_{12} (1 average burger) 56 g	2.5	0.2
Nuts, e.g. almonds, cashew, brazil (1 average serving), 25 g	1	0
Seeds, e.g. melon, pumpkin, sesame (1 average serving), 30 g	2	0
Curry powder (1 tsp), 3 g	3	0
Plain chocolate (1 bar), 50 g	1	0
Yeast extract (spread on 1 slice bread), 1 g	0	0.01

tbsp, tablespoon (15 mL); tsp, teaspoon (5 mL).
Source: Adapted from CompEat Pro nutritional database, based on Ref. [17].

UK began in the seventeenth century when the British East India Company first began trading with India [22]. Today the Asian community represents 34.9% of the ethnic groups in the UK [2]. Traditional dietary customs are largely based on the religious and cultural beliefs of the three main religious groups: Hindus, Muslims and Sikhs. Dietary variance has been observed within these groups, as income and geographical area have an influence on the diet.

Dietary customs of Hindus

Approximately 1.4% of the UK population are Hindu [2]. The majority originally came from the Gujarat region of India, although some are from the Indian Punjab and East Africa [22, 23].

Hindus classify foods into three groups [24]:

- sattvik (nutritious foods) such as milk, fruit, vegetables, nuts and whole grains
- rajasi (foods of strong emotions) such as meat, eggs, fish, spices, onions, garlic, hot peppers, pickles and other pungent or spicy foods
- tamsai (leftovers producing negative emotions), i.e. foods that are stale, overripe, spoilt or imperfect

Fasting is common among Hindus to help reinforce control over the senses and to achieve closeness to God. Fasting occurs for a few days during holy days, new moon days and festivals.

A restriction on eating beef was introduced between 1500 and 500 BC because Hindus regard the cow as sacred. It is also unusual for pork to be eaten as the pig is thought to be unclean. Devout Hindus believe in the doctrine of Ahimsa (not killing) and are vegetarian. Some will eat dairy products and eggs, while others refuse eggs because they are potential sources of life. A minority of Hindus practise veganism. Wheat is the staple food eaten by Hindus in the UK. It is used to make chapattis, puris and parathas. Oil and ghee (clarified butter), which is believed to sanctify food, are used extensively in cooking [22]. Traditional Hindus fast on 3 days a year to celebrate the birthdays of the Lords Shiva (March), Rama (April) and Krishna (August). Orthodox Hindus may also fast once or twice every week (often on Tuesdays and Fridays). Fasting lasts

Table 26.10 Age of introduction of solids by mother's ethnicity in Great Britain, 2010.

	% White	% Mixed	% Asian or Asian British	% Black or black British	% Chinese or other ethnic group	% Great Britain total
6 weeks	1	4	2	5	1	2
8 weeks	2	4	3	5	1	2
3 months	5	4	4	9	1	5
4 months	30	24	22	33	19	29
5 months	77	69	62	65	65	75
6 months	95	90	90	90	83	94
9 months	99	99	97	99	x	99

Source: Data.Gov.UK *Infant Feeding Survey – 2010* [10]. Licensed under Open Governement.

Table 26.11 Suitable vegetarian and vegan weaning foods.

Age	Foods
Around 6 months Initially foods may need to be pureed or mashed	Baby rice Cooked fruit and vegetable Weetabix Cooked pulses and lentils with rice or wheat foods Pudding or custards made with cow's milk or calcium fortified soya milk
7–9 months Introduce lumps and soft finger food	Whole grains Bread Pasta and rice Cooked pulses or lentils with rice or wheat foods Finely ground nuts Dried fruits Cheese made from cow's milk or calcium fortified soya curd Egg Tofu and Quorn
9–12 months Minced and chopped texture	As above

Table 26.12 Sample vegetarian or vegan meal plan for young children.

Breakfast	Breakfast cereal with milk or milk substitute Wholemeal or white bread, margarine, peanut butter, other nut butter or yeast extract *Egg
Midday meal	Beans, dhal, lentils, soya, **nut-based dish, *egg-based dish or *cheese-based dish Bread, chapattis, pasta, potatoes, rice, couscous or rice Fruit or fruit-based dessert
Evening meal	Alternative choices from above
Drinks	Dilute orange juice (not orange squash or juice drink) *Cow's milk or recommended milk substitute Water
Snacks	Nuts**, dried fruit, toast, fruit

*Not suitable for vegans.
**Whole nuts should not be given to children under 5 years of age as they are a choking hazard.

Table 26.13 Vegetarian sources of essential fatty acids.

	Energy (kcal (kJ))	α-Linolenic acid (g)	Linolenic acid (g)
Nuts and seeds			
Walnuts 6 nuts (24 g)	165 (681)	2	9
Sunflower seeds 1 tablespoon	57 (238)	0	3
Brazil nuts 3 nuts (15 g)	102 (422)	0	4
Flaxseed 1 tablespoon (13 g)	66 (274)	3	1
Sesame seeds 1 tablespoon (11 g)	66 (272)	0	3
Pumpkin seeds 1 tablespoon (12 g)	68 (281)	0	3
Peanuts (groundnuts)10 nuts	68 (281)	0	2
Almonds 12 nuts	70 (290)	0	1
Hazelnuts 10 nuts	68 (280)	0	1
Oils (10 mL)			
Safflower	90 (370)	0	6
Evening primrose	90 (371)	0	7
Sunflower	90 (370)	0	7
Soya	90 (370)	1	5
Walnut	90 (370)	1	6
Corn	90 (370)	0	5
Flaxseed	98 (363)	5	1
Sesame	90 (369)	0	4
Peanut (groundnut)	90 (370)	0	3
Rapeseed	90 (370)	1	2
Hazelnut	90 (370)	0	1
Palm	90 (370)	0	1
Olive	90 (370)	0	1

Source: Nutritics nutritional analysis software.

from dawn to dusk and varies from avoiding all foods except those considered pure (e.g. rice, fruit and yoghurt) to total food exclusion [22, 24].

Jainism has its roots in Hinduism. Jains practise non-violence to all living creatures, and their diet is a form of lacto-vegetarianism that includes the avoidance of root vegetables, with the exception of ginger and turmeric.

Table 26.14 Vegetarian sources of vitamin D.

Non-animal foods (1 average portion)	Vit D (μg)	Non-animal foods (1 average portion)	Vit D (μg)
Special K 31 g	1	Bran flakes 25 g	1
Ricicles 35 g	2	Sultana Bran 30 g	1
Rice Krispies 29 g	2	Coco Pops 40 g	2
Frosties 23 g	1		
All-Bran 31 g	1	Non-dairy margarine (for 1 sandwich filling) 8 g	0.5 m

Source: Nutritics nutritional analysis software.

Dietary customs of Muslims

Approximately 4.6% of the UK population are Muslim. With the majority originating from Pakistan and Bangladesh, more recently they have been joined by Muslims from African countries such as Somalia, Yemen, Sudan, Morocco, Syria and Lebanon [2].

The Koran provides halal guidelines [24]. Acceptable animal foods are beef, sheep, lamb, goat, deer, poultry and fish prepared and stored under halal conditions. Unclean foods are carnivores (except fish), pork, birds of prey, reptiles, amphibians, rodents, insects and maggots. Wheat, usually in the form of chapattis, is the staple cereal eaten by Muslims from Pakistan, whereas those from Bangladesh eat more rice. Cooking oil is used in preference to ghee.

Fasting for Ramadan occurs during the ninth lunar month of the Islamic year. Muslims fast between sunrise and sunset. The purpose is to purify oneself both spiritually and physically and to share the experiences of the poor and hungry. Children under the age of 12 years (puberty) and the elderly are exempt from fasting. People who are ill, pregnant,

Table 26.15 Vegetarian sources of calcium.

Milk, cheese, yoghurt and alternatives			
Foods	Calcium (mg)	Foods	Calcium (mg)
Milk, all types 200 mL	240	Soya milk, calcium enriched, 200 mL	240
Hard cheeses (1 slice), 40 g	240	Water/orange juice calcium enriched, 200 mL	292
Fruit yoghurt (1 medium pot), 150 g	240	Soya yoghurt, calcium enriched (1 pot), 125 g	150
Whole milk yoghurt (1 medium pot), 150 g	300		
Milky pudding, e.g. kheer/rice pudding (1 small serving), 140 g	120		
Rice dessert (1 pot), 228 g	196		
Bread, cereals and alternatives			
Foods	Calcium (mg)	Foods	Calcium (mg)
Naan bread (1), 170 g	240	Fortified breakfast bar (1 bar), 37 g	180
White or brown bread (2 slices), 60 g	120	Gluten-free bread (2 slices), 50 g	180
White flour, self-raising, (2 tbsp) 50 g	180	Swiss-style muesli (1 average portion), 60 g	60
Meat alternatives			
Foods	Calcium (mg)	Foods	Calcium (mg)
Nuts, e.g. almonds, brazils, pistachios (1 medium packet), 30 g	30	Baked beans (1 small tin), 220 g	120
Sesame and sunflower seeds (1 tbsp), 25 g	60	Bombay mix (1 medium packet), 100 g	60
Fruit and vegetables			
Products	Calcium (mg)	Products	Calcium (mg)
Spinach boiled (½ cup), 120 g	192	Dried figs (4), 40 g	92
Okra (½ cup), 92 g	68	Orange (1 medium), 160 g	40
Spring greens (½ cup), 85 g	64	Sultanas (1 portion), 18 g	12

tbsp, tablespoon (15 mL); tsp, teaspoon (5 mL).
Source: Nutritics nutritional analysis software.

menstruating or on a long journey are also excused, but are expected to fast later. Unfortunately, many pregnant women fast with the rest of the family during Ramadan as they find it more convenient. The Koran also dictates that children should be breastfed up to the age of 2 years.

Dietary customs of Sikhs

Approximately 0.6% of the UK population are Sikhs. Sikhism is a relatively new religion, originating as a reformist movement of Hinduism in the Indian Punjab in the sixteenth century [2].

Non-practising Sikhs are not usually vegetarian, but they will usually avoid beef, pork and their products. They will also avoid halal meats preferring animals that have been killed with a single stroke, i.e. the jhatka method. Sikhs who have undergone the amrit ceremony are usually lacto-vegetarians avoiding meat, fish, eggs and their products [24].

Punjabi food customs include a wide range of milk dishes from cream, white cheese, butter, ghee and yoghurt that include maize flatbread (roti), spinach, dhal and chickpeas.

Common South Asian dietary habits

Common dietary patterns across the three main groups (Table 26.16) include alcohol abstinence and the hot and cold properties of foods. Many of the Asian people in the UK share dietary customs, despite their varying religious and geographical background. Older members of the Asian community tend to retain traditional dietary customs, while second and later generations are consuming more Westernised foods, especially convenience foods. The extent of adoption of these foods is variable, tending to be greater in the younger generations who were born in the UK and in those who have lived in the UK for some time [22], although they may continue to eat traditional meals in the evening [25].

The traditional breakfast includes chapattis, parathas, bread and, occasionally, hard-boiled or fried eggs are eaten. The two main meals are based on staples, usually served with a vegetable, pulse or nut-based curry [23]. Most foods, including spices, are usually fried before adding to the curry, which is then served with home-made chutneys, side salads of tomatoes and onions and yoghurt. Very little hard cheese is eaten; paneer, an Indian soft curd cheese, is preferred. Meals are usually served with tea, which is made with hot milk and sugar, although English tea is becoming popular. Traditionally, Asians rarely eat snacks, although Western snack foods are increasing in popularity. Traditional Asian savoury snacks (usually reserved for celebrations only) are high in fat, and the sweets are often very high in refined sugar. Many Asians believe that foods have heating and cooling effects on the body. These hot and cold foods should be eaten in the correct balance to achieve a healthy state. Certain hot foods cause symptoms such as constipation, sweating and body fatigue, while certain cold foods lead to strength and happiness. Foods may also be used to treat a condition, e.g. hot foods should be avoided during pregnancy and cold ones avoided when breastfeeding [24].

Infant feeding

Early studies reported lower breastfeeding rates among Asians in the UK compared with the Caucasian population [26, 27] and Asians in the Indian subcontinent [28]. However, high incidences of breastfeeding among Asian mothers (49% at 6 months) compared with white mothers (32% at 6 months) have more recently been reported in the 2010 Infant Feeding Survey [10]. Interestingly, of mothers who were born outside the UK, 30%–40% who bottle fed initially or who stopped breastfeeding to bottle feed reported that they would have fed their babies differently had the babies not been born in the UK. Unfortunately, for some bottle feeding is perceived as the Western ideal and, therefore, better for the baby. This problem is compounded by communication difficulties and overcrowded housing [12], making it difficult for a mother to breastfeed in privacy.

Weaning

Grains, roots and tubers are the foods first introduced. A systematic review in 2018 found that early weaning was not uncommon among most Asian families, with about 70% starting before 3 months and almost all babies being weaned by 6 months of age. However, families from Pakistan introduce complementary feeding later than other Asian groups: 49% by 6 months of age and 15% after 7 months [29].

Nutritional problems commonly found in Asian children

Faltering growth

Dietary intake, family income, housing standards, maternal education, psychological distress and morbidity all influence growth [22, 26]. The incidence of lower birthweights in this population has decreased recently; longer birth intervals, fewer teenage pregnancies and improved nutrition are thought to be contributing factors [22]. Despite lower birthweights, some studies show that Asian babies and children grow as well as other groups [30, 31]. Table 26.17 shows birthweight by ethnic group.

Iron deficiency anaemia

Iron deficiency anaemia has been described in Asian infants. Contributing factors include maternal iron deficiency during pregnancy, premature delivery and low birthweight. Inadequate dietary intake of iron is commonly related to the early introduction and excessive use of unfortified cow's milk. Prolonged use of a baby bottle and the mother being born outside the UK have also been shown to have a negative influence on the iron status of Asian children [33]. Families should be advised on the use of foods rich in iron and vitamin C [34].

Table 26.16 Foods commonly eaten by the Asian population in the UK.

Food	Nutrient	Method of cooking
Cereals Breakfast cereals, wheat, bread, rice, semolina, ground rice, bajri (millet flour), puffed rice, rice flakes	Energy B vitamins	Baked, boiled, fried: chapatti, paratha, poppadom, bhaji, poori, pakora, porridges, samosa, sweetmeats
Tubers Arvi/colocasia root, cassava, taro tuber, yam	Energy	Boiled, fried, curries
Vegetables Ackee, amaranth (tanjurdo), aubergine (ringun), colocasia leaves, mustard leaves, radish leaves, cluster beans, mint leaves, fennel leaves, okra, brinjal pepper, cho cho/chayote, fenugreek leaves, bitter gourd (darela/dudhi/turia/gulka), kantola, patra leaves, spinach (palak), leeks, tomatoes	Vitamin A Riboflavin Folic acid Vitamin C Iron Calcium Fibre	Boiled, fried, curries, chutneys, pickles
Pulses Peas, beans, balor/valor/urad gram, chickpeas (chana dhal), lentils (masoor), black-eyed beans, whole urad dhal (black gram), whole mung dhal, sprouted pulses	Energy Protein B vitamins Iron Fibre	Curries, fried, snack
Seeds and nuts Sesame seeds, peanuts, dried coconut, pistachios, almond, cashew nuts	Energy Fibre Iron Essential fatty acids	Fresh, fried, snack
Fruits Banana, citrus fruits, unsweetened juices, dates, blackcurrants, figs, raisins, apricots, prune/prune juice, guava (jamphal), mango, sapodilla (sapota/chiku)	Vitamin A Vitamin C Fibre	Raw, curries, chutneys
Milk products Milk, yoghurt, cheese/paneer	Energy Protein Vitamin A	Milk drinks: boiled, fresh Cheese: fresh, fried
Eggs	Protein Riboflavin Nicotinic acid Vitamin D	Fried
Fats and oils Ghee/clarified butter Vegetable oil Margarine	Energy Essential fatty acids	Frying, spreading

Table 26.17 Percentage low birthweight by ethnic group.

	Asian			Black		White			
Birthweight	Bangladeshi	Indian	Pakistani	African	Caribbean	White British	White other	Other	Not Stated
Under 2.5 kg 2006	7.3	6.6	6.2	3.2	4.1	2.6	2.3	3.3	3.1
Under 2.5 kg 2015	5.6	5.6	4.7	2.8	4.3	2.4	2.0	3.0	2.7

Source: Office of National Statistics, 2017 [32]. Licensed under Open Government License.

Megaloblastic anaemia

Megaloblastic anaemia resulting from vitamin B_{12} deficiency has been observed in some strict vegetarian and vegan Asians [35, 36]. Education regarding vitamin B_{12} sources in the vegetarian diet is required, and supplementation may be needed in the vegan diet.

Rickets

The steady decline in rickets in the UK was halted in the late 1960s and early 1970s when a number of cases appeared in immigrant families, mainly of Asian origin [37–39]. There is evidence that the incidence that was once in decline is now resurging [40]. The weaning diets of infants

should include foods rich in vitamin D such as fortified milk products, eggs, oily fish, liver, fortified breakfast cereals and margarine. Vitamin D supplementation is advisable for infants, young children and deficient pregnant women to prevent neonatal hypocalcaemia and rickets [11]. In addition, children should be encouraged to play outside [41].

Dental caries

Traditionally, sugary foods are reserved for celebrations and, therefore, do not have a major role in Asian diets. However, with increasing Westernisation, over consumption of refined sugar leading to a high incidence of dental caries has been observed in Asian preschool children [42]. Asian mothers often add sugar to babies' bottles and give sweetened drinks via the bottle for prolonged periods. These drinks, as well as having high sugar content, are acidic, which can lead to tooth decay [43]. Education regarding infant feeding with the restriction of quantity and frequency of sugar intake, the use of fluoride-containing drops and toothpaste and frequent dental visits will help to reduce the incidence of dental caries.

Obesity and diabetes

With the increasing consumption of high sugar and high fat foods, the prevalence of obesity is increasing. The incidence of obesity and diabetes is higher in Asian children aged 10–11 years than in white children (Table 26.18). In addition to restricting these foods, advice on acceptable Asian food alternatives and appropriate cooking techniques must be given. The dietary fat intake can be reduced by avoiding deep-fried foods, reducing the amount of oil or ghee used in cooking and restricting or not adding fat to chapattis. Avoiding the popular sweet sugary tea and Asian sweetmeats will reduce dietary sugar.

Afro-Caribbean communities

The earliest migration from the Caribbean to the UK began in the eighteenth century with the trade in people. Small communities settled around the major British port cities of Bristol, Liverpool and London. In the second wave in the nineteenth century, there was recruitment from the Caribbean for both the Royal and Merchant Navy. The settled communities continued to serve in the First and Second World War. The final migration occurred after the Second World War when people from former British colonies were invited to the UK to support major industries, public services and the NHS [45]. The largest phase of migration from the Caribbean occurred in the 1940s and 1950s [46, 47]. Most were recruited to re-staff national transport and health services [45]. The Afro-Caribbean community is 1.1% of the UK population and 5.6% of ethnic minority groups in the UK [2].

Table 26.18 Prevalence of overweight and obesity (%) within ethnic groups in England, 2017/2018.

	Reception year (4- and 5-year-old children)	Year 6 (10- and 11-year-old children)
White	22.5	32.2
Mixed	21.5	36.2
Asian or Asian British	18.5	39.6
Black or black British	29.3	45.0
Chinese	18.3	30.1
Any other ethnicity	23.5	39.6
Unknown	22.9	35.0

Source: NHS Digital. [44]. Licensed under Open Governement.

Dietary customs

Most Afro-Caribbeans are Christians, such as Seventh-Day Adventists, Pentecostals, Baptists and Rastafarians. A high proportion of Afro-Caribbeans living in the UK has adopted the dietary patterns of the wider UK population than other ethnic groups. However, a small group retain traditional meal patterns.

Seventh-Day Adventists and Pentecostals aim to eat foods that are natural and have few dietary restrictions; they abstain from eating pork and fish without scales. Alcohol, caffeine and high intakes of sugar and salt are discouraged. Some Seventh-Day Adventists may also be lacto-vegetarians.

Rastafarians aim to eat food in their natural states (Ital foods). Some avoid meat completely to obey the commandment 'thou shalt not kill' and follow a lacto-ovo-vegetarian or vegan diet [48]. Vinegar, raisins, grapes and wine are also avoided by some Rastafarians as the Nazarite law states that fruits of the vine should not be eaten.

The two main meals are taken at breakfast time and in the evening [49]. Traditional breakfasts include fried plantain, cornmeal dumplings and fried dumplings. However, many dietary practices have now been adopted from British culture, with toast and breakfast cereals largely replacing these foods. The evening meal is more likely to contain traditional foods, especially with the younger generation who seem keen to retain their identification and culture. Cereals and tubers such as rice, green banana, yam and sweet potato form the main part of the diet [50]. These starchy foods are served with small amounts of meat or fish [49]. The tropical climate in the homeland makes it difficult to keep foods fresh, and, therefore, preserved meat, fish and milk are eaten. Peas, beans, nuts and green leafy vegetables are widely used, often being made into homemade soups and stews, which are well seasoned with herbs and spices [50].

Infant feeding

Infant feeding is mainly influenced by the place of birth, knowledge of traditional practices and advice from relatives. Over 95% of black or black British women breastfeed their babies initially, and 61% are still exclusively or mixed breastfeeding when their child is 6 months old; this is higher than the UK average of 35% [10].

Weaning

Infants use to be traditionally weaned as early as 1 month of age with 45% reported to be receiving solid food by 3 months of age [49, 50]. The 2010 Infant Feeding Survey [10] indicates that most black and black British women now delay the introduction of solids to between 4 and 6 months. Late weaning now only occurs in less than 10% of babies from this group. Common weaning solids include high starch foods with a low nutrient density such as cornmeal, oats or rice porridge. This practice may lead to energy, protein, vitamin and mineral deficiencies if continued for a long time [13–16, 18–54]. The common practice of adding thin porridge to bottles should be discouraged as it can lead to a delay in the weaning process. It is also common for infants to be given bush teas (infusions of herbs and leaves) as a cure for minor ailments [49]. Care should be taken to ensure that these are not given instead of milk. By the age of 9 months, most infants are eating family foods with the diet having both traditional and Western influences [49].

Nutritional problems found in Afro-Caribbean children

Obesity and diabetes

With the adoption of British dietary customs, there has been an increase in the consumption of high sugar and high fat convenience foods and drinks. This has led to an increased prevalence of obesity and diabetes in Afro-Caribbean children compared with white children.

Iron deficiency anaemia

Iron deficiency anaemia has been observed in Afro-Caribbean children living in the UK. The main causes were thought to be prolonged bottle feeding, late weaning onto foods with low iron content and the early introduction and excessive use of cow's milk [51]. However, late weaning now only occurs in less than 10% of babies from this group [10].

Megaloblastic anaemia

There have been reports of megaloblastic anaemia in Rastafarian children living in Jamaica [55, 56]. Vegan children may require vitamin B_{12} supplementation.

Rickets

Rickets is common among Afro-Caribbean children and vitamin D supplementation is beneficial.

Lactose intolerance

There is a high incidence of lactose intolerance because of hypolactasia among the Afro-Caribbean population. A reduction in, and occasionally the avoidance of, the consumption of milk and other foods containing lactose will usually reduce symptoms.

Chinese communities

Today Chinese people represent 0.7% of the UK population and 5.6% ethnic groups in the UK [2], with roots from the Caribbean, Hong Kong, Taiwan, China, Malaysia, Vietnam and Singapore [57]. The common religions include Buddhism, Confucianism, Taoism and Islam.

Dietary customs

Dietary habits vary according to the country and region of origin. Very few foods are avoided, with the exception of the Chinese Muslim population not eating pork. Eggs are highly valued as they are regarded as food for the brain. Northern China has a cool climate favouring the growth of wheat, maize, sorghum and millet. These staples are often made into steamed bread, dumplings, pancakes or noodles [24, 57]. Meals are often based on root vegetables such as sweet potato and turnip, with very little meat being eaten. In contrast, because of its high rainfall, rice is the staple in southern China. Fresh vegetables and fruit are also found in abundance [57]. In the East, because of the long coastline, fish and shellfish are plentiful. In the West, livestock are reared, and, therefore, the consumption of meat, milk and cheese is much higher [57].

Traditional breakfasts include rice porridge (congee), served either plain or with liver, meat, salted fish, salted eggs or Chinese cheese and a soup made from rice and meat [24, 57]. These traditional foods are, however, slowly being replaced by Western alternatives. The midday and evening meals consist of boiled rice or noodles and a variety of highly seasoned dishes such as fried or steamed meat and fish and stir-fried vegetables. Raw food is rarely eaten, as fertiliser in China commonly contains human manure. Meals are usually served with either China tea or a thin soup and then followed with fruit. Sweet foods are usually reserved for special occasions [24, 57]. The main health concern is the high salt intake associated with many of the preserved foods, seasonings and soya sauce. A high fat and refined sugar intake associated with the increasing consumption of Western foods, especially by the younger generation, is also of concern [57]. A high incidence of lactose intolerance, because of hypolactasia, is also becoming apparent with the increasing consumption of milk and other dairy products [57].

Yin and Yang foods

To Chinese people health is perceived as the maintenance of a sound body and mental state rather than absence of disease. In traditional Chinese medicine there is a balance between Yin (feminine energy, cold, passive) and Yang (masculine energy, hot, aggressive) [24, 57]. In illness the balance becomes disturbed and the body becomes either too hot or too cold. Tolerance of Yin and Yang increases with age. Thus, an adult can eat a much wider variety of foods than can a child. The classification of foods varies: in general meat, duck, goose, oily fish, potatoes, coffee, chocolate, sugar, nuts, herbs, spices, alcohol and fats are regarded as hot foods; chicken, milk, rice and some vegetables are neutral foods; fish, shellfish, soya beans, certain fruits and vegetables and barley water are cold foods. Stewing, deep fat frying, grilling and roasting make foods hotter, steaming neutralises, and boiling and stir frying have a cooling effect [24, 57]. The Chinese believe that a healthy diet should be three parts Yang and two parts Yin. The balance should be changed for certain illnesses (e.g. for hyperactivity more Yin foods should be eaten than Yang foods).

During pregnancy and after childbirth, the woman's body is thought to become cool, and, therefore, cold foods are avoided. Alcohol, ice cream, mutton, beef and fizzy drinks are also avoided. In addition, if the woman is breastfeeding, green vegetables and fruit are avoided because of concern that they may give the baby diarrhoea. Consequently, breastfeeding mothers often have a high protein intake [57].

Infant feeding

In the UK, Chinese women often return to work soon after childbirth, which has led to a decrease in the rate and duration of breastfeeding [58, 59]. Soya bean oil, which is a poor source of essential fatty acids, is a major source of fat in the Chinese diet. Because of this, breastmilk has been found to have a low concentration of DHA and arachidonic acid (AA) [60]. It has, therefore, been suggested that mothers who are breastfeeding their infants should supplement their diet with a good source of DHA and AA such as fish oil. Because infant formula is regarded as hot, bottle-fed babies are often given frequent cooling drinks such as water and barley water.

Most infants are weaned at 3 months of age. Traditionally, rice-based porridges were introduced, but commercial baby foods are being used [57]. A study examining Westernisation of the nutritional pattern of Chinese children living in France reported that at 1 year of age, Chinese children mainly consumed a traditional diet. The intake of dairy products and fresh fruit was very low and that of soft drinks high, resulting in suboptimal calcium and vitamin C intakes [58]. In general, infants are thought to have a hot equilibrium, and, therefore, neutralising or cooling foods are considered best for them. It is common practice for children to be given afternoon tea consisting of cooling foods such as bread, biscuits, cake, barley water and herb teas to counteract the heating effect of school meals [57].

Vietnamese communities

Some 75% of Vietnamese settlers in the UK are ethnic Chinese and, therefore, share many of the Chinese traditions [57]. Most arrived in the UK during the 1970s. Common religions among Vietnamese are Buddhism, Roman Catholicism and Confucianism.

Dietary customs

The Vietnamese diet is typically high in carbohydrate and low in fat [61]. Vietnam borders the ocean and has an extensive river system, and, therefore, fish and shellfish are staple parts of the traditional diet. There are no forbidden foods; however, certain unfamiliar foods such as lamb, ox liver, tinned or cooked fruit and some root vegetables may be avoided [24]. Rice is the main staple food and is served either boiled or fried with small amounts of meat or fish. Like Chinese food, main dishes are often heavily seasoned, and vegetables are lightly steamed or stir-fried in oil or lard. The resultant high sodium intake is the main health issue. Very little fresh milk, butter, margarine and cheese are used because of their lack of availability in Vietnam and the high incidence of lactose intolerance. Snacks of roasted nuts, sweet potatoes, rice or noodle soup, spring rolls and fresh fruit are frequently eaten. Common beverages include tea, coffee and fruit juice, and alcohol is taken on special occasions [24].

With increasing Westernisation, the intake of high sugar and high fat snack foods is increasing, especially in the younger generation. This has led to an increase in dental caries and obesity in the Vietnamese population, both in the UK [62] and other countries [63]. Unfortunately, obesity is traditionally seen as a sign of prosperity.

The Vietnamese people observe hot and cold food principles, similar to the Chinese. In contrast to the Chinese, however, pregnancy is regarded as a hot condition, and, therefore, women eat less red meat and fish. A traditional stew called Keung Chow, made from pigs' trotters, boiled eggs, vinegar and ginger, is given to women after childbirth to help recovery and to celebrate the birth of the child. After childbirth, women are encouraged to eat hot foods to regain their strength [24].

Infant feeding

Since their arrival in Westernised countries, including the UK, Vietnamese mothers have abandoned traditional infant feeding practices in favour of more modern bottle feeding methods [63–65]. In addition, many Vietnamese women believe that breastfeeding will cause their breasts to sag. Hence, the incidence of breastfeeding is low, and there is a need for culturally sensitive health education programmes to support breastfeeding in this group. Infants are typically given a rice-based porridge at around 6 months of age;

minced meat and vegetables are given at 9 months and more solid food at 1 year.

Iron, calcium and vitamin D

There is an increased risk of iron deficiency in young Vietnamese children [66]. This is particularly associated with a high milk intake and poor body weight.

Children are at risk of calcium deficiency, especially if minimal milk and associated products are eaten. The rice traditionally grown in Vietnam is a good source of calcium, but is unavailable in Britain. Traditional Vietnamese fruit and vegetables also contain more calcium than British varieties [24].

Vitamin D deficiency has been noted in Vietnamese children; supplementation is beneficial [24].

Somalian communities

Somalis first settled in the UK in 1914 when they were recruited to fight in the First World War. They are now thought to be the oldest African community in London. Later arrivals included Somalian asylum seekers who fled the civil unrest in their country and settled around the main cities in the UK. Today there are second-, third- and fourth-generation Somalis living in the UK.

Dietary customs

Somalis are of Arab-African ethnicity and their faith is Islam. Therefore, they share many of the Islamic (Muslim) dietary customs. Somalia was formed in 1960 from a British protectorate and an Italian colony. As a result, many southern Somalis eat Italian food, and spaghetti is a national dish. The Somalian diet tends to be relatively high in protein.

Breakfast usually consists of 2–3 pieces of injera (fermented pancake-like Somali bread made from corn and wheat) with ghee or butter and tea. Lunch is the main meal and usually consists of spaghetti or rice with a meat sauce (beef or goat) and mixed vegetables. Food is often flavoured with aromatic spices (cumin powder, cinnamon, cloves, cardamom, garlic, cilantro, parsley). Pork is avoided and chicken, fish and eggs are not usually eaten. The evening meal consists of injera or bread with butter and jam, or a traditional meal of rice, beans, butter and sugar. Desserts and snacks are not considered as part of the daily diet. Sweets are usually given to children, but are not usually eaten by adults. Children usually drink cow's or goat's milk three times or more each day. From the age of 3 years, sweetened tea is usually added to the milk. During pregnancy, Somali women tend to decrease their meals to ensure an easier delivery. They believe that too much food will make the baby grow too big, and it will be hard to deliver normally. The diet usually improves during the third trimester, although most women do not take prenatal vitamins.

Infant feeding

Almost all women breastfeed, often for 2–3 years. Breastmilk is not offered in the first 24 hours when infants may be given sugar water or fresh cow's or goat's milk. Colostrum is thought to have a poor nutritional value or to be unhealthy, and it often expressed and discarded. A mixture of rice and cow's milk is introduced at 6 months of age, and drinks from a cup are offered at 6–8 months.

Calcium and vitamin D

The traditional Somali diet is low in vitamin D and calcium and could give rise to poor bone mineralisation and the development of osteoporosis [67]. Vitamin D deficiency has been reported in 82% of Somalis living in Liverpool [67]. Dietary advice should focus on improving the intake of these nutrients from dietary sources with additional supplementation with vitamin D where appropriate.

Jewish communities

The dietary laws of the Jewish community (kashrus) are based around foods fit to eat (kosher) and foods that are forbidden (treifah) [68]. The laws of kashrus may be set aside for life-threatening conditions and only applies to food or substances that are ingested orally.

Kosher laws prescribe that only certain meat and fowl can be eaten and all must be slaughtered as humanely as possible and prepared in a way that ensures that as much blood has been removed as possible. Meat and milk products, or foods containing them, must be stored separately and cooked using separate utensils. Meat and milk foods cannot be eaten in the same meal, and there must be a break of a minimum of 3 hours before the other food can be eaten. Only milk from kosher animals that has been bottled under the supervision of a kashrus authority may be drunk.

Fish, fruit and vegetables are known as parev (neutral) because they do not contain meat or milk. These foods can be eaten with either meat or milk-containing foods. All fruits and vegetables are kosher; however, care must be taken to ensure that they do not contain any insects. With regard to seafood, only certain species that can clearly be recognised as 'fish' are kosher. Eels, crabs and shellfish are treifah.

The Really Jewish Food Guide (www.kosher.org.uk) lists commercially produced foods that are deemed to be acceptable for a kosher diet.

The prevalence of breastfeeding among Jewish families is very high; however, where infant formula is required, it should be kosher certified (Table 26.8).

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

27 Inherited Metabolic Disorders: Introduction and Rare Disorders

Fiona J. White

This chapter provides information on normal metabolic processes and how these are affected in inherited metabolic disorders (IMD). Also discussed are the basics of inheritance and how this relates to IMD, newborn screening (NBS), an overview of dietary treatment modalities for those disorders treatable with dietary manipulation and, briefly, the role of transplantation.

The final section covers IMD requiring nutritional support and management with a ketogenic diet.

Metabolism

Metabolism describes the chemical processes that occur in the body's cells to produce energy and other substances needed for normal body functioning. It comprises two elements:

- anabolism – the formation and storage of complex compounds needed for growth, tissue repair and energy storage from simpler molecules
- catabolism – the breakdown of large complex molecules to provide energy for cellular activity and smaller compounds, e.g. amino acids, needed for anabolic reactions or for elimination from the body

Commonly the term metabolism defines the digestion and absorption of food together with how its components (carbohydrates, fats and proteins) are transformed into energy via a sequence of chemical reactions (metabolic pathways), which are controlled by large numbers of different enzymes. Enzymes themselves are proteins. These biochemical reactions frequently involve cofactors, often vitamins, which help the specific enzyme function, e.g. vitamin B_6 is the cofactor for the enzyme cystathionine β-synthase, which converts the amino acid homocysteine into cystathionine.

Figure 27.1 illustrates the metabolic processes involved in the overall metabolism of carbohydrates, lipids and protein including the catabolic processes to produce energy and urea (the detoxification product of the nitrogen moiety of amino acids) and anabolic processes to form tissue protein and energy stores, glycogen and lipids. Together these processes are known as *intermediary metabolism*.

Carbohydrate metabolism

Cellular carbohydrate (CHO) metabolism involves both catabolic (glycolysis, glycogenolysis) and anabolic (glycogenesis, gluconeogenesis) processes. Carbohydrates, as monosaccharides (glucose, fructose, galactose), are absorbed in the intestine and then transported to the liver where excess glucose, galactose and fructose are converted to glucose-6-phosphate (G-6-PO_4). Depending upon energy needs, G-6-PO_4 undergoes either catabolism to form energy or anabolism to form glycogen, the storage form of glucose, in liver and muscles. To produce energy, G-6-PO_4 (derived from monosaccharides from dietary CHO or from glycogen degradation by glycogenolysis) undergoes glycolysis. A series of enzyme reactions in the glycolytic pathway convert G-6-PO_4 to form pyruvate or lactic acid and then to acetyl-CoA. Acetyl-CoA is also produced from fatty acid oxidation and degradation of the carbon skeleton of the glucogenic amino acids (Table 27.1). Acetyl-CoA enters the Krebs cycle, also known as the citric acid or tricarboxylic acid (TCA) cycle, within the mitochondria. Within the Krebs cycle acetyl-CoA, combined with oxaloacetate, undergoes cycles involving eight enzymes, when reducing equivalents are produced, which then enter the electron transfer chain for the production of energy as adenosine triphosphate (ATP). When cells do not require G-6-PO_4 for energy production, it undergoes glycogenesis to be stored as glycogen until required to restore blood glucose levels. G-6-PO_4 can also be produced via pyruvate from protein catabolism of several glucogenic

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

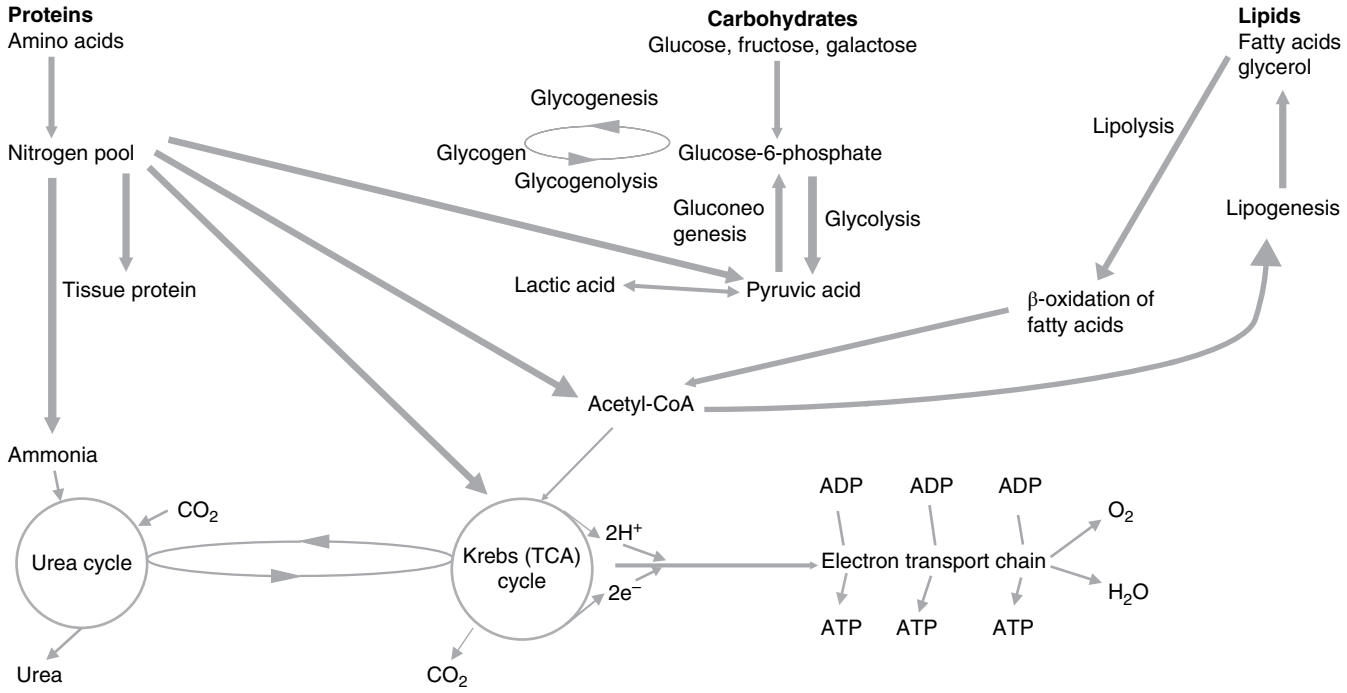


Figure 27.1 Summary of metabolism of carbohydrates, lipids and protein. TCA, tricarboxylic acid cycle; ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Table 27.1 Classification of amino acids.

Glucogenic only	Ketogenic only	Ketogenic and glucogenic
Alanine	Leucine	Isoleucine
Arginine	Lysine	Phenylalanine
Asparagine		Threonine
Aspartate		Tyrosine
Cysteine		Tryptophan
Glutamate		
Glutamine		
Glycine		
Histidine		
Methionine		
Proline		
Serine		
Valine		

amino acids or breakdown of glycerol from lipids, via glyceraldehyde-3-PO_4, both within the gluconeogenesis pathway (Table 27.1).

Lipid metabolism

Dietary fat is present mainly as long chain triglycerides, comprising a glycerol backbone and fatty acids. Dietary fats, and lipids produced endogenously from acetyl-CoA, are initially hydrolysed by lipases into glycerol and free fatty acids. Glycerol is then oxidised to acetyl-CoA via pyruvate. Lipid transport is a complex process and is discussed in Chapter 30. Long chain fatty acids enter the mitochondria via the carnitine transport cycle (medium chain fatty acids enter primarily independent of carnitine) into the β-oxidation spiral in which fatty acids, via a series of enzymes, produce acetyl-CoA and electron carriers. Acetyl-CoA can enter the Krebs cycle or form ketone bodies in the liver. Electron carriers (flavin adenine dinucleotide, $FADH_2$, and nicotinamide adenine dinucleotide, NAD) enter the electron transfer chain to produce ATP. Acetyl-CoA in excess of requirements for energy production via the Krebs cycle is converted via lipogenesis to stored lipids in adipocytes.

Protein metabolism

Dietary protein is broken down into 20 individual amino acids for absorption. Of these nine are essential or indispensable (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine) as they cannot be synthesised by the body. The other 11 (alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, serine, tyrosine) are classified as non-essential amino acids (NEAA), or dispensable, as they can be produced from the breakdown of essential amino acids (EAA) by transamination. A few of the NEAA become conditionally essential in certain disorders or at times of stress. These include arginine, cysteine, glutamine, glycine, proline and tyrosine and in such circumstances must be provided in the diet.

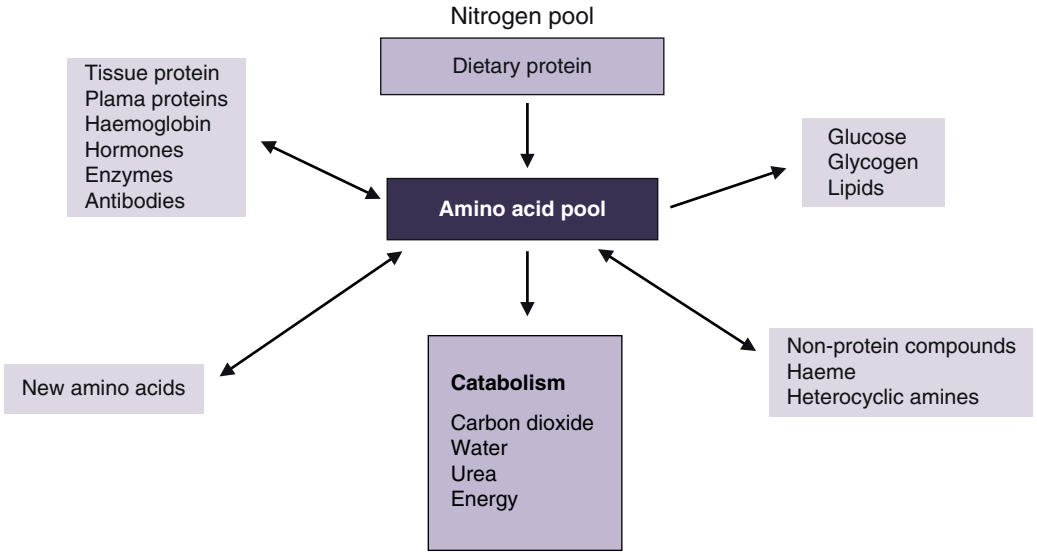


Figure 27.2 Function of the amino acid pool.

Amino acids enter the body's nitrogen pool (Figure 27.2) and are used to form proteins needed for growth and body tissue repair or are catabolised by transamination and deamination. The amine group (nitrogen moiety) undergoes transamination, in which it is transferred to a keto acid producing a new amino acid and a new keto acid, and then deamination to produce ammonia, which is detoxified via the urea cycle to produce urea, which is then excreted in urine. The carbon skeletons of amino acids (organic acids) are either glucogenic, ketogenic or both (Table 27.1).

Glucogenic amino acids degrade either:

- directly to Krebs cycle intermediates
- via acetyl-CoA or acetoacetyl-CoA to oxaloactetate, which is either used in the Krebs cycle or can be converted to phosphoenolpyruvate and used to produce G-6-PO_4 via gluconeogenesis
- to pyruvate, which can either be used to produce G-6-PO_4 via gluconeogenesis or converted irreversibly to acetyl-CoA by the pyruvate dehydrogenase (PDH) complex. Acetyl-CoA can then enter the Krebs cycle

Ketogenic amino acids degrade to acetoacetate or acetyl-CoA and are used in fatty acid synthesis or ketone body production (Figure 27.3).

Control and regulation of metabolism

To maintain homeostasis within cells, metabolic pathways have to be finely balanced (Figure 27.4). This is achieved by either:

- flux through pathways increasing or decreasing by intracellular self-regulation of reactions (feedback), by responding to concentrations of substrates or products, e.g. a low concentration of an essential product causes increased enzyme activity in the metabolic pathway, resulting in increased product production from the substrate
- responding to signals from other cells, involving hormones and growth factors

Influence of hormone regulation

Hormones are released according to metabolic status including whether in the fed or starved state and stress. Their regulation of metabolic pathways (Table 27.2) plays a crucial role by:

- altering the availability of substrates, e.g. the sympathetic nervous system response during exercise increases the mobilisation of glucose from glycogen, fatty acids from adipose tissue [1] and insulin being released in response to high blood glucose levels and glucagon being released when glucose levels are low
- influencing enzyme activity, e.g. adrenaline, a fight and flight hormone, increases phosphofructokinase (PFK) activity, an important enzyme in glycolysis. In addition glucocorticoids and thyroid hormones also affect energy metabolism

Inheritance

In 1911 Johannsen [2] introduced the theory that genes were responsible for inheritance, and in 1941 Beadle and Tatum hypothesised the one gene, one enzyme theory [3]. The molecular disease concept in which gene mutations alter protein structure by changing a single amino acid within the protein was introduced by Pauling *et al*. [4] and Ingram [5] with their work on sickle cell anaemia.

The structure of deoxyribonucleic acid (DNA), from which genes are formed, was described by Watson and Crick in 1953. DNA contains:

- information as a code made up of four chemical (nucleotide) bases: adenine, cytosine, guanine and thymine

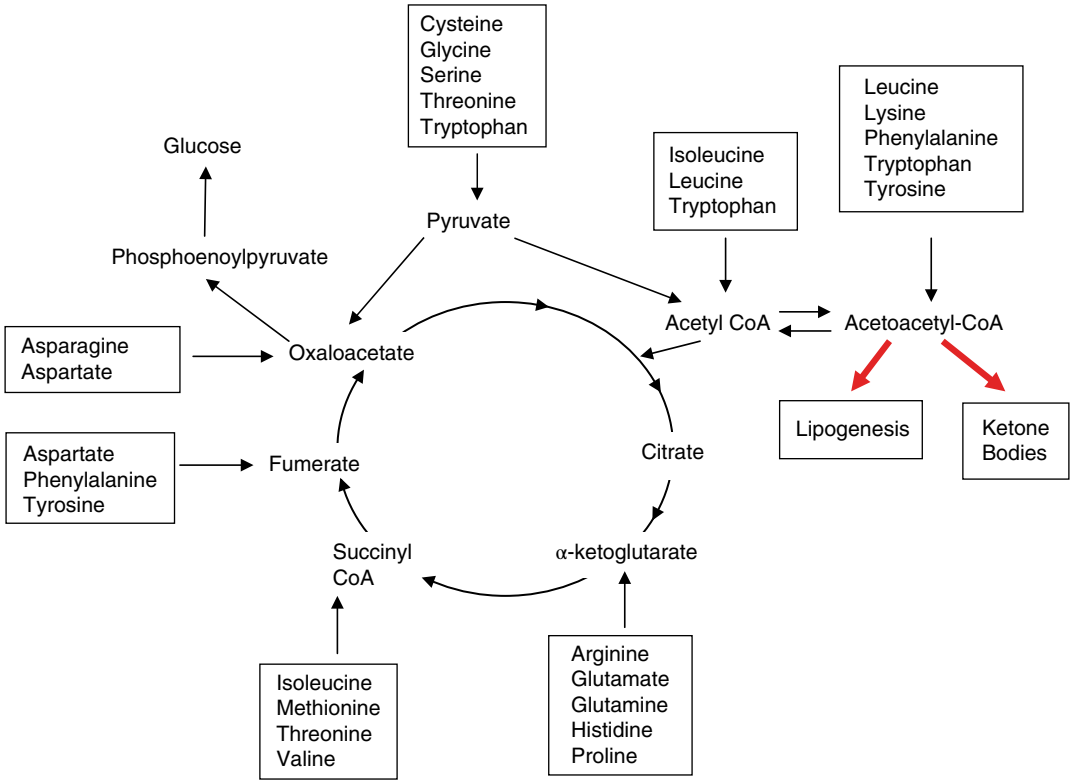


Figure 27.3 Catabolism of amino acids.

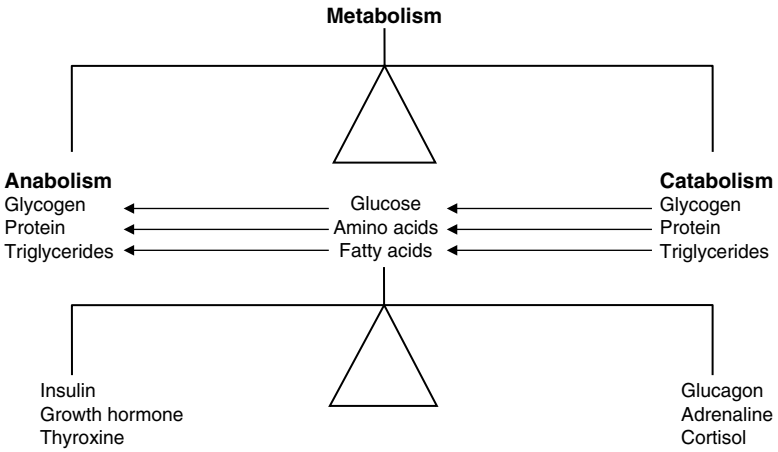


Figure 27.4 Hormonal regulation of metabolic balance.

- the sequence of bases provides information for building and maintaining body structures
- DNA sequences are made up of exons and introns:
  - exons are coding sequences that contain information to encode for a protein
  - introns, which occur between exons, do not code for proteins
- the process of a gene expressing for a protein involves two significant steps:
  - transcription, within the cell nucleus, which involves the transfer of information in the DNA to messenger ribonucleic acid (mRNA). mRNA carries this information out of the nucleus into the cytoplasm for translation
  - translation where ribosomes read the sequence of mRNA bases. Three base (codon) sequences code for specific amino acids (AA). Transfer RNA (tRNA) then assembles the protein by sequentially adding AA until a stop codon (a three-base sequence that does not code for an AA) is reached

Genetic disorders arise due to mutations (changes) in the DNA sequence:

Table 27.2 Summary of the action of hormones on metabolic pathways.

Hormone	Anabolic or catabolic	Stimulates	Inhibits	Blood levels: Glucose	Blood levels: Fatty acids	Blood levels: Amino acids
Insulin Released in response to: • Increased blood glucose • Increased blood amino acids	Anabolic	Uptake of glucose by muscle and adipose tissue • Glycolysis • Glycogenesis • Lipogenesis Cellular uptake of • Amino acids • Protein synthesis	• Gluconeogenesis • Glycogenolysis • Lipolysis • Fatty acid oxidation • Proteolysis • Ketogenesis	↓	↓	↓
Glucagon Released in response to: • Decreased blood glucose • Decreased blood amino acids	Catabolic	Glycogen breakdown and formation of glucose • Glycogenolysis • Gluconeogenesis Fat breakdown by • Lipolysis • Fatty acid oxidation	• Glycogenesis • Lipogenesis • Protein synthesis	↑	↑	⟺
Adrenaline (epinephrine) Released in response to: • Exercise • Strss (stimulates sympathetic nervous system)	Catabolic	Glucagon and cortisol release resulting in glycogen breakdown and formation of glucose • Glycogenolysis • Gluconeogenesis Fat breakdown: • Lipolysis	• Insulin release	↑	↑	⟺
Cortisol Released due to physiological and emotional stress Supports effects of decreased insulin and increased glucagon secretion	Catabolic	Decreased glucose, fatty acid and amino acid uptake by all tissues except brain • Gluconeogenesis • Lipolysis		↑	↑	↑
Growth hormone Released in response to • Hypoglycaemia • Increased plasma amino acid levels • Increased metabolism associated with growth, exercise	Anabolic	Muscle protein synthesis Mobilisation of free fatty acids • Lipolysis Reduced cellular glucose uptake • Gluconeogenesis	• Glucose uptake by muscles (glucose sparing)	↑	↑	↓
Thyroxine Slow response to metabolic changes Increases sensitivity to epinephrine, glucagon and growth hormone Increases basal metabolic rate	Catabolic	Increases ATP production by • Glycolysis • Glycogenolysis • Lipolysis • Fatty acid oxidation		Indirectly ↓		

ATP, adenosine triphosphate.

- an error in the coding sequence of a gene can result in no protein or an abnormal protein or enzyme being produced
- many mutations are benign (silent), whereas others lead to variable severity of defect (Table 27.3)
- gene mutations result in a genotype that predicts residual enzyme activity
- single genes do not function independently, but interact with other genes and the individual's environment, resulting in the disease phenotype
- there is not always an exact genotype–phenotype correlation

Further information can be obtained at https://ghr.nlm.nih.gov and www.genomicseducation.hee.nhs.uk/genetics101/genes.

Patterns of inheritance

Autosomal recessive inheritance

Features of autosomal recessive (AR) inheritance (Figure 27.5) are as follows:

- two faulty (mutated) copies of the gene have to be inherited for the disease to be expressed

Table 27.3 Types of mutations.

Mutation type	Change in amino acid (AA) code	Effect
Point	Single base pair change	Benign unless causes change in AA code
Missense	Single base pair change	Substitution of one AA for another in the protein chain. Can have serious consequences
Nonsense	Single base pair change or premature termination of AA code (stop codon)	Signals cell to stop building a protein, thus producing a shortened protein that may function improperly or not at all
Insertion	Adds a piece of DNA, which changes number of DNA bases	Protein product produced may not function correctly
Deletion	Removes piece of DNA	Function of resulting protein may be altered
Duplication	Piece of DNA abnormally copied once or multiple times	Resulting protein function may be altered from normal
Frameshift	Loss or addition of one or more DNA bases causing change in grouping of the triplet base pair coding for AA	Usually results in non-functioning protein
	Deletions, insertions and duplications can also result in frameshift mutations	
Splice site mutations	Introns (bulk of the DNA within a gene that is not translated) not spliced from mRNA	Incorrect protein is produced

- parents are obligate heterozygotes (carriers), but do not have the disease; they may carry the same or a different gene fault (mutation)
- affected offspring are either homozygous with two copies of the same gene fault (mutation) or compound heterozygotes with two different gene faults (mutations)
- there is a 25% (one in four) risk of having an affected child with each pregnancy
- unaffected children have a 66% (two out of three) chance of being a carrier
- many IMD are inherited in this way including phenylketonuria (PKU), maple syrup urine disease (MSUD), galactosaemia, glycogen storage disease (GSD) Ia and medium chain acyl-CoA dehydrogenase deficiency (MCADD)

Autosomal dominant inheritance

Features of autosomal dominant (AD) inheritance (Figure 27.6) are as follows:

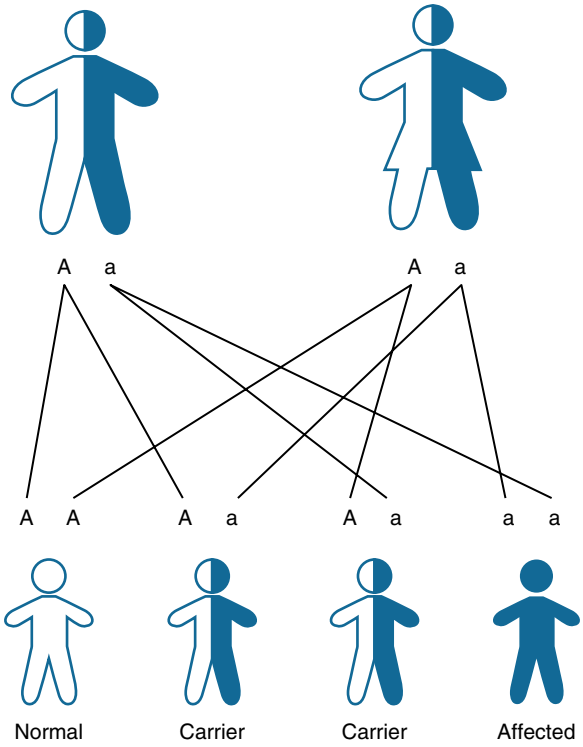


Figure 27.5 Autosomal recessive inheritance (http://www.geneticseducation.nhs.uk).

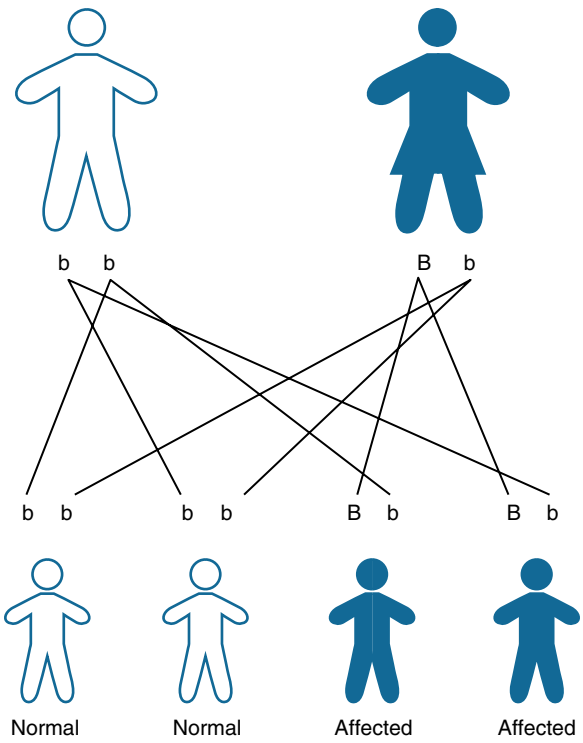


Figure 27.6 Autosomal dominant inheritance (http://www.geneticseducation.nhs.uk).

- it only requires one copy of a faulty (mutated) gene to inherit the disorder; this can be inherited from either parent
- there is a 50% risk of occurrence with each pregnancy
- Unaffected offspring will have two normal copies of the gene
- dominant mutations can occur sporadically (*de novo*) with both parents having no mutations. This is often seen in Glut 1 deficiency syndrome. Occasionally an AD disorder can occur as the result of a germ line mutation; this is where parents usually have a normal phenotype, but one of the parents has a mutation occur in some of his/her sperm/eggs
- AD conditions can occur in a homozygous state in which case they can be very severe or lethal
- familial homozygous hypercholesterolaemia (FH) is an AD disorder; heterozygotes are symptomatic, but homozygotes are more severe and often die from fatal myocardial infarction in early adult life
- individuals with heterozygous AD disorders (only one copy of the faulty gene) have a 50% chance of passing on the faulty gene. All children born to individuals with homozygous AD disorders will inherit the disorder

X-linked inheritance

Features of X-linked inheritance (Figure 27.7) are as follows:

- mutations occur in genes on the X chromosome
- X-linked recessive single gene defects affect males as they only have one X chromosome, and if the gene fault/mutation is passed on from a carrier mother then they are affected
- females carry the gene fault/mutation on one of their two X chromosomes. Depending upon the degree of X inactivation (how many of the mutant X chromosomes are active), females can be symptomatic to a greater or lesser extent, e.g. in ornithine transcarbamylase (OTC) deficiency, some carrier females present with hyperammonaemia
- males with X-linked disorders will pass on the faulty gene to all of their daughters; sons are unaffected
- examples of X-linked IMD include adrenoleukodystrophy, OTC deficiency and X-linked phosphorylase b kinase deficiency (GSD type IXa)

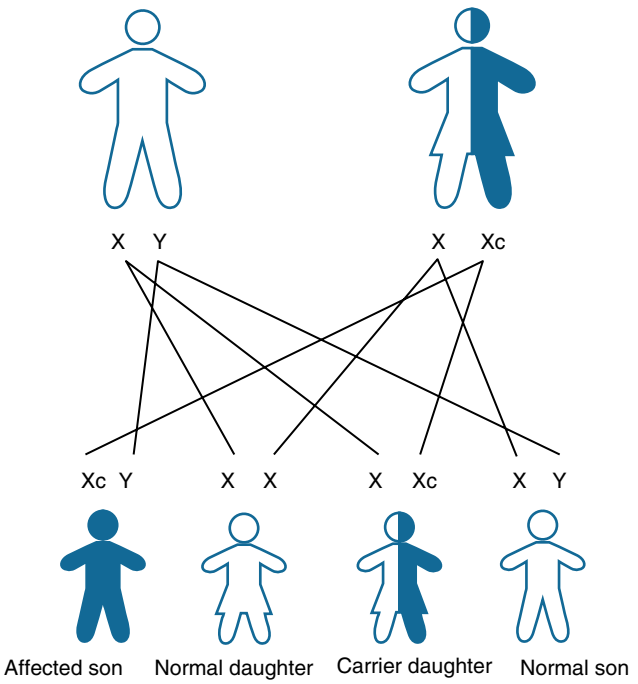


Figure 27.7 X-linked inheritance (http://www.geneticseducation.nhs.uk).

Mitochondrial inheritance

Features of mitochondrial inheritance are as follows:

- mitochondria contain their own DNA, which originates in the egg and encodes for enzymes involved in electron transport and energy metabolism
- some mitochondrial encoded polypeptides join with nuclear originated protein to form a complete enzyme
- Mitochondrial disorders can be inherited in maternal, recessive, X-linked or dominant fashion dependent upon the defective polypeptide
- cells contain multiple mitochondria and, therefore, many alleles for one gene. When some alleles are mutated the cells contain a mixture of normal and mutated alleles, known as heteroplasmy. Depending on the number of mutated mitochondria in the cell or tissue, diseases with the same mutation can be expressed differently
- examples of mitochondrial inherited IMD include Leigh syndrome, Pearson syndrome and mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS)

Inherited metabolic disorders

Inherited metabolic disorders are genetic biochemical disorders of specific enzymes or proteins causing a block in a normal metabolic process of protein, CHO or lipid metabolism. This results in an abnormality in the normal metabolic process and accumulation of intermediary metabolites, which cannot be further metabolised. Garrod described 'individualities of metabolism' in 1902 [6] and introduced his concept of IMD in 1908, describing such disorders as alkaptonuria, albinism, pentosuria and cystinuria [7], which are all inherited in an AR trait.

IMD can be categorised in a number of ways. Based on their pathophysiology they can be considered in three distinct groups:

1. **Disorders of intermediary metabolism leading to intoxication**
   As illustrated in Figure 27.8, these include disorders in which the enzyme deficiency leads to:
   - accumulation of intermediary metabolites proximal to the block (B)
   - formation of alternative products (D) producing acute or chronic toxic effects that result in disease manifestations
   - possible deficiencies of products downstream of the block (C)

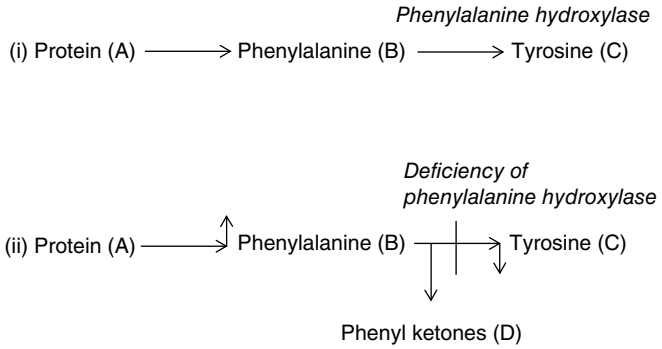


Figure 27.8 Metabolism of phenylalanine: normal (i) and in phenylketonuria (ii).

Examples of such disorders include:

- the amino acidopathies (PKU, MSUD, homocystinuria, tyrosinaemias, hyperornithinaemia-gyrate atrophy of the choroid and retina)
- organic acidaemias
- urea cycle disorders
- disorders of sugar intolerance (galactosaemia, hereditary fructose intolerance)
- metal intoxication disorders (Menkes disease, Wilson disease)
- porphyria

These disorders all have a symptom-free period after birth and then present with acute (either in the neonatal period or a later onset) or chronic signs of 'intoxication':

- acute symptoms can be triggered by dietary intake, catabolism, fever, intercurrent illness
- chronic, progressive presentations include developmental delay, failure to thrive, cardiomyopathy, hepatomegaly, lens dislocation

2. **Disorders of intermediary metabolism involving energy metabolism**
   These include disorders in which the enzyme deficiency results in lack of energy production or energy utilisation within organs including the liver, muscle, brain and myocardium. They can be subdivided into defects of:
   - mitochondrial energy metabolism, including disorders of fatty acid oxidation, ketone body defects, congenital lactic acidaemias and respiratory chain disorders
   - cytoplasmic energy metabolism, including disorders of glycolysis, glycogen metabolism, gluconeogenesis, glucose transport, hyperinsulinism and creatine metabolism

   Symptoms may include hypoglycaemia, lactic acidosis, hepatomegaly, cardiomyopathy, myopathy, hypertonia, failure to thrive and sudden infant death.
3. **Disorders involving complex large molecules**
   These are disorders in which complex molecules are incompletely catabolised and accumulate in organelles, resulting in a variety of symptoms including progressive loss of function of affected body systems, organomegaly and dysmorphic features. They include:
   - disorders of lipoprotein and cholesterol metabolism
   - lysosomal storage disorders
   - peroxisomal disorders
   - disorders of glycosylation
   - disorders of sterol synthesis
   - disorders of purine and pyrimidine metabolism

Management of IMD

A significant number of IMD are treatable, often by therapeutic dietary intervention. The main forms of nutritional therapy in IMD are as follows:

Substrate reduction in which the accumulating metabolite(s), due to the enzyme deficiency, is restricted (if it is an essential nutrient) or as far as possible removed from the diet. Such a treatment strategy is employed in managing:

- disorders of amino acid metabolism
- disorders of galactose and fructose metabolism
- lipoprotein disorders
- disorders of fatty acid oxidation
- some peroxisomal disorders, e.g. Refsum's disease
- the lysosomal storage disorder Infant onset lysosomal acid lipase deficiency

Provision of products normally produced downstream of the block which, as a result of the block, are conditionally essential to prevent deficiency, e.g.

- tyrosine supplementation in PKU
- arginine in urea cycle disorders
- maintaining normoglycaemia by regular feeding and/or CHO supplements in:
  - glycogen storage disorders
  - disorders of fatty acid oxidation
- cholesterol in Smith–Lemli–Opitz syndrome
- mannose in CDG 1b (phosphomannose isomerase deficiency)

Stimulation of residual enzyme activity by the use of pharmacological doses of cofactors, often vitamins, e.g.

- vitamin B_{12} in methylmalonic acidaemia
- pyridoxine (vitamin B_6) in homocystinuria
- riboflavin (vitamin B_2) in multiple acyl-CoA dehydrogenase deficiency
- sapropterin in some forms of biopterin responsive PKU

Providing alternative substrates

- use of glucose and medium chain triglycerides in long chain fatty acid oxidation disorders
- use of the ketogenic diet in Glut 1 deficiency syndrome to produce ketones as an alternative energy source to glucose for use by the brain

In many IMD the promotion of anabolism and avoidance of catabolism at all times is vital to prevent metabolic decompensation occurring with the risk of further irreversible damage, particularly neurological. In such IMD the use of emergency dietary regimens during illness or times of stress, e.g. surgery, is imperative (Chapter 31). Detailed discussion of dietary treatment approaches is given in the relevant sections of this and the following chapters.

Patients with IMD are invariably complex to treat, and it is important they are managed by an experienced metabolic team including doctors, specialist dietitians, clinical nurse specialists, biochemists, pharmacists and psychologists in a metabolic centre. Local professionals and hospital teams also form an integral part of the care for metabolic patients, and liaison between the metabolic centre and local health, education and social care is crucial.

Nutritional support and ketogenic diet in IMD

Some IMD require nutritional support for various reasons, or, on occasions, dietary advice is required to limit the intake of certain nutrients if there are dietary intolerances due to drug treatment, e.g. with the use of Miglustat in Gaucher disease. Infantile Refsum's disease requires both therapeutic diet and nutritional support. Other IMD may be treated with a ketogenic diet. Examples of nutritional interventions are given in Table 27.4.

Newborn screening

Early detection is important to ensure a good outcome in many IMD, starting treatment before significant or any damage is done. NBS aims to detect affected infants before symptoms occur to allow early implementation of treatment. Strict criteria have to be met in order to be considered for screening, with screening tests having a high positive prediction value and low numbers of false positive and false negative results (www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes):

- PKU was the first IMD to be part of NBS (from the end of the 1960s in the UK)
- Screening has been expanded in a number of countries to include a variety of other disorders, depending on local health policy
- In the UK NBS was expanded to include:
  - MCADD (2009 England, 2012 all UK)
  - homocystinuria, isovaleric acidaemia, glutaric aciduria type 1 and MSUD (2015 in England)
- Further information on NBS can be found at www.gov.uk/guidance/newborn-blood-spot-screening-programme-overview
- Metabolic Support UK have developed an app for parents receiving a positive NBS result 'INHERITED METABOLIC DISORDERS: A Guide for Parents of a Child Detected by Screening', which can be downloaded via their website www.metabolicsupportuk.org
- Clinical and dietetic management guidelines can be accessed from www.bimdg.org
- NHS Newborn Blood Spot Screening Programme – a laboratory guide to newborn blood spot screening for inherited metabolic diseases. Updated September 2017. Describes the screening and diagnostic pathway for all screened disorders
- TEMPLE (Tools Enabling Metabolic Parents Learning) is a resource for health professionals and families, covering many different IMD including all those part of NBS www.bimdg.org.uk/site/temple.asp
- Further information on the disorders and treatment is given in the disorder-specific sections of Chapters 28–31

Transplantation for inherited metabolic disorders

Solid organ transplants, e.g. liver, kidney and stem cell transplants are used in some IMD:

Liver transplantation

- If the enzyme affected by the IMD is limited to the liver, then liver transplantation would effect a cure. Such disorders include the urea cycle disorders, MSUD and GSD type Ia
- Transplantation improves the metabolic stability of patient, but continued IMD management is required post-transplant. Includes organic acidaemias, e.g. propionic acidaemia, methyl malonic acidaemia and GSDIb

Kidney transplantation

- Renal transplants can be required in methylmalonic acidaemia where the toxic effect of methylmalonic acid causes end-stage renal failure. IMD management is still required post-transplant

Haematopoietic stem cell transplantation (HSCT)

- HSCT is used as a means of cross correction whereby engrafted donor white blood cells make and secrete the deficient enzyme in the recipient that can be taken up and used by enzyme deficient host cells, thus correcting the enzyme deficiency [12]. HSCT is used in a number of IMD including MPS I (Hurler disease) and X-linked adrenoleukodystrophy

There are review papers on IMD and liver transplantation [13, 14], kidney [15], liver–kidney [16] and HSCT [12, 17].

Summary

There are over 500 different IMD currently identified. A significant number are treatable, often by therapeutic dietary intervention as the sole treatment or in combination with pharmacological agents. These are discussed further in Chapters 28–31.

Learning points: inherited metabolic disorders

- *Understanding of normal metabolism and hormonal control is key to the understanding of IMD of intermediary metabolism*
- *IMD are individually very rare, but as a group are not*
- *Therapeutic dietary treatment is the sole or a significant treatment modality in many IMD*
- *Ketogenic diet therapy is a treatment modality for the underlying metabolic defect in some disorders of energy production or glucose transport, as well as being used to treat epilepsy in some IMD*
- *Nutritional support is a part of the management of many non-treatable forms of IMD*

Table 27.4 Nutritional interventions in inherited metabolic disorders.

Disorder	Dietary management
Lysosomal storage disorders (LSD) A defect in a specific lysosomal enzyme usually results in accumulation of incompletely catabolised substrates. This can result in organomegaly, dysmorphic or other morphological features as well as neurological deficits. Includes: • Mucopolysaccharidoses (MPS) – result from incomplete breakdown of glycosaminoglycans; include MPS I (Hurler syndrome), MPS II (Hunter syndrome), MPS III (Sanfilippo syndrome), MPS IV (Morquio syndrome) • Mucolipidosis (ML) – has features of MPS and sphingolipidoses; includes I-cell disease • Oligosaccharidoses – result from incomplete breakdown of carbohydrate side chains from glycoproteins; includes mannosidosis • Sphingolipidoses – result from incomplete breakdown of ceramide-containing membrane lipids; includes GM gangliosidosis, Fabry disease, Gaucher disease, Krabbe disease, Niemann–Pick Type A/B, metachromatic leukodystrophy • Neuronal ceroid lipofuscinosis (NCL), e.g. Batten's disease • Lipid storage diseases, e.g. Niemann–Pick type C, Pompe disease (GSD type II), lysosomal acid lipase deficiency • Lysosomal transport defects, e.g. cystinosis Some LSD are treated with enzyme replacement therapy Some LSD, e.g. Fabry disease, Gaucher disease, Niemann–Pick type C, may be treated with Miglustat (substrate reduction therapy). This can cause diarrhoea initially due to malabsorption of disaccharides, particularly sucrose and maltose; lactose to a lesser extent	**Children with a LSD may require nutritional intervention as:** • Nutritional support including enteral tube feeding, particularly those with neurodegeneration – see Chapter 4 • Weight management. Some may have growth retardation as a part of the disorder, e.g. those with MPS IV have short stature • Low disaccharide diet if on Miglustat therapy [8] • Ketogenic diet if they have epilepsy, e.g. Batten's disease – see Chapter 17 Infant onset lysosomal acid lipase deficiency (Wolman disease) requires specific therapeutic dietary management – see Chapter 30

Defects in energy production
A number of different disorders that affect cellular energy supply (ATP)
Mitochondrial disorders – a heterogeneous group of disorders resulting in impaired energy production by the mitochondrial respiratory chain. Many may result in neurological deficits, epilepsy, gastrointestinal symptoms and involvement of unrelated organs over time. Includes:
• Alpers syndrome – progressive neuronal degeneration of childhood with liver disease
• Coenzyme Q_{10} deficiency – multisystem disease with nephropathy, encephalopathy including seizures, hearing loss
• Ethylmalonic encephalopathy (EME)
• Leigh syndrome (subacute necrotising encephalomyelopathy)
• Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episode (MELAS)
• Myoclonus, epilepsy, ragged red fibres (MERFF)
• Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
• Pearson syndrome
Further information in review papers:
Rahman S *Gastrointestinal and hepatic manifestations of mitochondrial disorders* [9]
Rahman S *Mitochondrial disease and epilepsy* [10]
 	
Disorders of pyruvate metabolism and Krebs cycle - includes:
Pyruvate dehydrogenase (PDH) deficiency
• PDH complex converts pyruvate to acetyl-CoA. Deficiency results in increased blood and cerebrospinal fluid (CSF) concentrations of pyruvate and lactate and lack of acetyl-CoA, thus decreasing availability of precursors feeding into the Krebs cycle and resulting in limitation of mitochondrial energy production.
Pyruvate carboxylase (PC) deficiency
• PC catalyses the conversion of pyruvate to oxaloacetate, a Krebs cycle intermediate, and is also needed for synthesis of aspartate required to transport reducing equivalents across the mitochondrial membrane and in the urea cycle.
There are currently no specific medical or dietetic therapies to effectively treat the underlying defect
Supportive therapies, including nutritional support, may be required in many cases to manage symptoms resulting from the underlying defect
 	
Disorder of glucose transport affecting brain energy metabolism
Glut 1 deficiency syndrome
• Lack of glucose transporter type 1 prevents normal transport of glucose across the blood–brain barrier and a consequent lack of glucose for brain energy metabolism. For a fuller description see Chapter 17
	Children with defects in energy production may require nutritional intervention as:
	• Enteral nutritional support, including enteral tube feeding, for poor growth, inadequate oral intake, unsafe swallow – see Chapter 4
	• Parenteral nutrition may be required in MNGIE due to severe gut dysmotility causing gastrointestinal pain with enteral intake, resulting in severe undernutrition and growth failure – see Chapter 5
	• Pearson syndrome may require pancreatic enzyme replacement therapy – see Chapter 12
	• Ketogenic diet may be used for:
	  ◦ Management of epilepsy
	  ◦ Management of milder cases of PDH deficiency
	  ◦ Management of Glut 1 deficiency syndrome – see Chapter 17

(continued overleaf)

Table 27.4 (*continued*)

Disorder	Dietary management

Peroxisomal disorders
A group of inherited heterogeneous disorders that result from either dysfunction of either the biosynthesis of peroxisomes or their function. Peroxisomes are involved in β-oxidation of very long chain fatty acids, production of plasmalogens (class of phospholipids) and bile acid synthesis.
There are two main categories of peroxisomal disorders:
• Single peroxisomal enzyme deficiency including:
  ○ X-linked adrenoleukodystrophy (X-linked ALD)
  ○ Refsum's disease
  ○ Rhizomelic chondrodysplasia punctate
• Disorders of peroxisomal biogenesis:
  ○ Zellweger spectrum disorders including neonatal adrenoleukodystrophy and Infantile Refsum's disease
  ○ Rhizomelic chondrodysplasia punctate (type 1)
For most of the peroxisomal disorders, there is no specific treatment other than supportive care. Exceptions:
• X-linked ALD – HSCT may be a possible treatment option if diagnosed before the onset of neurological symptoms
• Infantile Refsum's and Refsum's disease – a low phytanic acid diet
Further information on the peroxisomal disorders can be found in *Clinical Paediatric Dietetics* 4th edition [11]
	Children with peroxisomal disorders may have neurological impairment affecting feeding abilities and require nutritional intervention as:
	• Enteral nutritional support, including enteral tube feeding for poor growth, inadequate oral intake, unsafe swallow – see Chapter 4
	
	Children with Refsum's disease and some cases of Infantile Refsum's disease require a low phytanic acid diet
	• Phytanic acid is derived from the breakdown of chlorophyll by microbes in ruminant animals
	• The following foods rich in phytanic acid must to be avoided:
	  ○ Meat from ruminant animals (beef, calves' liver and kidneys, lamb, duck, goose, rabbit)
	  ○ Dairy products made from cow, sheep or goat milk apart from very low fat alternatives, e.g. skimmed milk, very low fat/fat-free yoghurts
	  ○ Fish, particularly oily types, shellfish, fish oil
	  ○ Baked products using butter
	  ○ Milk chocolate
	Further dietary information is available on the Adult Refsum's disease website
	https://refsumdisease.org/

Sterol biosynthesis disorders Multisystem disorders resulting from enzyme deficiencies in the biosynthesis of cholesterol and consequently the formation of bile acids, steroid hormones, cell membranes and vitamin D. This results in dysmorphic and skeletal dysplasias that have antenatal onset. Includes: • Smith–Lemli–Opitz syndrome (SLOS) • Desmosterolosis • Lathosterolosis Cholesterol supplementation is used for SLOS and in other sterol disorders where there is hypocholesterolaemia. In SLOS restoration of normal plasma cholesterol levels restores adrenal steroid and bile salt production. Cholesterol supplementation increases plasma cholesterol levels. In turn this provides feedback inhibition of HMG-CoA reductase, thus reducing flux through the endogenous cholesterol synthesis pathway with decreased production of 7-dehydrocholesterol and its isomer 8-dehydrocholesterol, which are toxic. Exogenous cholesterol cannot cross the blood–brain barrier and so cannot treat the biochemical defect in the brain.	**Children with SLOS and other sterol biosynthesis disorders may require nutritional intervention as:** • Enteral nutritional support, including enteral tube feeding for poor growth, inadequate oral intake, unsafe swallow – see Chapter 4
Congenital disorders of glycosylation A group of disorders resulting from defects in the glycosylation (addition of sugar molecules) of proteins or lipids to form glycoproteins and glycolipids. They affect multiple organs causing a range of symptoms including developmental delay, hypotonia, seizures in most and commonly gastrointestinal symptoms of diarrhoea and vomiting.	**Children with congenital disorders of glycosylation may require nutritional intervention as:** • Enteral nutritional support, including enteral tube feeding for poor growth, inadequate oral intake, unsafe swallow – see Chapter 4

GSD, glycogen storage disease; ATP, adenosine triphosphate; HSCT, haemopoietic stem cell transplantation.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

28 Disorders of Amino Acid Metabolism, Organic Acidaemias and Urea Cycle Disorders

Marjorie Dixon, Anita MacDonald and Fiona J. White

Protein requirements

Proteins provide an essential structural and functional role; amino acids are the building blocks of all vital organs, muscle (including heart muscle), hormones and biological fluids such as blood. Maintenance of growth and other physiological functions requires a constant intake of good quality dietary protein as the human body is incapable of maintaining reserves of protein. The body is in a dynamic state. Its proteins and other nitrogenous compounds are degraded and resynthesised continuously, a process that is not completely efficient (some amino acids are lost by oxidative catabolism) [1]. The magnitude of daily protein synthesis in adults is three- to fourfold greater than the intake of protein and five- to sixfold greater in growing children [2].

Anabolism, including protein synthesis, increases in tissues following food ingestion. Amino acids are used to support anabolism throughout the day, but especially following meal ingestion (foods containing carbohydrate, fat and protein). The form and nature of dietary proteins may influence amino acid utilisation within the body. L-amino acids do not require digestion and are directly available for absorption by the small intestine [3]. This leads to rapid absorption [4, 5] and may cause a transient imbalance among amino acids in the systemic circulation. Absorption of L-amino acids is different from that of whole protein, such as casein. Ingestion leads to a rapid increase and higher plasma concentrations, but they also decrease more quickly compared to whole protein [5]. In addition, nitrogen retention and weight gain following ingestion of L-amino acids is less efficacious than with casein-rich protein, suggesting a less efficient transfer of amino acids into tissue and plasma proteins [4, 6]. Increased oxidation has also been suggested when amino acid supplements are taken in large single doses [7].

Amino acid requirements in healthy infants and children

For healthy infants up to 6 months of age, the amino acid content of breastmilk is considered the best estimate of amino acid requirements. However, for infants with amino acid disorders, breastmilk given *ad lib* without supplementation with suitable L-amino acids would provide an intake in excess of their tolerance. The average essential amino acid (EAA) content of mixed human milk proteins is given in Figure 28.1.

The FAO/WHO/UNU report on *Protein and Amino Acid Requirements in Human Nutrition* used a factorial calculation approach to estimate the amino acid requirements of children (Table 28.1). These were based on growth rates and protein deposition for children of different age groups, the amino acid composition of whole body protein and efficiency of dietary protein utilisation [8]. Amino acid requirements are also determined using a stable isotopic technique: indicator amino acid oxidation (IAAO) method [9, 10].

In general, the results of the isotopic experimental method are similar to those derived by the factorial method, except for branched chain amino acids (BCAA) [9]. For school-aged children the estimated requirement for BCAA (leucine, valine, isoleucine combined) using the factorial approach is 96 mg/kg/day [8], and by the IAAO technique 147 mg/kg/day [11]. The factorial approach uses adult BCAA requirements plus the additional needs for growth, and it assumes that the maintenance requirements for dietary EAA are the same for children as adults [9]. More studies are required using the IAAO technique to demonstrate their reliability [12].

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

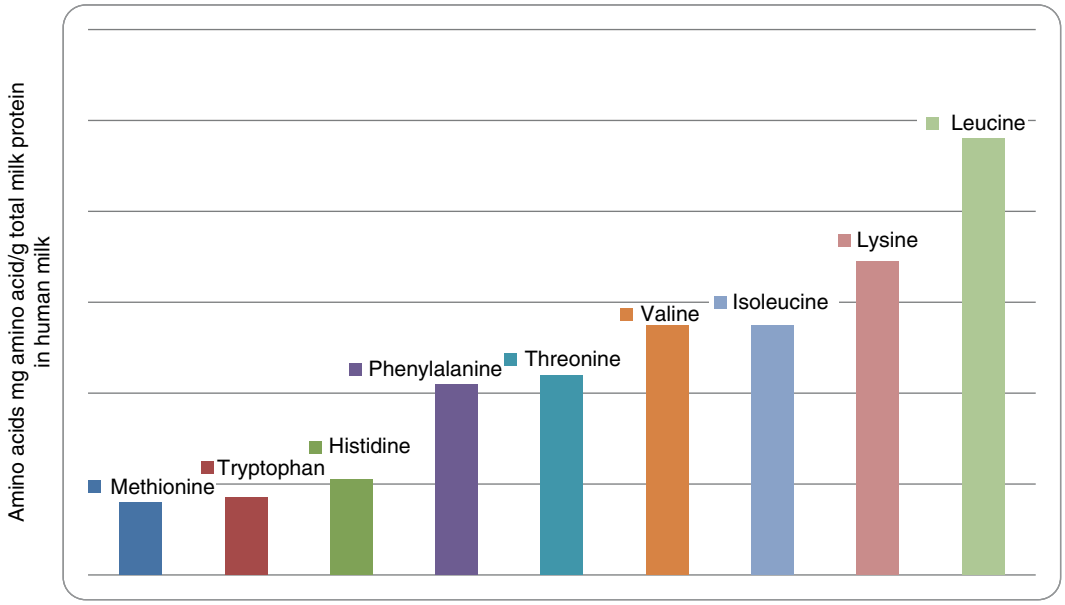


Figure 28.1 Amino acid composition of mixed human milk proteins [8].

Table 28.1 Amino acid requirements of healthy children determined using the factorial approach [8].

	Essential amino acid requirements (mg/kg/day)								
Age (years)	His	Ile	Leu	Lys	SAA	AAA	Thr	Trp	Val
0.5	22	36	73	64	31	59	34	9.5	49
1–2	15	27	54	45	22	40	23	6.4	36
3–10	12	23	44	35	18	30	18	4.8	29
11–14	12	22	44	35	17	30	18	4.8	29
15–18	11	21	42	33	16	28	17	4.5	28

His, histidine; Ile, isoleucine; Leu, leucine; Lys, lysine; SAA, sulphur amino acids (methionine, cysteine); AAA, aromatic amino acids (phenylalanine, tyrosine); Thr, threonine; Trp, tryptophan; Val, valine.
Source: Reproduced with permission of WHO.

Total protein requirement in amino acid disorders

Most patients with amino acid disorders require severe restriction of natural protein intake, and the provision of a suitable precursor-free supplement of L-amino acids (referred to as a protein substitute in this text) is essential to both prevent protein deficiency and optimise metabolic control. In most patients, it is likely that precursor-free protein substitute will supply >75% of the total protein intake [13].

Phenylketonuria

Anita MacDonald

Enzyme	Phenylalanine hydroxylase (PAH)
Biochemical defect	PAH catalyses the hydroxylation of phenylalanine to tyrosine, using tetrahydrobiopterin (BH4) as a cofactor. Deficiency leads to complete or partial inability to metabolise phenylalanine, causing increased phenylketones, and elevated blood phenylalanine concentrations that cross the blood–brain barrier and accumulate in the brain. Tyrosine, dopamine, norepinephrine and serotonin concentrations are lower (Figure 28.2). High levels of brain phenylalanine are possibly the main cause of neurotoxicity [14] by interfering with cerebral protein synthesis [15], increasing myelin turnover and inhibiting neurotransmitter synthesis [16].

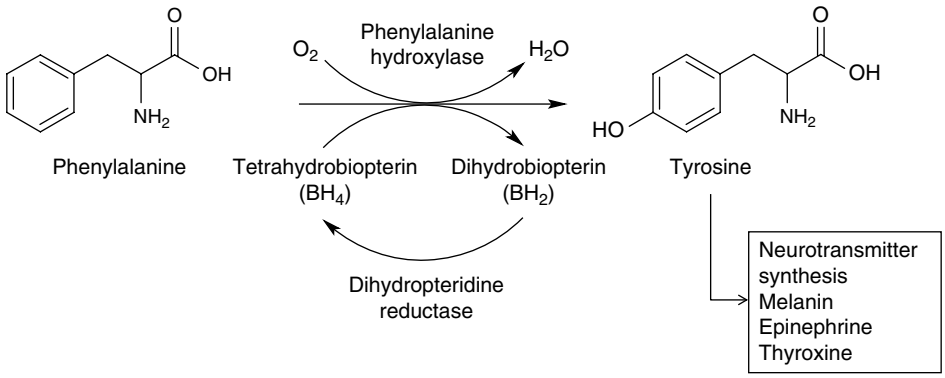


Figure 28.2 Hydroxylation of phenylalanine.

Genetics

- Autosomal recessive inheritance. The global prevalence in screened populations is approximately 1 in 12 000 births with an estimated carrier frequency of 1 in 55 [17], but it varies between populations. It is particularly common in Ireland and Turkey.
- Phenylketonuria (PKU) is caused by mutations in the gene encoding PAH. There are >1000 PAH gene variants and >2500 different genotypes [18]. There is a good correlation between genotype and phenotype [19].
- A small number of patients with so called severe PKU mutations have escaped intellectual disability despite having high blood phenylalanine concentrations and poor dietary control. They appear to have near normal brain phenylalanine content although other neurological, psychological and/or behavioural symptoms may occur [20].

Newborn screening

- Screening is by measurement of phenylalanine (≥240 µmol/L) in dried blood spots using tandem mass spectrometry. More information on UK screening, diagnostic and clinical management protocols can be found at www.bimdg.org and www.gov.uk *Newborn blood spot screening: laboratory guide for IMDs* (inherited metabolic diseases).
- UK infants are screened at around day 5 of life. European PKU guidelines 2017 [21] recommend the following:
  - Treatment should start by 10 days of age
  - All patients with untreated blood phenylalanine levels >360 µmol/L should be treated

Clinical onset presentation, features

Untreated PKU causes global intellectual disability, significant delays in developmental milestones, hyperactive behaviour with autistic features, seizures, movement problems, eczema, musty body odour and light pigmentation (eyes, hair and skin). If treatment is started within the first 3 weeks of life, irreversible intellectual disability is prevented.

Classification

There is a broad continuum of PKU phenotypes ranging from severe to milder forms. PKU is generally classified by the severity of hyperphenylalaninaemia at diagnosis:

- *Classical or severe PKU*: usually characterised by blood phenylalanine concentrations >1200 µmol/L. Phenylalanine tolerance may be ≤250 mg/day (5 g/day natural protein) to maintain phenylalanine concentrations <360 µmol/L
- *Moderate PKU*: classified with diagnostic phenylalanine concentrations of 600–1200 µmol/L. Most patients with moderate/severe PKU tolerate between 200 and 700 mg/day phenylalanine (4–14 g/day natural protein) while maintaining phenylalanine concentrations <360 µmol/L
- *Persistent hyperphenylalaninaemia or mild PKU*: patients present with phenylalanine concentrations between 120 and 600 µmol/L on a normal diet. They are likely to tolerate >750 mg/day phenylalanine (>15 g/day natural protein). European PKU guidelines 2017 recommend all patients with untreated blood phenylalanine between 360 and 600 µmol/L be treated during the first 12 years of life [21] and should remain on treatment >12 years if blood levels exceed 600 µmol/L. Any patient with a blood phenylalanine between 240 and 360 µmol/L should remain in long-term follow-up, particularly women due to later risks of maternal PKU. Young children require blood phenylalanine monitoring, particularly during the first year of life as levels may still increase in the late weaning period

About 1%–2% of hyperphenylalaninaemia is caused by mutations in genes coding for enzymes involved in tetrahydrobiopterin (BH4) cofactor biosynthesis or regeneration [22] affecting phenylalanine homeostasis and catecholamine and serotonin biosynthesis [23]. BH4 deficiencies are treated with neurotransmitters with or without BH4 supplementation (described in *Clinical Paediatric Dietetics* 4th edition). A low phenylalanine diet may be prescribed for hyperphenylalaninaemia.

Long-term complications and outcome

Neuropsychological and mental health

Children who commence early dietary treatment from newborn screening should be within the broad normal range of general ability, attain expected educational standards and lead independent lives as adults. However, outcome is dependent on the quality of blood phenylalanine control, and even children with good metabolic control have lower IQs (up to 6 points) than their unaffected siblings and children without PKU [21]. They may have deficits in selective and sustained attention, processing speed, fine motor skills, perception and visual–spatial abilities. Executive function (working memory, planning, mental flexibility, organisation and inhibitory control) may be impaired. Mental health problems (anxiety, depression, mood swings) have been associated with concurrent and historical high blood phenylalanine levels. Seizures, behavioural problems and movement disorders are reported in patients with long-term diet discontinuation [24].

Quality of life

An infant diagnosis of PKU may have a significant psychological impact on parents. The knowledge that their actions can affect the neurocognitive outcome of their child is a heavy responsibility. Dietary management of PKU by parents has a median time burden of 19 hours per week [25]. Stigmatisation and feeling socially excluded are common issues. Bullying about diet can affect a child's relationship with food, leading to disordered eating [26]. Eating away from home is a barrier to adherence.

Growth

Overall children with PKU have comparable growth patterns to healthy controls, although suboptimal growth has been noted, particularly in early childhood and adolescence [27, 28], with adults underachieving their final height [28]. Head circumference increase has been shown to align with natural protein intake [29]. Fat-free mass and improved body composition is also associated with higher intakes of natural protein intake [30, 31].

Overweight

Adults with PKU have a higher prevalence of overweight, and females are more overweight/obese than the general population [27, 32, 33]. Although factors associated with overweight in PKU include relaxation of strict diet therapy, a high carbohydrate intake and low activity levels [34], causes are probably multifactorial.

Bone health

Osteopenia and osteoporosis may occur, with a lower spine bone mineral density [35], but meta-analysis of early treated patients shows that while bone mineral density *z* scores were lower than healthy peers, they were within normal reference range [36].

Poor bone health is associated with amino acid imbalances; inadequate natural protein intake; low calcium, phosphorus, magnesium, vitamin D, *n*-3 polyunsaturated fatty acids intakes; low calcium/protein ratios; poor dietary adherence with micronutrient supplemented protein substitute; low plasma magnesium, zinc and copper concentrations; elevated blood phenylalanine concentrations and lack of weight bearing exercise [35–37].

Vitamin B_{12} deficiency

Vitamin B_{12} deficiency is mainly reported in adolescents or adult patients who have either relaxed their diet and are less adherent with protein substitutes or stopped diet but not eating a normal protein intake, particularly animal protein. Symptoms such as spastic paraparesis, tremor and slurred speech are associated with vitamin B_{12} deficiency in adults with PKU [38, 39].

Medical treatment

- Lifelong treatment with a low phenylalanine diet
- Care should be provided by a specialist multi-disciplinary team (medical doctor, dietitian, nurse, psychologist). Psychological support and family and patient education are essential
- Regular monitoring according to European PKU guidelines 2017 [21], assessing blood phenylalanine control, neurocognitive outcome and overall psychosocial well-being
- Diet history and growth: weight, length/height, body mass index (BMI) should be monitored at each clinic visit
- Assessment of bone mineral density in late adolescence only, providing adherence with dietary management, is satisfactory, and nutrient intakes meet requirements
- Optimisation of calcium, vitamin D and natural protein intake and regular exercise for bone health
- Effective transition processes between paediatric and adult services is essential

Other treatment options

New treatment options, either as an adjunct therapy to a low phenylalanine diet or to replace dietary treatment, are available or in development.

Biopterin-responsive phenylalanine hydroxylase deficiency

Sapropterin dihydrochloride (Kuvan) is an oral synthetic form of BH4, the natural cofactor of phenylalanine hydroxylase, which activates residual PAH enzyme activity. Only some mutant PAH enzymes show enhanced activity in the presence of pharmacological doses of sapropterin, so it is effective only in a subset of patients (around 20%–30%), mainly those with mild or moderate phenotypes. Sapropterin has been demonstrated to lower blood phenylalanine concentrations and improve phenylalanine tolerance. It is either given with a relaxed low phenylalanine diet, or it may replace diet therapy depending on the individual response to the drug [21].

Prior to treatment, responders are identified by evaluating the reduction in blood phenylalanine following treatment with 20 mg/kg/day of sapropterin for up to a 4-week period. A 30% reduction from baseline in mean phenylalanine blood levels is considered an effective response. Once responsiveness is established, the dosage may be adjusted within the range 5–20 mg/kg/day. Details of responsive testing are given by Muntau *et al*. [40, 41]. It is important to check that patients are prescribed phenylalanine to their full tolerance prior to sapropterin responsiveness testing and a treatment trial.

This drug is not routinely commissioned by the NHS in England, Scotland, Wales or Northern Ireland.

Pegvaliase (PEGylated recombinant [*Anabaena variabilis*] phenylalanine ammonia lyase [PAL]) (Palynziq)

An enzyme substitution therapy given by daily subcutaneous injection. PEGPAL converts phenylalanine into low levels of ammonia and non-toxic trans-cinnamic acid by-products. This allows patients with PKU to metabolise phenylalanine independently of PAH residual activity. It is approved by the USA Food and Drug Administration, and the European Medicines Agency has granted marketing authorisation for patients with PKU aged 16 years and over with blood phenylalanine levels >600 µmol/L. Its use has not yet been appraised in the NHS. Trial data has demonstrated that 61% of patients were able to achieve blood phenylalanine levels <360 µmol/L at 24 months of treatment [42] with substantially improved natural protein intake. Side effects include hypersensitivity type reactions including injection site reactions, anaphylactic episodes, headaches, and joint pain during the initial stages of dosing with the drug.

Other therapies

Those in development include genetically modified bacteria to lower phenylalanine levels [43] and genome-targeted gene therapy [44].

Dietetic management	• Primary aim – to prevent adverse neurocognitive and psychological outcomes by restricting protein from natural foods to maintain blood phenylalanine levels within the target range while providing enough phenylalanine to support protein synthesis and avoid catabolism • Secondary aim – to maintain a healthy nutritional status by providing sufficient low phenylalanine/phenylalanine-free protein substitute, energy and other nutrients to support physiological protein synthesis, counterbalance catabolism but without providing excess energy intake. Protein substitute may be from one of two sources: either phenylalanine-free L-amino acids or low phenylalanine glycomacropeptide (GMP) (p. 520)
Monitoring – biochemical	Blood phenylalanine levels should be measured weekly in the first year, once every 2 weeks from age 1–12 years and monthly >12 years of age. Blood phenylalanine levels should be reported within 5 working days from the time of home blood spot sampling [21]. For children aged 0–12 years, target blood phenylalanine levels are 120–360 µmol/L. For patients above the age of 12 years (exception pre-conception and pregnancy), European PKU guidelines 2017 suggest 120–600 µmol/L to be safe throughout adolescence and adulthood [21]. Parents should be taught by a specialist nurse how to collect heel or thumb prick dried blood spot samples at home. Blood samples are posted to the hospital and analysed, usually by tandem mass spectrometry (MS/MS), for phenylalanine (+/– tyrosine). For patients on dietary treatment, the dietitian should promptly inform the parents/patients of blood phenylalanine results on the same day of availability, discuss their interpretation and give instruction about any necessary dietary change. Blood phenylalanine levels should be taken at a standard time each day, preferably before the first dose of protein substitute in the morning when they are at their highest concentration after an overnight fast [45]. Annual measurement of plasma homocysteine and/or methylmalonic acid, haemoglobin, mean corpuscular volume (MCV) and ferritin [21]. Serum vitamin B_{12} concentrations within the reference range do not indicate a satisfactory vitamin status [38].
Clinical management guidelines	European PKU guidelines 2017 [21] includes evaluation/monitoring for cognitive and executive function, neurological involvement, psychosocial and mental health, biochemical nutritional monitoring and pregnancy.
Parent support groups	The National Society for Phenylketonuria (NSPKU) www.nspku.org The European Society for Phenylketonuria (ESPKU) www.espku.org

Dietary management of PKU

There are six key elements:

- In classical PKU, dietary phenylalanine (protein) restriction to 20% or less of normal intakes is necessary to maintain blood phenylalanine concentrations within target range. It is best to avoid high protein foods such as meat, fish, eggs and cheese in classical PKU as the amounts permitted would be very small. The percentage of phenylalanine in protein found in milk products, cereals, vegetables and fruits is given in Table 28.2.
- Daily allocation of dietary phenylalanine from measured quantities of natural protein foods to provide essential phenylalanine requirements is allocated by an exchange system: one food can be exchanged or substituted for another of equivalent phenylalanine content.
- Provision of a suitable protein substitute, with added tyrosine in order to meet nitrogen and tyrosine requirements.
- Maintenance of a normal energy intake by encouraging liberal use of foods naturally low in phenylalanine and special low protein foods such as bread and pasta.

Table 28.2 Percentage of phenylalanine found in milk products, cereals, vegetables and fruits [46].

Protein contributed by phenylalanine from cereals and milk products	Protein contributed by phenylalanine from vegetables	Protein contributed by phenylalanine from fruits
5%	3%–4%	3%

Source: Reproduced with permission of Elsevier.

- Provision of vitamins, minerals and docosahexaenoic acid to meet dietary requirements; these are usually added to the protein substitute or as separate modules.

Phenylalanine tolerance

The amount of phenylalanine tolerated will vary depending on the severity of the patient's phenotype (residual enzyme activity), age, use of sapropterin, dosage of protein substitute and non-protein energy ratio.

Natural protein/phenylalanine tolerance is defined as the amount that maintains the blood phenylalanine within a target treatment range. The amount of natural protein/phenylalanine from infant formula or food should be titrated against blood phenylalanine levels until levels are stable and within the target treatment range. Phenylalanine requirements are highest (mg/kg/day) in early infancy. After the age of 6 months, there is a slow and steady decline in tolerance per kilogram body weight, although the total daily amount may stay the same (Table 28.3). This is in parallel with decreasing growth rate and protein requirements. Phenylalanine is an EAA and its excessive restriction should be avoided. Deficiency, with very low blood phenylalanine levels, could lead to anorexia, alopecia, perineal rash, faltering growth, osteopenia and even death [21, 47, 48].

Exchange systems used to allocate dietary phenylalanine (natural protein)

- Systems for allocating phenylalanine vary throughout Europe [49]. In the UK, phenylalanine is allocated in

Table 28.3 Tolerance of phenylalanine throughout childhood.

Age	Phenylalanine (mg/kg)
0–6 months	25–60*
7–12 months	25–40
	Phenylalanine (mg/day)
1–10 years	200–700*
11–16 years	200–700*

This does not take into consideration the additional quantities consumed from low protein free foods and fruits and vegetables allowed without measurement/calculation in the diet.
*MacDonald A. Unpublished longitudinal clinical data in 100 patients with classical/moderate PKU over 20 years: maintaining plasma phenylalanine 120–360 µmol/L in children aged 1–10 years and 120–700 µmol/L in adolescents aged 11–16 years (data collected prior to European PKU guidelines 2017 [21] using target blood phenylalanine levels higher than these recommended guidelines for patients aged 10 years and older).

50 mg phenylalanine or 1 g protein exchanges. Generally, for all foods except fruit and vegetables, protein analysis can be used to calculate exchanges as 1 g protein provides 50 mg phenylalanine. Fruit and vegetables generally contain a lower concentration of phenylalanine (<50 mg/1 g protein) compared with their protein content, so phenylalanine analysis is used to calculate phenylalanine exchanges from fruits and vegetables.

- Each patient is allocated a total daily amount of natural protein/phenylalanine; the number of exchanges to make up this daily allowance is then calculated (Table 28.4) [49]. One food can be exchanged or substituted for another of equivalent phenylalanine content. No more than 50% of the natural protein/phenylalanine allowance should be given at any one meal. A guide to calculating the weight of 1 g protein exchange (50 mg phenylalanine) from protein food labels is given in Table 28.5. A guide to using protein/phenylalanine exchanges is given in Table 28.6.

Table 28.4 Examples of phenylalanine/protein exchange systems for PKU.

Exchange system	Approximate protein equivalent	Examples of number of daily phenylalanine exchanges allocated
50 mg phenylalanine	1 g	200 mg Phe daily 4 × 50 mg exchanges = 4 g protein/4 exchanges 300 mg Phe daily 6 × 50 mg exchanges = 6 g protein/6 exchanges

Phe, phenylalanine.

Table 28.5 Guide to calculating the weight of 1 g protein exchange (50 mg phenylalanine) from protein food labels.

100 ÷ by the amount of protein per 100 g food = 1 protein exchange

Breakfast cereal X contains protein 8.3 g/100 g

To calculate 1 exchange:

100 ÷ 8.3 g = 12 g *breakfast cereal X*

12 g *breakfast cereal X* = 1 g protein or 1 protein exchange

NB: Always use the protein analysis per 100 g of food and *not* protein analysis per stated food portion size. If using this method for estimating protein exchange from food portion sizes, see Table 28.7.

Challenging phenylalanine tolerance

From the age of 2 years, if blood phenylalanine control is stable, phenylalanine tolerance should be re-examined from time to time, but particularly at times of rapid growth. Some adolescents and adults with PKU have been reported to tolerate more natural protein than they had been prescribed [55]. Any challenge with additional phenylalanine should be conducted carefully, introducing small measured quantities (equivalent to 0.5–1.0 g/day natural protein) systematically, ensuring stable blood phenylalanine control within target limits before further changes are made. A minimum of three consecutive blood phenylalanine levels within target range should be achieved before further challenge is considered.

Low protein foods

There are some foods that are naturally very low in protein that can be eaten in normal portion sizes in the diet without measurement (Table 28.9). They are referred to as exchange-free foods [51].

The European Commission and Consumers Regulation (EU) No. 1169/2011 on the provision of food information for consumers states that manufacturers need not declare protein content if manufactured foods contain ≤0.5 g/100 g protein, and so foods may be listed as containing 0 g protein even if they have protein-containing ingredients. This has contributed to some unclear protein labelling on manufactured foods. However, the British Inherited Metabolic Disease Group (BIMDG) dietitians have examined the protein content of manufactured foods and have defined for each food group the foods that can be considered exchange-free in PKU (Table 28.9) [51].

Energy intake

It is important that age-related energy requirements are met for optimal dietary protein utilisation. Total energy intakes as a percentage of estimated average requirements (EAR) is similar to children without PKU [56], but from 12 months of age, children with PKU consume a higher intake of carbohydrate (CHO) providing almost 60% of energy requirements, with 15% from protein equivalent sources. There are concerns that a high CHO diet may impact on body composition

Table 28.6 Guide to using 1 g (50 mg phenylalanine) protein exchange foods.

1. Exchange foods are generally sourced from low biological protein foods such as potatoes, peas, sweetcorn, rice, pasta and breakfast cereals. Yoghurt or milk are useful protein sources in older infants and toddlers if appetite is poor
2. It is preferable to weigh foods with digital scales rather than using household measurements, which are not accurate
3. Ideally exchanges should be spread evenly throughout the day so that a phenylalanine load is not given at any one time [50]
4. It is useful to teach parents and patients to calculate 1 g protein exchanges directly from food protein labelling on packages. An example on how to calculate 1 g protein exchanges is given in Table 28.5. 'Pocket-size protein calculators' are helpful and are available from the NSPKU. Their website also provides a downloadable PKU exchange calculator www.nspku.org
5. If protein exchange amounts are calculated from food portion sizes listed on food labels, then the protein content per item should be rounded up or down to the nearest 0.5 g protein using the rule for rounding numbers (Table 28.7) [51]
6. All parents/caregivers should be advised to read food label ingredient lists. Occasionally food protein labelling errors occur that can be detected by checking the list of ingredients. For example, if a food states that it contains protein <0.5 g/100 g but the first or second ingredient is wheat flour, then the protein label is likely to be incorrect. Patients should be encouraged to report protein labelling errors to their dietitian and food supplier.
7. For foods such as ice cream, weight rather than volume should be used to calculate the protein exchange amount. The protein value may be expressed per 100 g or per 100 mL on food labels. The weight of 100 mL ice cream is not the same as 100 g ice cream because of the difference in density. The density is influenced by the 'free' air a manufacturer whips into the ice cream. Ice cream has a minimum density of approx. 50 g per 100 mL, but brands of ice cream that contain solid ingredients such as chocolate chips will have higher densities (up to 90 g per 100 mL)
8. Fruits and vegetables:
   - Fruits and vegetables containing phenylalanine >75 mg/100 g are counted as exchange foods. Phenylalanine content up to 75 mg/100 g are exchange-free [21] as they do not significantly elevate plasma phenylalanine concentrations and can be safely given free [52]
   - Fruits and vegetables containing phenylalanine 76–99 mg/100 g (e.g. cauliflower, broccoli) use a standard weight of 60 g as one phenylalanine exchange (Table 28.8)
   - Fruits and vegetables containing phenylalanine ≥100 mg/100 g (e.g. peas, sweetcorn) use the actual phenylalanine content per 100 g to calculate the weight of food to provide one phenylalanine exchange (Table 28.8) [53]
9. Potatoes should be calculated as part of the phenylalanine/protein allowance. They have a higher phenylalanine/protein ratio than most other fruits and vegetables. If potato products contain additional exchange ingredients, e.g. wheat flour or milk, then the protein analysis on the packet should always be used to determine their exchange amount
10. Cooked crisps (snacks) made from vegetables such as beetroot or parsnips are concentrated in phenylalanine and should be counted within the phenylalanine allowance
11. Theoretically any foods can be eaten as exchanges, but high protein foods can only be given in small amounts. Young children do not understand exchange systems and have difficulty in understanding why they cannot eat more of these foods. It would seem inappropriate to accustom their palate to high protein foods when they cannot eat adequate quantities to satisfy appetite

NSPKU, National Society for Phenylketonuria.

Table 28.7 Guidance for calculating protein exchange amounts [51] from food portion sizes on food labels.

Protein content per item when calculated from food label	Calculated exchange
0 g protein per food portion	Exchange-free
0.1 g protein per food portion	Exchange-free
0.2 g protein per food portion	Exchange-free (providing total amount consumed does not exceed 0.5 g protein)
0.3 g protein per food portion	Exchange-free (providing total amount consumed does not exceed 0.5 g protein). If a food is 0.3 g/per food portion, suggest one portion is exchange-free and two portions is ½ exchange
0.4–0.7 g protein per food portion	½ exchange protein
0.8–1.2 g protein per food portion	1 exchange protein
1.3–1.7 g per food portion	1.5 exchange protein
1.8–2.2 g per food portion	2 exchange protein
2.3–2.7 g per food portion	2.5 exchange protein
2.8–3.2 g per food portion	3 exchange protein

Table 28.8 Basic 50 mg phenylalanine exchanges for infant formula, fruits and vegetables (using phenylalanine analysis) and 1 g protein exchanges for dairy products.

Food	Amount of food for 50 mg phenylalanine exchanges [53, 54]	Food	Amount of food for 50 mg phenylalanine exchanges [53, 54]
Breastmilk	90 mL	Kale, cooked	35 g
SMA Pro First Infant Milk (from powder)	70 mL	Lentils, raw	5 g
Cow & Gate First Infant Milk (from powder)	90 mL	Lentils, boiled	12 g
Cow & Gate First Infant Milk – liquid	85 mL	Mangetout, raw or cooked	60 g
Aptamil Profutura First Infant Milk (from powder)	90 mL	Passion fruit	40 g
Aptamil Profutura First Infant Milk – liquid	85 mL	Peas, petit pois (fresh, frozen, tinned), boiled	25 g
Cow's milk	30 mL	Rocket, raw	35 g
Yoghurt (natural/flavoured)	20 g	Romanesco, cooked	35 g
Asparagus, boiled	60 g	Spinach, boiled	25 g
Baked beans (canned)	20 g	Spring greens, boiled	35 g
Bamboo shoots, raw or cooked	60 g	Sugar snap peas, cooked	60 g
Beansprouts, raw or cooked	60 g	Sweetcorn (canned), cooked	35 g
Broad beans, boiled	20 g	Sweetcorn (corn on the cob), cooked	4 cm
Broccoli, boiled	60 g	Vine leaves, cooked	30 g
Brussels sprouts, boiled	60 g	Whole hearts of palm, cooked	60 g
Cauliflower, boiled	60 g	Yam, boiled	60 g
Chestnut (sweet), tinned	40 g	Potato, main crop, boiled, jacket, flesh only (average value)	80 g
Choi Sum, cooked	35 g	Roast potatoes	55 g
Figs	60 g	Chipped potatoes	45 g

compared with normal diets although data around this topic is too limited to draw conclusions [56].

It has long been established that utilisation of dietary protein is influenced by energy intake [57–59]. Protein synthesis and catabolism are energy dependent and thus are sensitive to dietary energy deprivation. Insulin is secreted in response to CHO (and protein) promoting cellular uptake and the use of amino acids. Energy and/or glucose depletion will result in phenylalanine breakdown (gluconeogenesis) to meet minimal glucose requirements, which can ultimately lead to a loss of blood phenylalanine control. It is not uncommon to observe this in young children with classical PKU who may have poor appetites. Regular monitoring of energy intake is important.

Protein substitutes

Phenylalanine (Phe)-free or low Phe protein substitute is the primary source of protein or protein equivalent in a low phenylalanine diet, typically providing between 50% and 80% of the total protein intake, depending on the severity of PKU. It is derived from synthetic protein. Traditionally based on Phe-free L-amino acids, more recently casein glycomacropeptide (CGMP) is also being used in products for children aged 4 years and above.

The provision of protein substitute is essential. Its functions include:

- prevention of protein deficiency
- supporting growth
- provision of tyrosine
- optimisation of metabolic control by promoting anabolism and/or ability of individual large neutral amino acids (LNAA) to alter phenylalanine transport at gut epithelial level [60]
- 35%–50% of the total L-amino acids content is from LNAA; these provide competition with phenylalanine and block its transport across the blood–brain barrier [61], both decreasing brain phenylalanine and increasing brain tyrosine and tryptophan
- prevention of micronutrient deficiencies; most protein substitutes are supplemented with additional vitamins and minerals in amounts that meet requirements providing they are prescribed in adequate dosages

Casein glycomacropeptide

CGMP is a low Phe protein source used as an alternative to L-amino acids in the treatment of PKU. Found in cheese whey, it is associated with better taste and improved nitrogen retention [62]. In PKU mice studies, it has been shown to improve

Table 28.9 Foods that can be allowed without measurement (exchange-free) in PKU [51].

Food group	Examples of suitable exchange-free foods
Fruits and vegetables	• Fruits and vegetables given in Table 28.10 [21, 52, 54]
Fats	• Butter, margarine, ghee, vegetable oils
Starches	• Cassava flour, arrowroot, cornflour, custard powder, sago, tapioca and tapioca starch providing they contain protein ≤0.5 g/100 g
Vegan products	• Some vegan protein free cheeses (e.g. Violife), chicken substitutes (e.g. Violife), shrimp and salmon substitutes (e.g. Sophie's Kitchen) containing protein ≤0.5 g/100 g. They are based on vegetable oil and plant starches. Any vegan food products containing >0.5 g/100 g of protein should be calculated as part of the protein exchange system, e.g. modified soya-based cheeses
Sugars	• Sugar, glucose, jam, honey, marmalade, golden syrup, maple syrup, icing sugar, buttercream, sweets containing protein ≤0.5 g/100 g
Drinks	• All drinks must be free of aspartame.* Water, squash, lemonade, cola drinks, fruit juice; black tea, fruit tea, mint tea, green tea, coffee; tonic water, soda water, mineral water • Plant milks, e.g. rice† or coconut milk, should be counted as part of protein exchange system (unless protein content provides ≤0.1 g/100 mL) • Milk shake liquids and powders, e.g. Crusha, Nesquick, containing protein ≤0.5 g/100 g and aspartame-free
Pickles	• All clear pickles in vinegar, e.g. pickled onions, gherkins, red cabbage
Miscellaneous	• Vegetarian jelly, agar-agar, salt, pepper, herbs, spices, seasonings, vinegar, tomato and brown sauce, baking powder, bicarbonate of soda, cream of tartar, food essences and colouring. The protein content of some foods (e.g. herbs and spices) is relatively high, but because they are only used in small amounts, they are considered exchange-free • Gravy mixes containing protein ≤0.5 g/100 mL when diluted. Tabletop sauces and cook-in sauces containing protein ≤1.0 g/100 g • Soya sauces containing protein ≤1.5 g/100 g
Low protein special foods available on (ACBS) prescription	• A selection of low protein (LP) breads, flour mixes, pizza bases, pasta, biscuits, egg replacers and milk replacements are available on prescription (ACBS) in the UK • Most LP foods are exchange-free provided their listed ingredients are also exchange-free. If they do contain exchange ingredients such as milk, but total phenylalanine content is ≤25 mg/100 g, they are exchange-free • Some LP foods contain protein/phenylalanine ingredients. If their phenylalanine content is >25 mg/100 g, e.g. potato-based low protein snack pots, burger mixes, milk replacements, these should be calculated as part of the exchange system • A list of all low protein prescribable foods is available from the NSPKU website www.nspku.org • Age-based guidelines on the number of units of ACBS-approved low protein foods that can be prescribed each month are given on the NSPKU website. This is calculated to provide around 50% of daily energy intake
Energy supplements	If appetite is poor and energy intake is low, energy supplements such as glucose polymer, fat emulsions or combined energy/fat supplements may be needed to maintain phenylalanine control

ACBS, Advisory Committee on Borderline Substances.
*Aspartame (E951) is an artificial sweetener derived from a dipeptide composed of phenylalanine and the methyl ester of aspartic acid. It is added to squashes, fizzy drinks, chewing gums, sweets, desserts, tabletop sweeteners and some savoury snacks, e.g. flavoured crisps. It should be avoided in PKU. Other artificial sweeteners such as sucralose, saccharin or Acesulfame K are suitable.
†It is advisable not to give rice milk to less than 4½ years old children less than due to its high arsenic content.

bone health and acts as a probiotic [63]. Unmodified CGMP is low in some EAA or semi-EAA such arginine, cysteine, histidine, tryptophan, leucine, lysine and tyrosine. When CGMP is used as a protein substitute in PKU, it is supplemented with deficient amino acids (except phenylalanine). CGMP protein substitutes, usually with added vitamins and mineral, are available in powdered, liquid and bar presentations (Table 28.A.1). Almost all CGMP protein is sourced from one supplier, and UK CGMP substitutes adapted for PKU mainly provide 1.8 mg phenylalanine for each 1 g protein equivalent [63]. Taking 60 g/day of protein from CGMP substitutes (the average adolescent/adult dose) provides an extra 108 mg/day phenylalanine. It is established that if CGMP supplies the entire daily dose of protein substitute, it increases blood phenylalanine levels in well-treated children with PKU. Therefore, it is essential CGMP substitutes are systematically introduced when replacing Phe-free L-amino acids in children under 12 years of age [64, 65]. Only one dose of CGMP should replace one dose of Phe-free L-amino acids at any one time, and stability of blood phenylalanine control must be established (at least 3–4 serial blood phenylalanine concentrations within target range) before replacing a second dose. CGMP substitutes should not be used in children <4 years of age as there are no studies examining efficacy in this age group. Some brands of CGMP substitutes are higher in CHO and fat and provide a high energy intake. It is advisable not to mix powdered CGMP products with low protein milk, such as Prozero and SnoPro, as this will add extra energy.

Table 28.10 Fruits and vegetables that are exchange-free in PKU [53, 54].

Fruits		
Fresh, frozen or tinned in syrup (phenylalanine ≤75 mg/100 g)		
Apples	Jack fruit	Plums
Apricots	Kiwi fruit	Pomegranates
Bananas	Kumquats	Prickly pears
Bilberries	Lemons	Prunes
Blackberries	Limes	Quinces
Blackcurrants	Loganberries	Raisins
Blueberries		Raspberries
Clementines	Lychees	Redcurrants
Cherries	Mandarins	Rhubarb
Cranberries	Mangoes	Satsumas
Currants, black, red, white and dried	Melons	Sharon fruit
Custard apples	Medlars	Star fruit
Damsons	Mulberries	Strawberries
Dates	Nectarines	Sultanas
Dragon fruit	Olives	Tamarillos
Dried banana chips	Oranges	Tangerines
Dried fruit (not gogi berries)	Papaya	Watermelon
Gooseberries	Pawpaws	Mixed peel
Grapefruit	Peaches	Angelica
Grapes	Pears	Glace cherries
Greengages	Physalis	Ginger
Guava	Pineapples	
Vegetables		
Fresh, frozen or tinned vegetables (phenylalanine ≤75 mg/100 g)		
Artichoke	Dudhi	Parsley
Aubergine	Endive	Parsnip
Avocado	Eddoe	Peppers
Baby corn	Fennel	Plantain
Beans, French, green, runner	Garlic	Pumpkin
Beetroot	Gherkins	Radish
Cabbage, white	Gourd	Samphire
Carrot	Herbs, fresh and dried	Spring onion
Capers and caperberries	Karela	Squash, acorn, butternut, spaghetti
Cassava	Kohl rabi	Swede
Celeriac	Lady's finger (okra)	Sweet potato
Celery	Leek	Tomato
Chayote	Lettuce	Tomato purée
Chicory	Marrow	Turnip
Cress	Mooli	Watercress
Courgette	Onion	Water chestnut
Cucumber	Pak choi	

Source: Adapted from [53, 54].

Dosage of protein substitute

Precise requirements of protein substitute are unclear. The European PKU guidelines 2017 recommend that the total protein intake should supply 40% more than the FAO/WHO/UNU safe levels of protein intake for age [21], but this figure is arbitrary and unconfirmed by research. As most of the available protein substitutes are derived from Phe-free L-amino acid sources, MacDonald *et al*. recommend a higher dose is given to allow for inefficient absorption of natural/intact protein mainly derived from low biological value (LBV) plant protein, poor utilisation of L-amino acids or suboptimal energy intake [66]. This is supported by studies investigating metabolic control on differing dosages of free L-amino acids [66, 67]. Also, PKU data from European surveys suggest that most clinicians/dietitians recommend a higher amount of total protein in their clinical practice than the amount being recommended by the European PKU guidelines 2017 [68]. Higher intakes of protein substitute have been associated with better body composition (lower % fat mass) [31].

Recommended daily total protein intakes per kilogram body weight in the UK are given in Table 28.11.

Body weight, age, growth and the prescribed amount of natural protein/phenylalanine are considered when determining the dose of protein substitute. If an individual is obese, then the protein substitute requirement should be based on ideal body weight.

In one study, long-term intake of L-amino acids has been linked to proteinuria and decreased glomerular filtration rate (GFR) in PKU, although total protein intake was only 0.96 g/kg; 24% of patients were overweight, 13% were obese and 16% were not on dietary treatment from early infancy [13]. This area requires further controlled study [21].

Nutritional composition of protein substitutes

The composition of L-amino acid substitutes was originally based on the amino acid profile of breastmilk [69]. The amino acid composition of CGMP protein substitutes differs from conventional L-amino acid acids as they are naturally higher in some amino acids, such as threonine and isoleucine. Most protein substitutes for children aged >6 months contain added vitamins, minerals and long chain polyunsaturated fatty acids (LCPUFA), usually docosahexaenoic acid (DHA) ± eicosapentaenoic acid (EPA). Some also contain prebiotics. If an adequate dose is consumed, they should meet age-dependent nutritional requirements. If a smaller dose is prescribed than usually advocated (e.g. when sapropterin is prescribed and there is relaxed natural protein intake), vitamin and mineral intakes from diet and protein substitute need to be carefully assessed. Protein substitutes designed for children aged >3 years commonly have lower CHO added; the majority of energy requirements are provided by food. The decrease in CHO content is not usually associated with loss of metabolic control [70]. Some products contain minimal quantities of sodium and potassium, and adequate intake is expected to be provided by the diet. A small number of substitutes without added vitamins and minerals require separate supplementation.

The nutritional composition of protein substitutes is given in Table 28.A.1. Suitable infant amino acid formulas are discussed in the section on feeding and management of newly diagnosed infants (p. 525).

Table 28.11 Guidelines for total protein requirements for PKU (protein intake from protein substitute and natural protein/phenylalanine exchanges).

Age (years)	Total protein (g/kg body weight/day)
0–2	3.0
3–10	2.0
11–14	1.5
>14	1.0 (maximum 80 g/day)

Presentation of protein substitutes

From 6 months of age, there are spoonable semi-solid protein substitutes or powders prepared with added water available [71]. For children >12 months of age, protein substitutes are mainly presented as flavoured/unflavoured powders (cans, pre-measured sachets) or liquids. From the age of 3 years, ready to drink pouches, powders, bars or semi-solid protein substitutes are available, together with tablets for older patients. The various presentations of protein substitutes are given in Table 28.12.

Adherence with protein substitute

Adherence is an issue mainly associated with the bitter taste of the substitutes. Failure to take the prescribed amount is coupled with poor metabolic control. However, the improved range, taste, volume, presentation and availability (through home delivery) of protein substitutes for PKU has improved long-term adherence, particularly in teenagers taking liquid protein substitutes [72–74].

Timing of protein substitute intake

It is best to give protein substitutes in small frequent doses, 3–4 times spread evenly throughout the day rather than once or twice daily. Infrequent administration of large doses increases nitrogen excretion as well as amino acid oxidative utilisation, so this practice is not advocated [75]. Ideally, protein substitute should be taken with natural protein to improve the balance of amino acids, thereby increasing efficiency of dietary protein utilisation.

Administration of protein substitutes

- They are hyperosmolar, ranging from 600 to 2700 mOsm/kg H_2O (manufacturers' data), depending on their dilution with water. If they are given in a small volume of water or as a semi-solid, they may cause abdominal pain,

Table 28.12 Presentation of protein substitutes, based on L-amino acids.

Type of protein substitute	Advantages	Disadvantages
Powdered Phe-free infant formula	• Nutritionally similar to standard infant formula except Phe-free, tyrosine supplemented and higher in Phe-free protein content (approximately 2 g/100 mL formula) • Contain LCPUFA and may contain novel nutrients such as prebiotics • Usually similar preparation instructions to standard infant formula	• May not contain novel nutrients like prebiotics
Weaning/spoonable protein substitutes from 6 months of age. Designed to be given as a semi-solid consistency from a spoon	• Supplemented with vitamins and minerals ± DHA/EPA • Proven to be a successful way of administering L-amino acids but need to be introduced in this format early in a child's life (preferably from 6 months of age) [54, 55] • Useful to accustom a young child to the taste of L-amino acids in the weaning period • Low volume • Pre-measured in a sachet	• Concentrated so needs to be administered with extra water • Low energy so advice regarding adequate energy provided from solid foods is necessary • Poor taste but most infants adapt • Can be difficult to administer during teething and intercurrent illness • Some spoonable protein substitutes thicken on standing • Should be prepared immediately prior to administration • Less convenient than readymade protein substitutes; spoon and water always need to be available for administration
Protein substitutes suitable for children over 1 year of age. These powders are mainly presented as flavoured/unflavoured powders (in cans/ pre-measured sachets)	• Supplemented with vitamins and minerals ± DHA/EPA • Flexible as amount of water added can be varied to make a low volume concentrated drink or higher volume more dilute drink • Can be flavoured	• Should be administered with additional water as a drink • Poor taste • Can be difficult to administer during teething • Needs preparation immediately prior to administration; the smell may be stronger if left reconstituted for some time • Less convenient; always needs water available for preparation
Ready to drink bottles for children over 1 year	• Supplemented with vitamins and minerals ± DHA/EPA • Ready to use/convenient	• High volume • Poor taste • Can be difficult to administer during teething • More difficult to transport due to weight of liquids
Protein substitute powders suitable from 3 to 4 years or older	• Supplemented with vitamins and minerals ± DHA/EPA • Usually available in pre-measured sachets (convenient and easy to transport) • Concentrated in amino acids so low volume • Flexible as the amount of water added can be adjusted to prepare a low volume concentrated drink or higher volume more dilute drink • Can be flavoured or available in different flavours	• Poor taste • Less convenient; needs water available for preparation
Ready to use liquid pouches suitable from 3 years of age	• Supplemented with vitamins and minerals ± DHA/EPA • Pre-measured doses of protein substitute in low volume • Convenient • Different flavours available • Usually low CHO/low fat/low energy • Packaging presentation acceptable	• Poor taste • Smaller volume pouches need extra water given due to osmolality • More difficult to transport due to weight of liquids
Ready to use semi-solid protein substitutes	• Supplemented with vitamins and minerals ± DHA/EPA • Pre-measured doses of protein substitute in low volume • Convenient • Usually low CHO/low fat/low energy • Packaging presentation acceptable	• Poor taste • Small volume needs extra water given due to osmolality • More difficult to transport due to weight of product • Always need a spoon to administer
Tablets	• Only some are supplemented with vitamins and minerals • Taste of L-amino acids is masked in tablet format so useful for patients who do not like the taste of liquid or powdered products • Low energy	• Large number of tablets required • Needs to be administered with water • Not suitable for younger children
Ready to use semi-solid protein substitute bars	• Usually supplemented with vitamins and minerals • Novel presentation	• Taste fatigue • Large number of bars needed to meet requirements • Not palatable

Phe, phenylalanine; LCPUFA, long chain polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; CHO, carbohydrate.

Table 28.13 Strategies for encouraging protein substitute in children.

Caregivers should be patient, calm and encouraging while remaining persistent
Establish a routine for protein substitute: always give at the same time each day
Continue to offer protein substitute even when a child refuses or is unwell. Giving a child a 'day off' from protein substitute will adversely affect their metabolic control and give the wrong message. Stopping a protein substitute, even for 24 hours, may create difficulties with its reintroduction, particularly in young children
With young children, if taken with meals, it may be better to offer protein substitute before food while they are hungry
If more than one person administers the protein substitute, ensure that all caregivers involved apply the same strategies in the same way
It is good practice to ensure that no protein substitute is left behind in containers or pouches
An adult should always supervise the intake of protein substitute at home, nursery or school

diarrhoea or constipation. An additional drink of water should always be given with protein substitutes if they are diluted with less water than recommended.
- Artificial flavours should not be added to unflavoured protein substitutes before the age of 1 year.
- It is not usually advocated that protein substitute powders are added to food as this will spoil the taste of the food and it cannot be guaranteed that all the food will be eaten.

Useful strategies for parents/caregivers to encourage protein substitute are given in Table 28.13.

Tyrosine supplementation

In PKU, tyrosine is an indispensable amino acid because it is not supplied endogenously via phenylalanine hydroxylation, or only to a limited degree. L-tyrosine is important for the biosynthesis of the brain neurotransmitters (epinephrine, norepinephrine and dopamine), and melanin skin pigments. Tyrosine is added to all ACBS prescribable protein substitutes (9%–11% of the amino acids), and providing an adequate dose of protein substitute is prescribed, tyrosine requirements should be met. Additional supplementation should be unnecessary.

Blood tyrosine concentrations are difficult to interpret with accuracy as there are wide diurnal variations in blood tyrosine over 24 hours. Fasting tyrosine concentrations may be low, but then peak immediately following protein substitute intake [76].

Essential fatty acids and LCPUFA

A strict low protein diet is low in fat, α-linolenic acid, arachidonic acid and devoid of any sources of EPA and DHA [77]. Children with PKU are likely to have lower concentrations of DHA in plasma and membrane phospholipids compared with controls without additional supplementation. DHA ± EPA supplements should be given if not already added to the protein substitute (Table 28.A.1). The optimal dosage of DHA ± EPA in children is not established, but between 140 and 500 mg daily are provided by protein substitutes for children aged between 2 and 16 years.

Micronutrients

Vitamins and minerals are added to most protein substitutes, so providing an adequate dose is prescribed, no additional supplementation is necessary. If either a low dose of protein substitute is taken, or protein substitute does not supply vitamins and minerals, additional vitamin and mineral supplementation is essential. Vitamin and mineral deficiencies are now uncommon in PKU. Suitable supplements that can be prescribed are given in Table 28.14. To improve micronutrient availability, it is best to administer all vitamin and mineral supplements in two to three equal doses throughout the day.

Interpreting blood phenylalanine results

Guidelines on interpreting blood phenylalanine results are given in Tables 28.15 and 28.16.

Feeding and management of newly diagnosed infants with PKU

Blood phenylalanine concentrations consistently >360 μmol/L are treated [21].

Initial treatment depends upon the diagnostic phenylalanine concentration:

- *Phenylalanine concentration >1000 μmol/L*: The phenylalanine source (breastmilk or infant formula) is temporarily stopped and replaced by a Phe-free infant formula given at a minimum volume of 150 mL/kg/day. This is to achieve a rapid fall in plasma phenylalanine concentrations; a decrease of between 300 and 600 μmol/L/day is expected. For example, a diagnostic phenylalanine level >2000 μmol/L may take 2–3 days to fall to 1000 μmol/L.
- Breastmilk or 50 mg/kg/day phenylalanine from standard infant formula is introduced when phenylalanine concentrations are approaching 1000 μmol/L or below. This should be given with a Phe-free infant formula. While breastfeeding (BF) is stopped for a minimal time, mothers should be encouraged to regularly express their breastmilk. Mothers require a breastmilk pump and support from a midwife. Table 28.3 gives guidance on phenylalanine requirements. Table 28.8 shows the phenylalanine content of infant formulas.
- *Phenylalanine concentration 600–1000 μmol/L*: It is not necessary to stop the phenylalanine source. Either breastfeeds or 50 mg/kg/day phenylalanine from standard infant formula is given with a Phe-free infant formula. Blood phenylalanine should reach target treatment range in 2–3 days.

Table 28.14 Prescribable micronutrient supplements (UK).

Product	Company	Daily dosage	Age	Comments
FruitiVits	Vitaflo UK	6 g sachet	From 3 years	Orange-flavoured powdered vitamin, trace element and mineral mix. Contains minimal amount of carbohydrate, sodium and potassium. Mix with water
Paediatric Seravit	Nutricia	Suggested daily dose: • Age 0–6 months 14 g • Age 7–12 months 17 g • Age 1–7 years 25 g • Age 7–14 years 35 g	0–14 years	Powdered vitamin, trace element and mineral mix containing only trace amounts of sodium and potassium on a carbohydrate base; designed for infants and children; unflavoured and pineapple flavour. Mix with water or suitable fruit juice
Phlexy-Vits	Nutricia	7 g sachet or 5 tablets	>11 years	Unflavoured comprehensive vitamin and mineral supplement; does not contain sodium and potassium; available in powder and tablets. Powder can be mixed with water or fruit juice; better to consume immediately after mixing
Forceval Junior soluble tablet	Alliance Pharmaceuticals Ltd.	Recommended dose by manufacturer only one daily	>6 years	Effervescent tablet. Contains all vitamins and minerals but contains no calcium, phosphorus, sodium, inositol, choline and only a small amount of potassium and magnesium. If no other source of vitamins and minerals, 1 tablet dose is low in vitamins A, D, folic acid, iron, zinc, selenium and iodine. Dissolve in 125–200 mL water
Forceval soluble tablet	Alliance Pharmaceuticals Ltd.	Recommended dose by manufacturer only one daily	>12 years	Effervescent tablet. Contains all vitamins and minerals except vitamin K, inositol and choline but contains no sodium and only a small amount of potassium, calcium, phosphorus and magnesium. Dissolve tablet in 125–200 mL water.

Table 28.15 Interpretation of blood phenylalanine results: high concentrations.

Cause of high phenylalanine concentrations	Action
Fever/infection/trauma (illness management guidance for PKU p. 530)	1. Increase energy intake 2. Ensure intake of protein substitute 3. Identify and treat source of infection as clinically indicated 4. Antipyretics as clinically indicated
Excess natural protein intake	1. Check understanding/calculation of phenylalanine exchanges, dietary adherence and hidden sources of natural protein 2. Check that any low protein products are low protein, not gluten-free products
Inadequate intake of protein substitute	1. Check adherence (at home, nursery, school) 2. Timing of protein substitute administration: should be spread out evenly over 24 hours 3. Check adequate home supplies of protein substitute 4. Recalculate protein substitute and adjust the dosage appropriately
Incorrect protein substitute	Check type of protein substitute; occasionally the wrong type of protein substitute may accidentally be prescribed or delivered
No obvious reason	1. If phenylalanine blood levels are consistently high (≥3 consecutive levels), consider a reduction in natural protein by approximately 1 g/day protein or exchange equivalent; total daily natural protein should not be decreased below 3 g/day 2. It is good practice to recheck blood amino acids before reduction in natural protein

- *Phenylalanine concentration 360–600 µmol/L*: Minimal restriction of phenylalanine may be all that is necessary but depends on the individual baby. Initially breast or standard infant formula milk should provide approximately 75 mL/kg/day (estimated 50% 'normal' requirements); then phenylalanine intake is titrated according to blood levels.

Blood phenylalanine levels should initially be monitored twice weekly until stable.

Breastfeeding

BF (with a Phe-free infant formula) is associated with satisfactory blood phenylalanine control and growth.

- Breastmilk has several advantages for the infant with PKU:
  - It is low in phenylalanine
  - It contains LCPUFA

Table 28.16 Interpretation of blood phenylalanine results: low concentrations.

Cause of low blood phenylalanine levels	Action
Inadequate intake of natural protein	1. Ensure all prescribed intake of natural protein/exchanges are eaten 2. Check understanding of exchange system
Anabolic phase following an intercurrent infection	1. Ensure all prescribed intake of natural protein/exchanges are eaten and energy intake is adequate 2. Repeat blood phenylalanine level. If level is still low, consider an increase in natural protein by 1 g/day; careful blood phenylalanine monitoring is required as the increase in extra phenylalanine tolerance may be temporary
Rapid growth spurt such as puberty	1. Ensure all prescribed intake of natural protein/exchanges are eaten and energy intake is adequate 2. Repeat blood phenylalanine level; if level is still low, consider an increase in natural protein by 1 g/day; careful blood phenylalanine monitoring is required during any increase in natural protein intake

  - It is convenient and reduces the number of bottles that needs to be given and helps establish good mother–infant bonding
  - It gives the mother some control over the feeding process
- BF is based on the principle of giving a measured volume of a Phe-free infant formula before each breastfeed, so inhibiting the baby's appetite and, hence, suckling. This reduces the amount of breastmilk taken so lowering phenylalanine intake.
- Babies can still feed on demand, with a varying number of feeds from day to day, provided the Phe-free infant formula is always given first. The volume given at each feed changes according to blood phenylalanine concentrations and frequency of breastfeeds, from 30 to 50 mL per feed. Most breastfed infants will take 6–8 feeds of Phe-free infant formula daily.
- Once blood phenylalanine concentrations are stabilised within target treatment ranges, if phenylalanine levels then increase >360 µmol/L, the Phe-free infant formula is increased by 10 mL per feed; the amount of breastmilk decreases accordingly.
- If phenylalanine concentrations are <120 µmol/L, the Phe-free infant formula is decreased by 10 mL per feed, with breastmilk being increased by similar quantities.
- Local and international BF practices vary in PKU [78]. The baby should be weighed weekly for the first 6–8 weeks. BF can continue for as long as the mother and baby desire.

Bottle feeding

- Once phenylalanine concentrations are <1000 µmol/L, 50 mg/kg/day of phenylalanine from standard infant formula should be introduced (Table 28.8). The total daily amount of calculated infant formula is divided between 6 and 7 feeds.
- Traditionally, it is recommended standard infant formula is given first to ensure the entire phenylalanine source is given, followed by the Phe-free infant formula that can be fed to appetite, with guidance on an acceptable minimum volume to give.
- Alternatively, the calculated volume of standard infant formula and Phe-free infant formula can be mixed together, but it is then essential that the full volume is consumed. A disadvantage of mixing the source of phenylalanine (standard infant formula) with Phe-free infant formula is that the infant will not easily adapt to the taste of the Phe-free infant formula. Therefore, when phenylalanine from food exchanges is introduced and the quantity of standard infant formula is reduced, the Phe-free infant formula may be less acceptable and consequently refused.
- Ensuring a minimum volume of Phe-free infant formula is consumed is just as important as ensuring all the phenylalanine source is taken (some infants may require the Phe-free formula to be given first to ensure the minimum volume is consumed). The total volume provided by the two formulas should equate to a feed volume of 150–200 mL/kg/day. The Phe-free infant formula and source of phenylalanine (standard infant formula) should be given at the same feed to deliver the correct balance of all EAA.

The quantity of standard infant formula is adjusted by 25–50 mg phenylalanine/day according to blood phenylalanine concentrations. If blood phenylalanine concentrations are <120 µmol/L, the standard infant formula is increased. If the blood phenylalanine is >360 µmol/L, the daily dietary phenylalanine is decreased by 25–50 mg providing the infant is well, gaining weight and drinking adequate quantities of Phe-free infant formula.

An example feeding plan is given in Tables 28.17 and 28.18. A case study is given in Table 28.22.

Introduction of solids

- Solids should be introduced around 17–26 weeks of age starting with 1–2 teaspoons of natural low protein exchange-free foods such as homemade purée fruits and vegetables, e.g. apple, pear, carrot, butternut squash and parsnip. A wide variety of homemade weaning foods or commercial baby foods containing exchange-free ingredients only should be encouraged.

Table 28.17 Example of a daily feeding plan for a 4 kg infant with PKU having infant formula.

***Aim*: To provide 50 mg phenylalanine/kg/day and 3 g total protein equivalent/kg/day** (using natural protein and Phe-free infant formula)

- Total fluid intake = 200 mL/kg/day = 800 mL daily
- 90 mL Cow & Gate First Infant Milk (reconstituted from powder) = 50 mg phenylalanine
- Total number of feeds = 6

Phenylalanine requirement 50 mg/kg/day = 4 × 50 mg = 200 mg phenylalanine/day

- Daily formula intake from Cow & Gate First Infant Milk = 4 × 90 mL = 360 mL daily
- Total fluid requirement = 800 mL
- Fluid from Cow & Gate First Infant Milk = 360 mL
- Deficit = 440 mL (800–360 mL)

Feed deficit made up with Phe-free infant formula, e.g. PKU Anamix Infant, PKU Start = 440 mL/day

Feeding plan

First feed: 60 mL × 6 feeds of Cow & Gate First Infant Milk
Second feed: 75 mL × 6 feeds of PKU Anamix Infant/PKU Start (more can be given if the infant is hungry)
However, in this calculation, a 'generous' intake is already provided, and a variable daily volume of Phe-free infant formula may lead to an uneven blood phenylalanine profile

Table 28.18 Nutritional analysis of a daily feeding plan for a 4 kg infant with PKU having infant formula.
Aim: To provide 50 mg phenylalanine/kg/day and total protein equivalent 3 g/kg/day (using natural protein and Phe-free infant formula)

	Energy						
	kcal	kJ	Protein equivalent (g)	Phenylalanine intake (mg/day)	Carbohydrate (g)	Fat (g)	Fluid (mL)
360 mL Cow & Gate First Infant Milk (41 g dry weight)	238	990	4.7	191	26.6	12.2	360
450 mL PKU Anamix Infant (68 g dry weight)	311	1292	9	0	33.3	15.8	450
Total	549	2282	13.7	191	59.9	28	810
Intake per kg	137	571	3.4	48			202
% energy intake			10%	2%	41%	46%	

- Low protein weaning foods are usually offered after the breast or formula feeds, so it does not alter the volume of breastmilk/formula consumed. The intake of Phe-free infant formula should be carefully monitored to ensure the amount is adequate. At this stage, the low protein food is mainly offered for the infant to establish a taste for solids foods, and they usually accept these without difficulty [79].
- Many low protein weaning foods have a low energy density, so higher energy weaning foods should be encouraged: low protein rusks mixed with cooled boiled water to a smooth paste; low protein pasta meal as a 'porridge' replacement or low protein breakfast cereal; custard made with protein-free liquid milk replacements, e.g. Prozero, SnoPro. Weaning foods are gradually increased to three times daily.
- Once infants are taking 8–12 teaspoons at a time, natural protein exchange foods are given instead of the equivalent quantity of infant formula or a breastfeed. (One breastfeed in combination with Phe-free infant formula is likely to provide approximately 1.0–1.5 g natural protein, but this amount is determined by the number of breastfeeds consumed in 24 hours and the amount of Phe-free infant formula.) 1 g natural protein exchange should be introduced, gradually replacing all breast or formula feeds with the equivalent natural protein source from solid food. Foods such as purée potato, peas, yoghurt, ordinary rusks, baby rice or vegetable based weaning foods in jars or tins are useful protein exchange foods. Cheese-flavoured sauce mixes (given as exchange food) can be introduced from the age of 6 months.
- More textured food should be gradually introduced from 6 to 8 months with breakfast cereals, e.g. wheat biscuits or oat based cereal, and mashed potato for protein exchanges.
- Finger foods can be given from 7 months of age: fingers of low protein toast; soft fruits such as bananas, strawberries and peaches; soft vegetable sticks; fingers of low protein cheese; low protein bread sticks; low protein rusks and biscuits. The Phe-free infant formula or a protein-free milk replacement can be introduced from a feeder beaker at 7 months of age.
- From 9 months, low protein pasta dishes; sandwiches made with low protein bread; chopped low protein burgers or sausages; finger exchange foods such as mini-waffles, potato shapes and rice cakes.

Introduction of second stage protein substitute

As solids are introduced, an infant may be unable to drink adequate amounts of Phe-free infant formula and so, from the age of 5–6 months, will struggle to meet total protein requirements of 3 g/kg/day. At this stage, it becomes necessary to introduce a more concentrated, spoonable second stage/weaning Phe-free L-amino acid substitute (e.g. PKU Anamix First Spoon, PKU Gel, PKU Squeezie, PKU Explore). Most are powdered and reconstituted with water (1 g powder to 1 or 1.5 mL water depending on the product) and given as a paste before meals (PKU Squeezie is ready to use).

Spoonable protein substitutes are gradually introduced to meet protein equivalent requirements unmet by natural protein and Phe-free infant formula. Generally, spoonable Phe-free L-amino acid substitutes provide 2 g protein for each 5 g of product. A plan for introducing these products is given in Table 28.19. The entire Phe-free infant formula should not normally be replaced with the second stage Phe-free L-amino acid substitute until infants are at least 1 year old as they still require some Phe-free infant formula to ensure adequate energy intake. If the Phe-free infant formula is continued after 1 year, it is usually as a social drink, perhaps given in the morning or evening.

Parents need support when transitioning protein substitutes. It is essential that parents maintain a good daytime routine and consistency of approach and are persistent when administering spoonable protein substitute. Infants usually only exhibit difficulty in accepting it if they are unwell or when teething; but at the same time, they are usually refusing solid food [79]. Spoonable protein substitute is usually given unflavoured <1 year of age.

Feeding preschool and school children and young people

Issues to consider when feeding preschool and school children and teenagers and during transition to adult services are given in Table 28.20.

Parent/caregiver approach and support

- If more than one person is involved in feeding a child with PKU, there should be a family approach with all parents/caregivers applying the same strategies in the same way.
- Extended family members should help with food preparation, e.g. making low protein bread, cakes and biscuits. It is best all family members receive education about PKU.
- Parents should be encouraged to batch cook and freeze low protein meals, so there are always 'ready meals' that are suitable to eat.
- Parents should be assisted to support each other: swapping recipe ideas, cooking tips and management tips on difficult practical issues and organising local events such as toddler groups, cookery workshops, family picnics.

Good patient and parent education is essential. The NSPKU provides basic guidance on PKU management, picture lists of exchange-free/exchange fruits and vegetables, Christmas and Easter ideas, information packs for new parents, lists of ACBS prescribable low protein foods and booklets and leaflets about PKU. They also produce a helpful teaching skills guide 'Let's learn about PKU', designed to aid dietitians and nurse specialists. They also run annual and regional conferences that include low protein cookery demonstrations.

Table 28.19 Plan for introducing spoonable Phe-free L-amino acid substitutes in infants from the age of 5–6 months.
A boy aged 5–12 months with PKU on 4 g natural protein (200 mg phenylalanine) daily and 3 g/kg/day total protein equivalent

Age	5 months	6 months	8 months	12 months
Weight	7 kg	8 kg	9 kg	10 kg
	Protein equivalent (g/day)			
4 g/day natural protein from 4 × 50 mg phenylalanine exchanges	4	4	4	4
PKU Anamix Infant/PKU Start daily	12 (from 600 mL amino acid infant formula)	12 (from 600 mL amino acid infant formula)	12 (from 600 mL amino acid infant formula)	8 (from 400 mL amino acid infant formula)
PKU Anamix First Spoon/PKU gel/PKU Explore 5	5 (from approximately 12 g of product)	8 (from approximately 20 g of product)	11 (from approximately 28 g of product)	18 (from approximately 45 g of product)
Total protein equivalent	21	24	27	30
Protein equivalent intake kg/body weight/day	3	3	3	3

If the infant takes less Phe-free infant formula, then the amount of spoonable protein substitute should increase.

Table 28.20 Issues to consider when feeding different age groups of children with PKU.

Preschool children
- Avoid giving bottles with protein substitute after 1 year of age due to risk of dental caries/limiting appetite for solid foods. Intake of sweetened low protein drinks should also be controlled
- Encourage consistent and regular mealtime routines
- Encourage a variety of low protein foods, but it is not uncommon to find young children with PKU have food neophobia and are suspicious of new foods [80]
- Encourage families to eat together and share at least one low protein food item, e.g. low protein vegetable soup, exchange-free vegetables, fruit or sorbet for dessert. They should try to replicate the same food choices that the rest of the family are eating, e.g. low protein pizza instead of regular pizza
- Encourage children to eat with others, particularly at nursery
- Provide nursery with a care plan, and use different coloured food mats, plate and cups for food and drink to help staff identify the child with PKU. Adjust nursery menus so they are suitable for PKU. Ensure meals, snacks and protein substitute are carefully supervised and a record of food intake/protein substitute is kept for parents
- Young children should be encouraged to help in the kitchen from an early age, e.g. choosing toppings for low protein pizza, making low protein cakes. This helps to create an interest in food and their diet

Teenagers
- This is a challenging time. Young people want to be like their peers, and socialising is encumbered by a low phenylalanine diet. It is well established that blood phenylalanine control deteriorates with many unable to keep blood phenylalanine levels within target range
- From the age of 12 years, the process of transition to an adult clinic begins. Children will attend a transition clinic, they will be expected to learn several core skills about managing their condition and they will see the PKU team independently from their parents and from around the age of 14 years will be introduced to the adult PKU team. Education about teenage health issues is important

Core skills
- Knowledge about PKU
- Understanding of phenylalanine exchange/exchange free foods
- Understanding consequences of high phenylalanine levels
- Basic low protein cooking skills
- Learning how to take their own blood spots for phenylalanine
- Learning how to order their protein substitute and low protein food supplies
- Apps/phone alarms to remind them to take their protein substitute, count exchanges and to do blood tests may be helpful

School children
- School SENCO teachers need basic information about day to day practical implications of the PKU special diet. A care plan should be developed for each child including suitable drinks, snacks, school/packed lunches, mealtime supervision, school trips, breakfast clubs and after-school care. Guidance should be given on protein substitute administration
- If children take a packed lunch to school, guidance on suitable lunches is necessary, including choices of low protein bread, bread rolls, low protein wraps or crackers. Slices of low protein vegan cheese/meat alternatives, small packets of dried fruit and fresh fruit are useful. Hummus, cereal bars, crisps, popcorn are practical exchange foods
- School children should have some knowledge about PKU. They need ongoing education about the foods they can eat, 'exchange' foods, why they take their protein substitute and the need for blood tests. The PKU team should do one-to-one teaching or run group teaching sessions. Parents should encourage children to be involved in their own treatment to help aid future independence
- Encourage attendance at weekend holiday camps and other events specifically for PKU so that children socialise with their peers and share and discuss experiences of how they manage PKU

Teenage pregnancy
- In maternal PKU, high blood phenylalanine levels during pregnancy have a teratogenic effect on the developing foetus that can result in foetal intrauterine growth retardation, infant low birth weight, facial dysmorphism, microcephaly, developmental delay, intellectual disabilities and congenital heart disease
- The European PKU guidelines 2017 [21] state that from the age of 12 years, all females should receive systematic age-related sex education, with professional counselling about the risk of unprotected sexual contacts. They should be informed that unplanned pregnancy can occur even during the first menstrual cycle
- Teenage girls should feel comfortable discussing pregnancy and contraception issues with their PKU medical teams. It is essential that all discussions are conducted with an assurance of confidentiality. They may need signposting to local family planning clinics. GPs should be informed about the risks of maternal PKU
- Encouraging teenage girls to attend female health and pregnancy study courses run by adult PKU clinics is important. It is an opportunity for them to talk to women with PKU who have experienced pregnancy

SENCO, special educational needs coordinator; GP, general practitioner.

Management of illness

A formal emergency regimen (ER) is not normally necessary during illness as acute metabolic decompensation does not occur in PKU. However, to prevent an excessive rise in blood substrate amino acid concentrations, it is prudent to encourage L-amino acid substitutes and high CHO drinks during illness [21].

Factors to consider in the management of illness are given in Table 28.21.

Blood phenylalanine concentrations are likely to rise quickly during illness. For the immediate treatment of infections (until a suitable aspartame-free medication is sourced), it may be better to use aspartame-containing medications rather than leave a child without treatment. The amounts of phenylalanine in a medicine may be listed in its *Summary of Product Characteristics*, available via the Internet.

Learning points: phenylketonuria

- *In early treated PKU, outcome is dependent on the quality of blood phenylalanine control*
- *Lifelong treatment and follow-up is recommended*
- *Comprehensive European PKU guidelines for the medical and dietary management of PKU are available [21]*
- *The UK NSPKU produces practical resources to help patients with dietary management*

Table 28.21 Factors to consider in the management of illness in PKU.

Factors	Guidance
Protein substitute	Maintenance of protein substitute intake to support protein synthesis. It may be better for this to be given in smaller, frequent doses throughout the day. Try to control fever (temperature ≥38 °C) prior to administration to avoid vomiting
High carbohydrate intake	Encourage high carbohydrate fruit juices/glucose polymer solution
Natural protein intake	There is no need to formally omit natural protein. Catabolism will probably increase blood substrate amino acid concentrations more than natural protein. However, in practice, a reduced appetite leads to a lower natural protein intake
Fluids	Give regular drinks, particularly if there is high temperature, vomiting or diarrhoea. Oral rehydration solutions (aspartame-free) are suitable
Medications	All treatment specific medication should be continued during illness. Medications should be free of aspartame. Continue sapropterin if prescribed
Treat precipitating factors	For example, antipyretics for fever; antibiotics (aspartame-free) for infections

Table 28.22 Case study: a newborn screened infant with PKU being breastfed.

A healthy breastfed term infant
Day 5 of life: Newborn screening test taken
Day 9 of life: A presumptive positive screening result, blood phenylalanine level = 1200 µmol/L reported to the PKU team
The family were contacted by a specialist nurse from the PKU centre and general practitioner (GP) to explain the likely implications of this initial screening result.
The parents were given the 'PKU is suspected' leaflet www.bimdg.org.
A repeat blood spot was taken to confirm the diagnosis of PKU by the specialist nurse and returned to the PKU centre immediately so the result would be available for the hospital consultation with the family.
The parents and baby attended the PKU centre and were seen by a metabolic paediatrician, dietitian and nurse.
The repeat blood phenylalanine concentration = 1710 µmol/L
A blood sample for pterins was also taken to exclude tetrahydrobiopterin deficiencies (this was negative).
The infant weight = 3.2 kg. She was well and breastfed on demand. There were no issues with feeding.

Dietary intervention:
Breastfeeding was stopped for 24 hours only.
The infant was started on a Phe-free infant formula given on demand.
The mother kept a daily record of all formula taken (the amounts and times) to estimate total feed intake.
The mother was advised to express breastmilk at least 6 times in 24 hours, and her local midwife was contacted to provide support.
Supplies of the specialist formula were organised (with parental consent) through a home delivery company who liaised with the GP.

The infant drank 60–90 mL of Phe-free infant formula every 2–3 hours.
Twenty-four hours later, blood phenylalanine had rapidly lowered = 1210 µmol/L.
Breastfeeding was recommenced; 50 mL of Phe-free infant formula was introduced prior to each breastfeed.

Within a further 48 hours, the blood phenylalanine reduced = 210 µmol/L, the specialist formula was reduced to 40 mL prior to each breastfeed.
The mother was worried the baby was taking too little breastmilk, but with encouragement and reassurance she was happy to continue breastfeeding in combination with the Phe-free formula.

The baby was weighed weekly for the first 6 weeks and gained weight satisfactorily.
Blood spot phenylalanine concentrations were measured twice weekly, and within 2 weeks the parents had both learnt how to take blood samples.
The dietitian reported results to the parents on the same day of availability.

During the first 10 weeks of life, there was little variability in the blood phenylalanine concentrations, almost all = 120–360 µmol/L.
Gradually, phenylalanine concentrations increased to >300 µmol/L.
The baby was only taking six breastfeeds in 24 hours and was feeding for a longer duration at each feed. The Phe-free infant formula was increased to 50 mL and then 60 mL before each breastfeed until almost all phenylalanine concentrations were maintained well within the target treatment range.

The infant was weaned onto solids at 22 weeks.
At 26 weeks the number of breastfeeds was further decreased with phenylalanine from food (50 mg phenylalanine exchanges) replacing breastfeeds at breakfast, midday and evening meal.

The mother continued to give two to three breast feeds daily until the baby was 10 months old.

Maple Syrup Urine Disease

Anita MacDonald

Enzyme

Branched chain 2-ketoacid dehydrogenase (BCKD) complex that is composed of three catalytic enzymes (Figure 28.3). It is the second enzyme in the catabolic pathway of the branched chain amino acids (BCAA): leucine, isoleucine, valine.

Biochemical defect

The first step of BCAA catabolism is their transamination to form the branched chain keto acids. The second shared step in the degradation of the branched chain keto acids is irreversible and catalysed by BCKD enzyme. Deficiency results in maple syrup urine disease (MSUD) with:

- ↑ accumulation of plasma leucine, isoleucine and valine
- ↑ 2-ketoacids in plasma, urine and cerebrospinal fluid
- L-alloisoleucine is always present (≥5 μmol/L) and is pathognomic for MSUD
- ketonuria is present without treatment, poor metabolic control or catabolic stress
- ↑ molar ratio of leucine to other amino acids such as alanine, glutamine and tyrosine [81]

On presentation, plasma leucine levels are commonly 1000–5000 μmol/L (normal reference range 65–220 μmol/L). Non-classic forms of MSUD have lower presenting concentrations of BCAA.

Genetics

Autosomal recessive inheritance

- >260 mutations reported.
- Estimated prevalence is 1 in 150 000 worldwide but is more common in Saudi Arabia, Qatar and Malaysia [82].

Newborn screening

- Screening is by measurement of combined concentrations of leucine, isoleucine and alloisoleucine in dried blood spots using tandem mass spectrometry (MS/MS). More information on UK screening and diagnostic and clinical management protocols can be found at www.bimdg.org and www.gov.uk *Newborn blood spot screening: laboratory guide for IMDs* (inherited metabolic diseases).
- UK infants are screened aged day 5; infants with classic MSUD may be symptomatic before newborn screening (NBS) results are available
- NBS will detect patients with classic MSUD, but may not detect intermediate or intermittent forms that have a spectrum of clinical and biochemical severity; milder variant forms of MSUD may have normal leucine levels in the newborn period

Clinical onset presentation, features

Clinical phenotype can be divided into five types based on clinical presentation and severity; classical, intermediate, intermittent, thiamin-responsive and E3-deficient forms. The distinction between classic and intermediate type is not absolute [83].

Classification

- *Classic MSUD*: 0%–2% enzyme activity, presents at the age of 2–3 days with ketonuria, intense sweet malty caramel smell, irritability, poor feeding, vomiting, leading to lethargy, seizures, brain oedema, encephalopathic crisis, coma, central respiratory failure and even death
- *Intermediate MSUD*: 3%–30% of normal enzyme activity, may appear healthy as a neonate, but present with anorexia, developmental delay, faltering growth and metabolic encephalopathy triggered by intercurrent illness or other catabolic stress
- *Intermittent MSUD*: 3%–30% enzyme activity, presentation at any age, normal growth and neurological development, but may present with encephalopathy triggered by catabolic state (e.g. intercurrent illness or increased protein intake), between episodes plasma BCAA are normal
- *Thiamin-responsive*: A cofactor for BCKD complex with 2%–40% enzyme activity; thiamin-responsive phenotype is similar to intermediate MSUD
- *Dihydrolipoamide dehydrogenase deficiency (E3-deficiency)*: 8%–20% enzyme activity, early-onset neurologic phenotype: hypotonia, developmental delay, microcephaly, vomiting, hepatomegaly, lethargy, seizures, spasticity, Leigh-type encephalopathy and lactic acidosis

In MSUD, acute elevations of leucine and alpha-ketoisocaproic acid (αKIC) due to trauma, surgery, illness, excess protein intake and dietary non-adherence increase the risk of metabolic decompensation, causing acute metabolic encephalopathy and life-threatening cerebral oedema.

Long-term complications and outcome

Without early and effective treatment, children develop severe and permanent brain damage, including spasticity, and may die within the first few months of life. With early diagnosis and diligent dietary management, the outcome is improving. Children with milder variants of MSUD tend to have better outcomes [84], but all patients are vulnerable to rapid deterioration associated with catabolic stress. Treated individuals have average low IQs, inattention, hyperactivity, generalised anxiety, depression and movement disorders. Some attend normal schools and have normal IQ scores. Intellectual outcome is related to the length of time after birth that plasma leucine concentrations are >1000 μmol/L and quality of long-term metabolic control. High leucine levels are associated with psychological comorbidity (particularly long periods of leucine toxicity and recurrent acute decompensations) [85]. Pancreatitis has been documented during acute intercurrent illness/leucine intoxication [83].

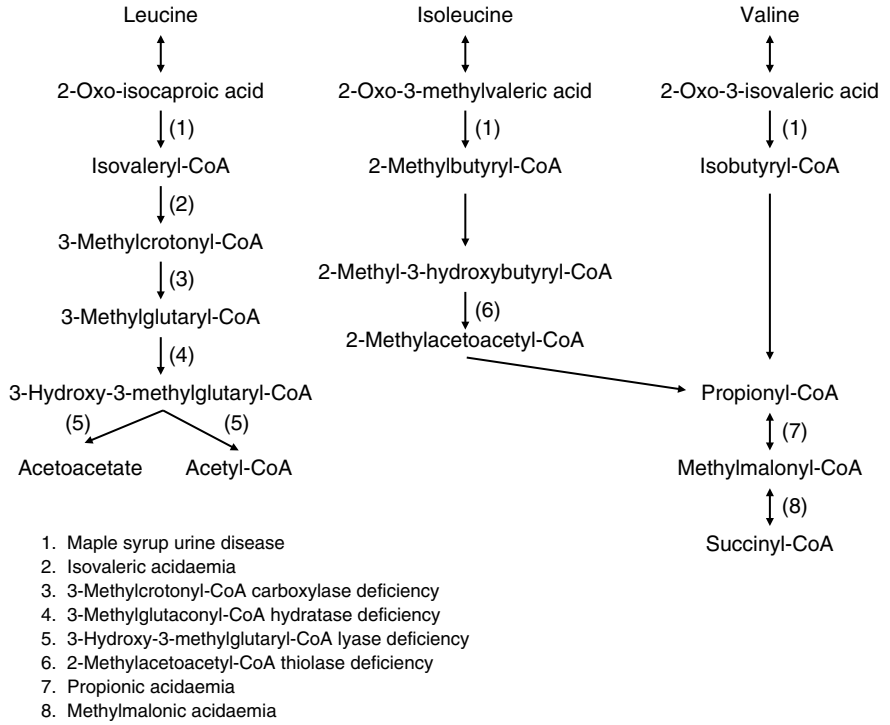


Figure 28.3 Selected inborn errors of the catabolic pathways of branched chain amino acids.

Growth and nutrition

There may be low height for age *z*-scores [86]. A higher BMI at the age of 5 and 10 years in children with MSUD compared with other IMDs treated with low protein diets was observed [87]. Energy intake in the early treatment years was >200% of predicted basal metabolic rate (BMR), contributing to long-term increased BMI and % fat mass [87]. Nutritional deficiencies may occur including valine and isoleucine deficiency [88], *n*-3 fatty acids [81], selenium as indicated by erythrocyte glutathione peroxidase measurements [89]. Chronic deficiency of BCAA may cause anaemia, acrodermatitis, hair loss, growth failure, arrested head growth, anorexia and lethargy. Low bone mineral density (BMD) is also reported in adolescents [83]. Bone fractures cause transient leucinosis [83]. Chronic imbalance of plasma BCAA or natural protein over-restriction can lead to abnormal brain amino acid uptake with subsequent decreased myelin and neurotransmitter synthesis, causing brain damage and possibly manifesting as chronic encephalopathy [90].

Medical treatment

- In classic MSUD, lifelong dietary treatment with a low BCAA diet is essential (except post-liver transplantation).
- Metabolic decompensation is a risk post-diagnosis and is triggered by trauma, surgery, illness and excess leucine intake. Meticulous treatment using an emergency regimen (ER) (p. 673) is necessary. It is essential to monitor biochemical and clinical status and prevent catabolism by providing adequate BCAA-free protein, energy and fluid. On diagnosis, rapid reduction of toxic metabolites is vital (p. 535).
- Care should be provided by a specialist multidisciplinary team consisting of medical doctor, dietitian, nurse and psychologist. Good family/patient education is essential.
- Assessment of developmental milestones and neurocognitive and neuropsychological outcome should be done at regular intervals such as preschool, primary, middle and senior school ages.
- Diet history and growth (weight, length/height, BMI) should be monitored at each clinic visit. Assessment of BMD should be conducted in adolescence. Calcium, vitamin D and natural protein intake should be optimised, with regular exercise for bone health.
- Effective transition processes between paediatric and adult services is essential.
- Consideration of liver transplantation. This is associated with an increase in BCKD activity; diet therapy should be unnecessary although acute metabolic decompensation has occurred in the early period after heterozygous living donor liver transplantation in a single case study [91]. Some advocate long-term monitoring of BCAAs, particularly at times of illness [92], and others recommend an ER during illness [93]. Even though there is no further neurocognitive deterioration following liver transplantation, any existing dysfunction cannot be reversed.
- In thiamin-responsive phenotype, pharmacological doses of thiamin may improve metabolic control and BCAA tolerance. In thiamin-responsive patients, leucine tolerance may increase, but patients are likely to require a BCAA restricted diet and ER during illness [94].
- Hepatocyte transplantation has been shown to correct selected neurometabolic abnormalities in MSUD mice [95].
- Sodium phenylbutyrate has been considered as an adjunct therapy increasing enzyme activity of BCKD and decreasing blood BCAA levels. However, patient data is limited [96, 97].

Dietetic management

- The aim is to maintain plasma BCAA concentrations within a target treatment range that is not associated with neurotoxicity (that can cause encephalopathy and cerebral oedema). Dietary restriction of leucine, valine and isoleucine is necessary while avoiding their deficiency.
- Dietary principles are similar to PKU. To ensure adequate protein synthesis, energy intake should meet estimated average requirements for age [98]. Low protein/exchange-free foods are similar as for PKU (Table 28.9). Generally, any foods containing protein ≤0.5 g/100 g weight are considered exchange-free. Suitable fruits and vegetables given without measurement are listed in Table 28.23.
- Low protein special foods (e.g. bread, pasta, cereals) are an important source of energy, but some contain higher amounts of leucine (Table 28.24); these should be calculated as part of the leucine exchange allowance.
- If appetite is poor, additional energy supplements such as glucose polymer or fat emulsions may be necessary to minimise catabolism. Tube feeding may be required in a few cases. Long periods of fasting should be avoided, particularly in young children as blood leucine increases with fasting.
- In classical MSUD, leucine tolerance is likely to vary from 400 to 700 mg/day in children [87] and is allocated in 50 mg leucine exchanges (this is equivalent to approximately 0.5 g protein) (Table 28.25).

The diet is supplemented with leucine, valine and isoleucine-free L-amino acids, with dosage and distribution similar to a low phenylalanine diet in PKU (p. 525). Age-specific MSUD amino acids are available, but the choice is more limited than for PKU (e.g. MSUD Anamix Infant, MSUD Anamix Junior, MSUD Gel, MSUD Lophlex LQ, MSUD Cooler 10, 15, 20, MSUD Maxamum). Total daily protein requirements are given in Table 28.26. They are usually supplemented with vitamins and minerals, and, if an adequate dose is prescribed, dietary reference values of micronutrients should be met. Details of presentation, composition, age suitability and preparation can be found on the manufacturers' websites: www.nutricia.co.uk, www.vitaflo.co.uk. Similar products are available outside the UK: www.abbottnutrition.com, www.meadjohnson.com, www.metax.org, www.milupa-metabolics.com. Separate flavour packs are also available.

Additional valine and isoleucine supplements are invariably necessary. Valine supplementation has a low affinity for the blood–brain barrier LAT1 transporter, and it is especially vulnerable to competitive inhibition by leucine [83]. Failure to provide adequate isoleucine and/or valine for protein synthesis during acute metabolic decompensation slows the rate at which blood leucine decreases. In infants and children, a suggested starting dose of 50–100 mg/day of valine and/or isoleucine should be given if isoleucine and/or valine are below target treatment range. The dose is then titrated according to plasma valine and isoleucine concentrations.

Separate valine (50 or 1000 mg) and isoleucine (50 or 1000 mg) supplements are available in pre-measured sachets (www.vitaflo.co.uk). A small amount of carbohydrate (CHO) (3.8 g/4 g sachet) is added to each 50 mg valine/isoleucine sachet. This CHO should be calculated in infant and ER feeds (dosage with ER feeds is given on p. 539 and in newly diagnosed infants on p. 535). Valine and isoleucine supplements should be given in three doses throughout the day and added to the BCAA-free amino acid substitute or low protein milk.

Non-classic MSUD dietetic management

- Intermediate MSUD: leucine restriction +/– branched chain free amino acids and an ER are necessary
- Intermittent MSUD: may only require moderate protein restriction (no branched chain free amino acids) and an ER
- Thiamin-responsive phenotype: leucine restriction +/– branched chain free amino acids and thiamin supplementation [94] and an ER; thiamin is required during illness, fasting, infection or surgery [101]
- E3-deficiency: a BCAA-restricted diet does not reverse or prevent ongoing symptoms, but can maintain blood BCAA concentrations within target ranges; ER is necessary

Monitoring biochemical

- In order to meet leucine requirements for protein synthesis and avoid protein deficiency, recommended target leucine concentrations are 100–300 µmol/L [83, 94]. In the UK, current recommended practice is to maintain leucine at 150–300 µmol/L, although this is challenging. Some recommend maintaining 2–3 hour postprandial leucine concentrations close to normal concentrations (80–200 µmol/L) [94], but this may result in leucine deficiency
- Recommended target valine and isoleucine concentrations are between 200 and 400 µmol/L
- Parents may be taught how to collect either dried blood spots or liquid blood samples. Different acceptable BCAA reference ranges may be used for dried blood spots versus plasma samples
- Ideally, following initial stabilisation in infancy, early morning fasting blood spots for BCAA should be taken weekly in the first 5 years, once every 2 weeks aged 6–12 years and monthly in teenagers
- BCAA results should be promptly reported to parents and interpretation discussed. The guidelines given in Table 28.15 can be used for adjusting leucine intake in accordance with blood BCAA levels. Principles are similar to PKU. Instead of increasing/decreasing protein intake by 1 g/day (as described for PKU), leucine intake should be increased/decreased by 50 mg/day (0.5 g/day protein) in response to low or high blood leucine levels. Factors such as illness, growth and dietary adherence should be taken into account as in PKU (Tables 28.15 and 28.16). If leucine intake is increased or decreased, it may similarly affect valine and isoleucine blood levels; therefore adjustment of valine and isoleucine supplements may be necessary
- Annual measurement of quantitative amino acids, plasma homocysteine and/or methylmalonic acid, haemoglobin, MCV and ferritin, plasma zinc, selenium and vitamin D

Clinical management guidelines

BIMDG Newborn Screening Guidelines www.bimdg.org.uk including MSUD clinical management guidelines, MSUD dietetic management guidelines, MSUD emergency regimen [102].
USA Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach [94].

Parent support groups

Metabolic Support UK www.metabolicsupportuk.org
Maple Urine Disease Family Support Group USA. www.msud-support.org

Table 28.23 Fruits and vegetables allowed without measurement in MSUD [46, 99].

Fruits		
Fresh, frozen or tinned in syrup (<1 g protein/100 g or <30 mg leucine/100 g)		
Apples	Guava	Oranges
Apricots	Kiwi fruit	Peaches
Blackberries	Lemons	Pears
Blackcurrants	Limes	Pineapples
Clementines	Loganberries	Plums
Cherries	Loquats	Pomegranates
Cranberries	Lychees	Raspberries
Damsons	Mandarins	Rhubarb
Fruit salad	Mangoes	Satsumas
Gooseberries	Melons	Starfruit
Grapefruit	Mangosteen	Strawberries
Grapes	Nectarines	Tangerines
Greengages	Olives	Watermelon
Vegetables		
Fresh, frozen or tinned (<1.5 g protein/100 g or <100 mg leucine/100 g)		
Artichoke[+]	Fennel[+]	Plantain[§]
Aubergine	Garlic[+]	Pumpkin
Beans, French, green[§]	Gherkins[#]	Radish
Beetroot	Gourd[#]	Samphire[§]
Cabbage[§]	Leek*	Spring onion
Carrot	Lettuce[§]	Squash, butternut[#]
Celery	Marrow[+]	Swede
Chicory	Mustard and cress	Sweet potato[§]
Chives[#]	Onions	Tomato
Courgette*	Parsley[+]	Tomato purée
Cucumber	Parsnip[§]	Turnip
Endive[+]	Peppers	Watercress[+]

*No leucine data are available for these fruits and vegetables.
[+]They are included on the free list because they contain <1 g protein/100 g or are consumed in small amounts infrequently.
[#] No leucine data are available for these vegetables, but they are consumed in small quantities.
[§]These vegetables contain 50–100 mg leucine/100 g, so it is better to use them in small quantities in the diet.
NB: The protein content of vegetables is 3%–6% leucine (i.e. 30–60 mg for 1 g protein); the protein content of fruits is 5% leucine (50 mg leucine for 1 g protein) [100].
Source: Adapted from [46, 99].

Management of infants with MSUD

The newly diagnosed infant is likely to be very sick, requiring admission to intensive care and ventilation. On presentation in infancy, rapid leucine reduction is required to achieve target treatment levels. The stimulation of a high rate of protein synthesis and to minimise catabolism is essential to aid removal of leucine from the plasma pool.

Treatment of the infant with MSUD includes the following:

- Immediate removal of toxic metabolites by continuous venovenous extra corporeal therapies (CECRT) including haemodialysis and haemofiltration [103], reducing leucine to almost 1000 µmol/L or lower within 24 hours irrespective of initial leucine concentration in neonates [104].
- Newborn screening by MS/MS may lead to earlier treatment and prevent the need for CECRT [105] with dietary treatment alone normalising leucine levels within 2–3 days.
- BF and infant formula (leucine source) are stopped temporarily.
- The rate of decrease of blood leucine concentrations should be >750 µmol/L per 24 hours [106]. CECRT is more effective than diet alone in reducing plasma leucine and can usually be stopped around 24–36 hours after commencement.
- Enteral feeding should be commenced early. BCAA-free infant formula (e.g. MSUD Anamix Infant) will stimulate protein synthesis. 150 mL/kg/day of BCAA-free infant formula (providing 2 g/100 mL protein equivalent) will provide 3 g/kg/day BCAA-free protein equivalent. If fluid is restricted, it may be necessary to supplement BCAA-free infant formula with additional concentrated BCAA-free amino acid mixes only (MSUD Aid 111 or MSUD Amino 5) to enable provision of 3 g/kg/day BCAA-free protein equivalent. A feeding plan is given in Table 28.27.
- A high energy formula (120–140 kcal [500–585 kJ]/kg/day), administered by a continuous tube feed or bolus, is necessary to promote anabolism. Glucose polymer is usually added to BCAA-free infant formula to provide a total of 10 g CHO/100 mL and 79 kcal (330 kJ)/100 mL. Fat emulsion (e.g. Calogen) is added, as necessary.
- If enteral feeds are not well tolerated, intravenous (IV) fluids are given – 10% dextrose with additional electrolytes and lipid (e.g. Intralipid at 2 g/kg/day). Any hyperglycaemia requires insulin administration. A continuous feed of BCAA-free amino acids (+ valine/isoleucine) may be tolerated (recipes are given at www.bimdg.org.uk) and will help plasma leucine decrease.
- Plasma leucine will not decrease if isoleucine and/or valine are deficient (as they become rate limiting for protein synthesis), and it has been suggested that 60–90 mg/kg/day (varying between 200 and 400 mg/day) of isoleucine and valine should be given to support maximal rates of protein synthesis. There is little toxicity associated with increased plasma concentrations of isoleucine and valine [105], and plasma levels are likely to fall quickly with haemodialysis/haemofiltration.
- Individual supplements of valine and isoleucine (50 mg/sachet) may be used. The contribution of energy and CHO (3.8 g/CHO per 4 g sachet) from these supplements should be calculated. These can be either added to the feed or mixed with water and given as a medicine, if there is a risk the full volume of enteral feed may not be given.

Table 28.24 Leucine content of low protein manufactured foods that should be calculated as part of leucine exchange system.

Product	Portion size	Amount of leucine (mg) per portion size	50 mg leucine exchanges
Nutricia Loprofin Drink	200 mL	40	1 exchange/200 mL
Nutricia SnoPro	200 mL	30	0.5 exchange/200 mL
Taranis Dalia Drink	200 mL	28	0.5 exchange/200 mL
Taranis Fish substitute	19 g portion	57	1 exchange per portion
Promin Low Protein Potato Pot, Sausage and Croutons	50 g pot	57	1 exchange per pot
Promin Low Protein Potato Pot, Bacon, Cabbage and Croutons	50 g pot	68	1 exchange per pot
Promin Low Protein Potato Pot, Onion and Croutons	50 g pot	68	1 exchange per pot

This is not a comprehensive list of low protein manufactured foods that should be counted as leucine exchanges. It is possible that the recipes of some manufactured products may change over time, so it is important to regularly recheck the leucine content of low protein manufactured foods.

Table 28.25 50 mg leucine exchanges for MSUD.

Food	Weight	Protein* (g)	Leucine† (mg)	Isoleucine† (mg)	Valine† (mg)
Milk					
Human milk, mature	40 mL	0.5	50	29	29
SMA Pro First Infant Milk‡	40 mL	0.5	52	26	29
Cow & Gate First Infant Milk‡	38 mL	0.5	52	32	29
Cow's milk	15 mL	0.5	50	27	36
Single cream	20 mL	0.5	48	26	36
Double cream	35 mL	0.6	52	30	38
Yoghurt (natural/flavoured)	10 g	0.4	57	31	34
Custard	15 mL	0.4	57	31	42
Cereals					
Rice, raw	10 g	0.7	56	26	39
Rice, boiled	25 g	0.6	47	22	32
Vegetables					
Asparagus, boiled as served	65 g	1.9	49		
Baked beans, canned	15 g	0.8	51		
Broccoli, boiled	45 g	1.5	51		
Brussels sprouts, boiled	35 g	1.1	53		
Cauliflower, boiled	40 g	0.8	53		
Mushrooms, fresh	50 g	0.8	53		
Okra, fried in oil	35 g	1.0	52		
Peas, boiled	15 g	0.8	45		
Petit pois, boiled	15 g	0.8	51		
Spinach, boiled	20 g	0.4	54		
Spring greens, boiled	25 g	0.5	51		
Sweetcorn, canned	15 g	0.4	50		
Yam, boiled	45 g	0.7	49		
Potato§					
Boiled, jacket	60 g	1.3	55		
Roast	45 g	1.2	53		
Chips	35 g	1.2	46		
Fruits (edible portion)					
Avocado	45 g	1.0	52		
Bananas	55 g	0.7	53		
Dried fruits¶	60 g	1.4	56		

Figures for the weight of food are rounded to the nearest 5 g, although many families use electronic scales which are accurate to between 1 and 2 g.
* [99].
† [46].
‡ Manufacturers' data for infant formulas.
§ Potato – the leucine content of potato varies between old, new and different varieties; an average figure has been used.
¶ Dried fruits – the leucine content of different dried fruits is similar, so an average figure has been used.

- Oral feeding can usually be re-established once the infant is extubated and leucine level is normalised. Leucine is given from standard infant formula/expressed breastmilk (EBM) when plasma leucine is <800 µmol/L. Although young infants often tolerate between 300 and 400 mg/day of leucine [107], it may be prudent to start with 200 mg/day (140 mL infant formula) of leucine (divided equally throughout the daily feeds) and increase/titrate intake according to blood concentrations, aiming for blood leucine 150–300 µmol/L.
- As leucine intake from infant formula increases, this natural protein will also provide a source of isoleucine and valine, and so these individual supplements should be reduced and adjusted to maintain them within target treatment reference ranges. A total protein intake of 3 g/kg/day from standard infant formula and BCAA-free infant formula is necessary. Once oral feeding is established, the BCAA-free infant formula and infant formula should be administered in separate feeding bottles (similar to PKU p. 527). A measured volume of infant formula is given (6–8 times/day) followed by BCAA-free infant formula.
- An infant with MSUD can be breastfed. During initial stabilisation, BCAA-free infant formula and valine and isoleucine supplements are given until leucine levels are <800 µmol/L, with the mother expressing breastmilk. Infants can then be breastfed on demand, but always with a measured quantity of BCAA-free infant formula first, with the volume titrated according to BCAA amino acid concentrations. This process for BF is similar to PKU (p. 526). There are few reports of BF infants with MSUD [108].
- Plasma BCAA should be monitored frequently, preferably daily in the early stages of management. Feeding plans are given in Table 28.28 and 28.29.

Table 28.26 Guidelines for total protein requirements for MSUD (protein intake from protein substitute and natural protein/leucine exchanges).

Age (years)	Total protein (g/kg body weight/day)
0–2	3.0
3–10	2.0
11–14	1.5
>14	1.0 (maximum 80 g/day)

Introduction of solids

The timing and principles of weaning is similar to PKU (p. 527). Start at one meal only with 1–2 teaspoons of homemade purée fruits and vegetables (e.g. apple, pear, carrot, butternut squash and parsnip). Commercial baby foods should contain exchange-free ingredients only (e.g. low leucine fruits and vegetables without rice or milk). Gradually increase to 3 times daily and progress from smooth purée to lumpier foods and suitable low protein finger foods (p. 528).

Many low protein weaning foods have a low energy density, so higher energy weaning foods should be encouraged: low protein rusks mixed with cooled boiled water to a smooth paste, low protein pasta meal as a 'porridge' replacement or low protein breakfast cereal and custard made with protein-free/leucine-free liquid milk replacements, e.g. Prozero (some low protein milk replacements contain leucine – Table 28.24).

As the intake of solids increases, gradually reduce the breastmilk/infant formula by 1 × 50 mg leucine exchange (e.g. 40 mL breastmilk; 38–40 mL infant formula depending on the brand), and replace with 1 × 50 mg leucine exchange of food (e.g. 40 g cauliflower or 45 g avocado). This process is continued until all the leucine from breastmilk or infant formula is replaced. The leucine exchanges should be divided between the three main meals.

Introduction of second stage protein substitute

As solids are introduced, an infant may be unable to drink adequate BCAA-free infant formula to meet total protein

Table 28.27 Example of daily feeding plan for an 8-day-old 3 kg infant with MSUD.

Newly diagnosed by newborn screening with leucine concentration of 1200 µmol/L

Ingredients	Amount	Energy (kcal (kJ)/day)	Protein equivalent (g/day)	CHO (g/day)	Fat (g/day)	Leucine (mg/day)	Valine (mg/day)	Isoleucine (mg/day)
MSUD Anamix Infant	450 mL	311 (1300)	9	33.3	15.8	0	0	0
Valine 50 sachets	16 g	60 (250)	0.2	15.2	0	0	200	0
Isoleucine 50 sachets	16 g	60 (250)	0.2	15.2	0	0	0	200
Total daily intake		431 (1800)	9.4	63.7	15.8	0	200	200
Intake kg/day		144 (600)	3.1			0		
Per 100 mL		96 kcal (400 kJ)	2.1 g	14.2 g	3.5 g	0	44 mg	44 mg

Administration: 19 mL/hour over 24 hours via nasogastric feeding tube.
Total CHO concentration of feed is high due to the CHO content of the valine/isoleucine 50 sachets. However, valine/isoleucine supplied by the supplementary sachets will decrease as natural protein is introduced from breastmilk or standard infant formula (according to tolerance/titrated according to blood leucine concentrations). This will decrease the overall CHO concentration of the feed.

Table 28.28 Example of daily feeding plan for 18-day-old 3.3 kg infant with MSUD.

Feeding 167 mL/kg/day, tolerating 80 mg/kg/day leucine (264 mg/day) and 200 mg/day of valine and isoleucine

Feeding plan
First feed: 25 mL × 3 × 8 feeds of Cow & Gate First Infant Milk
Second feed: 45 mL × 3 × 8 feeds of MSUD Anamix Infant

	Energy		Protein equivalent (g)	CHO (g)	Fat (g)	Leucine (mg)	Isoleucine (mg)	Valine (mg)
	(kcal)	(kJ)						
190 mL Cow & Gate First Infant Milk (26 g powder)	125	523	2.5	13.9	6.5	260	160	145
360 mL MSUD Anamix Infant (54 g powder)	248	1033	7.2	26.6	12.6	0	0	0
Valine 50 sachets (4 g dry weight)	15	63	0.04	3.8	0	0	0	50
Isoleucine 50 sachets (4 g dry weight)	15	63	0.04	3.8	0	0	50	0
Total	403	1682	9.8	48.1	19.1	260	210	195
Per 100 mL	73	306	1.8	8.7	3.5			
Per kg	122	510	3.0	14.6	5.8	79	64	59

Valine/isoleucine supplementation is titrated according to blood valine/isoleucine concentrations. One leucine exchange is equivalent to 50 mg.

Table 28.29 Example of daily feeding plan for a 2-month-old 4.5 kg infant with MSUD.

Feeding 165 mL/kg/day to provide 400 mg leucine (8 leucine exchanges) and 250 mg/day of both valine and isoleucine

Feeding plan
First feed: 50 mL × 6 feeds of Cow & Gate First Infant Milk
Second feed: 75 mL × 6 feeds of MSUD Anamix Infant

	Energy		Protein equivalent (g)	CHO (g)	Fat (g)	Leucine (mg)	Isoleucine (mg)	Valine (mg)
	kcal	kJ						
300 mL Cow & Gate First (41 g powder)	198	825	3.9	21.9	10.2	410	253	229
450 mL MSUD Anamix Infant (68 g powder)	311	1291	9	33.3	15.8	0	0	0
Total	509	2116	12.9	55	26	410	253	229
Per 100 mL	68	282	1.7	7.3	3.5			
Per kg	113	470	2.9	12.2	5.9	91	56	51

Valine/isoleucine supplementation is titrated according to blood valine/isoleucine concentrations. One exchange of leucine is equivalent to 50 mg.

requirements of 3 g/kg/day. From 6 months, and usually at the time of introducing leucine exchanges, it is necessary to gradually introduce a more concentrated spoonable second-stage/weaning BCAA-free L-amino acid substitute (e.g. MSUD gel; 5 g powder provides 2 g BCAA-free protein equivalent). This is reconstituted with approximately 1–2 mL water for each 1 g of product and is given as a paste before meals (as in PKU p. 529). At 1 year of age, the spoonable protein substitute may be replaced by a concentrated/low volume drink, e.g. MSUD Anamix Junior powder (10 g protein equivalent/29 g powder) and MSUD Anamix Junior LQ (10 g protein equivalent/200 mL).

BCAA-free infant formula should not normally be completely replaced by the second stage amino acid substitute until infants are at least 1 year old as the infant still requires some BCAA-free infant formula to ensure adequate energy intake.

Feeding preschool and school children and young people

Issues to consider when feeding preschool and school children and teenagers and during transition to adult services are given in Table 28.30.

Emergency regimens for management of intercurrent illness

During intercurrent infections, surgery and injury, plasma BCAA concentrations may rise rapidly, particularly leucine due to inadequate energy intake [109] and the direct catabolic effect of the infection [110]. This may cause rapid neurological deterioration, with neurotoxic levels of leucine and branched chain keto acids being reached within hours [107].

Table 28.30 Issues to consider when feeding different age groups of children with MSUD.

Preschool children	School children/teenagers
• Associated with a higher CHO diet, young children with MSUD may be at greater risk of dental caries causing decay, pain and distress. Encourage parents to take their child to see a family dentist as soon as their first teeth come through and at the latest by the age of 1 year, so preventative advice can be offered and children acclimatise to the dental surgery environment • Young children with MSUD will often eat a very limited diet, repeating the same narrow range of foods. It is important to build their confidence when eating. Avoid aversive food experiences. Introduce new foods by a graduated series of small changes around a food, beginning in child's comfort zone and expanding at a rate they tolerate. Working with a play therapist/psychologist is important. Allow plenty of time for mealtimes • If a young child requires tube feeding, it is particularly important that they are still offered low protein foods regularly during the day and experience the social aspects of eating. Children should be involved in cooking and food shopping from an early age • Parents may be reluctant to entrust their child's care to nursery workers. However, children should experience contact with other children to assist with learning development. It may be better to encourage half-day attendance at nursery for the first few months, so that staff only need administer suitable snacks and drinks. This will enable parents to build confidence in the nursery workers' ability to manage the condition. A strict care plan should be in place • Feeding problems, food refusal and gastro-oesophageal reflux can be an issue with some children. The use of gastrostomy is essential to prevent high leucine levels due to catabolism. Reflux should be treated with medications. Psychology support can help some families to overcome the stresses of food and amino acid substitute refusal and the anxiety associated with high leucine levels	• School-aged children with MSUD may be resistant to transitioning from an amino acid substitute for young children (e.g. MSUD gel) to a liquid pouch (which is easier to administer and has an age-appropriate micronutrient profile). Involving schoolteachers with this change may be helpful. Under the supervision of a teacher/teaching assistant, gradually introduce and increase the volume of an amino acid substitute from a small liquid pouch. This will help children become accustomed to the new taste, flavour and texture of the protein substitute. Only when at least 10 g protein equivalent is supplied by the new product should one daily dose of protein substitute be replaced. This usually takes considerable time • SENCO teachers will need comprehensive information about MSUD. A care plan should identify dietary needs, necessity for meal and snack time supervision, protein substitute administration, illness management, signs of metabolic decompensation (e.g. irritability, disorientation) and any additional educational needs. If a child has a gastrostomy *in situ*, a care plan should include necessary action if this is accidentally dislodged in school. The care plan should be reviewed annually and it may need to escalate to an 'education, health and care plan', if additional school resources are required • Children with MSUD become hungrier with age. Due to their rigid eating patterns, some children may want more of the foods they are used to, particularly leucine-containing foods such as potato products. Therefore, dietary adherence may be challenging. It is essential that children learn the basics of their dietary treatment, why they need to control leucine intake and take their protein substitute. Talking to the children (as well as parents) regularly will help them understand and accept their dietary treatment • Some children may be overweight, associated with their high CHO diet [87]. Encouraging daily exercise is important (e.g. dance, trampoline, swimming, football) • Some young people who are transitioning into adult care will have learning disabilities. It is important their individual care needs are carefully considered in the transition process enabling appropriate care packages to be in place when they are transferred to adult services

SENCO, special educational needs coordinator.
Also refer to Table 28.20.

Patients may present with symptoms such irritability, vomiting, dehydration and lethargy. Parents need to recognise early warning signs. They often report young children cannot sit up and fall to one side or fall over with walking, crying, being 'clingy' and poor feeding. Rapid neurological decline, including altered mental state (e.g. disorientation, speech disturbances, hallucinations), seizures and encephalopathy, may occur. Ketoacidosis and ketonuria is present. Any acute metabolic decompensation is considered a medical emergency [111]. The principles of ER are described on p. 673. The ER for MSUD is disorder specific.

It is essential to start the ER (Table 28.31) at the first sign of illness:

- Aim to provide the child's usual intake of branched chain free amino acids and at least the normal energy requirement for age [109]. If oral intake is poor, tube feeding should commence without delay.
- The usual leucine intake should be stopped or substantially decreased.
- Valine and isoleucine supplements should be added to the BCAA-free substitute. As a starting point, valine and isoleucine should replace the amount provided by the natural protein allowance and in addition to the usual valine and isoleucine supplements, but this may vary. Valine and isoleucine content of feeds should be titrated according to blood BCAA. A 50 mg leucine exchange from food or infant formula typically provides 25–30 mg isoleucine and 30–40 mg valine (Table 28.25).
- Daily monitoring of blood BCAA.
- Glucose polymer is added to the BCAA-free substitute meeting total CHO concentration as recommended for standard ER feeds (p. 677); addition of fat emulsion should be considered for additional energy, if necessary.
- BCAA-free L-amino acid substitutes made up according to manufacturer's instructions have a high osmolality. This needs to be considered when managing illness particularly if there is diarrhoea. If tolerance is poor, adding additional water to make them more dilute may help. Continuous feeds can help feed tolerance.

With timely introduction of the ER with mild or moderate illnesses, most patients can be safely managed at home [83]. It is essential to maintain close contact with parents/caregivers during illness management (at least 3 times a day) to assess if the prescribed ER feed is being achieved. If there is any feed intolerance and/or progression of clinical symptoms, the child should be admitted to hospital without delay.

Table 28.31 Emergency regimens in MSUD.

Diet	Essential	Guidance
BCAA-free amino acid substitute to support protein synthesis	Yes	Daily dose 0–3 years: 3 g/kg protein equivalent 4–5 years: 2.5 g/kg protein equivalent 6–10 years: 2 g/kg protein equivalent 11–14 years: 1.5 g/kg protein equivalent 15–16 years: 60 g/day protein equivalent
Valine and isoleucine intake	Yes	Valine and isoleucine to replace the amount provided by the natural protein allowance combined with the usual dose of valine and isoleucine supplements, but this may vary
Glucose polymer intake	Yes	CHO concentration and volume as per standard ER for age (p. 677)
Fat source	If tolerated	A high energy intake is required to promote anabolism. If fat is tolerated, the fat concentration could be 3–5 g per 100 mL of emergency feed. This can be added in the form of 50% fat emulsion; include any fat provided by the amino acid substitute in the calculation
Natural protein intake (leucine exchanges)	Stop or reduce by at least 50% (depending on severity of illness and BCAA results)	
Fluid	Yes	Fluid requirements as per standard ER for age (p. 677) Additional fluids may be necessary with diarrhoea or fever
Administration	Give orally or via a nasogastric or gastrostomy tube continuously over 24 hours. If there is poor tolerance of nasogastric/ gastrostomy feeding, consider administration via a nasojejunal tube	If oral feeds are not tolerated, administer concentrated BCAA-free amino acids (with valine/isoleucine) with IV glucose (ER feed recipes of concentrated BCAA-free amino acids are given at www.bimdg.org.uk)
Monitoring	Monitor BCAA concentrations to determine metabolic control/reintroduction of leucine and doses of isoleucine and valine Urine ketones (p. 540)	Daily during acute illness
Treat precipitating factors	For example, antipyretics for fever; antibiotics for infections	As prescribed by medical doctor

Dietary emergency guidelines with examples of age specific ER recipes are given at www.bimdg.org.uk.
BCAA, branched chain amino acids; CHO, carbohydrate; ER, emergency regimen, IV, intravenous.

Urine ketone monitoring

Ketonuria is a physiological result of catabolism in late infancy, childhood and even adolescence. In MSUD, daily home monitoring using standard test strips for ketonuria is useful in illness [83], and it is a surrogate marker for metabolic instability but should be used in combination with (and not replace) plasma BCAA monitoring. A positive result indicates catabolism, and the energy content of the ER should be increased, as tolerated. Usually the result is expressed as negative or positive with a grade of 1–4. Testing should be performed according to manufacturer's instructions on fresh uncontaminated urine. Urine test reagents deteriorate with exposure to air (so should be kept in a tightly sealed container) or if used after expiry date. The use of old or incorrectly stored test reagents may lead to false negative results.

Intravenous therapy

If emergency feeds are not tolerated and the patient's symptoms are vomiting, diarrhoea or very high temperature, then IV fluids (at least 10% dextrose) are given. Some patients may require higher concentrations of dextrose, insulin and Intralipid to promote anabolism [112]. Accompanying enteral BCAA-free amino acid acids (e.g. MSUD Aid 111 or MSUD Amino 5) providing up to a maximum concentration of 8 g/100 mL protein equivalent [113] together with valine and isoleucine supplements administered via a continuous tube feed are essential to promote protein synthesis. Pure BCAA-free amino acid acids without additional nutrients may be better tolerated than the usual BCAA-free amino acid substitute with added CHO, fat and micronutrients. If vomiting persists, consideration

should be given to nasojejunal feeding as, in the UK, there are no BCAA-free parenteral amino acid solutions available. Careful monitoring of hydration, electrolytes and neurological status is necessary to prevent cerebral oedema. Acute illness resulting in elevated plasma leucine is usually well managed without the need for CECRT. However, if the plasma leucine is >1000 µmol/L, CECRT should be considered [103]. If clinically safe, enteral nutrition including energy, fluid and BCAA-free amino acids with valine/isoleucine supplements should be given in combination with dialysis [83].

Introduction of natural protein post-illness

Studies suggest reintroduction of leucine when plasma leucine reaches the upper treatment target range [83]. Others recommend graded reintroduction over 3–4 days when leucine concentrations are <800 µmol/L (Table 28.32) (www.expandedscreening.org). Supplements of isoleucine/valine should be adjusted according to dietary intake and plasma BCAA concentrations.

Table 28.32 Introducing dietary leucine post-illness.

Plasma leucine concentrations (µmol/L)	Amount of dietary leucine to introduce
Leucine <800	25% usual leucine intake
Leucine >400 and <600	50% usual leucine intake
Leucine <400	75% usual intake
Repeat leucine <400	Usual leucine intake

Learning points: maple syrup urine disease

- *In early treated MSUD, outcome is dependent on prompt and effective control of plasma BCAA levels*
- *Lifelong dietary treatment and follow-up is required*
- *Supplementation with valine and isoleucine is commonly necessary*
- *Prompt and meticulous use of an ER is essential at any time there is a risk of metabolic decompensation*

Classical Homocystinuria

Fiona J. White

Enzyme

Cystathionine β-synthase. Expressed mainly in the liver and kidneys [114]

Biochemical defect

Deficiency of the enzyme cystathionine β-synthase (CBS) in the catabolic pathway of the essential amino acid methionine (Figure 28.4):

- Methionine is initially converted into the non-structural amino acid homocysteine by a series of enzyme dependent steps
- Homocysteine is not a constituent of protein and so not required for protein synthesis. Normally it undergoes either:
  - degradation through the trans-sulphuration pathway that converts homocysteine via cystathionine, with the addition of a serine group, to cysteine or
  - recycling back to methionine by the remethylation pathways [114] by either:
    i. methionine synthase, vitamin B_{12} and folic acid or
    ii. betaine–homocysteine methyltransferase – occurring in certain tissues, e.g. liver, kidney [115]

The first step in the trans-sulphuration of homocysteine requires CBS and pyridoxal-5-phosphate (vitamin B_6) as a cofactor. Deficiency of CBS results in:

- increased plasma concentrations of methionine, homocysteine and other sulphur-containing metabolites (mixed disulphides)
- low levels of plasma cysteine, cystathionine and serine
- homocysteine is present in large amounts in the urine, hence the condition being termed homocystinuria (HCU)

Homocysteine is present in plasma in several forms [116] with:

- 10%–20% present as free, non-protein bound homocysteine (fHcy) comprising homocysteine (reduced form <2%), homocystine (disulphide of homocysteine) and mixed disulphide (homocysteine–cysteine)
- 80%–90% present as protein (albumin)-bound homocysteine

Plasma total homocysteine (tHcy) concentration is the sum of all the different forms. Normally free homocysteine (fHcy) is undetectable, and tHcy level is 5–15 µmol/L [117]. fHcy only becomes detectable when tHcy exceeds 60 µmol/L [118]. At diagnosis plasma tHcy in HCU patients will be significantly elevated with levels often >200 µmol/L in non-screened patients. Additionally, plasma methionine levels are elevated and cysteine levels are low.

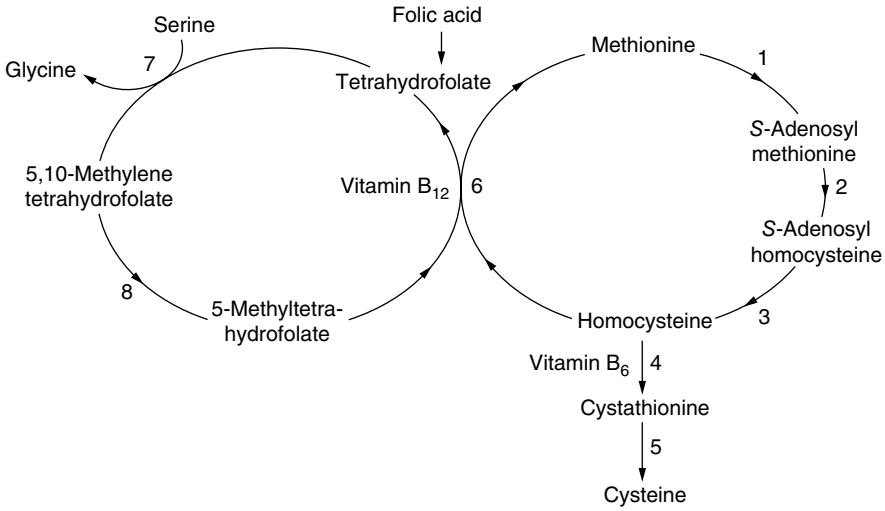


Figure 28.4 Metabolic pathways of homocysteine metabolism. 1: methionine adenosyl transferase; 2: SAM-dependent methyltransferase; 3: SAH hydrolase; 4: cystathionine β-synthase; 5: γ-cystathionase; 6: methionine synthase; 7: serine hydroxymethyltransferase; 8: methylenetetrahydrofolate reductase.

Genetics

Autosomal recessive inheritance

- Classical HCU was first described in 1962 [119, 120]. At least 160 mutations have been identified, with the majority being private (i.e. only occurring within that family) [121]
- Prevalence – The worldwide population prevalence varies, ranging from 1 in 1 800 to 1 in 900 000 [122], but there are large population differences, being highest in populations where there is a high level of consanguinity. In the Republic of Ireland, the prevalence is at least 1 in 65 000 [123]. DNA screening studies of newborn infants in a number of countries have shown that the overall prevalence may be as high as 1 in 20 000 [124]
- The highest reported incidence is in Qatar where there is a high carrier frequency (1% population) of a common mutation, with a prevalence of 1 in 1800 [125]

There are two distinct phenotypes:

- pyridoxine responsive HCU, which is the milder phenotype
- pyridoxine non-responsive HCU

There are some cases that show a partial pyridoxine responsive phenotype with tHcy levels decreasing to below 80% of baseline [122].

Newborn screening

Many countries undertake newborn screening (NBS) for HCU:

In the UK infants are screened on day 5 of life using a standard screening protocol with quantification of methionine, and then, if the level is above the cut-off, second tier testing with quantification of tHcy.

Only pyridoxine non-responsive HCU were thought likely to be identified on NBS, as those who are pyridoxine responsive are more likely to have methionine levels below the screening cut-off at that time. However, unpublished data from the European Network and Registry for Homocystinurias and Methylation Defects (E-HOD) shows that if the screening test is sufficiently sensitive, then pyridoxine responsive cases may be identified [122]. The author is aware of one case of pyridoxine responsive homocystinuria identified by NBS in England (personal communication).

More details on UK screening and diagnostic protocols can be found at www.gov.uk and www.bimdg.org.uk

Clinical onset presentation, features

- Individuals with HCU are clinically normal at birth.
- CBS deficiency results in accumulation of methionine, homocysteine and their *S*-adenosyl derivatives (*S*-adenosylmethionine (SAM), *S*-adenosylhomocysteine (SAH) and deficiency of cystathionine and cysteine.
- Without early diagnosis and treatment there is progressive onset of the clinical features of HCU, from the severe childhood onset of multisystem disease to those where symptoms only appear in adulthood [122].
- The pathogenesis is not fully elucidated. In addition to the accumulation of homocysteine, altered concentrations of other metabolites may play a role in the pathophysiology [122].

The major clinical features involve:

- the ocular system – lens dislocation, iridodonesis, myopia, glaucoma
- skeletal system – osteoporosis, scoliosis, elongation and thinning of the long bones, Marfanoid appearance
- vascular system – thromboembolisms, malar flush
- central nervous system – developmental delay, learning difficulties, electroencephalogram changes, epilepsy, psychiatric disturbance

Worldwide up to 50% of cases of CBS deficiency HCU are pyridoxine responsive. Pyridoxine responsiveness results in a decrease in tHcy <50 μmol/L [122] and elimination of homocysteine from urine [123, 126]. There are population differences with a much smaller percentage showing pyridoxine responsiveness in certain populations, e.g. UK and Ireland.

Long-term complications and outcome

Good long-term biochemical control in HCU can prevent the onset of complications in early diagnosed individuals and can curtail further progression, but not reversal, of the disorder in late diagnosed cases, apart from the eye disease [127]:

- No long-term data of tHcy levels over time and clinical outcome have yet been published.
- Published outcome data from follow-up of patients treated over many years show that lifelong median fHcy <11 µmol/L significantly reduces the probability of developing complications [123] and levels of fHcy <10 µmol/L indicate good biochemical control [127]. A median fHcy of around 10 µmol/L corresponds with a median tHcy around 120 µmol/L [122].
- Normal IQ has been reported [127, 128] in pyridoxine non-responsive HCU with good treatment adherence since diagnosis in the neonatal period.
- In a review of 46 patients [129] 65% were diagnosed from NBS (77% of whom had good/moderate control) with complication rates: 2% for those diagnosed on NBS and under good control; 17% for those diagnosed on NBS, but with poor control; and 45% for those not identified on NBS. Tertiary education was achieved by 84% of those diagnosed on NBS compared with 43% who were clinically presenting cases. Ectopia lentis (lens dislocation) is likely to develop where fHcy >12.3 µmol/L. Cognitive outcome in children is related to exposure to homocysteine and is best where cumulative exposure up to age 4 years is fHcy <100 µmol/L.
- Vascular events are the most common cause of death with risk of a vascular event at 25% <16 years of age and 50% by age 30 years in undiagnosed or poorly controlled HCU [130].
- Cardiovascular risk is greater in pyridoxine non-responsive HCU [126].
- Growth in a pyridoxine non-responsive HCU cohort has been reported [131]:
  - At 18 years of age cases, late diagnosed with learning disability had greater height and weight than those picked up through NBS. This appears related to early accelerated growth pre-diagnosis as rate of growth >10 years age was comparable. There was no relationship with metabolic control.
  - Compared with the general population, they were heavier and taller, with those diagnosed on NBS being closer to the general population.
- Osteoporosis, a known risk in HCU, can be prevented if diagnosed early and good biochemical control is maintained on treatment [122].
- Psychiatric conditions are more prevalent [122, 132].

Treatment

- Aimed at reducing homocysteine levels.
- Modality will depend upon factors such as pyridoxine responsive or non-responsive and age at diagnosis.
- All newly diagnosed patients should initially have a trial with a pharmacological dose of pyridoxine (vitamin B_6): 50 mg twice daily for 7–14 days in those diagnosed on NBS www.bimdg.org.uk; and 10 mg/kg/day (max 500 mg/day) in older children for 6 weeks [122], together with 5 mg folic acid to assess for pyridoxine responsiveness.

Pyridoxine responsive HCU

- The enzyme CBS requires pyridoxal-5-phosphate, formed from pyridoxine, as its cofactor.
- A significant number of CBS deficient individuals show clinical and biochemical response to pharmacological doses of pyridoxine, up to 500 mg/day [128].
- Pyridoxine supplementation should be kept to the minimum effective dose as doses >900 mg/day have been associated with peripheral neuropathy [122, 133, 134].
- The defect in pyridoxine responsive cases is still caused by mutations within the CBS protein and is not due to either deficient pyridoxine status or a disorder of pyridoxine metabolism. Pyridoxine, in this situation, is acting to increase residual CBS activity.

Pyridoxine non-responsive HCU

Plasma homocysteine levels do not fall following pharmacological doses of pyridoxine. Treatment strategies aim at reducing homocysteine levels by:

- decreasing the intake of the substrate methionine by the use of a methionine- or protein-restricted diet to reduce plasma methionine and therefore homocysteine levels
- giving an additional pharmacological dose of folic acid, 5 mg daily, to ensure adequate supply of folate for the remethylation pathway; vitamin B_{12} status should be monitored and, if suboptimal, supplementation given as it is required for folate metabolism
- utilising alternative pathways to remove homocysteine by giving betaine (a methyl donor) that remethylates homocysteine back to methionine and so reduces plasma homocysteine levels; if betaine is used, plasma methionine levels will usually be elevated

The decision on treatment option varies between metabolic centres, depending upon factors including age and mode of diagnosis, i.e. screened or clinically presenting, and previous treatment experiences. Those diagnosed on NBS are more likely to be solely diet treated, at least in the early years, than those clinically presenting at a later age.

Dietetic management

Principles are based on:

- substrate (methionine) reduction to decrease the load on the affected pathway
- supplementing deficient products beyond the metabolic block (cysteine)

Primary aims of dietary treatment are to correct abnormal biochemistry:

- decrease plasma methionine levels to within or slightly above the normal age-related reference range (unless on betaine therapy)
- decrease plasma homocysteine levels to target treatment levels
- increase plasma cysteine levels to within the normal range (Table 28.33).

Further details of dietary management are on p. 545.

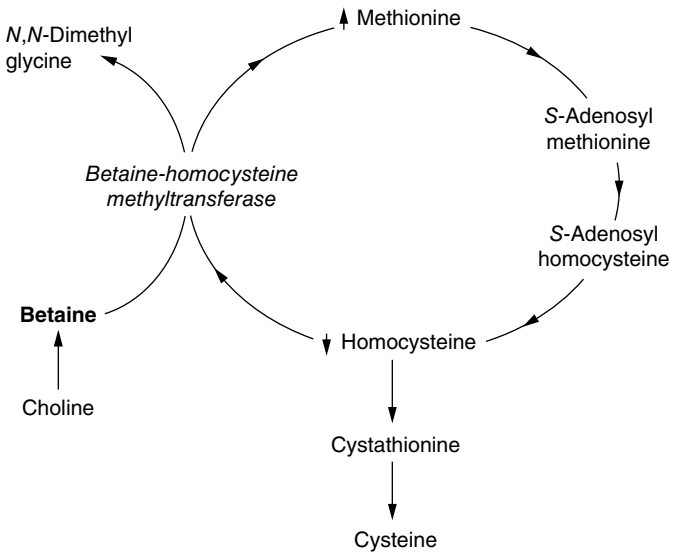


Figure 28.5 Methyl group donation by betaine.

Medications

Vitamin B_6 – Pharmacological doses used in pyridoxine responsive or partial responsive cases.
Folic acid – In CBS deficiency folic acid requirements can increase, due to increased flux through the remethylation pathway. It is recommended that low dose folate supplements are given although sufficient may be included within the methionine-free protein substitutes.
Betaine – A methyl donor, derived from choline, promotes the remethylation reaction of homocysteine to methionine via the enzyme betaine–homocysteine methyltransferase (Figure 28.5). Its use in HCU results in a decrease in plasma homocysteine and increase in plasma methionine [135]:

- Oral betaine can be useful, *as an adjunct to dietary therapy*, in improving biochemical control where dietary adherence is poor, e.g. adolescents, adults and those late diagnosed. However, adherence with betaine is not always good, with fHcy levels in 13 patients in one study not being significantly altered with betaine (mean 35 µmol/L pre-treatment and 33 µmol/L on treatment), and it is unlikely to replace dietary therapy [127], although a European survey [136] identified significant individuals treated with betaine alone.
- Initial dose in children – 100 mg/kg/day divided in two doses and adjusted depending upon response [122] should result in a decrease in plasma homocysteine levels and will normally result in plasma methionine levels being significantly increased, although this is not universal [135, 137].
- Pharmacokinetic studies demonstrated that doses of betaine above 200 mg/kg/day in two to three divided doses were of no additional value in decreasing tHcy levels [138, 139]. Giving betaine twice daily is adequate, with the half-life of betaine around 14 hours [139].
- Betaine alone as treatment of pyridoxine non-responsive HCU rarely achieves target Hcy levels [122]. This is also seen in CBS-deficient mice [140]. The response to betaine has been shown to be less efficient if plasma methionine is >80 µmol/L [141]; thus betaine should be used as an adjunct to a methionine-restricted diet and not as a sole treatment.
- The significantly raised plasma methionine levels that occur with betaine use do not appear to affect the pathophysiology of the disease [127]. Methionine levels should be monitored closely, and the dose reduced if levels exceed 1000 µmol/L as high levels have been associated with cerebral oedema [142, 143].

Monitoring

Dietary monitoring
Monitoring the diet by serial measurements of substrate blood amino acid levels is essential to assess metabolic control.

Treatment targets [122] (Table 28.33)
plasma tHcy <100 µmol/L in pyridoxine non-responsive cases
plasma tHcy <50 µmol/L in pyridoxine responsive cases

If dried blood spots (DBS) are used, the results will be lower than for plasma. Studies in non-HCU patients show the DBS method was approximately 40% of the plasma concentration [144, 145]. This may vary in clinical practice with HCU patients and so locally, by paired samples, the ratio of DBS to plasma levels should be determined. A correction factor can then be applied to enable results to be compared with target levels.

Methionine – Within the normal range except in cases on betaine where methionine should be maintained <1000 µmol/L. Excessive restriction of methionine that results in levels below the normal range could impair growth and neurodevelopmental outcome [122].

Cysteine – Aim for levels within the normal range, but this can be difficult to achieve. Low levels can be a reflection of poor homocysteine control, and improving this may improve cysteine levels.

Frequency of testing
Depends on age, severity, treatment adherence, previous complications [122]. Regular blood sample monitoring can be challenging as blood samples for total homocysteine require centrifugation within 1 hour of collection [146], so blood samples are usually taken at a local hospital. More recently DBS monitoring has become available in some centres that enables samples to be taken at home and therefore can be done more frequently as in PKU (p. 517).

Biochemical/haematological monitoring
- Vitamin B_{12} and folate status should be assessed as low levels of these could cause inadequate response to treatment due to their intimate roles in homocysteine metabolism
- Annual monitoring of full blood count (FBC), ferritin
- Other vitamins, minerals, trace elements, essential fatty acids as appropriate

Clinical monitoring
- growth – weight, length/height, BMI at each clinic review
- assessment for signs of any vitamin and mineral deficiencies (e.g. skin rashes, sparse hair)
- neurological and neurocognitive assessments
- DEXA (dual-energy X-ray) scans from adolescence to monitor bone health as risk of osteoporosis

Nutritional monitoring
- dietary assessment at all clinic reviews
- nutritional biochemistry as above

Guidelines	Morris *et al*. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency [122].
Parent Support Group	Metabolic Support UK www.metabolicsupportuk.org HCU Network Australia www.hcunetworkaustralia.org.au

Dietary management of classical HCU

Restriction of dietary methionine intake

Methionine is an EAA required for normal growth and body protein synthesis and so cannot be completely excluded from the diet. Methionine intake is restricted by restriction of dietary protein to maintain blood methionine and homocysteine levels within treatment targets (Table 28.37). In practice this will require the avoidance of high biological value (HBV) protein foods including meat, fish, eggs, cheese and pulses as they contain high amounts of methionine and, thus, the amounts permitted would be very small.

Methionine tolerance

- Individuals have a daily methionine allowance that maintains blood Hcy, methionine and cysteine within target values (Table 28.33).
- Methionine tolerance varies between individuals and is influenced by a number of factors (Table 28.34).

In the author's unit, a historical group (the majority identified by NBS), monitored using fHcy with target levels ≤10 µmol/L, had a median tolerance of methionine of 230 mg/day (range 160–900 mg/day). Current patients, diagnosed on NBS, monitored using tHcy, appear to require a lower methionine intake, around 80–160 mg/day to achieve target tHcy <100 µmol/L.

Table 28.33 Biochemical monitoring in HCU – treatment targets.

	Plasma methionine	Plasma cysteine	Plasma tHcy	Plasma fHcy
B_6 responsive	Normal range	Normal range	<50 µmol/L	<10 µmol/L
B_6 non-responsive, diet alone	Normal range	Normal range	<100 µmol/L	<10 µmol/L
B_6 non-responsive + betaine	<1000 µmol/L	Normal range	<100 µmol/L	<10 µmol/L

Table 28.34 Factors affecting substrate amino acid tolerance.

Residual enzyme activity
Growth rate
Degree of adherence to methionine (or natural protein) prescription
Adequacy of methionine-free, cysteine-enriched protein substitute
Adequacy of energy intake
Taking betaine in combination with methionine restricted diet
Target treatment substrate blood amino acid concentrations

Exchange system

To manage an individual's methionine allowance, an exchange system is used, predominantly consisting of foods of LBV protein:

- Each exchange contains 20 mg methionine equivalent to approximately 1 g protein; where the methionine content is not available, for example, in manufactured foods, the protein content is used
- Some centres use 1 g protein exchanges only
- Examples of basic 20 mg methionine exchanges are given in Table 28.35, and 1 g protein exchanges in Table 28.48

The guides for calculating exchanges in PKU can be adapted for use in HCU (Tables 28.5, 28.6 and 28.7).

Table 28.35 Basic 20 mg methionine exchanges for use in HCU [147, 148].

Food	Weight/volume
Milk and dairy	
SMA Pro First Infant Milk[#]	65 mL
Cow & Gate First Infant Milk[#]	70 mL
Aptamil Profutura First Infant Milk[#]	70 mL
Cow's milk	20 mL
Single cream*	30 mL
Double cream*	45 mL
Yoghurt (natural/fruit/flavoured)	20 g
Custard	20 g
Cereal	
Rice, raw	15 g
Rice, boiled	40 g
Vegetables	
Baked beans, canned in tomato sauce	35 g
Broad beans, boiled	75 g
Broccoli, boiled	45 g
Brussels sprouts, boiled	75 g
Cauliflower, boiled	65 g
Lentils, raw	10 g
Lentils, boiled	30 g
Mushrooms, fresh	35 g
Peas, petit pois (fresh, frozen, tinned), boiled	35 g
Spinach, boiled	20 g
Spring greens, boiled	100 g
Sweetcorn, canned	25 g
Yam, boiled	85 g
Potatoes	
Main crop, boiled, jacket, flesh only (average value)	70 g
Roast	45 g
Chips	35 g
Fruit	
Avocado	30 g
Dried fruits, e.g. raisins, currants, sultanas	75 g[‡]

[#] Manufacturers' data cards July 2019.
*There are a many different dairy creams available with variable fat content and therefore protein content. Always check protein content on the individual product nutritional analysis label.
[‡]This is an average amount for dried fruits.
Source: Adapted from [147, 148].

Low protein foods

Foods that are naturally very low in protein or protein-free are considered exchange-free and can be included in the diet in normal portion sizes without being weighed. They are important in ensuring adequate energy intake is achieved from the diet to meet normal energy requirements for age [98], thus supporting growth and preventing protein catabolism. These include the following:

Sugars, fats and some commercial foods (Table 28.9)

Work has been undertaken by the BIMDG Dietitians Group to classify exchange-free commercial foods in PKU. Generally foods with <0.5 g protein/100 g can be allowed freely unless a large portion is likely to be eaten. This definition may be used in HCU.

Fruits and vegetables (Table 28.36)

- fruits containing <1 g protein/100 g or <15 mg methionine/100 g
- vegetables with <1.0 g protein/100 g or <20 mg methionine/100 g

Very low protein manufactured foods (Table 28.9)

- These include flour mixes (all purpose, cakes), bread (loaves, rolls), pizza bases, pasta, rice, couscous, breakfast cereals and bars, savoury snacks, biscuits/crackers, soup sachets, low protein desserts, low protein energy bars and egg replacers
- The majority are available on prescription in the UK
- Manufacturers include Fate Special Foods, First Play Dietary Foods, Gluten Free Foods, Juvela, Metax, Mevalia, Nutricia, PK Foods, Promin, Taranis and Vitaflo
- The methionine/protein content of most of these foods is very low, but they should be checked as some may need to be counted as part of the daily methionine/protein allowance unless made completely with exchange-free ingredients
- These foods are an important part of the diet to provide energy and variety. Having a choice of low protein products is important, but cost and quantity should be considered if these are provided on prescription. The NSPKU have produced age-based guidelines on the monthly quantities to provide around 50% daily energy requirements that are applicable to HCU (www.nspku.org)
- Recipe booklets and online resources are produced by manufacturers

Energy supplements such as glucose polymers, fat emulsions or combined fat and glucose polymer supplements.

Methionine-free protein substitute

As the natural protein intake provided by the daily methionine allowance is inadequate to meet overall protein requirements, a methionine-free, cystine-enriched protein substitute is required to provide adequate nitrogen for protein synthesis and growth. This is used to make up total daily protein requirements (Table 28.37):

- A number of age-specific methionine-free, cystine-enriched protein substitutes are available; however, the range is less than that available for PKU due to the far smaller numbers of people with HCU. Examples include HCU Anamix Infant, HCU Anamix Junior, HCU Anamix Junior LQ, HCU Explore, HCU Lophlex LQ, HCU Cooler and HCU Express. The manufacturers' websites provide information on composition and usage www.nutricia.co.uk and www.vitaflo.co.uk. Outside the UK similar products are available from other companies, e.g. www.abbottnutrition.com, www.meadjohnson.com, www.metax.org and www.milupa-metabolics.com

Table 28.36 Fruits and vegetables allowed without measurement in HCU and tyrosinaemia.

Fruits		
Fresh, frozen or tinned in syrup (<15 mg methionine and/or <1 g protein/100 g)		
Apples	Guava	Pawpaws
Apricots	Kiwi fruit	Pears
Blackberries	Lemons	Pineapples
Blackcurrants	Limes	Plums
Clementines	Lychees	Pomegranates
Cherries	Mandarins	Raspberries
Cranberries	Mangoes	Rhubarb
Damsons	Melons	Satsumas
Fruit salad	Mulberries	Strawberries
Figs, green, raw	Nectarines – contain 36 mg methionine/100 g Allow up to 1 nectarine daily only in HCU	Tangerines
Gooseberries	Olives	Water melon
Grapefruit	Oranges	
Grapes	Passionfruit	
Vegetables		
Fresh, frozen or tinned (<20 mg methionine and/or <1 g protein/100 g)		
Artichoke	Fennel	Peppers
Aubergine	Garlic	Plantain
Beans, French, green	Gherkins	Pumpkin
Beansprouts	Gourd	Radish
Beetroot	Fennel	Spring onion
Cabbage	Leek	Swede
Carrot	Lettuce	Sweet potato
Celery	Marrow	Tomato
Chicory	Mustard and cress	Tomato purée
Courgette	Onion	Turnip
Cucumber	Parsley	Watercress
Endive	Parsnip	

Source: From [123, 124] and Leatherhead Food RA, Randalls Road, Leatherhead, Surrey, UK, 1994.

Table 28.37 Guidelines for total protein requirements for HCU (protein equivalent from protein substitute and natural protein/amino acid exchanges).

Age (years)	Total protein (g/kg body weight/day)
0–2	3.0
3–10	2.0
11–14	1.5
>14	1.0 (maximum 80 g/day)

- The administration and distribution through the day are similar to those in PKU (p. 523)
- Protein substitutes come in a range of presentations including powdered infant formula, spoonable products useful in weaning, powders and liquids (Table 28.12)
- Strategies are often required by parents/caregivers to encourage their child to take the protein substitute (Table 28.13)

Cystine supplementation in HCU

Cystine is a conditionally indispensable amino acid in HCU because of the metabolic block preventing the conversion of cystathionine into cysteine (Figure 28.4). Although all the methionine-free protein substitutes contain added cystine (30–50 mg/g protein equivalent), plasma cysteine concentrations are commonly low:

- Cysteine and homocysteine–cysteine is present in plasma in three different forms:
  - free cysteine
  - bound to homocysteine forming a mixed disulphide
  - bound to protein
- With increased concentrations of plasma homocysteine, the amount of cysteine present as the mixed disulphide homocysteine–cysteine increases, and cysteine and protein-bound cysteine decrease as cysteine is displaced from albumen by homocysteine [149]
- Monitoring plasma cysteine is problematic; most laboratories only measure free cystine, and if the sample is not deproteinised quickly, results may be falsely low [149]; ideally total plasma cysteine (free and bound) should also be assessed, but it is difficult to measure [149, 150]
- It has been reported that as biochemical control improves, with decreasing homocysteine concentrations, total cysteine levels increase [150]
- There are reports that deficiency of cysteine can lead to poor weight gain and growth despite adequate energy intakes [151] although one study did not find any association with low cysteine levels and height [131]
- Cystine has a poor solubility, so care is required to ensure it does not precipitate on solution when added to water; it has an unpleasant taste and can also cause gastrointestinal (GI) disturbance [131]
- Additional supplementation may not be warranted if tHcy is well controlled, as well as growth satisfactory; however, cysteine is essential for synthesis of glutathione that is an important antioxidant. Further research is needed to accurately assess cysteine status and whether supplementation to achieve normal levels affects outcome, for example, hHcy levels, glutathione status. Accurate monitoring of cysteine status is needed, and, if low, studies of supplementation in well-controlled patients and outcomes are needed

Micronutrients

Intakes of vitamins, minerals, trace elements, essential fatty acids and LCPUFA should be sufficient to meet age-appropriate requirements. Due to the restriction of dietary protein,

supplementation will be required. A number of methionine-free protein substitutes are already supplemented with these nutrients. Where they are not, separate supplements are required (Table 28.14).

Dietary management of newly diagnosed infants with HCU

Infants with HCU who fail to respond to a pharmacological dose of pyridoxine are commenced on dietary therapy. The dietary management guidelines pathway developed when NBS was introduced in England in 2012 is given in Figure 28.6.

Formula-fed infants

For infants with pyridoxine non-responsive HCU:

- initially all natural protein (methionine) intake is stopped, and the infant is fed entirely on a methionine-free infant formula, e.g. HCU Anamix Infant, aiming to give approximately 3 g methionine-free protein equivalent/kg body weight/day and normal energy requirements for age. (Other methionine-free formulas are available outside the UK: www.abbottnutrition.com, www.meadjohnson.com, www.milupa-metabolics.com.)
- subsequently a measured amount of natural protein, initially to provide 120 mg methionine/day (or 30 mg

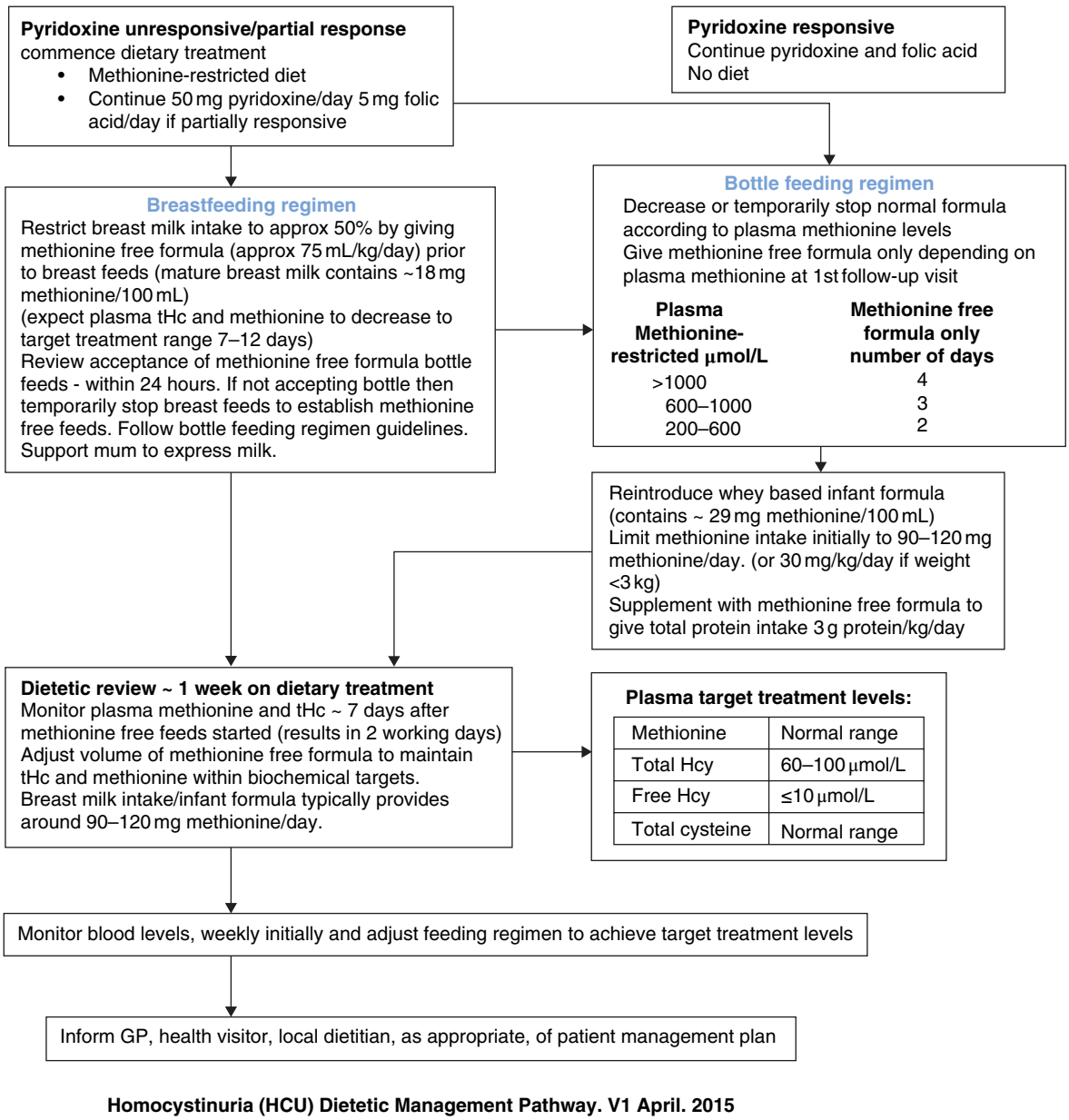


Figure 28.6 Homocystinuria (pyridoxine non-responsive) dietary management pathway. Source: www.bimdg.org.uk.

methionine/kg/day if weight below 3 kg), from standard infant formula is reintroduced, depending on initial biochemistry (Figure 28.6):
  - the standard infant formula is divided equally between several feeds (5–6 times daily) and is offered first followed by HCU Anamix Infant to appetite after each standard feed and at additional feeds as the infant demands. An example feeding plan is given in Table 28.38
  - the quantity of standard infant formula is adjusted according to subsequent plasma methionine and homocysteine levels, aiming to keep within the desirable limits (Table 28.33)

Breastfed infants

Early diagnosed infants (newborn or at risk screening) with pyridoxine non-responsive HCU can be breastfed using the principles employed in the management of PKU. The dietary management guidelines for pyridoxine non-responsive HCU (Figure 28.6) are as follows:

- If initial plasma methionine is >200 µmol/L, breastmilk should be withheld for 24–48 hours, and the infant fed solely methionine-free infant formula. The mother should be encouraged to express breastmilk regularly, around 6 times a day, to maintain supply. Following this, methionine-free infant formula should be decreased to approximately 75 mL/kg/day divided into 5–6 feeds and given prior to breastfeeds.
- If initial plasma methionine is <200 µmol/L, breastmilk intake should be decreased by approximately 50%. This is achieved by giving the infant 75 mL/kg/day of methionine-free infant formula divided into 5–6 feeds and given prior to BF.
- The prescribed quantity of methionine-free infant formula would then be increased or decreased according to blood methionine/homocysteine levels in order to manipulate the amount of breastmilk the infant takes.

This has been shown to be successful in practice, maintaining low plasma tHcy as long as adequate intake of methionine-free infant formula is taken [152].

Further dietary progression with the introduction of weaning solids and food exchanges and onto second stage protein substitute follows the same pattern as in PKU (p. 529).

Feeding issues can occur and parents can need support. Appropriate guidance around these issues is given on p. 529 and Table 28.20.

Interpretation of homocysteine, methionine and cysteine results

Regular monitoring of blood levels of homocysteine, methionine and cysteine should be carried out with samples taken at home (dried blood spots) or at the local hospital (venous

Table 28.38 Example of a daily feeding plan for a 4 kg infant with homocystinuria.

Aim: 120 mg methionine/day and 3 g total protein/kg
- Total fluid intake 180 mL/kg/day (= 720 mL daily)
- 70 mL Cow & Gate First Infant Milk = 20 mg methionine
- Total number of feeds = 6 daily

Methionine requirement: 120 mg/day = 6 × 70 mL Cow & Gate First Infant Milk = 420 mL daily
- Total fluid requirement = 720 mL
- Fluid from Cow & Gate First Infant Milk = 420 mL
- Deficit = 300 mL (720–420 mL)

Feed deficit made up with methionine-free protein substitute, e.g. HCU Anamix Infant = 300 mL/day

Feeding plan

6 feeds per day of
70 mL × 6 feeds of Cow & Gate First Infant Milk followed by
50 mL HCU Anamix Infant

Additional feeds of HCU Anamix Infant can be given if hungry

	Energy		Protein equivalent (g)	Carbohydrate (g)	Fat (g)	Fluid (mL)
	kcal	kJ				
420 mL Cow & Gate First Infant Milk	277	1155	5.5	30.7	14.3	420
300 mL HCU Anamix Infant	207	861	6.0	22.2	10.5	300
Total	484	2016	11.5	52.9	24.8	720
Intake per kg/day	121	504	2.9	13.2	6.2	180
			10% energy	44% energy	46% energy	
Energy requirement per kg/day	96	403				

samples). Target aims are given in Table 28.33. Depending upon blood results dietary manipulation may be required:

- If tHcy is towards the lower target range, then an increase in methionine/protein intake, by 10–20 mg methionine or 0.5–1.0 g protein per day, should be advised
- If tHcy is higher than target ranges, then a decrease in methionine/protein intake, by 10–20 mg methionine or 0.5–1.0 g protein per day, should be advised

It is better to consider trends in blood results before increasing/decreasing natural protein intake. It is advisable to adjust methionine/natural protein intake after more than one blood result is available unless blood concentrations are very low or very high. Factors such as illness, growth rate and dietary adherence should be taken into account. During illness, plasma tHcy and methionine increase due to catabolism. Tables 28.15 and 28.16 give guidance on interpretation of blood amino acid results.

Management of illness

Children with HCU do not have acute metabolic decompensation with intercurrent illness. A formal ER is not required. It is prudent, though, to try to prevent catabolism and excessive rise in blood homocysteine levels by:

- encouraging intake of methionine-free protein substitute
- giving methionine/protein exchanges to appetite
- giving high carbohydrate drinks
- ensuring good fluid intake

Development of acute venous thrombosis is a potential risk [122] that can be minimised by:

- avoiding dehydration and immobilisation
- giving intravenous fluids if there is intractable vomiting

Dietary management in later diagnosed cases of HCU

Individuals diagnosed late after the onset of clinical symptoms, or because of investigation following a sibling diagnosed with HCU, are commenced on treatment. Management depends on the individual's circumstances and may be by dietary methionine/protein restriction alone, dietary restriction with betaine or betaine alone.

In the author's unit the practice is to initiate dietary treatment in the following way:

- restricting methionine intake to 200 mg/day. If, from diet history, the normal dietary protein intake prior to diagnosis has been exceptionally high, a larger methionine allowance may be given
- giving an age-appropriate methionine-free protein substitute to make up the total protein requirement for age as in Table 28.37
- subsequent methionine allowance is adjusted according to plasma methionine and homocysteine levels so as to achieve acceptable control (Table 28.33)
- a sample menu plan is given in Table 28.39

Table 28.39 Menu plan for an 8-year-old boy with HCU.

Weight = 27 kg

10 × 20 mg methionine exchanges and methionine-free protein substitute to provide 2 g protein equivalent/kg

Total protein equivalent requirement = 54 g (10 g from natural protein/methionine exchanges and 44 g from protein substitute, e.g. 3 × HCU Cooler 15 or 2.5 HCU Lophlex LQ)

Breakfast
Methionine-free protein substitute, e.g. 1 × HCU Cooler 15 (130 mL) or 1 HCU Lophlex LQ (125 mL)

3 × 20 mg methionine exchange
105 g baked beans (3 exchanges)
Low protein toast
Fruit juice

Mid-morning
Fruit
Water

Midday
3 × 20 mg methionine exchange
Low protein pasta salad + 25 g boiled sweetcorn (1 exchange)
Chopped peppers or tomato or cucumber
Low protein bread and margarine
1 cereal bar (2 exchanges)
1 pear
Fruit juice or water

Mid-afternoon
Methionine-free protein substitute, e.g. 1 × HCU Cooler 15 (130 mL) or HCU Lophlex LQ (65 mL)

1 × 20 mg methionine exchange
1 packet crisps (1 exchange)

Evening meal
2 × 20 mg methionine exchange
Low protein pizza
Free salad vegetables
Low protein garlic bread (with garlic butter)
60 g ice cream (2 exchanges)
Fruit juice or water

Bedtime
Methionine-free protein substitute, e.g. 1 × HCU Cooler 15 (130 mL) or 1 HCU Lophlex LQ (125 mL)

1 × 20 mg methionine exchange
10 g cornflakes (1 exchange)
Protein-free milk replacement, e.g. Prozero, SnoPro

Dietary adherence in this group, in some cases, can be difficult to achieve because they are used to a normal unrestricted diet. Most will have learning difficulties, and so understanding the need for such a radical change in diet can be difficult to achieve. Individuals may 'cheat' with high protein foods, take additional methionine exchanges or refuse the methionine-free protein substitute. These problems need to be addressed. A positive family attitude and support from the multidisciplinary team, including clinical psychologist, are important if dietary treatment is to succeed.

For some late diagnosed individuals in whom all attempts to give the methionine-free protein substitute have failed, a modified low protein diet using the minimum safe level of protein intake [153] to minimise protein catabolism and poor growth is used in conjunction with oral betaine therapy.

In some cases, management with betaine alone is used. A European survey [136] of dietary practices in 181 patients showed wide variety in treatment with 62% on measured methionine/protein restriction (of whom 92% also had betaine), 34% on betaine alone and 3% on unmeasured, moderate protein restriction and betaine. The use of diet alone decreased with age with the converse for use of betaine only.

Learning points: classical homocystinuria

- *Pyridoxine non-responsive homocystinuria is part of the newborn screening programme in the UK and many other countries*
- *Dietary treatment (low methionine diet and methionine-free, cysteine-enriched protein substitutes) is required lifelong*
- *With lifelong good biochemical control of fHcy, clinical features of HCU can either be avoided or not worsened*

Hereditary Tyrosinaemias

Fiona J. White

Tyrosine is a non-EAA found in dietary protein and also endogenously synthesised from the hydroxylation of phenylalanine. It is used for protein synthesis as well as being a precursor for a number of important body chemicals including dopamine, epinephrine, norepinephrine, melanin and thyroxine. Tyrosine is catabolised by a series of enzyme-dependent reactions to fumaric acid and acetoacetate (Figure 28.7).

There are three inherited disorders of tyrosine catabolism: hereditary tyrosinaemia types I, II and III.

In addition to these, raised tyrosine levels can also occur in:

- neonates, particularly preterm infants. This is most commonly transient tyrosinaemia of the newborn probably due to immaturity of the enzyme 4-hydroxyphenylpyruvate dioxygenase (Figure 28.7) [154]. This may respond to vitamin C supplementation to induce enzyme activity, with rapid normalisation of tyrosine levels
- any severe liver disease where plasma quantitative amino acids can show raised tyrosine ± methionine
- infants fed unmodified goat's milk that has a high protein content and can give rise to suspicion of tyrosinaemia type I, with raised tyrosine and a metabolic acidosis [155, 156]

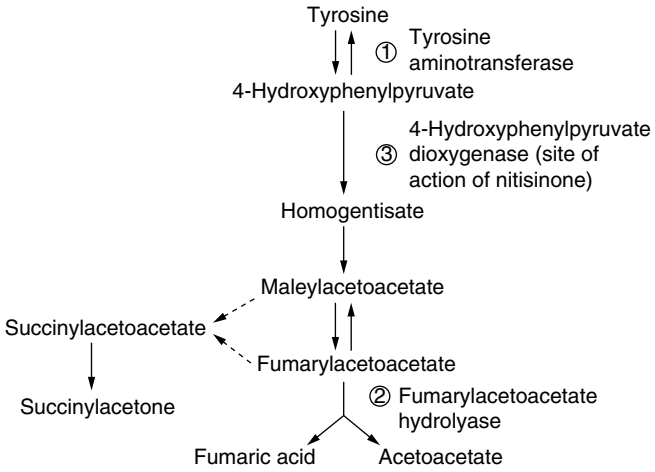


Figure 28.7 Pathways of tyrosine degradation. ① Tyrosinaemia type II. ② Tyrosinaemia type I. ③ Tyrosinaemia type III 4-hydroxyphenylpyruvate dioxygenase (site of action of nitisinone).

Tyrosinaemia Type I (hepatorenal tyrosinaemia, HTI)

Enzyme	Fumarylacetoacetate hydrolase (FAH)
Biochemical defect	FAH catalyses the final step of tyrosine degradation (Figure 28.7). Deficiency results in accumulation in both plasma and urine of the toxic metabolites: • Fumarylacetoacetate (FAA) which is further metabolised to produce succinylacetone (SA) and maleylacetoacetate (MAA) • Presence of SA is pathognomonic for HTI. It inhibits δ-aminolevulinic acid (δ-ALA) dehydratase (PBG synthase) resulting in accumulation of δ-ALA, which is excreted in high concentrations in urine • Plasma tyrosine levels are usually only moderately elevated, around 2–4 times the upper limit of normal (30–120 μmol/L), as the defect occurs in the terminal rather than early steps of tyrosine degradation • Plasma methionine concentration can also be markedly increased, due to liver dysfunction or secondary inhibition of *S*-adenosylmethionine synthetase [157] • The main diagnostic metabolite for HTI is SA measured in plasma, dried blood spot (DBS) or urine • Alpha-fetoprotein (AFP) levels are normally markedly raised, even in those identified on newborn screening (NBS), but this is not specific for HTI [158]

Genetics

Autosomal recessive inheritance

- Caused by mutations encoding for FAH. The gene is located on chromosome 15 with over 95 mutations having been identified [159].
- Prevalence – Certain FAH mutations occur more frequently in particular areas or ethnic groups including Mediterranean countries, Finns, Turks and Pakistanis, due to founder effects, leading to a higher prevalence within these populations [159, 160]. Whereas the worldwide population prevalence of HTI is approximately 1 in 100 000, it is higher in:
  - Quebec, Canada – around 1 in 1 846 in the French-Canadian region of Saguenay-Lac Saint-Jean (over 90% alleles are the same mutation) and Quebec overall 1 in 16 000
  - Finland – in particular the Pohjanmaa region 1 in 5000
  - Birmingham, UK – 1 in 20 791 that is associated with South Asian ethnicity and consanguinity
- There is no clear genotype–phenotype correlation [161].

Newborn screening

- HTI is not currently part of NBS in the UK, but is being considered www.gov.uk/government/groups/uk-national-screening-committee-uk-nsc
- Because tyrosine can be raised in a number of situations, on its own it is unhelpful as a screening marker for HTI. In areas where NBS is carried out, this is based on initial detection of high tyrosine with second tier testing for the presence of SA

Clinical onset presentation, features

- Individuals with HTI are clinically normal at birth
- Most affected infants will present clinically unless:
  - born in a region where NBS for HTI is performed
  - had early testing due to an affected sibling
  - identified on NBS with high tyrosine ± phenylalanine/methionine levels and then SA measured
- can present clinically at any age from the neonatal period until adulthood although biochemical abnormalities may be present soon after birth, including raised SA and AFP levels
- although most infants rarely present with clinical symptoms in the first few days, some neonates can have rapid onset of symptoms
- can manifest with a variety of clinical symptoms and severity and is usually classified according to age of onset of symptoms, broadly correlating with severity of disease [158, 162]:
  - *acute* – the most common form presents before 6 months of age with acute liver failure, the most severe before 2 months
  - *subacute* – presents between 6 months and 1 year of age with progressive liver failure, hepatosplenomegaly, coagulopathy, faltering growth and rickets
  - *chronic* – presents over 1 year of age with chronic liver and renal disease, rickets or porphyria-like episodes; some may also have cardiomyopathy or pancreatic cell hypertrophy that can cause hyperinsulinism [163]
- FAA, MAA and SA, possibly through binding to sulphydryl groups and resulting in tissue injury [163], are considered responsible for the clinical features of:
  - progressive liver failure with increased risk for hepatocellular carcinoma (HCC)
  - renal tubular dysfunction causing a 'Fanconi picture' with aminoaciduria, phosphaturia and renal tubular acidosis; phosphate loss results in hypophosphataemic rickets
- δ-ALA is responsible for a porphyria-like syndrome [158, 164]

Management

Acute management

If HTI is suspected because of liver disease, then once appropriate investigations (including plasma amino acids, urine organic acids, investigations for galactosaemia and, if age appropriate, for hereditary fructose intolerance which can both also present with acute liver failure) are undertaken:

- start nitisinone (suppresses the production of the toxic metabolites)
- a low tyrosine, low phenylalanine diet should also be commenced pending confirmatory results
- while waiting for diagnostic results, galactose and fructose should also be withheld from the diet until galactosaemia and hereditary fructose intolerance are excluded [158]

Chronic management

HTI is managed with:

- nitisinone
- dietary restriction of tyrosine and phenylalanine

Historically HTI was treated with a low tyrosine, low phenylalanine diet to minimise formation of toxic metabolites. Methionine intake was also restricted if plasma levels were high. Dietary treatment improved renal tubular dysfunction, growth and to some extent liver function, in particular prothrombin time, but dietary management could not completely prevent the production of toxic metabolites or the development of HCC. Most patients diagnosed early in life, pre-1992 and the introduction of nitisinone, either died from progressive liver failure or lethal porphyric crises unless they received a liver transplant that was the only effective treatment.

Treatment of HTI has been revolutionised since the use of nitisinone (2-(2-nitro-4-trifluoromethyl-benzoyl)-1,3-cyclohexanedione, NTBC, Orfadin) was described in 1992 [165].

Nitisinone treatment

- inhibits 4-hydroxyphenylpyruvate dioxygenase, the second enzyme in tyrosine catabolism (the defect in tyrosinaemia type III), blocking the tyrosine degradation pathway upstream of the enzyme defect (Figure 28.7) that:
  - suppresses the formation of FAA, MAA and SA
  - increases plasma tyrosine as the degradation pathway is blocked earlier

- in studies on healthy volunteers, given a single dose of nitisinone, plasma tyrosine concentrations increased from around 10 µmol/L at baseline to approximately 1100 µmol/L [166]
- as high plasma tyrosine concentrations are considered the probable cause of the oculocutaneous manifestations in tyrosinaemia type II and may also be associated with cognitive impairment [167], restriction of dietary tyrosine and phenylalanine is necessary
- leads to rapid improvement in hepatic and renal function and prevents neurological dysfunction in most patients [168]
- when started early in life, nitisinone markedly reduces the risk of early development of HCC. For patients who start this treatment late, there remains a considerable risk for liver malignancy [169, 170]
- is established as a very effective alternative to liver transplantation
- treatment must continue without interruption; otherwise serious complications, including acute liver failure, neurological crisis or malignant liver changes, may occur [158]
- the usual dose of nitisinone is 1 mg/kg/day in two divided doses. Based on the half-life being 54 hours in healthy adults, the frequency of dosing has been examined as less frequent could be beneficial in improving adherence and metabolic control, as compliance issues have been reported [171]. However experience is divided: a single daily dose could maintain adequate plasma NTBC levels [172]; but detectable levels of SA were found in those on once but not twice daily dosing [173]

Dietetic management

Principles are based on:

- substrate reduction (tyrosine, phenylalanine) to decrease the load on the affected pathway. Phenylalanine has to be restricted as it is catabolised to tyrosine

The primary aims of dietary treatment are to correct abnormal biochemistry:

- decrease plasma tyrosine to target treatment levels (Table 28.40)
- maintain blood phenylalanine within the normal range. This may require additional L-phenylalanine supplementation as described on p. 556

Further details of dietary management are given on p. 554.

Monitoring

Dietary monitoring

Monitoring the diet by serial measurements of substrate blood amino acid levels is essential to assess metabolic control. The European recommendations 2013 [158] are to maintain:

- blood tyrosine levels between 200 and 400 µmol/L
- blood phenylalanine concentration within the normal reference range. However, it is suggested to maintain phenylalanine concentration >50 µmol/L to compensate for the daily fluctuation in blood phenylalanine level [174]

Very high tyrosine concentrations are risk factors for neurotoxicity and corneal opacities [175]. Eye complications are said to be rare with tyrosine concentrations <800 µmol/L [158]. However, there is a case report of a nitisinone-treated HTI patient with photophobia and 'burning eyes', with tyrosine levels around 600 µmol/L. Corneal deposits resembling those seen in hereditary tyrosinaemia type II were confirmed [176].

Frequency of testing

Regular monitoring of blood or plasma tyrosine and phenylalanine concentrations should be undertaken. Generally DBS are taken at home and sent in to the laboratory for analysis. The European recommendations 2013 do not give any recommendations on frequency of monitoring [158]. A guide would be:

- weekly in infants because growth is rapid, or in newly diagnosed patients until stable
- every 1–2 weeks in 1- to 4-year-olds
- monthly thereafter or more frequently if levels are unstable

Biochemical/haematological monitoring

- regular monitoring of nitisinone levels and SA. Methods for determining nitisinone levels in DBS have been developed that enable easier monitoring with samples being able to be sent from home
- SA and AFP at clinic reviews
- liver and renal function tests, clotting, bone profile, FBC
- plasma quantitative amino acid profiles
- iron studies
- annual monitoring of other vitamins, minerals, trace elements, essential fatty acids as appropriate [158]

Clinical monitoring

- growth – weight, length/height, BMI at each clinic review
- assessment for signs of any vitamin and mineral deficiencies (e.g. skin rashes, sparse hair)
- neurological and neurocognitive assessments
- eye examination especially if high tyrosine levels
- bone mineral density (DEXA), especially if there is renal tubular disease

Nutritional monitoring

- dietary assessment at all clinic reviews
- nutritional biochemistry as above

Long-term complications and outcome

Prior to nitisinone treatment, survival rates were clearly related to age of onset of symptoms with death from liver failure, neurological crisis or HCC usually by 10 years of age [162] (Table 28.41).

Nitisinone is now the mainstay of treatment for HTI. A small proportion of patients presenting acutely with liver failure do not respond after a week of nitisinone. These cases should be referred for liver transplant assessment [158].

Survival and morbidity

Treatment with nitisinone and a low tyrosine/phenylalanine diet have resulted in an over 90% survival rate with normal growth, improved liver function, prevention of cirrhosis and correction of the renal tubular dysfunction [177] and the absence of porphyria-like crisis [171].

Cognition

- Neuropsychological outcome appears affected in nitisinone-treated HTI [170, 171, 178–180] in particular affecting IQ scores, especially performance skills, executive functioning and social cognition.
- Outcome studies on 46 French [171], 10 Belgian [178], 19 Dutch [179] and 7 German (>3 years of age) [181] patients treated with nitisinone and diet show high incidence of educational difficulties and cognitive impairment, in up to:
  - 35% of the French cases of school age
  - 30% of the Belgian cases
  - 32% of the Dutch cases
  - five of the seven German cases
- The cause of the cognitive deficits is unclear, but may be the result of high tyrosine levels due to poor adherence with the dietary treatment as chronic high tyrosine levels are associated with cognitive difficulties in HTII and most cases of HTIII [171, 178]. Tyrosine is a precursor for the neurotransmitters dopamine and norepinephrine, and high tyrosine levels may alter the synthesis of these [178].
- Some patients have low plasma phenylalanine concentrations [178, 182]. There is a known association in PKU between low phenylalanine levels and low IQ [178] where patients with the lowest IQ had mean phenylalanine <40 µmol/L in the first 2 years of treatment. Phenylalanine and tyrosine are both large neutral amino acids, and they compete for entry at the blood–brain barrier; thus high tyrosine levels with low phenylalanine concentrations will limit the amount of phenylalanine transported into the brain, potentially being rate limiting for brain protein synthesis.
- Recent work from the Netherlands [183] looked at plasma and, by calculation, presumptive brain influx of tyrosine and phenylalanine. Presumptive brain influx of phenylalanine was decreased more than expected from plasma levels but could be increased with phenylalanine supplementation; however to achieve adequate presumptive brain phenylalanine influx in HTI plasma phenylalanine levels probably needs to be above the current thresholds for hypophenylalaninaemia of 30–40 µmol/L [184, 185].

Guidelines

European 2013 – Recommendations for the management of tyrosinaemia type 1 [158]
US/Canadian 2017 – Diagnosis and treatment of tyrosinaemia type I: a US and Canadian consensus group review and recommendations [180]

Parent Support Group

Metabolic Support UK www.metabolicsupportuk.org/

Dietary management of HTI

Restriction of dietary protein intake

Tyrosine is present in protein containing foods and produced from phenylalanine catabolism. Both tyrosine and its precursor phenylalanine have to be restricted to control blood tyrosine. Some natural protein is required to cover requirements for phenylalanine to support growth and body protein synthesis. In the UK information on tyrosine content of foods is not available, so the overall protein content of foods is used. Individuals are prescribed a daily natural dietary protein intake allowance, thereby limiting both tyrosine and phenylalanine intakes. This is altered on an individual basis according to blood tyrosine concentrations to maintain levels within target treatment ranges (Table 28.40). An exchange system is used whereby one exchange is equivalent to 1 g protein.

Table 28.40 Biochemical monitoring in HTI.

Blood tyrosine	Blood phenylalanine
200–400 µmol/L	>50 µmol/L

Table 28.41 One- and two-year survival probability after the onset of symptoms prior to 1992 [162].

	Survival rates	
Age of onset of symptoms	1 year (%)	2 years (%)
Very early onset <2 months	38	29
Early onset 2–6 months	74	74
Late onset >6 months	96	96

Source: Adapted from John Wiley & Sons.

Exchange system

Foods used to provide daily protein allowance are mainly of low biological value protein as foods with a high biological value protein contain high amounts of tyrosine and phenylalanine and thus the amounts permitted would be very small. Each exchange provides 1 g protein. Examples of basic 1 g protein exchanges are in Table 28.42. A more extensive list is

Table 28.42 Basic 1 g protein exchanges for tyrosinaemia [54].

Food	1 g protein exchanges
SMA Pro First Infant Milk[#]	80 mL
Cow & Gate First Infant Milk[#]	75 mL
Aptamil Profutura First Infant Milk[#]	75 mL
Cow's milk	30 mL
Single cream*	30 mL
Double cream*	60 mL
Yoghurt (wholemilk natural/flavoured)	25 g
Rice, raw	15 g
Rice, boiled	45 g
Baked beans in tomato sauce, canned	20 g
Broccoli tops, boiled	30 g
Brussels sprouts, boiled	35 g
Cauliflower, boiled	50 g
Lentils, raw	5 g
Lentils, boiled	12 g
Peas, petit pois (fresh, frozen, tinned), boiled	15 g
Spinach, boiled	30 g
Spring greens, boiled	55 g
Sweetcorn kernels	40 g
Yam, boiled	60 g
Potato, old, boiled	55 g
Potato, new, flesh and skin, boiled	55 g
Jacket baked potato, flesh only	45 g
Jacket baked potato, flesh and skin	40 g
Roast potato	40 g
Chips	30 g

[#] Manufacturers data cards July 2019, based on protein.
*There are a many different dairy creams available with variable fat content and therefore protein content. Always check protein content on the individual product nutritional analysis label.
Source: Adapted from Finglas et al. [54]. Licensed under Open Government UK.

in Table 28.48. The guides for calculating exchanges in PKU can be adapted for use in HTI (Tables 28.5, 28.6 and 28.7).

Natural protein tolerance

The amount of natural protein tolerated varies between patients. From a peak of 1.8–2.4 g protein/kg/day at 4–5 months, it decreases to around 1 g protein/kg/day in late infancy [186]. This high peak of protein intake could be related to catch-up growth following diagnosis. Thereafter, once the patient has stabilised, the total protein intake usually varies little, irrespective of age, except during growth spurts. This scenario is also observed in the author's centre's cohort of HTI patients where natural protein allowance changes little with increasing age, even in the most adherent patients:

- Average natural protein intake per kilogram decreases with age in this cohort, average intakes being at:
  - 1–4 years age 0.6 g/kg/day (median 8 g/day)
  - 5–10 years 0.4 g/kg/day (median 8 g/day)
  - ≥11 years 0.2 g/kg/day (median 14 g/day, the majority in this age group always having an intake around this).
- There is intra-individual variation in natural protein tolerance, as observed in all disorders of amino acid metabolism, with intakes varying between 7 and 16 g/day. One centre has reported that daily natural protein intake increased with age in 6 of 11 patients [187]; however, median intakes were not dissimilar to the author's patient group. Tolerance is influenced by a number of factors (Table 28.43).

Table 28.43 Factors affecting tyrosine tolerance.

Residual enzyme activity
Growth spurt/catch-up growth
Adequacy of tyrosine- and phenylalanine-free protein substitute
Adequacy of energy intake
Taking nitisinone
Target treatment tyrosine and phenylalanine concentrations

Low protein foods

Foods that are naturally very low in protein or protein-free are considered exchange-free and can be included in the diet in normal portion sizes without being weighed. They are important to ensure adequate energy intake is achieved from the diet to meet normal energy requirements for age, thus supporting growth and preventing protein catabolism. These include:

- sugars and fats
- some commercial foods (Table 28.9); generally foods with <0.5 g protein/100 g can be allowed freely unless a large portion is likely to be eaten
- some fruits and vegetables (Table 28.10)
- very low protein manufactured foods:
  - these include flour mixes (all purpose, cakes), bread (loaves, rolls), pizza bases, pasta, rice, couscous, breakfast cereals and bars, savoury snacks, biscuits/crackers, soup sachets, low protein desserts, low protein energy bars and egg replacers
  - the majority are available on prescription in the UK
  - manufacturers include Fate Special Foods, First Play Dietary Foods, Gluten Free Foods, Juvela, Metax, Mevalia, Nutricia, PK Foods, Promin, Taranis and Vitaflo
  - the protein content of most of these foods is very low, but they should be checked as some need to be counted as part of the daily protein allowance unless ingredients are completely exchange-free

  - these foods are an important part of the diet to provide energy and variety. Having a choice of low protein products is important, but cost and quantity should be considered if these are provided on prescription. The NSPKU have produced age-based guidelines on the monthly quantities to provide around 50% daily energy requirements that are also applicable in HTI (www.nspku.org.uk)
  - recipe booklets and online resources are produced by manufacturers
- pure energy supplements, such as glucose polymers, fat emulsions or combined fat and glucose polymer supplements, may be needed if appetite is poor

Tyrosine- and phenylalanine-free protein substitute

As the natural protein allowance is inadequate to meet overall daily requirements, a tyrosine- and phenylalanine-free protein substitute is given. The combined intake of natural protein and protein equivalent from the protein substitute provides the daily protein requirement shown in Table 28.44:

- A number of age-specific tyrosine- and phenylalanine-free protein substitutes are available; however the range is less than that available for PKU due to the far smaller numbers of people with HTI. Examples include Tyr Anamix Infant, Tyr Anamix Junior, Tyr Anamix Junior LQ, Tyr Explore, Tyr Lophlex LQ, Tyr Cooler and Tyr Express. The manufacturers' websites provide information on composition and usage www.nutricia.co.uk and www.vitaflo.co.uk. Outside the UK similar products are available from other companies, e.g. www.abbottnutrition.com, www.meadjohnson.com, www.metax.org, www.milupa-metabolics.com
- The administration and distribution through the day are similar to those in PKU (p. 523)
- Protein substitutes come in a range of presentations including powdered infant formula, spoonable products useful in weaning, powders and liquids (Table 28.12)
- In the future it is likely that there will be protein substitutes for HTI based on glycomacropeptide (GMP), which is very low in tyrosine and low in phenylalanine (p. 520)
- Strategies are often required by parents/caregivers to encourage their child to take the protein substitute (Table 28.13)

Table 28.44 Guidelines for total protein requirements for HTI (protein equivalent from protein substitute and natural protein exchanges).

Age (years)	Total protein (g/kg body weight/day)
0–2	3.0
3–10	2.0
11–14	1.5
>14	1.0 (maximum 80 g/day)

Phenylalanine supplementation in HTI

Low plasma phenylalanine concentrations have been observed in HTI patients on low tyrosine/phenylalanine intakes [182]. If plasma phenylalanine concentrations remain low, they may become rate limiting for protein synthesis, and plasma tyrosine levels will remain high. It is important to monitor phenylalanine concentrations and to supplement with additional phenylalanine if consistently low. There is significant diurnal variation between morning (highest) and afternoon (lowest) blood phenylalanine concentrations [174, 184]:

- Supplementation, starting with 50 mg/day of phenylalanine, should probably be given if fasting phenylalanine concentration is consistently (two consecutive tests) below 50 µmol/L [174]
- Supplementation can be achieved either by increasing natural protein intake by 1 g, if tyrosine concentration also low (1 g protein contains around 50 mg phenylalanine), or by using an L-phenylalanine powdered supplement, e.g. Phenylalanine 50 (Vitaflo) (50 mg phenylalanine in a 4 g sachet)
- Care needs to be taken as additional phenylalanine from extra natural protein or pure phenylalanine powder may increase tyrosine concentrations. Any supplementation should be carefully monitored

Micronutrients

Intakes of vitamins, minerals, trace elements, essential fatty acids and LCPUFA should be sufficient to meet age-appropriate requirements. Due to the restriction of dietary protein, supplementation will be required. Most tyrosine- and phenylalanine-free protein substitutes provide these. If not separate supplements are required (Table 28.14).

Dietary management of newly diagnosed infants with HTI

Breastfed infants

Infants with HTI can be successfully breastfed while maintaining satisfactory biochemical control [188]. The principles of BF in PKU can be used in HTI. A measured amount of tyrosine- and phenylalanine-free infant formula, e.g. Tyr Anamix Infant, is given prior to BF.

A starting point is:

- to provide 1 g protein equivalent/kg/day from Tyr Anamix Infant divided into 5–6 feeds per day
- breastfeed to appetite following the Tyr Anamix Infant feed
- additional breastfeeds to appetite can be given if required

Tyrosine levels are monitored regularly:

- If tyrosine is >400 µmol/L, the volume of Tyr Anamix Infant is increased to suppress breastmilk intake
- If tyrosine is <200 µmol/L, the volume of Tyr Anamix Infant is decreased to stimulate appetite for breastmilk

Formula-fed infants

Initial management will depend upon plasma tyrosine levels.

Initial plasma tyrosine level is <500 µmol/L:

- decrease natural protein intake to 1 g/kg/day, divided into 5–6 feeds
- give Tyr Anamix Infant to appetite after each feed and at additional feeds as the infant demands
- aim to give a total of 3 g protein equivalent/kg body weight/day and normal energy requirements for age

Initial plasma tyrosine levels are >500 µmol/L, which may be the case particularly if nitisinone has been commenced prior to dietary treatment:

- All natural protein (tyrosine and phenylalanine) intake is stopped
- Give Tyr Anamix Infant to normal fluid requirements, providing around 3 g protein equivalent/kg body weight/day and a normal energy intake
- Subsequently, as plasma tyrosine levels fall, a measured amount of natural protein, initially to provide 1 g protein/kg/day as standard infant formula, is reintroduced
- An example feeding plan is given in Table 28.45. The quantity of standard infant formula is adjusted according to subsequent plasma tyrosine levels, aiming to keep within target treatment range (Table 28.40)

Further dietary progression with the introduction of weaning solids, food exchanges and onto second stage protein substitute follows the same pattern as for PKU (p. 529).

Feeding issues can occur. Some guidance around this as well as how to manage the diet during different stages of childhood is given in the PKU section (p. 529 and Table 28.20).

Interpretation of blood tyrosine and phenylalanine results

Regular monitoring of blood levels of tyrosine and phenylalanine should be carried out with samples taken at home (DBS). Target aims are given in Table 28.40. Depending on blood results, dietary manipulation may be required:

- If phenylalanine levels are low (<50 µmol/L) on two consecutive measurements, supplement initially with 50 mg/day of phenylalanine (p. 556)
- It is better to consider trends in blood results before increasing/decreasing natural protein intake. Once there is stability on diet following diagnosis, it is advisable to adjust natural protein intake after more than one result is available unless blood concentrations of tyrosine or phenylalanine are very low or very high
- Factors such as illness, growth rate and dietary adherence should be taken into account when assessing and interpreting blood monitoring results. Guidance on interpretation of tyrosine results is given in Table 28.46

Table 28.45 Example of a daily feeding plan for a 4 kg infant with HTI.

Aim: 1 g natural protein/kg/day and 3 g total protein/kg/day

Total fluid intake 180 mL/kg/day = 720 mL daily
- 80 mL SMA Pro First Infant Milk = 1 g protein
- Total number of feeds = 6 daily

Protein requirement: 1 g/kg/day = 4 × 1 g = 4 g protein/day = 4 × 80 mL SMA Pro First Infant Milk = 320 mL daily

Total fluid requirement = 720 mL
- Fluid from SMA Pro First Infant Milk = 320 mL (55 mL × 6)
- Deficit = 400 mL (720–320 mL) of tyr/phe-free infant protein substitute (65 mL × 6)

Feeding plan
6 feeds per day of
55 mL × 6 of SMA Pro First Infant Milk followed by
65 mL Tyr Anamix Infant

Additional feeds of Tyr Anamix Infant can be given if hungry

	Energy		Protein equivalent (g)	Carbohydrate (g)	Fat (g)	Fluid (mL)
	kcal	kJ				
330 mL SMA Pro First Infant Milk	221	924	4.3	23.4	11.9	330
390 mL Tyr Anamix Infant	269	1119	7.8	28.9	13.7	390
Total	490	2043	12.1	52.3	25.6	720
Intake per kg/day	123	511	3	13.1	6.4	180
			10% energy	43% energy	47% energy	
Energy requirement per kg/day	96	403				

Table 28.46 Manipulation of diet based on blood tyrosine levels.

Blood tyrosine level	Protein intake
>400–700 µmol/L	Decrease intake by 1–2 g protein/day
<200 µmol/L	Increase intake by 1 g of protein/day

Management of Illness

Children with HTI do not have acute metabolic decompensation with intercurrent illness. A formal ER is not required. It is however prudent to try to prevent catabolism and excessive rise in blood tyrosine levels by:

- encouraging intake of the usual tyrosine and phenylalanine protein substitute
- giving protein exchanges to appetite
- giving sugary/high carbohydrate drinks

Dietary management of later diagnosed cases of HTI

Individuals diagnosed late after the onset of clinical symptoms, or as a result of investigation following a sibling being diagnosed with HTI, are commenced on dietary treatment and nitisinone:

- Initially natural protein intake is decreased to 0.5–1.0 g/kg body weight/day, and an age-appropriate tyrosine- and phenylalanine-free protein substitute is introduced to maintain an age-appropriate total protein intake/kg/day (Table 28.44)
- Natural protein intake is then adjusted according to plasma tyrosine results (Table 28.46) to maintain within target treatment ranges (Table 28.40)

Learning points: tyrosinaemia type I (hepatorenal tyrosinaemia)

- *HTI is a treatable disorder since the introduction of nitisinone*
- *Dietary restriction of tyrosine and phenylalanine is required lifelong*
- *Long-term outcome knowledge is still being accrued as nitisinone has only been available for 27 years*

Tyrosinaemia Type II (Richner–Hanhart syndrome, HTII)

Enzyme

Tyrosine aminotransferase (TAT)

Biochemical defect

Hepatic tyrosine aminotransferase catalyses the first step of the tyrosine degradation pathway (Figure 28.7); deficiency results in:

- gross accumulation of tyrosine with plasma tyrosine concentrations usually >1200 µmol/L (normal reference range 30–120 µmol/L) at presentation
- tyrosine levels also increased in cerebrospinal fluid
- increased excretion of its phenolic derivatives in urine [154]. If the tyrosine concentration is less markedly increased, HTIII should be considered

Genetics

Autosomal recessive inheritance

- Most cases of HTII have not been confirmed by enzyme or mutation analysis; therefore some cases may actually be HTIII not HTII [154]

Clinical onset presentation, features

TAT deficiency results in tyrosine accumulation

- Usually present in the first few months of life with painful hyperkeratotic plaques on soles and hands
- High concentrations of tyrosine result in tyrosine crystals depositing within cells causing inflammation and leading to some of the clinical features that may affect the eyes and skin (oculocutaneous tyrosinaemia) and cognitive development [154]:
  - ocular lesions – occur in around 75% cases; corneal damage is due to tyrosine crystals disrupting corneal epithelial cell function and leading to an inflammatory response
  - skin lesions – occur in around 80% of cases and affect pressure areas, most commonly the palms and soles; this is possibly caused by excessive intracellular tyrosine causing structural abnormalities of the epidermal keratinisation [189]
- No liver or renal disease as the biochemical defect is early in the tyrosine degradation pathway, so the toxic metabolites found in HTI are not formed

Long-term complications and outcome

- With dietary treatment, the skin and eye problems usually improve rapidly. Skin and eye symptoms do not generally occur if tyrosine concentrations are <800 µmol/L [154]
- Neurological complications occur in around 60% cases with varying degrees of developmental delay including seizures, self-mutilation and behavioural difficulties [190]

Dietetic management

Principles of dietetic management used for HTI (p. 554) are also used in HTII:

- Low tyrosine and phenylalanine-restricted diet including tyrosine- and phenylalanine-free protein substitute
- Target treatment blood levels: tyrosine 200–400 µmol/L
  phenylalanine >50 µmol/L

	• The target for tyrosine is lower than that needed to treat the skin and eye lesions to minimise possible risk of high tyrosine levels contributing to developmental delay [191]
Monitoring	**Frequency of blood tyrosine and phenylalanine monitoring** Regular monitoring of blood tyrosine and phenylalanine concentrations should be undertaken. Generally DBS are taken at home and posted to the laboratory for analysis: • weekly in infants because growth is rapid, or in newly diagnosed patients until stable • every 1–2 weeks in 1- to 4-year-olds • monthly thereafter or more frequently if levels are unstable **Clinical monitoring including** • growth – weight, length/height, BMI at each clinic review • assessment for signs of any vitamin and mineral deficiencies (e.g. skin rashes, sparse hair) • neurological and neurocognitive assessments • eye examination especially if high tyrosine levels • skin examination (fingers/soles of feet especially if high tyrosine levels) **Nutritional monitoring** • dietary assessment at all clinic reviews • nutritional biochemistry including plasma quantitative amino acids, FBC, iron studies, annual monitoring of other vitamins, minerals, trace elements, essential fatty acids as appropriate
Parent Support Group	Metabolic Support UK www.metabolicsupportuk.org/

Learning points: tyrosinaemia type II (Richner–Hanhart syndrome, HTII)

- *HTII is extremely rare*
- *Treatment with a low tyrosine and phenylalanine diet with tyrosine and phenylalanine protein substitute, as in HTI, will reduce the accumulation of tyrosine crystals*
- *Neurological outcome is compromised in many cases with learning difficulties, challenging behaviour and seizures*

Learning points: tyrosinaemia type III

- *HTIII is extremely rare*
- *Treatment with a low tyrosine and phenylalanine diet with tyrosine- and phenylalanine-free protein substitute although needed initially may not be required long term to achieve target treatment blood levels*
- *Neurological outcome is compromised in most cases*

Tyrosinaemia Type III

Enzyme	4-Hydroxyphenylpyruvate dioxygenase (4-HPPD) Expressed in the liver and kidney
Biochemical defect	4-HPPD catalyses the second step in the tyrosine degradation pathway (the step that is inhibited by nitisinone in the treatment of HTI) (Figure 28.7) resulting in: • elevated plasma tyrosine • increased excretion of its phenolic derivatives in urine [154]
Genetics	Autosomal recessive inheritance • Mutations in the enzyme 4-HPPD gene located on chromosome 12 • Five mutations have been described [154], but without specific genotype–phenotype correlation • It is a very rare disorder with only 13 cases described in the literature to date • In some enzymatically diagnosed cases, no mutations have been identified [192]
Clinical onset presentation, features	• Neurological symptoms include developmental delay, ataxia, microcephaly, seizures, increased reflexes [154] • Liver and renal function are normal, and there are no reports of the oculocutaneous features seen in HTII [192] • Plasma tyrosine levels are usually in the range 300–1000 µmol/L • Urine organic acids show increased excretion of phenolic compounds • Diagnosis is possible by enzyme analysis of liver or kidney biopsy or mutation analysis [154]

Long-term complications and outcome	• There are reports that after infancy many patients with HTIII are able to maintain tyrosine levels within the target treatment range without the need for dietary treatment [193]. This has also been observed in the author's unit • Intellectual impairment is the most common long-term complication reported in 75% of cases [192, 194]
Dietetic management	Principles of dietetic management used for HTI (p. 554) can be applied to HTIII: • low tyrosine and phenylalanine diet • tyrosine and phenylalanine protein substitute • target treatment levels: tyrosine 200–400 µmol/L phenylalanine >50 µmol/L
Monitoring	**Frequency of blood tyrosine and phenylalanine monitoring** Regular monitoring of blood tyrosine and phenylalanine concentrations should be undertaken. Generally DBS are taken at home and posted to the laboratory for analysis: • weekly in infants because growth is rapid, or in newly diagnosed patients until stable • every 1–2 weeks in 1- to 4-year-olds • monthly thereafter or more frequently if levels are unstable **Clinical monitoring including** • growth – weight, length/height, BMI at each clinic review • assessment for signs of any vitamin and mineral deficiencies (e.g. skin rashes, sparse hair) • neurological and neurocognitive assessments • eye examination especially if high tyrosine levels, although this has never been described **Nutritional monitoring** • dietary assessment at all clinic reviews • nutritional biochemistry including plasma quantitative amino acids, FBC, iron studies, annual monitoring of other vitamins, minerals, trace elements, essential fatty acids as appropriate
Parent Support Group	Metabolic Support UK www.metabolicsupportuk.org

Organic Acidaemias and Urea Cycle Disorders

Marjorie Dixon

Dietary management: general principles of low protein diets

Introduction

A low protein diet forms an essential part of the management of organic acidaemias (OAA), e.g. methylmalonic acidaemia (MMA), isovaleric acidaemia (IVA), glutaric aciduria type 1 (GA1) and the urea cycle disorders (UCD), e.g. citrullinaemia, ornithine carbamoyl transferase deficiency. These disorders arise due to enzyme defects in the catabolic pathways of certain amino acids (in the case of OAA) and of waste nitrogen excretion (in the case of UCD). The aim of the low protein diet is to limit the substrate load (amino acids in OAA and nitrogen in UCD) on the 'blocked' metabolic pathway to reduce the production of toxic metabolites that can cause neurological sequelae and organ damage. As such, these are classified as 'intoxication type disorders' of intermediary metabolism.

This section describes the provision of a low protein diet and acute management, common to these disorders. Dietary treatment is generally combined with pharmacological treatment to reduce the substrate load on the pathway (e.g. nitrogen scavengers in UCD) or to increase excretion of toxic intermediates (e.g. carnitine and glycine to excrete isovaleric acid in IVA) or to replace a deficient product (e.g. arginine in UCD). Medical aspects and disorder-specific dietary treatments are described under each separate condition. Patients with an OAA or UCD are invariably complex to treat, and it is essential they are managed at specialist metabolic centres. Local professionals and hospital teams should also form an integral part of their care package.

Protein requirements

Proteins are large complex molecules. Different proteins work as antibodies, enzymes, messenger proteins such as some types of hormones and structural components and in transport and storage. The body does not maintain reserves of protein; thus a constant supply is needed (p. 513).

Low protein diets should provide at least the minimum amount of protein, nitrogen and indispensable (essential) amino acids to meet the body's requirements. 'Safe level of protein intake' (Table 28.47) and requirements for indispensable amino acid intake have been set by FAO/WHO/UNU

Table 28.47 'Safe level of protein intake' for infants, children and adolescents.

Age	Safe level (g protein/kg/day)
For infants < 6 months of age (months)	
1	1.77
2	1.5
3	1.36
4	1.24
6	1.14
For weaned infants (sexes combined) (years)	
0.5	1.31
1	1.14
1.5	1.03
2	0.97
3	0.9
4	0.86
5	0.85
6	0.89
7	0.91
8–9	0.92
10	0.91
Girls	
11	0.9
12	0.89
13	0.88
14	0.87
15	0.85
16	0.84
17	0.83
18	0.82
Boys	
11	0.91
12–13	0.90
14	0.89
15	0.88
16	0.87
17	0.86
18	0.85

Source: Adapted from [8].

expert committees, most recently in 2007, based on nitrogen balance studies [8]. Protein intakes (g/kg/day) decrease with age throughout childhood. The 'safe level of protein intake' has been calculated as the mean requirement +2 standard deviations (SD), so as to meet or exceed the requirements of most individuals. However, for some, a protein intake below the safe intake may be adequate for growth, particularly if protein is mainly from HBV sources. More recent advances in determining protein and amino acids requirements in humans is by a stable isotope method: indicator amino acid oxidation [195]. Using this technique, mean and safe protein intake in children aged 6–10 years is reported to be 1.3 and 1.55 g/kg/day that is much higher than current FAO recommendations. However, while experts continue to debate the accuracy of alternative methodologies used to determine protein requirements [12, 196, 197], the FAO guidelines for protein continue to be used to guide low protein intake prescriptions in OAA and UCD, although some countries use local reference value guidelines. Ideally the protein source in low protein diets should be mainly from HBV protein. However, this is not necessarily common practice because a greater variety of foods and a higher energy intake per gram of protein can be provided from LBV protein foods. Children on low protein diets who frequently consume a limited range of LBV protein foods (plant foods) may be at risk of one or more indispensable amino acids becoming rate limiting for protein synthesis, e.g. lysine in predominantly cereal-based diets. It is, therefore, important that a variety of LBV protein foods (potato, cereals, rice, pasta, pulses, vegetables) are eaten to ensure an adequate intake of all indispensable amino acids. If the protein tolerance and prescription is generous enough, more HBV proteins should be included to improve the protein quality of the diet. A new method of calculating protein quality was published by the FAO in 2013 [198]. However, without more up to date and extensive amino acids analysis of foods, this is difficult and time consuming to calculate. There are no publications describing an optimal ratio of HBV to LBV foods in low protein diets for these disorders. Dietary practice surveys in UK and Europe report that HBV foods typically provide at least some of the daily protein allowance in patients with UCD [199], and the OAA, propionic acidaemia (PA) [200] and IVA [201].

Protein allowance (g/day) varies depending on the disorder, residual enzyme activity of the specific disorder, growth rate, age and prescribed medicines. During early infancy, growth is at a maximum, so protein requirements per kg body weight are greatest at this time. Clinical and biochemical monitoring are essential to help prevent protein and amino acid deficiencies, which can cause severe cutaneous lesions (babies and young children are particularly vulnerable), and to guide protein prescription (refer to specific disorders).

Protein intake may need to be temporarily increased:

- during periods of catch-up growth
- if the usual daily protein intake is repeatedly interrupted, e.g. some MMA patients have frequent episodes of metabolic decompensation and acidosis and require intravenous (IV) 10% glucose and ER instead of usual feeds. It is important to monitor days off with less than usual or zero protein intake
- during episodes of severe pancreatitis (as seen in MMA, PA, IVA), when protein catabolism can be substantial in response to severe inflammation, protein requirements are increased (p. 186)

Provision of a low protein diet

Protein

In OAA and UCD a daily protein allowance is prescribed. Protein intake (g/kg/day) decreases with age, but the total intake (g/day) increases (Table 28.47). Protein is provided from breastmilk or infant formula for infants and food for older children (unless they are tube fed). Protein intake from LBV protein foods can be measured by an exchange system, where one exchange equals the amount of each food that provides 1 g of protein. This system allows greater variety in the diet as foods can be substituted for each other and still provide a similar protein content and the same total daily protein intake.

Table 28.48 provides a list of 1 g protein exchange weights and energy content for basic foods such as potato, rice, pasta, pulses, vegetables and some infant formulas. Protein can also be provided by manufactured foods such as bread, pitta, chapatti, breakfast cereals, biscuits, cake, potato-based foods and vegetable fingers. The protein content on the nutritional label is expressed as grams of protein/100 g food and sometimes per portion. Parents should be taught how to interpret the food label and calculate exchanges. For manufactured foods one exchange (1 g protein) is calculated as follows:

- 100 ÷ (g protein per 100 g of food)
- if more than 1 g protein is desired, this is multiplied by that number of exchanges, e.g. cornflakes = 7 g protein per 100 g
- 100 ÷ 7 = 14 g cornflakes = 1 g protein
- if 2 g of protein is required, then 14 g × 2 = 28 g cornflakes

Ideally the protein intake should be evenly distributed between main meals with some allocated for snacks to avoid giving a protein load at any one meal. Protein food exchanges should be weighed using digital scales that weigh in 1 g increments, at least initially. If parents cannot cope with the concept of protein exchanges or weighing, then a set menu with handy measures or a pictorial food chart can be used. Often parents become familiar with portion sizes that provide 1 g of protein and stop weighing food; however, it remains important to check accuracy by weighing regularly.

The energy provided by exchange foods has a wide variation, e.g. an exchange (1 g protein) of baked beans provides 20 kcal (85 kJ) and crisps 110 kcal (460 kJ). It may be helpful, particularly if the child has a poor appetite, to give parents advice on choosing protein exchanges that are more energy dense and provide >60 kcal (250 kJ) per exchange.

HBV protein foods can be incorporated in the diet as 3 or 6 g protein exchanges (i.e. one exchange is the amount of food which provides 3 or 6 g protein). Table 28.49 provides a list of 6 g protein exchange weights for higher protein foods. This is more useful for older children or those with milder disorders who are on a much more generous protein allowance.

Some vegan, plant-based foods are as high in protein as HBV foods; however, some are lower in protein and can help provide more choice in a low protein diet. Parents should be encouraged to spend time looking at different product choices in the supermarket.

Protein substitutes (L-amino acid supplements)

Precursor-free L-amino acid supplements (i.e. disorder-specific amino acid supplements that do not contain the amino acids that cannot be metabolised) are used by some centres in the treatment of some OAA (further discussed under the specific disorders as their role and use varies between disorders). The use of EAA supplements in UCD is discussed on p. 590. Administration of amino acid supplements (termed protein substitutes) for disorders of amino acid metabolism is discussed on p. 523. Although smaller amounts are used in OAA and UCD, the practical aspects are generally still applicable.

Energy

Energy requirements need to be adjusted for the individual's needs considering metabolic stability, rate of weight gain and physical activity. Inadequate energy intake must be avoided as it causes poor growth and metabolic instability with endogenous protein catabolism, leading to an increased production of toxic metabolites, e.g. ammonia in UCD, and must be avoided. The aim is to provide around normal energy requirement for age and sex, except for those with physical disability who are likely to have lower energy requirements due to reduced mobility, such as children with MMA who have had a metabolic stroke and, in others who may have increased energy requirements, such as children with GA1 with severe dystonia.

Dietary energy can be provided by both the protein exchanges and the following groups of foods that are allowed without restriction in the diet:

- foods naturally low in or free of protein: sugar, fats and a few commercial foods (Table 28.9). The classification guideline for exchange-free commercial foods in PKU can also be used for low protein diets. Generally foods with <0.5 g protein/100 g can be allowed freely unless a large portion is likely to be eaten
- fruits and vegetables with <1.0 g protein/100 g (Table 28.50)
- specially manufactured very low protein foods; these include bread (loaves, rolls), pizza bases, pasta, rice, couscous, pasta, flour mixes (for cakes, savoury), breakfast cereals and bars, savoury snacks, biscuits/crackers, soup sachets, low protein desserts, low protein energy bars and egg replacers. In the UK most of these foods are available on prescription, endorsed Advisory Committee on Borderline Substances (ACBS). Manufacturers of low protein foods include Fate Special Foods, First Play Dietary Foods, Gluten Free Foods, Juvela, MetaX, Mevalia, Nutricia, PK Foods, Promin, Taranis and Vitaflo. The protein content of most of these foods is very low, but they should be checked as some may need to be counted

Table 28.48 Basic list of 1 g protein exchange foods for low protein diets.

	Food	Weight (g) = 1 exchange = 1 g protein	Energy (kcal/g protein)	Energy (kJ/g protein)
Infant formula	SMA Pro First Infant Milk	80 mL	54	224
	Cow & Gate First Infant Milk	75 mL	50	208
	Aptamil Profutura First Infant Milk	75 mL	50	208
Milk and dairy	Cow's milk	30 mL	19	79
Coconut	Single cream	30 mL	58	243
	Double cream	60 mL	298	1251
	Yoghurt* (whole milk, fruit)	25	27	114
	Fromage frais*	20	20	83
	Ice cream*	~30	88	370
	Milk chocolate*	15	78	326
	Plain chocolate*	20	102	428
	Philadelphia*	20	45	186
	Boursin*	12	48	201
	Dairylea*	10	21	88
	Coconut, creamed, block	15	100	420
Potatoes and starchy vegetables†	Potato, old	55	33	138
	Potato, new (flesh and skin)	55	35	148
	Jacket (baked) potato (flesh only)	45	37	155
	Jacket (baked) potato (flesh and skin)	40	39	163
	Chips cooked	30	61	256
	Roast potato	40	65	270
	Crisps	15	74	311
	Sweet potato	90	76	317
	Plantain	125	32	136
	Yam	60	59	247
	Butternut squash (baked)	110	35	147
Pulses†	Baked beans in tomato sauce*	20	15	63
	Beans: aduki, haricot, black-eye, chick peas, red and white kidney	12	14	59
	Beans: broad, butter	20	10	42
	Beans: soya	7	10	42
	Tofu (soya bean steamed)	12	9	38
	Lentils	12	12	50
	Peas	15	12	50
	Marrowfat peas	15	13	55
	Hummus*	15	37	154
Vegetables†	Asparagus	30	8	34
	Beansprouts, mung (raw)	35	11	46
	Brussels sprouts	35	12	50
	Broccoli tops	30	8	34
	Cauliflower	50	15	63
	Curly kale	40	10	42
	Mangetout	30	8	34
	Okra	40	11	46
	Spinach, fresh baby and frozen	30	6	25
	Spring greens	55		
	Sweetcorn kernels	40	10	42

(continued overleaf)

Table 28.48 (*continued*)

	Food	Weight (g) = 1 exchange = 1 g protein	Energy (kcal/g protein)	Energy (kJ/g protein)
Fruits and dried fruits (varies depending on the fruit, check individually)	Avocado	55	95	399
	Banana flesh, no skin	85	69	290
	Raisins	50	136	571
	Sultanas	40	110	462
	Apricots dried	25	63	265
	Figs	30	63	265
Cereals	Cornflakes*	10	58	243
	Rice Krispies*	15	58	243
	Honey Monster Puffs*	20	53	224
	Weetabix*	10	36	152
	Oatmeal	10	36	152
	Rice white, long grain			
	raw	15		
	boiled	35	46	193
	Pasta white: fusilli, twists, spaghetti (dried, then boiled)	20	28	118
	Noodles rice	55	49	206
	Semolina (raw)	10		
	Couscous (cooked)	15	27	113
	Flour: white, wholemeal, plain or self-raising	10	35	147
Breads	White*	12	29	120
	Wholemeal*	10	22	92
	Rolls (soft, crusty)*	10	29	120
	Chapatti*	15	43	180
	Nan*	15	40	164
	Pitta*	10	28	118

* For manufactured foods the weight for one exchange and energy value will be more accurate if calculated from the nutritional label on the food. The figures given can be used as a guide.
† The weight of one exchange for vegetables, potatoes and pulses is for cooked (boiled) weight (except for baked beans) unless otherwise stated.
Source: From Finglas et al. [54]. Licensed under Open Government UK.

as part of the daily protein allowance. Availability of choice is important for quality of life and dietary adherence, but cost of products and quantity used should be considered if obtained on prescription. Manufacturers produce recipe booklets and online resources for their low protein food products, e.g. www.lowproteinconnect.com, www.vitafriendsmsud.com/recipes

- energy supplements: glucose polymer, fat emulsions or combined fat and glucose polymer supplements

Manufactured low protein foods are not always necessary or popular with children on low protein diets although low protein milk replacements, e.g. Prozero and Loprofin Drink, are useful and can be well accepted. Some children obtain sufficient energy from normal foods and prefer to eat these. In contrast others with a poor appetite, inability to suck or swallow due to neurological disability, or vomiting, gastro-oesophageal reflux (GOR) and retching depend on energy supplements as their main energy source, which are invariably part of a modular tube feed. If energy supplements are needed, it is important to maintain a healthy balance between fat and carbohydrate (CHO) energy.

Vitamins, minerals and trace elements

Mineral deficiencies, particularly associated with low protein diets, have been reported in patients with OAA and UCD [202–204]. Vitamin and mineral supplements are invariably essential as dietary intake will be severely limited. Adequate intake of vitamins A and C and folic acid can be provided by fruits and vegetables, if eaten in amounts recommended for healthy children. Iron, zinc, copper, calcium,

Table 28.49 Basic list of 6 g protein exchange foods for low protein diets.

Food	Weight (g) = 1 exchange = 6 g protein
Egg (hen's)	1 medium egg
Meat, trimmed of all fat, e.g. beef, pork, lamb, chicken	20–25 depending on cut
Processed meats, e.g. sausage, burger, salami, ham, chicken nuggets	Vary – calculate from nutritional label
Fish	
White fish, e.g. cod, haddock, plaice, baked	25
Oily fish, e.g. salmon, mackerel, sardines	30
Shellfish, e.g. prawns, crab	30
Scampi in breadcrumbs	Approx. 60 – calculate from nutritional label
Fish fingers, fish cakes	Vary – calculate from nutritional label
Cheese	
Cheddar, Edam, Gouda	25
Feta	40
Cottage cheese	Approx. 60 – calculate from nutritional label
Nuts	
Peanuts	25
Peanut butter	25
Cashew	30
Chestnuts	50

Source: From Finglas et al. [54]. Licensed under Open Government UK.

vitamins B_{12} and D are most likely to be deficient in low protein diets based mainly on LBV protein foods. Children who are less mobile and those who are less exposed to sunlight or with dark skin are at greater risk of vitamin D deficiency. Together, the diet and vitamin and mineral supplement should provide at least the reference nutrient intakes (RNI) for vitamins and minerals [205], except for children with MMA who have chronic kidney disease (CKD) (p. 262).

The amount of supplement required varies depending on the child's diet and must be assessed for the individual, including those on modular tube feeds [206]. The supplement is best given as a divided dose to enhance absorption. A list of ACBS prescribable micronutrient supplements is provided in Table 28.14. These vary in format (powders, capsules, effervescent tablets). Paediatric Seravit (unflavoured or pineapple flavour) provides a comprehensive vitamin and mineral supplement (except for sodium, potassium and chloride). The unflavoured powder can be added to infant formula or modular tube feeds, taking into account what the feed already provides, or mixed into a strong flavoured drink to mask its flavour. FruitiVits is a comprehensive supplement, an orange flavoured powder that is dissolved in water and can be used from age 3 years. Alternatively for older children Forceval Soluble Junior (suitable from age 6 years) or Forceval Soluble or Capsules (suitable from age 12 years) can be given. Forceval Soluble Junior does not contain calcium, phosphorus or sodium, inositol and choline and only small amounts of magnesium. A separate calcium supplement must be given. Forceval Soluble and Capsules differ in composition from Soluble Junior; they contain no sodium or vitamin K and only a small amount of calcium, phosphorus and potassium. An additional calcium supplement is needed. Phlexy-Vits (powder or tablets) is a comprehensive vitamin and mineral supplement suitable from age 11 years. The powder is generally taken mixed with a strong flavoured drink. If commercial vitamin and mineral supplements available from supermarkets and pharmacies are used, it is essential their composition is checked as this varies greatly between brands and invariably will not provide an adequate intake of all necessary micronutrients. Supplements should be given with a drink of water or mixed with water to dilute (as recommended by manufacturer).

Essential fatty acids

Children on low protein diets may be at risk of inadequate intakes of essential fatty acids (EFA) and their longer chain derivatives docosohexaenoic acid (DHA) and arachidonic acid (AA). LCPUFA deficiency, specifically DHA, has been reported in patients with UCD and MMA, and supplementation recommended [207]. Low plasma and red cell DHA concentrations in patients with UCD and branched chain organic acidurias have also been reported [208]. Low protein diets and modular feeds [206] need to be assessed for EFA and LCPUFA content. In the UK at least 1% of total energy intake from linoleic acid and 0.2% from α-linolenic acid is recommended for infants [205]. FAO/WHO 2008 [209] recommends for children >6 months, 3%–4% linoleic acid and 0.4%–0.6% α-linolenic of daily energy intake, and DHA for infants to be based on amounts in breastmilk and for children: 100–150 mg for 2–4 years; 150–200 mg for 4–6 years; 200–300 mg for 6–10 years. Red cell and plasma fatty acid profiles should be measured if there are concerns about possible deficiency. Red cell measurements more accurately reflect long-term EFA and LCPUFA status. DHA is added to some of the disorder-specific precursor-free amino acid supplements used in treatment of OAA such as the Infant Anamix and Cooler ranges. KeyOmega and Doc Omega are AA and/or DHA supplements that can be added if dietary or modular feed sources are inadequate.

Monitoring a low protein diet

Clinical and biochemical

Nutritional adequacy of the low protein diet needs to be carefully monitored as deficiency states have been reported [202–204]. The following are necessary at clinic appointments: clinical examination (skin, looking specifically for

Table 28.50 Low protein fruits and vegetables allowed freely in the diet.

Fruits		
Fresh, frozen protein/100 g or tinned (fruit only weight) <1 g protein, unless stated otherwise. Fruits with >1 g protein/100 g may need to be counted as part of the daily protein intake if eaten in large portions. Many dried fruits are higher in protein content and need to be counted.		
Apples	Jack fruit	Pineapples
Apricots	Kiwi fruit	Plums
Bilberries	Kumquats	Pomegranates (1.3 g protein/100 g)
Blackberries	Lemons	Pears
Blackcurrants	Limes	Prunes
Blueberries	Loganberries	Quince
Clementines	Lychees	Raisins
Cherries	Mandarins	Raspberries (1.4 g protein/100 g)
Cranberries	Mangoes	Redcurrants
Damsons	Melons	Rhubarb
Dragon fruit	Medlars	Satsumas
Figs, not dried	Mulberries	Sharon fruit
Figs, green, raw	Nectarines (1.4 g protein/100 g)	Star fruit
Gooseberries	Olives	Strawberries
Grapefruit	Oranges	Tamarillos
Grapes	Passion fruit (2.6 g protein/100 g)	Tangerines
Greengages	Papaya	Water melon
Guava	Peaches	Mixed peel
Vegetables		
Fresh cooked (vegetable weight only) <1 g protein/100 g, unless stated otherwise. Vegetables with >1 g protein/100 g may need to be counted as part of the daily protein intake if eaten in large portions.		
Artichoke	Cucumber	Parsley
Aubergine	Fennel	Parsnip (1.6 g protein/100 g)
Beans, French, green	Garlic	Peppers
Beetroot boiled (2.3 g protein/100 g)	Gherkins	Pumpkin
Cabbage boiled (1.5 g/100 g)	Herbs	Radish
Carrot	Leek (1.2 g protein/100 g)	Rocket, raw (3.6 g protein/100 g)
Capers	Lettuce, raw (1.2 g/100 g)	Squash, butternut (0.9 g protein/100 g)
Cassava	Marrow	Swede
Celeriac	Mustard and cress	Tomato
Celery	Mushrooms, raw (1 g protein/100 g)	Tomato purée
Chicory	Onion	Turnip
Courgette (2 g protein/100 g)	Spring onion	Watercress (3 g protein/100 g)

Source: From Finglas et al. [54]. Licensed under Open Government UK.

signs of protein deficiency such as rashes, hair and nails), anthropometric measurements, biochemical assessment (such as quantitative amino acids and electrolytes) and dietary assessment (checking all nutrients). At least annual assessment of the following is also important: plasma status of vitamins A, D, E, B_{12}, minerals (ferritin, Hb), trace elements (copper, zinc, selenium) (Table 1.6), bone mineral density scans (by DEXA) and plasma and red cell status of EFA and LCPUFA.

Growth

Poor growth can occur in some of these disorders and may be attributed to the disorder and low protein diet; therefore, regular monitoring is essential. It has been demonstrated [210] that a protein-energy ratio range of 6%–12% correlates with an optimal growth, BMI and % fat mass in OAA and UCD on a restricted natural protein diet (median natural protein intake at or above safe intakes [8], without use of L-amino acids). However, no description of type or amount

of HBV or LBV protein was given. It was recognised that a protein intake at the upper end of this ratio may not be possible due to the underlying metabolic defect. Data on 263 MMA/PA patients from the European registry and network for Intoxication type Metabolic Diseases (E-IMD) [211] showed that a higher natural protein energy prescription ratio and plasma L-valine and L-arginine levels were positively associated with height *z*-score, but negatively associated with amount of synthetic protein prescription and age at visit.

The nutritional intake of infants needs to be monitored frequently as they grow rapidly during the first few months and year of life. Newly diagnosed neonates and young infants should be weighed 1–2 weekly at local baby clinics; this can usually be decreased to monthly intervals by one year of age if growth is satisfactory. Parents should initially be contacted every 1–2 weeks to review weight gain and assess feed intake; thereafter, the frequency can be based on progress. Adjustments to composition and volume of low protein feeds are then made based on weight gain (to give the safe level of protein intake, provided the child is metabolically stable) and guidance given on the feeding pattern, including frequency of feeding. This regular contact can also identify any feeding problems at an early stage.

Initial dietary treatment of the critically unwell, newly diagnosed patient

Patients with 'intoxication type disorders' generally present following a symptom-free period, which can be acute or chronic. Neonates and young infants may present with a history of poor feeding, lethargy, hypotonia with relentless deterioration and progression to coma. Older children, or even adults, may present acutely at the time of an intercurrent infection or other catabolic event. The newly diagnosed patient may be very sick with metabolic encephalopathy, in intensive care with a severe metabolic acidosis and/or hyperammonaemia requiring ventilation and extracorporeal procedures and drug management to remove toxic compounds. Reversal of catabolism is essential to prevent further production of toxic metabolites and to help stabilise the child's condition.

The principles of dietetic treatment to promote anabolism are similar for both OAA and UCD:

- Stop all protein sources (to reduce the production of toxic metabolites from exogenous sources) for the minimum time possible to avoid protein deficiency and catabolism.
- Give a protein-free, high energy intake to promote anabolism: IV fluids comprising 10% glucose and electrolytes, combined with or progressing to continuous nasogastric (NG) feeds of 10%–20% glucose polymer (depending on age) ± fat emulsion; infants can be given a protein-free feed such as Energivit, as tolerated, or for older children, Basecal. Some patients progress directly to introduction of protein (see below) and may not have a period of protein-free feeds, once stabilised.
- Fluid restrictions in the ventilated child and sometimes poor tolerance of enteral feed can make provision of an adequate enteral energy intake difficult; a higher energy intake can often be achieved from parenteral nutrition (PN) via a central venous catheter (CVC) or peripherally inserted catheter (PICC) and may be preferable during the initial stabilisation period. Assess for the individual.
- Reintroduce protein within 24–48 hours of stopping and before if the acute metabolic derangement, including acidosis, has been corrected and plasma ammonia is <100 µmol/L (normal <40 µmol/L). This may be delayed in very sick infants on dialysis.
- Protein is usually commenced at 0.5 g protein/kg body weight/day and increased to the final safe level of protein intake (Table 28.47) within a few days (typically 2–3 days), depending on blood biochemistry. An age-appropriate feed is used: for infants either infant formula or EBM; for older children a paediatric enteral feed.
- If enteral feeds are not tolerated, PN is given (p. 71). A standard parenteral amino acid solution such as Vaminolact or Vamin can be used, but only the desired amount of protein (amino acids g/kg/day) given.
  For example: to provide 2 g amino acids/kg for a 3.5 kg infant
  Vaminolact provides 65.3 g amino acids (9.3 g nitrogen = 58 g protein)/1000 mL
  110 mL provides 7.2 g amino acids = 2 g/kg.
  Vaminolact, glucose and electrolytes solutions are given together, as well as lipid and vitamin solutions; combined they provide the total energy and nutrient requirements.
- As the child stabilises the IV fluids or PN can be gradually decreased, and enteral feeds (providing the same protein and energy content) increased concurrently. A PN titration plan is calculated to decrease both solutions that enables tolerance to be assessed and an adequate energy intake and the desired protein prescription to be constantly provided.
- The titration plan is based on the volume and administration rate of each PN solution and the volume of enteral feed to be given.
- Electrolytes (sodium and potassium) may need to be added to the feed to provide normal requirements for age, taking into account any contribution of these from IV fluids and medicines such as sodium bicarbonate (to treat acidosis) and sodium benzoate (to treat hyperammonaemia). Blood electrolytes should also guide intake.
- For infants, if the mother wishes to breastfeed, she should be encouraged to express several times a day to maintain a good supply of breastmilk until the baby becomes more metabolically stable; then BF can be reintroduced. This changeover from NG feeds to BF may take a few days in a baby who is still not fully alert post-extubation, has been encephalopathic and has never established full BF due to poor feeding prior to presentation. Initially a combination of some BF and NG/oral feeds may be best with progression towards full BF as the infant's oral feeding improves. Careful monitoring is necessary to ensure the infant receives an adequate intake during this period. EBM can be used to provide the protein requirement

until BF is fully established. Protein-free feeds are usually given in combination with BF while metabolic stability is being established and often long term to limit protein intake (see below).
- For children who present at an older age, a low protein tube feed (short or long term), particularly for those with a severe neurological insult or to establish a low protein diet, may be needed. When starting a low protein diet, taking a diet history is important as some children may already self-select a low protein diet and/or have specific eating habits and food choices. This is seen typically, but not exclusively, in those with UCD. This information is useful to plan the low protein diet and to help the family cope. It may be possible to continue with a self-selected low protein diet and just ensure adequate protein-free energy, vitamins and minerals are given.
- Once the child transitions from acute to chronic management, the principles of a low protein diet (p. 562) should be followed. Practical aspects of feeding and ongoing dietary treatment are described below.
- Prior to discharge the parents need to be fully educated and given clear written instructions about the dietary treatment and emergency regimen for management of illness (discussed in detail under specific disorders) and a list of contact information for the metabolic team. Liaison with local healthcare professionals, such as health visitors and the local hospital team, is also an essential part of the ongoing care package.

Examples of low protein feeds and diets for the management of OAA and UCD are given in Tables 28.51 and 28.52 (infant feeds), Table 28.53 (older child's diet) and Tables 28.54 and 28.55 (tube feeds).

Table 28.51 Standard infant formula and Energivit (protein-free feed) for 3-month-old male infant.

Weight = 5 kg, to provide 1.36 g protein/kg, 150 mL/kg (total volume = 750 mL)

	Energy				
	(kcal)	(kJ)	Protein (g)	CHO (g)	Fat (g)
540 mL SMA Pro First Infant Milk (68 g powder)	362	1520	7	39	19
250 mL Energivit	185	777	–	25	9.5
Total	547	2297	7.0		
Per kg	109	459	1.4	–	–
Energy requirement per kg*	96	403			
	480/day	2106/day			
Safe protein intake¶			1.36 g/kg/day		
Energy %			5.1	47	47

*Dietary reference values for energy, SACN [212].
¶ FAO/WHO/UNU safe level of protein intake (Table 28.47). Provides only 5% of daily energy (see p. 566).

Table 28.52 Protein-free modular feed.

	Energy						
	(kcal)	(kJ)	CHO (g)	Protein (g)	Fat (g)	Sodium (mmol)	Potassium (mmol)
55 g Maxijul	209	888	52	—	—	0.5	0.1
40 mL Calogen	180	756	—	—	20	0.1	—
10 g Paediatric Seravit*	30	126	7.5	—	—	0.1	0.1
25 mL Normasol						3.9	
5 mL KCl solution (2 mmol/mL)							10.0
Plus water to 600 mL							
Total	419	1770	61	—	20	4.6	10.2
Per 100 mL	70	295	10.2	—	3.3	0.8	1.7

*The dose of Paediatric Seravit is adjusted according to normal recommendations [205] taking into account the amount provided by infant formula (i.e. the protein source).
Sodium and potassium per 100 mL is similar to standard infant formula.

Infant feeding

Breastmilk or a whey-based infant formula should provide the main protein source for infants. Some centres choose to provide some of the daily protein allowance as EAA for UCD infants or precursor-free amino acids for MMA/PA/IVA infants; this will be discussed in the disorder-specific sections.

Breastmilk has many immunological and nutritional benefits. In the normal population breastfed babies produce significantly less propionic acid compared with formula-fed babies [213], so theoretically breastfed infants with MMA or PA may have the additional benefit of reduced gut propionate production. Despite only a few published reports of BF in babies with UCD and OAA [214–216], demand BF can be successful provided there is regular monitoring of growth and metabolic status. BF can be difficult to establish in a baby who has been sick and not breastfed for several days; mothers need support and encouragement to express. They may feel anxious about not knowing how much protein the breastmilk is providing. If demand BF provides too much protein, this can be reduced by supplementary protein-free bottle feeding before some or all breastfeeds. The volume of protein-free infant formula to give before breastfeeds can be calculated: (daily fluid requirements) − (volume of breastmilk to provide prescribed amount of protein) = volume of specialised infant formula required.

For example, for a 4 kg infant, age 1 month:
Total daily fluid requirements = 170 mL/kg/day; safe level of protein intake = 1.77 g/kg/day (Table 28.47) = 7 g protein/day
Daily fluid requirements = 680–540 mL breastmilk (1.3 g protein/100 mL = 7 g protein) = 140 mL protein-free infant formula given as 35 mL before four breastfeeds

If a whey-based infant formula is used, the volume is adjusted to provide at least the safe level of protein intake for age, or more if clinically indicated, and combined with a protein-free infant formula (Table 28.51). If not available, a modular low protein feed that is similar in composition to standard infant formula, but protein-free, can be used (Table 28.52); this is more complex for parents. Several nutritional companies (e.g. Abbott, Mead Johnson, MetaX, Milupa, Nutricia) produce protein-free infant formulas, but only Energivit (Nutricia) is available in the UK. The protein-free formula can be either mixed with the standard formula or given on demand after each protein feed. It is useful to specify a minimum amount the infant should consume.

Dietary management of GA1 differs. The amount of natural protein from breastfeeds or standard infant formula is based on lysine intake and combined with a lysine-free, low tryptophan infant formula (p. 583).

Introduction of solid foods

Normal weaning practices are followed, starting at the usual time of around 6 months (26 weeks) of age: solids are introduced at one meal then two and three times per day and the infant progresses from smooth purées to lumpier foods and finger foods during the first year. The first solids given are protein-free such as fruit or low protein vegetable purées (Table 28.50) or very low protein manufactured foods such as Aminex rusk and Promin low protein pasta meal that are available on ACBS prescription, or commercial baby foods containing <0.5 g protein/100 g (predominantly fruit purées), so, if refused, the total protein intake is not affected. Once these are accepted, protein-containing solids are introduced from either commercial baby foods or homemade foods such as potato, vegetables or cereals. Protein exchanges should be gradually introduced, and intake carefully monitored to ensure adequate is being provided at all times from a combination of feed and food and thus avoid risk of protein deficiency. It is best to have a flexible approach as to when the protein food should be given; some infants may take this best before (if not too hungry) or between feeds. One gram of protein from infant formula is replaced by 1 g of protein from solids. This is less easy to regulate in the breastfed infant as the protein intake is not known. Therefore, an aim for total protein intake (usually the safe level of protein intake) is set; each breastfeed will then equate to an amount of protein, e.g. one feed = 2 g protein, and as the protein exchanges from solids are introduced, the number of breastfeeds is reduced to compensate.

It is important to ensure that an adequate energy intake is provided by exchanges and free foods; otherwise breastfeeds will not be reduced sufficiently; each 1 g protein from breastmilk provides around 52 kcal (217 kJ). The energy content of protein exchanges can be increased by adding butter or margarine to savoury foods. In both the bottle and breastfed infant, this process of introduction of solids is continued throughout the first year of life or so and is dictated by what the infant can manage, until all the protein is provided by solid food. Ideally the protein exchanges should be evenly distributed between main meals. During this changeover period, it is important to ensure that vitamin and mineral intake is adequate, the supplement being introduced or increased with the progressive change to solids, as these foods are a poorer source of micronutrients than infant formula and breastmilk.

Some patients never progress onto solids or take very small amounts because of feeding difficulties. This is discussed in more detail in disorder-specific sections. If precursor-free L-amino acids form part of the diet, progression to a product suitable for older infants or children is appropriate. If the infant does not progress onto solid foods, then a change from infant formula to a paediatric enteral feed during early childhood is indicated to provide the base (and protein source) of a low protein feed. This may be an oral or tube feed or combination of both.

Diet in childhood

Throughout childhood protein intake is increased to provide around the safe level (Table 28.47) for age or more if clinically indicated. This is given in conjunction with an adequate energy, vitamin and mineral intake for age as described

above. It is important to ensure the child consumes a variety of LBV protein foods (Table 28.48). HBV foods, if the daily protein intake allows, can provide some protein (Table 28.49). Choices could include thin sliced meats (ham, chicken or turkey), fish in oil, cheeses (processed cheese triangles, cream cheese), hot dog sausages, fish fingers, Quorn products, eggs, fromage frais and yoghurt (choosing the highest energy varieties) and custard-style desserts. If the daily protein allowance as food is not all eaten, it should be replaced with fluids; a measured volume of cow's milk with added glucose polymer to 15%–20% final CHO concentration is often the simplest way to do this. Some children are poor eaters and will not achieve an adequate energy intake from the diet. Some ideas to help are:

- frying foods, adding butter, margarine, vegetable oil, mayonnaise or double cream (1 g protein and 270 kcal [1.1 MJ] per 60 mL) to savoury foods such as pasta, rice or potato
- adding sugar, glucose polymer or double cream to desserts
- high CHO drinks (>10% concentration) or adding glucose polymer to drinks to a final concentration of 15%–25% CHO, depending on age
- low protein crisps, e.g. cassava snacks, prawn crackers, corn curls
- very low protein milks, e.g. Prozero, SnoPro, can be used to make milkshakes and desserts and can be poured onto breakfast cereals

Table 28.53 provides an example of a low protein diet.

Table 28.53 Low protein diet for 6-year-old girl.

Very low protein foods such as fruits and some vegetables are allowed freely and not counted as part of the daily protein intake.

Weight = 18 kg, to provide safe protein intake = 0.89 g protein/kg (16 g protein)

	Protein (g) (using 1 g protein exchanges)
Breakfast	
20 g Cornflakes and sugar	2
Protein-free milk*	
Potato waffle (weight will vary)	1
Mid-morning	
Biscuit, crisps, cake	2
Packed lunch	
2 thin slices bread	4
Butter or margarine	
Lettuce, tomato, cucumber and mayonnaise	
Violife cheese	0
40 g fromage frais	2
Portion fresh fruit	
Evening meal	
105 g cooked rice fried with chopped onion, garlic, tomato, green beans	3
40 g sweetcorn	1
30 g ice cream	1
Tinned fruit in syrup	
Bedtime	
Protein-free milkshake*	

Energy supplements: A daily dose of glucose polymer and/or fat emulsion may be necessary if insufficient energy is provided by the diet.

Low protein special foods: Can provide extra energy and variety in the diet as necessary.

Vitamin and mineral supplement: e.g. 1 sachet of FruitiVits or 25 g Paediatric Seravit is recommended for this age, but a lower dose may provide an adequate intake depending on vitamins and minerals provided by the diet.

*Protein-free milk alternatives, e.g. ProZero, SnoPro, Loprofin Drink.

Feeding problems and tube feeding

Some children with UCD [199, 217, 218] and OAA [206, 219, 220] have extensive feeding difficulties, and tube feeding is necessary to maintain metabolic stability and promote normal growth, which can be difficult. Feeding issues may be due to neurological impairment, poor appetite, slow feeding and food refusal, vomiting, retching, GOR and biochemical instability. Some of these problems can be present from diagnosis or be acquired, particularly during episodes of metabolic decompensation. Poor appetite, limited food variety and lengthy mealtimes have been reported as the main feeding problems identified by caregivers of children with OAA and UCD [221]. This pilot study also identified inadequate attention to the social aspects of eating as a key issue, with most children regularly eating alone. Involvement of a speech and language therapist and a psychologist at an early stage may help manage some feeding and behavioural problems. Issues to consider when feeding different age groups of children with PKU are provided in Table 28.20 and some of these suggestions may be useful.

If tube feeding is necessary, a low protein modular feed is designed to meet the specific therapeutic dietary needs of the child's disorder. A measured volume of a standard paediatric feed is used to provide the prescribed protein intake, with other single ingredients added to meet normal energy and nutrient requirements: glucose polymer, fat emulsions, vitamins, minerals and electrolytes. Alternatively, a protein-free feed such as Basecal, which is a similar composition to paediatric feeds but protein-free, can be used and is easier for parents and helps ensure overall nutritional adequacy [206, 222]. It is important to ensure adequate fluids and fibre are given (using a paediatric feed containing fibre or adding a fibre supplement to the feed). Some children have increased fluid requirements, including those with GA1 who have increased muscle tone or those with MMA and CKD. The

additional fluid is given as water, either between feeds or extra water with tube feed flushes; this is often better tolerated than adding to the feed volume. Examples of low protein feeds are shown in Tables 28.54 and 28.55. Gastrostomy feeding is recommended in preference to NG feeding for children who require long-term tube feeding. It is important that parents and caregivers have adequate training in safety aspects of home enteral feeding and regular training updates as incorrect practices may increase a child's risk of metabolic decompensation [221]. PEG-J (percutaneous endoscopic gastro-jejunostomy) feeding is a useful option for those with ongoing vomiting problems.

Table 28.54 Low protein tube feed for a 4-year-old girl.
Weight = 15 kg

	Energy						
	(kcal)	(kJ)	CHO (g)	Protein (g)	Fat (g)	Sodium (mmol)	Potassium (mmol)
550 mL PaediaSure	556	2335	60	15.4	27.5	14.3	15.4
120 g Maxijul	456	1915	114	–	–		
60 mL Calogen	270	1134	–	–	30.0	0.2	–
5 g Paediatric Seravit	24	102	6.0	–	–	–	–
16 mL NaCl (1 mmol/mL)						16	
8 mL KCl solution (2 mmol/mL)							16.0
Plus water to 1200 mL							
Total	1306	5486	180	15.4	57.5	32	31.6
Per 100 mL	108	457	15	1.3	4.8	2.7	2.6
Per kg	87	365		1.0		2.1	2.1
Energy requirement per kg*	85 1275/day	357 5.3 MJ/day				12–30	15–28
Safe level of protein intake†				0.86 g/kg/day			
Energy %			55	5	40		

Electrolytes, vitamins and minerals need to be individually determined considering any additional intake from food or medicines.
* Dietary reference values for energy, SACN [212].
† FAO/WHO/UNU safe level of protein intake (Table 28.47).

Table 28.55 Low protein tube feed for a 10-year-old boy.
Weight = 32 kg

	Energy						
	(kcal)	(kJ)	CHO (g)	Protein (g)	Fat (g)	Sodium (mmol)	Potassium (mmol)
1040 mL Nutrini	1040	4368	128	29	46	27	29
215 g Basecal (5 sachets)	1000	4195	150	–	44.5	18	25
Plus water to 1800 mL							
Total	2040	8563	278	29	90.5	45	54
Per 100 mL	113	475	15.4	1.6	5	2.5	3
Per kg	64	268		0.91			
Energy requirement per kg*	64	270				15–50	24–50
	2030/day	8.5 MJ/day					
Safe level of protein intake†				0.91 g/kg/day			
Energy %			54	6	40		

* Dietary reference values for energy, SACN [212].
† FAO/WHO/UNU safe level of protein intake (Table 28.47).

Disorders of propionate metabolism: methylmalonic acidaemia (MMA) and propionic acidaemia (PA)

Enzyme

MMA – methylmalonyl-CoA mutase-apoenzyme or its cofactor 5-deoxyadenosylcobalamin (vitamin B_{12})
PA – propionyl-CoA carboxylase

Biochemical defect

Defects in the final steps of the catabolic pathways of the four EAA isoleucine, valine, threonine and methionine. Cholesterol side chain and thymine and uracil metabolism are also affected but are of lesser significance (Figure 28.8):

- PA results from mutations in the PCCA or PCCB genes encoding the α- and β-subunits, respectively, of propionyl-CoA carboxylase, a biotin-dependent enzyme which catalyses the conversion of propionyl-CoA to D-methylmalonyl-CoA. Metabolites increased include high plasma propionylcarnitine, glycine, alanine and urinary methylcitrate and 3-hydroxypropionate [223].
- MMA results from mutations in either the MUT locus encoding the methylmalonyl-CoA mutase-apoenzyme causing low to moderate (mut^-) or absent (mut^0) activity or one of the proteins involved in the synthesis of its active cofactor adenosylcobalamin, classified as cobalamin (cbl) A, B, D (variant 2, which is very rare) deficiency. The conversion of methylmalonyl-CoA to succinyl-CoA (for entry into the Krebs cycle) is impaired, so methylmalonyl-CoA accumulates with greatly increased amounts of methylmalonic acid in plasma and urine. The compounds found in propionic acidaemia also accumulate (as above) [223].

Propionate (in the form of propionyl-CoA) is formed from three main sources, not just from amino acid catabolism, approximately:

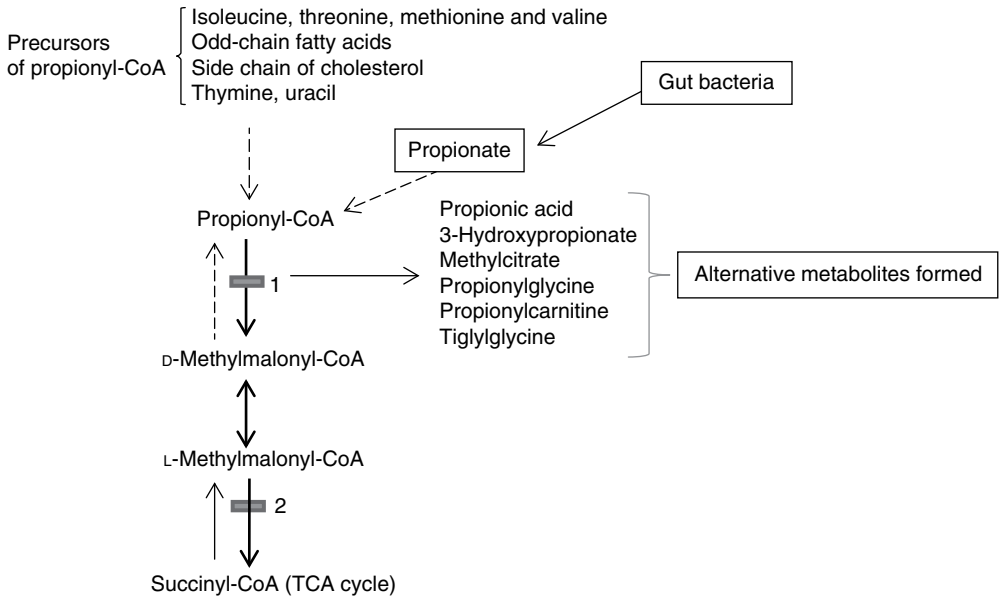
- 50% from the catabolism of the precursor amino acids isoleucine, valine, threonine and methionine [224]
- 25% from anaerobic bacterial fermentation in the gut [224]
- 25% from the oxidation of odd-numbered long chain fatty acids (C15 and C17) [225] and other metabolites. These odd-chain fatty acids are synthesised by the normal pathway of fatty acid synthesis, but propionyl-CoA acts as the primer instead of acetyl-CoA – hence the additional odd number of carbons in the chain [226]

Genetics

Autosomal recessive inheritance

Newborn screening

No newborn screening in the UK. The impact and clinical benefits of screening in other countries continue to be discussed [227, 228].



1 Propionic acidaemia due to deficiency of propionyl-CoA carboxylase, a biotin dependent enzyme
2 Methylmalonic acidaemia due to deficiency of Methylmalonyl-CoA mutase, an adenosylcobalamin dependent reaction

Figure 28.8 Disorders of propionate metabolism.

Clinical onset presentation, features

Patients can present at any age with acute or chronic symptom, but usually in the neonatal period: 65% PA, 48% MMA [229]. Common biochemical and clinical features occur due to accumulation of propionyl-CoA and other metabolites:

- *early-onset form:* acute deterioration with poor feeding, vomiting, lethargy, hypo- or hypertonia and dehydration that can progress to coma and death if untreated; biochemical findings include a severe metabolic acidosis with elevated anion gap (although not always) [228, 230], ketoacidosis, lactic acidosis and hyperammonaemia
- *late-onset form:* later in infancy or childhood with less severe symptoms including failure to thrive and developmental delay, recurrent vomiting, ketoacidosis, acute metabolic decompensation; a movement disorder may also develop [223]

Long-term complications and outcome

Outcome varies widely – The mechanisms of toxicity are complex and not completely understood; for detailed reviews of the pathophysiology, refer to Kölker *et al*. [231] and Haijes *et al*. [232]. Accumulating toxic metabolites and mitochondrial impairment are considered causative factors. Survival rates have improved in the last decade, but early deaths still occur [220, 233, 234]. Early onset is associated with poorer outcome. Outcome in MMA is best predicted by vitamin B_{12} responsiveness, enzymatic subgroup, age at onset and birth decade. Mut° and cblB patients have the poorest outcome, mut⁻ and vitamin B_{12} responsive patients have a much better long-term outcome, although they remain at risk of metabolic decompensation and long-term complications such as CKD [233, 234].

Multiple body systems – Can be affected in both disorders even with current treatment strategies. Recognised complications include acute injury of the basal ganglia (known as metabolic stroke) causing mental and motor retardation and movement disorders, epilepsy (more prevalent in PA), cardiomyopathy [235] and long QT syndrome (more prominently in PA) [236], pancreatitis [237], optic nerve atrophy [238], immune dysfunction, recurrent infections and pancytopenia and CKD (in MMA) [239, 240]. These complications may arise during episodes of metabolic decompensation and/or are due to a more chronic deterioration of organ function [241].

IQ/developmental outcomes – Range from normal to significant intellectual disability in both disorders [233, 234, 241]. In PA the frequency of metabolic crises is reported to be negatively correlated with IQ [220].

Faltering growth is common – The causative factors are likely to be multifactorial and remain to be fully elucidated [220, 234]. Early-onset and progressive growth retardation is seen in PA [220]. Growth retardation is also reported in MMA [211, 241]; CKD may be one of the contributing factors as this is a feature of CKD *per se* [242]. Failure to thrive is reported as more common in MMA mut° patients than the other enzymatic subgroups [233].

Acute management

The newly diagnosed patient may be very sick, with a severe metabolic acidosis (with increased anion gap), ketoacidosis, lactic acidosis and hyperammonaemia in intensive care requiring ventilation and extracorporeal detoxification (to remove ammonia and toxic compounds). Protein intake is stopped, and IV glucose (at least 10%) is given to reverse catabolism and is a crucial part of the initial management to help stabilise the child (p. 567), [241].

Medical treatment

Pharmacotherapy

Treated with some or all of these medications:

- L-Carnitine 100 mg/kg/day – conjugates with propionic acid to form propionylcarnitine and increases its excretion in urine. A lower carnitine dose may be given in MMA patients who have deteriorating kidney function and have high plasma concentrations of propionylcarnitine.
- Sodium benzoate – for treatment of hyperammonaemia.
- Vitamin B_{12} – pharmacological doses by intramuscular (IM) injection are given routinely to MMA B_{12} responsive patients.
- Sodium bicarbonate – to correct any acidosis in MMA.
- Carglumic acid (*N*-carbamylglutamate) – for treatment of hyperammonaemia during acute decompensations. Carglumic acid combined with nitrogen scavengers is reported as more effective in reducing plasma ammonia concentrations [243]. It may also be used in long term management.
- Metronidazole (antibiotic) – to suppress gut production of propionate [244]. It is usually given intermittently, but administration between centres varies. Its clinical efficacy has never been proven in randomised controlled trials. Metronidazole is not used by all centres routinely.
- Additional medicines are given to treat specific complications such as CKD in MMA, or in PA-related cardiomyopathy, CoQ_{10} supplementation may help [245].

Transplantation

Liver transplant in PA and in MMA, kidney, liver or combined liver and kidney transplants [246–248]; however, these are associated with significant risk at the time of transplant. Peri- and post-operative planning of nutritional management is crucial to avoid catabolism and possible metabolic decompensation [249]. Liver transplant is not a cure, but minimises risk of further decompensation and improves quality of life [241]; however metabolic complications may still arise, such as metabolic stroke [250]. With liver transplant some relaxation of protein is possible, but patients still have increased concentrations of plasma organic acids; ongoing close monitoring of diet is essential [249–251]. MMA children with kidney transplant need to remain on a low protein diet.

Dietetic management

The main aim is to reduce production of the toxic organic acids by:

- restriction of precursor amino acids (isoleucine, valine, threonine and methionine) by limiting natural protein intake
- avoidance of fasting to limit lipolysis and thus the oxidation of odd-chain fatty acids with release of propionyl-CoA
- provision of an adequate energy intake to limit catabolism

Parenteral nutrition should be administered when enteral protein is not tolerated at diagnosis, episodes of pancreatitis, intolerance of enteral feeds

Monitoring

Biochemical, nutritional and anthropometric monitoring are essential for optimisation of medical and dietetic management. These are described in detail (p. 577).

Emergency regimen	• During intercurrent illnesses or episodes of vomiting and GOR with intolerance of enteral feeds, patients become catabolic and are at risk of developing metabolic decompensation • Standard emergency regimen (ER) (p. 673) and/or IV fluids (10% glucose and electrolytes) are given; the usual medicines are continued (or increased) to help prevent decompensation (www.bimdg.org)
Clinical management guideline	Baumgartner *et al*. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidaemia [241]. Reid Sutton *et al*. Chronic management and health supervision of individuals with propionic acidaemia [252]. Chapman *et al*. Acute management of propionic acidaemia [253]. Jurecki *et al*. Nutrition management guidelines for propionic acidaemia: An evidence and consensus-based approach [254]. Aldubayan *et al*. Acute illness protocol for organic acidaemias, methylmalonic and propionic acidaemia [255].
Parent support group	www.metabolicsupportuk.org/

Dietary management

Low protein diet

The precursor amino acids (isoleucine, valine, threonine and methionine) do not accumulate in plasma so it is not possible to use measurement of their plasma levels to determine the intake of natural protein. Treatment is to limit dietary protein intake to around the safe level of protein for age (g/kg/day) (Table 28.47). Dietary protein is increased according to age, weight, clinical condition and quantitative plasma amino acid concentrations. However, it can be difficult to achieve a balance between provision of sufficient protein and avoiding an excess of protein that may precipitate metabolic decompensation. Too low a protein intake can have serious effects, such as poor growth, skin rashes, hair loss, vomiting and metabolic decompensation [202–204, 241]. Practical aspects of provision of low protein diets and feeds have been discussed (p. 560).

Precursor-free amino acids

Some centres provide part of the total protein intake from precursor-free L-amino acid (PFAA) supplements (no methionine, threonine, valine, isoleucine) to further reduce their intake from natural protein in an effort to improve metabolic stability, improve the quality of the low protein diet or achieve protein requirements. This appears to be a more common practice in some central European metabolic centres [200, 256, 257] and the USA [258] but is seldom used in UK centres. Prescription of PFAA supplements is highly variable and may provide up to 40%–50% of total protein intake [220, 256, 259]. However, the clinical value of PFAA remains controversial. A retrospective review of MMA/PA (137 patients) [219] concluded that PFAA supplementation did not seem to have an important role in the long-term nutritional and developmental outcome. Concerns have been raised about the high leucine content of PFAA [258]; cross-sectional data on 61 patients with MMA identified iatrogenic amino acids deficiencies (low plasma isoleucine and valine) and poor growth outcomes attributable to increased leucine intake. Data from the E-IMD registry on 250 MMA/PA patients [256] also identified low plasma valine and isoleucine levels mainly in those receiving PFAA and related this with the high leucine content of these products. Single amino acids (isoleucine and valine) are prescribed by some centres to correct low plasma levels [256, 258]; it seems ironic to have to supplement the amino acids that cannot be catabolised.

The 2014 MMA/PA guideline [241] advises PFAA should form part of the total protein intake if natural protein tolerance is below 2007 FAO/WHO/UNU safe levels of protein intake [8], making up any deficit. The 2019 PA guideline from the USA [254] recommends for individuals tolerating <100% of the dietary reference intake from intact protein to consider adding PROP medical food (i.e. PFAA) to meet 100%–120% of total protein requirement.

Metabolic balance can be achieved without PFAA; they are unpalatable and can be difficult to administer to children unless they are tube fed. If used, the amount prescribed should provide only part of the total protein intake and be based on growth and biochemical parameters, including protein status such as plasma amino acids. Dietary intakes of isoleucine, valine, threonine and methionine should be calculated and compared to FAO/WHO/UNU [8] requirements to avoid deficiency states. Leucine intake should also be calculated to avoid a high ratio of leucine to other large neutral amino acids that could cause imbalance.

PFAA supplements are available as infant formula, drink mixes, gels or pure amino acids designed for different ages. For details of presentation, composition, age suitability and preparation, refer to the manufacturers' websites: www.nutricia.co.uk, www.vitaflo.co.uk. Similar products are available outside the UK (www.abbottnutrition.com, www.meadjohnson.com, www.milupa-metabolics.com).

Avoidance of fasting

It is recommended that long fasts are avoided to limit the production of propionyl-CoA from the oxidation of odd-numbered long chain fats [225]. Mobilisation of fatty acids can be suppressed by regular 3–4 hourly daytime feeding and overnight tube feeding. Currently, overnight tube feeding is not used universally although many do receive this because of feeding problems.

Energy requirements

Resting energy expenditure (REE) is reported to be decreased in some patients when they are well [260]; however, others have described no difference between predicted and reported

REE [261]. Standard predictive equations of REE may not be a good guide to energy requirements in children with MMA as they can have an altered body composition (increased fat mass, reduced fat-free mass) and decreased renal function, which are both known to affect REE [262].

MMA B_{12} responsive patients

Vitamin B_{12} (as hydroxycobalamin) is given as an IM injection or, rarely, as an oral supplement. The dose frequency is individualized. In a cohort of 11 patients from the author's centre, this ranged from every 1–7 days (median 2 days) [263]. On treatment, urine and plasma methylmalonic acid decreases to low but not normal concentrations. Some urinary methylmalonic acid (UMMA) is still produced; concentrations vary between patients and may typically range from 200 to 900 μmol/mmol creatinine (normal 0–30 μmol/mmol) that is significantly less than non-responsive patients where concentrations can be >20 000 μmol/mmol creatinine. Horster *et al*. describe no kidney disease (creatinine clearance <60 mL/min/1.73 m^2 with UMMA excretion <2000 μmol/mmol creatinine [233]). Plasma methylmalonate (PMMA) is also much lower in B_{12} responsive compared with non-responsive patients. In the author's cohort of 11 patients, PMMA ranged from 4 to 482 μmol/L (median 44 μmol/L), normal 0–0.29 μmol/L [263]. Concentrations of PMMA increase with loss of kidney function. Dietary treatment with a low protein diet and ER is the same as for B_{12} non-responsive patients, although a more generous protein allowance may be possible.

Complications of methylmalonic acidaemia and propionic acidaemia

MMA and chronic kidney disease

Impaired renal function is a common complication in B_{12} non-responsive MMA, manifesting initially with a defect of urinary concentrating and acidification ability due to renal tubular dysfunction [264]. Glomerular failure can develop at an early age with progression to chronic and then end-stage renal failure (ESRF) during childhood or adolescence [233, 240, 265]. Deterioration of kidney function is likely to be multifactorial with methylmalonic acid itself considered nephrotoxic [266]. Development of CKD correlates with urinary MMA excretion, manifesting earlier in those with highest mean MMA concentrations [233] and in those with mut° or cobalamin B [234]. Kidney function can deteriorate markedly during episodes of dehydration, which can be caused by GI complications such as vomiting and GOR, inadequate fluid intake, repeated illness and metabolic decompensations. At the author's centre the glomerular filtration rate is measured by the IOHEXOL method, 1–2 yearly from age 2 years in MMA patients. The management of MMA and CKD (undertaken jointly with nephrologists) can be particularly challenging and involves ongoing modification of nutrient intakes, fluids and medicines based on biochemical monitoring results and clinical symptoms.

Dietary manipulations

The low protein diet used for MMA is also appropriate dietary treatment for CKD:

- Increased fluids are needed to prevent dehydration. The amount given is determined by kidney losses, blood pressure, blood urea and electrolytes. Additional water is given separate from the feed to ensure the full volume of feed is delivered. In our experience families find it easier to give water flushes between feeds rather than adding extra fluid to the feed.
- Phosphate, calcium and vitamin D. Renal bone disease is complex and begins even in the milder stages of CKD, seen biochemically as a rise in parathyroid hormone (PTH). Renal bone disease is managed by a combination of medicines and diet:
  - vitamin D analogues, e.g. 1α-hydroxycholecalciferol (alfacalcidol) to increase calcium absorption from the gut
  - if plasma phosphate is increased, dietary phosphate is restricted, although intakes may already be low because patients are on tube feeds or do not eat high phosphate foods because of protein restriction. Phosphate binders are given to lower plasma phosphate, either calcium-based (e.g. calcium carbonate) or a calcium-free binder if there is hypercalcaemia (e.g. sevelamer hydrochloride)
- In children with CKD (non-MMA), it is suggested that total calcium intake from nutritional sources and phosphate binders be in the range of 100%–200% of DRI for calcium for age (p. 253).
- Electrolytes
  - Supplements of sodium bicarbonate are often needed both to replace sodium losses and reduce acidosis.
  - If blood pressure is raised, dietary sodium intake may need to be reduced.
  - Hyperkalaemia is not usually a problem until the end stages of kidney disease when potassium intake may need to be reduced.
- Vitamin A can accumulate in serum in CKD, and this may be linked to hypercalcaemia [267]. In the UK a practice guideline suggests that vitamin A intake in CKD (non-MMA) should be less than twice the RNI; however, recent work suggests even this amount may be too high [268]. In MMA vitamin A intake should be assessed, particularly the contribution from vitamin and mineral supplements and any precursor free amino acid supplements. Intake of vitamin A around the RNI seems sensible, but this may need to be reduced if plasma concentrations are raised.
- Anaemia is a chronic complication of CKD and is treated with iron supplements and injections of erythropoiesis stimulating agents: erythropoietin β or darbepoetin α. It is important to ensure adequate iron is provided from the low protein diet (most likely to be provided from a combination of feeds and vitamin and mineral supplements).

Haemodialysis or peritoneal dialysis can result in symptomatic and biochemical improvement, with fewer episodes of metabolic decompensation [239, 269–271]. On dialysis the dietary restrictions remain necessary and are modified according to biochemical results; protein intake may be slightly increased compared with intake pre-dialysis. Glucose absorbed from the perotineal dialysis fluid contributes to the daily energy intake and should be taken into considered when assessing energy intake (p. 258).

Kidney transplant

Peri- and post-operative planning of nutrition is crucial to avoid complications of catabolism and metabolic decompensation. Haemodialysis is performed pre-kidney transplant to improve biochemical parameters. IV fluids, at least 10% glucose, are given during surgery. Post-transplant the child's usual enteral feeds and protein intake can normally be introduced immediately in the first few days based on clinical progress. PN may be used by some centres, initially. MMA children need to remain on a low protein diet.

Gastrointestinal problems

Gastro-oesophageal reflux, recurrent vomiting and retching are common in MMA B_{12} non-responsive patients and often necessitate hospital admission. In the author's cohort, 7 of 14 patients had GI symptoms; all were treated with anti-reflux medicines, and additionally a continuous overnight feed with slow daytime bolus feeds given via an enteral feeding pump was beneficial [272]. A hydrolysed protein feed helped some with GI symptoms, including diarrhoea.

Constipation is a problem observed in some, particularly in patients with PA. Maintenance of gut motility to prevent constipation is important as it may reduce propionate production. In a small study of four children, Senokot (vegetable laxative) was reported to be biochemically beneficial and to increase transit time [257]. Guidelines recommend that constipation should be treated promptly [241], and laxatives have been recommended for PA [252]. Movicol is the laxative of choice at the author's centre. Adequate fluids and feeds containing fibre (in tube fed patients) may also help prevent constipation. Probiotics may be useful to restore and balance intestinal flora [241, 254], but evidence to support this in MMA and PA is lacking.

Feeding problems and tube feeding

Anorexia and feeding problems of varying degrees are almost invariably present in children with more severe disorders. Feeding problems can be present at diagnosis and may not improve with treatment. Food and fluid refusal can be acquired during the course of the disease and is frequently associated with repeated intercurrent infections. The causative factors of feeding problems are unclear, but increased plasma propionate is a possibility. Many children have a poor appetite for solid foods. Some will only eat a few selected foods in very small amounts, occasionally changing the type of foods that they will eat. Some are difficult feeders; parents complain of children being slow, fussy, retching or self-inducing vomiting. Children with MMA have a preference for salty foods, e.g. crisps, tomato ketchup, chips and salt, and may select these to compensate for increased urinary losses of sodium.

Achieving optimal growth in MMA and PA can be difficult and although considered to be attributable to the low protein diet, other factors may also contribute. Enteral feeding via gastrostomy (particularly if there is vomiting) or NG tube is essential to provide an adequate dietary intake, to prevent metabolic decompensation and to help the parents cope with a child who is difficult to feed. In the author's centre 12 of 14 patients with B_{12} non-responsive MMA had feeding problems, and 11 required long-term tube feeding; feeding problems were much less common in MMA B_{12} responsive patients, and only 1 was tube fed [272]. In a European cohort, gastrostomy feeding was necessary in 27 of 55 patients with PA to ensure growth and metabolic stability [220]. European surveys of dietary practices in PA report 63% (117/186) [200] and in MMA 42% (90/215) patients [273] were tube fed. Early insertion of a gastrostomy in infants and young children has been recommended [252]. A PEG with a jejunal extension tube (PEG-J) can also be helpful in the management of episodes of vomiting and pancreatitis.

Pancreatitis

Pancreatitis is a recognised complication of both MMA and PA and may be either a single acute episode or recurrent acute episodes [220, 234, 237]. In some cases it is associated with an intercurrent illness. The pathophysiology of pancreatitis is not clear. The child's usual dietary restrictions should continue irrespective of the feeding intervention used to treat pancreatitis. A period of PN (in mild and severe) is likely to be needed. Alternatively NG/gastrostomy/jejunal feeds may be possible. A standard parenteral amino acid solution such as Vaminolact or Vamin can be used but should only provide the desired amount of protein (amino acids g/kg/day). However, in severe pancreatitis additional protein may be needed as protein catabolism can be substantial in response to the severe inflammation and, thus, increase requirements [274]. Further details about the dietetic management of pancreatitis can be found on p. 186.

Emergency regimens for management of intercurrent illness

During intercurrent illnesses or episodes of vomiting and GOR with intolerance of enteral feeds (common in some), patients are at risk of developing metabolic decompensation. Development of new neurological signs, including metabolic stroke, are reported following episodes of acute metabolic decompensation [220, 275]. In MMA there is the added risk of dehydration and deterioration of kidney function. To help prevent catabolism and metabolic decompensation, the

standard ER (p. 673) and extra fluid are given, and usual medicines are continued (e.g. carnitine, sodium bicarbonate); doses may be increased and additional medicines given if ammonia levels are high. It is important to treat pyrexia. If the child is vomiting at home and the full volume of ER is not able to be administered or tolerated, the child should be admitted to hospital without delay, because of risk of metabolic acidosis, for treatment with IV fluids (10% glucose and electrolytes) (www.bimdg.org). The usual protein intake is stopped for the minimum time possible to prevent protein deficiency, which could greatly exacerbate the effects of illness. Protein is normally reintroduced early (within 24–48 hours) and over a period of 1–2 days depending on biochemical results (such as ammonia, blood pH and gas, bicarbonate, ketones) and the clinical condition of the child. Obviously, a more rapid reintroduction of protein is beneficial. Practical advice on protein reintroduction is given on p. 678. Continuation of an adequate energy intake is important throughout this period.

Emergency regimen – fluid recommendations

In MMA a generous fluid intake needs to be given to prevent dehydration and deterioration of kidney function. The ER should provide the child's usual maintenance fluid intake and more (this needs to be assessed on an individual basis taking into account the child's kidney function); 24 hour continuous tube feeds are suggested to administer the full fluid intake. The usual dose of sodium bicarbonate may need to be increased. For IV fluids the BIMDG emergency protocols suggest that 120% maintenance fluids are given. If a child becomes dehydrated, more fluids will be needed, the daily amount usually guided the nephrologist.

Table 28.56 Routine biochemical monitoring in methylmalonic acidaemia and propionic acidaemia.

Blood	Comments
Quantitative plasma amino acids	Glycine is usually increased
	Alanine is generally increased if lactate is increased
	If precursor amino acids or or other essential amino acids are low, consider increasing natural protein
Plasma acylcarnitines	Propionyl carnitine is increased
	Higher concentrations are seen in MMA as kidney disease progresses
	Other acylcarnitines can also be increased, e.g. free carnitine, acetyl carnitine
Plasma methylmalonate (MMA only)	Increases to higher concentrations as kidney function deteriorates in MMA
Urea, creatinine and electrolytes	Urea is often low on a restricted protein diet
	Urea and creatinine increase as kidney function deteriorates in MMA
Full blood count	May have neutropenia, particularly during illness
Blood gas, bicarbonate	Possible metabolic acidosis
Ammonia	May be raised
Lactate	May be raised
Urate	May be raised, treated with allopurinol
Amylase and lipase	Will be raised during episodes of pancreatitis
GSH, GSSG	Not routinely measured in all centres, a measure of oxidative stress
GSSG oxidised and reduced	Concentrations can be low [276]
MMA only – urine monitoring	
Urine MMA/creatinine μmol/mmol	Much lower concentrations in B_{12} responsive MMA
Urine methylcitrate/creatinine μmol/mmol	Much lower concentrations in B_{12} responsive MMA
MMA only – to monitor kidney function	
PTH, vitamin D, calcium, phosphate, alkaline phosphatase	To monitor renal bone disease
Ferritin, Hb, TIBC, TSAT	To monitor iron status and anaemia of chronic kidney disease
Vitamin A in MMA	Can be raised
Lipids – triglycerides and cholesterol	Can be raised
Glomerular filtration rate	1–2 yearly from age 2 years, less frequently may be appropriate in B_{12} responsive MMA

MMA, methylmalonic acidaemia; GSH, glutathione; GSSG, glutathione disulfide; PTH, parathyroid hormone; Hb, haemaglobin; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

Parenteral nutrition

Inadequate nutrition in these disorders leads to catabolism, making the metabolic disturbance worse. Some patients can have frequent episodes of vomiting and acidosis and need repeated hospital admissions. If protein reintroduction is often interrupted or delayed or not possible, an early resort to PN is essential as there is risk of catabolism and deficiency. PN can reverse the catabolic spiral and improve the metabolic state. Provision of PN in these disorders is described p. 567. Placement of a portacath may be considered in any child who has frequent episodes of illness and if their IV access is difficult. However, this needs to be carefully considered because of the risk of line infection precipitating metabolic decompensation [252].

Clinical and biochemical monitoring in MMA and PA

Monitoring of the nutritional aspects of a low protein diet has been discussed (p. 565). Routine biochemical monitoring is shown in Table 28.56. Baseline DEXA is recommended at age 10 years and follow-up according to bone health status [241].

Learning points: methylmalonic acidaemia and propionic acidaemia

- *Dietary management is a restricted protein diet (further manipulations of diet and fluids are needed when there is chronic kidney disease) and emergency regimen for use during intercurrent illness*
- *Outcome varies with Mut° and cblB patients having the poorest outcome, followed by mut⁻ and cblA*
- *Vitamin B_{12} responsive patients have a much better long-term outcome*
- *Multiple body systems can be affected with complications including cardiomyopathy, chronic kidney disease, pancreatitis and optic nerve atrophy*
- *Episodes of metabolic decompensation need to be treated promptly to help prevent further organ damage and neurological insult*

Isovaleric acidaemia

Enzyme	Isovaleryl-CoA dehydrogenase
Biochemical defect	Deficiency of isovaleryl-CoA dehydrogenase, which catalyses the third step of leucine catabolism: the conversion of isovaleryl-CoA to 3-methylcrotonyl-CoA (Figure 28.3). Isovaleryl-CoA, isovaleric acid, isovaleryl (C5) carnitine and other metabolites accumulate. During remission the majority of isovaleryl-CoA is conjugated to glycine to form isovalerylglycine that is not toxic and is excreted in large amounts in urine. Similarly isovaleryl-CoA is also conjugated to carnitine to form isovalerylcarnitine and excreted in the urine. During acute episodes the natural capacity of this detoxification pathway is exceeded, and isovaleryl-CoA is deacylated to produce large amounts of toxic isovaleric acid, which may cause an overwhelming illness [277]. The mechanism of toxicity is not clear, but accumulating toxic metabolites are known to cause synergistic inhibition of the TCA cycle and ureagenesis [229].
Genetics	Autosomal recessive inherited disorder. Mutations in the IVD gene are highly heterogeneous, and no genotype–phenotype correlation has been identified [277], except in those diagnosed on newborn screening (NBS) with the c.932C>T mutation, who have a much milder phenotype [278].
Newborn screening	NBS on day 5 of life in the UK. Screening is by measurement of C5 acylcarnitines in dried blood spots using tandem mass spectrometry. More information on UK screening, diagnostic and clinical management protocols can be found at www.bimdg.org and www.gov.uk. *Newborn blood spot screening: laboratory guide for IMDs* (inherited metabolic diseases). Some infants present clinically before the screening test or the results are reported.
Clinical onset presentation, features	*Early-onset (acute) form:* Neonates present within the first days/weeks of life [279], commonly with poor feeding, vomiting, metabolic acidosis, hyperammonaemia and lethargy progressing to coma. Their subsequent course follows the chronic intermittent course. A characteristic smell of 'sweaty feet' may occur when the child is unwell. *Late-onset (chronic) form*: Children may present with more chronic, non-specific symptoms of failure to thrive and/or developmental delay or mental retardation. Late onset can also present with vomiting, impaired consciousness and acute metabolic crises. The spectrum of presentation with chronic forms is wide. The E-IMD registry provides detailed information about symptoms seen at the presentation in early- and late-onset patients with isovaleric acidaemia (IVA) (n = 52) [229].
Long-term complications and outcome	Outcome is variable ranging from normal neurocognitive outcome/psychomotor development and less commonly to severe mental retardation [279]. Neonatal presentation is associated with high mortality, but those who survive the acute episode have a better neurocognitive outcome than patients with a late diagnosis [279]. Expanded NBS may improve the mortality of neonatal onset, provided screening is done early; those with neonatal onset will present within the first week. IVA is not considered to be a progressive disorder. There are no reported major long-term complications. Acute pancreatitis is reported in a few cases both pre- and post-diagnosis. [279, 280]. The author is aware of several other unpublished cases in the UK.

Acute management	The newly diagnosed, clinically presenting infant is likely to be very sick with metabolic acidosis (with elevated anion gap), hyperammonaemia, elevated lactate and urinary ketones and requires intensive care. Initial management to stabilise the infant is to promote anabolism by giving IV glucose 10% and to reduce production and increase excretion of isovaleric acid by giving IV carnitine. Protein intake is stopped temporarily.
Medical treatment	*Pharmacotherapy* L-glycine and L-carnitine, either or both, may be prescribed: • L-glycine (150–300 mg/kg/day) • L-carnitine (50–100 mg/kg/day) [281] Both conjugate with isovaleric acid producing non-toxic conjugates (isovalerylglycine, isovalerylcarnitine) that are excreted in urine; hence isovaleric acid levels are reduced [282–284]. These medicines are particularly important during periods of metabolic decompensation. The need for both medicines in a stable child is controversial [284–286], and prescribed doses vary [279]. Medicines should be individually prescribed as response can vary [287, 288].
Dietetic management	The aim is to minimise the formation of isovaleric acid by: • limiting dietary intake of leucine (protein). Leucine does not accumulate in plasma so measurement of this cannot be used to determine protein intake • provision of adequate energy intake to prevent catabolism and promote normal growth and development Mutation c.932C>T is a mild phenotype – protein restriction is not necessary, but an ER for management of illness is recommended [278].
Monitoring – biochemical and nutritional	There is no established laboratory marker for monitoring therapeutic control. Plasma amino acids and carnitine should be monitored at routine clinic reviews. Plasma leucine is normal; it does not accumulate. Plasma glycine is increased in patients taking glycine. Isovalerylcarnitine concentrations are increased. Monitoring of the nutritional aspects of a low protein diet has been discussed (p. 565).
Emergency regimen for management of illness	• During intercurrent infections, catabolism greatly increases production of isovaleric acid with risk of metabolic decompensation • The standard ER of frequent 2 hourly drinks/feeds of glucose polymer is given day and night to prevent catabolism (p. 673) • Protein intake is stopped temporarily (24–48 hours) • Glycine and carnitine continue to be given; doses may be increased temporarily as necessary • Hospital admission for IV fluids (10% glucose, saline 0.45%) is necessary if ER is not tolerated (www.bimdg.org) • IV carnitine can be given; no IV glycine preparation exists • If pancreatitis develops the usual dietary restrictions should continue irrespective of the feeding intervention used to treat the pancreatitis • PN may be necessary; alternatively NG or NJ feeds may be possible (see p. 186) Episodes of metabolic decompensation appear to be less frequent with age [289] with no reported episodes beyond age 9 years in 21 patients [279]. However, the author is aware of episodes in older children in UK metabolic centres.
Clinical management guideline	Currently there are no published consensus treatment guidelines for IVA. European proposed guidelines using SIGN methodology for IVA can be accessed from E-IMD [290]
Parent support group	Metabolic Support UK www.metabolicsupportuk.org

Dietary management

A European survey [201] of 133 patients from 38 centres reports that dietary management varies and natural protein intake does not always provide the FAO/WHO/UNU safe level of protein intake [8]. Leucine-free L-amino acid (LFAA) supplements were prescribed by 18 centres (none from UK). The data was collected prior to the E-IMD web-based IVA guidelines [290], which recommend limiting natural protein intake to provide at least the safe intake of protein. No recommendation to supplement LFAA is given. In the author's experience, the use of LFAA is generally not warranted as metabolic stability is achievable on natural protein restriction alone, plus carnitine and/or glycine.

Practical aspects

- Practical management of low protein diets and feeds is described on p. 560
- Natural protein should be limited, but to provide at least the FAO/WHO/UNU 2007 safe intake of protein for age [8, 290]. A more relaxed protein intake than this is often possible (around 2 g/kg in infants and young children, decreasing to between 1.5 g and 1 g/kg in older patients, although some have higher intakes and remain metabolically stable)
- Some patients, often those who present later, are not on a 'counted' protein intake and remain stable on a self-selected low protein diet, or they just avoid high protein foods, which can be the case in older patients who are on a more relaxed diet [291]

- Infants can be exclusively breastfed and remain stable. If necessary a small volume of protein-free formula can be given pre-breastfeeds to limit protein intake (p. 569)
- An adequate energy intake provided to promote anabolism and normal growth and development and to help limit production of isovaleric acid
- Vitamin and mineral supplements are usually needed even in those on a relaxed protein diet. Intakes should be assessed and biochemically monitored (p. 565)
- Most children with IVA appear to have a reasonable appetite and grow normally, but major feeding problems can occur in some, and tube feeding may be necessary [279, 289]. Only 8 of 133 patients were reported to be tube fed in a European survey of feeding practices [201]

Learning points: isovaleric acidaemia

- *Dietary management is a restricted protein diet and emergency regimen during illness*
- *L-carnitine and L-glycine are given to conjugate with toxic isovaleric acid*
- *Outcome varies from normal neurocognitive outcome/psychomotor development to, less commonly, severe mental retardation and is better in early-onset compared with late-onset presentation*

Glutaric aciduria type 1

Glutaric aciduria type 1 (GA1) is a neurometabolic disorder, first described in 1975 [292].

Enzyme	Glutaryl-CoA dehydrogenase
Biochemical defect	A deficiency of the enzyme glutaryl-CoA dehydrogenase (GCDH) in the catabolic pathway of the amino acids L-lysine, L-hydroxylysine and L-tryptophan that catalyses the dehydrogenation of glutaryl-CoA to glutaconyl-CoA and its decarboxylation to crotonyl-CoA (Figure 28.9). Biochemically there is accumulation of the metabolites glutaric acid, 3-hydroxyglutaric acid, glutaryl-CoA, glutaconic acid (to a lesser extent) and glutaryl carnitine in body fluids (urine, plasma and cerebrospinal fluid) and tissues [293]. Lysine and tryptophan do not accumulate. Patients can have either low or high urinary excretion of metabolites, termed low or high excretors; irrespectively they both remain at the same risk of striatal damage.
Genetics	An autosomal recessive disorder due to mutations in the GCDH. Worldwide the incidence is reported as 1 in 100 000 although there is a much higher incidence in some specific communities: Irish travellers [294], the Amish community in Pennsylvania, USA [295] and the Canadian Oji-Cree Indians [296]. There is no genotype/clinical phenotype correlation although there is some correlation with biochemical phenotype; those with residual GCDH activity have a low urinary metabolite excretion, while those with high excretion have no residual GCDH activity; this does not, however, predict severity [297].
Newborn screening	NBS on day 5 of life in the UK by measurement of glutaryl acylcarnitine (C5-DC) in dried blood spots using tandem mass spectrometry. More information on UK screening, diagnostic and clinical management protocols can be found at www.bimdg.org and www.gov.uk *Newborn blood spot screening: laboratory guide for IMDs* (inherited metabolic diseases).
Clinical onset presentation, features	*Clinical presentation* – Babies with GA1 who present clinically usually appear normal in the first months of life, although some have macrocephaly. The majority of patients typically present before 2 years of age with a median age of 9 months [298] following an intercurrent illness such as a respiratory or GI illness, which precipitates an acute encephalopathic crisis. Characteristically this causes irreversible striatal damage and a complex movement disorder. Severely affected patients are consequently left with a severe dystonic–dyskinetic disorder that is similar to cerebral palsy and ranges from extreme hypotonia to choreoathetosis to rigidity and spasticity [298, 299]. There is loss of mobility (partial), swallowing difficulties and dysarthria. Intellectual function is generally preserved initially. Morbidity and mortality is high in patients who have had a crisis. Some cases of GA1 never present clinically and may only be diagnosed on sibling screening following presentation of the index case [300, 301].

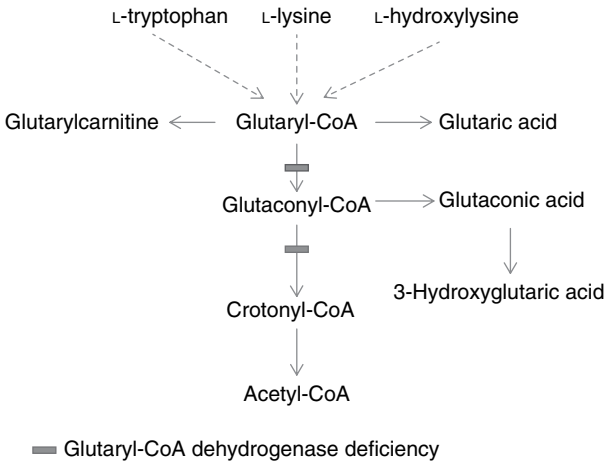


Figure 28.9 Glutaric aciduria type 1 – catabolic pathway of lysine, hydroxylysine and tryptophan.

Insidious onset – A minority of patients have a more insidious onset with no obvious encephalopathic episode preceding the development of the movement disorder [293, 302].
Late onset – Patients diagnosed after age 6 years who present with non-specific and sometimes longstanding symptoms but no dystonia; on MRI there are no striatal lesions, but predominantly white matter changes [303].
Newborn screening – Patients diagnosed on expanded newborn screening are asymptomatic [304].

Long-term complications and outcome

Patients appear to be at greatest risk of striatal injury during a finite period of brain development, between birth and 6 years. The neuropathogenesis of GA1 is not fully delineated; an overview is given by Jafari *et al*. [297]. Intraneuronal accumulation of high concentrations of glutaric acid (GA) and 3-hydroxyglutaric acid (3-OH-GA) formed by *de novo* synthesis in the central nervous system during catabolic episodes is considered to be the most important factor in precipitating neuronal damage, probably via several mechanisms: excitotoxic cell damage, impairment of energy metabolism and oxidative stress [297]. As the transport capacity for GA and 3-OH-GA across the blood–brain barrier (BBB) is low, they accumulate in very high concentrations during catabolic episodes (10- to 1000-fold higher than in plasma) and are 'trapped' in the brain [305]. Studies in GCDH-deficient mice provide evidence that lowering lysine intake and L-arginine (or homoarginine) supplementation and an increased glucose intake reduces the concentration of GA and 3-OH-GA in brain; carnitine supplementation increases formation of non-toxic glutarylcarnitine, but does not alter GA and 3-OH-GA production [306, 307].

Early detection by NBS and pre-symptomatic initiation of treatment can greatly improve the outcome, preventing the neurological handicap that develops with the clinical presentation and onset of neurological crises, provided there is good adherence to dietary treatment and emergency regimen [304, 308]. A study of 87 patients diagnosed by NBS identified that delayed emergency treatment in 12 patients caused acute-onset motor disorder (mostly severe and moderate) and of those who did not strictly follow maintenance treatment 8 of 16 developed an insidious-onset dystonia (moderate to mild) without a preceding acute event [304]. Even with good adherence, cerebral changes can still be seen on neuroimaging [309], and some may still have fine motor and speech deficits [310]. Chronic kidney disease has been reported and may manifest irrespective of treatment and good adherence [304].

Medical treatment

Carnitine supplementation: 100 mg/kg/day to facilitate production of non-toxic glutarylcarnitine from glutaryl-CoA and to avoid secondary carnitine deficiency as a consequence of its increased formation. Carnitine is also reported to have antioxidant benefits [311]. A higher dose may be needed if free carnitine levels are low. A lower dose is given beyond 6 years of age (30–50 mg/kg/day) [293].
Management of any movement disorder: Is complex and beyond the scope of this publication; recommendations are made in the 2017 guideline [293].

Dietetic management

Lowering cerebral lysine influx and lysine oxidation limits production and accumulation of neurotoxic GA and 3-OH-GA and is considered neuroprotective in pre-symptomatic patients who have not experienced a neurological crisis [308, 309].
Dietetic management is the same for high and low excretor patients and those with insidious onset:

- restriction of lysine and tryptophan (protein) intake
- lysine-free, low tryptophan amino acid supplements (LFAA) containing arginine
- provision of an adequate energy intake to limit catabolism, specifically lysine oxidation

Emergency regimen

Emergency treatment is probably the most important aspect of treatment. Prompt implementation of an ER during intercurrent illness is essential to prevent striatal injury and onset of a complex movement disorder [304]:

- The standard ER of frequent 2 hourly drinks/feeds of glucose polymer is given day and night to prevent catabolism (p. 673)
- Usual dose of LFAA continues to be given
- Usual carnitine dose is doubled (up to 200 mg/kg/day in infants and young children)
- Aggressive and prompt treatment of pyrexia

Monitoring – biochemical and nutritional

- Nutritional monitoring of low protein diets is discussed on p. 565. Severe protein and mineral deficiencies have been reported in those on low protein diets [312, 313].
- Biochemical monitoring of maintenance treatment is difficult as there is no reliable biochemical marker. Urine GA, 3-OH-GA and plasma glutarylcarnitine do not correlate with outcome [314]. Lysine and tryptophan do not accumulate in plasma.
- The 2017 guideline [293] recommends routine biochemical monitoring and frequency (1–6 monthly in children <6 years of age): quantitative plasma amino acids (in particular lysine, tryptophan) to assess nutritional status, carnitine to check depletion and adherence, full blood count, liver function tests and albumin and bone chemistry.
- Plasma lysine should be maintained in the normal reference range [293], although it can be in the lower normal reference range [314], and this is the author's practice. If plasma lysine is lower than this, the diet is reviewed as an increase in natural protein or change in type of food may be necessary, i.e. more milk-based foods if the diet is high in cereal content.
- Growth needs to be regularly monitored, particularly in dystonic patients as weight gain can be significantly reduced [314].

Clinical management guideline

Boy *et al*. Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type 1: second revision [293].

Parent support group

Metabolic support UK www.metabolicsupport.org.uk

Dietary management

The low lysine diet recommendations in the 2017 GA1 guideline [293] are based on the original 2007 [312] and 2004 [315] publications:

- A diet based on lysine is considered to be more precise than a low protein diet because the lysine content of protein-containing foods varies considerably. The original recommendations for lysine and tryptophan intake (mg/kg/day) are based on clinical practice from Germany and published safe intakes at that time for the normal population (Table 28.57) [315].
- More recent publications (FAO/WHO/UNU 2007) [8] set lysine requirements lower (Table 28.57). However, the use of these values has not been reported in clinical practice, and it is, therefore, not known if further restriction of lysine has any therapeutic advantage. It should also be borne in mind that a good outcome can be achieved with the current guideline recommendations.
- From age 6 years the risk of striatal damage diminishes; relaxation of the low lysine diet to a diet based on safe levels of protein intake is, therefore, possible and recommended [293]. However, no guidance on further relaxation of diet with increasing age is given.
- Recommendations for total protein intake (g/kg/day) (from natural protein and amino acid supplement) were given in the 2007 guideline [312], but not in the 2017 revised guidelines [293] because the natural protein intake varies widely depending on the type of food consumed to provide lysine.
- Supplements of lysine-free, tryptophan-reduced amino acids are recommended to ensure an adequate intake of all EAA [293]. Amino acid intakes (g/kg/day) from supplements are given in Table 28.57.
- If the diet is not supplemented with LFAA, natural protein intake should provide the safe levels of protein intake or more, if necessary, to ensure adequate daily lysine intake.
- A potential benefit of giving amino acid supplements is that they provide a good source of arginine. Lysine and arginine share the same cerebrovascular cationic transport system (y+system), and arginine competes with lysine for uptake at the BBB and inner mitochondrial membrane. However, high dose arginine is not recommended as a low lysine diet is considered to be more effective in lowering cerebral toxic metabolites [293].

Low protein (lysine) diet: practical aspects

The analysis of lysine content of foods in the UK is very limited and old [46]. It is, therefore, not easy to provide a low lysine diet, except in early infancy when the lysine and tryptophan content of infant formula and breastmilk is known. As weaning on to solid food progresses, a low protein diet based around the safe level of protein intake may be a more practical option to limit lysine intake. As low protein foods vary in lysine content (Table 28.58), a combination of cereal-, vegetable- and milk-based foods is needed to ensure an adequate lysine intake. If the diet contains predominantly cereal foods, lysine intake will be less than recommended. The low protein diet is combined with lysine-free, low tryptophan amino acid supplements given according to, or at least in similar amounts to, the guideline recommendations (Table 28.57).

Table 28.57 Maintenance dietary treatment for glutaric aciduria type 1.

Treatment	Age				
Low lysine diet	0–6 months	7–12 months	1–3 years	4–6 years	>6 years
Lysine (natural protein source)* (mg/kg/day)	100	90	80–60	60–50	Recommendation 6 [293] After age 6 years dietary treatment should follow an age-adapted, protein controlled protocol based on safe levels for protein intake
FAO/WHO/UNU 2007 [8] (lysine (mg/kg/day))	119–65	64 (6 months)	45 (1–2 years) 35 (3 years+)	35	
Tryptophan* (mg/kg/day)	20	17	17–13	13	
FAO/WHO/UNU 2007 [8] (tryptophan (mg/kg/day))	29–16	16	6.4 (1–2 years) 4.8 (3 years+)	4.8	
Lysine-free, low tryptophan amino acid supplement (g/kg/day)	1.3–0.8	1.0–0.8	0.8	0.8	
Protein (natural)† (g/kg/day)	1.4–1.3	1.5–1.3	1.4–1.3	1.3–1.1	
FAO/WHO/UNU 2007 [8](safe level of protein intake (g/kg/day))	1.77–1.14 (1–6 months)	1.31–1.14 (6 months–1 year)	1.14–0.9	0.9–0.89	
Protein (total)† (g/kg/day)	2.7–2.1	2.5–2.1	2.2–2.1	2.1–1.9	

* Lysine and tryptophan recommendations are based on the 1st European Workshop on GA1 (Heidelberg, 1993) and international dietary recommendations available at that time [315].
† Recommendations were given for protein and total protein intake in the 2007 guideline only [312].
Source: Adapted from [293, 312, 315].

Table 28.58 Lysine content of selected food groups.

Food	Lysine mg/g protein
Fish	90
Nuts	80
Meat	70
Milk, cheese, yoghurt	70
Eggs	60
Potato	60
Vegetables	50
Cereal/baked goods	50
Rice/barley/oats	40
Bread/pasta	30

Source: Data adapted from [312, 315].

An alternative approach to providing the low lysine diet is to provide the daily lysine intake as a prescribed number of protein exchanges from cereal-based foods and milk and milk-based foods (Table 28.58). At the author's centre, LBV protein foods are averaged to 40 mg lysine/100 g (foods shaded in grey in Table 28.58), and milk and milk based foods 70 mg lysine/g protein. More protein is given from cereal-based foods as this is more practical and manageable. Using this method the natural protein generally exceeds the safe level of protein intake; the total protein figures included in the 2007 guideline also show this (Table 28.57).

Example calculation of a low lysine diet for a 2-year-old boy, weight = 12 kg

Diet to provide: 70 mg lysine/kg/day (Table 28.57) = 840 mg lysine
Milk and milk-based foods = 5 × 1 g protein exchanges (70 mg/g protein) = 350 mg
Cereal-based foods = 12 × 1 g protein exchanges (40 mg lysine/g protein) = 560 mg
Total = 350 mg + 560 mg = 840 mg lysine
Natural protein = 17 g/day = 1.4 g/kg
Safe intake of protein [8] = 12 g protein/day = 1 g protein/kg/day

Lysine-free, low tryptophan L-amino acid supplements

Lysine-free, low tryptophan amino acid supplements are available as infant formula, e.g. GA1 Anamix Infant, or for older infants and children in a variety of formats such as gel mixes, powdered drinks, ready to drink liquid bottles, e.g. GA gel from 6 months; GA1 Anamix Junior powder from 1 year; GA Express15 from 3 years. These products contain added energy as CHO ± fat and vitamins and minerals. The tryptophan content of amino acid supplements available in the UK is 4–6 mg/g of amino acids and arginine 69–78 mg/g of amino acids. GA amino5 and XLYS TRY Glutaridon are pure amino acid supplements. As Glutaridon is tryptophan-free, it is essential that the diet provides the requirement for tryptophan as deficiency can induce neurological dysfunction [315]. Table 28.57 provides the FAO/WHO/UNU 2007 requirements [8] for tryptophan; these are mostly lower than the 2017 guideline recommendations [293]. For details of presentation, composition, age suitability and preparation of these supplements refer to the manufacturers' websites: www.nutricia.co.uk, www.vitaflo.co.uk. Similar products are available outside the UK www.abbottnutrition.com, www.meadjohnson.com, www.metax.org, www.milupa-metabolics.com.

Biochemical and haematological nutritional status are reported to be better in those taking lysine-free, low tryptophan supplements with added vitamins and minerals [316].

Infant feeding

On receipt of a positive newborn/diagnostic screening result, treatment (diet and carnitine) should be commenced promptly even before confirmation of diagnosis by enzyme and/or mutation analysis. Infants can be breastfed and/or bottle fed. The BIMDG guidelines recommends that from diagnosis to age 1 year, lysine intake is restricted to 114 mg/kg/day (1.3 g natural protein) and 1.3–1.4 g protein equivalent from LFAA, these being slightly higher than the GA1 guideline (Table 28.57). Full details can be accessed from www.bimdg.org. Lysine intake from either breastfeeds or standard infant formula is restricted by giving supplementary lysine-free, low tryptophan infant formula, e.g. GA1 Anamix Infant formula. A BF regimen will give more natural protein as lysine content is lower than in standard infant formula (89 vs. 114 mg/100 mL).

Breastfed infant

Breastmilk provides around 68 mg lysine/g of protein or 89 mg lysine/100 mL [8]. Demand BF of 150–200 mL/kg/day would provide 133–178 mg/kg/day of lysine. To limit lysine intake from breastmilk, the lysine-free, low tryptophan infant formula is given before breastfeeds; the total volume is divided and distributed evenly before five to six breast feeds.

Example of a breastfeeding regimen for an infant age 3 weeks, weight = 4 kg

Aim: Limit lysine to 114 mg/kg/day (456 mg lysine) from natural protein
Total fluids = 170 mL/kg = 680 mL/day
Estimated intake of breastmilk = 510 mL = 114 mg lysine/kg/day = 6.6 g protein (1.6 g/kg/day)
GA1 Anamix Infant = 170 mL (680 – 510 mL) = 3.4 g protein equivalent/kg = 0.9 g/kg/day)
Feeds: 35 mL × 5, before five breastfeeds, followed by breastfeeding on demand
Total protein = 6.6 g natural and 3.4 g protein equivalent = 10 g = 2.5 g/kg/day

Bottle-fed infant

Standard infant formula provides around 88 mg lysine/g of protein or 114 mg lysine/100 mL. Demand feeding of infant formula at 150–200 mL/kg would provide 171–228 mg/kg/

day of lysine. The volume of standard infant formula is limited to restrict lysine to around 114 mg/kg/day and divided between six to eight feeds, depending on feeding frequency. Lysine-free, low tryptophan formula, e.g. GA1 Anamix Infant, is then fed to appetite after the standard infant formula.

Example of a bottle feeding regimen for an infant aged 2 months, weight = 5 kg

Aim: Limit lysine to 114 mg/kg/day (570 mg lysine) from natural protein

Total fluids = 170 mL/kg = 850 mL/day

Standard infant formula 500 mL = 570 mg lysine = 114 mg/kg/day = 6.5 g protein (1.1 g/kg/day)

GA1 Anamix Infant 350 mL (850 mL – 500 mL) = 7 g protein equivalent = 1.4 g/kg/day

Feeds: 140 mL × 4 hourly × 6 feeds

First feed of 80 mL standard infant formula followed by second feed of 60 mL GA1 Anamix Infant to appetite (more is given if the infant is hungry)

A nutritional analysis for the daily feed plan is given in Table 28.59.

Weaning

Weaning onto solid foods is started at the usual time of around 6 months (26 weeks) of age and proceeds in a similar method to low protein and amino acid diets, described in more detail on p. 569. Normal weaning practices are followed: solids are introduced at one meal and then given 2–3 times per day, and the infant progresses from smooth purées to lumpier foods and finger foods during the first year. An overview of weaning stages:

- Introduce free weaning foods, e.g. fruits, vegetables (Table 28.50), low protein manufactured foods (p. 562).
- Introduce 1 g protein exchanges to provide the lysine requirement (90 mg/kg/day) or at least the safe level of protein intake for age from a variety of cereal, vegetable and dairy foods (p. 582 and Table 28.58). Protein from standard infant formula or breastmilk is replaced by food, gradually introducing 1 g exchanges of natural protein at a time using: purée potato, pasta, rice, lentils, vegetables or commercial weaning foods (dried or wet varieties in jars, pouches, packets) such as ordinary rusks, baby cereals or vegetable-based savoury foods and yoghurt and milk-based desserts.
- Start second stage lysine-free, low tryptophan amino acid supplement, e.g. GA Gel. Practical aspects of introducing more concentrated amino acid supplements are given on p. 529. Less supplement is required in GA1 compared to the amino acid disorders. One teaspoon of GA Gel is introduced from around 6 months at one meal, gradually increasing the quantity and giving at two and then three meals before solids. As Gel is increased, less GA1 Anamix is given but ensuring adequate energy, vitamins and minerals are provided by the diet and lysine-free, low tryptophan supplement. GA1 Anamix Infant feeds may continue to be given on waking and before bed until around 1 year of age. The guideline recommends 1.0–0.8 g protein equivalent/kg/day from the supplement for infants aged 7–12 months, e.g. for a 10 kg child, aged 1 year, one sachet of GA Gel provides 10 g protein equivalent = 1 g/kg and 67 mg tryptophan (=6.7 mg/kg/day), which does not provide the guideline amount of 17 mg/kg/day (Table 28.57), but does provide the more recent recommendation of 6.4 mg/kg/day [8]. The diet will provide more tryptophan. GA1 Anamix Junior powder given as a drink mix can be used from 1 year of age, each sachet providing 5 g protein equivalent and 40 mg tryptophan. Some centres introduce before 1 year.
- Low protein manufactured foods can be given to provide extra energy and variety, if necessary, e.g. low protein rusk or cereal (p. 562).

Table 28.59 Nutritional analysis of daily feed plan for male infant with glutaric aciduria type 1.
Age 2 months, weight = 5 kg

	Energy						
	kcal	kJ	Protein (g)	Protein equivalent (g)	Lysine (mg/day)	Tryptophan (mg/day)	Fluid (mL/kg)
500 mL Cow & Gate First Infant Milk (68 g powder)	330	1386	6.5	—	569	103	100
350 mL GA1 Anamix Infant (54 g powder)	251	1004		7	—	36	70
Total	581	2390	6.5		569	139	
Intake per kg/day	116	478	1.3	1.4	114	20	
Aim per kg/day	96*	403		1.3†	100†	20‡	170
					114♯	29§	

*Ref. [212].
†Ref. [293].
‡Refs. [312, 315].
§Ref. [8].
♯www.bimdg.org

- Vitamins and minerals will be provided by the lysine-free, low tryptophan supplement (if enriched with vitamins and minerals), but depending on dose may not provide the full requirements. It is important to assess the additional contribution from the diet and supplement as necessary.

Young children

During early childhood the diet is provided by a combination of foods to provide the recommended lysine intake (Table 28.57) or the safe level of protein intake (Table 28.47) for age. The LFAA supplement should provide around 0.8 g/kg/day of protein equivalent (Table 28.57). The LFAA supplement plus protein exchange foods will provide adequate tryptophan.

Diet after 6 years of age

As striatal damage occurs only during a finite period of brain development, the low lysine diet can be relaxed beyond 6 years of age; the GA1 guideline recommends avoidance of an excessive intake of natural protein and to use protein sources with a low lysine content according to safe levels of protein intake [293]. For some the natural protein intake may, however, already be greater than the safe intake, depending on food choice. No specific guidance is given on continued use of LFAA supplements. Lysine intakes of children on relaxed diet in the seventh year of life are reported to be mean ± SD 135 ± 50% of the recommendation for 4–6 year olds (60–50 mg lysine/kg/day) and a decreased LFAA intake of mean ± SD 88 ± 17%; no information of actual natural protein intake was given [314].

Current practice varies, with some centres continuing the LFAA supplement and others changing to a more relaxed controlled protein intake without using supplements. It is important relaxation of diet, and LFAA is discussed with families, and they are able to make an informed choice based on current evidence.

Dietary management of symptomatic patients

Dietary treatment in symptomatic patients who have presented with encephalopathy and neurological crises is reported to be of no or limited neurological benefit [298, 317, 318]. It is known that protein restriction cannot reverse neurological damage that has already occurred and dietary protein restriction alone is not sufficient to prevent brain injury [317–319]. The rationale for a restricted lysine or protein diet in symptomatic patients is unclear, but for some it may be helpful in prevention of any possible progressive neurological deterioration [299, 319] and is used in some centres.

Feeding problems

Feeding problems are common in the group of patients with neurological disease and include chewing and swallowing difficulties, due to dyskinesia, and GOR and vomiting, due to truncal hypotonia. The extent of these feeding problems is related to the severity of the neurological disease, with acute onset being much worse than insidious onset. Dietary advice is tailored to the individual child's needs: the use of thickened fluids, energy dense foods of the correct consistency and energy supplements may be required to achieve an adequate energy and fluid intake. Tube feeding is often essential to maintain an adequate energy intake and to achieve satisfactory growth. Nissen fundoplication (and insertion of gastrostomy) may be necessary in some patients for treatment of GOR and vomiting. Assessing energy requirements in this group of patients can be difficult; the worst patients cannot walk so should need less energy, but often energy expenditure is reported to be increased due to high muscle tone and dystonic movements and to disturbances in temperature control [299], thus emphasising the need for adjusting the diet to the requirements of the individual. Additional fluids may be required in patients who have disturbances in temperature control with excessive sweating. An example of a low protein/lysine tube feed for a symptomatic patient is given in Table 28.60. Not all patients are on protein restricted feeds.

Emergency regimens for management of intercurrent illness

Prompt and aggressive treatment of intercurrent illness by implementation of a high energy ER is critical to prevent neurological damage in pre-symptomatic patients and further injury in symptomatic patients [293, 308]. Delayed treatment can have serious consequences with irreversible striatal damage and a complex movement disorder [304]. Strategies to help prevent this need to be in place and include written treatment protocols for home and local hospital and adequate education and training of parents/caregivers [293]. With increasing age, and in particular from 6 years of age, the risk of acute neurological insult appears to be reduced; however, the use of an ER is an important part of management. The GA1 guideline provides comprehensive emergency treatment guidelines and detailed strategies to prevent its delayed implementation. GA1 emergency management can also be accessed from www.bimdg.org.

The main aim of the ER is to reduce production and accumulation of neurotoxic GA and 3-OH-GA by:

- provision of a high energy intake, at least normal requirements for age to prevent catabolism; 120% of daily energy requirement is recommended by some centres [294]
- omitting or temporarily reducing (by 50%) natural protein intake
- provision of usual dose of lysine-free, low tryptophan amino acids
- double dose of usual carnitine supplementation (carnitine can be given IV)

The general principles of implementation, administration of the ER and reintroduction of usual diet are the same as the standard ER (p. 673). It is particularly important to

Table 28.60 Low protein/low lysine gastrostomy feed for a girl with glutaric aciduria type 1.
Age 4 years, weight = 13 kg

	Energy										
	kcal	kJ	Protein (g)	Protein equivalent (g)	Lysine (mg/day)	Tryptophan (mg/day)	CHO (g)	Fat (g)	Sodium (mmol)	Potassium (mmol)	Fluid (mL)
450 mL PaediaSure Fibre	454	1899	12.6	–	945	180	50.4	22.4	12	12.7	450
GA1 Anamix Junior (54 g)	198	831	–	15	–	120	16.2	6.9	15.0	8.4	
Duocal (85 g)	418	1751	–	–	–	–	62	19	<0.8	<0.1	
Add water to 1200 mL											
Total	1070	4481	12.6	15	945	300	128.6	48.3	27	21.1	
per 100 mL	83	373					10.7	4.0	2.1	1.6	
Intake/kg/day			1.0	1.1	73	23					
Aim per day	81/kg*	340/kg	0.86†	0.8‡	60–50‡	13‡			30*	28*	1200
	1053	4422									

Additional electrolytes may be necessary. Electrolytes from Duocal are not included in calculation. Adequate vitamins and minerals are provided from the combination of PaediaSure Fibre and Anamix Junior. A fibre-containing feed is used to help maintain normal bowel function.
*Refs. [205, 212].
†Ref. [8]. Safe level of protein intake.
‡Refs. [293, 312].

implement the ER for any fever (high temperature). Episodes of vomiting and diarrhoea (even if no fever) necessitate hospital admission. For very minor illnesses, ER may not always be required, and continuation of the usual diet is appropriate. It is essential that this provides the normal energy intake (extra energy supplements may be needed) and the usual amount of lysine-free, low tryptophan amino acids.

Administration, composition and practical aspects of the ER:

- Stop natural protein intake temporarily for 24 hours to a maximum of 48 hours
- Provide ER feed, a combination of the usual LFAA and glucose polymer solution ranging from 10% to 25%, as per for age (p. 676).
- For children <6 years old, give around 1 g/kg/day protein equivalent from their usual LFAA supplement
- Alternatively pure lysine-free, low tryptophan amino acids products such as GA amino5 are suitable for all age groups and can be easily added directly to the glucose polymer solution (10%–25% CHO depending on age)
- Amino acid supplements are hyperosmolar (see manufacturers' information) and need to be considered if the child has a GI illness, e.g. GA1 Anamix Junior, osmolality >1220 mOsm/kg H_2O
- In children aged ≥6 years, there is no consensus about the use of LFAA supplements, but it may be advantageous to continue to give if this helps prevent catabolism and limits lysine uptake across the BBB
- Fluid volume is the same as for standard ER
- The ER can be implemented at home, but patients need to be reassessed by professionals several times per day with a low threshold for hospital admission
- NG feeding can help ensure the full volume of ER is given, but parents must be competent in doing this [320]
- If the ER is not tolerated, it is crucial that the child is admitted to hospital without delay for IV therapy of 10% dextrose/0.45% saline and carnitine. The BIMDG provides emergency protocols for IV management and can be accessed at www.bimdg.org
- A low volume, continuous tube feed of pure LFAA (e.g. XLYS TRY Glutaridon, GA amino5) to provide 1 g protein equivalent/kg/day can be given along with IV fluids, as tolerated. A concentration of 8–10 g amino acids/100 mL, as necessary, can be given. It may also be possible to add glucose polymer to 10% CHO or higher
- In the UK there are no PN solutions designed specifically for GA1
- Once the child begins to improve, the usual natural protein intake and diet/feed is reintroduced as for standard ER, ensuring an adequate energy intake at all times

A calculated example of an ER for a 9-month-old infant who is unwell is given in Table 28.61. Examples of other feed recipes can be accessed from www.bimdg.org.

Learning points: glutaric aciduria type 1

- *Newborn screening and early treatment, with strict adherence, can prevent striatal damage and onset of movement disorder*
- *Management is low lysine diet, carnitine and emergency regimen (during catabolic stress)*
- *A high energy emergency regimen is critical to prevent neurological damage in pre-symptomatic patients and further injury in symptomatic patients*
- *Low lysine diet can be relaxed >6 years of age, but the emergency regimen is still needed*

Table 28.61 Emergency regimen feed for an unwell infant with glutaric aciduria type 1.

Age 9 months, weight = 8 kg
Unwell with temperature of 38 °C, mild diarrhoea, no vomiting
Aim: Provide 1 g protein equivalent/kg/day from LFAA formula and at least energy intake for age. 120% of EAR for energy would be 86 kcal (360 kJ)/kg and is appropriate for infants

	Energy		Protein natural (g)	Protein equivalent (g)	Lysine (mg/day)	CHO (g)	Fat (g)	Sodium (mmol)	Potassium (mmol)
	kcal	kJ							
GA1 Anamix Infant 400 mL	276	1148	–	8	Nil	29.6	14	4.8	7.6
Maxijul 100 g	380	1615	–	–	–	95	–	tr	tr
Total volume 1200 mL	656	2763		8		124			
per 100 mL	55	230		0.7	–	10.4	1.2	0.4	0.6
Intake per kg/day	82	345		1.0					
Aim per kg/day	72*	302*	–	1.0†					
Administration	Feed: 100 mL every 2 hours day and night or 50 mL/hour as continuous tube feeds								

EAR, estimated average requirement; LFAA, lysine-free amino acid.
† Refs. [293, 312].
* Ref. [212].

Urea cycle disorders

The urea cycle (UC) has two main functions:

- converts toxic ammonia, formed from waste nitrogen compounds, via a series of biochemical steps to form non-toxic urea for excretion by the kidney. Waste nitrogen is generated from dietary amino acids and obligatory endogenous protein catabolism
- biosynthesis pathway for arginine, which is the precursor for the synthesis of several important metabolites including nitric oxide (NO), creatine and glutamate

Enzymes and disorders

Normal function of the UC depends on a series of six consecutive enzymatic reactions, and inborn errors at each step have been identified (Figure 28.10):

- *N*-acetylglutamate synthetase deficiency (NAGS)
- carbamoyl phosphate synthetase 1 deficiency (CPS1)
- ornithine transcarbamoylase deficiency (OTC)
- argininosuccinate synthetase deficiency (ASS) or citrullinaemia
- argininosuccinate lyase deficiency (ASL) or argininosuccinic aciduria (ASA)
- arginase deficiency

The ASS and ASL enzymes additionally form part of the overlapping nitric oxide production pathway.
There are also disorders of transport proteins of UC intermediates because the cellular steps are in two cellular compartments:

- citrin deficiency or citrullinaemia type II (CTLN2) (due to glutamate/aspartate antiporter citrin deficiency)
- hyperornithinaemia, hyperammonaemia, homocitrullinaemia (HHH) syndrome (due to ornithine/citrulline antiporter ORNT1 deficiency)

These are rare disorders and are discussed in *Clinical Paediatric Dietetics 4th edition* [321].

Biochemical defect

Any enzyme deficiency in the UC reduces flux through it blocking normal ureagenesis; waste nitrogen accumulates as ammonia in blood and brain, which is neurotoxic and may cause a severe encephalopathy. Secondary metabolic changes also contribute to central nervous system (CNS) toxicity, such as increased glutamine. Plasma ammonia is raised and can be very high, e.g. in acute neonatal onset patients it can be >1000 µmol/L (normal <40 µmol/L). Plasma amino acids are deranged, glutamine and alanine accumulate and arginine is low, except in arginase deficiency where it accumulates. Citrulline accumulates to high concentrations in citrullinaemia and similarly argininosuccinic acid in ASA. These metabolites are excreted in urine and provide alternative pathways for nitrogen excretion.

The pathology is complex and an overview of current understanding is given by Braissant [322]. Arginase deficiency is distinct from the other disorders and is discussed separately.

Genetics

All are inherited as autosomal recessive traits apart from OTC deficiency, which is X-linked and the most common of these disorders. There is a wide phenotypic spectrum within each disorder, with some ability to predict the course of some based on mutations [323].

Legend

	Enzyme	Name of disorder
1.	Carbamoyl phosphate synthetase 1	CPS 1 deficiency
2.	Ornithine transcarbamoylase	OTC deficiency
3.	Argininosuccinate synthetase	ASS deficiency or citrullinaemia type 1
4.	Argininosuccinate lyase	ASL deficiency or argininosuccinic aciduria (ASA)
5.	Arginase	Arginase deficiency or hyperargininaemia
6.	*N*-Acetyl glutamate synthetase (NAGS)	NAGS deficiency
	Transporters	
7.	Mitochondrial aspartate-glutamate carrier (AGC2)	Citrin deficiency
8.	Mitochondrial ornithine transporter (ORT1)	HHH syndrome

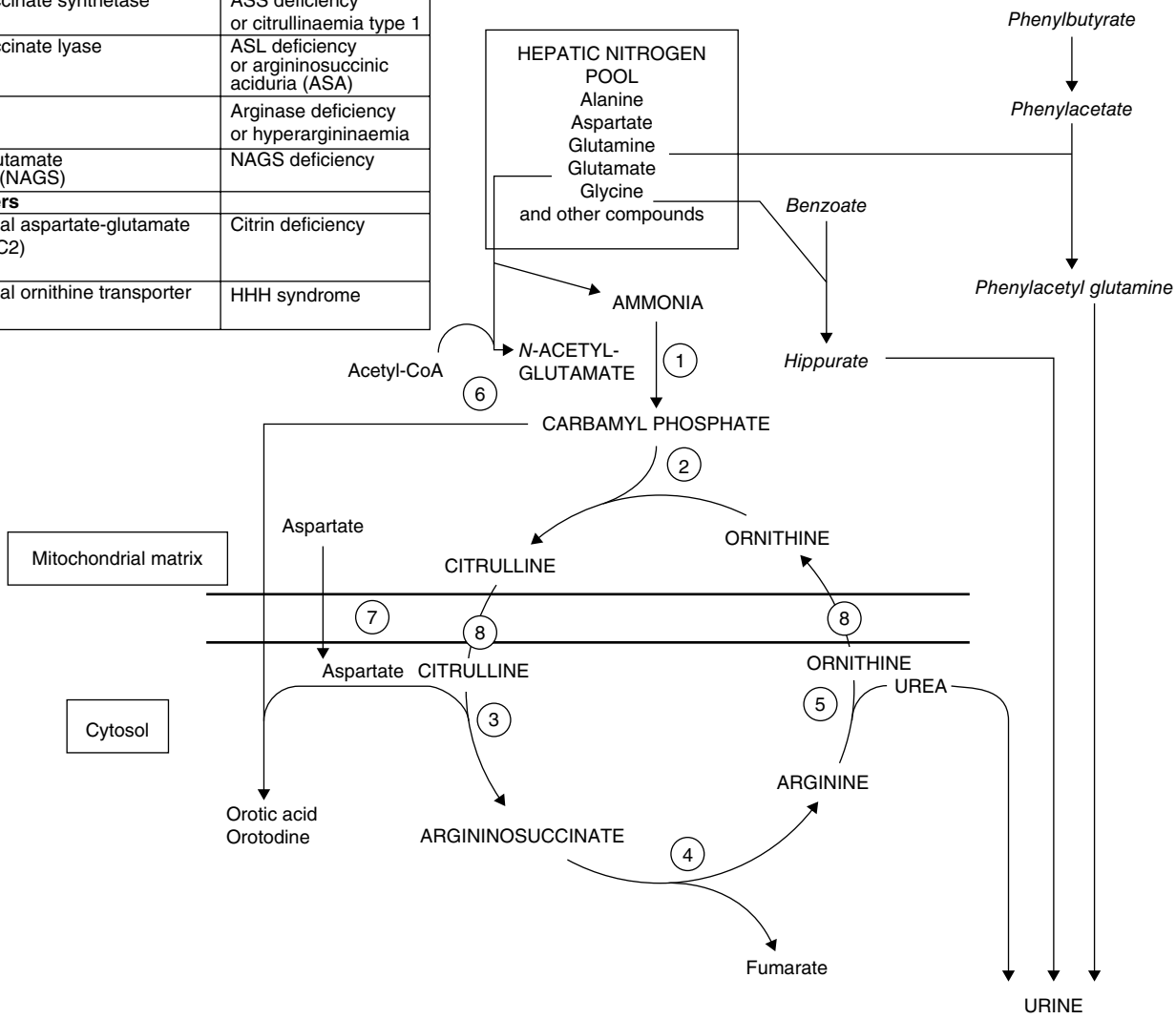


Figure 28.10 Disorders of urea cycle and related disorders.

Newborn screening

No newborn screening in the UK. Expanded NBS is problematic, suitable screening markers and their specificity being key issues [323].

Clinical onset presentation, features

Presents at any age from the neonatal period, throughout childhood and in adulthood. A detailed review of clinical symptoms and presentation is described by Haberle *et al*. [323]:

- Presentation may be acute, chronic or, rarely, acute intermittent. Signs and symptoms can be neurological (most frequently), hepatic–gastrointestinal and psychiatric
- Most severe defects present acutely with hyperammonaemia in the neonatal period, most commonly within the first 7 days of life, or later at any age (which may be precipitated by a catabolic event such as an intercurrent infection), and may cause a severe neurological handicap or even death
- Loss of appetite, poor feeding, lethargy and vomiting are common in all ages
- In the newborn there is often respiratory distress with signs of hyperpnoea, altered level of consciousness and seizures, acute encephalopathy and collapse [324]
- Respiratory alkalosis is initially present in about 50% of acute onset patients [325]
- In later onset, confusion, headache, disorientation, abnormal behaviour, ataxia, focal neurological signs or coma can occur, and in some there is also delayed physical growth and developmental delay [324]
- Protein aversion as revealed in diet histories of later presenting patients is common in urea cycle disorders (UCD), with selective avoidance of high protein foods [326]
- Heterozygote OTC deficient females can present with postpartum psychosis

Long-term complications and outcome

High mortality and morbidity are associated with UCD [325, 327, 328]. The outcome is related to duration of coma at presentation and peak ammonia levels. The outlook for infants is very poor if the ammonia level is >1000 µmol/L, and a decision not to treat may be made [323]. The neurodevelopmental outcome can range from mild to profound cognitive deficits [325, 327, 329]. In late-presenting patients many have some degree of learning and neurological disability [325, 330]. Patients with ASL deficiency have poorest cognitive outcome, and this supports the theory that toxins other than ammonia may affect this, such as argininosuccinate [327, 331, 332], increased guanidinoacetate concentrations or deficiency of nitric oxide production. Some develop hepatic complications [331], systemic hypertension [332], GI problems [333] and renal tubulopathy [333, 334].

Liver transplant is successful in preventing further episodes of metabolic decompensation in UCD, but cannot reverse any neurological damage. Low protein diet and UCD medicines are not required post-transplant [335].

Cell-based therapies, gene therapy and enzyme replacement therapy are currently under trial as alternative possible treatment options [323].

Medical treatment

Pharmacotherapy

- Sodium benzoate and sodium phenylbutyrate (phenylacetate) conjugate with specific amino acids destined for ammonia formation and thus reduce the nitrogen load to the UC (Figure 28.10). They are termed alternative pathway medicines or nitrogen scavengers because of their mode of action. Both are available in different formats. They are unpleasant tasting and can cause mucositis and gastritis, so it is important they are taken with meals and plenty of fluids to help prevent this. Some patients have a gastrostomy tube specifically to administer these. Standard doses provide a significant sodium load to infants, which can be a problem.
- Phenylbutyrate is metabolised *in vivo* to form phenylacetate that is conjugated with glutamine in liver and kidney to form phenylacetylglutamine. If the reaction were complete, then 2 moles of nitrogen would be excreted for each mole of phenylbutyrate given. However, more recent studies indicate only 1 mole is excreted [336, 337]. Phenylbutyrate is also reported to deplete BCAA. Careful monitoring of plasma amino acids is essential to avoid deficiency, and supplementation of BCAA may be necessary.
- Sodium benzoate is conjugated with glycine in the liver and kidney to form hippurate so that 1 mole of nitrogen is excreted for each mole of sodium benzoate given.
- Glycerol phenylbutyrate is a new alternative to sodium phenylbutyrate. It has the added benefits of being sodium-free and tasteless and may be more effective [338].
- Practices differ with choice of nitrogen scavenger (one or both may be given), and doses vary; this to some extent depends on the severity of the disorder and the patient's tolerance. Higher doses may be used temporarily during episodes of acute hyperammonaemia.
- Arginine becomes an essential or semi-EAA in UCD because its synthesis is greatly reduced [339]. Arginine can be administered orally or IV. It is available in liquid, powder or tablet form for oral use. It is given as a divided dose and usually in conjunction with the other medicines.
- In OTC and CPS deficiencies, arginine supplements of 100–200 mg/kg body weight/day are given to replace that which would normally be formed. The aim is to increase the flux through the UC and urea synthesis and to maintain a normal plasma arginine concentration (normal reference range 40–120 µmol/L). Alternatively in OTC, in order to meet the arginine requirements, supplements of citrulline can be given as it is rapidly converted to arginine via the intact part of the UC. Also, citrulline contains one less nitrogen atom than arginine, thereby reducing waste nitrogen production; however, it is more expensive than arginine.
- In citrullinaemia and ASA deficiency, arginine is given, up to 100–300 mg/kg/day [323], to replenish ornithine supply; traditionally, higher doses have been given. The carbon skeleton of ornithine is needed for the formation of citrulline and argininosuccinic acid that accumulate and are excreted in citrullinaemia and ASA, respectively, and provide another method for nitrogen removal. Argininosuccinic acid is more effective than citrulline as it carries two waste nitrogen atoms and has a higher renal clearance. Arginine, however, increases plasma concentrations of both citrulline and argininosuccinic acid, the full consequence of which is unknown; concerns have been expressed that high concentrations of argininosuccinic acid in ASA deficiency may have adverse effects on the brain and be hepatotoxic [340–342] and is a main reason why lower arginine doses are prescribed, nowadays.
- *N*-Carbamyl-L-glutamate (or carbamylglutamate or carglumic acid) – Defects of NAGS affect production of *N*-acetylglutamate. Patients with NAGS deficiency are treated with carbamylglutamate, the orally active form of *N*-acetylglutamate that is essential for activation of CPS1 (first step of the UC).
- Carbamylglutamate – Can be given during acute neonatal hyperammonaemia as an emergency drug to help lower ammonia levels.

Dietetic management

The aim (in combination with medicines) is to reduce the nitrogen load to the UC and prevent hyperammonaemia and consequent neurological sequelae:

- restrict natural protein intake to provide around the safe levels of protein intake for age [8] (Table 28.47)
- EAA supplementation if natural protein tolerance is below the safe level of protein intake, with poor growth and metabolic instability [323]
- branched chain amino acid (BCAA) supplementation in patients on high doses of sodium phenylbutyrate who have persistently low plasma BCAA
- provision of an adequate energy intake to ensure normal growth and prevent endogenous protein catabolism. Energy requirements in ASA may be lower than other UCD and could be related to an imbalance of the Krebs cycle [343]
- regular feeding and avoidance of prolonged fasts to help maintain good biochemical control. Plasma glutamine and ammonia concentrations increase with fasting and catabolism

Acute management	Patients who present acutely with hyperammonaemia are generally very sick, in intensive care requiring ventilation and haemodiafiltration to remove ammonia. Reversal of catabolism and prevention of hyperammonaemia is a crucial to help stabilise the child. Treatment must be initiated promptly to reverse catabolism and hyperammonaemia, as outcome is correlated with duration of coma and peak ammonia levels [344]. *Immediate management is to*: • stop protein intake • start IV 10% glucose and electrolytes • give IV medicines – nitrogen scavengers, arginine and carbamylglutamate (in some) • start protein-free feeds once the child is stabilised (dietetic management of a newly diagnosed neonate, infant or child is discussed on p. 567) • protein reintroduction may induce hyperammonaemia; an EAA supplement may be given to reduce waste nitrogen (p. 590) and then replaced with natural protein once the patient is more stable
Monitoring – biochemical and nutritional	Clinical and biochemical monitoring are essential to assess metabolic stability and to guide treatment, protein intake and medicine doses [323]. *Clinical monitoring*: Includes growth, assessment for signs of any vitamin and mineral deficiencies (e.g. skin rashes, sparse hair), liver ultrasound, blood pressure (in ASLD), neuroimaging, neurological and neurocognitive assessments *Dietary assessment*: The nutritional monitoring of low protein diets has been discussed on p. 565. *Biochemical monitoring of plasma concentrations*: Ammonia, glutamine, arginine and amino acids, particularly BCAA, argininosuccinic acid in ASS, citrulline in ASL, creatine
Emergency regimen	Prompt implementation of an ER during intercurrent illness is essential to prevent catabolism and hyperammonaemia: • Stop natural protein intake and EAA supplements • Give standard ER of frequent 2 hourly drinks/feeds of glucose polymer (p. 673) • Give at least the usual doses of medicines (nitrogen scavengers and arginine) • Admit to hospital, if not tolerating or not improving on ER
Clinical management guideline	Haberle *et al*. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision [323]. US Urea Cycle Disorders Consortium guidelines www.rarediseasenetwork.epi.usf.edu.
Parent support group	Metabolic support UK www.metabolicsupport.org.uk

Dietary management

Low protein diet

The major route for excretion of waste nitrogen is urea. Its production and excretion are linearly related to increasing protein intake [345]. A low protein diet will reduce the accumulation of waste nitrogen as ammonia, glutamine and alanine. A reduction of 0.1 g/kg/day of protein reduces the nitrogen load on the urea cycle by 16 mg/kg/day [346]. Even on the minimum protein intake for normal growth and maintenance, there is always some flux through the UC, as tissue protein is constantly being synthesised and broken down [8]. For those with severe defects the dietary protein intake is reduced to around the safe level of protein intake (Table 28.47), but this needs to be titrated against biochemical parameters (ammonia, glutamine and EAA [323]). Patients with milder defects will tolerate more protein than the safe intake; these patients are also likely to be on lower doses of one of the nitrogen scavengers. Protein requirements per kilogram bodyweight are highest during early infancy (at 1 month, 1.77 g/kg) and decrease with age to 0.8 g/kg/day in late adolescence. Neonates may tolerate and need higher protein intakes of 2–2.5 g/kg/day to achieve growth (author's experience). The E-IMD registry study [256] reported the median natural protein intake of 289 patients on protein restricted diets to be close to or above the WHO recommended daily allowance (RDA). However for certain disorders, some patients who were on EAA supplements had a natural protein intake less than WHO, RDA.

The practical management of a low protein diet for infants and children is described on p. 562.

Essential amino acid and branched chain amino acid supplements

A 2013 study of dietary treatment practices across Europe reported that 38% (174/464 patients) were prescribed EAA supplements [347] and that doses varied widely: 10%–90% of total protein intake. More recent data from the E-IMD registry [256] reported 32% (114/361patients) were prescribed EAA supplements, with a mean dose of EAA (including single amino acids) of 28%–31% of total protein prescription and a median protein prescription of 0.28 g/kg/day (range 0.04–1.17 g/kg/day). Plasma amino acids levels were reported in 277/361 of all patients, 20%–30% had BCAA levels below reference ranges, but no differences were observed between those prescribed EAA or not. Sodium phenylbutyrate dose correlated with low BCAA levels. It is important to note the many limitations of this cross-sectional study.

EAA supplements as part of the total daily protein intake may be beneficial because, theoretically, by limiting the intake of non-EAA, waste nitrogen is utilised to synthesise these and hence nitrogen destined for excretion as urea will be reduced. This, however, has never been proven in clinical studies and is not routine practice across Europe. The UCD guidelines [323] suggest EAA supplements of 20%–30% of total protein intake be given only when natural protein tolerance is below safe protein intake for age and too low to achieve normal growth and metabolic stability. This contrasts with US recommendations of use from diagnosis and to give at a higher dose of 25%–50% of total protein as EAA in severe defects [348] and in infancy to give 50% of protein as EAA; as growth rate slows, the percentage is decreased

[349]. The rationale for use during infancy is not completely clear as protein requirements per kilogram per day are highest and nitrogen retention is at a maximum, but this could be related to using nitrogen scavengers. There are no studies that compare the two methods of management.

A trial of EAA supplements may be useful if:

- blood biochemistry (glutamine, alanine, ammonia) cannot be corrected by altering the medicines because the child is either on maximum doses of medicines or refusing to take more and the protein intake is around the safe intake and cannot be reduced further
- plasma amino acids are persistently low, with poor growth and metabolic instability
- biological value of a low protein diet is lacking in one or more EAA, which may occur if the protein is provided from a limited range of LBV protein foods
- natural protein intake is inadequate due to poor oral intake (a tube may be the preferred option to provide adequate natural protein)
- metabolic control is poor, or there are repeated episodes of metabolic decompensation
- needed temporarily to help stabilisation in newly diagnosed patients

EAA are generally given as a divided dose between feeds or two or three meals. Products differ in composition and age suitability (Table 28.62). It is important to be aware that all EAA provide a source of nitrogen (8.5%–13.7%), but this is lower than the nitrogen content of food that ranges from 13.4% to 19.1% depending upon its amino acid composition [347]. Similar products are available outside the UK (www.abbottnutrition.com, www.meadjohnson.com, www.milupa-metabolics.com).

Sodium phenylbutyrate is reported to selectively lower plasma BCAA, and supplementation with BCAA has been recommended [350, 351]. A possible mechanism for this is the ability of phenylbutyrate to cause an enhanced flux through the branched chain α-keto acid dehydrogenase complex, which catalyses the reversible oxidative decarboxylation of the BCAA [352]. The effects of lowered BCAA are unknown, but it may cause patients to be less stable [353]. Despite these reports, BCAA supplement use across Europe is uncommon; cohort studies from 2013 to 2019 report only 3% patients were prescribed supplements [256, 347], which suggests little change in practice during this period. BCAA or single amino acid supplements can be given; there is no BCAA product readily available in the UK.

Feeding behaviour and tube feeding

Protein aversion (before and after diagnosis), poor appetite, food refusal and poor variety of foods eaten, frequent vomiting and abnormal eating behaviour are features of some children with UCD [217, 256, 326]. Some children may have an inadequate oral energy and nutrient intake due to mechanical feeding problems and unsafe swallow associated with neurological handicap or severe developmental delay, caused by hyperammonaemia or poor appetite. If a child is unable to take sufficient orally, NG or gastrostomy feeding is essential to prevent hyperammonaemia and metabolic decompensation. In a European study of feeding practices [256], <20% received enteral tube feeds, and in a UK study 25% [199]. Tube feeding may also be used specifically for administration of EAA and/or medicines, although the need for this appears to be limited. The provision of a low protein tube feed has been described on p. 570.

Nutritional and biochemical monitoring

Recommended clinical, nutritional and biochemical monitoring of the diet is described (p. 565). In a study of 311 UCD patients, height *z*-score was positively associated with the

Table 28.62 Essential amino acid products used in urea cycle disorders.

Product (manufacturer)	Amino acids g/100 g	Protein equivalent g/100 g	Energy kcal (MJ)/100 g	CHO g/100 g	Fat g/100 g	Vitamins and minerals	Comments
Dialamine (Nutricia)	30	25	360 (1.5)	65†	nil	‡	Orange flavoured. Suitable from 6 months Can be added to a feed, drink or given as a paste
Essential Amino Acid Mix (Nutricia)	94.5	79	316 (1.3)	nil	nil	nil	Suitable for infants under 6 months
EAA supplement (Vitaflo)	48	40	288 (1.2)¶	31.8	0.1	**	Tropical flavour. Suitable from age 3 years 12.5 g/sachet
UCD amino5 (Vitaflo)	94.85	75.4	302 (1.28)	nil	nil	nil	Unflavoured. Suitable from 3 years 6.6 g sachet

EAA, essential amino acids.
Refer to manufacturers' data information for full nutritional composition of products.
†Contains a mixture of glucose polymer and sugar.
‡Contains vitamin C and trace amounts of sodium, potassium, chloride, calcium, phosphorus and magnesium.
¶Contains glucose polymer, sugar and sweeteners.
**Contains a comprehensive range of vitamins, minerals and trace elements.

natural protein-energy ratio, and low plasma leucine and valine associated with height *z*-score < – 2SD [211]. Although there are limitations to this study, it serves to highlight the importance of ongoing monitoring, careful interpretation and management decisions. Frequency of monitoring depends on the child's overall metabolic stability in relation to treatment and compliance. Younger and more severe patients need more frequent monitoring, 3–4 monthly being typical for most patients who are stable. A 24 hour profile of plasma ammonia and glutamine can be helpful in patients who are difficult to manage. Timing of the blood sample is important as there is variation in relation to meals and medicines. Ideally, samples should be obtained at the same time and at trough levels 3.5–4 hours after a meal. This will avoid high concentrations of amino acids (seen following consumption of EAA supplements at mealtimes) and low concentrations being missed [354]. However, it is not always possible to collect samples under optimal conditions, so results need to be interpreted in the light of the conditions. Plasma ammonia may be falsely elevated due to poor or difficult blood sample collection. The overall aim is to maintain plasma concentrations: ammonia (normal), glutamine (normal range or at least <1000 μmol/L), arginine (high, normal) and amino acids, particularly BCAA, within normal reference ranges to achieve normal growth and the best possible development [323, 354] (Table 28.63). It is important to be aware that plasma glutamine does not directly influence brain glutamine concentration, as this is synthesised mainly in the brain. It is not known if this is altered if plasma glutamine concentrations are high [354].

Changes to dietary protein, EAA intakes, arginine and medicines (sodium benzoate and phenylbutyrate, and arginine in ASA and citrullinaemia) are based on the results of these investigations, and alterations vary depending on the disorder (Table 28.63). Blood results need careful interpretation (particularly if they are unsatisfactory) because they are influenced by a number of different factors that need to be considered before implementing any change to diet or medicines: growth, dietary intake, type and doses (including timings and frequency) of medicines, compliance with diet and medicines, age (puberty can be a difficult time), use of EAA, use of ER and timing of blood sample in relation to foods/EAA intake. Looking for patterns in results over time can be helpful.

High concentrations of glutamine and ammonia in plasma may be caused by:

- inadequate medicines, too high or too low a protein intake (causing catabolism); both factors may be a compliance issue. It is also important to ensure that medicines are given as divided doses over the 24 hour day.
- periods of chronic catabolism caused by either an inadequate energy and protein intake due to poor appetite or repeated use of ER; so growth and clinical status must always be considered when interpreting the results.

Poor appetite is observed in some children [355], with high glutamine levels implicated, possibly causing an increased influx of tryptophan (the precursor of serotonin) into the brain and promoting serotonin synthesis. Serotonin increases a feeling of satiety [356]. If plasma glutamine is maintained within the normal range, then, in some children, appetite may improve. Low plasma BCAA may be due to phenylbutyrate (p. 591). Good biochemical control may be difficult to achieve during periods of slow growth before and particularly after puberty [355]. When the adolescent stops growing, there may be a period of instability because protein is no longer needed for growth; protein intake and medicines may require adjustment to restore stability.

Argininosuccinic acid accumulates in ASA and high dose arginine will also increase its production; the full consequences of this are not known, or if there is a specific plasma concentration, that ASA should be kept below. A high plasma arginine may also be harmful by causing an increased cerebral guanidinoacetate concentration [357]; a fasting plasma arginine concentration of up to 70–120 μmol/L is considered acceptable [323]. Liver

Table 28.63 Guide to management decisions for urea cycle disorders (excluding arginase deficiency).

All influencing factors should be considered before making changes to diet or medicines.			
Ammonia (μmol/L) normal reference range <40	Glutamine (μmol/L) normal reference range 400–800	Quantitative plasma amino acids	Suggested action
>80–100	>1000	Low EAA/BCAA	Increase medicines in OTC and CPS* Increase medicines in ASA and citrullinaemia;† Increase natural protein or EAA
>80–100	>1000	Normal	Increase medicines in OTC and CPS* Increase medicines in ASA and citrullinaemia† No change to diet
<80	<1000	Low EAA/BCAA	No change to medicines. Increase natural protein
<80	<1000	Normal	No change to medicines or diet

EAA, essential amino acids; BCAA, branched chain amino acids; OTC, ornithine transcarbamoylase deficiency; CPS, carbamoyl phosphate synthetase deficiency; ASA, argininosuccinic aciduria.

†ASA and citrullinaemia – arginine, sodium benzoate or phenylbutyrate. If plasma arginine is much above the normal reference range 40–120 μmol/L, arginine dose is not increased; sodium benzoate and/or phenylbutyrate would be increased instead. If plasma citrulline or argininosuccinic acid is too high, arginine is not increased; sodium benzoate and/or phenylbutyrate would be increased instead.

*OTC and CPS – sodium benzoate and/or phenylbutyrate.

functions tests (LFT) are routinely monitored in ASA to detect the presence of liver disease early. A lower dose of arginine may help normalise LFT; however, nitrogen scavengers will need to be increased to compensate [357]. Arginine is necessary for the synthesis of creatine (Cr), which is used in energy storage and transmission. Decreased Cr levels have been reported in OTC deficiency, citrullinaemia and HHH syndrome; in contrast, in ASA Cr levels are increased [358]. It is not yet known if altered Cr metabolism effects CNS function in UCD. Monitoring of Cr may help to guide the dose of arginine in UCD as both high and low plasma levels of arginine may have adverse effects [358]. Dietary Cr intake may also be reduced on low protein diet as meat is the main source.

Emergency regimens for management of illness

- The standard ER of frequent feeds of glucose polymer (p. 673) is given to prevent the effects of illness and accumulation of ammonia and glutamine and to promote anabolism.
- Protein intake is stopped temporarily, and a high energy intake is given from glucose polymer. The need to completely stop protein has been challenged [359]; the majority of patients studied were protein deficient on admission with hyperammonaemia. However, there are no reports of undertaking this in practice.
- The usual doses of sodium benzoate, phenylbutyrate and arginine are administered. If necessary during acute illness, the dose of both benzoate and phenylbutyrate can be temporarily increased to 500 mg/kg/day.
- Protein is usually reintroduced within 24–48 hours of starting the ER and over a period of 1–2 days depending on the child's clinical condition and biochemical results.
- Practical advice on protein reintroduction is given on p. 678.
- If the child is not improving at home or does not tolerate oral/enteral ER and medicines, which is common, they should be admitted to hospital without delay for IV 10% dextrose and medicines. The BIMDG (www.bimdg.org) provides emergency protocols for IV management.
- Oral fluids can usually be recommenced within 24–48 hours, with a gradual changeover from IV to oral, thus always ensuring an adequate energy intake.
- Plasma ammonia should be measured frequently to help guide protein reintroduction. Once the plasma ammonia is falling and is <80–100 µmol/L, protein is gradually reintroduced usually over the same 24–48 hour period. This should not be delayed as inadequate protein will cause catabolism and increase ammonia levels further.
- If hyperammonaemia is induced during protein reintroduction, giving an EAA supplement temporarily may help.

Learning points: urea cycle disorders

- *Dietary management is a restricted protein diet with emergency regimen during illness*
- *Nitrogen scavengers reduce waste nitrogen load to the urea cycle and thus ammonia*
- *Arginine becomes an essential or semi-essential amino acid*
- *Monitoring of plasma amino acids is essential to make medical and dietetic management decisions*

Arginase deficiency

Enzyme	Arginase 1 (ARG1)
Biochemical defect	ARG1 catalyses the conversion of arginine to urea and ornithine (Figure 28.10). Hyperargininaemia and a mild hyperammonaemia occur due to defective hydrolysis of arginine.
Genetics	Autosomal recessive inheritance, very rare disorder
Newborn screening	No newborn screening
Clinical onset presentation, features	Arginase deficiency is distinct from the other UCD. Patients rarely present in the neonatal period but typically present with first symptoms between 2 and 4 years of age [360]. It is characterised by a progressive spastic paraplegia and cognitive impairment (mild to severe mental retardation) that may continue to deteriorate, seizures and poor growth [360–362]. Episodes of hyperammonaemic encephalopathy can occur and appear to be more common than previously reported [361]. Similar to other children with UCD, some patients self-limit protein prior to diagnosis. Interestingly, it has been reported that this has been observed in children by their parents only after the age of 5 years [362].
Long-term complications and outcome	Treatment should help prevent further neurological damage and may induce a partial recovery of skills over time [360, 363, 364]. Three patients treated from birth are reported to be largely without symptoms but are still at an age when they are usually asymptomatic [361, 365]. In patients who already have spastic diplegia, dietary treatment will not improve this, but can help prevent hyperammonaemia. The pathophysiology is yet to be fully delineated, but arginine and its guanidino metabolites and alterations in NO synthesis are possible factors [360, 361, 366].
Medical and dietetic management	Management is to prevent accumulation of arginine and ammonia by: • a low protein diet (to limit dietary arginine), usually provided as a combination of natural protein and EAA supplements • provision of an adequate energy intake (to prevent catabolism) • sodium benzoate sodium or glycerol phenylbutyrate to provide an alternative pathway for waste nitrogen excretion Clinical trials of enzyme replacement therapy are underway https://clinicaltrials.gov/ct2/show/NCT03921541.

Monitoring	Clinical, nutritional and biochemical monitoring is same as for other UCD (p. 565, 591). The diet is monitored by regular measurements of plasma ammonia and plasma amino acids, including arginine. Distinct from the other UCD, plasma arginine is raised. The aim is to maintain plasma arginine levels <200 μmol/L (normal reference range 40–120 μmol/L), which is extremely difficult to achieve, and a near normal plasma ammonia (normal range <40 μmol/L).
Emergency regimen	Prompt implementation of an ER during intercurrent illness is essential to prevent hyperargininaemia and hyperammonaemia and implemented as described for other UCD (but with no arginine medication): • Stop natural protein intake and EAA supplements • Give standard ER of frequent 2 hourly drinks/feeds of glucose polymer (p. 673) • Give at least the usual doses of medicines (nitrogen scavengers) • Admit to hospital, if not tolerating or not improving on ER
Clinical management guideline	Haberle *et al*. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision [323].

Dietary management

All dietary nitrogen has the potential to be converted to arginine, this source being considerably greater than the small amount of arginine that is naturally present in protein. In the past, in order to restrict nitrogen intake, diets comprised an EAA supplement with a very limited intake of natural protein. Nowadays, by giving sodium benzoate and phenylbutyrate, a more generous intake of natural protein may be possible while still maintaining acceptable plasma arginine and ammonia levels. Protein is restricted to the safe level of intake (Table 28.47), and is provided by a low protein diet, or some of the protein as an EAA supplement, which is more common practice. Studies report: 17/23 patients had EAA supplements, providing 25%–50% of total protein intake in children <16 years of age [347]; in 10/19 patients providing a median 0.65 g/kg/day range 0.25–0.9 g/kg/day [361]. The precise composition of protein intake must be determined by the balance of requirements for growth and the medicines necessary for good biochemical control. A combination of 50%–75% as natural protein and 25%–50% as EAA has been suggested [323, 365]. The practical management of the low protein diet and EAA supplementation are provided on pp. 562 and 590.

Other metabolic disorders

The following rarer disorders are discussed in *Clinical Paediatric Dietetics 4th edition* [321]: lysinuric protein intolerance (p. 507), gyrate atrophy of the choroid and retina (ornithine amino transferase deficiency) (p. 510), guanidinoacetate methyltransferase deficiency (p. 513), alkaptonuria (p. 515), isolated sulphite oxidase deficiency (p. 516), non-ketotic hyperglycinaemia (p. 517), trimethylaminuria or fish odour syndrome (p. 519), glucose-6-phosphate dehydrogenase deficiency and favism (p. 523).

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

28.A Appendix

Table 28.A.1 Types of protein substitute available on prescription (ACBS) for PKU in the UK.

Name	Company	Unit size	Protein source	Protein g/100 g	Protein g per unit size	Phe content mg per unit size	Energy kcal per unit size	CHO g per unit size	Fat g per unit size	Vitamins and minerals	LCPUFAs	Age suitability flavours
PKU Anamix Infant	N	100 mL	L-Amino acids	13.1	2.0	0	70	7.5	3.5	Yes	DHA, AA	Infant formula Contains prebiotics
PKU Start	V	100 mL*	L-Amino acids	14.3	2.0	0	68	7.2	3.5	Yes	DHA, AA	Infant formula
PKU Anamix First Spoon	N	12.5 g	L-Amino acids	40	5	0	41	4.8	0.2	Yes	DHA, AA	From 6 months to 5 years Unflavoured
PKU Anamix Junior LQ	N	125 mL	L-Amino acids	8/100 mL	10	0	118	8.8	4.8	Yes	DHA	From 1 to 10 years Unflavoured, orange, berry flavours
PKU Anamix Junior	N	36 g	L-Amino acids	27.8	10	0	135	11.5	4.5	Yes	DHA	From 1 to 10 years Unflavoured, orange, berry, vanilla, chocolate flavours
PKU Explore 5	V	12.5 g	L-Amino acids	40	5	0	43	5.3	0.2	Yes	DHA, AA	From 6 months to 5 years Unflavoured
PKU Explore 10	V	12.5 g	L-Amino acids	40	10	0	83	9.8	0.4	Yes	DHA, AA	From 12 months to 5 years Orange, raspberry flavours
PKU Gel	V	24 g	L-Amino acids	41.7	10	0	81	10.3	0.02	Yes	No	From 6 months to 10 years Unflavoured Orange, raspberry flavours from 12 months to 10 years
PKU Squeezie	V	85 g	L-Amino acids	12	10	0	135	22.5	0.5	Yes	DHA, AA	From 6 months to 10 years Apple, banana flavours
PKU Express 15	V	25 g	L-Amino acids	60	15	0	74	2.4	0.05	Yes	No	From 3 years Unflavoured, orange, lemon, tropical flavours
PKU Express 20	V	34 g	L-Amino acids	60	20	0	101	3.3	0.07	Yes	No	From 3 years Unflavoured, orange, lemon, tropical flavours
PKU Cooler 10	V	87 mL	L-Amino acids	11.5/100 mL	10	0	65	4.4	0.8	Yes	DHA	From 3 years Orange, purple, red, white and yellow flavours
PKU Cooler 15	V	130 mL	L-Amino acids	11.5/100 mL	15	0	97	6.6	1.2	Yes	DHA	From 3 years Orange, purple, red, white, yellow flavours
PKU Cooler 20	V	174 mL	L-Amino acids	11.5/100 mL	20	0	130	8.9	1.6	Yes	DHA	From 3 years Orange, purple, red, white, yellow flavours

(continued overleaf)

Table 28.A.1 (*continued*)

Name	Company	Unit size	Protein source	Protein g/100 g	Protein g per unit size	Phe content mg per unit size	Energy kcal per unit size	CHO g per unit size	Fat g per unit size	Vitamins and minerals	LCPUFAs	Age suitability flavours
PKU Air 15	V	130 mL	L-Amino acids	11.5/100 mL	15	0	75	2.0	0.8	Yes	DHA	From 3 years Yellow (mango breeze), gold (coffee fusion, contains <20 mg of caffeine per pouch), white (Caribbean crush), green (citrus twist), red (berry blast) flavours
PKU Air 20	V	174 mL	L-Amino acids	11.5/100 mL	20	0	100	2.6	1.0	Yes	DHA	From 3 years Yellow (mango breeze), gold (coffee fusion, contains <20 mg of caffeine per pouch), white (Caribbean crush), green (citrus twist), red (berry blast) flavours
PKU Lophlex LQ 10	N	62.5 mL	L-Amino acids	16/100 mL	10	0	58	4.4	Nil added	Yes	DHA	From 4 years Juicy orange, juicy berry, juicy tropical, juicy citrus, berry, orange flavours
PKU Lophlex LQ 20	N	125 mL	L-Amino acids	16/100 mL	20	0	115	8.8	Nil added	Yes	DHA	From 4 years Juicy orange, juicy berry, juicy tropical, juicy citrus, berry, orange flavours
XPHE Jump 10	M	63 mL	L-Amino acids	16/100 mL	10	0	63	5	0.3	Yes	DHA (except unflavoured)	From 3 years Cola (without caffeine), wild berries, orange flavours Neutral (unflavoured)
XPHE Jump 20	M	125 mL	L-Amino acids	16/100 mL	20	0	126	10	0.6	Yes	DHA (except unflavoured)	From 3 years Cola (without caffeine), wild berries, orange flavours Neutral (unflavoured)
PKU Easy Liquid	G	130 mL	L-Amino acids	11.5/100 mL	15	0	98	2	0.5	Yes	DHA, EPA	From 3 years Orange/citrus, mixed berries flavours
PKU Easy Shake and Go	G	34 g	L-Amino acids	45	15	0	125	14	0.1	Yes	No	From 3 years Orange flavour
PKU Lophlex Powder	N	27.8 g	L-Amino acids	72	20	0	91	2.5	0.1	Yes	No	From 8 years Unflavoured, berry, orange flavours
PKU Lophlex Sensation	N	109 g	L-Amino acids	18.3	20	0	166	20.2	0.4	Yes	DHA	From 3 years Berry flavour
Glytactin Bettermilk 15 Original	C	49 g	CGMP	31	15	23	160	23	4.5	Yes	DHA	From 3 years Neutral flavour Contains probiotic

Glytactin Bettermilk 15	C	52 g	CGMP	29	15	24	200	26	3.9	Yes	DHA	From 3 years Strawberry crème, orange crème flavours Contains probiotic
Glytactin Build 10	C	16 g	CGMP	63	10	10	54	2.1	0.6	Yes	No	From 3 years Neutral flavour Contains probiotic
Glytactin Bettermilk Lite 20	C	46 g	CGMP	43	20	35	150	12	2	Yes	DHA	From 3 years Neutral flavour Contains probiotic
Glytactin Complete 15 Fruit Frenzy	C	81 g	CGMP	19	15	32	330	35	12	Yes	No	From 3 years Fruity taste chewy bar
Glytactin Complete 15 Peanut Butter	C	81 g	CGMP	19	15	37	320	42	8	Yes	No	From 3 years Peanut butter taste chewy bar
Glytactin RTD 10 Original	C	250 mL	CGMP	4	10	18	153	21	3.5	Yes	No	From 3 years Original, chocolate flavours
Glytactin RTD 15 Original	C	250 mL	CGMP	6	15	27	200	23	5	Yes	No	From 3 years Original, chocolate flavours
Glytactin Restore Powder 5	C	20 g	CGMP	25	5	9	73	14	0	No Incomplete	No	From age 3 years. Orange, berry flavours
Glytactin Restore Lite Powder 10 Orange	C	19 g	CGMP	53	10	18	65	6.4	0	No Incomplete	No	From 3 years Orange flavour
GMPro	N	33.3 g	CGMP	30	10	18	128	12.5	3.9	Yes	DHA	From 3 years Use with caution 3–6 years Vanilla flavour
GMPro LQ	N	250 mL	CGMP	4	10	18	112	8.5	4	Yes	DHA, EPA	From 3 years Use with caution 3–6 years Vanilla flavour
PKU sphere 15	V	27 g	CGMP	56	15	28	91	4.9	1.3	Yes	DHA	From 4 years Red berry, vanilla, chocolate flavours

(continued overleaf)

Table 28.A.1 (*continued*)

Name	Company	Unit size	Protein source	Protein g/100 g	Protein g per unit size	Phe content mg per unit size	Energy kcal per unit size	CHO g per unit size	Fat g per unit size	Vitamins and minerals	LCPUFAs	Age suitability flavours
PKU sphere 20	V	35 g	CGMP	56	20	36	120	6.3	1.6	Yes	DHA	From 4 years Red berry, vanilla, chocolate flavours
PKU synergy	N	33 g	L-Amino acids	60.6	20	<5	98	3.5	0.33	Yes	DHA	From 10 years Citrus flavour
Phlexy 10 Drink mix	N	20 g	L-Amino acids	42	8.3	0	69	8.8	Nil added	No	No	From 8 years Apple and blackcurrant, tropical surprise, citrus burst flavours
Phlexy 10 tablets	N	10 tablets	L-Amino acids	58	8.3	0	38	0.7	0.2	No	No	From 8 years
PK Aid 4	N	100 g	L-Amino acids	79 g	79 g/100 g	0	71	Nil	Nil added	No	No	For infants, children and adults Unflavoured

ACBS, Advisory Committee for Borderline Substances; PKU, phenylketonuria; Phe, phenylalanine; CHO, carbohydrate; LCPUFA, long chain polyunsaturated fatty acids; N, Nutricia; V, Vitaflo; M, MetaX; Galen; C, Cambrooke Therapeutics; DHA, docosahexaenoic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; GCMP, casein glycomacropeptide.
All nutritional analysis is for unflavoured products.
* Pack size = 400 g.

29 Disorders of Carbohydrate Metabolism

Anita MacDonald, Marjorie Dixon and Fiona J. White

Disorders of Galactose Metabolism

Anita MacDonald

Galactosaemia

The common forms of galactosaemia are classical galactosaemia and biochemical (Duarte) variant galactosaemia.

Enzyme	Galactose-1-phosphate uridyl transferase (GALT)
Biochemical defect	An inability to metabolise galactose in the Leloir pathway, leading to hypergalactosaemia [1] (Figure 29.1). Galactose-1-phosphate increases and is metabolised to galactitol and galactonate, both accumulating in abnormal quantities in tissues. Galactose is a hexose monosaccharide that has an important role in energy delivery and in the biosynthesis of complex carbohydrates, glycoproteins and glycolipids [2]. Abnormal glycosylation of glycoproteins and glycolipids may occur.
Genetics	Autosomal recessive inheritance. Incidence in Western Europe is estimated to be 1 in 16 500–44 000. The most common classical galactosaemia mutation in Caucasian populations is Q188R (c.563A N G), associated with null red blood cell GALT activity. Patients with Duarte variant galactosaemia have one GALT allele that is severely impaired and a second GALT allele (Duarte-2, D2) that is partially impaired [3].
Newborn screening	No newborn screening (NBS) in the UK. No universal agreement about NBS.
Clinical onset presentation, features	The common forms are: • classical galactosaemia - is associated with neonatal symptoms and long-term complications • biochemical (Duarte) variant galactosaemia - infants and children may rarely present with this milder form. Patients are usually asymptomatic and mainly identified due to abnormal NBS with moderate elevations in total blood galactose and decreased GALT activity [4]. It is not associated with an increased risk of developmental abnormalities and does not require dietary treatment [3]

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

Classical galactosaemia presents in the newborn period with life-threatening illness when fed either breastmilk or milk-based infant formula (both contain galactose):

- Symptoms and signs include poor feeding, vomiting and diarrhoea, weight loss, jaundice, hypotonia, hepatic failure and coagulopathy. Without urgent treatment, infants are at risk of *Escherichia coli* sepsis, multi-organ failure and death [5].
- Biochemical findings include abnormal liver function tests, abnormal clotting, hypoglycaemia, raised plasma amino acids and renal tubular dysfunction. Rapid improvement occurs on stopping galactose-containing feeds.
- Rarely, patients may present after the newborn period with faltering growth and developmental delay.

Long-term complications and outcome

Despite early diagnosis and strict galactose-restricted diet, many treated patients develop one or more long-term complication(s).

Speech defect: Delayed speech vocabulary and childhood apraxia of speech are common [1]. More general speech/language delays also occur associated with producing, rather than understanding, speech and language [4].

Cognitive development, executive and neurological function: Cognitive development, memory and executive functions are commonly in the low average range, but there is a range of ability with some achieving university education and attaining higher degrees.

Psychiatric symptoms: These include obsessive–compulsive disorder and autism spectrum disorder [6]. Anxiety and depression may occur.

Primary ovarian dysfunction (POI): Ovarian damage resulting in POI occurs in 80% of women with classical galactosaemia despite treatment [7], and the severity is variable [8]. Despite the high prevalence of POI, several spontaneous pregnancies are documented, both in classical galactosaemia [9] and women with milder mutations. A small number of women with galactosaemia have successfully breastfed their infants.

Reduced bone mineral density: 10%–25% of patients with classical galactosaemia are at risk of low bone mass density (BMD *z*-score <–2) as compared with the general population [10]. Diet restriction and ovarian insufficiency in women both increase risk of compromised bone health. Blood vitamin D levels are commonly in the low reference range.

Growth disturbance: Growth may be delayed in childhood and early adolescence, but final height is usually normal, although decreased height *z*-scores compared to mid-parental target height is described [11]. There is also a decrease in fat mass and lean tissue mass compared with actual height *z*-scores [12].

Medical treatment

If galactosaemia is suspected, a galactose-free formula should be given instead of breastmilk or standard infant formula. Long-term management includes:

- assessment of developmental milestones, intellectual development and speech and language should be done at regular intervals such as preschool, primary, middle school and senior school ages according to International Galactosaemia Guidelines [3]
- ophthalmological screening/follow-up is necessary for cataracts
- many females need puberty induction and/or hormone replacement therapy to prevent sequelae of POI

The case study in Table 29.11 provides an example of initial medical management.

Dietetic management

Galactose-restricted diet. Glucose and galactose form the disaccharide lactose, present in most animal milks. It is also available as free and bound galactose in carbohydrates such as oligosaccharides and polysaccharides, glycoproteins and glycolipids.
The International Galactosaemia Guidelines [3] recommend a lifelong galactose-restricted diet that only eliminates sources of lactose and galactose from dairy products. At present there is insufficient evidence to support a specific age-related recommendation for the quantity of galactose allowed in the diet.

Monitoring – biochemical

There is no consensus as to the most relevant biomarker(s) for monitoring as there is no clear association between galactose metabolites, other markers and the development of both acute and long-term complications:

- Red cell galactose-1-phosphate is widely used to monitor dietary adherence and should be measured at diagnosis after 3 and 9 months, then annually [3]. More frequent measurements are only necessary if there is poor dietary adherence.
- Galactose-1-phosphate is high at diagnosis and falls progressively after commencing galactose-free formula/diet, but can take up to 1 year or even longer to decrease to the local treatment reference range (laboratories use varying target ranges). Concentrations do not decrease to normal levels found in healthy individuals [3].
- Vitamin D status: serum 25-hydroxyvitamin D, 25(OH)D, levels should be measured annually in children [3].
- Dual-energy X-ray (DEXA) scans: every 4–5 years from onset of puberty.

Clinical management guidelines

International Galactosaemia Guidelines 2016 [3].

Patient support group

The European Galactosaemia Society (EGS) www.galactosaemia.eu
The UK Galactosaemia Support Group www.galactosaemia.org

Endogenous production of galactose

Significant amounts of endogenous galactose are produced in patients with galactosaemia, being several-fold higher for body weight in infants than in adults [13] who produce approximately 13 mg/kg body weight/day compared with approximately 41 mg/kg body weight/day in newborns [14]. Endogenous galactose is thought to originate from the transformation of glucose and from the recycling of glycosylated proteins and lipids. It is considered a major cause of late complications [15].

Dietary management: galactose-restricted diet

The International Galactosaemia Guidelines (2016) [3] recommend: 'treating patients with classical galactosemia with a life-long galactose-restricted diet that only eliminates sources of lactose and galactose from dairy products but permits galactose from non-milk sources that contribute minimal dietary galactose. Within this definition we accept that small amounts of galactose are present in specific mature cheeses and caseinates. At present there is insufficient evidence to support a specific age-related recommendation for the quantity of galactose allowed in the diet'.

Sources of galactose

Lactose

Lactose is the main source of dietary galactose; it cleaves to glucose and galactose when digested. Cow's milk is the main dietary source of galactose and contains approximately 2400 mg galactose/100 mL, and high amounts are found in yoghurt, soft cheese and other dairy foods [16]. All milk and manufactured foods containing milk need to be avoided (Tables 29.1 and 29.2). Constituents of milk are likely to be found in foods such as biscuits, some sweets and tinned and processed meats (Table 29.3). Many spreads (including reduced fat) and mayonnaise include milk components to improve their flavour. The lactose content of whey derivatives such as whey powder is high, comprising 70% of total solids.

There are exceptions in a galactose-restricted diet:

- caseinates: foods containing caseinates are permitted as they contain trace amount of lactose only. They are used in coffee whiteners, meat products and baked goods. The Casein and Caseinates Regulations [18] state that the maximum anhydrous lactose content of casein should not exceed 1% by weight
- butter oil and ghee: these contain minimal lactose and galactose and are permitted in the diet for galactosaemia in the UK. Butter oil is used by the food industry for the following functions: flavour, flavour carrier, food gloss, creaming, air incorporation, anti-staling and shortening [19]
- non-milk derivatives that may be added to food products are shown in Table 29.4. These do not need to be

Table 29.1 Lactose and galactose content of foods [17].

Food	Lactose content (g/100 mL or g/100 g)	Galactose content (g/100 mL or g/100 g)
Milk, skimmed	4.4	2.2
Milk, whole	4.5	2.3
Cream, single	2.2	1.1
Yoghurt, low fat, fruit	4.4	2.2
Butter	0.6	0.3
Milk chocolate	10.1	5.1
Ice cream, dairy	5.2	2.6
Lactofree milk (Arla)*	0.02	1.65

*Data analysed by UK Galactosaemia Support Group.
Source: Licensed under Open Government.

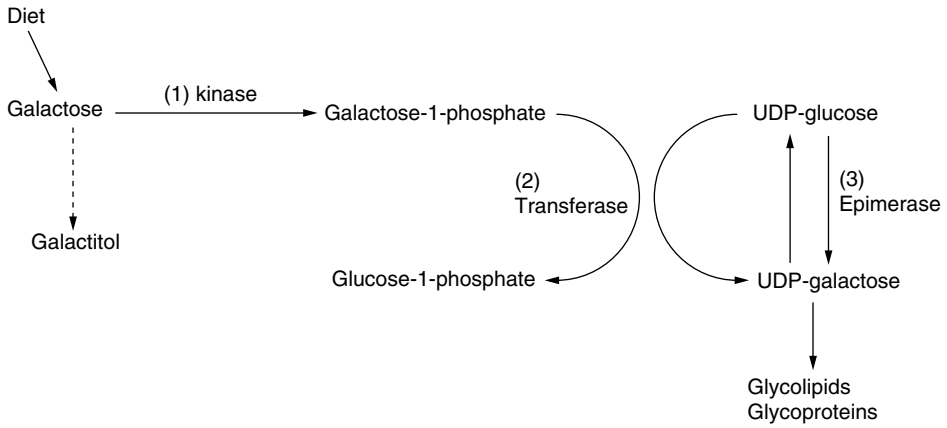


Figure 29.1 Pathways of glucose metabolism.

Table 29.2 Milk, milk products and milk derivatives that should be avoided in galactosaemia.

Milk and milk products
Cow's milk, goat's milk, sheep's milk
Cheese, cream, butter
Ice cream, yoghurt, fromage frais, crème fraiche
Chocolate
Milk derivatives
Skimmed milk powder, milk solids, milk protein, non-fat milk solids, separate milk solids
Whey, hydrolysed whey protein, margarine or shortening containing whey, whey syrup sweetener, casein, hydrolysed casein, sodium caseinate, calcium caseinate
Lactose*
Buttermilk, butter, artificial cream
Cheese powder
Filtrated/enzymatically treated low lactose dairy products (containing galactose)
Low lactose milk, cheese, yoghurt, cream and spreads
Lactose as a filler may be used in
Flavourings
Tabletop or tablet artificial sweeteners
Medicines

*Lactose powder is added to a diverse range of food products including bakery goods, confectionery, dry mixes, dried vegetables and crisps. It is added:

- To prepared foods to prevent caking or as a coating
- To bakery goods to enhance browning and to reduce sweetness (it has one sixth the sweetness of sucrose)
- As a filler and flowing agent in seasoning mixes for foods such as instant pot noodles or as a carrier for flavours and seasonings
- Maybe to ham, bacon and salami
- To some artificial tabletop or tablet sweeteners

avoided except for lactitol, a polyol made from galactose. Some residual galactose is left after its fermentation in the gut, so it is unsuitable

Galactosides

The α-galactosides are part of the oligosaccharides (raffinose, stachyose and verbascose) and are a potential source of galactose. They are found in foods such as peas, beans, lentils, soya beans, cocoa, nuts, wheat, oat flour and vegetables (Table 29.5).

Studies investigating the effects of galactosides in galactosaemia are rare, include limited numbers of subjects and are short term and inconclusive. The α-galactosidase linkage in oligosaccharides is not hydrolysable by the human small intestinal mucosa *in vitro* or *in vivo*. Instead, the galactosides are rapidly degraded and fermented by the caecal microflora to produce volatile short chain fatty acids. Galactosides are not avoided in the diet.

The International Galactosaemia Guidelines (2016) [3] recommend 'allowing any amount and type of fruits, vegetables, legumes, unfermented soy-based products. Although higher in galactose, all fermented soy-based products can be allowed in the small quantities that are typically used in the diet'.

Table 29.3 Galactose-restricted diet.

Manufactured foods that contain or could contain milk or milk derivatives are shown in italics. Food labels should always be checked as constituents change
Milk, milk products and milk derivatives
These should all be avoided (Table 29.2)
Plant and cereal milks
Infant soya formula
Liquid soya milk, other plant milks (e.g. almond, coconut, oat, rice*) – calcium enriched (not before 1 year of age)
Fats and oils
Milk-free margarine
Many margarines and low fat spreads contain milk
Vegetable oils
Lard, dripping, suet, ghee
Meat and fish
Meat, poultry, fish, shellfish (fresh or frozen)
Ham and bacon (lactose may be used as a flavour enhancer – see ingredient label)
Fish fingers
Quorn
Tofu
Many meat or fish products such as sausages, burgers, pies, breaded or battered foods or in sauce may not be suitable
Eggs
Cereal, flour, pasta
All grains; wheat, oats, corn, rice, barley, maize, sago, rye, tapioca
Pasta, spaghetti, macaroni, dried noodles, couscous
Tinned pasta such as spaghetti hoops may contain cheese
Flour: plain, self-raising; cornflour, rice flour, soya flour, pastry products
Semolina
Carob
Breakfast cereals
Most are suitable, e.g. Weetabix, cornflakes, Rice Krispies
Some cereals may contain chocolate derivatives or milk
Bread and yeast products
Most bread is suitable
Milk bread and naan bread contain milk, croissants and brioche
Pitta, chapatti
Muffins, crumpets and teacakes may not be suitable
Cakes, biscuits, crackers
Many cakes, biscuits and crackers contain milk
Desserts
Sorbet, jelly, soya/plant desserts, soya/plant ice cream, soya/plant yoghurt
Most desserts/dessert mixes contain milk in some form
Fruit
All fresh, frozen, tinned or dried fruit
Vegetables
All fresh, frozen, tinned or dried vegetables
Most dried and tinned pulses, e.g. red kidney beans, chickpeas, lentils
Baked beans and ready-made vegetable dishes such as coleslaw and potato salad may contain milk
Savoury snacks
Plain crisps, poppadom
Nuts, peanut butter
Flavoured crisps may not be suitable because they contain cheese or lactose as a filler in the flavouring
Dry roasted nuts and popcorn may contain milk/butter
Seasonings, gravies
Pepper, salt, pure spices and herbs, mustard

Table 29.3 (*continued*)

Marmite, Bovril, Bisto *Gravy granules and stock cubes may contain milk*
Soups *Tinned, packet and carton soups may contain lactose*
Sugar, sweet spreads Sugar, glucose, fructose Pure artificial sweeteners *Powdered and tablet artificial sweeteners may contain lactose* Jam, syrup, honey, marmalade, lemon curd
Confectionery Boiled sweets, most mints, marshmallow, plain fruit lollies, chewing gum *Milk chocolate, most plain chocolate, butterscotch, fudge and toffee contain milk* *Plain or carob chocolate may contain milk*
Drinks Soya, plant or nut drinks *Milk shake syrup or powders may contain milk* Fizzy drinks, squash, fruit juice Cocoa, tea, coffee *Drinking chocolate may contain milk* *Instant milk drinks and malted milk drinks – avoid*
Miscellaneous – used in baking Baking powder, yeast, gelatine, marzipan
Flavourings Lactose may be used as a 'carrier' for flavourings, particularly in crisps and similar snack foods. In sweets lactose is rarely used for this purpose except in some dairy flavours See Table 18.4

*Not recommended for children <4½ years old due to its high arsenic content.

Table 29.4 Non-milk derivatives.

Lactic acid E270, sodium lactate E325, potassium lactate E325, calcium lactate E327
Lactalbumin, lactoglobulin, lycasin, stearoyl lactylates, glucono-delta-lactone, monosodium glutamate, cocoa butter, non-dairy cream

Table 29.5 Dietary sources of galactosides.

Galactosides	Peas, beans, lentils, legumes, chickpeas, dhal, gram flour, spinach Texturised vegetable protein Soya (other than soya protein isolates), soya beans, soya flour Fermented soya products, e.g. soya sauce Cocoa, chocolate Nuts

Free and bound galactose

Free galactose is present in many fruits, vegetables and legumes (Table 29.6). Free galactose content may vary from <0.1 mg/100 g to 40 mg/100 g [21]. In selected plant materials, it ranges from 2 ± 0.1 mg/100 g in red potato to 39.7 mg/100 g in red pepper. The free galactose content of most fresh or processed fruits, vegetables and legumes is <50 mg/100 g serving [22], and an adult diet rich in fruits and vegetables was found to contain only 54 mg of galactose per day [23]. Free and bound galactose food sources are not restricted in the diet. Fermented soybean products (e.g. soya sauce, miso, tempeh) contain a greater concentration of free galactose since the fermentation process can release galactose from various oligosaccharides; they are still permitted in small quantities [3].

Table 29.6 Free galactose in fruit and vegetables (mg/100 g).

Food	UK*	USA
Tomato	10	23
Grape	<10	2.9
Cucumber	20	4.0
Banana	10	9.2
Watermelon		14.7
Kiwi fruit		10

*Unpublished data analysed by UK Galactosaemia Support Group [20].

Galactose storage organs

Offal is a source of galactocerebrosides and gangliosides. Small amounts of galactose may be present in free form and bound to proteins as glycoproteins and galactolipids. Cell lipids and proteins continuously undergo degradation, releasing glycerol, fatty acids, amino acids and their carbohydrate components, including galactose [24]. Their galactose content is unknown, but there is no evidence of any harmful effects in galactosaemia. In the UK they are not avoided, although the International Galactosaemia Guidelines suggest they be taken in moderation only [3].

Practical management of a low galactose diet

As the main source of galactose in foods, the avoidance of lactose is the key element in a galactose-restricted diet.

Milk substitutes

Breastfeeding and cow's milk-based infant formulas are contraindicated because they contain galactose. It is important that infants and young children be given a suitable nutritionally adequate formula.

Soya infant formula

The Medical Advisory Panel of the Galactosaemia Support Group (GSG) and the British Inherited Metabolic Disease Group (BIMDG) recommend that soya infant formula continues to be used as the first-choice low galactose infant formula for galactosaemia. While it is accepted that it contains a source of phytoestrogens with its associated mild risk of oestrogenicity, the potential disadvantages of other formulas far outweigh any concerns about the phytoestrogen content of soya infant formula. It is widely used by other countries and it has been safely given to infants with galactosaemia for

over 40 years. Nevertheless, caregivers should be informed about the phytoestrogen content of soya infant formula and be reassured about its safety for their infant.

Nutritionally complete soya infant formula, e.g. SMA Wysoy, is lactose-free. There is no evidence soya infant formula is a factor in the fertility problems seen in galactosaemia.

Low lactose and protein hydrolysate formulas

Other suitable infant formulas include low lactose formulas and casein hydrolysate formulas (Table 29.7). Medium chain triglyceride (MCT)-based casein hydrolysate infant formula, such as Pregestimil Lipil, may be advantageous when there is significant liver disease and should be administered until this complication has resolved.

All low lactose and protein casein hydrolysate formulas based on cow's milk protein contain some residual lactose, and the amounts vary. Manufacturers of these formulas declare their lactose content at <10 mg/100 kcal (420 kJ) as defined by the European Food Safety Authority [25]. A 5 kg infant taking 200 mL/kg of formula would have <14 mg/kg/day (or a maximum of 69 mg/day) of galactose from this source. Whey hydrolysate formulas contain a higher concentration of residual lactose and are unsuitable. Enteral feeds for older children based on whey hydrolysates are also unsuitable.

Table 29.7 Low lactose, casein hydrolysate and amino acid formulas for infants with galactosaemia.

Infant formula	Protein source	Lactose content (per 100 mL)
Low lactose		
Galactomin 17 (Nutricia)	Caseinate	6 mg
Casein hydrolysate		
Nutramigen 1 with LGG (Mead Johnson)	Enzymatically hydrolysed casein	<5 mg
Nutramigen 2 with LGG (Mead Johnson) (not suitable for infants under 6 months)	Enzymatically hydrolysed casein	<5 mg
Pregestimil Lipil (Mead Johnson)	Enzymatically hydrolysed casein	<5 mg
Similac Alimentum (Abbott Laboratories)	Enzymatically hydrolysed casein	<5 mg
Amino acids		
Alfamino (Nestle Health Science)	L-Amino acids	Nil
Neocate LCP (Nutricia)	L-Amino acids	Nil
Neocate Syneo (Nutricia)	L-Amino acids	Nil
Nutramigen Puramino (Mead Johnson)	L-Amino acids	Nil
Infant weaning food		
Neocate Spoon (Nutricia) (not suitable for infants under 6 months)	L-Amino acids	Nil

Amino acid-based formulas

Amino acid-based formulas are lactose-free and used by some centres. They are more likely than soya infant formulas to be fortified with novel nutrients, such as long chain polyunsaturated fatty acids, but are considered less palatable.

Plant, cereal and nut drinks for children over 1 year of age

Many commercial nutritionally enriched plant, cereal and nut drinks (e.g. soya, oat, rice, coconut, hazelnut and almond) are suitable. Most contain approximately 120 mg/100 mL of calcium and 0.8 µg/100 mL of vitamin D. There are also nutritionally enriched follow-on soya milks designed for children >1 year with added calcium, iron, vitamin D, some B vitamins and an energy profile similar to cow's milk (e.g. Alpro Soya Growing Up milk). Calcium absorption from soya drinks is similar to that from cows' milk.

Rice milk, which is suitable in galactosaemia, contains traces of inorganic arsenic, and the UK Food Standards Agency recommend children aged between 1 and 4½ years should avoid rice milk.

Unsafe milks/drinks

Since lactose is the carbohydrate source in animal milks, e.g. goat's and sheep's milks, these are unsuitable. A low lactose dairy drink, Lactofree (Arla), where approximately half the lactose content is removed by filtration and the remainder is removed enzymatically, is available. However, it contains a significant quantity of galactose, rendering it unsuitable for galactosaemia (Table 29.1) [20].

Lactase enzyme drops, which reduce the lactose content of cow's milk, are also unsuitable as the drops digest the lactose into glucose and galactose.

Cheeses

Hard mature cheeses

Cheese is a good source of calcium and other nutrients and provides additional variety in the diet. The International Galactosaemia Guidelines [3] recommend that any mature cheese with a galactose content <25 mg/100 g is suitable (Table 29.8). The fermentation process and bacterial fermentation lower the lactose content. Most mature cheese types have high levels of casein (which contains no more than 1% lactose) and low levels of whey (which contains 70% lactose). The lactose content is reduced by the removal of whey by

Table 29.8 Types of mature cheese allowed in galactosaemia (galactose content <25 mg/100 g).

Extra mature cheddar (typically 12–15 months old)
Vintage cheddar (typically 15–18 months old)
Emmental
Gruyere
Jarlsberg
Comte
Italian parmesan (Parmigiano Reggiano and Grana Padano)

These cheeses have been extensively tested for their lactose and galactose content [26] and have been shown to contain minimal lactose and galactose on repeated analysis.

drainage (during this stage approximately 98% of the lactose will be removed). The type of starter culture, coagulating enzyme and the acid produced can all alter lactose content by influencing the properties of the curd and the degree of whey expulsion.

For harder cheeses the curd is cut into small cubes, which allows fluid to drain from the individual pieces of curd. Any residual lactose in cheese curd is metabolised during its ripening process [27], and, generally, the longer the cheese has matured, the lower its lactose content.

Other cheeses are not permitted. Specific analysis has been commissioned by the UK Galactosaemia Medical Advisory Panel to test gouda, edam and some soft and processed cheeses, but all contain lactose and galactose and are not suitable [26].

Plant cheeses

Plant cheeses are suitable. They are dairy-free and made from nuts, such as cashew, almond and pine nuts; soybeans; coconut oil; rice; and other ingredients. However, some are low in protein and other nutrients, such as calcium.

Enzyme-treated cheese products

Lactofree cheese produced from Lactofree milk is not recommended.

Manufactured foods

Interpreting galactose on food labels

As galactose is found in milk sources, it is important to teach caregivers and patients how to identify milk on food labels. It is mandatory that a milk source is identified on the ingredient list of pre-packed foods (listed either in bold, in an alternative colour or by underlining). The word 'milk' does not need to appear if a milk product such as cheese, cream, yoghurt or butter is an ingredient because these foods, legally, can only be made from animal milks. It is mandatory to identify milk when the reference is to a less familiar dairy product or ingredient, e.g. quark (**milk**) and whey (**milk**).

Cross-contamination of manufactured foods with milk

Both milk-free and milk-containing foods may be manufactured in the same plant or even using the same machinery. Cross-contamination with milk is always possible, and if there is a risk of a food product being cross-contaminated, the label should include one of the following statements: 'may contain milk' or 'not suitable for someone with milk allergy'.

The UK Galactosaemia Support Group Medical Advisory Panel permits foods that are labelled with a risk of cross-contamination with milk. It is likely the quantity of milk is minimal.

Vitamin and mineral supplementation

Many nutrients are involved in optimum bone metabolism, particularly calcium, phosphate and vitamin D. Vitamin K also has an important role, acting as a cofactor in the post-translational carboxylation of osteocalcin, which has a regulatory role in the mineralisation and remodelling of bone [28]. Vitamin K supplementation may be beneficial when combined with an adequate intake of calcium and vitamin D, but currently there is not enough evidence to recommend this.

Calcium and vitamin D

It is important to ensure the reference nutrient intake (RNI) for all bone-related nutrients is provided. Calcium intake may be low. The UK RNI for calcium varies between 325 and 1000 mg daily in children and teenagers [29]. Wherever possible, calcium requirements should be achieved from food. Soya infant formula can provide RNI for calcium (age 0–2 years) provided an adequate amount is taken. With advancing age it may be necessary to change to a calcium-enriched plant drink (preferably supplemented with vitamin D). Suitable food sources should be encouraged to ensure adequate intake: low galactose cheese, plant yoghurts, sardines, mackerel, sesame seeds and lentils (Table 29.9).

A calcium supplement may be needed. This can be challenging mainly because of the size, type of presentation (mostly tablets rather than liquid) and nutritional composition available for children. Additional vitamin D supplementation will aid calcium absorption, e.g. Healthy Start vitamin drops (Table 1.22). Alternatively, there are several prescribable calcium supplements with added vitamin D (Table 29.10). The latter are mainly chewable or dissolvable in water. They are bulky and unpopular with children and adherence is an issue. There are no suitable liquid calcium supplements listed in the British National Formulary (BNF) for children. If the diet as a whole is poor, it may be necessary to give a more comprehensive vitamin and mineral supplement, e.g. Paediatric Seravit or FruitiVits (suitable from 3 years of age). Ideally calcium supplements should be co-administered with vitamin D and given in more than one

Table 29.9 Food sources of calcium for galactosaemia [17].

	Calcium (mg)	Vitamin D (µg)
	per 100 mL/100 g	
Calcium/vitamin D enriched soya drinks	100–140	0.8
Soya dairy-free yoghurts	120	Variable
Low lactose hard cheese	730	0.3
Whitebait	860	Not available
Sardines in oil/brine	500	5
Pilchards	250	14
Sesame seeds	670	0
Red kidney beans	100	0
Bread	170	0
Spinach	170	0
Apricots	73	0

Source: Licensed under Open Government.

Table 29.10 Suitable calcium supplements for galactosaemia.

	Presentation	Available calcium (mg)	Vitamin D (μg)
Adcal-D3 (Kyowa Kirin Ltd). Calcium carbonate. Chewable tablet/effervescent tablets. Not licensed for children under 12 years.	Tablet	600	10
Cacit-D3 (Warner Chilcott UK Ltd). Calcium carbonate. Granules. Not licensed for use in children.	Sachet	500	11
Calceos (Galen). Calcium carbonate. Chewable tablet.	Tablet	500	10
Calcichew D3 (Takeda UK Ltd). Calcium carbonate. Chewable tablet.	Tablet	500	5
Calcichew D3 Forte (Takeda UK Ltd). Calcium carbonate. Chewable tablet.	Tablet	500	10
Natecal D3 (Chiesi Ltd). Calcium carbonate. Chewable tablet.	Tablet	600	10

Information from manufacturers' data cards.

daily dose. The International Galactosaemia Guidelines (2016) [3] recommend 'an annual dietary assessment of calcium and vitamin D intake with measurement of plasma total 25-OH-vitamin D levels. Both calcium and vitamin D should be supplemented as necessary following the age-specific recommendations for the general population'.

Iodine

Cow's milk is usually a rich source of iodine in the diet (depending on dairy farming practices). Many plant milks are not fortified with iodine [30]. If patients with galactosaemia use these, it is important to encourage alternative dietary sources such as seafood and eggs. An iodine-containing supplement (not kelp or seaweed owing to risk of iodine excess) may need to be considered. A 3-day dietary food record to assess iodine intake should be undertaken annually.

Lactose in medications

Lactose is an excipient with properties that make it ideal as a tablet filler or binder, and it is found in many medications; for most the amount of lactose is unlikely to be significant, particularly if the medication is being used for a short time period [31], but it is still important to check the amount. Lactulose contains high quantities of lactose and galactose: 1 mL contains <100 mg galactose and 67 mg lactose [32] and is contraindicated in galactosaemia.

Contraceptive pills prescribed for oestrogen insufficiency contain lactose as an excipient and provide approximately 20–65 mg lactose/day (manufacturers' data sheets).

Some toothpastes and shampoos may contain milk derivatives. No recommendation is given to avoid these. Although young children may swallow some toothpaste, the amount should only be small.

Long-term dietary treatment

A lifelong galactose-restricted diet is recommended for galactosaemia although there is debate about how strict dietary treatment should be in teenage years and beyond. Overall there is little evidence to support the safety of discontinuation of the galactose-restricted diet.

UK Galactosaemia Support Group

The UK Galactosaemia Support Group (www.galactosaemia.org) produces a wide range of educational materials for parents and caregivers including a galactose-restricted diet guide for children and adults, a small dietary shopping card, Easter and Christmas lists of suitable treats, information about healthy bones and a glossary of food ingredient definitions. It has also commissioned the analysis of several foods for their lactose and galactose content and employs a dietitian who produces much of the dietary information.

Dietary restriction in pregnancy

There is no advantage to restricting milk in the mother's diet during pregnancy.

Case study

A case study demonstrating the dietary management of an infant diagnosed in the neonatal period is given in Table 29.11.

Learning points: galactosaemia

- *Galactosaemia usually presents as a life-threatening illness in infancy and early symptoms resolve with a galactose restricted diet*
- *Comprehensive international guidelines for the medical and dietary management of galactosaemia are available [3]*
- *The UK Galactosaemia Support Group produces practical resources to help patients with dietary management*

Galactokinase deficiency and UDP-galactose-4-epimerase

These are very rare disorders of galactose metabolism. Clinical, biochemical and dietetic overview can be found in the 4th edition of *Clinical Paediatric Dietetics* [33].

Table 29.11 Case study: clinical presentation of galactosaemia in the neonatal period.

Baby boy, born full term, discharged home from local hospital on day 3
Fully breastfed, birthweight = 4.5 kg
Appeared well except for jaundice
Feeding deteriorated and he started vomiting
Admitted to a local hospital, diagnosed with a urine infection and commenced antibiotics. However, he was also found to have liver dysfunction with deranged clotting and intermittent hypoglycaemia and was transferred to a paediatric liver ward. Galactosaemia was suspected; breastfeeding was stopped; soya infant formula was given; fluids were restricted
Over the next 3 days, fluid intake was gradually increased to normal requirements; liver function similarly improved; he tolerated the soya infant formula and his clinical symptoms ameliorated within 48 hours
Classical galactosaemia was diagnosed with a galactose-1-phosphate concentration >2000 μmol/L and determination of galactose-1-phosphate uridyltransferase activity. He was homozygous for the Q188R mutation.
Discharged home on a galactose-restricted diet only
He drank soya infant formula without difficulty, and galactose-restricted solids were introduced at 20 weeks of age. Parents gradually expanded his diet according to his age, introducing low lactose cheese, plant yoghurts and other suitable products
His galactose-1-phosphate concentration only slowly lowered to within treatment range during the first year despite excellent dietary adherence
He continued to feed well and gained weight appropriately
At the age of 2 years, he was changed onto a toddler calcium and vitamin D enriched commercial soya drink. His weight and length were adequate, as were his intakes of calcium and vitamin D
At the age of 3 years, his clinical progress is good, but speech is slightly delayed. His nutrient intake, growth and galactose-1-phosphate concentrations are assessed twice per year

Glycogen Storage Disorders

Marjorie Dixon and Fiona J. White

Introduction to glycogen metabolism

Glycogen, the storage form of carbohydrates (CHO), is found predominantly in the liver and skeletal muscle; minor stores are found in the heart and brain. It is a large molecule containing up to 60 000 glucose moieties that are linked in straight chains with α-1,4 glycosidic bonds, and branched with α-1,6 glycosidic bonds, at intervals of 4–10 glucose residues, thus forming a glucose reservoir. Glycogen is a major fuel source. In the fed state glucose forms glycogen (glycogenesis). Glycogen synthase catalyses the formation of the α-1,4 linkages between glucose molecules, enabling the glucose chain to elongate, forming amylose. Glycogen branching enzyme then catalyses the formation of the α-1,6-linked branch points to enable assembly of side chains of glucose molecules, amylopectin, resulting in the polymer, glycogen. In the fasting state liver glycogen is degraded (glycogenolysis) to glucose-6-phosphate via a series of enzymatic reactions. Phosphorylase kinase activates glycogen phosphorylase, the rate-limiting step in glycogenolysis, which shortens the unbranched outer α-1,4 links of the glycogen molecule to release glucose-1-phosphate and leave four glucosyl units at the α-1,6 branch point. The debrancher enzyme then performs two catalytic functions: the transferase component transfers three glucose residues (from the shortened glycogen branch) to the end of a neighbouring glycogen branch (which glycogen phosphorylase then shortens), leaving one glucose moiety at the α-1,6 branch point, and the glucosidase component releases the single glucose moiety and breaks the branch point – hence the name debrancher enzyme. Phosphoglucomutase then converts glucose-1-phosphate into glucose-6-phosphate (G6P). Skeletal muscle glycogen is predominantly degraded to glucose-6-phosphate where it is used by muscle fibres during contractions and converted to lactate, as detailed below.

G6P has three fates:

- conversion to free glucose via glucose-6-phosphatase, which occurs predominantly in the liver, for release into the bloodstream
- as the initial substrate for energy production via glycolysis, forming pyruvate. Under aerobic conditions pyruvate is oxidised to form ATP; under anaerobic conditions in active muscle tissue, it is converted to lactate. Lactate generated from muscle glycogen or glucose can be transported via the bloodstream to the liver and, via the gluconeogenic pathway, to reform glucose. This recycling pathway is known as the Cori cycle
- processed by the pentose phosphate pathway to yield NADPH and ribose derivatives

Gluconeogenesis is the reversal of glycolysis and is another major pathway for glucose formation via G6P from

lactate, pyruvate, gluconeogenic amino acids and glycerol. Fructose and galactose can also enter the gluconeogenic pathway to form glucose or, via glycolysis, forms pyruvate and lactate (Figure 29.2). A more detailed review of glycogen metabolism is given elsewhere [34].

Defects of most enzymatic reactions involved in glycogen metabolism have been identified and collectively are known as the glycogen storage disorders (GSD). These are notated by a Roman numeral, the deficient enzyme or the person who first described the disorder (Figure 29.2, Table 29.12). In this section the hepatic GSD are discussed as these are treated primarily by diet. Treatment ranges from complex intensive feeding routines with overnight tube feeds to more straightforward avoidance of fasting and management of illness.

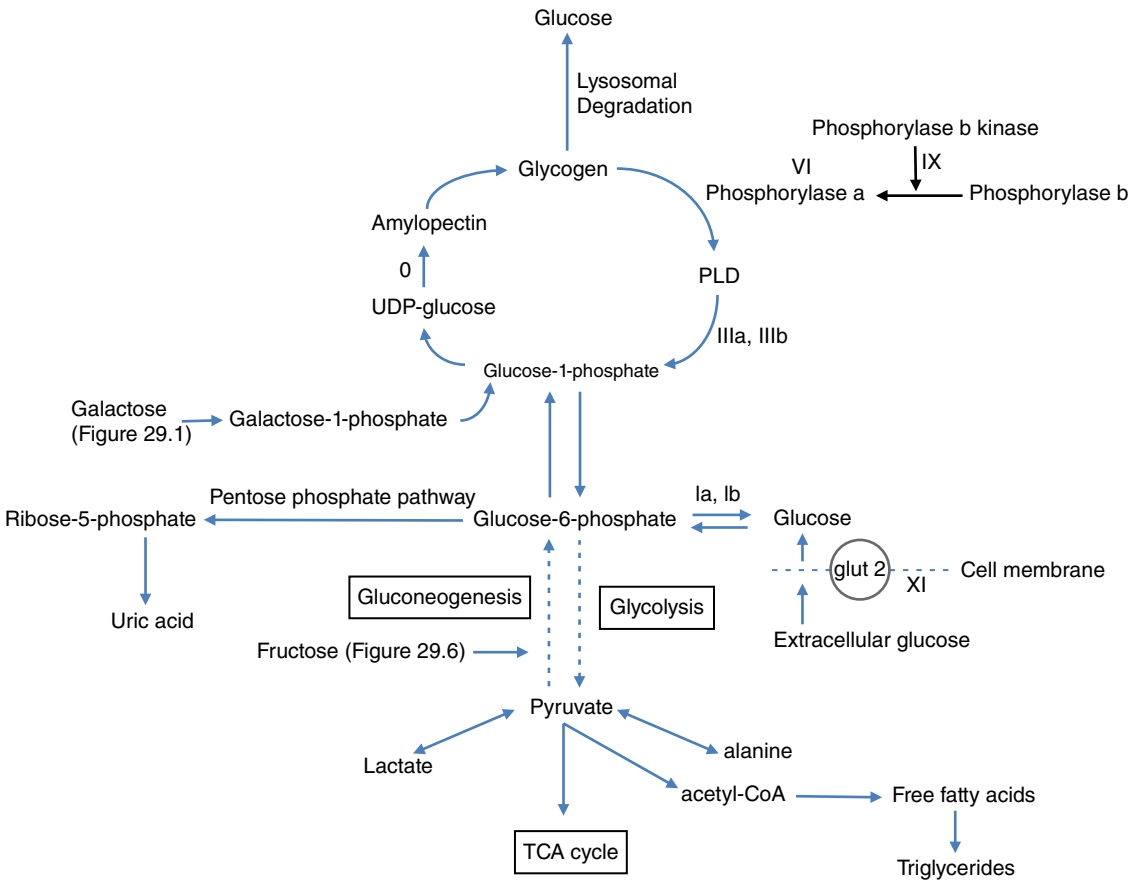


Figure 29.2 Pathway of liver glycogen metabolism. UDP-glucose, uridine diphosphate glucose; PLD, phosphorylase limit dextrin; TCA, tricarboxylic acid.

Table 29.12 Hepatic glycogen storage disorders, nomenclature and main organs involved.

Type	Eponym	Enzyme deficiency	Principal organs involved
0		Glycogen synthase	Liver
Ia	Von Gierke	Glucose-6-phosphatase	Liver, kidney
Ib		Glucose-6-phosphatase translocase	Liver, kidney and leucocytes
III a/b	Cori, Forbes	Debranching enzyme and subtypes	Liver +/– muscle
VI	Hers	Phosphorylase	Liver
IX		Phosphorylase kinase and subtypes	Liver and/or muscle
XI	Fanconi Bickel	Glut 2	Liver, kidney

Glycogen storage disease type I

Marjorie Dixon

Enzyme

Glucose-6-phosphatase system

Biochemical defect

Two subtypes:

- GSD type Ia – Deficiency of glucose-6-phosphatase that hydrolyses G6P into glucose and inorganic phosphate. Expressed in liver, renal cortex and intestinal mucosa, but not muscle.
- GSD type Ib – Deficiency of glucose-6-phosphate transporter protein (G6P translocase) that transports G6P from the cytoplasm across the endoplasmic reticulum membrane into the lumen for hydrolysis [35]. Expressed ubiquitously.

The glucose-6-phosphatase system is the final common pathway reaction for endogenous glucose synthesis from both glycogenolysis and gluconeogenesis (Figure 29.2). Glucose production is inadequate if either enzyme is deficient. Hypoglycaemia results after relatively short periods of fasting when exogenous glucose sources are depleted, typically around 2 hours. As G6P cannot form glucose, there is increased glycolytic flux, which leads to secondary metabolic derangements of lactic acidosis (with or without hyperventilation), hyperuricaemia and hyperlipidaemia, with triglycerides more markedly elevated than cholesterol [36]. Hyperlipidaemia is likely due to increased *de novo* lipid synthesis from excess acetyl-CoA (formed from pyruvate) and decreased lipid serum clearance [37]. Hyperuricaemia is caused by decreased renal clearance due to competition with lactate for excretion and increased breakdown of adenine nucleotides to uric acid [38]. Ketone body production, as an alternative fuel during fasting, is reduced because excess acetyl-CoA leads to increased concentrations of malonyl-CoA, which promotes lipid synthesis rather than oxidation of fatty acids to form ketones.

Genetics

GSD types Ia and Ib are autosomal recessive inherited disorders. GSDIa occurs more frequently (about 80% of GSDI patients) than type Ib and is the most common of the hepatic GSD.

Clinical presentation, features

Can present in the neonatal period, but more typically occurs later in infancy between 4 and 6 months when periods of fasting are extended, particularly overnight. The resulting fast-induced hypoglycaemic episode can cause seizures and lactic acidosis. Features include growth retardation, truncal obesity and muscle wasting, rounded doll-like facies and hepatomegaly (causing a protuberant abdomen) due mainly to fatty infiltration of the liver; bruising and bleeding can occur due to platelet dysfunction [38, 39]. These features can also be seen in treated patients, but generally to a lesser extent.
Additionally in type Ib, there is chronic neutropenia and impaired neutrophil function, which increases susceptibility to recurrent bacterial infections, oral and intestinal mucosal ulcerations and a chronic inflammatory bowel disease (IBD) similar histopathologically to Crohn's disease [40–43]. Neutropenia is considered due to increased apoptosis of mature neutrophils and the movement of neutrophils from blood to inflamed tissues.

Long-term complications

Renal disease (both glomerular and tubular dysfunction) and hypertension in some [44]; hepatic tumours (mostly benign adenoma, but with the potential for malignant transformation), which develop predominantly during and after puberty [45]; low bone mineral density and osteopenia [46, 47]; anaemia [48]; polycystic ovaries in females [49, 50]. GSDIa patients are at risk of developing insulin resistance and metabolic syndrome [51, 52]. There are only a few reports of diabetes in the literature [53].

Medical treatment

Acute management of hypoglycaemia and correction of biochemical abnormalities. Medicines are prescribed to correct the latter and to help prevent long-term complications, e.g. allopurinol if plasma urate is raised, an ACE inhibitor for persistent microalbuminuria, both to help preserve kidney function. There are reports of successful liver [54, 55] and hepatocyte transplants [56] in GSDI patients. Liver transplant corrects the metabolic derangement, but some type Ib patients still experience frequent infections [55, 57]. Hematopoietic stem cell transplant is an option to treat neutropenia and neutrophil dysfunction in GSDIb, but the need for intensive dietary treatment remains [58]. Post-liver transplant dietary treatment is no longer indicated, but tube feeding may still be necessary because of ongoing feeding problems [59].

Type Ib
Granulocyte-colony stimulating factor (G-CSF) treatment increases neutrophil count and decreases fever, infection and severity of IBD; however, splenomegaly with abdominal pain is a complication and limits dosage [40, 58]. Vitamin E supplementation, given for its antioxidant properties, is reported to improve neutrophil function, reduce infections and enable a decrease in G-CSF doses [60, 61].

Dietetic management

Infants and children need a frequent supply of CHO both day and night to maintain normoglycaemia. Provision of CHO varies by age and fasting tolerance; typically 2 hourly daytime feeds for infants and young children. From around 1 to 2 years: introduction of uncooked cornstarch (UCCS) may extend fasting tolerance; for older children: continuous tube feeds or UCCS at night. Post-puberty, CHO therapy is still needed, but may be less frequent.

Emergency regimen

During intercurrent infections, glucose polymer solution is given to maintain normoglycaemia and prevent hypoglycaemia and lactic acidosis. The emergency regimen (ER) should provide at least adequate CHO to meet endogenous glucose production rates for age (Table 29.13) or the child's usual CHO requirement. A standard ER may provide too much glucose and cause hyperglycaemia and thus risk of rebound hypoglycaemia.

Monitoring

Clinical, anthropometric and biochemical monitoring is essential to assess efficacy and guide dietary treatment, which aims to promote normal growth, minimise secondary biochemical abnormalities and help delay the onset and severity of long-term complications. More detailed clinical and biochemical monitoring is given on p. 617.

Clinical management guideline	Kishnani P, Austin SI, Abdenur JE et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med.* 2014, 16(11) e1 [63]. Rake JP, Visser G, Labrune P et al. Guidelines for management of glycogen storage disease type I – European Study on Glycogen Storage Disease Type I (ESGSDI). *Eur J Pediatr.* 2002, 161(1) S112–119 [64]. Visser G, Rake JP, Labrune P et al. Consensus guidelines for the management of glycogen storage disease type 1b – European Study on Glycogen Storage Disease type 1. *Eur J Pediatr*, 2002, 160(1) S120–3 [40].
Parent support group	Association for Glycogen Storage Disease (UK) (www.agsd.org.uk)

Dietary management

Aims are to:

- maintain a constant normal blood glucose concentration without large swings. Hypoglycaemia carries the risk of neurological complications [65], and hyperglycaemia can cause hyperinsulinism and, long term, may lead to insulin resistance [52, 53]
- help correct secondary biochemical abnormalities by maintenance of normoglycaemia, though it is recognised that these cannot be completely normalised [66]; hyperlipidaemia is frequently observed on treatment [36, 37]
- optimise and promote normal growth and maintain a healthy body mass index (BMI) as overweight and obesity is a common problem [51, 67, 68]
- promote exercise, although it is recognised that exercise capacity can be reduced in some [69]; less active children should have a lower energy intake
- help delay or prevent long-term complications

Provision of carbohydrate

- Per cent energy intake of the diet in children who are eating is typically: 40% from UCCS and glucose polymer and from food 20%–30% CHO, 20%–30% fat and 10%–15% protein
- glucose intakes are calculated to be similar to normal hepatic endogenous glucose production rates [62, 70–72], but should be adjusted to achieve good biochemical control (p. 617); more or less glucose may be needed.
- glucose requirements (g/kg/hour or mg/kg/min) decrease with age (Table 29.13)
- insufficient CHO leads to high plasma lactate levels and growth retardation; excessive CHO induces peripheral body fat storage due to glycogen overload and hyperlipidaemia

Table 29.13 Glucose requirements based on endogenous glucose production rates [62].

Age	Glucose (mg/kg/minutes)	Glucose (g/kg/hour)	
		Day	Night
Infants	8–9	0.5	0.5
Toddlers and children	5–7	0.3–0.4	0.3–0.4
Adolescents and adults	2–4 at night		0.2–0.25

- large quantities of glucose exacerbate swings in blood glucose levels and make patients more prone to hyperglycaemia and rebound hypoglycaemia [64]
- CHO usually needs to be given at 2 hourly intervals or more often in infants and young children not on UCCS and Ib patients who often have a poor response to UCCS
- CHO is given during the day as infant formula and glucose polymer, complex CHO from food and UCCS
- CHO is given overnight as continuous tube feeds (infant formula, paediatric enteral feed with glucose polymer or just glucose polymer) or UCCS
- guidance on amounts of CHO foods to eat at each meal and snack should be given, as around 40% of energy intake may be provided by night feeds, UCCS and glucose polymer
- avoidance of foods with a high sugar content is important to prevent swings in blood glucose levels and excessive glucose and energy intake
- vitamin and mineral supplements are necessary because of the high energy intake from pure starch and glucose

Fructose and galactose

- fructose and galactose are not metabolised to G6P for glucose production, but instead may lead to increased lactate production via glycolysis [73]
- there is no consensus about the need to restrict these sugars, and management between countries differs [63]; UK centres generally do not limit these sugars
- a mildly elevated blood lactate level of up to 4.0 mmol/L is considered acceptable by some because lactate provides an alternative source of energy to the brain and, therefore, has a protective effect against fuel depletion [74]
- hypoglycaemia can have a detrimental impact on brain function [65]
- some children have near-normal plasma lactate despite including dietary fructose and lactose
- intake of these sugars will inadvertently be reduced because pure starch (UCCS) and glucose polymer provide around 40% of energy intake
- if plasma lactate is persistently elevated on an unrestricted diet, a trial of reducing fructose and galactose may be warranted
- as the intake of fruit, vegetables, milk and dairy products is limited, vitamin and mineral supplements (specifically calcium and vitamin D) are necessary

Fat

- fat intake needs to be decreased to compensate for increased CHO intake
- replacement of saturated with polyunsaturated fats is recommended by some in an attempt to improve hyperlipidaemia, but this is much less important than supplying a frequent CHO intake and avoiding overtreatment
- despite persistent hyperlipidaemia, no evidence of endothelial dysfunction or premature atherosclerosis has been observed [75–77]; however, others suggest patients may be at increased risk of cardiovascular disease [78]
- two small cohort studies [79, 80] have reported that using MCT as a fuel may allow a reduction of energy from CHO; concerns have been raised about the possible benefits of all the biochemical changes from adding MCT [52]
- MCT is not standard dietary treatment of GSDI

Tube feeding overnight

- continuous gastrostomy feeding is used to provide overnight feeds in type Ia, but gastrostomy is contraindicated in type Ib because of infection risk and poor wound healing [65]
- continuous nasogastric (NG) feeding is used to provide overnight feeds in type Ib, but there are risks, including aspiration [81]. Some families have a care package for home with a healthcare professional to manage and monitor the overnight NG tube feeding
- parents need to undergo competency training for any form of tube feeding
- the feed pump must accurately control flow rate and alarm immediately if there is electrical or mechanical failure; fatalities have been reported because of unplanned cessation in delivery of the glucose feed or failure to switch on the pump delivering the feed [81]
- to prevent any leaks, the tubing used for feed delivery must be secure
- an enuresis alarm may be helpful in identifying any leakage of feed into the bed
- some parents use baby alarms to hear if their child is restless or wakens during the night as this can be a sign of problems with the overnight feed or hypoglycaemia
- continuous overnight feeds usually continue until the child stops growing when it may be possible to maintain normoglycaemia overnight with UCCS; more than one dose overnight may be required

Diet for infants

Newly diagnosed infants will be managed in hospital where fasting tolerance needs to be determined:

- most infants need to be fed at 2 hourly intervals with some needing feeds every 90 minutes (often type Ib)
- bedside blood glucose monitoring is used to guide dietary treatment; ideally 24 hour blood glucose and lactate profile (1–2 hourly measurements) should be done before discharge
- infants <4–6 months of age require around 0.5 g glucose/kg/hour (Table 29.13), which can be provided by the lactose in standard infant formula fed at normal volumes of 150–180 mL/kg; both galactose and glucose contribute towards the glucose requirement
- glucose polymer is added to infant formula if:
  - the normal fluid volume for age and weight provides insufficient glucose
  - inadequate feed volume is consumed
  - blood glucose and lactate control is not optimal
- NB: adding glucose polymer increases energy content; therefore, the feed volume may need to be decreased to maintain a normal energy intake and avoid overfeeding. Maintenance of adequate protein and micronutrient intake is essential; supplements may be required if feed volume limits these. Alternatively, a modular feed could be considered with reduced fat to compensate for the increased CHO energy and thus to achieve a normal total energy intake
- some centres use a soya infant formula to avoid galactose and provide all the glucose as glucose polymer
- at night the feed is given continuously via a pump, usually administered for 8–10 hours. At the beginning and end of the night feed, an oral or bolus feed providing sufficient glucose to last for 30 minutes is given (i.e. 50% of the volume given for 1 hour from the night feed)
- breastfeeding is possible though is demanding for a mother: at least 2 hourly daytime feeding is necessary; a very small volume top-up feed of 10%–20% glucose polymer solution with each breastfeed may be necessary to maintain normoglycaemia. Expressed breastmilk can be used for the continuous overnight feed or infant formula could be given instead. Additional breastfeeds may be given during the night
- regular 1–2 weekly monitoring of growth is essential to adjust feeds and optimise management

An example of an infant's feeding regimen is shown in Table 29.14.

Weaning onto solid foods

The introduction of solid foods can begin around 6 months (26 weeks) of age:

- continue to provide 0.5 g glucose/kg/hour
- often the infant is not hungry because of the frequent day and overnight feeding; establishing food intake is often difficult and invariably there is reliance on tube feeding
- solids should contain complex CHO foods such as baby rice, oat/wheat-based cereal, rusk, potato, pasta to provide glucose and low fat protein foods such as chicken, lean red meat, white fish and pulses
- as starchy food intake increases, it can replace part or all of the infant feed at main meals as the source of glucose for the following 2 hours
- parents need to count CHO to ensure sufficient is given at each meal and to avoid excess; a list of the weights of starchy foods that will provide specified amounts of CHO for 2 hours is given, and parents are taught to

Table 29.14 Example feeding regimen for a female infant, age 10 weeks, with GSDI.

	Aim 0.5 g* glucose/kg/hour (Table 29.13)					
		Energy				
Weight = 5 kg	Fluid (mL)	(kcal)	(kJ)	CHO (lactose) (g)	Protein (g)	Fat (g)
SMA PRO 1	840	562	2352	60	10.5	30
Amount/kg	170	112	470	12.0	2.1	
Amount/kg/hour				0.5*		
Amount/hour				2.5		
% energy intake				43%	8%	48%

Daily feed distribution

Day:	Oral feeds 70 mL
	06.30, 08.00, 10.00, 12.00, 14.00, 16.00, 18.00, 20.00 = 560 mL
Night:	Continuous nasogastric feeds 35 mL every hour from 22.00, finishing at 06.00 = 280 mL
	Bolus nasogastric feeds 20 mL at 22.00 and 06.30 (extra to calculated fluid requirement)

*Lactose = 0.25 g glucose and 0.25 g galactose. Glucose polymer can be added to provide more glucose, as indicated by blood glucose and lactate results.

calculate and weigh the amount of food required using the CHO analysis on food labels, for example, an infant weighing 8 kg requires 0.5 g glucose/kg/hour, which equates to 8 g CHO for 2 hours:
  - Step 1: Look at total CHO content per 100 g of food (on nutrition analysis label)
  - Step 2: Then 100 ÷ by the CHO content per 100 g of food
  - Step 3: Multiply the answer by 8 (or other amount of CHO required) = weight of food, which provides 8 g CHO (or other amount of CHO required)
- if insufficient food is eaten, then a full feed or a top-up feed of infant formula with a total concentration of 12%–15% CHO is given to provide the 2 hourly CHO requirement
- boluses of pure glucose polymer are best avoided because it is rapidly absorbed, may cause swings in blood glucose and may not maintain blood glucose for 2 hours in some patients
- for the overnight feed the volume of infant formula is decreased, and glucose polymer added to provide around 0.5 g glucose/kg/hour, with the ultimate aim of providing all CHO as glucose polymer from about 1 year of age, provided weaning is well established and the child has a good food intake
- the daily feeding regimen must be nutritionally adequate and meet protein requirements; this can be compromised in patients on high CHO diets and who also do not eat well. Vitamin and mineral supplements are often necessary

An example of a weaning diet is shown in Table 29.15.

Diet for children

- provide 0.3–0.5 g glucose/kg/hour (Table 29.13)
- under 2 years of age the daytime glucose continues to be given at 2 hourly intervals (or more often) either from a meal or snack containing complex CHO or a paediatric enteral feed with added glucose polymer
- starchy foods such as potato, rice, pasta, bread and breakfast cereals are encouraged in preference to sugary foods as these are more slowly digested to produce glucose
- from around 1 year of age the night feed is changed to a solution of glucose polymer up to 15% CHO concentration in 1 to 2 year olds, providing weaning is well established; 20% CHO for 2 to 6 year olds; 25% up to a maximum of 30% CHO for older children. Often a vitamin and mineral supplement is added to this feed
- occasionally, a paediatric enteral feed is administered at night in preference to glucose polymer alone, particularly if growth or food (and nutrient) intakes are inadequate
- many children find it very difficult to eat breakfast due to being fed overnight; CHO may need to be provided from simple sugar such as glucose polymer, milk or fruit juice as a drink or mixed with the dose of UCCS
- in type Ib bacterial infections, oral and intestinal mouth ulcers and chronic IBD may necessitate further dietary manipulation
- mouth ulcers can make oral feeding difficult and painful; meals and snacks may need to be temporarily replaced with nutritionally complete fluid supplements, and if necessary these can be given via NG tube

Table 29.15 Example of a diet for a 10-month-old infant with GSDI.

Weight = 8 kg	Aim 0.5 g glucose/kg/hour (4 g CHO/hour) (Table 29.13)						
						Energy	
Time	Food or drink	Total CHO (g)	CHO* (g/kg/hour)	Protein (g)	Fat (g)	(kcal)	(kJ)
08.15	½ Weetabix (10 g) 100 mL semi-skimmed milk	6.5 2.9	0.4 0.2	1.1 2.2	0.2 1.1	34 30	143 125
10.00	100 mL SMA PRO 2	7.9	0.5	1.3	3.2	67	280
12.00	Baby pouch (130 g) chicken casserole and rice	11.8	0.7	4.3	1.3	80	336
14.00	Small banana (40 g)	8	0.5	0.5	0.1	36	151
16.00	1 potato waffle (58 g) 1 grilled fish finger (28 g) salad: cucumber, tomato, lettuce	13 6.0	0.8 0.4	1.4 3.5	5.1 2.3	106 61	445 256
18.00	Fromage frais (60 g) Raspberries 70 g	4.9 3.2	0.3 0.2	2.5 1.0	1.1 0.2	41 22	174 93
20.00 to 08.00 12 hours	SMA PRO 2 (200 mL) + glucose polymer (30 g) + water to 360 mL (13.3 g CHO/100 mL) 30 mL hourly	48.0	0.5	2.6	6.4	254	1067
20.00 and 08.00	SMA PRO 2 (recipe above) 15 mL bolus	4.0		0.2	0.5	21	89
Total		116		21	22	752 94 kcal/kg	3158 395 kJ/kg
% energy intake		62		12	26		

*The portion size of CHO foods (appropriate for age) will make the CHO content of main meals in excess of the specified requirement of 0.5 g/kg/hour (calculated as a combined intake).

Uncooked cornstarch

UCCS, 'household cornflour', is a branched chain glucose polymer (92% CHO) made up of amylose (linear chain) and amylopectin (branched chain). The ratio can vary; some have a high amylopectin to amylose ratio. Uncooked, it is slowly digested, primarily by pancreatic amylase to gradually release glucose into the circulation. In GSDI it is given to help maintain normoglycaemia [82]. When compared with glucose polymer feeding, a smoother blood glucose profile is produced, and less glucose is required [83, 84]. Lee *at al*. reported only achieving satisfactory glycaemia for a median of 4.25 hours (range 2.5–6.0) [85]. The variation in response may be due to malabsorption [86]. Glycosade is a hydrothermally processed high amylopectin starch, which is a slow-release CHO. A number of studies [87–90] have reported improvements in duration of fasting, glucose and insulin profile in some older children and adults, when compared with UCCS. Further trials are underway to assess response in younger children. UCCS is usually introduced between 1 and 2 years of age. In younger children it may not be adequately digested to maintain normal blood glucose because pancreatic amylase activity only reaches mature levels between 2 and 4 years of age, although its activity is reported to be induced by oral starch [91]. Once UCCS is introduced and 2 hourly fasting tolerance is extended, feeding problems often gradually begin to abate.

UCCS practical aspects: dose and frequency of administration

UCCS should be given in the following way:

- uncooked; cooking or heating disrupts the starch granules by hydrolysis and thus makes it much less effective
- ideally mixed with cold water or milk; it has a chalky taste
- mixed with squash or carbonated drinks is reported to make it less effective because of increased insulin production [83, 84]
- can be mixed with semi-liquid food such as yoghurt, fruit purée and thin cold custard or mixed with milk and then poured onto breakfast cereal, but this provides more bulk for the child to eat and is also a source of sugars
- can be given via feeding tube if refused orally, but the oral route should still be encouraged; it can block the feeding tube so needs to be administered with adequate fluids and the tube flushed afterwards
- it settles out on standing and needs to be mixed or shaken prior to consuming

Dosing of UCCS:

- a dose is typically required every 3–6 hours, but this is based on the results of the UCCS load test (see below)
- each dose is up to 2 g/kg body weight in young children, decreasing to around 1.5 g/kg in older children and 1 g/kg in adolescents who have stopped growing
- overweight and obese children are given lower doses based on ideal rather than actual weight for height
- responses differ and need to be individually assessed; low doses even in young children should be tried and used if possible to lower energy intake from pure CHO
- dose and frequency need to be reviewed regularly and tailored to requirements taking into consideration growth velocity, frequency of hypoglycaemia and biochemical results. It should only be increased as indicated rather than routinely based on increasing body weight
- success has been reported in children <2 years of age using smaller more frequent doses [92–94]
- small doses added to 2 hourly day feeds has helped to maintain blood glucose levels in older infants rather than by increasing glucose polymer (Figures 29.3 and 29.4)
- using the standard doses/kg appear to be less effective in maintaining normoglycaemia in type Ib compared with Ia (personal experience); smaller more frequent doses may be beneficial
- the diet usually comprises two or three doses of UCCS during the daytime, after breakfast, lunch and sometimes evening meal depending on the time the night feed starts
- some families prefer to use UCCS at night as it is less complicated and more socially acceptable than tube feeding, but the main disadvantage of this for young children is the need to wake frequently at around 4 hourly intervals, thereby interrupting sleep. Parents also need to wake up to give the dose and rely on an alarm clock to do so. Failure to waken does occur and is a risk [81]
- if UCCS is given at night, a larger dose compared with the usual daytime dose, to extend normoglycaemia, is suggested; this should be trialled in hospital
- some families routinely give overnight continuous tube feeds, but for certain circumstances, e.g. holidays or sleepovers, will instead give UCCS

Example of continuous glucose monitoring before and after introduction of small dose of UCCS

A 12-month-old child with GSDIb had 2 hourly feeds of Cow & Gate 1 infant formula with added glucose polymer to 11% total CHO concentration, providing 0.45 g glucose/kg/hour during the day and overnight feeds providing 0.41 g glucose/kg/hour. During the day blood glucose levels fluctuated with hypoglycaemia and hyperglycaemia (Figure 29.3). A dose of 2.5 g of UCCS was added to each 2 hourly daytime feed. Blood glucose results improved with a smoother blood glucose profile and maintenance of normoglycaemia (Figure 29.4).

UCCS load test

When initiating UCCS treatment, a fasting 'UCCS load test' takes place in hospital to assess the child's metabolic response by serial hourly measurements of blood glucose and lactate, initially hourly, but more frequently as blood glucose concentration falls. The process is as follows:

- prior to the load test, UCCS is introduced at home to test its palatability and acceptance; this may be helped by giving a small amount from a young age, around 12–18 months
- the dose is gradually increased to a maximum of 2 g/kg (or other target lower dose/kg) at one meal, beginning with 5 g and increasing by 5 g every week to the required dose with no change to usual regimen
- some patients may experience side effects such as diarrhoea, abdominal distension and flatulence, but these are usually transient
- the load test in hospital should use the UCCS brand the family use at home

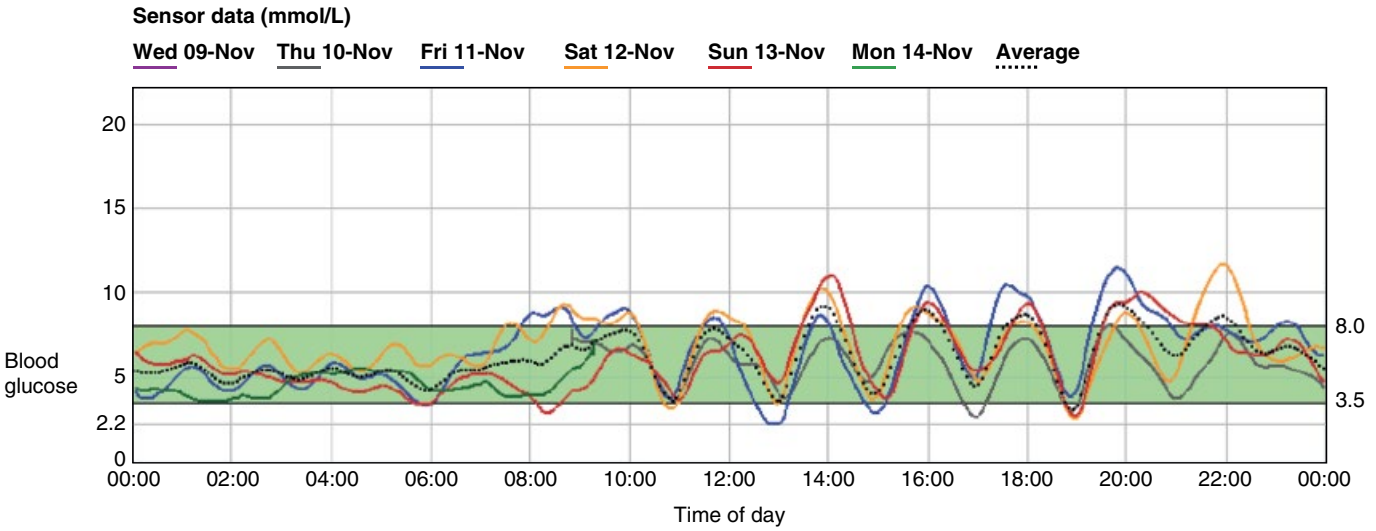


Figure 29.3 24 hour continuous glucose monitoring before uncooked cornstarch. Normoglycaemia is shown by shaded grey band.

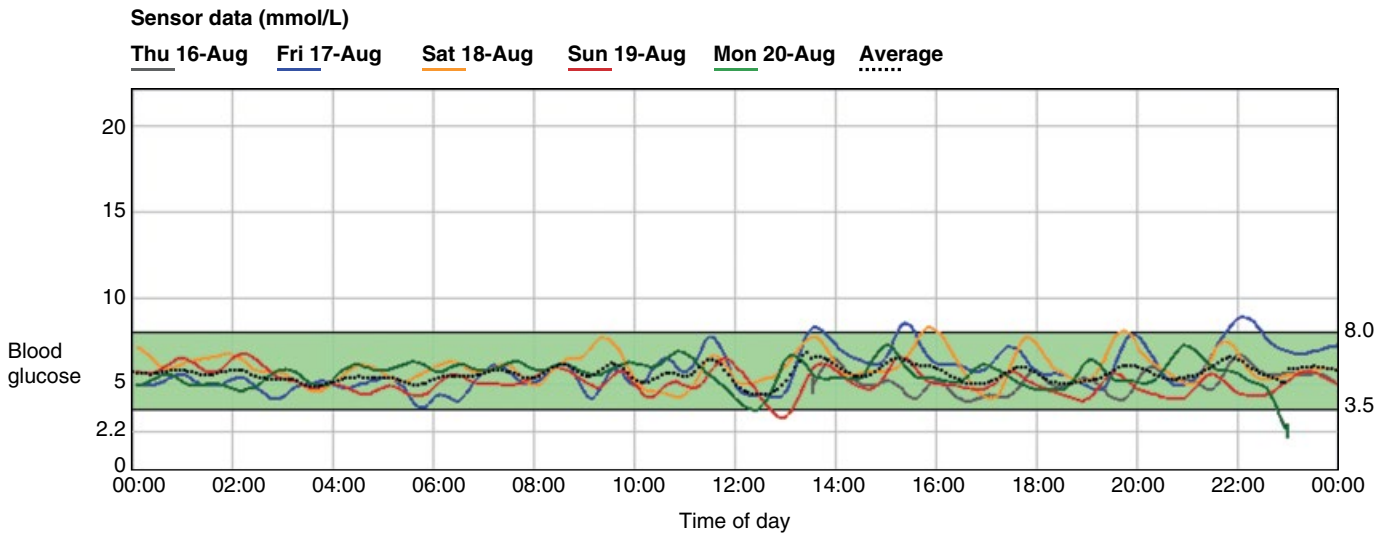


Figure 29.4 24 hour continuous glucose monitoring after uncooked cornstarch. Normoglycaemia is shown by shaded grey band.

- an example of the results of an UCCS load test is given in Figure 29.5. Over time blood glucose decreases and lactate increases. The test is stopped when blood glucose is <3 mmol/L and/or the child has symptoms of hypoglycaemia
- the biochemical test results are used to determine the frequency and quantity of UCCS doses
- some children have a poor response to UCCS; in young children the maximum fasting period is usually 3–4 hours, but this usually improves with increasing age
- if fasting tolerance to a standard dose of UCCS for age is short, giving a larger dose is unlikely to extend the time
- ideally patients should have 24 hour glucose and lactate profiles and UCCS load test repeated annually. UCCS load test is performed on initiation of UCCS, increasing age, consideration of discontinuation of night feed, poor growth or biochemical indices and starting or changing school
- when planning the UCCS regimen, it is important to be aware it can take around 30 minutes before glucose is released
- UCCS is best given after a meal so it does not reduce appetite; actual timings need to be planned around the child's daytime routine

An example of a diet incorporating UCCS is given in Table 29.16.

Cornflour, Glycosade (from age 2 years) and glucose polymer are approved by the Advisory Committee on Borderline Substances (ACBS) for prescription. Cornflour is usually a shop brand and, therefore, is food rather than pharmaceutical grade. The dose of cornflour is measured either by scoops or more accurately by weighing. Glycosade is presented in a sachet: each 60 g sachet provides 53 g CHO (which equates to a dose of 55 g UCCS); the required dose is then measured.

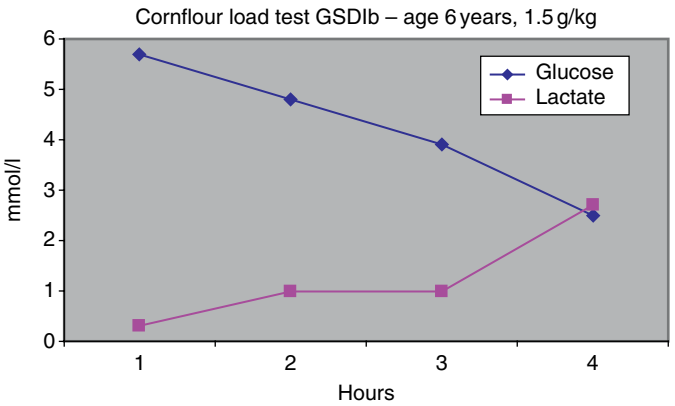


Figure 29.5 Uncooked cornstarch (cornflour) load test.

Adolescents

- after puberty some form of nocturnal glucose therapy needs to continue to prevent fasting hypoglycaemia and biochemical abnormalities [95]
- adolescents should be reassessed at this time to determine their fasting tolerance as this may differ from that in childhood
- discontinuing the overnight tube feed can be difficult even when growth ceases, as UCCS does not maintain normoglycaemia for sufficiently long periods

Vitamins and minerals

- vitamin and mineral deficiencies can occur particularly as a high percentage of the dietary energy intake is provided as glucose polymer and pure starch
- thiamin is essential for normal glucose metabolism and at least the RNI for age should be supplied
- inadequate calcium intakes and reduced bone mineral density (BMD) has been found [47, 96] although this also occurs with normal calcium intakes in GSD [97]

Table 29.16 Example diet for a 7-year-old boy with GSDI.

Weight = 27 kg 75th–91st centile, ideal body weight = 22 kg 25th–50th centile.

Aim 0.3 g glucose/kg/hour overnight and cornflour 1.5 g/kg/dose (using ideal body weight)

Time	Food or drink
08.00 **Breakfast**	CHO foods, e.g. breakfast cereal, bread; often only small amount eaten 35 g cornflour mixed with up to 100 mL water or semi-skimmed/skimmed milk
10.30 **Mid-morning**	Snack if no breakfast eaten to provide 10 g CHO, e.g. portion fruit, small slice bread with margarine, 1 semi-sweet biscuit
12.00 **Lunch** suggestions	CHO foods to provide 20–30 g CHO, e.g. bread, pitta, wrap as sandwich Fillings, e.g. ham, low fat cheese, egg, chicken, tuna and salad vegetables Fruit or low fat/low sugar yoghurt
13.00	35 g cornflour mixed with up to 100 mL water or semi-skimmed/skimmed milk
17.00 **Evening meal** suggestions	CHO foods to provide 20–30 g CHO, e.g. potato, pasta, rice, chapatti, couscous, noodles Meat, chicken, eggs, fish, dhal Vegetables or salad Fruit or low fat/low sugar fromage frais
19.00 **Bedtime snack** suggestions	CHO foods to provide 10–15 g CHO, e.g. toast, crackers, crumpet, muffins, semi-sweet biscuit, cereal and semi-skimmed milk
20.00 to 07.30	20% glucose polymer 35 mL hourly (provides 0.3 g CHO/kg/hour)
20.00 and 07.30	15 mL bolus of 20% glucose polymer

Energy requirement = 71 kcal (295 kJ)/kg/day = 1562 kcal (6.5 MJ)/day (Scientific Advisory Committee on Nutrition. *Dietary Reference Values for Energy*, 2011).
Provide around 60% daily energy intake from CHO = 937 kcal (3.9 MJ)/day.
% CHO energy intake from UCCS and glucose polymer = 616 kcal (2.6 MJ)/day, 154 g CHO = 40% energy.
% CHO energy from food limited to 20% energy = 321 kcal (1.3 MJ), 80 g CHO.
The meal plan suggests amounts of CHO to give at main meals and snacks.

- vitamin D and calcium intakes need to be adequate together with good metabolic control to optimise bone health [46, 47]

Quality of life

The intensive 24 hour feeding regimen is demanding and time consuming for parents, particularly if feeding 2 hourly. It is disruptive to normal living during the day and particularly night for both parents and child, with potentially serious consequences if treatment is not adhered to [81]. Management requires constant watching of the clock and great attention to detail as delay in feeding will result in hypoglycaemia; human errors do occur including forgetting to switch on the pump or alarm clock [81]. Feeding problems are common and can manifest as a poor food intake or quality of diet and overfeeding because of concern about hypoglycaemia. A lower quality of life has been reported in GSDI patients; this study also highlights the burden of care on parents [98]. Disordered eating and body esteem is also reported [99]. Support from a paediatric psychologist is valuable.

Exercise

A major reduction in exercise capacity in adult patients with GSDI has been reported, with mean blood glucose levels for patients showing a progressive decrease throughout exercise and recovery [69]. Children are likely to require additional CHO with prolonged exercise. Parents often report the need to give food or sugary drinks before, during or after exercise. Pre-exercise dietary treatment may need to be adjusted according to the intensity and duration of the exercise being undertaken with complex CHO for low to moderate intensity and a sugary snack/drink for high intensity. Guidance is required on quantities as too much sugar will result in hyperglycaemia. It is important that children are encouraged to be physically active to help prevent overweight or obesity and associated risks of diabetes and cardiovascular disease.

Hypoglycaemia

Hypoglycaemia occasionally occurs and may be related to delayed meals/drinks/UCCS, illness, poor dietary compliance or prolonged exercise. Parents should contact the metabolic team if there is repeated hypoglycaemia. Parents need to recognise early warning signs such as sweating, pallor, irritability or drowsiness and respond by immediately giving a sugary or glucose polymer drink orally or via the tube and, on recovery, some starchy foods. Excessive amounts of glucose can cause rebound hypoglycaemia; 10–20 g glucose is usually adequate. Dextrose gels such as Glucogel (40% dextrose) can be rubbed into the buccal cavity and is an invaluable treatment for the semiconscious or uncooperative child. If the child is unresponsive or fitting, emergency services should be urgently called. Patients with GSDI do not respond to glucagon (as it normally increases blood glucose

via glycogenolysis and gluconeogenesis); IV glucose (10%) or a dextrose gel (as above) is necessary to treat a child with hypoglycaemia who is unconscious.

Managing the unwell child: emergency regimen for GSDI

During intercurrent infections, adequate glucose must be maintained to prevent hypoglycaemia and, in GSD type I, lactic acidosis:

- the standard ER concentrations of glucose polymer for age used for management of illness in other metabolic disorders (p. 677) may provide too much glucose, particularly at 20%–25% glucose polymer concentration, resulting in hyperglycaemia and potential rebound hypoglycaemia when discontinued
- the ER glucose solution for GSD1 should provide the endogenous glucose production rate for age or the child's usual hourly glucose intake (Table 29.13) and an adequate intake of fluids (similar volumes to standard ER)
- often 24 hour continuous tube feeds of glucose polymer will replace either the usual 2 hourly dietary regimen or UCCS
- IV fluids may be necessary and must provide adequate, but not excessive, glucose compared to the usual requirement of g glucose/kg/hour or mg/kg/min (Table 29.13)
- an overall adequate glucose intake must be given when titrating from IV fluids back to the usual feeding plan
- if IV fluids have provided more glucose than the usual overnight feed, there is a risk of hypoglycaemia; this needs to be considered when planning the titration plan and blood glucose should be monitored

An example of an ER is given in Table 29.17.

Clinical and biochemical monitoring

Clinical, anthropometric and biochemical monitoring is essential to assess the efficacy of dietary treatment and to guide the composition of the diet (Table 29.18):

- Continuous glucose monitoring is a useful tool (p. 629). Blood glucose monitoring at home may be useful, but is not perceived essential for daily management.
- Biochemical aims of dietary treatment are:
  - preprandial blood glucose >3.5 mmol/L. Hypoglycaemia is defined as a blood glucose <3.0 mmol/L. Some children may not be symptomatic at these blood glucose levels as lactate may be providing an alternative fuel source. Single blood glucose and lactate levels in a routine clinic appointment are not a good indicator of long-term metabolic control
  - plasma lactate <4.0 mmol/L. Some centres aim to maintain lactate in the normal reference range: 0.5–1.0 mmol/L (mild to moderate hyperlactataemia: 2.0–4.0 mmol/L). This can be very difficult to achieve in some patients, and a moderately increased lactate may be beneficial as it provides fuel to the brain when blood glucose is low [74]. Lactate can be chronically elevated despite seemingly good dietary treatment. The concentration at which lactate contributes to long-term complications is not known
  - plasma triglycerides (TG) <6 mmol/L [64], normal fasting levels 0.5–2.2 mmol/L. The American College of Medical Genetics and Genomics (ACMG) guidelines [63] do not suggest an aim for plasma TG. Wang *et al*. [45] reported significantly increased adenoma progression in patients with a mean 5-year TG value of >5.6 mmol/L. TG can be chronically raised and probably reflect decreased metabolic control [36]. Ideally TG should be as near normal as possible
- Weight and height should be monitored regularly and BMI calculated. BMI should ideally be normal range, but this can be difficult to achieve in some patients. The suggested aim is to maintain BMI between 0 and +2 standard deviation scores [64]. Mid-upper arm circumference is another useful assessment tool particularly if there is hepatomegaly, but is not standard practice.
- Growth retardation occurs with inadequate treatment and even on intensive treatment [100, 101]. Mundy *et al*. have reported improved growth with intensive dietary treatment, but a subset within their patient group who, despite therapy, have poor growth. These patients had measured endocrine responses similar to those reported for untreated patients, but the reasons for this are not yet clear [100]. Interestingly, the more obese patients were tallest, although as a group they were significantly shorter than average.
- Regular biochemical monitoring of vitamin and minerals, in particular calcium and vitamin D, is recommended because of risk of low BMD and osteopenia. BMD should be assessed by DEXA scan from 5 years of age every 1–2 years [64].

Table 29.17 Example of an emergency regimen for a 3-year-old girl with GSDI.

ER to provide 0.4 g glucose/kg/hour. Body weight = 14 kg
Calculate the daily amount of glucose = 0.4 g × 14 kg × 24 hour = 134 g (5.6 g glucose/hour)
Recipe for 24 hours:
140 g glucose polymer
+ water added up to 1400 mL (10% CHO concentration)
Feed 60 mL/hour continuously for 24 hours = 0.4 g CHO/kg/hour

Learning points: glycogen storage disease type I

- *Dietary treatment involves avoidance of fasting, frequent provision of glucose day and night, with individualised feeding regimens*
- *Diet regimens are particularly demanding in young children*
- *Maintenance of normoglycaemia is essential to normalise blood biochemistry, although this is difficult to achieve, and to delay onset or prevent long-term complications*

Table 29.18 Biochemical monitoring for GSDI.

Checked at each outpatient appointment unless otherwise indicated					
GSD type	0	Ia/b	IIIa/b	VI and IX	Fanconi Bickel syndrome
CGM	*	*	*	*	*
Glucose +/– lactate profiles in hospital	*	*	*	*	*
UCCS load test	*	*	*	*	*
Glucose	√	√	√	√	√
Lactate	√	√		√	√
Ketones	√		√	√	√
Creatinine kinase			√ (IIIa)		
Liver profile	√	√	√	√	√
Urate		√			
Triglycerides	√	√	√	√	√
Cholesterol	√	√	√	√	√
Bone profile, vitamin D†	√	√	√	√	√
FBC, WBC, iron status	√	√	√	√	√
Renal profile	√	√	√	√	√
Urine protein–creatinine ratio (or equivalent)		√	√		

CGM, continuous glucose monitoring; UCCS, uncooked cornstarch; LFT, liver function tests; FBC, full blood count; WBC, white blood cells.
*Glucose and lactate profiles, CGM and UCCS load test are usually performed annually, but may vary as clinically indicated.
†Vitamin D – annually.

Glycogen storage disease type III

Enzyme

Debrancher enzyme is bifunctional with two catalytic sites (p. 609, Figure 29.2).

Biochemical defect

Two main subtypes:

- debrancher enzyme deficiency in liver, skeletal muscle and heart (GSD type IIIa, 85% of cases)
- debrancher enzyme deficiency in liver only (GSD type IIIb, 15% of cases) [38]

Production of free glucose from glycogenolysis is limited, and the partially degraded glycogen is stored as an abnormal structure, termed 'limit dextrin'. The gluconeogenic pathway, however, is functional for endogenous glucose production, and this prevents the development of profound hypoglycaemia during fasting, although it can still occur. Glycolysis proceeds normally. Functionally these patients have only partial glycogenolysis, while glycolysis and gluconeogenesis are preserved.

Genetics

Autosomal recessive inherited disorder. A high predicted prevalence is reported in the Faroese (approximately 1 in 3100) [102] and North African Jews from Israel (1 in 5400) [103].

Clinical onset presentation, features

Presents in infancy and early childhood (usually before 18 months) with predominantly liver-related features: fasting intolerance, severe hepatomegaly (due to both glycogen and fat accumulation) and markedly elevated liver transaminases, hyperlipidaemia (triglycerides and cholesterol), ketotic hypoglycaemia and failure to thrive [104]. Lactate is normal. Biochemical abnormalities improve on treatment, but may not normalise.

Long-term complications and outcome	Cardiac manifestations and skeletal myopathy may develop with increasing age. Accumulation of limit dextrin may be involved in their pathogenesis. Cardiac involvement is variable, typically manifesting as asymptomatic left ventricular hypertrophy starting in the first decade of life [104], which can progress to symptomatic hypertrophic cardiomyopathy, severe cardiac dysfunction, congestive heart failure and (rarely) sudden death [105–108]. Predictive features for cardiac outcome are not known. Skeletal myopathy presents as weakness and wasting and gradually progresses, being a greater problem for adults [107, 109]. Many children, however, tire easily with exercise. Skeletal muscle glycogen normally provides an essential energy source to contracting muscle, especially at high intensities. Exercise intolerance in six GSDIIIa patients has been attributed to a block in muscle glycogenolytic capacity [110]. Creatine kinase (CK), a marker of muscle damage, may increase as children become more active; the ISGSDIII study data reports a raised CK at some time point in 100/124 patients, median age 10 years (range 0.3–56.1 years) [104]. CK in adult patients, although often still above the normal reference range, is reported to decrease, probably due to progressive muscle loss [109]. Whole-body muscle magnetic resonance imaging is a useful monitor of muscle involvement; signal alteration was predominant in the lower limbs and postural muscles in a cohort of 15 patients (age 16–59 years) [111]. Liver symptoms improve with age; thus hypoglycaemia is less of a problem. A small number of patients develop hepatic cirrhosis and adenomas and, rarely, hepatocellular carcinomas, but this is much less than in type I [107]. BMD is markedly reduced in GSDIII with type IIIa patients being much worse than IIIb [112]. A high incidence of bone fractures in paediatric patients is reported [104], suggesting reduced BMD may develop early. Melis *et al*. [113] propose the pathogenesis of impaired bone mineralisation is multifactorial, attributable to poor metabolic control. Hyperlipidaemia occurs, but complications of pancreatitis and atherosclerosis are not reported [104]. Poor growth can also be seen in childhood, although spontaneous catch-up growth usually occurs during puberty [114]. Overweight and obesity are recognised complications [68, 104]. Liver transplant has been reported [54, 107, 109].
Acute management	Initial acute management may necessitate management of hypoglycaemia and correction of biochemical abnormalities with IV fluids and/or frequent feeds.
Dietetic management	Dietary management is the primary treatment. The aims are to: • prevent hypoglycaemia and ketosis in the infant and young child • promote normal growth and BMI • help delay onset of cardiac manifestations and muscle myopathy in type IIIa • pre-exercise dietary management to prevent risk of hypoglycaemia Infants who present with hypoglycaemia and poor fasting tolerance require a more intensive dietary regimen with increased CHO, similar to GSDI (p. 610). Children who present later with short stature and hepatomegaly are treated with UCCS or Glycosade, which is given to try and improve their growth rate. Symptomatic hypoglycaemia is generally not a problem. As gluconeogenesis is functional, the gluconeogenic precursors such as the glucogenic amino acids, lactate and glycerol can be converted to glucose. High protein and high fat diets are being used to reverse hypertrophic cardiomyopathy as the traditional high CHO diet may actually be harmful due to accumulation of limit dextrin. As gluconeogenesis is functional, it is not necessary to limit fructose and galactose containing foods.
Monitoring	Clinical, anthropometric and biochemical monitoring is essential to assess the efficacy of dietary treatment, to guide composition of the diet and to promote normal growth. Most of the guidelines given for GSDI (p. 617) can be used for GSDIII, taking into account any differences. Table 29.18 provides guidelines for biochemical monitoring. Other recommendations for monitoring include echocardiography (for ventricular hypertrophy), neuromuscular assessment, DEXA scans and liver ultrasound [107]. CK is a useful measure of muscle damage (see above).
Emergency regimen	During illness a frequent supply of glucose must be maintained to prevent hypoglycaemia and ketosis. The ER information for managing the unwell child with GSDI can also be used for patients with GSDIII (p. 617).
Clinical management guideline	Kishnani PS, Austin SL, Arn P et al. *Glycogen storage disease type III diagnosis and management guidelines. Genet Med.* 2010, 12 446–463 [107].
Parent support group	Association for Glycogen Storage Disease (UK) (www.agsd.org.uk)

Dietary treatments: high CHO, high protein or high fat diets

Controversy surrounds which dietary therapy is best for patients to maintain normoglycaemia and also to improve or prevent cardiomyopathy and skeletal muscle myopathy. Either CHO intake can be increased to provide a continuous supply of glucose (similar to GSDI) or protein intake can be increased to enable gluconeogenesis to provide the main source of glucose.

High CHO diet

Provision of a regular high CHO intake using UCCS can maintain normoglycaemia and reduce the need for production of glucose via gluconeogenic substrates [115–117]. This treatment may be as effective as the high protein diet, provided overtreatment is avoided. One small crossover study of five children over a period of 2.5 years compared UCCS diet with a high protein diet and showed unchanged glycaemic control, liver function tests and lipid profiles with both regimens, but better growth and reduced liver spans when using UCCS. Two of the patients with muscle involvement showed increased creatine phosphokinase levels on UCCS diet; no cardiac data were given [118].

High protein diet

Studies recommending a high protein diet are limited. Studies from the 1980s [119–121] report an increased demand for gluconeogenesis with loss of muscle amino acids (supported by observations in change of plasma alanine, a major gluconeogenic precursor) may be a contributory factor to the skeletal myopathy seen in some patients with GSDIIIa. Slonim *et al*. [119] reported a high protein daytime diet and night feed (20%–25% energy from protein) improved muscle strength in myopathic patients, but six of seven patients studied were not on any dietary treatment, and so perhaps similar improvements could have been achieved with a high CHO diet and night feed. Fernandes and van de Kamer demonstrated that protein, galactose and fructose induced a rise in blood glucose concentration using hexose and protein tolerance tests in five children with GSD [122]. These early studies did not distinguish between type IIIa/b. Two more recent adult case reports describe reversibility of hypertrophic cardiomyopathy (demonstrated by echocardiography) with a high protein diet. The diets had different macronutrient energy ratios: case 1, an adult, was given 30% protein (no data were given on CHO and fat) [123]; case 2, an obese adult, was given 37% protein, 2% lipid, 61% CHO and total energy intake reduced to 900 kcal (3.8 MJ)/day [124]. It is not possible to distinguish which element of the diet was of most benefit. These studies implicated a high CHO diet and UCCS as possible contributing factors to the development of cardiomyopathy as excess CHO can cause deposition and accumulation of abnormal glycogen in heart [108, 124].

High fat diets

High CHO diets in GSDIII suppress lipolysis. A newer approach to reverse cardiomyopathy and improve muscle myopathy is the ketogenic or modified Atkins diet, which provides fatty acids and ketones instead of CHO as the main energy source. Fatty acids are the principal energy source for cardiac muscle and skeletal muscle in the resting state and during prolonged exercise. Ketone bodies can be used by most tissues including the brain, and the heart uses ketones in preference to glucose.

Current published literature describes different approaches:

- an infant (2 months) with asymptomatic hypertrophic cardiomyopathy, whose sibling had GSDIII and died at 11 months from cardiac arrest, was given a 2 : 1 ketogenic diet (65% energy from lipid, 15% from protein, 20% from CHO) and synthetic ketone bodies as D,L-3-OH butyrate, which resulted in permanent ketosis. Cardiomyopathy improved and muscle strength remained normal [125]
- an infant (7 months) with hypertrophic cardiomyopathy was given a high fat (60% energy), high protein (20% energy), low CHO (20% energy) diet. The cardiomyopathy fully resolved after 7 months of treatment and has not recurred; fasting tolerance improved [126]
- two siblings (5 and 7 years) were given a high fat (60% energy), high protein (25% energy energy) (unchanged), low CHO (15%) diet. Heart wall thickness decreased and biochemistry improved; UCCS could gradually be stopped [127]
- two boys (9 and 11years) were given a modified Atkins diet (10 g CHO per day, unrestricted protein increased from 3 to 7 g/kg/day, fat from 1.6 to 8 g/kg/day); UCCS was gradually stopped. The % energy intake was not provided in the paper (the author has calculated the values as 1.6% CHO, 71% fat, 27% protein for comparison). Cardiac function, stamina and CK improved [128]

Diet choice: high CHO or high protein?

Intermittent administration of either UCCS or a high protein supplement is necessary throughout 24 hours with both diets; acceptance of either can be difficult. Achieving a high protein intake from food may be more difficult than a high CHO diet in a young child. Both diets can maintain normoglycaemia. There are no long-term published data to determine which diet therapy is best for patients with myopathy. On current evidence it is not yet clear if a high protein diet is more beneficial than high CHO in treating/delaying onset of cardiac manifestations and muscle myopathy in type IIIa patients. No cohort studies of high protein diets have been reported in infants or young children. Such a high protein intake may not be tolerated or warranted in this age group. A gradual increase in protein intake with age, or if there is evidence of myopathy, may be more appropriate. The final choice of dietary management for children with GSDIII will also vary depending on the severity of the disorder and ultimately what is practically achievable for the child and family. The diet needs to be individually tailored to the child's specific clinical features. A high protein diet in GSD type IIIb patients may not be warranted as they do not develop myopathy.

The optimal macronutrient composition of the diet in GSD III is unknown; various differing energy ratios are reported in the literature. Problems and the long-term complications may result when too much CHO is given; any increase in protein or fat intake should decrease CHO intake. Bhattacharya *et al*. suggest both macronutrient ratio and quality of CHO are important; lower glycaemic index foods are preferable [129].

Practical provision of high CHO, high protein diet

Infants who present early with hypoglycaemia and poor fasting tolerance require a more intensive dietary regimen with increased CHO, as for GSDI (p. 610). The suggested energy ratio in GSDI is 60%–70% from CHO, 20%–25% from fat and 10%–15% from protein. At night, continuous tube feeding is used and regular 2 hourly feeding or UCCS during the daytime. The feed regimen examples for GSDI (p. 612) can be used for GSDIII if the patient is not on a very high protein diet. Starchy foods should be used in preference to simple sugars to limit peak glucose excursions and insulin release. As discussed, there should perhaps be greater emphasis on the inclusion of high protein foods and lower CHO in the diet, particularly if a child has or develops a cardiac or skeletal myopathy. Table 29.19 gives guidance on provision of combinations of high CHO diet, high protein and low fat diet. The ACMG guidelines [107] recommend a high protein diet and refer to the energy ratios used by Slonim *et al*. (20%–25% energy from protein, 50%–55% from CHO and 20%–25% from fat) [119–121]. These protein intakes are very high, e.g. 100 g protein provides 25% of energy in a diet providing 1600 kcal (6.7 MJ). High protein foods at meals and snack times need to be increased and parents need guidance on portion sizes, suitable low fat foods such as skimmed milk, low fat yoghurt and fromage frais. Achieving a sufficiently high protein intake, even from protein rich foods, is very difficult, and pure protein supplements such as Protifar (concentrated milk protein powder, 89% protein) are likely to be necessary. Protifar can be added to UCCS and skimmed milk drinks and to a continuous overnight feed of skimmed milk, replacing some of the glucose polymer (gram of CHO for gram of protein). This latter change should be instituted in hospital, so blood glucose can be formally monitored. Most high protein drinks or dessert supplements are too high in energy intake to be very useful. Exceptions are ProSource Plus Liquid (neutral and flavoured), which provides 15 g protein, 11 g CHO, 100 kcal (420 kJ) in 30 mL and can be given orally or by tube, and ProSource Jelly with 20 g protein, <2 g CHO, 90 kcal (375 kJ) per 118 g serving. Older children may be able to replace nocturnal feeds with UCCS before they have stopped growing if their fasting tolerance is >6–8 hours. Fasting tolerance should be assessed in hospital, as described for GSDI, and can then be monitored at home using continuous glucose monitoring (CGM).

It is important to carefully monitor the energy distribution of the diet and when making changes to macronutrient energy intakes. CGM can be used to further monitor these changes at home. Further CHO reductions can be made if blood glucose is at upper level of normal. Too high an energy intake from CHO can cause rebound hypoglycaemia [130]. If a child has limited exercise capacity, this should be considered when planning the overall energy intake to avoid excess weight gain.

Children who present later with short stature and hepatomegaly are treated with UCCS or Glycosade to try and improve their growth rate. Symptomatic hypoglycaemia is

Table 29.19 High CHO, normal protein, low fat diet or high protein, normal/reduced CHO, low fat diet for GSDIII.

Carbohydrate foods (starch and sugar)	
Starchy foods At least one serving at three main meals and bedtime snack, e.g. bread, chapatti, pitta, cereal, potato, rice, pasta, fruit, plain biscuits or crackers, tea cake, muffins	
Sugar and sugary foods These are allowed, but should be kept to a minimum, e.g. table sugar, sweets, cakes, ice cream, preserves	
High protein, low fat foods*	
Milk	Semi-skimmed or skimmed milk, low fat fromage frais or yoghurt
Meat	Lean red meat (5%–10% fat content), trim off all visible fat
Poultry	
Fish	White fish instead of oily
Cheese	Low fat cheese, e.g. cottage, edam type, half-fat cheddar, quark
Pulses	Beans, lentils, peas (and sweetcorn)
Eggs	
Meat alternatives	Tofu, Quorn
Fats	
High fat foods should be used sparingly, e.g. butter, margarine, vegetable oil, animal fats, cream (double, whipping, single), imitation cream, mayonnaise, salad dressings, pastry, batter and breaded foods	
Avoid fried or roasted foods. Spread butter or margarine thinly on bread	
Snack foods	
Most children choose high fat or sugary snack foods, e.g. crisps, nuts, sweets and chocolate. Low fat, high protein or high carbohydrate snack foods should be used instead, e.g. yoghurt, fromage frais, crackers and low fat cheese, glass of milk for the high protein diet or sandwich, plain biscuits, crumpet, fruit for the high starch diet	

*High protein diet for GSD III – at least one serving of high protein, low fat food at three main meals and bedtime snack. Generous intakes of milk should also be given.
High CHO diet for GSD III – one serving of high protein, low fat foods at two meals. Can include milk (or milky foods) in the daily diet.

generally not a problem for these children, although after an overnight fast they may have high ketones. Frequency of administration and dose of UCCS (1–2 g/kg/dose) will vary depending on fasting tolerance, age, growth rate and response. Usually a dose is given before bed, and sometimes daytime doses are necessary to improve growth. Children should have regular meals and a bedtime snack that contain both starchy and protein food. Fat intake should be decreased to compensate for the increased CHO intake and for weight control.

A high starch, normal protein, low fat diet and high protein, normal/reduced starch, low fat diet for GSDIII is given in Table 29.19.

Vitamins and minerals

Vitamin and mineral intakes need to be regularly assessed. If a high percentage of the dietary energy intake is provided as pure starch or glucose polymer, there is greater risk of vitamin and mineral deficiencies. Calcium and vitamin D intakes are particularly important because of risk of decreased BMD [112, 113].

Alcohol

Adolescents and adults must be made aware that alcohol is a potent inhibitor of gluconeogenesis and even quite moderate amounts may reduce glucose production. Alcohol intake should be limited and must always be taken in combination with food [131].

Exercise

Exercise intolerance is attributed to severely limited ability to breakdown glycogen [110]. If a child fatigues and tires early with exercise, giving CHO pre-exercise, as described for GSDI, may help. Preisler *et al*. [132] report exercise tolerance improved with fructose ingestion in three adults with GSD III.

Hypoglycaemia

The guidelines given for management of GSDI can also be used for patients with GSD type III (p. 616).

Managing the unwell child: emergency regimen information for GSDIII

The guidelines given for management of GSDI can also be used for patients with GSD type III with the aim to prevent hypoglycaemia and ketosis (p. 617). As not all children with GSDIII are tube fed, glucose polymer drinks need to be given orally, 2–3 hourly day and night, depending on usual fasting tolerance.

Learning points: glycogen storage disease type III

- *Infants who present with hypoglycaemia are managed with a high CHO diet and frequent 2–3 hourly feeds during the daytime and continuous tube feeds overnight*
- *Children who present later need a less intensive feeding regimen*
- *UCCS is introduced from around 1 to 2 years of age*
- *High protein, high fat diet and low CHO diets are being trialled to help prevent complications, but the optimal macronutrient ratio is not yet defined*

Glycogen storage disease type VI

Fiona J. White

Enzyme	Glycogen phosphorylase (Figure 29.2)
Biochemical defect	Deficiency of glycogen phosphorylase: • prevents release of glucose-1-phosphate from the linear chains of α-1,4-linked glucose molecules, thus limiting the production of glucose by glycogenolysis • glucose can still be produced via gluconeogenesis, which helps prevent significant hypoglycaemia during prolonged periods of fasting, e.g. overnight
Genetics	Autosomal recessive inheritance resulting from mutations encoding for the enzyme hepatic glycogen phosphorylase (PYGL, EC 2.4.11). There is a common mutation in the Mennonite population where the incidence is around 1 in 1000 [133].

Clinical onset, presentation features

Usually presents in childhood, around 2–3 years of age, with:

- abdominal distension, hepatomegaly (due to increased liver glycogen storage) and growth retardation. Clinical presentation is the same as in hepatic forms of GSDIX (p. 624) and similar, but generally milder to that seen in GSDIII
- there may be some muscle or central nervous system involvement with symptoms such as mild hypotonia, delayed motor development, muscle weakness and cramps [134]
- significant ketosis may be present particularly after an overnight fast or during illness. This represents inadequate production of glucose from liver glycogen with stimulation of counter-regulatory hormones, glucagon, adrenaline and growth hormone to maintain normoglycaemia, which reduce insulin levels and increase lipolysis and further ketosis [135]. Cases with normoglycaemic ketonaemia have been described [136]
- mild increase in liver transaminases, alkaline phosphatase and gamma-GT [135]. Blood lipids, particularly triglycerides, are usually raised. Normal uric acid and lactate levels [137]
- large glucose loads may increase postprandial lactate levels; this was seen in 6/6 patients following a glucose loading test [134]

Long-term complications and outcome

Clinical symptoms generally improve with age; hepatomegaly has usually resolved by puberty [133] and complete catch-up in final height achieved:

- osteoporosis is a risk factor if there is chronic ketosis [38]
- GSD VI was thought to be a benign condition, but long-term complications have been reported with cases of likely liver fibrosis and hepatocellular carcinoma [138, 139] as well as mild cardiomyopathy [138]

Initial management

Assessment of any hypoglycaemia or significant ketosis on the usual dietary intake by serial blood glucose monitoring and early morning ketone measurement. This can be done in hospital or at home with a period of CGM (p. 629) and early morning ketone measurement:

- hypoglycaemia is not always symptomatically obvious and may only become apparent if monitored overnight or after an overnight fast. If hypoglycaemia is present, it is usually less severe than in GSDI or GSDIII
- hyperketosis may be present after an overnight fast indicating the occurrence of lipolysis to preserve blood glucose and the need for additional CHO intake overnight, even if absolute hypoglycaemia has not occurred

Dietetic management

Dietary manipulation is the primary treatment aiming to:

- maintain normal blood glucose levels and prevent ketosis
- correct hyperlipidaemia
- promote normal growth and maintain a healthy BMI

Dietary advice is based on fasting tolerance:

- many patients do not require specific dietary treatment
- depending on fasting tolerance management ranges:
  - from regular meals and a bedtime snack that are high in complex CHO and with generous protein, with ER for illness
  - to those additionally requiring daily UCCS therapy at night to prevent hypoglycaemia or ketonaemia
- a high protein intake may be advantageous in providing precursors for gluconeogenesis and reducing reliance on CHO, thus decreasing glycogen storage
- avoidance of both under- and overtreatment is important. Undertreatment results in hyperketosis due to utilisation of lipolysis, β-oxidation and ketogenesis +/– hypoglycaemia as gluconeogenesis and fatty acid oxidation are functional. Overtreatment with excess food, milk formula or UCCS results in excess liver glycogen storage and peripheral body fat storage.

Alcohol

It is important to discuss alcohol intake with adolescents as it is a potent inhibitor of gluconeogenesis. Recommendations for GSDIII can be used (p. 622).

Hypoglycaemia

Guidelines for GSDI can be used (p. 616).

Monitoring

Clinical, anthropometric and biochemical monitoring is essential in assessing dietary treatment efficacy, dietary composition changes and promoting normal growth. Most of the monitoring described for GSDIII (p. 619) is applicable, accounting for any differences in dietary treatment and affected biochemistry. Biochemical monitoring guidelines are detailed in Table 29.18. Abdominal ultrasound of the liver or, in older children, magnetic resonance imaging (MRI) is performed every 12–24 months to assess for complications of liver cirrhosis and adenoma [135].

Emergency regimen

Illness or prolonged fasting, e.g. for surgery, could precipitate hypoglycaemia. It is essential that a supply of glucose is given frequently:

- ER guidance for GSDI can be used for GSDVI (p. 617)
- ER drinks need to be taken 2–3 hourly depending upon usual fasting tolerance

Clinical management guidelines

Kishnani PS, Goldstein J, Austin SL *et al*. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2019, 21(4) 772–789. [135].

Parent support group

Association for Glycogen Storage Disease (AGSD) (https://agsd.org.uk/)

Learning points: glycogen storage disease type VI

- *GSDVI is generally a less severe form of hepatic GSD*
- *Ongoing monitoring is needed due to reports of fibrosis, hepatocellular carcinoma and cardiomyopathy*

Glycogen storage disease type IX

Enzyme	Phosphorylase b kinase (PHK) (Figure 29.2) • PHK is composed of four copies each of four subunits (α, β, γ, and δ), encoded by four separate genes (PHKA1, PHKA2, PHKB, PHKG2), and deficiency can be present in the liver, liver and muscle or, rarely, in muscle only. There are five different subtypes depending upon clinical presentation and mode of inheritance [38, 140].
Biochemical defect	Deficiency of PHK (Figure 29.2) prevents activation of glycogen phosphorylase, thus limiting the production of glucose by glycogenolysis: • glucose can still be produced via gluconeogenesis, which helps prevent significant hypoglycaemia during prolonged periods of fasting, e.g. overnight
Genetics	• X-linked hepatic PHK deficiency, GSDIXa (type IX alpha), is caused by a wide range of mutations in the PHKA2 gene and is the most frequent form occurring in approximately 75% cases of GSDIX [141], with a mild phenotype often thought to be benign, but in some cases there may be a more severe phenotype • X-linked muscle glycogenosis, GSDIXd, is due to mutations in the PHKA1 gene and results in a mild phenotype • combined liver and muscle PHK deficiency, GSDIXb (type IX beta), results from mutations in the PHKB gene, with autosomal recessive inheritance, and is usually a mild phenotype • autosomal recessive liver PHK deficiency, GSDIXc (type IX gamma), results from mutations in the PHKG2 gene located on chromosome 16 and results in a severe phenotype • autosomal recessive muscle PHK deficiency, GSDIXe, has a mild phenotype
Clinical onset presentation, features	Types IXa (alpha), IXb (beta) and IXc (gamma), present with hepatomegaly, growth retardation, fasting hypoglycaemia, ketosis, hypercholesterolaemia, hypertriglyceridaemia and elevated liver transaminases: • hypoglycaemia may not always be pronounced as both gluconeogenesis and fatty acid oxidation are functional and ketosis may be more significant • hyperlacticacidaemia, usually postprandial, is also observed in some cases, especially in GSDIXc They are in general milder disorders than GSDIII, but there is wide variation in severity of symptoms. Although hypoglycaemia is usually mild, only occuring after prolonged fasting or infection, in some, particularly GSDIXc (gamma), there can be severe hypoglycaemia, ketosis and raised transaminases as seen in GSDI or GSDIII [138, 140]. There is gross accumulation of glycogen in the liver.
Long-term complications and outcome	Usually a late growth spurt allows complete catch-up in final height [142–144]. There is usually normalisation of liver enzymes in the majority and most adults will be entirely asymptomatic with a normal life expectancy: • the more severe GSDIXc (gamma) form is associated with liver fibrosis, which can progress to cirrhosis and development of adenoma [138, 140] • hypertrophic cardiomyopathy has also been reported in GSDIXc [138] • uncommonly X-linked GSDIXa (alpha) has also been associated with liver fibrosis and cirrhosis [141, 145]
Initial management	• as for GSD type VI (p. 623) • some cases with the severe form GSDIXc (gamma) may have severe nocturnal hypoglycaemia

Dietetic management	• as for GSD type VI (p. 623)
	• depending on fasting tolerance management ranges:
	  ◦ from regular meals and bedtime snack with ER for illness
	  ◦ to those additionally requiring daily UCCS therapy at night to prevent hypoglycaemia or ketonaemia
	• a high protein intake may be advantageous in providing precursors for gluconeogenesis and reducing reliance on CHO, thus decreasing glycogen storage
	• some cases with the severe form GSDIXc (gamma) may have severe nocturnal hypoglycaemia and shorter fasting tolerance than in milder forms. To maintain normoglycaemia, prevent fasting ketosis and improve growth [138], they need:
	  ◦ a more intensive regimen, as in GSDI or severe GSD III, with overnight continuous tube feeding, or
	  ◦ 1–2 doses of UCCS plus protein (as gluconeogenesis is functional) overnight and daytime UCCS plus protein (p. 625)

Alcohol	It is important to discuss alcohol intake with adolescents as it is a potent inhibitor of gluconeogenesis. Recommendations for GSDIII can be used (p. 622).
Hypoglycaemia	Guidelines for GSDI can be used (p. 616).
Monitoring	As for GSDVI (p. 623).

Emergency regimen	Illness or prolonged fasting, e.g. for surgery, could precipitate hypoglycaemia. It is essential that a supply of glucose is given frequently: • ER guidance for GSDI can be used for GSDIX (p. 617) • ER drinks need to be taken 2–3 hourly depending upon usual fasting tolerance • where a feeding tube is *in situ*, ER can be given continuously
Clinical management guidelines	Kishnani PS, Goldstein J, Austin SL *et al*. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2019, 21(4) 772–789. [135].
Parent support group	Association for Glycogen Storage Disease (AGSD) (https://agsd.org.uk/)

Learning points: glycogen storage disease type IX

- *The majority of cases of GSDIX will be male with X-linked forms and are generally mild disease*
- *GSDIXc (gamma) is a severe form and may require intensive dietary management as in GSDI or severe GSDIII*
- *Ongoing monitoring is needed due to reports of liver adenomas and cirrhosis*

Dietary management principles for GSD types VI and IX

The aim is to maintain normoglycaemia, which reduces the need for lipolysis and fatty acid oxidation and so prevents the development of ketosis:

- **Avoidance of hypoglycaemia and significant ketosis**. These can normally be managed by regular 3–4 hourly daytime meals and a bedtime snack comprising complex CHO and generous protein (Table 29.19). The precise ideal energy distribution of the diet is not known. Additional protein may be useful:
  - to provide gluconeogenic precursors
  - to be a direct fuel for muscles
  - simultaneously replacing the energy from additional protein with a reduction in CHO energy may reduce glycogen storage [129, 135]

  ACMG guidelines recommend an overall diet relatively high in complex CHO (45%–50% energy), generous protein (2–3 g/kg/day, 20%–25% energy) with reduced fat (approx. 30% energy) [135]. It can be difficult to achieve high protein intakes solely from food protein and protein supplements may be required (p. 621):
- If there is overnight hypoglycaemia or significant early morning ketosis (>0.5 mmol/L), UCCS should be introduced, approx. 1 g/kg/dose given at bedtime or late evening (p. 613). A second dose of UCCS may be required overnight to adequately maintain blood glucose and prevent ketosis. UCCS dosing requirements may be determined by an UCCS load test (p. 614) or by monitoring of early morning (pre-breakfast) blood glucose and ketone levels.
- Cases of GSD type IXc may require more intensive treatment as in GSDI or severe GSDIII.
- It is suggested that even where there is no hypoglycaemia or ketosis, UCCS at night is beneficial in improving any delayed growth [38].
- Micronutrient intakes should be optimized.

Severe GSDIXc

A more intensive dietary regimen will be required to maintain euglycaemia, prevent ketosis and promote growth, similar to GSDIII (p. 619).

Diet for infants with GSD VI, GSD IX and GSD0

Presentation in early infancy would be unusual apart from those of an affected older sibling; thus there is little experience of the practical management in such situations. In theory, from knowledge of the disorders and their management, cases identified in infancy would require:

- regular feeding at 3–4 hourly intervals throughout the 24 hour period to maintain normoglycaemia and prevent ketosis
- a controlled fast with monitoring of blood glucose, lactate and ketones could be used to determine the safe maximum fasting time between feeds
- monitoring of blood glucose, lactate (in GSD0) and ketones could be used to assess the adequacy of the frequency of feeding and volumes taken
- breastfed infants may need supplementary feeds of infant formula or glucose polymer if breastfeeds alone are insufficient to maintain euglycaemia
- weaning onto solid foods would be advised to start as normal around 26 weeks of age; as the intake of solids containing complex CHO and protein increase these can replace some of the milk feeds
- frequency of feeding, particularly overnight, needs reassessing regularly throughout infancy as fasting tolerance may increase

Glycogen storage disease type 0

Enzyme

Glycogen synthase (Figure 29.2)
- there are two isoforms, a hepatic isoform (GSY2) and a muscle isoform (GSY1). Only the hepatic form is discussed

Biochemical defect

Deficiency of glycogen synthase, the rate-limiting enzyme in glycogenesis (Figure 29.2), results in
- reduced availability of glycogen for the production of glucose via glycogenolysis during fasting periods. Although this is in contrast to the other hepatic GSD where glycogenolysis is disrupted, the clinical phenotype is similar to other forms of hepatic GSD [38]

Genetics

Autosomal recessive inheritance resulting from mutations in the GSY2 gene that encodes the enzyme glycogen synthase. The gene is located on chromosome 12. To date 18 mutations have been described [146]:
- many mutations are unique to particular families
- only one common mutation (c.736C >T) has been reported, found throughout Europe and North and South America [147]
- GSD0 appears rare, or under-diagnosed, as from its initial description to 2006, only 20 cases had been published [148]. A review of mutation analysis of 50 children with ketotic hypoglycaemia, from a single centre, only identified one case of GSD0 with no mutations found in the other 49 patients [146]

Clinical onset presentation, features

GSD0 typically presents in late infancy or early childhood with fasting ketotic hypoglycaemia, precipitated by increased length of overnight fast, intercurrent illness with a lack of dietary intake, or gastrointestinal symptoms of vomiting and/or diarrhoea causing reduced energy intake:
- despite significant hypoglycaemia some patients may be relatively asymptomatic as the high levels of blood ketones can provide an alternative fuel for brain energy metabolism
- seizures are uncommon; developmental delay has only been described in 22% of cases [148], and neurological sequelae appear infrequent [147]
- growth retardation may be present due to chronic ketosis
- a review of the 20 published cases identified a variety of presenting clinical symptoms, the most common being seizures 5/20, hypoglycaemia 2/20, short stature/faltering growth 2/20 and family history 5/20 [147]
- the diagnosis should be considered not only in cases of ketotic hypoglycaemia but also if hyperglycaemia and glycosuria occur that are not caused by diabetes mellitus
- the youngest age of diagnosis reported is in an 8-month-old child presenting with recurrent hypoglycaemic seizures [149]

Biochemistry at presentation

- in infants and young children overnight hypoglycaemia is a common feature
- blood glucose monitoring may reveal postprandial hyperglycaemia
- due to absence of stored glycogen, prolonged fasting will result in:
  - hypoglycaemia
  - hyperketonaemia and elevated free fatty acids
  - low levels of lactate and alanine (skeletal muscle release of alanine is inhibited by high levels of free fatty acids and ketones); thus precursors for gluconeogenesis are reduced, further exacerbating the risk of hypoglycaemia [147, 150]
- in the fed state, as a result of the reduced ability to produce glycogen in the liver, glucose derived from the diet is mainly channelled into the glycolytic pathway, resulting in the postprandial biochemical picture of hyperglycaemia, hyperlactataemia and hyperlipidaemia [151]; a standard oral glucose tolerance test produces an excessive rise in blood glucose and lactate (Table 29.20)

Long-term complications and outcome

- long-term outcomes have yet to be described
- fasting tolerance may improve with increasing age although there is considerable individual variation and it may remain a significant problem, particularly with prolonged fasting, illness, pregnancy and increased physical activity [147]

Initial management

- as for GSD type VI (p. 623)

Dietetic management

Aims:
- maintain normal blood glucose level, preventing both hypoglycaemia and hyperglycaemia
- correct secondary biochemical abnormalities of postprandial lactic acidosis and fasting ketosis by maintenance of normoglycaemia
- promote normal growth and maintain a healthy BMI

Normoglycaemia can be achieved by provision of complex CHO, which will minimise postprandial rise in blood glucose and lactate:
- simple CHO may cause a transient sharp rise in blood glucose and an increase in blood lactate; thus intake of highly refined CHO, e.g. sugary drinks, fruit juice, confectionery, cakes, sweet biscuits and high sugar cereals, should be limited
- a high protein intake is beneficial by providing substrate for glucose production via gluconeogenesis; maintenance of normoglycaemia limits fatty acid oxidation, thus preventing free fatty acid and ketone accumulation

Dietary management is based on fasting tolerance and advice centres on:
- regular meals, including a bedtime snack, containing complex CHO and protein
- managing overnight hypoglycaemia or significant early morning ketonuria (>0.5 mmol/L) with UCCS (p. 613) introduced at bedtime/late evening at a dose of 1.0–1.5 g/kg/dose. One or two doses of UCCS may be required overnight, determined by a UCCS load test (p. 614) and/or by monitoring of early morning (pre-breakfast) blood glucose and ketone levels
- continuous overnight tube feeds if UCCS is not tolerated or fails to maintain blood glucose levels adequately. There is one case report [146] of a child requiring overnight feeds of 25% glucose polymer as 6 hourly UCCS overnight failed to prevent hypoglycaemia

Alcohol	It is important to discuss alcohol intake with adolescents as it is a potent inhibitor of gluconeogenesis. Recommendations for GSDIII can be used (p. 622).
Hypoglycaemia	Guidelines for GSDI can be used (p. 616).
Monitoring	As for GSDVI.
Emergency regimen	Illness or prolonged fasting, e.g. for surgery, could precipitate hypoglycaemia. It is essential that a supply of glucose is given frequently: • ER guidance given for GSDI can be used for GSD0 (p. 617) • ER drinks need to be taken 2–3 hourly depending upon usual fasting tolerance • the CHO concentration may need to be reduced from the standard age-related ER to prevent hyperglycaemia and maintain blood sugars within a reasonable range (3.5–8 mmol/L)
Clinical management guidelines	None published
Parent support group	Association for Glycogen Storage Disease (AGSD) (https://agsd.org.uk/)

Table 29.20 Blood glucose and lactate following an oral glucose load in a 6-year-old patient as part of the diagnostic workup for GSD0.

Time (minutes)	Blood glucose mmol/L (reference range 3.3–5.5 mmol/L)	Blood lactate mmol/L (reference range 0.6–2.5 mmol/L)
0	2.5	1.42
+40	2.6	Haemolysed
+70	7.8	8.15
+120	6.9	8.18

Learning points: glycogen storage disease type 0

- *GSD0 is generally a less severe form of GSD*
- *Usually requires management with regular meals of complex CHO and protein, limiting intake of refined CHO*
- *UCCS may be required at night to prevent nocturnal hypoglycaemia and hyperketosis*

Fanconi Bickel syndrome (FBS, GLUT 2 defect, GSDXI)

Transporter	Glucose transporter 2 (GLUT2), a facilitative glucose (and galactose) transporter expressed in pancreatic islet cells, on the basolateral aspect of small intestine epithelial and proximal convoluted renal tubular cells and in hepatocytes
Biochemical defect	• deficiency of GLUT 2 • deficiency affects glucose homeostasis [152] due to GLUT 2's involvement in intestinal glucose uptake, renal reabsorption of glucose, glucose sensing in the pancreas and hepatic uptake and release of glucose (and galactose). It is essential for glucose entry into pancreatic islet cells, a process that is insulin dependent [153]
Genetics	• autosomal recessive inheritance due to mutations in the SLC2A2 gene • >70% of cases are in consanguineous families • >100 mutations have been described [153, 154], the majority being private, i.e. unique to a single family [155]
Clinical onset presentation, features	• clinically FBS presents in early childhood in those with a severe phenotype: hepatomegaly and nephromegaly due to glycogen accumulation in liver and kidney • growth failure with severe short stature • delayed bone age • hypophosphataemic rickets • delayed motor development • bone deformities, including genu valgum and kyphosis, may be present • malabsorption is not always a presenting feature; in a review of cases [156], 16% had intestinal symptoms including chronic diarrhoea or failure to thrive in infancy • cognitive development is normal • some cases may be identified on NBS for galactosaemia with galactosuria • cataracts, due to hypergalactosaemia, have been seen in a few cases although they were not found in the original patient despite a large milk intake throughout his life [153] • symptomatic hypoglycaemia in untreated patients is rare, presumably due to increased blood levels of ketone bodies and lactate

Biochemistry at presentation

Biochemical features of Fanconi Bickel syndrome (FBS) are of glucose and galactose intolerance and a Fanconi-type nephropathy:
- postprandial hyperglycaemia caused by decreased glucose uptake by the liver and low insulin secretion due to impaired glucose sensing by pancreatic β cells
- fasting hypoglycaemia due to altered glucose transport from hepatocytes [157] with ketosis
- tubular nephropathy results in glycosuria, galactosuria, amino aciduria and increased renal losses of bicarbonate, phosphate, calcium and potassium
- urine testing for amino acids and galactose is usually diagnostic in these patients, in conjunction with the clinical phenotype
- increased gluconeogenesis increases intracellular glucose, which cannot exit the cells, and inhibits glycogenolysis; this results in glycogen accumulation within the liver, enterocytes and renal tubular cells
- hydrogen breath tests following a glucose load are normal indicating that intestinal uptake of monosaccharides is not impaired; an additional transport system for glucose, SLGT1 (sodium-dependent glucose co-transporter) in the apical membrane and at the basolateral membrane, a vesicle mediated pathway, appears to enable intestinal glucose uptake [156]

Long-term complications and outcome

Despite careful management of symptoms FBS, due to its severe phenotype, is difficult to manage:
- the clinical symptoms of the original patient described persisted into adulthood and he had severe short stature [158]
- four cases had extremely poor linear growth (well below the 0.4th centile), severe tubulopathy and persistent nephrocalcinosis; heptomegaly, although reduced in 2/4 cases, remained along with abnormal glucose control, particularly postprandial hyperglycaemia [159]. Similar outcome is seen in cases in the author's unit
- UCCS has been proposed to improve metabolic control and growth [160]; however, the beneficial effects on growth seen in other GSD with the use of UCCS do not appear to be replicated in FBS
- in two siblings with a mild phenotype [161], the elder boy, diagnosed at 9 months, presented with faltering growth; his younger sister was investigated in the neonatal period and never had clinical symptoms. They have never had the classic symptoms of hepatomegaly, nephromegaly or hyperphophataemic rickets and only had mild glycosuria and proteinuria. Both had elevated blood galactose levels. At age 9½ and 4½ years, they achieved normal growth on frequent feeds of a diet restricted in glucose and galactose and avoidance of prolonged fasting. UCCS, 0.5 g/kg, was given at bedtime for the first 2 years. There have been no other published cases of mild phenotypes with good clinical outcome; other mild cases may exist as a cause of isolated glycosuria
- a first case of hepatocellular carcinoma has been described, which did not appear associated with hepatic adenomas, as is the case in other hepatic GSD [162]

Initial management
- assess fasting tolerance and institute dietary therapy to maintain normoglycaemia and prevent ketosis
- assess renal tubular losses of glucose, galactose, amino acids, calcium, phosphate, potassium and bicarbonate
- assess plasma calcium, vitamin D and phosphate status

Medical treatment
- renal tubulopathy requires supplementation of bicarbonate, potassium and phosphate
- calcium and vitamin D supplementation may be required
- adequate fluids must be given because of polyuria

Dietetic management

Management of FBS is based on symptomatic treatment. Dietary aims:
- maintaining normal blood glucose level, preventing both hyperglycaemia and hypoglycaemia
- preventing ketosis
- correcting hyperlipidaemia
- promoting normal growth and maintaining a healthy BMI

Control of blood sugars is managed by frequent intake of complex CHO, UCCS and, in some cases, continuous overnight feeds:
- large intakes of glucose and galactose (including that provided from sucrose and lactose) at a single time should be minimised to help prevent hyperglycaemia
- frequency of feeding can be determined by fasting tests, but is usually at least 3 hourly
- fasting tolerance may be improved by using UCCS
- euglycaemia and prevention of ketosis overnight might be possible with several doses of UCCS
- if overnight continuous feeding is required, the composition of the feed depends on daytime nutritional intake and growth, varying from glucose polymer to a nutritionally complete feed
- increased protein intake is needed to compensate for aminoaciduria
- there are no definitive recommendations to restrict galactose
- fructose can be tolerated as part of the diet as it is absorbed in the intestine via GLUT5, a transporter specific to fructose that is found in both the apical and basolateral membranes of the enterocyte [153]. Fructose may, therefore, be useful as an alternative monosaccharide to enable reduction in glucose intake, e.g. in overnight feeds. Fructose does not need to be converted to glucose for release from cells and is released by a different pathway to glucose [163]

Alcohol

It is important to discuss alcohol intake with adolescents as it is a potent inhibitor of gluconeogenesis. Recommendations for GSDIII can be used (p. 622).

Hypoglycaemia

Guidelines for GSDI can be used (p. 617).

Monitoring

Regular clinical and biochemical monitoring is important to evaluate the adequacy and efficacy of current dietary treatment, appraise if any dietary management changes are required and assess the family's understanding and delivery of the management. Monitoring is required to ensure:
- adequate provision of CHO and protein from diet
- adequate dosing of UCCS if required (this may be based on results of biochemical monitoring)
- nutritional adequacy of vitamin and mineral intake
- normal growth
- appropriate management of illness and that ER is updated for age and weight
- appropriate management of hypoglycaemia

Further monitoring is as for GSDI (p. 617). Routine biochemical and annual monitoring and aims are shown in Table 29.18.

Emergency regimen	The CHO concentration may need to be reduced from the standard age-related ER to prevent hyperglycaemia and maintain blood sugars within a reasonable range (3.5–10 mmol/L). Illness or prolonged fasting, e.g. for surgery, could precipitate hypoglycaemia. It is essential that a supply of glucose is given frequently: • ER guidance given for GSDI can be used for FBS (p. 617) • the CHO concentration may need to be reduced from the standard age-related ER to prevent hyperglycaemia and maintain blood sugars within a reasonable range (3.5–10 mmol/L) • additional fluids may be required if there is significant polyuria • ER drinks need to be taken 2–3 hourly depending upon usual fasting tolerance or given as a continuous infusion where a feeding tube is *in situ*
Clinical management guidelines	None published
Parent support group	Association for Glycogen Storage Disease (AGSD) (https://agsd.org.uk/)

Learning points: Fanconi Bickel syndrome (FBS, GLUT 2 defect, GSDXI)

- *FBS is a rare form of GSD caused by a defect in transporting glucose into cells*
- *Both hypoglycaemia and hyperglycaemia can occur and require management with regular meals with complex CHO and may require inclusion of UCCS to extend fasting period or continuous overnight tube feeding*
- *In addition to the defect in glucose homeostasis, there is also a Fanconi picture resulting in increased renal losses of fluid, glucose, galactose, amino acids, calcium, phosphate and potassium; supplementation to replace losses is essential*

Continuous glucose monitoring in glycogen storage disorders

Assessment of blood glucose control is pivotal to the management of hepatic GSD forming an integral part of the broader clinical and biochemical monitoring (Table 29.18). Regular assessment of the child's dietary intake, growth and relevant biochemistry is essential to optimise treatment and outcome by avoidance of under- and/or overtreatment [39].

Historically assessment of appropriateness of treatment regimens, in most UK and European metabolic centres, has been an annual inpatient admission for a 24 hour blood glucose +/− lactate profile, other relevant biochemical parameters and growth measurements. Although such admissions are able to provide true blood glucose +/− lactate measurements, their benefit is limited due to:

- giving only single point in time measurements, typically pre- and post-meals or as a maximum every 1 or 2 hours, with no indication as to the trajectory of glucose levels
- the hospital environment differing from home and the inability to reproduce normal home life, e.g. mealtimes and types of food are different, and normal activity levels at home and school cannot be maintained
- changes in dietary regimens may need a further period of inpatient assessment

Continuous glucose monitoring (CGM) has become a valuable tool in the routine monitoring of GSD patients to assess metabolic control and appropriateness of the dietary regimen. CGM allows an individual's glucose levels to be continually monitored over a period of time by an indwelling glucose sensor. It is a relatively non-invasive technique. There are advantages over intermittent glucose monitoring in that information on direction, magnitude, duration and frequency of fluctuations in blood glucose levels is also obtained [164, 165].

Initial reports in small numbers of GSD patients demonstrated that CGM provided useful longitudinal data on blood glucose concentrations rather than single time points [166] and the detection of unrecognised hypoglycaemia [167]. A study including an audit of 55 profiles in 26 patients (mainly children) showed 95% of profiles produced meaningful data and highlighted the usefulness of CGM, in association with diet diaries +/− lactate and ketone measurements and growth data, in optimising GSD biochemical parameters and nutritional management [164]. A further study of CGMS in 20 patients (40% ≥17 years old) showed the usefulness of the technique throughout the age continuum [168]. In addition to its role in detecting subclinical hypoglycaemia, the study also highlighted the detection of periods of hyperglycaemia, which equally need to be recognised and managed to prevent longer-term consequences of chronic hyperglycaemia (obesity, metabolic syndrome, type 2 diabetes).

Continuous glucose monitoring systems

How they work

- continuous glucose monitoring systems (CGMS) consist of an indwelling glucose sensor attached to a wireless data recorder
- the sensor, a very fine microelectrode coated with glucose oxidase, is inserted under the skin, usually into the abdomen although other areas can be used, e.g. upper arm and buttock, and connected to a small recorder
- the sensor measures glucose concentrations indirectly via an electrical signal produced by a glucose-oxidase electrochemical reaction in the interstitial fluid. Measurements are taken every 10 seconds, and an average reading every

5 minutes is recorded and wirelessly transmitted to the data recorder, producing up to 288 measurements per day
- sensor signals are converted to glucose concentration by a calibration process utilising finger stick blood glucose measurements [169]:
  - to reduce errors in calibration, capillary blood samples should be taken at times when these should be more stable, e.g. preprandial
  - a major cause of sensor error is calibration with capillary glucose levels that are rapidly changing as there is a lag time between changes in plasma and changes in interstitial glucose levels [170]. This, in addition to the sensor reaction time for glucose to diffuse into the sensor and for a signal to be processed, give an overall lag time of 5–15 minutes [171]
- retrospective and 'real-time' systems are available. In GSD management the use of 'real-time' systems is discouraged as this may result in families making frequent management changes, without discussion, which may not be appropriate [164]

Practicalities of using CGM

- sensors can remain *in situ* for around 6–14 days depending on type
- blood glucose meter measurements are taken four times daily prior to main meals and before a bedtime snack, start of continuous overnight feed or evening dose of UCCS
- a daily food diary is kept throughout the study and is essential for accurate interpretation of CGM results (Table 29.21)
- lactate and ketone monitoring, as clinically relevant, is done alongside CGM. Lactate meter measurements are done concurrently with blood glucose measurements. Ketones (urine or blood using a dual-purpose blood glucose/ketone meter) are usually measured before breakfast only:
  - measurement of blood lactate is particularly relevant in GSDI. The Lactate Pro portable meter has been validated in GSDIa [172]
  - lactate measurements, however, can be inaccurate particularly if the blood sample was not free flowing and results should be interpreted with some caution, particularly if they appear unusually abnormal for the child. For example, if blood glucose and lactate levels are well controlled, a one-off very high lactate level would be unusual, but following a period of hypoglycaemia, a high lactate level would be in keeping. Lactate, however, can be high in seemingly well-managed patients, despite normoglycaemia; in these cases lactate levels may be more consistently raised
- CGM profiles should be carried out with normal activities, including school days and sports, and no changes to dietary intake unless advised
- following the monitoring period, the sensor data are downloaded using specific computer software, and the data are then reviewed:
  - lower and upper limits for glucose levels are defined, which the software uses to look at time periods above and below the target glucose range. In the author's centre these are set at a lower glucose limit of 3.5 mmol/L and upper limit of 8 mmol/L, except for Fanconi Bickel syndrome where the upper limit is set at 10 mmol/L due to the extremes of hyperglycaemia observed in the condition
- data generated includes:
  - individual daily graph of glucose profile
  - overlay of each day's profile on one graph
  - data on total number, highest, lowest and average sensor values and standard deviation (SD) of glucose readings – the lower the SD, the less fluctuation there is in glucose values
  - accuracy criteria, which includes correlation between sensor and calibration capillary glucose measurements and the mean absolute difference (% MAD). MAD is the average % difference between sensor and capillary glucose values. Values <28% are optimal or <18% if glucose is maintained within a narrow range [173]
  - excursion summary, which describes the number of glucose levels above or below target glucose levels
  - duration distribution, giving % time below, within and above target in 24 hours
- CGM profiles should be reviewed looking at trends and the presence of repeated patterns rather than relying on single measurements, in conjunction with all other test results to inform management advice

Table 29.21 Home monitoring indicating the different parameters monitored according to disorder.

GSD type	0	Ia/b	IIIa/b	VI and IX	FBS
CGM	✓	✓	✓	✓	✓
Blood glucose (capillary) meter levels	✓	✓	✓	✓	✓
Lactate	✓	✓			
Ketones	✓		✓	✓	✓
Food diary • Time • Quantities	✓	✓	✓	✓	✓

CGM, continuous glucose monitoring.

An example of the use of CGM in practice is shown in Figures 29.3 and 29.4. Home monitoring for types of GSD is shown in Table 29.21.

Benefits of CGM

- avoidance of hospital admissions and associated repeated venepuncture
- may be inserted and removed at home by nurses trained in CGMS
- improved representation of normal lifestyle including dietary intake, activity patterns and adherence to prescribed dietary regimens

- allows comparison of weekend and school day profiles
- profiles provide significantly more information and are more 'visual' than a list of numbers produced during a standard inpatient blood glucose profile
- information gained includes confirmation of the adequacy of the usual dietary regimen or identification of trends indicating regimen changes are needed, e.g. glucose levels falling overnight or before feeds, even if the level is not below the lower target glucose range, indicate the potential for hypoglycaemia and the need to re-evaluate the dietary regimen
- ability to adjust and compare different dietary regimens during a profile period, which is valuable in attempting to optimise an individual's treatment without the need for repeated inpatient admissions, over a period of time, to assess different regimens
- glucose profile results are a visual educational tool for families; they can highlight adherence issues that can be addressed to improve biochemical control or illustrate specific foods that may cause high blood glucose levels, typically refined CHO
- increased information on overall dietary intake that can inform targeted advice on improving nutritional adequacy of the diet
- the process is positively accepted by the families
- is well tolerated by all age groups of patients

CGM should normally be done at least annually. In infants and young children with the most severe forms of GSD requiring intensive regimens, or in newly diagnosed or unstable patients, more frequent CGM will be needed to evaluate the effectiveness of management. In very stable or mild patients less frequent CGM may be acceptable.

Hereditary Fructose Intolerance

Fiona J. White

Hereditary fructose intolerance (HFI) is a very rare, possibly under-diagnosed, inherited metabolic disease.

Enzyme	Aldolase B (fructose-1, 6-bisphosphate aldolase) found in the liver, kidney and small intestine
Biochemical defect	Block in the conversion of fructose-1-phosphate (F-1-P) to glyceraldehyde and dihydroxyacetone. This results in accumulation of F-1-P and lack of intracellular phosphate/ATP causing inhibition of glycogenolysis and gluconeogenesis and reduced glucose production (Figure 29.6).
Genetics	Autosomal recessive inheritance. There are some common mutations in the ALDOB gene that can be analysed initially if HFI is suspected.
Clinical onset presentation, features	Generally presents after weaning when fructose-containing foods are introduced. May have an aversion to sweet foods and sugar-containing medicines, which may delay the diagnosis for years. Presenting clinical features can vary between: • acute severe presentation with hypoglycaemia, seizures and coma following ingestion of fructose, sucrose or sorbitol. In neonates this may lead to acute liver failure, kidney failure and death [174]. Acute presentation is less likely before weaning when infants are fed non-fructose-containing feeds, i.e. breastmilk or infant formulas where lactose is the carbohydrate source. However, there are case reports of neonates presenting, precipitated by being fed sucrose-containing formula [175] • non-specific features of poor feeding, vomiting, abdominal distension, restlessness, lethargy and growth faltering. A good diet history in these situations may reveal self-avoidance of sweet foods and drinks and vomiting with sugar-containing medications and gives a clue to the diagnosis • progressive liver dysfunction, hepatosplenomegaly, hypoglycaemia and renal tubular dysfunction
Long-term complications and outcome	The long-term prognosis is good provided a fructose-free diet is followed, although hepatomegaly and fatty changes in the liver may persist [176]. The diet needs to be continued for life.
Acute management	IV dextrose to correct any hypoglycaemia Avoidance of IV fluids containing fructose or sorbitol (this is not an issue in the UK)
Dietetic management	Minimal fructose, sucrose and sorbitol diet (Table 29.22) Supplementation of vitamin C and folic acid to meet requirements
Medications	Pharmacy check regarding suitability of medicines as they can contain sucrose, fructose, sorbitol and artificial sweeteners.
Monitoring	• growth • dietary adherence • liver and renal function tests, full blood count, plasma folate and iron status (haemoglobin and ferritin) • clinical assessment of skin and gums, checking for signs of vitamin C deficiency (swollen tissue, tender and bruises easily and bleeding gums). Vitamin C status can be measured in white blood cells, but analysis is not performed routinely by all laboratories (www.clinbiochem.info). Adult range: 26.1–84.6 μmol/L (there is no paediatric range); deficiency level: <11.1 μmol/L • vitamins A, E and D, selenium and zinc to measure general nutritional status as indicated • plasma lactate, urate and urinary protein to assess renal tubular dysfunction as indicated

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Baker P, II, Ayres L, Gaughan S, Weisfeld-Adams J Hereditary fructose intolerance. In: *Adam MP*, Ardinger HH, Pagon RA *et al.* (eds) GeneReviews. Seattle: University of Washington, 2015. [177] www.ncbi.nlm.nih.gov/books/NBK333439/.

Parent support group Metabolic Support UK (www.metabolicsupportuk.org/)

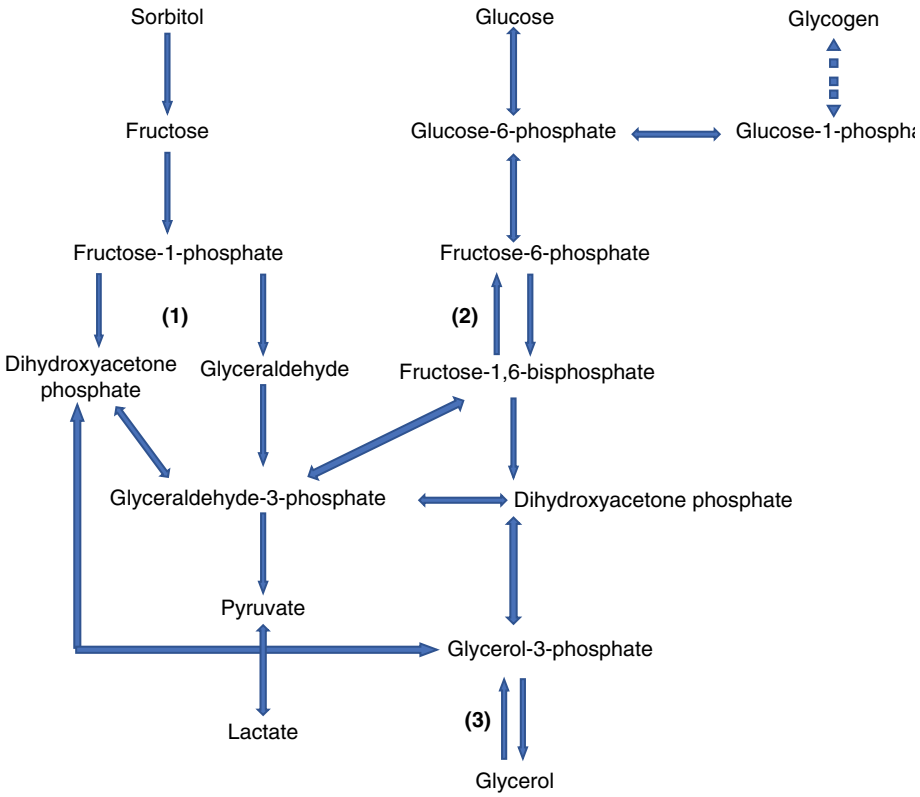

Figure 29.6 Fructose and glycerol metabolism.

Dietary treatment

HFI is managed primarily by avoidance of fructose, sucrose and sorbitol in the diet and in medicines (Table 29.22). Dietary aims are:

- the complete elimination of fructose, sucrose, sorbitol and other potential sources of fructose. However, this is not realistic or possible as very small amounts of fructose are found in many staple foods, particularly plant-based foods
- in practice fructose intake is restricted to <2 g/day from all sources, i.e. the lowest intake that is practically achievable (Table 29.22). On these intakes patients remain symptom free

In adults with long-term daily intakes of up to 2.5 g sucrose/day (1.25 g fructose, approx. 15–20 mg/kg), symptoms did not develop [181].

Carbohydrates that can be included in the diet

- starch
- glucose – can be used as an alternative sweetener to sucrose and can also provide a useful source of energy:
  - glucose has only half the sweetness of sucrose, so additional sweetening can be added to baked goods using as intense sweetener, e.g. Sweetex can be successfully added to cooked food; others that decompose on heating, e.g. aspartame, are not suitable for baking
  - in practice this may not be necessary as children with HFI generally dislike and avoid sweet tasting foods
  - glucose is not prescribable for treatment of HFI
- lactose
- polyols: erythritol, xylitol and lactitol
- sucralose (E955), previously known as Splenda, is about 600 times as sweet as sucrose. It is increasingly used in

Table 29.22 Minimal fructose, sucrose and sorbitol diet (aim <2 g fructose/day).

Analysis of fructose and sucrose content of foods [178–180]

Foods allowed	Foods to avoid
Sugars, sweeteners and preserves	
Glucose, glucose polymers, glucose syrup, dextrose, lactose, starch, maltose, maltodextrin, malt extract, glycerol Saccharin, aspartame, acesulfame K, Sweetex (aspartame and saccharin), sucralose (E955) Polyols: erythritol, xylitol, lactitol	Sugar or sucrose (cane or beet) – white, brown, caster, icing Fruit sugar, fructose, laevulose Honey, treacle, molasses Polyols: sorbitol, maltitol, mannitol, isomalt, Lycasin Golden syrup, corn syrup, invert syrup, high fructose or isoglucose syrups, hydrogenated glucose syrup, maple syrup Jam, marmalade, lemon curd
Fruits	
Avocado, rhubarb (occasionally)	All other fruits and fruit products
Vegetables	
Seaweed, vine leaves allowed freely See Table 29.23	Beans (French, green, runner), beetroot, Brussels sprouts, carrots, gherkins, green beans, kohl rabi, okra, onion, parsnip, peas, pepper, plantain, shallots, spring onion, squash, sweetcorn, sweet potato, tomato, tomato purée
See Table 29.23	Baked beans, tinned vegetables with added sugar, mayonnaise or salad cream, coleslaw Flavoured crisps Pickles, chutney
Milk and dairy products	
Infant formula and follow-on milk (check there is no added sucrose, fructose or honey)	Flavoured milk, condensed milk, milkshake powders and syrups
Cow's milk, unsweetened evaporated milk	Liquid soya milk
Coffee mate, dried milk powder	Aerosol cream
Cream	Cheese with added ingredients, e.g. nuts, fruit
Cheese, plain cottage cheese	Fruit and flavoured yoghurt, fromage frais
Natural yoghurt	Ice cream
Eggs	
Meat and poultry	
All fresh meat and poultry	Processed meats that have added sucrose, e.g. meat pastes, frankfurters, salami, pâté, sausages, tinned meat
Processed meat products (check there is no added sucrose, fructose or honey)	Tender sweet meats, e.g. ham, honey cured meats Ready-made meat meals (possible sources are gravies, sauces, vegetables, breadcrumbs, batter, pastry)
Meat substitutes	
Soya products, tofu, Quorn	Ready-made meals with these products may contain sucrose
Fish	
Fresh and frozen fish	Fish tinned in tomato sauce
Shell fish	Fish paste
Fish tinned in brine, oil or water	Fish cakes, fish fingers Ready-made fish meals (possible sources are sauces, vegetables, breadcrumbs, batter, pastry)
Flour and cereals	
Flour (white in preference to wholemeal), buckwheat, cornflour, custard powder, sago, semolina, tapioca, oatmeal, barley	Bran, wheat germ
Flaky pastry, filo pastry, shortcrust pastry (not sweetened)	Dessert pastry
Pasta and rice	
Spaghetti, macaroni, other pasta (white in preference to wholemeal)	Pasta tinned in tomato sauce
Noodles, egg noodles Rice (white in preference to brown)	Pot savouries, e.g. pot noodle
Breakfast cereals	
Porridge, Puffed Wheat, Ready Brek, Shredded Wheat	Most manufactured breakfast cereals

(continued overleaf)

Table 29.22 *(continued)*

Analysis of fructose and sucrose content of foods [178–180]	
Foods allowed	Foods to avoid
Bread and crackers	
White bread (pre-packed), tortilla wraps Baker's bread (check if sugar is added to dough mixture) Cream crackers, matzo crackers, water biscuits, Ryvita, plain rice cakes Crumpets (not all are suitable, check label)	Wholemeal bread, sweetened breads, e.g. malt bread, soda bread, currant bread, malt loaf, brioche, pain au chocolat Savoury snack biscuits
Cakes, biscuits and pastries	
Home-made – using permitted ingredients and sweeteners	All cakes, muffins, pancakes, waffles, biscuits and pastries
Desserts	
Home-made – using permitted ingredients, e.g. custard sweetened with glucose, choux pastry	Most desserts, e.g. jelly, meringue, mousse, gateaux, fruit pie or crumble, yoghurt, ice cream, sorbet, ice lollies
Fats and oils	
Butter, margarine, vegetable oils (including olive oil), lard, suet	
Drinks	
Lucozade Original (not fruit flavoured), soda water, mineral water (not fruit flavoured) Squashes and fizzy drinks flavoured with saccharin or aspartame only (free from sugar, sorbitol, fruit flavourings or comminuted fruits) Tea, coffee, cocoa, herbal teas (no sugar)	Fruit juices, vegetable juices, fruit squash, fizzy drinks, diabetic squash containing sorbitol or fructose, tonic water, fruit ice, Slush Puppie Drinking chocolate, malted drinks Instant tea mixes, coffee essence Fruit teas
Confectionery	
Lucozade Sport Glucose Energy tablets – original	Sweets, chocolate, toffee, jelly, ice lollies, chewing gum, diabetic sweets (sweetened with fructose or sorbitol)
Dextro energy – dextrose and maltodextrin Glucotabs (BBI healthcare)	Flavoured glucose tablets
Gravies, sauces and soups	
Marmite, Bovril White or cheese sauce made with milk, flour, fat and cheese only	Gravy granules, stock cubes Bottled sauces and dressings, e.g. tomato ketchup, horseradish sauce, mint sauce, soy sauce, sauce mixes, e.g. sweet and sour, curry Mayonnaise, salad cream All soups (packet, tinned or fresh)
Herbs, spices, nuts and seeds	
Pure herbs, mustard and spices, salt, pepper Sesame seeds Pumpkin and sunflower seeds (maximum 10 g per day)	Nuts, peanut butter, marzipan
Baking products	
Baking powder, bicarbonate of soda, yeast, arrowroot, food colourings, food essences, gelatine	
Alcohol (*not suitable for children*)	
Beer – bitter, lager, mild, pale ale, stout (Guinness), strong ale/barley wine	Low alcohol bitter, alcohol free/low alcohol lager, shandy, fruit beers
Note: Sucrose or fructose may be added to bottled, canned or keg beers to adjust the sweetness of the final product	Cider
Sucrose is usually added to cask conditioned beers (sometimes referred to as 'real' beers) to generate secondary fermentation within the container	
Wine – red only	Wine – champagne, mulled wine, rose, white fortified wines – port, sherry, tonic wine, vermouth
Spirits	Liqueurs Alcopops

- Always read the label of manufactured foods to check for sucrose, fructose, sorbitol, polyols or unsuitable sweeteners.
- Check toothpaste for sorbitol.

Table 29.23 Vegetables allowed in a minimal fructose, sucrose and sorbitol diet [180].

Total daily fructose intake from vegetables should not exceed 1.0–1.5 g/day
Group 1 – potatoes (old)
1 portion = approximately 0.3 g fructose
Boiled – 2 small egg size (100 g)
Jacket (flesh only) – 1 medium (100 g)
Mashed – 2 tablespoons (100 g)
Roast potatoes – 2 small (100 g)
Chips – medium portion (120 g)
Plain crisps – 2 small packets
*Potato waffles (1)
*Potato croquettes (2)
*Check to ensure does not contain sugar
Group 2 – vegetables containing <0.5 g fructose/100 g
1 portion = approximately 0.15 g fructose where a small portion is 1 tablespoon (30 g) unless indicated otherwise
Celery
Globe artichoke (1 globe, 50 g)
Mange tout
Mushrooms
Sauerkraut
Spinach
Watercress ($^1/_2$ bunch)
Beans, e.g. haricot, mung, red kidney
Lentils
Yam – boiled or baked (amount = ½ small potato)
Dried split peas
Group 3 – vegetables containing 0.5–1.0 g fructose/100 g
1 portion = approximately 0.3 g fructose where a small portion is 1 tablespoon (30 g) unless indicated otherwise
Aubergine – 1 slice (30 g)
Asparagus – 2 spears (50 g)
Bean sprouts
Broccoli – 1 spear (50 g)
Cabbage
Cauliflower
Cucumber – 8 thin slices (40 g)
Fennel – (45 g)
Jerusalem artichoke – (40 g)
Celeriac – (35 g)
Leeks – $^1/_4$ medium (30 g)
Lettuce – 4 small leaves (25 g)
New potato – 1 small (50 g)
Pumpkin
Radish (red) × 4 (40 g)
Spring greens
Swede
Turnip
Beans – black eye, broad, butter, soya
Peas – marrowfat, mushy, processed peas in water
Chickpeas or hummus

Source: Licensed Under CC BY 4.0.

products including medicines. Pharmacokinetic studies in humans given sucralose showed that the majority was recovered unchanged, predominantly in faeces [182]. It would appear unnecessary to exclude sucralose in HFI because the amount added to foods is likely to be extremely small, it is mostly not absorbed, and its intense sweetness will probably be disliked

Sources of fructose that need to be avoided in HFI

Sugars

In addition to fructose *per se*, fructose is also derived from sucrose and sorbitol. A number of compounds can also be potential sources of fructose and need to be avoided:

- fructose is the natural sugar present in fruits, vegetables and honey
- sucrose, a disaccharide, is cleaved in the small intestine by sucrase-isomaltase forming a molecule each of glucose and fructose. Sucrose is found in:
  - small amounts in fruits and vegetables
  - sugarcane or beet, refined to produce table sugar that is used extensively in baking and in food manufacture as a sweetener and bulking agent
  - cakes, biscuits, desserts and soft drinks
  - commercial foods (e.g. stock cubes, tinned meats, bottled sauces, savoury snack biscuits) contain sugar, but are much less obvious sources. Indeed, very few manufactured foods are suitable for inclusion in the diet
  - high fructose corn syrup is used as a sweetener, particularly in the USA where it is a large contributor [183, 184]
- sorbitol and other polyols. Polyols are sugar alcohols, classed as sugar-free, low energy bulk sweeteners that are used in many foods and medicines. They are potential sources of sorbitol and fructose. Their absorption is slow and incomplete, for example, only 10%–30% of sorbitol is absorbed. Although sorbitol does not contain fructose, in the liver it is rapidly converted via sorbitol dehydrogenase to fructose in the sorbitol-aldolase or polyol pathway. Polyols are thus a possible source of fructose or sorbitol [185].The most widely used and to be avoided in HFI are sorbitol (E420, derived from dextrose), mannitol (E421, derived from fructose), maltitol (E961, derived from maltose) and isomalt (E953, derived from sucrose)
  - foods and medicines, e.g. sugar-free syrups, lozenges and jelly preparations, suitable for children may contain these - check for suitability

  - there are different brands of polyols available, e.g. Lycasin (contains maltitol) and Neosorb (contains sorbitol). Polyols should be declared on the food ingredient and nutritional labels in the UK, making them relatively easy to identify
  - some toothpastes contain sorbitol - avoid as young children may swallow toothpaste
- oligosaccharides, raffinose (trisaccharide) and stachyose (tetrasaccharide) comprise fructose and glucose to which galactose is linked in an α-galactosidic linkage; it is thought that in humans these are not hydrolysed due to the absence of α-galactosidase [186]. They are found in small quantities in food: raffinose in sunflower seeds, chicory, onions and other vegetables (about 1 g/100 g food or less); legumes are the richest source of stachyose (1–5 g/100 g food)
- fructans and fructo-oligosaccharides. Inulin is a fructan found in various plants, e.g. artichokes and chicory [187]. Fructo-oligosaccharides (FOS), also known as oligofructose, are produced through enzymatic hydrolysis of inulin. Both inulin and FOS are primarily sources of dietary fibre. Being resistant to hydrolysis by digestive enzymes, they are not absorbed, but instead are fermented by anaerobic bacteria in the colon. However, as they have an energy value of 1.5–2 kcal (6–8 kJ)/g, it is possible that some fructose may be absorbed and that commercial inulin and oligofructose syrups may contain small amounts of fructose and sucrose:
  - FOS, as prebiotics, are added to some infant formulas and enteral feeds to promote the growth of intestinal flora similar to that of the breastfed baby [188, 189]. It is also added to weaning foods and functional foods. At low doses it is unlikely to cause adverse effects [175, 181]
  - the ingredients of special infant formulas and enteral feed products should be checked for sucrose and fructose. In the EU only lactose as a carbohydrate source is allowed in normal infant formulas [190]. However, this may not be the case in other countries; Li *et al*. reported four cases of acute liver failure in neonates fed fructose-containing formulas, subsequently diagnosed with HFI [175]
- flavourings can be another potential source of sucrose and fructose as these sugars are sometimes used as carriers for flavouring compounds, which will not necessarily be labelled

Vegetables

Vegetables contain significant amounts of fructose (as fructose and sucrose) so most must be avoided, and only vegetables with a very low fructose content, predominantly containing starch, can be included in the diet in restricted amounts only (Table 29.22). The total daily fructose intake from vegetables should not exceed 1–1.5 g/day as small amounts of fructose from cereals in the diet will increase the total intake to around the 2 g/day maximum. As the total fructose content (fructose plus half the sucrose content) varies between different vegetables, they have been divided into three groups:

- Group 1 – potatoes
- Group 2 – vegetables containing <0.5 g fructose/100 g
- Group 3 – vegetables containing 0.5–1 g fructose/100 g

Within each group portion sizes are indicated to provide a certain amount of fructose. These can then be used to calculate daily fructose intake from vegetables.

It is important to note the difference in fructose content between raw and cooked vegetables:

- cooking causes a loss of free sugars; consequently cooked vegetables have a lower fructose content and are recommended in preference to raw
- water from boiled vegetables should be discarded and not used to make gravy or sauces
- new potatoes have a higher fructose content than old (0.65 g/100 g vs. 0.25 g/100 g)
- sucrose content of stored potatoes has previously been reported to both decrease and increase on storage [191, 192]. Information from the Institute of Food Research, Norwich, reports that potatoes in cold storage (<8 °C) have a higher fructose content compared with those stored in warm temperatures (>15 °C)

Manufactured foods

Ingredient labels on manufactured foods should be checked for the presence of sucrose, fructose or sorbitol and other polyols or unsuitable sweeteners (Table 29.22). In the UK regulations on sugar labelling are available at www.legislation.gov.uk/uksi/2003/1563/contents/made. Products covered by these rules include:

- white sugars, dextrose, glucose syrups and fructose
- where a product is labelled to contain 'sugar' this indicates the ingredient is sucrose
- where glucose syrup or dried glucose syrup contains more than 5% fructose, 'fructose' will be indicated as an ingredient

Flour, bread, rice

- wholemeal flour and other wholegrain foods, e.g. brown rice and wholemeal pasta, contain more fructose than white versions because the germ and bran contain sucrose
- no accurate analysis for the fructose content of bread is available; however, it would appear prudent to choose white in preference to wholemeal. Bread has previously been restricted in the diets of children with HFI. Nowadays this restriction is probably unnecessary because most flour improvers for bread making do not contain sugar. If the bread does contain sugar, it has to be declared on the ingredient label. If there is any doubt about suitability of a particular bread, the manufacturer should be contacted. Caution should be applied where richer doughs are used (e.g. in soft rolls) because often the flour improver does contain sugar in these instances. Bread bought from craft bakers may also contain sugar. Under EU law products sold loose are

under no legal obligation to declare this information to the consumer as sucrose, fructose and sorbitol are not allergens [193]

Nutritional problems

Nutritional deficiencies may arise in children with HFI:

- risk of vitamin C and possibly folic acid deficiency due to the exclusion of the major dietary sources of these vitamins, i.e. fruits and vegetables [194]
- supplementation with vitamin C and folic acid is necessary to provide reference nutrient intake [29]
- commercial vitamin and mineral preparations should be checked to ensure ingredients do not contain sucrose, fructose, sorbitol, sucralose or other polyols
- lack of dietary fibre may also be a problem. This can be overcome by including pulses and oats, which contain only very small amounts of fructose, or inclusion of Resource Optifibre (Nestle); the fibre source is guar gum

Learning points: hereditary fructose intolerance

- *Many patients will have self -selected a low fructose diet prior to diagnosis*
- *A good diet history taken can alert healthcare professionals to the possibility of HFI in undiagnosed patients*
- *Dietary avoidance of fructose continues lifelong to avoid deleterious effects on liver and kidney*

Fructose-1,6-Bisphosphatase Deficiency

Anita MacDonald

Enzyme	Fructose-1,6-bisphosphatase (FBPase)
Biochemical defect	FBPase is a key gluconeogenic enzyme that catalyzes the hydrolysis of fructose-1,6-bisphosphate to fructose-6-phosphate and inorganic phosphate (Figure 29.6) [195]. Deficiency affects gluconeogenesis by impairing the formation of glucose from all gluconeogenic precursors including dietary fructose [196]. Hypoglycaemia occurs after prolonged fasting when glycogen stores are depleted [195].
Genetics	Autosomal recessive inheritance. It is caused by mutations within the FBP1 gene on chromosome 9q22.2–q22.3 and consists of 8 exons; incidence is rare, but is more common in countries with higher rates of consanguinity [197].
Presentation	Signs and symptoms include hypoglycaemia, ketoacidosis, lactic acidosis, hepatomegaly, coma and tachypnoea (occurs in neonates, about 50% of cases) or later during fasting or induced by fructose (approx. 1 g/kg body weight in one dose), especially after fasting [174]. Diagnosis may be delayed, and children may have experienced more than one episode of acute metabolic decompensation. Poor appetite, intercurrent infections, vomiting and prolonged fasting can precipitate metabolic decompensation.
Long-term complications and outcome	Mortality is high in the neonatal period, usually before diagnosis is made [196]. Once the diagnosis is established, the outcome is generally good. Children remain asymptomatic between acute episodes of metabolic decompensation. Growth and development of patients are usually normal. However, profound hypoglycaemia may lead to neurological deficits. Fasting tolerance should improve with age [199], and the frequency of acute metabolic decompensations decrease [174]. Symptoms have been reported in adulthood associated with illness and fasting during Ramadan [200], pregnancy [201], alcohol consumption [202], weight loss and extensive exercise training (the latter requires careful management) [203].
Dietary management	Dietary management is not well characterized, but should prevent hypoglycaemia and lactic acidosis. There is a dependence on exogenous sources of glucose, and the primary dietary goal is to avoid prolonged fasting. Fasting: • in infants and young children fasting times are limited, and infants commonly develop clinical symptoms following withdrawal of night feeds • infants should be fed 3–4 hourly until fasting tolerance is established (NB: fasting tolerance of only 3 hours has been reported in some case studies in infancy [196]) • in children >1 year of age regular meals containing starchy foods is important, including a bedtime snack, and breakfast should not be missed • in childhood it is often reported that fasting does not exceed 8 hours, but individual fasting tolerance varies [204] and should improve with age [205] Cornstarch (UCCS): • a late evening single dose of UCCS (household cornflour) is recommended by some centres to provide a source of slow-release glucose overnight [206] • the mean dose by age reported is as follows: 1–10 years, 1.2 g/kg; 11–16 years, 1.3 g/kg; >16 years, 1.0 g/kg) [205] • there is little data to support its effectiveness in FBPase deficiency • if UCCS is not given, a bedtime snack containing complex CHO, e.g. bread or cereal, is advocated

	Further information about provision of UCCS is given on p. 613. Fructose and sucrose restriction: • although fructose is a gluconeogenic precursor, the severity of sucrose and fructose restriction remains undefined, and dietary practices vary [205] • loading tests with fructose induced hypoglycaemia [207], suggesting reduced fructose tolerance; however, in non-catabolic states, fructose (sweet food) is generally tolerated in children when distributed over the day [200] • although many international centres avoid an excessive intake of confectionery and sugary drinks, particularly in young children [199, 205], most (64%) UK centres do not restrict fructose, sucrose or sorbitol intake when patients are well [208] Alcohol: • care must be taken if alcohol is consumed as it inhibits gluconeogenesis and in excess may precipitate hypoglycaemia; therefore, it should be taken in moderation only and always with food [209]
Clinical and biochemical monitoring	*Clinical*: somatic findings (liver size) *Neurological*: cognitive function, developmental monitoring *General monitoring*: growth, nutritional status, dietary intake *Biochemistry*: liver function, assessment of fasting tolerance *Illness*: glucose (low), lactate (high), pH, blood gases, full blood count
Emergency regimen and acute management	• Metabolic decompensation occurs during illness, trauma and surgery because the gluconeogenic pathway for glucose production is blocked. During acute episodes, there is lactate accumulation, decreased pH and an increased lactate/pyruvate ratio, hyperalaninaemia and glucagon-resistant hypoglycaemia [199]. • Treatment aims to prevent metabolic decompensation by giving glucose orally or IV. If tolerated, the standard oral ER for age should be given (Tables 31.1 and 31.2). The ER should be glucose polymer only; sweetened squash or other drinks should not be added as fructose, sucrose and sorbitol should be temporarily avoided during the acute illness. Fat should be avoided during decompensation as glycerol may exacerbate the illness. • Some patients may decompensate rapidly, becoming very ill with marked acidosis. If the child is unwell, a bolus of IV glucose is immediately administered [210] before providing an infusion of IV glucose (10%) at maintenance fluid requirements. Metabolic acidosis is treated by giving sodium bicarbonate. This treatment should promptly ameliorate symptoms [208]. In acute metabolic decompensation, IV administration of fructose is contraindicated and may lead to death [199]. • Once the child improves, a normal diet can be resumed, with a gradual reintroduction of fructose and sucrose. During the recovery period, extra glucose polymer drinks should continue to be given, particularly at night. • Fructose, sugar- and sorbitol containing medications should be avoided during intercurrent illness. Only sugar-free medicines should be given, but constituents should still be checked. • In Asian countries, including Japan, IV glycerol therapy may contain fructose, and this can cause hypoglycaemia and metabolic acidosis, even under stable conditions in patients with FBPase deficiency [208].

Learning points: fructose-1,6-bisphosphatase deficiency

- *Clinical symptoms of FBPase deficiency may overlap with many other metabolic disorders, and diagnosis is commonly delayed*
- *Dietary management in infancy and early childhood is avoidance of prolonged fasting +/– bedtime UCCS (for children >1 year of age)*
- *The standard ER is essential at all ages to prevent metabolic decompensation during illness and prolonged fasting*
- *Fructose, sucrose and sorbitol should be avoided during acute metabolic decompensation*

Glycerol Kinase Deficiency (GKD)

Marjorie Dixon

Enzyme	Glycerol kinase
Biochemical defect	Glycerol kinase catalyses the phosphorylation of glycerol to yield glycerol-3-phosphate (G3P) and ADP (Figure 29.6); around 70%–90% of G3P is oxidised to dihydroxyacetone phosphate and enters the glycolysis or gluconeogenic pathway at the level of glyceraldehyde-3-phosphate; 10%–30% of G3P combines with free fatty acids to form triglycerides [211]. Glycerol kinase deficiency (GKD) is characterised by hyperglycerolaemia and glyceroluria. Normal plasma glycerol levels (<0.2 mmol/L) may increase to 8 mmol/L, resulting in urine levels >150 mmol/L (normally undetectable) [212]. In non-fasting situations, glycerol (via gluconeogenesis) contributes little to hepatic glucose production. In prolonged fasting conditions, its contribution increases to about 20% energy as gluconeogenesis and fatty acid oxidation become essential to meet energy needs [211].
Genetics	GKD1 is an X-linked recessive disorder resulting from the deletion or mutation of the gene for the enzyme glycerol kinase [211].
Clinical onset presentation, features	There are three clinical forms: Infantile form • GK deficiency, or the 'GK complex', results from the Xp21 contiguous gene deletion syndrome with congenital adrenal hyopoplasia and/or Duchenne muscular dystrophy and is associated with severe developmental delay [211, 213] Adult form • 'isolated GK deficiency', benign with pseudohypertriglyceridaemia [214] Juvenile form • 'isolated GK deficiency' occurs in the first few years of life and is often precipitated by catabolism due to illness or poor feeding and can include episodic vomiting, metabolic acidosis, ketotic hypoglycaemia, lethargy, hypotonia, seizures and unconsciousness
Dietetic management	Juvenile form only – isolated GK deficiency: • avoidance of prolonged fasting • during illness the standard ER (p. 673) is given to provide glucose as an energy source • glucose is needed to prevent hypoglycaemia as the capacity to convert glycerol to glucose via gluconeogenesis is limited • if IV fluids are required, only glucose should be given and not lipids • refer to www.bimdg.org for IV management

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

30 Disorders of Mitochondrial Fatty Acid Oxidation and Lipid Metabolism

Marjorie Dixon, Rachel Skeath and Fiona J. White

Disorders of Mitochondrial Fatty Acid Oxidation and Related Disorders

Marjorie Dixon

Introduction to fatty acid oxidation

Fatty acids are a major fuel source for most tissues of the body, especially during fasting, when glucose supply is limited. They are the principal energy source for cardiac muscle and skeletal muscle in the resting state and during prolonged exercise. Fatty acid oxidation is also essential for the production of ketone bodies, another important fuel, which can be used by all tissues, particularly the brain during prolonged fasting as it cannot use fatty acids to generate energy. Ketones are also the preferred fuel for the heart.

Most naturally occurring fatty acids have a chain length of 16–18 carbon atoms (long chain fatty acids [LCFA]). Fat metabolism begins in adipose tissue in response to falling levels of blood glucose. Insulin activates hormone-sensitive lipase, which promotes the release of free fatty acids from triglycerides into the blood stream. Fatty acids are then transported to the tissues bound to albumin. In tissues where they are used, fatty acids enter the mitochondria bound to carnitine via the carnitine cycle pathway. Within the mitochondria, β-oxidation is the primary breakdown pathway of fatty acids to produce acetyl-CoA and electron carriers. Acetyl-CoA can enter the citric acid cycle or form ketone bodies in the liver. Ketones are also formed from the ketogenic amino acids (p. 503). Electron carriers ($FADH_2$ and NAD) enter the electron transfer chain to produce ATP. Enzyme defects can occur in the carnitine and fatty acid oxidation pathways, in the transfer of electrons and in the production and utilisation of ketone bodies, with resultant inadequate energy production (Figure 30.1).

The metabolic disorders that manifest in these pathways are treated primarily by diet. Some aspects of management are universal, but others vary with the underlying disorder, age at onset and severity. The main aim of treatment is to ensure an adequate energy intake and avoidance of fasting to minimise the oxidation of fatty acids and by using an emergency regimen (ER) during illness. Additionally, in more severe long chain fatty acid oxidation disorders (LC-FAOD), a minimal long chain fat diet, with increased carbohydrate (CHO) intake and supplements of medium chain triglyceride (MCT), is needed. In other disorders, such as medium chain acyl-CoA dehydrogenase deficiency and the ketone body disorders, MCT is best avoided.

Metabolic Support UK (www.metabolicsupportuk.org) is the UK patient organisation for inherited metabolic disorders; it encompasses all FAOD and offers bespoke support to families and patients.

Clinical Paediatric Dietetics, Fifth Edition. Edited by Vanessa Shaw.

Companion website: www.wiley.com/go/shaw/paediatricdietetics-5e

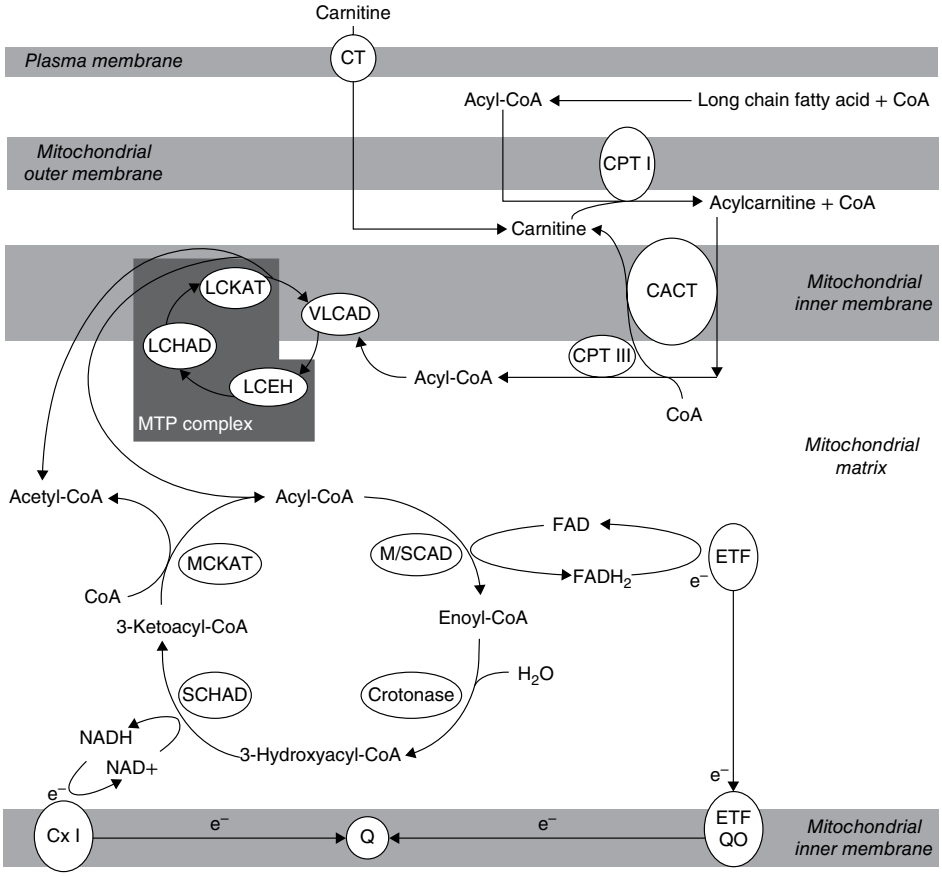

Figure 30.1 Biochemical pathways of mitochondrial fatty acid oxidation.
Enzymes involved: CT, carnitine transporter; CPTI, carnitine palmitoyltransferase I; CACT, carnitine acylcarnitine translocase; CPTII, carnitine palmitoyl transferase; VLCAD, very long chain acyl-CoA dehydrogenase; LCEH, long chain enoyl Co-A hydratase; LCHAD, long chain 3-hydroxyacyl-CoA dehydrogenase; LCKAT, long chain ketoacyl-CoA thiolase; MTP, mitochondrial trifunctional protein; M/SCAD, medium or short chain acyl-CoA dehydrogenase; SCHAD, short chain acyl-CoA dehydrogenase; MCKAT, medium chain ketoacyl-CoA thiolase; CxI, complex I of respiratory chain; Q, ubiquinone; e–, electrons; ETF, electron transfer flavoprotein; ETFQO, electron transfer flavoprotein ubiquinone oxidoreductase. Reprinted with permission of Springer.

Medium chain acyl-CoA dehydrogenase deficiency (MCADD)

Enzyme	Medium chain acyl-CoA dehydrogenase (MCAD) (Figure 30.1).
Biochemical defect	MCAD is necessary for the oxidation of medium chain fatty acids (MCFA) (C6–C12). Deficiency results in reduced energy and ketone body production. MCFA accumulate as their acyl carnitines and CoA esters, specifically octanoyl carnitine (C8) with an increased C8/C10 ratio, and are considered responsible for the clinical sequelae.
Genetics	Autosomal recessive inheritance. In Northern Europeans, the c.985A > G mutation is common and associated with classical clinical disease. In the UK all babies are treated irrespective of mutation.
Newborn screening	MCADD is included in the UK NBS programme. The prevalence in England is about 1 in 10 000 [1]. The screening test is the quantitative assay of C8 and decanoylcarnitine (C10). More details on screening and diagnostic protocols can be found at www.gov.uk and www.bimdg.org.
Clinical onset presentation, features	In countries without NBS, MCADD usually presents between 6 months and 4 years of age, but neonatal and adult onset also occur. Some may never present. Patients present with a 'hypoketotic' hypoglycaemia that can lead to encephalopathy and is precipitated by metabolic stress such as fasting, gastrointestinal (GI) illness or respiratory infections [2, 3]. Alcohol intoxication as a cause is described in adults [4]. Early symptoms may be poor feeding, lethargy and drowsiness. Hypoglycaemia is a late finding.
Outcome	There is risk of high morbidity and mortality if not treated promptly; some patients die suddenly, probably due to cardiac arrhythmias [2, 3]. Between episodes patients are usually completely well. Once diagnosed the outcome is very good [5].
Acute management	Intravenous (IV) 10% glucose – www.bimdg.org/guidelines
Dietetic management	Under normal conditions oxidation of MCFA is normal due to overlapping enzyme substrate specificity [6]. The problem arises when there is increased demand for fatty acids to produce energy such as during fasting and illness. Management is to avoid prolonged fasting and provide a regular endogenous energy supply to inhibit mobilisation of fatty acids. Fatty acid oxidation increases after a shorter duration of fast in infants, so they need to be fed more frequently. There remains a paucity of published data on safe fasting times [7]. The 2009 UK safe fasting times (Table 30.1) are based on the limited available evidence at the time of writing. Added MCT needs to be avoided because their oxidation is reduced.
Emergency regimen	The standard ER of frequent feeds of glucose polymer is required during intercurrent illness (p. 673).
Clinical guidelines	Clinical, dietary management guidelines and information leaflets for screened patients can be accessed from www.bimdg.org.uk.

Dietary guidelines for managing an at risk neonate with a family history of MCADD

Neonatal deaths have been reported in breast- and formula-fed babies who were undiagnosed [8]. Newborns are at greatest risk during the first 72 hours of life, especially if they are being breastfed. A prospective birth plan should be made to avoid any delay in screening or clinical problems. Management of MCADD at birth can be found online (www.bimdg.org):

- Any at risk baby should be screened at 24–48 hours, and results made available promptly
- A term baby should be fed at least 4 hourly and, if preterm, 3 hourly day and night until a diagnosis of MCADD is confirmed or excluded
- Special or preterm formulas that contain added MCT should be avoided (see below)
- Top-up feeds of formula milk are recommended for a breastfed baby (www.bimdg.org) as the energy content of breastmilk is low for the first few days of life and only small volumes are consumed
- If there are concerns about feeding volumes, the baby should be transferred to the neonatal unit and fed by nasogastric tube or given an IV infusion containing 10% glucose

Dietary guidelines for managing the well infant with MCADD

Infants (under 1 year of age)

- Breastfeeding or normal infant formula is suitable
- Long fasts should be avoided (Table 30.1)
- Demand feed every 3–4 hours throughout the day
- Night feeds should be given according to guidelines for 'maximum safe fasting times' (Table 30.1)
- Wean onto a normal diet at the usual time around 6 months (26 weeks) of age
- Encourage a regular intake of starchy foods as weaning progresses
- Restriction of long chain triglycerides (LCT) is *not* necessary [5]
- The vegetable oils added to standard infant formula contain only very small amounts of MCT, so this is not a problem
- Avoidance of special infant formulas or preterm formulas, which contain *added* MCT, e.g. Pregestimil Lipil and SMA Gold Prem 1 (refer to manufacturers' data on C8, C10 fatty acid content)
- If for any medical reason parenteral nutrition (PN) is required, the volume of lipid solution to be administered should be decided on an individual basis, and those that contain MCT, e.g. SMOF, should not be given

Table 30.1 Medium chain acyl-CoA dehydrogenase (MCAD) deficiency: guidelines for 'maximum safe fasting times' for the well child.

Age	Time in hours
Positive screening result to 4 months of age*	6
From 4 months	8
From 8 months	10
From 12 months onwards	12

*Around 2 weeks of age.
Source: www.bimdg.org.

Dietary guidelines for managing the well child with MCADD

Children (from 1 year of age)

- Advise a healthy balanced diet with regular meals (three main meals, including breakfast, which must not be missed)
- Restriction of LCT is *not* necessary
- Fast for a maximum of 12 hours overnight (Table 30.1)
- Include a bedtime snack containing starchy foods such as bread, crumpets, muffins, rice cakes, crackers, biscuits, pitta bread, chapatti or cereals
- Replace missed meals with a starchy snack, if necessary
- Maintain a 'healthy lifestyle' through diet and exercise; a CHO snack can be given before or after exercise if necessary, but is not always essential
- If teenagers consume alcohol, the amount should be limited and always taken in combination with food (see below)
- Avoidance of special feeds or energy supplements that contain added MCT, e.g. most paediatric hydrolysed protein feeds and some enteral feeds (refer to manufacturers' data on C8, C10 fatty acid content)
- If for any medical reason PN is required, the volume of lipid solution to be administered should be decided on an individual basis, and those containing MCT, e.g. SMOF, should not be given

Alcohol

Alcohol inhibits gluconeogenesis, so both fatty acid oxidation and gluconeogenesis, which provide fuel during fasting, will be impaired. Excessive alcohol intake can lead to inadequate food intake and vomiting, which can be life threatening [4]. Alcohol intake should be limited and always taken in combination with food. If a teenager does start to vomit, they must be admitted promptly to hospital for IV fluids and glucose. Friends should be made aware that the individual has MCADD, so they know to get medical help promptly enabling more rapid treatment.

Coconut

Coconut oil contains 13% and coconut 5% of the total fatty acid composition as C8 and C10. This amount of MCT is small and unlikely to cause any problems. If coconut oil were to be consumed in large amounts, suitability should be considered. Coconut based foods (e.g. coconut flakes, chunks, yoghurt, water, spreads) or foods with coconut as an added ingredient do not need to be avoided as these will contain only small amounts of MCT.

Carnitine

Carnitine is found mainly in muscle (98% of total body carnitine) and in blood (<1%). Blood carnitine reflects only a small percentage of total body carnitine. Some children with MCADD may sometimes have a decreased amount of free carnitine in their blood. There is no strong evidence to prove that carnitine supplements improve the general condition, and it is, therefore, not routinely prescribed in the UK.

Dietary guidelines for managing the unwell child with MCADD

Illness in any child is usually associated with loss of appetite and prolonged fasting, and fatty acid oxidation rates increase to provide energy. In MCADD this process is limited, and the child is at risk of serious illness and encephalopathy. Sudden death has been reported in screened patients specifically associated with vomiting [9]. To help prevent metabolic decompensation, the standard ER needs to be given. The ER will provide energy, stimulate insulin secretion and thereby minimise lipolysis and fatty acid oxidation. ER guidelines (IV and oral) for hospital use can be accessed from www.bimdg.org.uk. A Canadian study reported that children with MCADD have increased use of health services (in- and outpatient care) compared with children in the general population, although this diminishes beyond 24 months [10].

ER information specific for MCADD:

- Follow the standard ER guidelines for age of very frequent feeds/drinks of glucose polymer solution, day and night (p. 673)
- Avoidance of fat during the acute period (although there is little evidence to support if this is absolutely essential)
- Monitoring of blood glucose at home is not recommended because precision is poor at low concentrations and hypoglycaemia is a relatively late finding during illness; the child can be very unwell before the blood glucose falls [11]
- If for any reason the child needs to be commenced on a special infant formula or paediatric enteral feed during illness, it should not contain *added* MCT

Learning points: medium chain acyl-CoA dehydrogenase deficiency (MCADD)

- *The standard ER is given during illness*
- *Long fasts need to be avoided*
- *Feeds with added MCT are contraindicated*

Long chain fatty acid oxidation disorders (LC-FAOD)

LC-FAOD include:

- disorders of the carnitine cycle: carnitine palmitoyl transferase deficiency I and II (CPTID and CPTIID) and carnitine acylcarnitine translocase deficiency (CACTD) (Figure 30.1)
- disorders of the mitochondrial β-oxidation pathway: very long chain acyl-CoA dehydrogenase deficiency (VLCADD), mitochondrial trifunctional protein deficiency (MTPD) and long chain 3-hydroxy acyl-CoA dehydrogenase deficiency (LCHADD) (Figure 30.1)

Enzymes	Carnitine palmitoyl transferases I and II Carnitine acylcarnitine translocase (CACT) Very long chain acyl-CoA dehydrogenase Mitochondrial trifunctional protein complex (encompasses the three MTP enzymes) Long chain 3-hydroxy acyl-CoA dehydrogenase (enzyme within the MTP complex)
Biochemical defects	The enzymes of the carnitine cycle are required to transport LCFA into the mitochondria, and the enzymes of the four-step spiral pathway of mitochondrial β-oxidation to breakdown LCFA to produce energy (Figure 30.1). Oxidation of fatty acids produces acetyl-CoA that enters the Krebs cycle to produce ATP or is converted into ketone bodies (in the liver). Enzyme deficiencies lead to inadequate energy and ketone body production, toxic intermediates (such as long chain acylcarnitines) accumulate; these are all considered responsible for the clinical features.
Genetics	All are autosomal recessive inherited disorders. The clinical spectrum is very heterogeneous. Prevalent mutations have been identified in some, e.g. in LCHADD most Caucasian patients are homozygous for the c.1528G > C mutation. Three different isoforms of CPTI exist, CPTIa (liver and kidney) only identified in man, CPTIb (muscle and heart). Paradoxically, cardiac problems or raised creatine kinase (CK) are seen in some CPTIa patients [12]. CPTIa is very common in the Inuit population [12]. Three phenotypes of CPT II deficiency are known: a lethal neonatal form, a severe infantile hepatocardiomuscular form and a mild myopathic form. Muscle CPT II deficiency is the most frequent type of CPT II deficiency [13].
Newborn screening	LC-FAOD are not screened for in the UK but are included in NBS panels elsewhere worldwide.
Clinical onset presentation, features	LC-FAOD vary in severity and may present at any time from the neonatal period, during infancy, childhood to adulthood with associated mortality and possible morbidity. Attenuated forms are seen in CPTII and VLCAD deficiencies. The organs affected are the heart, liver and skeletal muscles. The clinical presentation for all disorders commonly includes one or all of these problems [12, 14, 15]:

	• an acute 'hypoketotic' hypoglycaemia and encephalopathy with associated liver failure, hyperammonaemia and hyperlactacidaemia • cardiomyopathy and arrhythmias (often in infancy) • skeletal muscle involvement that may cause hypotonia, weakness, muscle pain and exercise intolerance with acute episodes of muscle breakdown (rhabdomyolysis) and high CK; in CPTID and CACTD rhabdomyolysis does not occur • muscle CPT II deficiency is the most frequent type of CPT II deficiency; it more commonly presents in early childhood (1–12 years) than adolescence and adulthood; symptoms of myalgia, myoglobinuria and muscle weakness occur intermittently and are triggered mainly be exercise or intercurrent illness [12] • rhabdomyolysis can be the only clinical symptom in patients with mild VLCADD • some patients with CPTI have renal tubular acidosis during infancy
Outcome	Most patients with LCHADD or MTPD develop pigmentary retinopathy and/or a progressive peripheral neuropathy (more of a problem in MTPD). Patients with LCHADD have a more severe chorioretinopathy than MTPD [16]. Diet may help delay the onset and progression, but not prevent retinopathy [16]. Retinopathy is also reported to be milder and develop later in those diagnosed by NBS [17]. Early diagnosis and diet therapy may also delay onset and severity of peripheral neuropathy [18]. Outcome data from a cohort of 14 Austrian patients with LCHADD (9 confirmed by NBS), all with common mutation, reports normal growth and psychomotor development in 12 patients (except for 2 born premature) and less frequent hospitalisations with age [19]. Children may develop muscle pain with exercise, and some have a very limited exercise capacity. Patients with partial deficiencies of VLCADD often remain asymptomatic throughout childhood and sometimes throughout life. Longitudinal outcome data on VLCADD from the IBEM-IS USA database reported that most newborns identified by NBS remain asymptomatic and cardiomyopathy is uncommon. Elevations in CK as a marker of rhabdomyolysis associated with illness were common and typically first appeared in 1- to 3-year-olds [20]. CPTII neonatal form is lethal.
Acute management	Clinically diagnosed infants may be very sick and be managed in intensive care. IV 10% glucose is essential to reverse lipolysis and promote anabolism.
Dietetic management	Treatment is primarily by diet and varies depending upon the severity of the disorders and the centre treating the child. Nevertheless, the main aim is to minimise lipolysis and LCFA oxidation and to prevent the accumulation of potentially toxic acyl-CoA intermediates and the acylcarnitines formed from these. The abnormal metabolites that accumulate are disorder specific and present in higher concentrations during times of metabolic stress such as illness. Abnormal plasma acylcarnitines are not seen in CPTID [12]. Avoidance of long fasts and illness and exercise management are needed in those with mild and severe onset defects. For CPTIID the treatment recommendations for VLCADD (mild to severe) can be used [21]. In more severe defects in the carnitine cycle and β-oxidation pathway, typically those presenting early, a minimal long chain fat diet, with increased CHO intake and supplements of MCT and regular feeding, is needed. Overnight tube feeding in infants and young children is used in the UK and some other countries, such as Finland [18], to limit fatty acid oxidation overnight, but this is not universal practice. In CPTI deficiency relaxation of a strict diet may be possible if there are normal CK and liver transaminase levels (personal communication). During exercise additional CHO and/or MCT is required to provide an endogenous energy supply to exercising muscles.
Emergency regimen	During illness patients are at risk of metabolic decompensation due to increased lipolysis and fatty acid oxidation. To help prevent this the standard ER (p. 673) for age of frequent feeds of glucose polymer with or without MCT is given to provide energy.
Monitoring	Key monitoring is biochemical, nutritional and cardiac, additionally in LCHADD and MTPD nerve conduction studies and ophthalmology.
Clinical management guidelines	*Treatment recommendations in long chain fatty acid oxidation defects: Consensus from a workshop*, 2009 [21]. *VLCAD Nutrition management guidelines:* Genetics Metabolic Dietitians International, 2019 (access at www.gmdi.org), based on a Delphi consensus. There are no clinical management guidelines for disorders of the carnitine cycle.

Dietary management of LC-FAOD

Long chain triglycerides

Long chain fat intake is restricted because LCFA cannot be either transported into the mitochondria or undergo β-oxidation, depending on the enzyme defect. The safe upper limit for long chain fat intake is unknown and varies with the severity of the disorder. Normalisation of acylcarnitine profiles is observed in LCHADD and MTPD when LCT intake is <10% total energy and MCT are given [22]. In those with a milder myopathic form of VLCADD or CPTIID, LCT restriction may not be necessary.

The *Treatment recommendations in long chain fatty acid oxidation defects: consensus from a workshop* by Spiekerkoetter *et al*. [21] advises:

- *LCHADD and MTPD*: *Asymptomatic and symptomatic patients* should limit long chain fat intake as low as possible. There is evidence that diet may delay onset and progression of peripheral neuropathy and retinopathy [15–19]. Infants should be started on a low LCT, high MCT infant formula. Once on solid food, fat intake should be 25%–30% of total energy with 20%–25% of this as MCT, although in practice more typically 15% is LCT, including 3%–4% essential fatty acids (EFA), and 15% is MCT

For infants with VLCADD at NBS:

- *VLCADD*: *Asymptomatic infant's* treatment depends on the clinical presentation and biochemistry: if normal CK and liver transaminases, a combination of half breastmilk (or standard infant formula) and half low LCT infant formula can be given. Some asymptomatic newborns, whose acylcarnitines normalised after 1 week, have remained on normal feeds without VLCADD symptoms so far. After age 4 months and solid food introduction, fat energy should be 30%–40% of total energy of which 10%–15% is MCT
- *VLCADD*: *Symptomatic infants* or those with abnormal CK or transaminases should be started on a low LCT, high MCT infant formula. After age 4 months and solid food introduction, fat energy should be 25%–40% of total energy of which 20% is MCT and 3%–4% is EFA; therefore, LCT could range from 5% to 20% of total daily energy intake

Genetic Metabolic Dietitians International (GMDI): *VLCAD Nutrition management guidelines* (www.gmdi.org) advise:

- *VLCADD*: restriction of LCT intake in moderate form to be 15%–30% and in severe form to be 10%–15% of estimated total daily energy needs and that decreasing below 10% may provide no additional clinical benefit

For infants with VLCADD at NBS:

- *mild phenotype and asymptomatic:* to allow breastfeeding without MCT supplements
- *severe or moderate phenotype and asymptomatic:* to consider a combination of breastfeeds with a low LCT, high MCT infant formula
- *severe phenotype and symptomatic:* the primary source of nutrition should be a low LCT high MCT feed, considering allowing some breastmilk

A *Proposal for an individualized dietary strategy in patients with VLCADD* by Bleeker *et al*. [23] suggests choice of dietary treatment for those identified by NBS be based on results of fatty acid oxidation (FAO) flux score in fibroblasts:

- if >90%, no diet or ER
- if 10%–90%, mild diet (no fat restriction or MCT supplements), ER during illness
- if 10% strict diet (LCT restricted, MCT supplements, restricted fasting), ER during illness

Medium chain triglycerides

Dietary MCT are mainly absorbed through the hepatic portal vein; they pass directly into the mitochondria primarily independent of the carnitine cycle. They are then rapidly converted to ketone bodies, bypassing the long chain β-oxidation enzymes. Ketones inhibit the mobilisation of fatty acids from adipose tissue and the oxidation of fatty acids by cardiac muscle [24]. MCT (C8, C10) is a useful energy source, 8.3 kcal (35 kJ)/g, and may also have other beneficial effects in some disorders, as discussed below. MCT supplements need to be added to the diet, as the normal diet contains insignificant amounts.

β-oxidation disorders

- MCT have led to the resolution of cardiomyopathy in patients with VLCAD and LCHAD deficiencies [25, 26].
- MCFA may also suppress LCFA oxidation without being converted to ketone bodies; they have been shown to inhibit the accumulation of potentially toxic long chain intermediates in cultured skin fibroblasts from LCHAD and MTP deficient patients [27].
- The optimal amount or ratio of C8 and C10 fatty acids to provide is not known. Skin fibroblast studies have shown that C10 undergoes elongation prior to oxidation, so it has been suggested that C8 may be preferable [28, 29].
- The *Treatment recommendations in long chain fatty acid oxidation defects: consensus from a workshop* by Spiekerkoetter *et al*. [21] suggest 20%–25% total daily energy intake be provided from MCT for severe LCHADD, MTPD and VLCADD.
- Genetic Metabolic Dietitians International (GMDI): *VLCAD Nutrition management guidelines* (www.gmdi.org) recommendation is total fat intake (LCT and MCT) should not exceed the dietary reference intake (DRI) for age. The amount of MCT to give will, therefore, depend on prescribed LCT intake. In severe VLCADD they suggest daily energy intake from MCT to be 30%–45% energy for infants aged 0–6 months; 25%–30% for 7–12 months; 10%–30% for 1–3 years and 15%–25% for 4–18 years.

Carnitine cycle disorders

The role of MCT is slightly less clear in defects of the carnitine cycle:

- In several infants with CPTI deficiency, renal tubular acidosis has only resolved when they have been changed to an MCT-based feed [30].
- MCT has also been used with apparent benefit in patients with mild CACTD. However, in cases of severe CACTD and CPTIID, MCT has been reported to have caused markedly abnormal blood acylcarnitines and dicarboxylic aciduria and suggests that MCT may need to be limited and dose adjusted because it may in part enter the mitochondria by a carnitine-dependent mechanism [31, 32].
- It has also been suggested that MCT should be low in C10 due to evidence that C10 requires CACT for oxidation [31]. The C8 and C10 contents of available products vary, but the amount of C10 is always lower than C8 (Table 30.6).
- In the author's centre and others (personal communications), MCT has been added to the diet in a similar way to the long chain β-oxidation disorders with both severe and mild onset, using currently available MCT infant formula and energy supplements.

Triheptanoin

Triheptanoin is a synthetic, odd-carbon, medium chain triglyceride oil (C7, heptanoate), which is being trialled as an alternative energy source to MCT. The use of MCT leads to the production of acetyl-CoA, but it is hypothesised that a

shortage of oxaloacetate prevents this from being oxidised in the citric acid cycle. Heptanoyl-CoA is oxidised by medium chain fatty acid enzymes to generate acetyl-CoA and propionyl-CoA as well as 4- and 5-carbon ketone bodies. Propionyl-CoA is converted to oxaloacetate, which acts as an 'anaplerotic' substrate for the citric acid cycle and may help to restore the energy deficiency state, so triheptanoin appears to be superior to MCT [33]. Clinical trials are under way to study the efficacy of C7. Results from an open-label phase 2 study in 29 patients with severe LC-FAOD suggest that there appear to be some benefits: decreased major clinical events and reduced hospitalisations due to rhabdomyolysis compared to existing treatments including MCT [33]. Triheptanoin is not yet widely available outside the USA.

Frequency of feeding

Frequent feeding is recommended to reduce lipolysis. The safe duration of fasting for different disorders and ages has not been well defined, and practices, including the need for night feeds, differ between countries and centres. A stable isotope study used to assess fasting intolerance in LCHADD (five children aged 5.5–9.5 years) demonstrated increased lipolysis and accumulation of long chain acylcarnitines after 4 hours of fasting, which occurred before hypoglycaemia. The authors suggest fasting tolerance may be more limited than previously suggested and fasting assessment should be related to the complete metabolic situation and not only hypoglycaemia [34]:

- The *treatment recommendations in long chain fatty acid oxidation defects: consensus from a workshop* [21] suggest in VLCADD, MTPD and LCHADD during stable metabolic condition to feed 4 hourly during the day and a maximum safe fasting time at night of 4 hours for <3 months of age if the infant is well nourished, then 6 hours from 3 months of age, 6–8 hours from 6 months of age and 10–12 hours from 12 months.
- The GMDI *VLCAD Nutrition management guidelines* (www.gmdi.org) suggest maximum fasting times to be 3–4 hours for age 0–4 months, 4–6 hours for age 4–6 months, 6–8 hours for age 6–9 months, 8–10 hours for age 9 to <12 months of age and 10–12 hours for >12 months. Fasting times for more severe phenotypes should be set at the lower end of the recommended range.
- In the UK, fasting is more limited in severe defects to help reduce the risk of cardiomyopathy and in LCHADD and MTPD the onset and progression of long-term complications of retinopathy and neuropathy (although there is little evidence for this). Children with severe defects are fed 3–4 hourly during the day, and nasogastric (only bolus) or continuous gastrostomy feeding overnight, or the child is woken for feeds during the night. Overnight feeding is not standard practice; the literature suggests that some countries do this [17], but others consider management should be achievable without this [19]. It is difficult to be sure whether overnight feeding is necessary, particularly in older children who have larger glycogen stores. However, in LCHADD this may be more important to delay retinopathy and peripheral neuropathy [17, 18].
- Uncooked cornstarch (UCCS) is used by some centres, including the author's, to provide a source of 'slow release glucose' to help limit fasting [35]. In older children continuous tube feeding overnight may be replaced with UCCS (personal practice). This may be a better option than stopping overnight feeds completely. Before use, the metabolic response to UCCS should be assessed since this varies between patients [35]. The GMDI *VLCAD Nutrition management guidelines* (www.gmdi.org) suggest that there is little evidence to support the use of UCCS at night and advise a complex CHO snack at bedtime, if necessary.
- There are no published studies comparing the metabolic profiles of patients with LC-FAOD on overnight feeds or on UCCS and those who fast overnight or comparing the long-term outcome of these different treatments.
- Patients with milder defects are likely to tolerate overnight fasting without problems.

Prevention of deficiencies on a low LCT diet

Patients on minimal LCT diets require supplements of fat-soluble vitamins, EFA and long chain polyunsaturated fatty acids (LCPUFA). Additional supplements such as B_{12} and iron may be needed depending on food choices. An adequate calcium intake is usually provided from low fat dairy foods.

EFA and LCPUFA

In the UK at least 1% total energy intake from linoleic acid and 0.2% from α-linolenic acid are recommended [36]. Others recommend a much higher intake of 4.5% daily energy intake in infants <4 months of age, decreasing to 3% from age 4 years [21]. The joint FAO/WHO 2008 report on fatty acids recommends an adequate daily intake for children >6 months to be linoleic acid 3%–4% and α-linolenic 0.4%–0.6% of daily energy intake [37].

Most sources of EFA (such as walnut oil) do not provide LCPUFA, such as arachidonic acid (AA) and docosahexaenoic acids (DHA), but these are expected to be synthesised from the parent EFA that are provided. However, it may be prudent to add DHA and AA supplements on very low LCT diets to ensure adequate intake, avoiding the need to increase walnut oil and, hence, LCT intake. It has also been suggested that DHA deficiency may contribute to the pathogenesis of chorioretinopathy of LCHADD, although this is not prevented by supplementation [38]. Nevertheless supplements of DHA at a dose of 60 mg/day in children <20 kg and 120 mg/day in children >20 kg are recommended in MTPD and LCHADD [21]. FAO/WHO [37] recommends an adequate daily intake of DHA for normal children to be:

- the amounts found in breastmilk for infants
- 100–150 mg for children aged 2–4 years
- 150–200 mg for children aged 4–6 years
- 200–300 mg for children aged 6–10 years

Fat-soluble vitamin supplements
Vitamins A, D and E are essential for those on low LCT diet. Vitamin E deficiency is associated with a peripheral neuropathy, which is one of the long-term complications of MTPD and LCHADD and should, therefore, be provided in normal requirements for age, at least.

Carnitine

It remains uncertain whether carnitine supplements should be given to patients with LCFA oxidation disorders. Plasma-free carnitine concentrations are often below the normal range, particularly after episodes of illness, but tissue levels are probably not low enough to affect fatty acid oxidation. Supplements may facilitate the excretion of metabolites, but, by increasing the level of long chain acylcarnitines, it is possible that they may increase the risk of arrhythmias [39].

Energy distribution of the diet in severe defects

As LCT is restricted, more energy needs to be provided from CHO and supplements of MCT. The optimal distribution of energy intake from CHO and MCT is not known. The following provides a guide to the typical energy distribution and long chain fat intake of the diet in severe defects (based on personal practice):

- 60%–65% energy from CHO (CHO energy will vary depending on LCT and MCT intake)
- 10%–15% energy from protein
- 20%–25% energy from medium chain fat (depending on the disorder)
- 1.2%–2% energy from EFA (based on FAO/WHO [37]; higher intakes may be appropriate)

LCT is often expressed as g/day.

Infants 0–6 months: 2–7 g LCT/day (4%–7% of daily energy intake) if either Monogen or Lipistart (Table 30.2) provides the sole source of nutrition. LCT intake will increase with the introduction of solid food.

Older infants and children: It is possible to continue to restrict intake of long chain fat to provide ≤6% total energy intake, ≤7 g LCT/1000 kcal (4.2 MJ), excluding EFA. Similar dietary practices are reported to be used by others [39]. This is a very strict diet and not all agree this is warranted.

Minimal long chain fat diet

Infants

Infants with severe long chain defects (diagnosed clinically or by NBS, not in the UK) need a minimal LCT feed supplemented with MCT such as Monogen or Lipistart; both are nutritionally complete infant formulas with minimal LCT content (Table 30.2).

As previously discussed it is possible MCT cannot be fully oxidised in some severe CACTD or CPTIID [31, 32], and a modular feed without fat (long or medium chain) may be required. Whey protein powder does contain small amounts of LCT but can be used as the protein base with glucose polymer and added minerals and vitamins, EFA and LCPUFA to provide recommended intakes (p. 646). Suitable commercial minimal fat feeds with no added MCT are Low Fat Module (0.14 g fat/100 mL) and basic-f (<0.1 g fat/100 mL) (Table 30.2).

Clinically diagnosed infants are likely to be very sick, managed in intensive care and receiving IV 10% glucose and electrolytes. Once clinically stabilised, nasogastric feeds should be introduced and titrated against IV fluids to maintain adequate energy intake and prevent further metabolic decompensation. The feed should be distributed evenly over 24 hours to limit fasting and provide energy from both CHO and MCT regularly, e.g. for an infant weighing 6 kg feeding 150 mL/kg/day (900 mL):

- 120 mL 3 hourly × 5 feeds during the day (at 8 am, 11 am, 2 pm, 5 pm, 8 pm)
- 300 mL given at 40 mL/hour continuously overnight for 8 hours from 10 pm to 6 am (the night feed can be commenced 2 hours after the last day feed and discontinued up to 2 hours before the morning feed)

Weaning diet
Weaning is commenced at the normal time around 6 months (26 weeks) of age. Feeding problems have been reported in children with LCHADD, particularly in early childhood, despite good metabolic and clinical condition [40]. With age these problems either improved or resolved in this cohort.

An example of a suggested menu plan for infants is provided in Table 30.3. Solids should have a minimal fat content and be high in CHO. Rice, cereal, potato, fruit and vegetables are suitable as first weaning foods. Low fat, high protein foods can also be given, e.g. chicken or turkey breast, white fish, lentils, very low fat cottage cheese and yoghurt. Commercial baby foods can be included in the diet: wet baby foods (fat content <0.5 g/100 g) and dried baby foods (fat content <2 g/100 g) can be given freely. Baby foods with a higher fat content need to be counted as part of the daily fat intake. Parents can be taught how to calculate the amount of fat a food provides from the nutritional labelling (p. 649). As solid food increases, it can replace some of the 3 hourly day feeds, ensuring it provides at least the same amount of energy as the feed. MCT oil/emulsion/ powder (p. 651) is incorporated gradually into the diet to maintain MCT at 20%–25% of daily energy intake. As weaning progresses, the volume of infant formula should be decreased, and glucose polymer ± MCT added to provide the required amount of energy. Eventually the night feed can contain glucose polymer and MCT only.

Monogen or Lipistart, as the sole source of nutrition, provides more than the UK suggested requirement for EFA. As infant formula decreases, an additional source of EFA is needed. Walnut oil provides a good source of EFA and allows minimum LCT to be given (Table 30.4). The dose of oil to give should be calculated taking into account the EFA from the infant formula. To provide the UK suggested

Table 30.2 Low LCT infant formulas per 100 mL.

		Monogen (Nutricia)	Lipistart (Vitaflo)	basic-f (Milupa)*	Low Fat Module (Nutricia)
Dilution		17.5%	15%	13%	18%
Scoop size		5 g	5 g	4.3 g	6 g
Energy	kcal	74.6 (314 kJ)	69 (290 kJ)	49 (207 kJ)	67.3 (286 kJ)
Protein	g	2.2 (12% E)	2.1 (12% E)	1.8	1.6
Carbohydrate	g	11.6 (62% E)	8.3 (48% E)	10.2	14.9
Fat	g	2.2 (26% E)	3.1 (40% E)	<0.1	0.14
MCT	g % fat E % total E	1.8 84% 16%	2.48 80% 30%	Nil	Nil
C8	g	1.0	1.5		
C10	g	0.67	0.93		
LCT	g % fat E % total E	0.35 16% 4%	0.57 18% 7.4%		
Linoleic acid	mg % E	151 1.9%	259 3.4%	Nil	Nil
α-Linolenic acid	mg % total E	28.6 0.35%	36 0.5%	Nil	Nil
DHA	mg	10.1	15	Nil	Nil
AA	mg	10.1	30	Nil	Nil
Vitamins					
E	mg	0.82	1.7	0.3	0.4
A	mg	54.6	69.9	52	71.3
D	mg	2	1.4	0.9	1.2

E, energy; MCT, medium chain triglycerides; LCT, long chain triglyceride; DHA, docosahexaenoic acid; AA, arachidonic acid.
- Reconstitution: Monogen 1 scoop added to 25 mL water.
- Reconstitution: Lipistart 1 scoop added to 30 mL water.
- In UK only Monogen and Lipistart are prescribable.

*Not available in the UK.
Source: Manufacturers.

Table 30.3 Minimal long chain fat weaning diet. Sample menu.

8 am breakfast	*Commercial baby cereal mixed with Lipistart or Monogen
11 am	Lipistart or Monogen
1 pm lunch	Purée turkey, chicken (white only), white fish or lentils Purée or mashed potato, sweet potato Pasta, rice Purée or mashed vegetables *Commercial baby savoury foods
4 pm tea	Purée or mashed fruit and sugar or *commercial baby fruit dessert Very low fat yoghurt or fromage frais Milk pudding (custard, cornflour, ground rice) made with infant feed or skimmed milk
7 pm	Lipistart or Monogen
9 pm to 6 am	Continuous overnight feed for a 7 kg infant (270 mL): Monogen: 30 mL/hour provides 0.5 g CHO/kg/hour (197 kcal, 825 kJ) Lipistart: 30 mL/hour provides 0.36 g CHO/kg/hour (186 kcal, 782 kJ) but provides more energy from MCT than Monogen
Extra feeds or baby juice can be given with meals	
Finger foods may be introduced from 6 to 9 months: soft cooked vegetables, soft ripe fruit (pasta, bread and cereals may also be suitable, but LCT content must be checked first)	

*Suitable commercial baby foods (p. 647). Baby foods with a higher fat content are best avoided.

Table 30.4 Walnut oil. Essential fatty acid composition.

1 mL walnut oil provides	
Energy	8.4 kcal 35 kJ
Fat	0.93 g
Linoleic acid	0.58 g
α-Linolenic acid	0.12 g
Ratio *n*6:*n*3 fatty acids	4.5

For analysis of other oils, see Fatty acids, 7th Supplement to *McCance and Widdowson's The Composition of Foods*, 5th edn. Cambridge: Royal Society of Chemistry and London: Ministry of Agriculture, Fisheries and Food, 1992.

requirement of EFA, the dose of walnut oil needed is 0.1 mL/56 kcal (235 kJ). The walnut oil is administered as a single dose and given as a medicine from a spoon or via the feeding tube. Other oils such as sunflower, safflower (mainly linoleic acid), soya and flax are also rich sources of EFA, and a combination of these can also be used if walnut oil is disliked. Monogen (600 mL) and Lipistart (400 mL) provide the suggested intake of 60 mg DHA/day advised for LCHADD [21]. An alternative source of LCPUFA (such as KeyOmega) can be given as less or no infant formula is given.

Fat-soluble vitamin supplements are likely to be required once the intake of low LCT infant formula falls below 500 mL/day (Table 30.2).

Children

Long chain triglycerides

Children need a minimal LCT diet with an energy distribution as previously outlined (p. 647). Inevitably, daily intake of long chain fat increases with age. The figures quoted are based on the lowest possible long chain fat intake that is practicably achievable for a given age. However, as the safe upper limit for long chain fat is not known, such a low LCT intake may not be of clinical benefit and, therefore, unnecessary (p. 644). Ideally, the diet should be a combination of starchy foods (e.g. rice, pasta, potato, bread, cereals) and very low fat sources of protein, such as white fish, white chicken or turkey meat and pulses (Table 30.5). To enable suitable low fat food choices, parents need guidance on interpreting food labels, in particular to understand words used to describe the fat content of food, which can be misleading (reduced fat, low fat, virtually fat-free, 90% fat-free), and that different types of fat (monounsaturated and polyunsaturated) are all long chain fat and total fat content should be used to calculate fat intake.

Nutritional labelling expresses the total fat content as grams of fat per 100 g and often grams of fat per portion. Manufactured foods that have a fat content <0.5 g/100 g can generally be allowed in the diet freely, unless large amounts are being consumed. Those with a higher fat will need to be counted as part of the daily fat allowance. Foods with a fat content of up to 5 g fat/100 g are more likely to be suitable to include in the diet and given as a reasonable portion. Parents can be taught to calculate and then weigh the amount of food that provides a certain amount of fat. This also makes it easier to monitor the daily fat intake, for example:

$$\text{Weight of food to provide 1 g fat} = \frac{100}{\text{fat content per 100 g of food}}$$

Medium chain triglycerides

A daily intake of 20%–25% of total energy intake is advised. The optimal timing of administration has not been defined; however, it is common practice to divide the dose and give three to four times a day, as it is rapidly absorbed and used and high doses may cause GI symptoms in some patients. In young children MCT often remains part of the night feed. MCT can be added to the diet as an oil, emulsion or powder (Table 30.6). MCT oil can increase the palatability of the diet. It has a low smoke point compared with other cooking oils. Care must be taken when cooking foods in MCT oil to ensure it does not burn or become overheated as it develops a bitter taste and an unpleasant odour. The optimum cooking temperature for MCT is 160 °C. MCT oil can also be used in baking, e.g. cakes, biscuits and pastry, and can be added to a variety of foods such as pasta and soups. MCT emulsion, e.g. Liquigen, can be easily mixed into food and liquids without separating such as skimmed milk, low fat yoghurt, desserts and sauces, and used in baking. MCT Procal powder comes in pre-measured sachets and can be added to hot or cold food or drinks (not fruit juice as it curdles) and used in baking recipes. Recipes are available for all products from their manufacturers. Table 30.7 gives an example of how to provide the daily intake of MCT.

Other nutrients

EFA can be added as walnut oil or combinations of other oils as described for infants. LCPUFA can be given as KeyOmega (1 sachet = 100 mg DHA, 200 mg AA) and DocOmega (1 sachet = 200 mg DHA) as needed to provide the daily requirements [37].

The choice of fat-soluble vitamin supplement will depend on need, age and desired format: powder, tablets or soluble tablets are available. Ketovite tablets and liquid provide an adequate intake of fat-soluble vitamins and B_{12} and are suitable for all ages. Alternatively, more complete vitamin and mineral supplementation can be provided: FruitiVits (from age 3 years), Paediatric Seravit (all ages), Phlexy-Vits sachets or tablets (from age 10 years), Forceval Soluble Junior (from age 6 years) and Forceval Soluble (from age 12 years) (p. 524). Intakes of iron, zinc and B_{12} should be regularly calculated as these can also be low in minimal LCT diets.

Frequency of feeding

Lipolysis can be minimised by 3–4 hourly feeding during the day and continuous overnight tube feeds. If feeding overnight, the amount of energy required is not known. One approach to minimise overfeeding is to provide glucose polymer to equal basal glucose production rates for age

Table 30.5 Minimal long chain fat diet.

	Foods allowed	Foods to avoid
Milk	Skimmed milk, condensed skimmed milk Natural yoghurt, very low fat yoghurt and fromage frais (<0.2 g/100 g) Low fat cottage cheese (<0.5 g/100 g) *Very low fat cheeses Quark (skimmed milk soft cheese) Low fat ice cream	Full fat and semi-skimmed milk Cream (all types) Full fat yoghurt and fromage frais Full and half fat cheeses †Ice cream
Egg	Egg whites, egg white replacer, meringue	Egg yolks
Fish	White fish (no skin), e.g. haddock, cod, sole, plaice Crab, crabsticks, tuna, prawns, shrimps, lobster Tinned: tuna in brine or water, crab, prawns, shrimps	Oily fish, e.g. sardines, kippers, salmon, mackerel Fish in breadcrumbs, batter, sauces, pastry Tinned: fish in oil
Poultry	*Chicken, *turkey (white breast meat, no skin)	Chicken, turkey (dark meat and skin), basted poultry, duck, goose Chicken in breadcrumbs, batter, sauces, pastry
Meat	*Lean red meat (<5% fat content)	Fatty meat, sausages (normal and low fat), burgers, meat paste, paté, salami, pies
Meat substitutes	Soya mince, *Quorn, *tofu	
Pulses	Peas, e.g. chick peas, split peas Beans, e.g. red, white, borlotti, black-eyed	None, unless in made-up dishes containing fat
Fats/oils	Medium chain triglyceride oil as advised	Butter, margarine, low fat spread, vegetable oils, lard, dripping, suet, shortening
Pasta and rice	Spaghetti, macaroni, other pasta, noodles, couscous, rice (white)	Wholemeal pasta, pasta in dishes, e.g. macaroni cheese, carbonara Brown rice, egg noodles
Flours and cereals	Flour (white), cornflour, custard powder, semolina, sago, tapioca	Flour (wholemeal), soya flour, oats, bran Foods made with flour that contain fat, e.g. pastry, sauces, cake, biscuits, batter, breadcrumb coatings
Breakfast cereals	Many are suitable Wholewheat cereals, e.g. Weetabix, Bran flakes, are higher in fat content than non-wholewheat cereals, e.g. Rice Krispies, cornflakes	Cereals with nuts and chocolate, e.g. muesli All-bran, Ready Brek
Bread and crackers	*White bread, white pitta, crumpets, muffins. Some crackers have a low fat content, e.g. rice cakes, matzos, Ryvita (not sesame)	Wholemeal, wholegrain breads, naan bread, chapatti made with fat, croissants, oatcakes, cheese crackers, †crackers
Cakes, biscuits and pastry	Only those made from low fat ingredients 95% fat-free cakes and biscuits	†Cakes, †biscuits, buns, pastry for sweet and savoury foods, e.g. apple pie, quiche
Desserts	Jelly, meringue, sorbet, very low fat ice cream, skimmed milk puddings, e.g. rice, custard	Most desserts, e.g. whole milk puddings, trifle, cheesecakes, gateaux, †mousse, fruit pie or crumble
Fruit	Most varieties – fresh, frozen, tinned, dried	Avocado pears, olives, yoghurt/chocolate covered dried fruit, banana chips
Vegetables	All vegetables and salad Very low fat crisps	Chips, †crisps, †low fat crisps, roast potato, potato or vegetable salad in mayonnaise or salad dressing, †coleslaw
Herbs and spices	Pickles, chutney Herbs, spices, salt, pepper	
Nuts and seeds		Nuts, peanut butter, seeds, e.g. sesame, sunflower
Sauces and gravies	Tomato ketchup, brown sauce, soy sauce, Marmite, Oxo, Bovril, very low fat gravy mixes Fat-free dressings and mayonnaise Minimal fat sauces (jars, tins, packets)	†Gravy granules, †stock cubes Salad cream, mayonnaise, oil and vinegar dressings †Sauce mixes (jars, tins, packets)
Soups	Some low calorie and 'healthy eating type' soups are very low fat	Most soups, cream soups
Confectionery	Boiled sweets, jelly sweets, fruit gums, pastilles, marshmallow, mints, ice lollies	Chocolate, chocolate-covered sweets, toffee, fudge, butter mints
Sugars and preserves	Sugar, golden syrup, jam, marmalade, honey, treacle	Lemon curd, chocolate spread
Baking products	Baking powder, bicarbonate of soda, yeast, arrowroot, essences, food colouring	
Drinks	Fruit juice, squash, fizzy drinks, milkshake flavourings, tea, coffee	†Instant chocolate drinks, cocoa, malted milk type drinks, e.g. Horlicks

*Intake of these foods may need to be restricted because of their fat content.
†These foods in the 'avoid list' often have very low fat equivalents, which can be included in the diet.

Table 30.6 Medium chain triglyceride products.

Product	Energy kcal (kJ)	MCT	MCT g/100 g fatty acids			
			C8	C10	C12	Other nutrients
MCT oil (Nutricia)	855 (3.6 MJ)/100 mL	94 g/100 mL	58	38	1.7	Nil
Liquigen emulsion (Nutricia)	450 (1.9 MJ)/100 mL	50 g/100 mL	82.1	15.9	1.3	Nil
MCT Procal powder (Vitaflo)	657 (2.7 MJ)/100 g 105 (440 kJ)/16 g sachet	62.2 g/100 g 10 g/16 g sachet	54	39	–	Per sachet: 2 g protein, 3.3 g CHO

MCT, medium chain triglyceride.
Other MCT products such as MCT margarine can be sourced from www.ceres-mct.com or www.drschar.com. These are not prescribable in the UK.

Table 30.7 Example providing daily medium chain triglyceride intake.

Daily MCT intake for a 4-year-old girl
Estimated average requirement for energy for age = 1400 kcal (5.9 MJ)/day [36]
Provide 20%–25% energy from MCT = 280–350 kcal (1.2–1.5 MJ) ÷ (8.3 kcal, 35 kJ/g MCT) = 34–42 g/day

Breakfast	20 mL MCT emulsion (10 g MCT) added to breakfast cereal
Lunch	1 sachet MCT Procal (10 g MCT) added to very low fat yoghurt at school
Evening meal	10 mL MCT oil (10 g MCT) added to cooked pasta

Another 10 g of MCT added to the night feed (Table 30.8) from MCT emulsion

Table 30.8 Examples of an overnight feed for long chain fatty acid oxidation disorders.

Overnight feed for a 6-year-old boy, weight = 22 kg

25% CHO from glucose polymer, administered at 25 mL/hour from 10 pm to 6 am via gastrostomy

Fluid 200 mL

Energy 200 kcal (840 kJ)

Glucose polymer 53 g (95% CHO)

CHO 0.3 g CHO/kg/hour

Or

Glucose polymer and MCT feed, administered at 25 mL/hour from 10 pm to 6 am via gastrostomy

Fluid 200 mL

Energy 200 kcal (840 kJ)

Glucose polymer 30 g (95% CHO) = 114 kcal (479 kJ)

MCT = $^1/_4$ of daily dose (10 g MCT) as 20 mL Liquigen (= 5 g MCT/100 mL) = 90 kcal (370 kJ)

CHO, carbohydrate; MCT, medium chain triglyceride.

(around 0.3–0.4 g CHO/kg/hour) (p. 610). Addition of MCT as an energy source should enable the energy from CHO to be reduced. Table 30.8 gives examples of overnight feeds. Fasting tolerance increases with age; therefore, in older children it may be possible to stop overnight feeds completely or substitute with one or more doses of UCCS. Typical doses of UCCS used are 1–1.5 g/kg/dose. It is first introduced at home to test its palatability and tolerance, similar to the process in glycogen storage disease (p. 613). Before changing management, it is good practice [35] to assess the child's metabolic response under controlled conditions in hospital by serial measurement of plasma-free fatty acids, blood glucose, acylcarnitines and CK on their usual regimen and after a dose of UCCS. The results of these studies are used to plan how frequently a dose of UCCS is given.

Exercise management

Glucose is the initial fuel during any exercise. Under normal circumstances CHO is the main fuel used for moderate to high intensity exercise such as sprinting, whereas fatty acids are the main fuel for low to moderate intensity exercise. Patients with VLCADD, LCHADD, MTPD and CPTIID can experience muscle pain, rhabdomyolysis, elevated CK and, in severe cases, myoglobinuria with exercise. These episodes may begin to occur in children as they become more active and want to play sports for longer periods. Some children may not be able to do prolonged periods of exercise without developing muscle pain, so it has to be avoided. The symptoms may occur due to limited ability to oxidise LCFA as a fuel source for exercising muscle or the accumulation of toxic intermediates. Short burst exercise may be more suitable than prolonged low intensity exercise because CHO will be used in preference to LCFA. As yet, no treatment has conclusively been shown to prevent rhabdomyolysis, but several papers suggest that dietary modification may reduce the risk of this. Some patients with CPTIID appear to benefit from taking a diet rich in polysaccharides pre-exercise [41]. Pre-exercise boluses of MCT (0.3–0.4 g/kg/dose) have been reported to improve exercise capacity in patients with various FAOD [42]. Dietary treatment may need to be adjusted according to the intensity and duration of the exercise being undertaken. CHO foods and/or MCT can be trialled before or during or even after exercise to see if this exercise capacity is improved. MCT can be given as a prescribed dose of Liquigen, or MCT Procal, and CHO can be given from food such as a low fat cereal bar, banana, bread or a glucose polymer drink. If a child does develop muscle pain during or, more likely, following exercise, this

must be treated promptly as there is a risk of rhabdomyolysis, myoglobinuria and subsequent renal failure. The standard glucose polymer ER ± MCT, with extra fluids, should be implemented. Rest is important until symptoms resolve. Children are likely to find it very difficult and painful to walk for the first 24–48 hours. It is essential that parents and patients know to look for signs of myoglobinuria (dark, cola-coloured urine) and to go to their local hospital and make immediate contact with their metabolic team for further management advice. Plasma CK can be markedly elevated during episodes of rhabdomyolysis and is helpful in determining the extent of muscle damage and management needed. ER guidelines (IV and oral) for hospital use can be accessed from www.bimdg.org.uk.

Dietary monitoring

Once an infant or child is established on dietary treatment, families need continued support and advice. Regular monitoring of this complex diet is essential to:

- ensure the diet is nutritionally adequate, particularly for fat-soluble vitamins, EFA and LCPUFA
- ensure the overnight feeds provide adequate CHO (or energy) for age
- check the intake of LCT and MCT
- provide new ideas and information on low fat manufactured foods
- assess exercise tolerance and provide advice on CHO/MCT intake
- check the ER for CHO concentration and volume and parents' understanding of its use

Clinical monitoring

This should include a review of weight, growth and development. There has been little documented on the growth of children with LC-FAOD. Gillingham *et al*. reported excess weight gain with time in most of their LCHADD and MTPD patients [43], but others have not observed this, including the author's centre [17, 35]. If a child is overweight, this needs to be managed carefully as weight loss could precipitate metabolic decompensation. A gradual reduction in energy intake is needed. If a child develops muscle pain with exercise, this can make weight management more difficult. Cardiomyopathy usually resolves on institution of a minimal LCT diet supplemented with MCT. Thereafter, cardiac function (echo and electrocardiogram) should be monitored annually. Liver ultrasound is also performed annually to assess for steatosis. In LCHADD and MTPD annual ophthalmological (electrophysiology) and neurophysiological follow-ups are important.

Biochemical monitoring

Blood acylcarnitine concentrations may correlate with outcome in these disorders, but this is not certain. For example, in LCHAD deficient patients, cumulative long chain 3-hydroxyacylcarnitine concentrations appear to correlate with the progression of retinal disease [44]. Monitoring of acylcarnitines may, therefore, be useful in guiding dietary management. Plasma-free carnitine levels should also be monitored, although there is dispute about supplementing carnitine if levels are low (p. 647), except in OCTN2. Plasma transaminases and CK are helpful markers of clinical status. CK increases markedly during episodes of exercise or illness-induced rhabdomyolysis and returns to normal once treated. Fat-soluble vitamins and EFA and LCPUFA concentrations should be monitored annually and more often if there are concerns about dietary deficiencies. Erythrocyte measurements of EFA/LCPUFA are a better marker of long-term nutritional status than plasma. Other nutritional markers such as iron and B_{12} status may also be necessary if there are concerns about nutritional adequacy of the diet.

Dietary guidelines for managing the unwell child with a LC-FAOD

Illness in any child is usually associated with loss of appetite and prolonged fasting, and fatty acid oxidation rates increase to provide energy. In LC-FAOD this process is limited, and the child is at risk of serious illness. The ER needs to be started promptly to inhibit the mobilisation of fatty acids and to prevent rhabdomyolysis and myoglobinuria, as there is risk of acute renal failure. The standard ER guidelines should be used for LC-FAOD.

LC-FAOD specific ER information

- Follow the standard ER (p. 673) of very frequent feeds/drinks of glucose polymer, day and night
- Long chain fat is strongly contraindicated
- MCT can be added for extra energy if it forms part of the usual diet
- Parents and patients must look for signs of rhabdomyolysis and myoglobinuria (dark, cola-coloured urine); admission to hospital is essential for IV fluids if there is myoglobinuria
- Patients with cardiomyopathy should be admitted to hospital as there is a risk of deteriorating cardiac function
- IV carnitine should not be given because long chain acylcarnitines may be arrythmogenic
- Plasma CK can be markedly elevated at 20 000–40 000 U/L and higher (50–240 U/L is the normal range, local laboratory figures) during episodes of rhabdomyolysis with myoglobinuria; daily measurement of CK can be used to guide management of hyperhydration, which is necessary to increase myoglobin excretion and help prevent acute renal failure
- Rest is important until rhabdomyolysis symptoms resolve

- Blood glucose monitoring by parents at home is not recommended as a marker of metabolic status, since hypoglycaemia is a relatively late finding, and treatment should be initiated long before this develops [11]

Learning points: long chain fatty acid oxidation disorders (LC-FAOD)

- *Dietary treatment varies depending on the severity*
- *In severe defects opinions differ about dietary management, particularly the use of overnight feeds and uncooked cornstarch (p. 646)*
- *In all disorders the use of an ER is essential during illness to prevent metabolic decompensation*
- *Additional CHO and/or MCT is needed for pre-exercise in some patients*

Carnitine transporter deficiency

Patients with carnitine transporter deficiency (CT or OCTN2; Figure 30.1) have low plasma and intracellular concentrations of carnitine. This impairs fatty acid oxidation as carnitine is necessary for the transport of LCFA into the mitochondria. Abnormal plasma acylcarnitines are not seen in OCTN2. Patients generally present between 1 and 7 years of age with the typical features of an LC-FAOD; other patients remain asymptomatic [12]. Heart failure is a common presentation that can rapidly deteriorate with risk of death if patients are not treated with carnitine (around 100 mg/kg/day divided into two or three doses). No dietary treatment is necessary except during illness when there is a risk of metabolic decompensation. The standard ER of frequent glucose polymer drinks day and night should be given to prevent increased lipolysis (p. 673). A more detailed overview of clinical manifestations, diagnosis and management is described elsewhere [45].

Multiple acyl-CoA dehydrogenase deficiency (MADD)

This disorder is also known as glutaric aciduria type II.

Transfer protein	Electron transferring flavoprotein (ETF) or ETF ubiquinone oxidoreductase ETFQO (Figure 30.1)
Biochemical defect	Due to defects of ETF or ETFQO that carry electrons from dehydrogenation reactions (in β-oxidation, lysine, tryptophan, branched chain amino acids, choline) to the mitochondrial respiratory chain. Results in an energy deficiency.
Genetics	Autosomal recessive inheritance. ETF: mutations in ETFA, ETFB. ETFQO: mutations in ETF dehydrogenase gene
Clinical onset presentation, features	MADD ranges in clinical severity. Some patients are completely responsive to riboflavin [46]. Severe MADD presents within the first few days of life with hypoglycaemia, hyperammonaemia, acidosis, hypotonia and hepatomegaly; some also have congenital malformations, and cardiomyopathy may develop. The less severe form may present from infancy to adulthood with hypoglycaemia, liver problems and muscle weakness [12].
Outcome	Neonatal onset cases do not survive. Sudden death can occur at any time.
Drug treatment	Trial of riboflavin (some cases are completely responsive). Oral sodium D-3-hydroxybutyrate is given to more severe patients [47]. CoQ10 supplements are recommended for late onset ETFQO [48].
Dietetic management	Little is published on dietary treatment of MADD. In patients with severe congenital malformations, no treatment is effective or appropriate. If riboflavin is responsive, no dietary modification is necessary. Patients with more severe MADD are commenced on: • a low fat, protein-restricted diet as the dehydrogenase enzymes of β-oxidation and some amino acids are affected • regular feeding during the day with a high CHO intake to provide an adequate energy intake and limit lipolysis • overnight fasting should be limited; young children are given continuous overnight feeds that can be replaced by UCCS in older children to provide a 'slow release' source of glucose; it is essential to assess tolerance individually • MCT should be avoided as they may precipitate problems [49]. Medium chain fatty acids enter the mitochondria primarily independent of carnitine so bypassing CPTI, the step at which β-oxidation is normally regulated; therefore, high concentrations of toxic metabolites could be generated • typical energy distribution of the diet in severe defects (based on personal practice): – 65%–70% energy from CHO – 8%–10% energy from protein (at least the safe level of protein intake for age [50] – 20%–25% energy from fat (the use of MCT is probably best avoided) – frequent feeding For infants a modular feed with the above energy ratio is given, ensuring it provides all nutrients including EFA and LCPUFA in recommended amounts. Partial breastfeeding is possible when combined with a fat-free modular feed [51]. The diet can be based on protein and fat exchange foods: each 1 g protein exchange should provide a maximum of 3 g fat. Additional fat may be necessary if the protein exchanges are very low in fat. Very low protein and fat and high CHO foods can be given freely, e.g. fruit, most vegetables, sugar. Some low protein manufactured foods are suitable and can provide additional energy, e.g. low protein pasta, rice, flour.
Monitoring – nutritional	Regular monitoring is essential to ensure nutritional adequacy and normal growth. There is no useful biochemical marker to determine the response to diet. Even on diet, acylcarnitine profiles generally remain abnormal but in less severe disease can be normal. Routine biochemical nutritional monitoring should be undertaken for patients on low fat diets similar to LC-FAOD (p. 652). If the child is on a very low protein diet, monitoring of plasma amino acids may be indicated.
Emergency regimen	During illness the standard ER (p. 673) of very frequent feeds, day and night, of glucose polymer should be given (oral or tube) to minimise protein catabolism and increased fatty acid oxidation, thereby reducing risk of metabolic decompensation. Fat should be avoided during the acute period.

Learning points: multiple acyl-CoA dehydrogenase deficiency (MADD)

- *Dietary management is a low fat, protein-restricted diet; MCT is best avoided*
- *Catabolism is limited by providing regular daytime and overnight feeding*
- *Use of an ER is essential during illness to prevent metabolic decompensation*

Malonyl-CoA decarboxylase deficiency

This disorder is also known as malonic aciduria.

Enzyme	Malonyl-CoA decarboxylase (MLYCD)
Biochemical defect	MLYCD catalyses the decarboxylation of malonyl-CoA to form acetyl-CoA and regulates the intracellular concentration of malonyl-CoA, which is involved in the regulation of fatty acid oxidation through inhibition of CPTI [52]. Biochemically there is raised malonylcarnitine in the blood and high urinary excretion of malonic and methylmalonic acids.
Genetics	Autosomal recessive inheritance: MLYCD gene
Newborn screening	No NBS in the UK
Clinical onset presentation, features	Clinical features are of variable presentation and severity: cardiomyopathy (around 40% of cases), muscle weakness, developmental delay, seizures, short stature, hypoglycaemia and metabolic acidosis [53]. Malonic acid is found mostly in heart muscle, skeletal muscles and central nervous system.
Drug treatment	Carnitine, as total and free carnitine concentrations in plasma are low
Dietetic management	A trial of a low fat, MCT-supplemented diet may be indicated in MLYCD deficiency patients who have cardiomyopathy. Improvement in cardiac function and biochemical response to diet has been reported in some published cases [54–57]. MCT primarily enter mitochondria directly, bypassing CPT1, and can provide an alternative fuel for the heart. There is limited detail and description of the diet used for many of the published cases. The author's centre reported improvement of cardiac function in a child when MCT provided around 25% of energy intake and LCT was minimal; she was also on an angiotensin-converting enzyme (ACE) inhibitor [54]. It is not known at the molecular level which patients may develop cardiomyopathy. There is inadequate evidence to know if diet may help in prevention of onset of cardiomyopathy in patients diagnosed early or via NBS or on relaxation of diet with age, once cardiac function has normalised.
Monitoring	Biochemistry: acylcarnitines, including plasma malonyl carnitine, malonic and methylmalonic acid excretion. Echocardiography
Monitoring - diet	Refer to guidelines for monitoring low LCT diets for LC-FAOD (p. 652)
Emergency regimen	During illness the standard ER (p. 673) of very frequent feeds, day and night, of glucose polymer should be given to prevent metabolic decompensation

Disorders of biosynthesis of ketones (ketogenesis) and ketone body utilisation (ketolysis)

The biochemical pathways of ketogenesis and ketolysis and site of metabolic defects described are shown in Figure 30.2.

Enzymes	*Enzymes involved in ketogenesis:* • 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase • 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL) *Enzymes involved in ketolysis:* • succinyl-CoA 3-oxoacid-CoA transferase (SCOT) • beta-ketothiolase (mitochondrial acetoacetyl-CoA thiolase)
Biochemical defects	Ketone bodies are formed from acetyl-CoA, produced mainly from the oxidation of fatty acids, but also from the ketogenic amino acids leucine and isoleucine (Figure 30.2). *Disorders of ketogenesis (defects in biosynthesis of ketone bodies):* • HMG-CoA synthase deficiency. Necessary for ketone body formation from fatty acid oxidation • HMGCL deficiency. Necessary for ketone body formation from fatty acid oxidation and final step of leucine degradation *Disorders of ketolysis (defects in utilisation of ketone bodies):* • succinyl-CoA 3-oxoacid-CoA transferase (SCOT) deficiency. Necessary for the utilisation of ketone bodies • beta-ketothiolase, T2 deficiency (also involved in the isoleucine degradation pathway). Necessary for the utilisation of ketones bodies A more detailed description of the biochemical pathway for these disorders can be found elsewhere [58, 59].
Genetics	Autosomal recessive inheritance

Newborn screening	No NBS in the UK
Clinical onset presentation, features	Ketone bodies (acetoacetate and 3-hydroxybutyrate) are an important energy source for all tissues, particularly the brain during fasting. Ketone body production increases during physiological stress situations such as illness. Excess ketones results in ketoacidosis. *Disorders of ketogenesis*: Typically present with vomiting and lethargy with a 'hypoketotic' hypoglycaemia, acidosis, elevated transaminases and hepatomegaly (not seen in all HMGCL cases) and hyperammonaemia (in HMGCL) [60]. HMGCoA synthase deficiency typically presents in the first or second year of life [61, 62], whereas HMGCL presents primarily within the first year of life with around half as neonatal cases [60]. In both disorders there is risk of death at the initial presentation. *Disorders of ketolysis*: Typically present with vomiting and high levels of ketones (which cannot be utilised), 'hyperketotic hypoglycaemia' (which can cause a severe ketoacidosis), a reduced level of consciousness and dehydration. In T2 deficiency typical onset of a first ketoacidotic episode is between 6 and 36 months and commonly precipitated by an intercurrent illness; neonatal onset is rare [62]. SCOT deficiency can present in the neonatal period and early childhood [63]. In all disorders, following diagnosis not all cases will experience a further episode of metabolic decompensation.
Outcome	Clinical outcome is generally good if identified early with prompt treatment and avoidance of further acute episodes, except in HMGCL deficiency. However, neurological complications are reported in T2 deficiency, including a few cases with no metabolic crises [64]. In HMGCL deficiency many patients develop long-term neurological complications, which include epilepsy, muscular hypotonia and spasticity [60].
Acute management	Acute decompensation is treated by IV glucose to suppress ketogenesis; refer to BIMDG emergency guidelines (www.bimdg.org).
Drug treatment	HMGL deficiency: L-carnitine supplementation 75–100 mg/kg/day to avoid secondary deficiency
Dietetic management	*Ketogenesis and ketolysis disorders* Between episodes of metabolic decompensation, most patients are likely to be clinically asymptomatic. Once diagnosed some cases never experience another episode. In the well child avoidance of prolonged fasts and provision of adequate energy is important to limit catabolism. There are no published guidelines on safe fasting times for these disorders; therefore, as clinical severity varies, it is important to establishing fasting tolerance on an individual basis, particularly in infants and young children. Infants should have regular feeds, day and night, and it seems reasonable to continue a middle-of-the-night feed until the age of 1 year. Older children should tolerate overnight fasting (10–12 hours) without problems, but they should be given a starchy bedtime snack and not miss breakfast. Missed meals should be replaced with a starchy snack or high CHO drink if there is any risk of impending illness. *HMG-CoA lyase deficiency* A moderate protein restriction (1–2 g protein/kg/day) has been recommended to reduce leucine load [65, 66]. In addition to protein restriction, some centres add leucine-free amino acids to the diet of some patients [60]. In some cases protein restriction has been combined with a modest fat restriction [60, 65]. However, opinions differ about the necessity of these dietary manipulations. Stable isotope studies suggest that protein catabolism contributes little to the abnormal metabolites and that fatty acid catabolism may be more important [67]. In the well child it is reasonable to suggest a generous CHO intake and avoidance of a high protein and fat intake. Avoidance of alcohol consumption has been recommended in HMGCL because it can precipitate Reye-like syndrome episodes [68]. *T2 deficiency* Mild protein restriction (1.5–2.0 g/kg/day) to reduce isoleucine load is theoretically considered reasonable, but is not evidence based, and benefit is unproven [63]. *SCOT deficiency* Mild protein restriction (1.5–2.0 g/kg/day) has been described, probably to limit increased concentrations of ketones being formed from the ketogenic amino acids, and avoidance of a fat-rich diet which would cause ketosis [63, 69]. In the well child it is reasonable to suggest a generous CHO intake and avoidance of a high protein and fat intake. *Medium chain triglycerides* MCT are best avoided as either they cannot be used to form ketones or they will add to the total ketone load, which cannot be utilised. Theoretically, in SCOT and T2 deficiencies, MCT may increase concentrations of ketones (which cannot be utilised) and inhibit long chain fatty acid oxidation, thus contributing to the energy deficit. In HMGCoA synthase and HMGCL, the conversion of MCT to ketones may be limited and so will not provide an energy source. Special infant formulas or paediatric feeds with added MCT should be avoided.
Emergency regimen	During illness the standard ER (p. 673) of frequent glucose polymer feeds, day and night, should be given to minimise fatty acid oxidation and endogenous protein catabolism (specifically the ketogenic amino acids) and suppress ketogenesis. If specialised infant formulas or paediatric enteral feeds are needed, due to inadequate oral intake, MCT-containing feeds should not be given. *Disorders of ketogenesis* The ER will help prevent hypoglycaemia and limit the production of potentially toxic metabolites. Blood glucose monitoring by parents is not recommended, since hypoglycaemia is a relatively late finding and treatment should be initiated long before this develops. *Disorders of ketolysis* The ER will help prevent illness from leading to ketoacidosis. Patients can become anorexic at an early stage if refusing ER drinks. Early admission to hospital is essential for administration of ER via tube or IV fluids. Sodium bicarbonate may be necessary to correct acidosis and extra fluids to correct dehydration, which is common in the ketone body utilisation defects.
Clinical management guidelines	Guidelines for diagnosis and treatment for patients with ketone body utilisation disorders have been produced based on clinical information from Japan and worldwide [70].

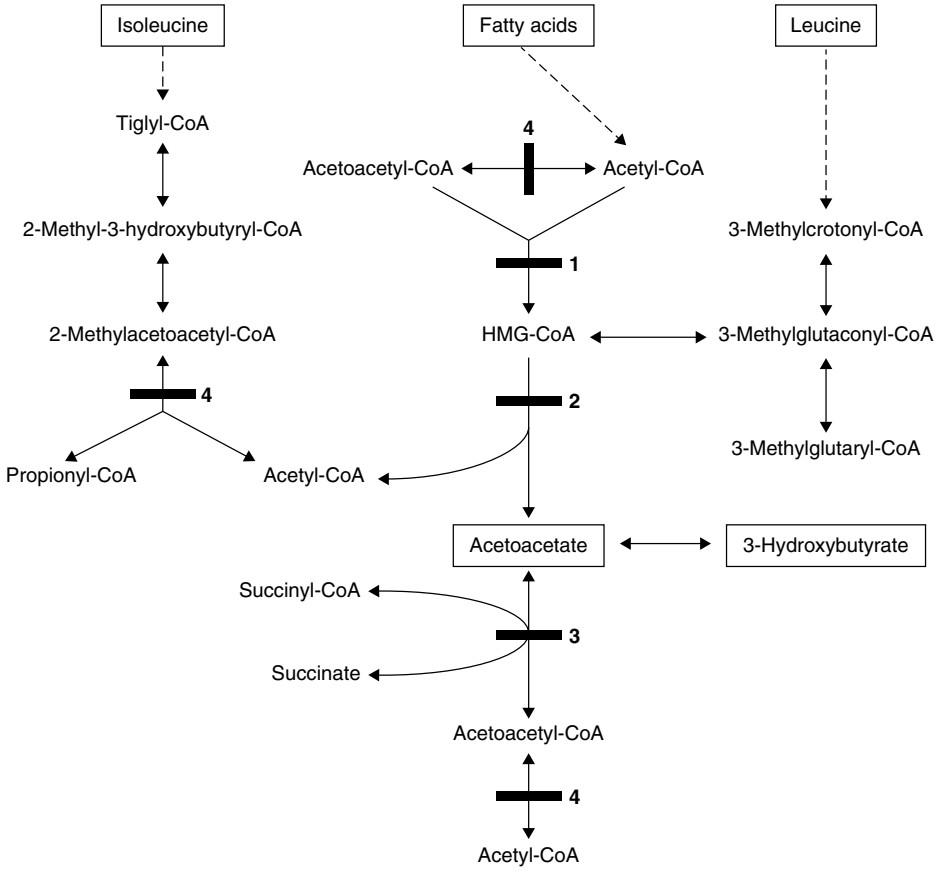

Figure 30.2 Biochemical pathways of ketogenesis and ketolysis. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A. 1, Mitochondrial(m) HMG-CoA synthase; 2, HMG-CoA lyase; 3, succinyl-CoA 3-oxoacid CoA transferase (SCOT); 4, mitochondrial acetoacetyl-CoA thiolase (T2). Reprinted with permission of Springer.

Learning points: disorders of biosynthesis of ketones (ketogenesis) and ketone body utilisation (ketolysis)

- *Management is avoidance of fasting, particularly during physiological stress, and treatment with standard ER or IV glucose (10%) (www.bimdg.org)*
- *Mild protein restriction is advised, but supporting evidence is limited*
- *MCT are best avoided*

Disorders of Lipid Metabolism

Rachel Skeath

Introduction

Triglycerides, cholesterol and phospholipids are the three main forms of lipid in the body. Their production and transport through the body is based on three interrelated pathways known as the exogenous, the endogenous and the reverse cholesterol transport pathways (Figure 30.3, Table 30.9). Lipids are transported in plasma as lipoproteins, which have a hydrophobic core of triglycerides and cholesteryl esters with hydrophilic molecules (phospholipids, cholesterol and proteins known as apolipoproteins) on the surface. The four main classes of lipoproteins are classified according to their density (Table 30.9). Apolipoproteins enable the packaging and transport of lipids; they are also cofactors for enzymes and ligands for lipoprotein receptors [71].

Disorders of lipid metabolism managed by dietary intervention can be categorised into:

- hypolipoproteinaemias: serum lipoproteins are deficient or absent
- hyperlipoproteinaemias: serum lipoproteins are increased

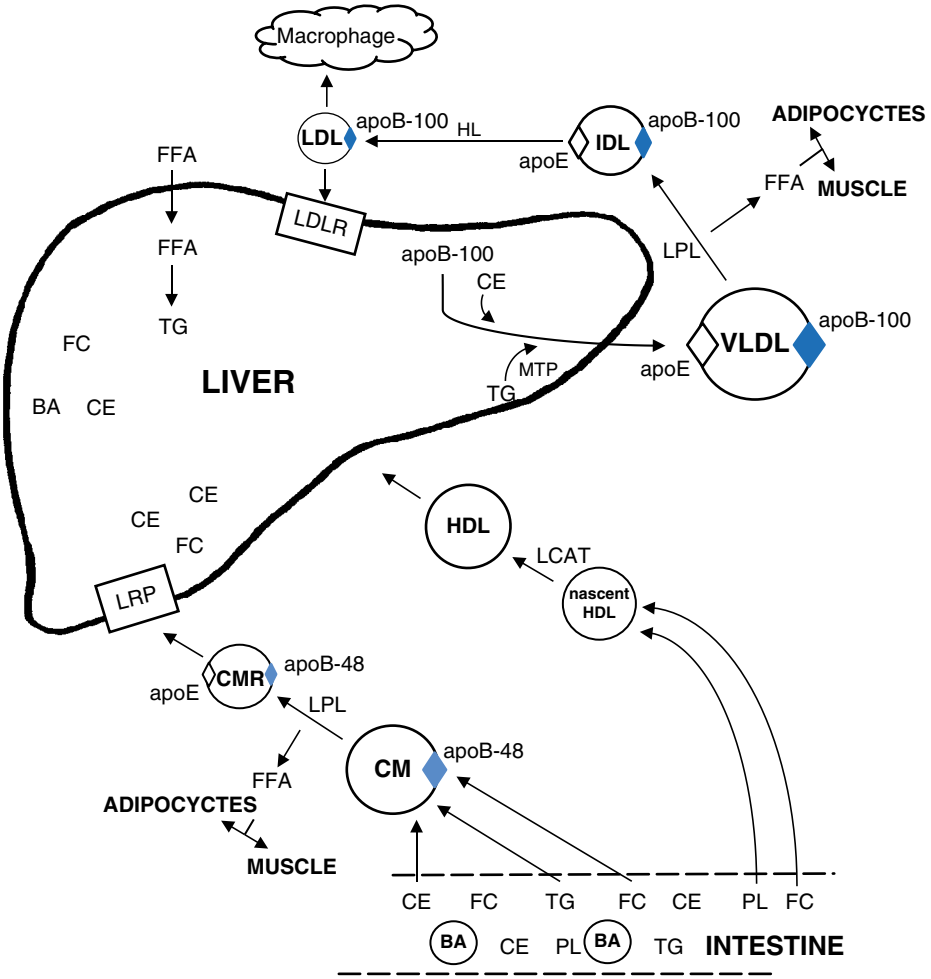

Figure 30.3 Lipid transport. Adapted from Kwiterovich *et al.* [72].
BA, bile acid; C, cholesterol; CE, cholesterol ester; CM, chylomicrons; CMR, chylomicron remnants; FC, free cholesterol; FFA, free fatty acid; HDL, high density lipoproteins; HL, hepatic lipase; IDL, intermediate density lipoproteins; LCAT, lecithin cholesteryl acyl transferase; LDL, low density lipoproteins; LDLR, LDL receptor; LPL, lipoprotein lipase; LRP, lipoprotein receptor-related protein; MTP, microsomal triglyceride transport protein; PL, phospholipid; TG, triglyceride; VLDL, very low density lipoproteins.

Table 30.9 Lipoprotein composition and function.

Lipoprotein	% wt from TG	% wt PL	% wt C+CE	Apolipoproteins	Function
CM	90	6	3	ApoB-48, ApoA-I, A-IV	Secreted from enterocytes. CM transport dietary TG and FC from the intestine. CE, FC and TG are hydrolysed by pancreatic lipase in the intestine, emulsified by BA, absorbed into enterocytes and then packaged into CM. TG in the CM is hydrolysed by endothelium-bound LPL in adipose tissue and muscle. CMR taken up by liver delivering CE and FC *(endogenous pathway)*
VLDL	55	15	22	ApoB-100, ApoC-I, C-II, C-III, ApoE	Secreted from hepatocytes. TG (synthesised in liver) is packaged with CE and apoB-100 to form VLDL and then transported to adipose tissue and muscle *(endogenous pathway)*. TG on VLDL is hydrolysed by LPL
LDL	5	25	50	ApoB-100	Catabolic product of VLDL formed by activity of HL. LDL transport cholesterol from liver to peripheral tissues (*endogenous pathway*). LDL normally removed by LDLR on liver, excess taken up by macrophages
HDL	5	25	20	ApoA-I, A-II, ApoC-I, C-II, C-III, ApoE	Transport cholesterol from peripheral tissues to liver *(reverse cholesterol transport)*. FC and PL form nascent HDL, which becomes a larger HDL particle through action of LCAT. Low levels of HDL are associated with higher risk of cardiovascular disease

BA, bile acid; C+CE, sum of cholesterol and cholesterol ester; CM, chylomicrons; CMR, chylomicron remnants; FC, free cholesterol; HDL, high density lipoproteins; HL, hepatic lipase; LCAT, lecithin cholesteryl acyl transferase; LDL, low density lipoproteins; LDLR, LDL receptor; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very low density lipoproteins, wt, weight.
Source: Adapted from Kwitervich PO [73].

Schaefer and Levy [74] describe grouping disorders of lipid metabolism by the lipid profile characteristic of the condition. Further classification becomes more complicated as similar phenotypes can result from different underlying causes. Advances in understanding lipoprotein metabolism continue to be made, assisted by the ongoing discovery of cases with novel mutations. Table 30.10 summarises the disorders reported in children.

Table 30.10 Overview of lipid metabolism disorders reported in children.

Disorder	Defect/problem	Lipid and lipoprotein profile	Dietary management
Deficiencies in apoB lipoproteins (gene involved is shown in italics)			
Abetalipoproteinaemia (ABL) (*MTP*)	Defect in the MTP protein responsible for processing of apoB lipoprotein	↓↓ CM, ↓↓ VLDL, ↓↓ LDL, ↓↓apoB, ↓↓ TG	Low LCT Although <20%–30% energy from LCT is recommended [75], in clinical practice a very much lower intake is necessary (p. 660) Adequate energy Caution in use of MCT High dose vitamin E EFA and fat-soluble vitamin supplements
Familial (heterozygous) hypobetalipoproteinaemia (*APOB*)	Decreased levels of functional apoB-100 lipoprotein, involved in VLDL and LDL structure	↓ LDL, ↓ apoB, normal TG	Usually asymptomatic – normal diet
Primary (homozygous) hypobetalipoproteinaemia (HBL) (*APOB*)		↓↓ CM, ↓↓ VLDL, ↓↓ LDL, ↓↓ apoB, ↓↓ TG	Low LCT Although <20%–30% energy from LCT is recommended [75], in clinical practice a very much lower intake is necessary (p. 661) Adequate energy MCT added to diet High dose vitamin E EFA and fat-soluble vitamin supplements
Chylomicron retention disease (CRD) (*SAR1B*)	Defect in the intracellular transport of CM	↓↓ CM, ↓↓ LDL, ↓↓ HDL, ↓↓ apoB, normal TG	Low LCT Although <30% energy from LCT is recommended [76], in clinical practice a very much lower intake is necessary (p. 661) Adequate energy MCT added to diet High dose vitamin E EFA and fat-soluble vitamin supplements
Disorders of reverse cholesterol transport			
Tangier disease	Defect in ABCA1 protein that is essential for exporting cholesterol and phospholipids to nascent HDL	↓↓ HDL, ↓ TC, ↓ apoA-I, normal TG or slightly ↑ TG	Low LCT
Lecithin-cholesterol acyltransferase deficiency	Unable to esterify cholesterol to produce HDL	↓↓ HDL, ↓ apoA-I, ↑ TG	
Exogenous hypertriglyceridaemia			
Familial lipoprotein lipase deficiency *(LPL)*	Defective or absent LPL causing accumulation of CM	↑↑ TG, ↑↑ CM, ↓ HDL, ↓ LDL, normal VLDL	Approximately 10–15 g LCT/day MCT added to diet EFA and fat-soluble vitamin supplements
ApoC-II deficiency (*APOC2*)	Defect in apoC-II that is a co-factor for LPL		
Defective glycosylphosphatidylinositol (*GPIHBP1*)	Defect in the GPIHBP1 protein that is involved in binding LPL		
apoAV deficiency (*APOA5*)	Exact mechanism of apoAV is unclear but is a modulator of TGs [77]		
Lipoprotein maturation factor 1 (*LMF1*)	LMF1 aids in LPL folding and transport		

(continued overleaf)

Table 30.10 *(continued)*

Disorder	Defect/problem	Lipid and lipoprotein profile	Dietary management
Endogenous hypertriglyceridaemia			
Familial hypertriglyceridaemia (*APOA5 and LIPI*)	Abnormal hydrolysis of TG Usually later onset Present in childhood if secondary risk factors for hyperlipidaemia are present	↑↑ TG, ↑ VLDL	10–15 g LCT/day MCT added to diet EFA and fat-soluble vitamin supplements
Combined exogenous and endogenous hypertriglyceridaemia			
Dysbetalipoproteinaemia/type III hyperlipoproteinaemia	Defective apoE *(APOE)* that binds CM, IDL and VLDL to LDLR Usually later onset. Presents in childhood if secondary risk factors for hyperlipidaemia are present	↑ TG, ↑ CM remnant, ↑ IDL remnant, ↑ VLDL remnant	10–15 g LCT/day MCT added to diet EFA and fat-soluble vitamin supplements
Hepatic lipase deficiency (*LIPC)*	Reduced hydrolysis of TG from IDL, LDL and HDL	↑↑ TG, ↑ VLDL, ↑ HDL, normal LDL	
Hyperlipidaemia due to disorders of LDL removal			
Familial hypercholesterolaemia (FH) (heterozygous) (*LDLR*)	Defective LDLR function	↑ LDL	Fat <30% of energy Saturated fatty acids <10% of energy Cholesterol <300 mg/day Oily fish once/week Fruit and vegetables – five portions/day
FH (homozygous) *(LDLR)*	Defective LDLR function	↑↑ LDL	
Familial defective apoB-100 (*APOB*)	Defective apoB-100 protein which decreases binding to LDLR	↑ LDL	
Autosomal recessive hypercholesterolaemia *(LDLRAP1)*	Defective internalisation of LDLR	↑ LDL	
PCSK9 disorders *(PCSK9*)	Decreased LDLR activity	↑ LDL	
Other hyperlipidaemias			
Sitosterolaemia (also known as phytosterolaemia) [78–80] Increased absorption and decreased biliary excretion of plant sterols and cholesterol	Defect in ATP-binding cassette transporter ABCG5/8 that transports sterols back into gut for excretion	↑↑ plant sterols in blood and tissues, ↑ LDL	Low saturated fat diet Avoid foods high in cholesterol, plant sterols and sterol fortified foods [78–80] https://ndb.nal.usda.gov/ Ezetimibe therapy (sterol absorption inhibitor) (p. 667) ± bile acid sequestrants
Lysosomal acid lipase deficiency Infant onset (Wolman disease)	Defect in lysosomal degradation of cholesteryl esters and triglycerides	↑ TG, ↑ LDL, ↓ HDL (less marked increases than in cholesterol ester storage disease, CESD)	See Wolman disease (p. 669)
Lysosomal acid lipase deficiency Childhood/adult onset (CESD)	Defect in lysosomal degradation of cholesteryl esters and triglycerides	↑ TG, ↑ LDL, ↓ HDL	May require modified lipid diet

CM, chylomicrons; EFA, essential fatty acids; HDL, high density lipoproteins; HL, hepatic lipase; IDL, intermediate density lipoproteins; LCT, long chain triglyceride; LDL, low density lipoproteins; LDLR, LDL receptor; LPL, lipoprotein lipase; MCT, medium chain triglyceride; MTP, microsomal triglyceride transport protein; TG, triglyceride; VLDL, very low density lipoproteins.

Hypolipoproteinaemias

Abetalipoproteinaemia (ABL)

Protein	Microsomal triglyceride transfer (MTP) protein
Defect	Defect in MTP protein resulting in impaired processing of apoB. Dysfunctional apoB causes impaired CM packaging and formation of VLDL and consequently LDL. Overall, it leads to the defective secretion, i.e. low levels, of the plasma lipids: chylomicrons, VLDL, LDL and fat-soluble vitamins.

Genetics	Autosomal recessive inheritance Incidence: <1 in 1 000 000 [81]
Clinical onset presentation, features	Age of onset is within first 24 months of life, typically the first few weeks. Biochemical features: • very low levels chylomicrons, VLDL, LDL, apoB and TG in plasma • deficiency of fat-soluble vitamins (vitamin E levels are almost undetectable [82]); deficient EFA levels • anaemia due to iron and folate deficiencies secondary to fat malabsorption • elevated prothrombin time and in severe cases gastrointestinal bleeding associated with vitamin K deficiencies Clinical symptoms involve many organ systems and include: • gastrointestinal: diarrhoea and steatorrhoea leading to faltering growth, abdominal distension • neurological: areflexia, ataxia, dysarthria and possible cognitive decline due to vitamin E deficiency; EFA deficiency may also be a contributing factor [82]; symptoms tend to develop by 10 years [81], and, left untreated, individuals can become immobile [82]; neurological symptoms are worse in ABL than HBL [75]. • ophthalmic: retinitis pigmentosa and less commonly corneal ulcers, ptosis and ophthalmoplegia due to vitamin E, A and EFA deficiency • liver: steatosis and elevated serum transaminases with hepatomegaly; although rare, hepatic complications such as cirrhosis has been reported [83, 84] • acanthocytosis: spiky red blood cells
Long-term complications and outcome	Prognosis is good with adherence to diet and vitamin supplementation. Early recognition and treatment can delay or prevent further deterioration of the presenting symptoms. GI symptoms resolve on commencing a low LCT diet. Vitamin E supplementation reduces retinal degeneration [81]. Hepatic steatosis is not uncommon, but further complications such as fibrosis or cirrhosis are rare [75]

Hypobetalipoproteinaemia (HBL)

Protein	ApoB protein
Defect	Defect in the synthesis of apoB (the step before the defect in ABL) causing impaired apoB. Leads to low levels of plasma LDL and fat-soluble vitamins
Genetics	Autosomal co-dominant inheritance. Mutation in *APOB* gene causes an error in the translation of apoB protein. Most mutations in *APOB* cause a truncated apoB protein, but some mutations affect intracellular transport of apoB. Another mutation in *PCSK9* gene causes upregulation (reduced degradation) of the LDL receptor that causes increased clearance of VLDL and LDL cholesterol [81]. Inheritance of one mutation in *APOB* gene causes heterozygous HBL, inheriting two mutations causes compound heterozygous or homozygous HBL (the term homozygous HBL will be used throughout to include compound heterozygotes). Heterozygous HBL has a milder clinical presentation than homozygous HBL. Incidence heterozygous HBL: 1 in 1000–3000 [85] Incidence homozygous HBL: 1 in 1 000 000 [81]
Clinical onset presentation, features	**Heterozygous HBL:** Usually asymptomatic; there is a three- to fivefold greater liver fat content than the general population; some develop hepatic steatosis. Biochemical features: LDL cholesterol and apoB level are one quarter to one third normal [81]. **Homozygous HBL:** Onset is within first 24 months of life; biochemical and clinical features are indistinguishable from ABL [85]
Long-term complications and outcome	The long-term outcome in heterozygous HBL is unknown; ongoing follow-up, particularly monitoring liver function, is recommended. In homozygous HBL early recognition and treatment with fat-soluble vitamins can slow the progression of neuromuscular and ophthalmological degeneration [81]. Malabsorption resolves with a fat-restricted diet. Hepatic steatosis may be more prevalent in HBL than ABL [75].

Chylomicron retention disease (CRD)

Protein	Sar 1b protein
Defect	Product of *SAR1B* gene is needed for intracellular trafficking of CM particles. The mutation causes accumulation of lipid (pre-CM transport vesicles) in the enterocytes and decreased, but not absent, LDL and apoB.

Genetics	Autosomal recessive inheritance. Mutation in *SAR1B* gene. Incidence 1 in 1 000 000 [81]
Clinical onset presentation, features	Clinical features normally present in early infancy and are similar to ABL [81] Biochemical features: • low levels (approximately 50% less than normal [76]) of total cholesterol, LDL, HDL, chylomicrons, but normal TG • elevated CK in many cases especially those with muscle complications • fat-soluble vitamin and EFA deficiency; plasma vitamin E levels are very low; omega-3 deficiency was less of a problem than omega-6 in one study population [76] • anaemia due to iron and folate deficiencies secondary to fat malabsorption • elevated prothrombin time and in severe cases GI bleeding associated with vitamin K deficiency Clinical symptoms involve many organ systems and include: • gastrointestinal: diarrhoea, steatorrhoea, abdominal distension and faltering growth • neurological: areflexia, ataxia, myopathy and muscle pain and sensory neuropathy have been reported [76] less severe than in ABL and HBL and tend to occur in those with a delayed diagnosis or poor compliance to treatment • ophthalmological: if present, mild compared to ABL and HBL • liver: hepatomegaly and steatosis in a few cases; cirrhosis has not been reported [81] • cardiomyopathy: has been described in adults [76]
Long-term complications and outcome	With early diagnosis, catch-up growth can be achieved. Diarrhoea and steatorrhea resolve with dietary modifications. Long-term data on outcome is lacking; ongoing follow-up is required.

ABL, HBL, CRD: Summary of management

Dietetic management	Low LCT diet Adequate energy MCT supplements Fat-soluble vitamin supplements; vitamin E in pharmacological doses; long-term EFA and/or LCPUFA supplements
Monitoring – biochemical and nutritional	Total cholesterol, LDL, HDL cholesterol Liver function tests, clotting factors, albumin, uric acid Vitamins A, D, E, K, B_{12}, folate, calcium, phosphate
Monitoring	Growth, stool output, abdominal distention Neurological examination, nerve conduction studies Ophthalmology Bone mineral density by dual energy X-ray absorptiometry (DEXA) Hepatic ultrasound Echocardiography
Clinical management guidelines	Lee J, Hegele RA Abetalipoproteinaemia and homozygous hypobetalipoproteinaemia: a framework for diagnosis and management. *J Inherit Metab Dis*, 2014, **37** 333–339 [75] Peretti N, Sassolas A, Roy CC *et al*. Guidelines for the diagnosis and management of Chylomicron Retention Disease based on a review of the literature and the experience of two centers. *Orphanet J Rare Dis*, 2010, **5** 24 [76]

Dietary management of ABL, HBL and CRD

Low LCT diet

Lee and Hegele [75] recommend in ABL that total fat intake, particularly LCT, should be <30% of energy intake and if possible closer to 20%; however, this differs markedly from clinical practice: GI symptoms generally only resolve on a much lower LCT intake. Homozygous HBL resembles ABL and so requires a similar LCT restriction. Children with heterozygous HBL are usually able to absorb the fat provided by a normal diet without restriction [86]. Peretti *et al*. [76] recommend in CRD that total fat intake should be <30% energy intake; this too differs in clinical practice as a very much lower intake is necessary to prevent GI symptoms. LCT restriction needs to be individually determined to relieve the GI symptoms of diarrhoea, steatorrhoea and abdominal distention and typically varies from 5 g fat/day in infants up to 20 g/day in older children. The diet is based on low fat carbohydrate foods such as white fish, lean meat, pulses, fruit and vegetables and very low fat dairy products such as skimmed milk and very low fat yoghurt. The LCT fat allowance should be distributed evenly through the day.

Adequate energy

Faltering growth at presentation needs correction. Throughout childhood energy deficit caused by LCT restriction should be compensated for with an increase in energy from low LCT, carbohydrate-based foods and MCT supplements.

Medium chain triglycerides

Medium chain triglycerides (C8 and C10) do not require chylomicrons for their absorption as they are absorbed and transported directly from the intestine to the liver via the hepatic portal system. MCT oil or MCT supplements (Table 30.6) can partially replace dietary LCT to enable more choice, improve palatability and provide additional energy. For example, MCT oil can be used in baking to make biscuits or pastry in place of margarine or used for frying foods. Further information on using MCT oil and alternative products can be found on p. 649.

Historically, the use of MCT as an energy source in ABL was controversial due to case reports of it possibly causing hepatic fibrosis [87, 88]. However, there are single case reports of children who developed cirrhosis independent of using MCT oil [75, 84]. Furthermore, there are case reports of benefit of MCT for catch-up growth and absence of adverse effects with its use [89]. Some metabolic centres, including the author's, include MCT in the diet with caution, in prescribed amounts; regular liver ultrasound scans and biochemical monitoring of liver function are required. Similar concerns have not been reported in HBL or CRD.

Fat-soluble vitamins

Vitamin E and beta-carotene are fully reliant on transport in apoB-containing lipoproteins for their delivery to the tissues of the body. Vitamins A, D and K, however, especially if taken in sufficiently large doses, are understood to be able to utilise the MCT transport pathway [75, 83].

Recommendations for supplementing fat-soluble vitamins are:

- vitamin E: 67–200 mg/kg/day [75, 90]
- vitamin A: 30–120 µg/kg/day [75] or 450 µg/day [76]
- vitamin D: 20–30 µg/day [75, 76]
- vitamin K: 5–35 mg/week [75] or 15 mg/week [76]

Long-term supplementation of vitamin E in high doses increases serum vitamin concentrations, but levels remain low in ABL, often <30% of the lower limit of normal [76, 91] and in CRD [83]. Different oral vitamin E preparations (liquid, tablets) are available including water-soluble forms. Liquid preparations are often in an oil-based suspension and in larger doses contribute to the daily LCT fat allowance. In the author's centre alpha-tocopherol acetate is mainly used (1 mL contains 100 mg vitamin E and l400 mg castor oil).

In contrast, deficiencies of Vitamin A, D and K seen at presentation can be corrected. The initial dose of vitamin A is high so it is important to monitor accordingly, as there is risk of toxicity [75, 84]. Fat-soluble vitamin supplementation should be given orally as this route is effective. There have been reports of hepatic complications in patients with ABL who have received parenteral vitamin supplementation; however, the association is not explicit [75]. At the author's centre, once initial deficiencies have been corrected, ongoing supplementation of vitamins A, D and K is provided through standard multivitamin and mineral supplements such as Ketovite tablets and liquid, Dalivit, Paediatric Seravit and FruitiVits (p. 526). Plasma concentrations are monitored to guide whether doses need to be adjusted beyond this.

Essential fatty acid supplements

EFA intake is restricted when following a low fat diet. In CRD neither intravenous (IV) nor oral supplementation with EFA was able to normalise plasma concentrations [76]. Plasma levels did not seem to impact outcome as, despite low plasma omega-6 fatty acid levels, the cohort of patients described still made very good clinical progress. There are no specific guidelines for EFA supplementation in HBL; therefore, supplementation with walnut oil (EFA) and KeyOmega (LCPUFA) to provide at least population requirements should be given (p. 646). Regular monitoring of EFA is essential with biochemical analysis of red blood cell (RBC) membrane fatty acids, rather than plasma fatty acids. RBC fatty acids reflect long-term fatty acid balance in tissues and are not influenced by recent dietary fat intake [92]. If tolerated the fat derived from walnut oil is not included as part of the daily fat allowance, although this practice may differ between centres.

Infant feeds

Newly diagnosed cases are often referred via gastroenterology services, with a history of having been fed various specialist formulas in an attempt to manage the malabsorption caused by fat-laden enterocytes. Infants should be fed from diagnosis with a minimal LCT formula. Diarrhoea may continue for several weeks, but the infant begins to thrive with the minimal LCT formula. If MCT is tolerated, a formula supplemented with MCT may be given, e.g. Monogen or Lipistart; both are nutritionally complete and contain 1.8–2.5 g MCT per 100 mL (Table 30.2). Exclusive feeding with Lipistart or Monogen will provide approximately 0.5–0.9 g LCT/kg based on an intake of 150 mL/kg.

If MCT is to be avoided, basic-f and Low Fat Module (Table 30.2) are suitable products on which to base a feed. Both require addition of vitamins, minerals and EFA supplements to meet requirements; basic-f also needs added glucose polymer to meet energy requirements. A minimal fat modular feed may be just as practical to use; an example providing approximately 5 g LCT is outlined in Table 30.11. The modular feed requires a minimal fat protein source (e.g. Protifar, Hydrolysed Whey Protein/Maltodextrin Mixture, Complete Amino Acid Mix), glucose polymer (e.g. Polycal, Vitajoule), electrolytes, EFA (e.g. walnut oil), LCPUFA (e.g. KeyOmega) and vitamins and minerals (e.g. Paediatric Seravit). If necessary a restricted amount of LCT (e.g. Calogen fat emulsion) may be added to the feed as an additional source of energy. Alternatively, and probably preferably, the amount of walnut oil can be increased until it provides all the allowance of LCT as invariably EFA levels remain low. As walnut oil is not a fat emulsion, it should not be added to the feed, but given as a bolus divided into 2–3 equal doses through the day.

Historically, breastfeeding has been considered to be contraindicated in ABL, HBL and CRD; however, a small amount

Table 30.11 Minimal fat feed (approx. 5 g LCT) when MCT is to be avoided.

A 16-week-old boy, prior to weaning. Weight = 5.4 kg (2nd centile). Length = 60 cm (9th centile)

Daily requirements:

Fluid 150 mL/kg. Energy 96–130 kcal (400–545 kJ)/kg. Protein 1.8 g/kg

EFA given as walnut oil to meet requirements (p. 646)

Feed volumes: 140 mL × 6

	Energy (kcal)	Protein (g)	CHO (g)	LCT (g)	Na (mmol)	K (mmol)
Vitajoule 120 g	456 (1908 kJ)	–	114	–	1.1	–
Protifar 20 g	74 (310 kJ)	17.4	0.2	0.3	1.0	0.7
Paediatric Seravit 10 g	30 (126 kJ)	–	7.5	–	0.1	0.1
Walnut oil 5 mL	42 (176 kJ)	–	–	4.7	–	–
KeyOmega 4 g sachet	18 (74 kJ)	0.1	3.2	0.5	0.3	0.3
KCl 7 mL (2 mmol/mL)	–	–	–	–	–	14.0
NaCl 1.5 mL (5 mmol/mL) + water to 900 mL	–	–	–	–	7.5	–
Per 100 mL	69 (289 kJ)	1.9	13.9	0.6	1.1	1.7
Per kg	107* (435 kJ)	2.9	21.6	0.9	1.7	2.6
% of energy		11	80	8		
Total per 24 hours (840 mL)	580 (2427 kJ)	16.3	116.6	5.7	9.3	14.1

*A higher energy intake may be needed in infants with faltering growth.

of breastfeeding may be possible in combination with a minimal or fat-free formula. Breastmilk intake needs to be restricted based on LCT allowance, e.g. 120 mL breastmilk can be estimated to provide 5 g LCT. Close monitoring is required, and the ratio of breastfeeding to formula feeding altered according to biochemical parameters, clinical symptoms and growth.

Glucose polymer, such as Maxijul or Vitajoule, can be added to infant formula to increase the energy density of the feed for those with faltering growth. Feed volumes may also need to be increased to provide additional energy; if the extra feed volume results in exceeding the LCT allowance, additional feeds of glucose polymer and a protein source should be given instead.

Weaning diet

Transition to solid foods can begin as usual at around 26 weeks of age with a minimal fat diet consisting of baby cereal mixed with the minimal fat feed, fruits and vegetables (excluding avocados and olives), pulses, meats and fish naturally low in fat. Families need to be taught how to calculate daily fat intake. As a guide for using commercial baby foods, wet baby foods and dried baby foods containing ≤0.5 g fat/100 g and ≤2 g fat/100 g, respectively, are allowed freely if given in typical portion sizes. Other baby foods with a higher fat content need to be counted as part of the total daily fat allowance. Families can be taught to calculate fat content of food from nutritional food labels (p. 649). A sample menu for a low LCT weaning diet is given in Table 30.3 (excluding the advice regarding overnight feeding, which is not necessary for these disorders; additional feeds can be given during the day instead).

Children

A fat (LCT)-restricted diet needs to continue into childhood. Daily fat allowance may increase slightly as already discussed. A guideline for achieving a minimal fat diet in children is to aim for main meals to contain ≤3 g fat per meal, snacks ≤0.5 g fat per item and desserts ≤0.5 g fat per portion. The LCT content of suitable foods is given in Table 14.14. A sample menu providing ≤10 g fat/day is given in Table 30.12.

Older children and adolescents

It can be particularly difficult to achieve an adequate energy intake for growth and development on such a low fat diet in this age group. Foods such as skimmed milk (made into milkshake with low fat flavouring), very low fat yoghurts, low fat breakfast cereals, fruit (including dried), fruit juices, meringue, jelly, jam and sorbet are suitable low fat sources of energy. Low fat food brands designed for weight loss can be useful and are increasingly available in the supermarkets; their fat content per portion needs to be considered before including in the diet. Standard recipes (e.g. for biscuits, cakes and savoury foods) can be adapted to make low fat versions. MCT oil will help to improve the palatability and the energy density of the diet (used with caution in ABL). See p. 648 for further details of using MCT supplements. Glucose polymers (e.g. Maxijul, Polycal, Vitajoule) may need to be used if adequate energy cannot be achieved with food alone. Finding suitable snack foods can be a particular challenge,

Table 30.12 A sample minimal fat menu providing ≤10 g fat/day.

Quantities will vary according to age and appetite	
Breakfast	Low fat cereal (<2 g fat/100 g, per 30 g serving = 0.5 g fat) e.g. cornflakes, Rice Krispies with skimmed milk Very low fat yoghurt (<0.2 g fat/100 g) White bread* toast (no spreading fat) and jam/honey/marmalade Fruit juice
Lunch	Sandwich made with bread*/bread roll* with filling of chicken/lean ham/tuna in brine or spring water/low fat cheese spread and salad OR baked beans and jacket potato OR egg white omelette with peppers and mushrooms with boiled potatoes Fruit/jelly/very low fat yoghurt
Snack	Fruit/vegetable sticks/suitable low fat snack items, e.g. low fat cereal bar
Evening meal	Chicken/turkey (light meat)/very lean beef (<5% fat) with fat drained or removed/white fish Vegetables or salad Boiled/jacket/mashed potato or boiled pasta/rice/chapattis (no fat) Meringue and very low fat yoghurt/milk pudding made with skimmed milk
Bedtime	Glass of skimmed milk Low fat cereal with skimmed milk

*Check fat content of product.

especially when out with friends. Advice should be given to families about minimal LCT choices when eating out.

Ongoing dietary assessment and monitoring is required to ensure the diet remains nutritionally adequate. EFA and fat-soluble vitamin supplements continue to be needed. To achieve adequate calcium intake, minimal fat calcium sources should be encouraged in the diet, e.g. skimmed milk (0.1% fat) and very low fat yoghurt (<0.2 g fat/100 g). Haemoglobin and ferritin levels should be monitored in view of the low intakes of haem sources (particularly red meat) in the diet.

Adherence to a low fat diet can be difficult, and young people and their families need ongoing support. As young people get older and more independent, they need to learn to manage the diet themselves. This requires them to understand the reasons for the diet as well as receiving education on a practical level to enable suitable dietary choices as they move to adulthood.

Learning points: hypolipoproteinaemias

- *ABL, HBL and CRD are very rare*
- *Treatment is a low LCT diet with supplementation of fat-soluble vitamin and essential fatty acids*
- *MCT can be used, but with caution in ABL*
- *Vitamin E is supplemented in very high doses, but plasma levels remain low in ABL*

Hyperlipoproteinaemias

Primary hyperlipoproteinaemias present due to genetic disorders, whereas secondary hyperlipoproteinaemias are acquired due to another underlying disease or environmental factors, e.g. diabetes, obesity and excessive alcohol intake.

As many of the primary hyperlipoproteinaemias are very rare, only the two most prevalent disorders are discussed: familial lipoprotein lipase (LPL) deficiency (type I hyperlipidaemia) and familial hypercholesterolaemia.

Familial lipoprotein lipase (LPL) deficiency

Protein	LPL
Biochemical defect	Defect in LPL gene causing decreased activity of LPL. Results in increase in chylomicrons, triglyceride, total cholesterol and inability to clear dietary fat
Genetics	Autosomal recessive inheritance Incidence of homozygous: 1 in 500 000–1 000 000 [93]
Clinical onset presentation, features	Heterozygous carriers are usually asymptomatic Homozygous: Presents in first year of life Biochemical features: • very high plasma TG, up to 10 000 mg/dL (114 mmol/L) [71] (normal fasting levels 0.5–2.2 mmol/L) • high levels of CM, low HDL, low LDL, with normal VLDL Clinical symptoms at presentation include: • creamy blood • abdominal pain • eruptive xanthomas, hepatosplenomegaly and lipaemia retinalis • pancreatitis • immune dysfunction has also been hypothesised [94] in a case report of a child who appeared to develop immunodeficiency with altered neutrophil function
Long-term complications and outcome	Episodes of pancreatitis can be life threatening. The role of plasma TG as an independent risk factor for coronary heart disease (CHD) in the general population is unclear due to insufficient evidence looking at TG in isolation from other plasma lipids [95, 96]. Kwiterovich [71] states that premature atherosclerosis does not occur in LPL deficiency.

Acute management	If there is pancreatitis at presentation, this will need to be treated foremost. If there is no pancreatitis at presentation, chronic dietary management can be commenced.
Medical treatment	Aim to control plasma triglyceride levels to avoid pancreatitis.
Dietetic management	Low LCT diet Adequate energy MCT supplements Fat-soluble vitamins EFA and LCPUFA supplements Aim plasma TG <10 mmol/L
Monitoring – biochemical and nutritional	Total cholesterol, TG, LDL, HDL Liver function tests, albumin, clotting factors Vitamins A, D, E, K, B_{12}, folate, calcium, phosphate, iron Pancreatic enzymes (amylase, lipase)
Monitoring tests	Liver ultrasound, not always done routinely

Dietary management of LPL deficiency

The aim of dietary treatment is to control plasma triglyceride levels and avoid pancreatitis.

Restricted LCT intake

Restriction of LCT to 5 g/day will result in optically clear fasting serum and lowering of serum triglycerides. Such severe fat restriction is difficult to maintain in the long term, so fat allowance should be determined by individual tolerance. A restriction of dietary fat to 10%–15% of total energy, or up to 25 g LCT fat/day, is usually sufficient to reduce plasma triglyceride levels and avoid pancreatitis [97, 98]. Plasma triglycerides will not normalise; the aim is to maintain at a level <10 mmol/L, although a more realistic target for some will be <20 mmol/L provided there is no abdominal pain. Experience from the author's centre suggests abdominal symptoms can occur with TG >15 mmol/L and pancreatitis with TG >20–30 mmol/L or higher. The diet is similar to that described for the hypolipoproteinaemias (p. 661).

MCT intake

MCT oil and supplements can be included in the diet as MCT do not require chylomicron formation for transport [98]. They are a useful energy source and can be added to the diet as discussed for the hypolipoproteinaemias (p. 662).

Carbohydrate intake

Some centres in the USA advise reducing intake of simple carbohydrate [98]. This approach is used in the general population where hypertriglyceridaemia is associated with high carbohydrate diets [99]. In the UK restrictions on carbohydrate intake are not applied in children with primary hypertriglyceridaemia.

Fat-soluble vitamins

Due to the low fat diet, fat-soluble vitamin supplements (e.g. Ketovite, Dalivit) are needed to provide UK recommended nutrient intakes [36]. Additional mineral supplements such as calcium and iron may also be needed if the diet does not provide sufficient sources. Plasma levels are monitored to guide any adjustments that need to be made. Be aware that fat-soluble vitamin levels may be falsely elevated in the presence of high levels of circulating triglyceride.

Essential fatty acids

EFA supplements are needed as requirements will not be provided by the fat-restricted diet. At the author's centre, walnut oil is given to provide EFA and KeyOmega to provide LCPUFA to meet population requirements (p. 646). There are individual case reports of LPL deficient patients responding to treatment with 15–30 g MCT oil or 4 g omega-3 fatty acids daily with a dramatic decrease in fasting plasma triglycerides [100–102]. One case was found to respond with an increase in mass and activity of LPL [100]. The mechanism for these findings is not fully understood, but is likely to be due to a unique genotype rather than the more common genetic defects seen in classical LPL [100].

Acute episodes

During episodes of acute abdominal pain or pancreatitis, a strict minimal LCT diet providing <5 g/day should be commenced with adequate energy from MCT and complex carbohydrate (Tables 14.13 and 14.14).

As discussed on p. 664, prompt enteral feeding (oral/nasogastric/nasojejunal) rather than extended periods of nil by mouth should be attempted in cases of pancreatitis [103, 104]. The author's experience of one patient without pancreatitis, but with severe abdominal pain, was that a short period (24–48 hours) of IV glucose fluids was all that could be tolerated initially due to the pain. Skimmed milk and glucose polymer may be taken orally to support dietary intake. If a child requires enteral tube feeding, 'juice'-style oral nutritional supplements, e.g. PaediaSure Plus Juce, Ensure Plus Juce, Fortijuce and Fresubin Jucy, can be given (Table 12.5); these are fat-free. Alternatively, a low LCT modular feed similar to that detailed in Table 30.11, but containing MCT such as Liquigen in place of some of the

glucose polymer, could be given. If PN is required due to intolerance of enteral feeds, lipid will need to be restricted.

Infants

A minimal LCT formula supplemented with MCT such as Monogen or Lipistart can be given and is nutritionally complete if given at age appropriate amounts. They include EFA and fat-soluble vitamins, so additional supplements should not be needed. Partial breastfeeding (although a source of LCT) may be possible in combination with a minimal LCT formula, aiming to maintain TG levels <10 mmol/L.

Weaning

When solid foods are introduced, a minimal LCT diet should be followed as discussed for the hypolipoproteinaemias (p. 663). Minimal LCT infant formula, Monogen or Lipistart, should continue during infancy. EFA and fat-soluble vitamin supplements will be needed as the volume of infant formula decreases as more food is eaten.

Children and adolescents

LCT restriction continues into childhood and adolescence. Concerns about ensuring adequate energy intake as discussed for the hypolipoproteinaemias also apply in LPL deficiency. MCT supplements can be used to improve the energy content and palatability of the diet as well as broadening choice. Issues with dietary adherence are relevant in LPL deficiency, and it is important that young people are enabled to take responsibility for their dietary choices, so they avoid complications such as pancreatitis and nutritional deficiencies.

Learning points: familial lipoprotein lipase deficiency

- *Treatment aim is to maintain TG <10 mmol/L to prevent pancreatitis*
- *Dietary treatment is a low LCT diet with MCT supplements, fat-soluble vitamins and essential fatty acids*
- *Pancreatitis develops when TG are high*

Familial hypercholesterolaemia (FH)

Protein	LDL receptor
Defect	LDL cholesterol uptake and clearance by hepatocytes is reduced, and so cholesterol accumulates with deposition in the blood vessels, causing progressive atherosclerosis. Caused by a defect in the LDL receptor or defective binding of the LDL particles to an intact receptor [105].
Genetics	Autosomal dominant inheritance. Mutation in low density lipoprotein receptor (LDLR) or apolipoprotein B-100 (APOB) or proprotein convertase subtilisin/kexin type 9 (PCSK 9) genes [77]. FH exists in homozygous and heterozygous forms. See p. 507 for an explanation of inheritance. The term homozygous FH is often used to include compound heterozygous FH [106].
Screening	Population screening strategy through cascade testing following a positive FH diagnosis. Early detection of FH is important as prompt treatment is likely to be more effective. Screening by measurement of serum cholesterol is most effective if done in early childhood between 1 and 9 years when a high detection rate can be achieved with a false positive of only 0.1% [107]. The 2017 National Institute for Health and Care Excellence (NICE) Clinical Guideline 71 [106] recommends that: • primary care records are systematically searched to identify people younger than 30 years with a total cholesterol concentration >7.5 mmol/L and people 30 years or older with a total cholesterol concentration >9.0 mmol/L; this will enable early detection of those at highest risk of FH • in an index case a diagnosis of FH should be made using the Simon Broome Criteria or Dutch Lipid Clinic Network (DLCN) criteria; an outcome of possible or definite FH on the Simon Broome criteria, or a DLCN score >5, should pre-empt referral for DNA testing • if a genetic diagnosis is made, cascade screening of first-, second- and third-degree biological relatives should be undertaken • in children at risk of FH due to an affected parent, DNA tests should be carried out before 10 years of age; if confirmed, children should be referred to a specialist centre with management expertise for this age group Homozygous FH is more severe and much less common. Prevalence is at least 1 in 500 (perhaps up to 1 in 250) for heterozygous FH and 1 in 1 000 000 for homozygous FH [105].
Clinical onset presentation, features	Presenting features include elevated levels of LDL cholesterol and total cholesterol in the blood and deposits of cholesterol in the peripheral tissues, tendon and skin xanthomas and corneal arcus. Total cholesterol will be >6.7 mmol/L or LDL cholesterol >4.0 mmol/L in a child <16 years with heterozygous FH. If total cholesterol is >11 mmol/L, homozygous FH can be suspected. Most children with heterozygous FH are clinically asymptomatic [105] but can begin to show signs of atherosclerosis, e.g. endothelial dysfunction, even before puberty [108].
Long-term complications and outcome	Premature atherosclerosis leading to cardiovascular disease (CVD). Early identification allows initiation of therapy in order to prevent CVD and can minimise progression [105, 108]. Heterozygous FH causes a >50% risk of CHD by the age of 50 years in men and at least 30% in women by the age of 60 years [109–111]. In homozygous FH there can be either a total absence of or defect in LDL receptors, so individuals usually develop coronary artery disease in the second decade; severity of hypercholesterolaemia may determine disease course (based on the outcome of a small number of cases) [112].
Acute management	Treatment is a combination of dietary intervention, drug therapy and lifestyle modification. More aggressive treatment, such as plasma LDL apheresis or liver transplantation, may need to be considered for homozygous FH [112, 113].

Medical treatment	The aim of treatment for both heterozygotes and homozygotes is to lower plasma LDL levels and reduce the risk of CVD [106]. The aim for adults is to reduce LDL cholesterol by 50%; no specific target is given for children. Statins (HMG-CoA reductase inhibitors): • The first choice of drug therapy [114] and offered lifelong • NICE recommends statins offered to children with FH by the age of 10 years or at the earliest opportunity thereafter; not all are licensed for this age group • Systematic reviews [115–117] summarise that statins are well tolerated and effective (reduce LDL cholesterol levels by 20%–40%) and are not associated with increased risk of adverse effects in children (aged 8–18 years) in the short term • The need for longer-term studies is recognised Other lipid lowering drug therapies: • bile acid sequestrants: bind bile acids in the intestine, causing upregulation of bile acid synthesis and, therefore, utilisation of cholesterol • fibrates: reduce triglyceride levels and increase HDL • ezetimibe: a cholesterol absorption inhibitor that impairs dietary and biliary cholesterol absorption from the small intestine [118] These may all be used in cases of intolerance to statins or in combination with statins for management of homozygotes or exceptional circumstances, such as a family history of heart disease at a very young age. Until the use of statins, bile acid sequestrants were the preferred treatment in children; however, due to poor tolerance long-term adherence was low [105].
Dietetic management	NICE Clinical Guideline 71 recommends a lipid-modified diet. Due to insufficient data on the effectiveness of lipid lowering diets in FH, this recommendation is based on three high quality reviews of dietary interventions in the general population [119–121]. NICE Clinical Guideline 71 [106]: • total fat intake 30% or less of total energy intake • saturated fats 10% or less of total energy intake • intake of dietary cholesterol <300 mg/day • saturated fats replaced by increasing the intake of monounsaturated and polyunsaturated fats Additional recommendations: • include at least five portions of fruit and vegetables a day • eat two portions of fish a week, one of which should be oily fish; do not routinely recommend omega-3 fatty acid supplements • if food products containing plant stanols and sterols are consumed, these products need to be taken consistently to be effective If bile acid sequestrants are used long term, then supplementation with fat-soluble vitamins (A, D and K) and folic acid should be considered.
Monitoring – biochemical and clinical	Fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides Liver enzymes (transaminases), bilirubin and CK if on statins Weight and body mass index Carotid artery assessment, carotid intermedia thickness and carotid plaque score may be measured to monitor progression of disease in homozygous FH; it is not routinely monitored in clinical practice in heterozygous FH
Monitoring – nutritional	If a modified lipid-lowering diet is followed, fat-soluble vitamin supplements should not be required; however, it is assiduous to check fat-soluble vitamin levels annually. If lean red meat is restricted, then iron stores need to be monitored. Calcium intakes should be assessed, and supplements given if there is poor intake of low fat dairy products.
Clinical management guideline	NICE Clinical Guideline 71 www.nice.org.uk/guidance/CG71 [106]
Parent support group	www.heartuk.org.uk/ [122]

Lifestyle modification

It is important that families are given information about exercise, smoking, alcohol and weight management alongside lipid-modifying drug therapy and dietary intervention. Where relevant, support should be given to individuals about weight reduction to achieve a healthy weight, as obesity is a further risk factor for CHD. Further details of the lifestyle interventions can be found in the NICE CG71 [106] with some practical resources including increasing activity levels and healthy eating recipe ideas on the NHS Live Well website www.nhs.uk/live-well/ [123] and Heart UK www.heartuk.org.uk/ [122].

Dietary management of FH

Total fat intake <30% of energy intake

Assessing each child's diet individually is essential. Some families may already follow a 'healthy' diet and achieve the recommended guidelines for total fat intake because a parent has FH. Others will require education and help to interpret food labels. As a guide and in line with NHS Live Well, a high fat food contains >17.5 g fat/100 g, and a low fat food contains <3.0 g fat/100 g or 1.5 g fat/100 mL for liquids [123]. In order to achieve this, simple adjustments in the diet can be made, such as using low fat dairy products. Full fat milk

(3.5% fat) can be replaced with skimmed milk (0.1% fat), 1% fat milk or semi-skimmed milk (1.7% fat). Decreasing the intake of hidden sources of fat in manufactured foods, such as from cakes and biscuits, will help in achieving the target fat intake. Some centres advise reducing intake of red meat and replacing with alternative protein sources such as beans, pulses, poultry (light meat, no skin) and white fish (not fried). Suggestions for making suitable food choices when eating out should also be given as required. Table 30.13 gives a suggested meal plan for a 10-year-old boy with newly diagnosed FH.

Saturated fatty acids (SFA) intake <10% of energy intake

Meta-analyses have shown that manipulating the type of fat in the diet of the general population can modify serum lipid profiles [99, 121]. Changes in plasma total cholesterol concentrations are largely achieved through changes in LDL level [124]. An increased intake of SFA raises plasma levels of total and LDL cholesterol [99]. As a guide, foods low in SFA contain ≤1.5 g/100 g or 0.75 g/100 mL for liquids [123]. Foods high in SFA contain ≥5.0 g/100 g and include foods such as:

- fatty cuts of meat, meat products such as sausages and pies
- butter, ghee and lard
- cheese, especially hard cheese
- cream, soured cream and ice cream
- savoury snacks, e.g. crisps and salted nuts
- chocolate confectionery, biscuits, cakes and pastries
- palm oil, coconut oil and coconut cream

Table 30.13 A suggested meal plan for a 10-year-old boy newly diagnosed with familial hypercholesterolaemia.

Weight = 31 kg (50th centile). Height = 143 cm (75th centile)	
Breakfast	Large bowl of low fat breakfast cereal with skimmed milk and chopped fruit 2 slices wholemeal toast/bagel + olive oil-based margarine or margarine enriched with plant stanol/sterols + honey Glass of water
Mid-morning snack	Banana Glass of water
Lunch	Tuna in spring water (drained) with 'extra light' mayonnaise and cucumber slices in a tortilla wrap* OR a mini baguette filled with low fat hummus and tomato slices Low fat crisps* OR low fat cereal bar* Carrot or celery sticks Apple Low fat yoghurt Glass of water
Mid-afternoon snack	1 slice wholemeal bread toast + olive oil-based margarine or margarine enriched with plant stanol/sterols Handful of grapes Diluted squash
Evening meal	Chicken curry (using light meat) with onions, green beans in a tomato-based sauce cooked in rape seed oil with boiled rice (white or brown) OR grilled salmon and new potatoes with steamed carrots, peas and sweetcorn Meringues and low fat yoghurt with chopped strawberries OR fruit and low fat custard made with skimmed milk Glass of water
Bedtime	Cereal* and skimmed milk OR hot chocolate using low fat drinking chocolate and skimmed milk OR a glass of skimmed milk

*Check nutrition label for fat content.

Dietary cholesterol <300 mg/day

A reduction in dietary cholesterol has only a small effect on plasma cholesterol levels. This is thought to be due to the body's feedback mechanism that alters endogenous production depending on exogenous intake [121]. Dietary cholesterol is found in eggs, high fat dairy products, shellfish and offal. Foods containing dietary cholesterol need not be restricted unless they also have a high SFA content. There is no recommended limit on egg consumption. They can be included in a healthy balanced diet, but the method of cooking needs to be considered, boiling or poaching instead of frying or scrambling with butter. Reducing the SFA intake often has the secondary effect of decreasing dietary cholesterol intake.

Increasing monounsaturated fats and polyunsaturated fats

Polyunsaturated fats (PUFA) and monounsaturated fats (MUFA) have been shown to have a hypocholesterolaemic effect when substituted for SFA in the diet in the general population [97, 99]. Replacement of SFA with PUFA reduces both HDL and LDL cholesterol, whereas MUFA reduces LDL, but has less of an impact on HDL. Omega-6 PUFA are found in sunflower oil, corn oil and soya oil. These oils can replace saturated fats and oils in the diet for use as a spread and in cooking. LCPUFA from fish oils (omega-3 fatty acids), compared with other PUFA, cause HDL cholesterol to rise and TG to decrease [77]. Oily fish such as pilchards, mackerel or salmon should be included in the diet at least once a week. MUFA are found in avocados, olive oil, rapeseed oil (a cheaper alternative to olive oil) and fat spreads made from these oils.

Plant stanols and sterols (phytosterols)

Sterols and stanols are components of cell membranes and produced in both animals and plants. All sterols and stanols, whether animal or plant, contain a sterol ring (in stanols this ring is saturated, in sterols it is unsaturated) [125]. Phytosterols, therefore, resemble cholesterol (an animal sterol), and their ingestion competes with cholesterol absorption in the intestine [126]. Several small and short-term studies have shown that incorporation of phytosterol-containing

foods in the diet of children with FH reduces LDL cholesterol by 10%–15% [108, 127]. This was achieved by taking 2.3 g/day plant sterol and 2.8 g/day plant stanol as enriched spreads. They need to be taken consistently to be effective. The opinion of NICE [106] is that the evidence is insufficient to draw definitive conclusions regarding effectiveness of phytosterols, and as longer-term use is very limited, further research is recommended. No evidence of associated vitamin deficiencies has been identified with the use of plant sterols or stanols in children.

A variety of phytosterol-enriched products can be found in supermarkets, the Flora ProActiv and Benecol ranges being widely available. Esters of sterols and stanols tend to be used for food fortification as they are more easily incorporated into food. Products vary in the amount they contain, e.g. 10 g of fortified spread contains 0.5–0.7 g of sterol/stanol per 10 g and a serving (68–100 g) of yoghurt drink contains 2 g sterol/stanol. Yoghurts, bars and chewy sweets are also available. These products are a significant expense for families as they need to be consumed regularly.

Fruit and vegetables

Families should be encouraged to increase their intake of fruit and vegetables (fresh, frozen or tinned), aiming for five portions a day and a wide variety. For children, as a guide, a portion is the amount that fits in the palm of their hand. Fruit juice (150 mL) counts as one portion a day.

Complex carbohydrates

Starchy foods such as cereals, bread, pasta, rice, chapattis, noodles and potatoes should be included at most meals. Encouraging sources of fibre is beneficial for general health, but soluble fibre, e.g. oats or linseed, may also have a lipid-modifying effect. Good quality evidence in FH is limited; one small study in adults with FH showed a significant reduction in LDL [126], which is consistent with studies in hypercholesterolaemia [128]. Beta-glucan, found in oats, may lower cholesterol by the formation of a gel in the digestive tract that binds to cholesterol and bile salts, so preventing cholesterol absorption [129]. Some starchy foods can be bulky and increase satiety levels and may have the undesired effect of reducing energy intake in some children.

Other supplements

Psyllium-enriched cereal, garlic, omega-3 fatty acids and soy protein are just some of the other foods or supplements that have been assessed for benefits in FH. The studies that have been undertaken to date are small and inconclusive, and no recommendations for practice can be made currently.

Learning points: hypercholesterolaemia

- *NICE Clinical Guideline 71 provides recommendations on the management of familial hypercholesterolaemia [106]*
- *Treatment aims to reduce total and LDL cholesterol levels through dietary intervention, drug therapy and lifestyle modification*
- *Statins are a safe and effective treatment for children with FH; they should be offered to children by the age of 10 years or the earliest opportunity [106]*
- *Adherence with dietary intervention is variable as symptoms are not experienced during childhood; motivation may be higher in families with a history of parental death from CHD*

Infant Onset Lysosomal Acid Lipase Deficiency (LAL-D)

Fiona J. White

This disorder is also known as Wolman disease.

Enzyme	Lysosomal acid lipase (LAL)
Biochemical defect	Deficiency of LAL prevents the normal lysosomal degradation of cholesteryl esters and triglycerides to produce free cholesterol and fatty acids, which are released into the cell's cytoplasm. To compensate for the apparent lack of cytoplasmic free cholesterol, it is thought there is upregulation of endogenous cholesterol synthesis causing increases in blood lipid levels and further lysosomal storage [130].
Genetics	Autosomal recessive inheritance
Clinical onset presentation, features	Infant LAL-D is a multisystem disorder in which lipids accumulate in organs and tissues, particularly the liver, gastrointestinal tract, spleen, macrophages, blood vessel walls and lungs: • onset of gastrointestinal symptoms, diarrhoea and vomiting, from the first weeks of life resulting in cachexia and severe growth failure and at presentation fulfil the WHO definition for severe acute malnutrition [131, 132] • distended abdomen due to hepatosplenomegaly, progressing to liver failure without treatment • anaemia • deranged clotting (vitamin K deficiency) and other fat-soluble vitamin deficiencies (A, D, E) • calcified adrenal glands • systemic inflammatory disease with high ferritin levels; some cases may have been thought to have haemophagocytic lymphohistiocytosis (HLH) at presentation but is in fact secondary to infant onset LAL-D [133]

Long-term complications and outcome	Infant LAL-D has only had a licenced treatment, enzyme replacement therapy (ERT), since 2015, so long-term outcome data is not yet available: • historically infants with LAL-D died before a year of age, median 3.7 months [134] • with ERT and dietary therapy, survival and growth are improving [131, 135, 136]; the oldest patient surviving of those in the initial clinical trial is 7 years old, functioning normally and attending mainstream school (as of May 2019, author's centre) • although there is improvement in gastrointestinal function, severe dietary fat-restriction remains necessary • oral feeding aversion and reliance on long-term enteral tube feeding is common
Acute management	At diagnosis most infants will be extremely sick due to the underlying disease process and malnutrition. Acute management will depend upon the individual's clinical state, but as a minimum will include: • stopping all dietary lipid intake • correcting any dehydration • correcting any haematological and clotting abnormalities • starting ERT as soon as possible
Drug treatment	ERT: weekly IV infusion of KANUMA® (sebelipase alfa) Supportive treatment for any associated medical issues Fat-soluble vitamin supplementation
Dietetic management Rationale *This is the practice of the author's centre, which other centres treating infant onset LAL-D have also used*	Dietary management is essential alongside ERT. It is based on management of the consequences of abnormal lipid storage due the underlying enzyme defect including: • lipid storage in macrophages within the lamina propria of the small intestine results in blunting and expansion of villi; digestive enzymes and absorptive capacity are reduced causing decreased digestion and absorption of nutrients and persistent frequent diarrhoea [137]: **minimal fat, amino acid, monosaccharide feed** • evidence of protein losing enteropathy (increased faecal alpha-1- antitrypsin) and gut inflammation (increased faecal calprotectin): **high protein intake** • persistent vomiting, probably due to gut dysmotility, and abdominal distension due to hepatosplenomegaly and 'intestinal gas' compromise the feed volume tolerated: **small, frequent or continuous tube feeds are better tolerated** Further details on the practical dietary management are discussed on p. 670:
Nutritional monitoring	• growth: weight, length, occipital frontal circumference (OFC) and mid-upper arm circumference (MUAC) (probably the best growth parameter to measure as it is not affected by organomegaly) • gastrointestinal symptoms • nutritional bloods including: o fat-soluble vitamin status – monthly until levels have normalised and then 3 monthly o red cell EFA status – 3 monthly initially
Emergency regimen	Onset of increased vomiting and/or diarrhoea to the child's norm can rapidly lead to dehydration and should be treated quickly: • stop usual feeds and start oral rehydration solution (ORS) at 120% of child's usual maintenance fluids • take to the emergency room for assessment of dehydration (weight loss), hypernatraemia (urea and electrolytes [U&Es]), acidosis (blood gas): o if blood results are normal, continue with ORS, daily weights and U&Es; reintroduce feeds after 24 hours o if blood results are abnormal, stop enteral feeds. Treat with IV fluids including correcting deficit and any hypernatraemia. Reassess every 12–24 hours. Once diarrhoea reverts to 'normal for individual', reintroduce usual feeds; this can be over 24 hours, titrating with IV fluids. If diarrhoea persists, but weight regained, U&Es and blood gas normal, introduce enteral ORS and reassess in 24 hours • if not re-established on usual feeds within 3 days, consider modified PN as nutritional status can decrease quickly
Clinical management guideline	Not yet published
References	Jones SA, Rojas-Caro S, Quinn AG *et al*. Survival in infants treated with sebelipase Alfa for lysosomal acid lipase deficiency: an open-label, multicenter, dose-escalation study. *Orphanet J Rare Dis*, 2017, **12**(1) 25 [135] Jones SA, Valayannopoulos V, Schneider E *et al*. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. *Genetics Med*, 2015, **18** 452 [134]
Parent support group	www.mpssociety.org.uk/

Dietary management of infant LAL-D

The following is based on the author's practice and experience with the largest single cohort of infant onset LAL-D worldwide and has been used by other centres.

Nutritional intake aims, at least initially, are to provide through modified feeds:

- protein: minimum 4 g/kg/day to account for increased losses and rapid catch-up growth
- lipid: it is probably prudent to avoid giving any fat before ERT starts:
  - LCT is very restricted to provide only EFA and LCPUFA (p. 646)
  - MCT may be tolerated as it is thought to be mainly absorbed through the hepatic portal vein directly to

the liver where it used for energy. Intakes of up to 2 g/kg/day have been used, at least initially, to provide an additional energy source

- carbohydrate: usually as glucose polymer, up to 20% concentration. If increased gradually, from an initial 10%, higher concentrations are tolerated. High CHO concentrations are required for catch-up and maintenance of growth as fat energy intake is very restricted
- sodium: 6–8 mmol/kg/day. Infants usually have low plasma sodium levels and are likely to have increased losses due to diarrhoea. Glucose requires sodium for absorption, so it would, therefore, seem that a high glucose intake will require additional sodium [138]. Urinary sodium measurements can provide a guide to sufficiency of sodium status. Where there are continued fluid and electrolyte losses, i.e. continued diarrhoea, maintaining a urinary sodium–potassium ratio of at least 2:1 is important [139]. The aim is to maintain urinary sodium >20 mmol/L
- micronutrients: ensure meeting reference nutrient intakes (RNI) [36]. Additional supplements of fat-soluble vitamins are often required
- fluids: tolerance of feed volume may be compromised with an enlarged abdomen due to hepatosplenomegaly, and large volume feeds may affect respiratory function. Small frequent feeds or continuous tube feeds are often better tolerated

Lipid intakes long term

It is not known how much fat can be tolerated. Despite ERT and minimal fat intakes, there appears to be ongoing lipid storage in the gut:

- LCT: tolerance to dietary LCT appears extremely limited. In the author's and others' experience, increases in LCT either intentionally, in very small increments, or inadvertently have resulted in worsening clinical condition with onset of increased gastrointestinal symptoms, worsening liver function and declining growth.

  For patients who remain fully reliant on enteral feeds, LCT intake can be restricted to that providing for EFA and LCPUFA requirements. In those who eat LCT, intakes should be as minimal as possible, e.g. 0.5 g/kg/day to a maximum of 5 g/day
- MCT: it is unclear whether some MCT is tolerated or not long term. Small amounts, a maximum of 2 g/kg/day, have been used in infancy and appear to be tolerated. In some cases where growth has remained poor, even with increased total energy intake, removing MCT has improved growth even if the energy deficit is not made up with additional carbohydrate or protein energy [131]

Initial dietary management

Change of feed to an amino acid, monosaccharide (glucose polymer) and minimal LCT feed with moderate MCT content:

- In the UK this requires individualised modular feeds as no suitable amino acid (or peptide)-based commercial feeds are suitable, all having too high LCT and total fat content. Commercial feeds that are available in some countries are Vivonex T.E.N. and Tolerex (Nestle). Practical details for modular feed are given in Tables 30.14 and 30.15
- Many infants will have intestinal failure and, even when changed to an appropriate amino acid-based feed, will continue to have diarrhoea and vomiting and become dehydrated. There should be a prompt decision to stop enteral feeds and start modified PN

Modified PN aiming to provide:

- protein: 4 g protein (0.64 g nitrogen)/kg/day
- glucose: start with approximately 12 g/kg/day and increase by 2 g/kg/day up to approximately 25 g/kg/day;

Table 30.14 Amino acid, monosaccharide (glucose polymer) and minimal LCT feed with moderate MCT content (per 100 mL, based on full feeds of 100 mL/kg/day).

	Amount g	Energy kcal (kJ)	Protein g	CHO g	LCT g	MCT g	Na mmol	K mmol
Complete Amino Acid Mix (Nutricia)	5	16 (67)	4.1	0	0	0	0	0
Glucose polymer, e.g. Vitajoule (Vitaflo)	18	68 (284)	0	17.1	0	0	0	0
Liquigen (Nutricia)	4	18 (75)	0	0	0	2	0.05	0
ORS, e.g. Dioralyte powder (Sanofi)	2.5	7 (29)	0	1.8	0	0	6	2
KeyOmega (Vitaflo)	4 g*	2 (8)	0	0.3	0.08	0	0.06	0
Paediatric Seravit (Nutricia)	5	1 (4)	0	1.3	0	0	0	0
+ water to 100 mL	Per 100 mL	112 (467)	4.1	20.5	0.08	2	6.1	2

ORS, oral rehydration solution.
*Can be added to 1 feed per day or to the full 24 hour volume.

Table 30.15 Commercially available amino acid, monosaccharide and minimal LCT formulas (available in some countries outside UK).

Per 100 mL Standard dilution	Energy kcal (kJ)	Protein g	CHO g	LCT g	MCT g	Na mmol	K mmol
Vivonex T.E.N. (Nestle Health Sciences)	100 (420)	3.83	20.6	0.3	0	3.2	2.3
Tolerex (Nestle Health Sciences)	100 (420)	2.05	22.6	0.2	0	2.2	3.0

this will depend on energy needs to gain weight and grow. Blood glucose levels should be monitored
- lipid: avoid any lipid until ERT has been started:
  - restrict fat to 1 g/kg/day using a lipid source containing MCT, e.g. SMOF (30% MCT); there are other MCT lipid emulsions available
  - account for the lipid content of the fat-soluble vitamin source in the total lipid intake
- sodium: increased requirements, usually at least 6 mmol/kg/day

Once diarrhoea subsides (vomiting usually stops too), trophic feeds (1 mL/kg/hour) of ORS should be started to maintain gut integrity either by continuous enteral feed or orally if the infant will take it, divided into 6–8 feeds over the day (total 24 mL/kg/day). This fluid should be additional to that provided by the PN.

Re-establishing oral/enteral feeds once growth rate is satisfactory:

- Enteral feeds are started, using an amino acid- and monosaccharide-based, minimal LCT and MCT feed as described above and in Table 30.14
- The feed should be increased gradually as tolerated, e.g. by 1–2 mL/hour every 24–48 hours as tolerated
- Decrease PN as enteral feeds are increased

It is important to be aware that vomiting and increased stool output will occur with the reintroduction of oral/enteral feeds. Feeds should not be decreased unless either dehydration is occurring (indicated by significant weight loss or biochemical evidence) or MUAC is static or decreasing.

Ongoing dietary management

Introduction of whole protein, disaccharide-containing minimal fat feeds can be considered once gastrointestinal symptoms are very much reduced, and growth is satisfactory. This may be after many months or even years. Feed changes should be made slowly, titrating with the current feed, e.g. starting with 10% of the new feed and 90% of the current feed with 10% increases weekly as tolerated. Some may not tolerate the change and get onset of increased diarrhoea; the introduction should be stopped and a return to the previously tolerated feed. Suitable formulas would be:

- Low Fat Module (Nutricia), basic-f (Milupa), minimal fat feeds (Table 30.2)
- a modular feed based on skimmed milk powder
- fat-free 'juice-style' enteral supplements (>1 year age), e.g. PaediaSure Plus Juce (Abbott), Ensure Plus Juce (Abbott), Fortijuce (Nutricia) and Fresubin Jucy Drink (Fresenius) (Table 12.5)

Probiotics have helped abdominal distension, due to large amounts of 'gas' seen in many infants and older children.

Weaning onto a very low fat diet can start around 6 months of age or once re-established on enteral feeds:

- suitable very low fat weaning foods (Table 30.3, excluding the advice regarding overnight feeding)
- continuing a minimal fat diet as weaning progresses; for discussion of long-term lipid intake, see p. 671. Tables 14.13 and 14.14 provide information on free foods for a minimal LCT diet and LCT content of foods. Table 30.5 gives information on a minimal LCT diet, and a sample minimal fat meal plan containing ≤10 g LCT is given in Table 30.12. Portion sizes may need controlling to maintain the daily LCT allowance. Parents can be taught how to calculate portion size from nutritional information given on food labels (p. 649)
- depending upon growth and intake of solids, it may be possible to reduce feed volume; generous protein intakes >RNI [36] should probably be continued
- the addition of fibre to feeds should be considered if the child does not eat any significant amount; in older children who no longer have watery diarrhoea, but have unformed stools, the addition of fibre has helped
- oral feeding aversion is common, particularly if there has been a very protracted period of frequent vomiting

Learning points: infant onset lysosomal acid lipase deficiency

- *Treatment is a combination of enzyme replacement and dietary therapy*
- *Nutritional therapy is complex*
- *Any changes in dietary therapy must be made quickly if things are going wrong and slowly and gradually when things are going well*
- *Treated infant onset LAL-D is a new phenotype; knowledge and evidence for best management is being gained; consensus guidelines on management are in progress*

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

31 Emergency Regimens for Inherited Metabolic Disorders

Marjorie Dixon

Introduction

This chapter provides information on emergency regimens (ER), which form an essential part of the management of some disorders of intermediary metabolism, both the intoxication type and those involving energy metabolism (p. 508). Idiopathic ketotic hypoglycaemia (IKH) is also included in this chapter. For metabolic disorders treated by ketogenic diets, e.g. glut 1 deficiency syndrome (GLUT1DS) or pyruvate dehydrogenase deficiencies (PDHD), illness and excess ketone management plans are discussed elsewhere (p. 344).

For some inborn errors of intermediary metabolism, any physiological stress situation, such as intercurrent infection, surgery or trauma, combined with a poor oral intake and fasting can precipitate severe metabolic decompensation with possible neurological sequelae. Metabolic decompensation, the accumulation of disorder specific toxic metabolites causing metabolic encephalopathy, is primarily a consequence of the effects of catabolism and/or the failure to utilise or produce sufficient energy. Under normal conditions, as fasting continues, glycogen stores are depleted, and gluconeogenesis and ketogenesis become the main energy supply. This process occurs more rapidly in infants and younger children. To help prevent metabolic decompensation, an ER is given to provide energy and to minimise fasting in situations when dietary energy intake is reduced, commonly illness [1]. The correct use of ER can be extremely effective and is known to reduce hospital admissions and episodes of metabolic decompensation [2, 3].

Emergency regimen guidelines

Disorder specific emergency regimen guidelines can be accessed from www.bimdg.org. These provide information on the disorder and intravenous (IV) and oral ER management for use by an emergency department or paediatric assessment unit/ward. They are due to be updated in 2020.

Principles of the emergency regimen

The ER provides an exogenous energy source to promote anabolism and:

- prevent an energy deficit and hypoglycaemia when energy substrates cannot be produced from their usual metabolic pathways, e.g. glucose from glycogenolysis and/or gluconeogenesis in glycogen storage disorders, ketones in defects of fatty acid oxidation and glucose via gluconeogenesis in fructose 1,6-bisphosphatase deficiency
- reduce production of toxic metabolites from protein and amino acid catabolism, e.g. ammonia in urea cycle disorders (UCD), leucine in maple syrup urine disease (MSUD) and organic acids in methylmalonic acidaemia (MMA), propionic acidaemia (PA), isovaleric acidaemia (IVA) and glutaric aciduria type 1 (GA1)
- reduce production of potentially toxic metabolites from lipolysis, e.g. accumulation of long chain acyl carnitines and free fatty acids in long chain fatty acid oxidation disorders

The child's usual metabolic treatment medicines are continued but may temporarily be increased in some disorders to help reduce accumulation of toxic metabolites, e.g. nitrogen scavengers to prevent hyperammonaemia in UCD, L-carnitine in GA1 to form glutarylcarnitine and so prevent high concentrations of glutaric acid. Medicines are also adjusted based on results of blood levels monitored during illness, e.g. blood gases in organic acidaemias (OAA).

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Some blood tests can be monitored at home, such as glucose and ketones, and help in making decisions about ongoing management. Trials are currently under way to assess the use of home blood ammonia monitors. Additional medicines are given to treat the underlying illness, such as antipyretics for fever.

Disorders requiring ER are described in (Table 31.1) as:

- standard ER only
- standard ER with disorder specific instructions, such as branched chain-free amino acids in MSUD, additional fluids in MMA. Disorder specific therapies are described in the chapters detailing the treatment of these disorders
- non-standard ER for citrin deficiency (p. 589), infantile onset lysosomal acid lipase deficiency (Wolman disease) (p. 669)

Detailed information about disorders and management are provided in the related chapter.

Composition of emergency regimens

The standard ER is a solution of glucose polymer, simple to administer, rapidly absorbed, usually well tolerated and suitable for most disorders. The carbohydrate (CHO) concentration (10%–25%) of the solution given depends upon the age of the child, with the lowest concentrations given to infants and younger children (Table 31.2). The standard ER must not be continued for long periods of time (ideally 24–48 hours) because it does not provide adequate nutrition. If use is prolonged and/or frequent, protein depletion, particularly in children on low protein diets, can develop surprisingly rapidly. Severe lactic acidosis caused by acute thiamin deficiency has been reported in two patients with PA who had high energy parenteral nutrition (PN) to restore anabolism, but no vitamins were given [4].

Energy

The precise energy requirements to prevent catabolism in metabolic patients during illness are not known. Energy requirements increase during illness and specifically with a fever, so they are likely to exceed the child's usual energy intake. Bodamer *et al*. [5] reported that resting energy expenditure was increased by up to 30% in two children with MMA during acute illness. At lower CHO concentrations, standard ER solutions do not always provide the estimated average requirement (EAR) for energy for age [6]. Therefore, a higher concentration of CHO or greater volume may be necessary to prevent catabolism. The standard ER may, however, be adequate to prevent hypoglycaemia providing feeding is frequent. Van Hove *et al*. [2] recommend higher concentrations of glucose polymer solutions be given to younger children to provide more energy (Table 31.2). Enteral ER is preferable to IV management as higher CHO concentrations, therefore, more energy can be given and it is less invasive. Nevertheless, IV fluids are essential in certain circumstances, such as vomiting, metabolic acidosis and hyperammonaemia seen in OAA.

Fat

Fat can provide an additional energy source but may be less well tolerated, particularly in the child who is vomiting as gastric emptying will be delayed. However, some metabolic centres successfully use a protein-free feed containing fat, such as Energivit, in OAA and UCD. The ER for MSUD and GA1 may contain fat from the protein substitute, protein-free milk substitute or Calogen. Fat (long and/or medium chain) is contraindicated in some disorders of fatty acid oxidation (Chapter 30).

Fluids

The daily fluid volume of glucose polymer solution given depends on age, weight and clinical condition of the child. The suggested figures are maintenance fluid requirements (Table 31.2). Higher fluid volumes will be needed in certain circumstances such as dehydration caused by diarrhoea and/or vomiting, rhabdomyolysis with myoglobinuria in long chain fatty acid oxidation disorders (LC-FAOD), and in MMA to prevent dehydration and protect the kidneys.

Oral rehydration solutions

In cases of acute diarrhoea, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [7] recommends oral rehydration for 4 hours, reassessment and then a return to normal diet. A longer period of rehydration may be necessary. The energy content of oral rehydration solutions (ORS) is very low (approximately 7 kcal [30 kJ]/100 mL) and, therefore, insufficient to prevent catabolism. If an ORS is prescribed for a metabolic patient, then parents need to seek advice from their metabolic team about using this alongside the ER. It is likely that any metabolic child with gastroenteritis will require admission to hospital for IV fluids. For mild gastroenteritis reconstituted ORS sachets can be given in addition to the standard ER feeds. ESPGHAN recommends an osmolality of 200–250 mOsm/kg H_2O for an ORS; adding glucose polymer would increase the osmolality. Too concentrated a solution of glucose polymer will be hyperosmolar, worsen diarrhoea and exacerbate the effects of the illness. ORS with glucose polymer added to a final concentration of 10% CHO has an osmolality of approximately 320 mOsm/kg H_2O. Such a feed will be low in energy and may not be suitable for all patients. Van Hove *et al*. [2] report successful use of such feeds in patients with mild diarrhoea. In addition, generous amounts of sodium will be provided from medicines such as sodium benzoate in UCD, sodium bicarbonate in MMA and ketone bodies in multiple acyl-CoA dehydrogenation deficiency (MADD).

Practical provision of ER

Glucose polymer is available as a powder, e.g. Maxijul, Polycal, and Vitajoule. Pure liquid glucose polymer solutions such as Polycal liquid have a very high CHO content

Table 31.1 Inherited metabolic disorders requiring an emergency regimen.

Disorder group	Disorder	Emergency regimen Usual medicines and doses	Disorder specific therapy
Organic acidaemias (Chapter 28)	Propionic acidaemia	ER* Usual medicines may be increased, e.g. carnitine	
	Methylmalonic acidaemia B_{12} responsive and B_{12} non-responsive	ER* Usual medicines may be increased, e.g. sodium bicarbonate, carnitine	Usual daily fluids or ≥120% maintenance fluids if there is chronic kidney disease
	Isovaleric acidaemia	ER* Usual medicines may be increased, e.g. carnitine and/or glycine	
	Glutaric aciduria type 1	ER** Carnitine, double standard dose	Lysine-free, low tryptophan amino acids, usual dose, if usually on supplements Aggressive treatment of pyrexia to prevent neurological damage [3]
Amino acid disorders (Chapter 28)	Maple syrup urine disease	ER**	Branched chain-free amino acids supplements, usual dose Isoleucine and valine supplements, at least usual dose, often increased
Urea cycle disorders (Chapter 28)	NAGS, CPS, OTC deficiencies, ASA, citrullinaemia	ER* Nitrogen scavengers and arginine may be increased. Carbaglu in NAGS	
	Arginase deficiency	ER* Nitrogen scavengers may be increased	
	Hyperornithinaemia, hyperammonaemia, HHH	ER* Nitrogen scavengers may be increased	
	Citrin deficiency (p. 589)	Non-standard ER	No glucose polymer ER – high fat and protein, low CHO Full fat cow's milk has suitable energy ratio (protein 20%, fat 53%, CHO 27%) IV fluids to be CHO-free
	Lysinuric protein intolerance (p. 594)	ER Citrulline and nitrogen scavengers, may be increased	
Fatty acid oxidation defects (Chapter 30)	β-oxidation defects: LCHAD, VLCAD, MTP deficiencies	ER*	No long chain fat
	Carnitine pathway disorders: CPTI, CPTII, CACT deficiencies	ER*	No long chain fat
	Carnitine transporter deficiency	ER*	
	Multiple acyl-CoA dehydrogenase deficiency	ER*	No long chain fat
	Malonyl-CoA decarboxylase deficiency	ER*	No long chain fat
	Medium-chain acyl-CoA dehydrogenase deficiency	ER*	No MCT

(continued overleaf)

Table 31.1 *(continued)*

Disorder group	Disorder	Emergency regimen Usual medicines and doses	Disorder specific therapy
Disorders of ketolysis (Chapter 30)	HMG-CoA synthase deficiency HMG-CoA lyase deficiency	ER*	Avoid MCT
Ketone body utilisation defects (Chapter 30)	SCOT deficiency beta-ketothiolase (T2) deficiency	ER*	Avoid MCT
Glycogen storage disorders (Chapter 29)	Glycogen storage disorders (GSD) types 0, I, III, VI, IX, Fanconi Bickel syndrome (Glut2 deficiency)	ER*	ER to provide at least adequate CHO to meet basal glucose requirements or child's usual requirement Avoid excess CHO to prevent hyperglycaemia. Usual CHO requirement
Miscellaneous			
Fructose 1,6-bisphophatase deficiency (Chapter 29)		ER*	Avoid fructose, sucrose and sorbitol (drinks and medicines) and fat during acute period
Glycerol kinase deficiency (Chapter 29)		ER*	Avoid fat during acute period
Ketotic hypoglycaemia (Chapter 31)		ER*	

NAGS, *N*-acetylglutamate synthase; CPS, carbamoyl phosphate synthetase; OTC, ornithine transcarbamylase; ASA, argininosuccinic aciduria; HHH, hyperornithinaemia, hyperammonaemia, homocitrullinuria; CHO, carbohydrate; IV, intravenous; LCHAD, long chain 3-hydroxyacyl-CoA dehydrogenase; VLCAD, very long chain acyl-CoA dehydrogenase; MTP, mitochondrial trifunctional protein; MCT, medium chain triglycerides; CPT, carnitine palmitoyltransferase; CACT, carnitine-acylcarnitine translocase; HMG, 3-hydroxy-3-methylglutaryl-CoA synthase or lyase; SCOT, succinyl-CoA:3-oxoacid-CoA transferase.
*Emergency regimen is the standard emergency regimen shown in Table 31.2.
**Emergency regimen is based on standard emergency regimen plus precursor-free amino acids (see related chapter for specific disorder).

Table 31.2 Standard emergency regimens.

Age (years)	Glucose polymer concentration (% CHO) [1]	Energy/100 mL (kcal)	Energy/100 mL (kJ)	Osmolality* (mOsm/kg H_2O)	Suggested daily fluid volumes for age/weight
Up to 1	10	40	165	103	<6 months 150 mL/kg up to a maximum of 1200 mL
					7–12 months 120–150 mL/kg up to a maximum of 1200 mL
1–2	15	60	250	174	11–20 kg: 100 mL/kg for first 10 kg, plus 50 mL/kg for next 10 kg
2–9	20	80	335	245	>20 kg: as above for first 20 kg + 25 mL/kg thereafter up to 2500 mL maximum
>10	25	100	420	342	
Administration of ER		Divide total volume over 24 hours: give 1–3 hourly orally or via feeding tube (bolus or continuously)			
Van Hove *et al*. [2] suggest alternative glucose polymer % CHO: 0–12 months 15%, 1–3 years 20%, 3–6 years 25%, 6–12 years 25% or 30%, 12–15 years 30%, >15 years 30%					

*Data provided by Scientific Hospital Supplies International Limited, *Clinical Paediatric Dietetics*, 3rd edn.

Table 31.3 Example emergency regimen for a 4-year-old girl with idiopathic ketotic hypoglycaemia.

A 4-year old with ketotic hypoglycaemia who is unwell with a sore throat and not eating well
Weight = 16 kg
ER: 20% glucose polymer solution
Preparation: 1 sachet of S·O·S 20 (or 4 × 5 g scoops of glucose polymer*), add water to 200 mL, flavour with squash as desired
Fluids: 1300 mL/24 hours of glucose polymer solution
Day and night: 110 mL × 2 hourly × 12 drinks or 160 mL × 3 hourly × 8 drinks
ER provides: 1040 kcal (4.4 MJ), EAR for energy = 1290 kcal (5.4 MJ) [6]
Day 1: Give full ER for 24 hours and encourage to eat, if appropriate
Day 2: On recovery, reintroduce usual diet, continue some ER drinks, particularly at night, with guidance on volume and frequency, until eating normally again

*Glucose polymer powders contain approximately 95% CHO; if using 20 g powder the CHO concentration is 19%.

(61.9%) and are not suitable for ER. Parents should be taught to measure glucose polymer powder accurately using handy scoop measurements or weighing scales and then to add water to a final volume (usually 200 mL). Recipes for individual feeds/drinks or larger volumes should be provided. Pre-measured, colour-coded sachets of glucose polymer are available: S·O·S 10, 15, 20, 25; the numbers indicate the percentage of CHO concentration once prepared. One sachet is made up with water to 200 mL. Sachets are more accurate than using scoops or weighing [8]. They are more convenient, portable and easily stored for use in an emergency situation at, e.g. nursery or school. It is worthwhile trialling the glucose polymer solution when the child is well in a non-emergency situation to ascertain if they will take it and to familiarise the parent with the reconstitution process. Glucose polymer solution can be flavoured with squash to help palatability. Table 31.3 gives an example of an ER for a 4-year-old girl with ketotic hypoglycaemia.

Commercial drinks

Some children dislike the taste of glucose polymer (even when flavoured) and prefer commercial drinks, but the CHO concentrations of these are lower than the standard ER. Commercial drinks can be used but with caution. Glucose polymer powder must be added to the required CHO concentration, e.g. to make a 20% CHO ER drink with fruit juice, 10 g glucose polymer (using a scoop to measure) is added to 100 mL fruit juice (10 g CHO/100 mL). Written instructions on preparation of the chosen commercial drink need to be given. As CHO concentrations of drinks can change and alternative flavours and formats of the same product have different CHO concentrations, parents must be taught to read the nutrition information label for the CHO concentration per 100 mL and to always check before using. Low calorie, sugar-free drinks and no added sugar drinks contain very little or no CHO and should be avoided. Parents need to be informed of this and to seek advice from their metabolic team if prescribed locally.

Implementation of ER: guidelines

At home

- Commence the ER at home at the first signs of illness, particularly if appetite is reduced or usual feeds not tolerated (e.g. colds, flu-like symptoms, viral infections, any illness associated with fever >37 °C, chest infection, tonsillitis, gastroenteritis)
- For minor illnesses the child should be assessed by their primary care team
- Give ER orally or via tube or both depending on intake and tolerance
- Administer frequently at 2–3 hourly intervals day and night to optimise energy intake and reduce the period of fasting
- 2–3 hourly overnight feeding may be difficult to achieve, particularly if there is no feeding tube, and more realistic targets should be considered, if feasible
- For most disorders the child's usual diet or feed should be reintroduced within 24–48 hours of commencing the ER
- While the child's appetite is returning to normal, some ER feeds should still be given to reduce the period of fasting (particularly at night) and to maximise energy intake
- Children with OA and UCD on low natural protein diets are often managed in hospital when unwell, but if at home a guide is:
  - day 1: ½ full ER volume and ½ usual protein feed or natural protein intake
  - day 2: return to full protein allowance (or more rapidly if clinically indicated), taking care to ensure an adequate energy intake
- Vitamin and mineral supplements should also be restarted, if they have been stopped
- Close liaison, at least daily with the metabolic team, is essential when a child is unwell at home to assess progress, tolerance and intake of ER and clinical state and to advise on reintroducing the usual diet

Tube feeding

- Tube feeding should be used if oral ER volume is insufficient; this may necessitate a hospital admission
- Continuous nasogastric (NG) feeding is generally better tolerated than bolus feeds, but is not safe at home for overnight feeds
- Some parents prefer to be taught to do NG feeding at home solely for provision of ER
- Parents need to remain confident and competent in passing an NG tube to administer the ER feed
- Some children may have a tube passed in the local hospital, observed for a few hours and discharged to continue this treatment at home if already trained to give NG feeds

Hospital admission

- If the child persistently vomits and is not recovering, they should go to their local hospital promptly for assessment
- For most disorders stabilisation with IV fluids of 10% glucose and 0.45% saline by peripheral drip or more concentrated glucose through a central line is needed
- The metabolic team should contact the local paediatric services to inform them the child needs urgent medical assessment, thus avoiding delay in starting appropriate treatment
- Placement of a portacath may be considered in those who have frequent episodes of illness and if IV access is difficult. There is a risk of line infection precipitating metabolic decompensation, so the benefits need to be carefully considered
- The oral ER or usual fluids/diet is reintroduced once metabolically stabilised. This needs to be done promptly as typically it will be beyond the recommended 24–48 hour period of ER only
- If the child has a low protein feed, ideally the usual full strength feed (not ER, as this prolongs protein deprivation) should be titrated directly against the IV 10% glucose fluids, gradually as tolerated, back to normal feeds before discharge
  Titration example: start with 10 mL/hour of usual feed concurrently decreasing IV fluids by 10 mL/hour; then continue to increase and decrease each respectively by 10 mL/hour every 4 hours until full usual feeds are established. Volumes to titrate can be lower or higher depending on the age of child, usual feed volume and expected tolerance. This process may take more than 24 hours
- If oral or enteral feeds cannot be re-established, then an early resort to PN is indicated, e.g. pancreatitis and metabolic acidosis with vomiting are common indications for PN in MMA and PA
- Weaning from PN to the usual low protein feeds needs to be carefully planned. Ideally the PN prescription will be similar in composition to the enteral feed. Clear guidance on volume rate decreases of the Vamin/glucose solution and lipid solution vs. feed volume increases will be required. This will ensure the correct protein and adequate energy is always achieved
- Poor growth and nutritional deficiencies will occur in patients on low protein diets who have repeated infections and are frequently on their ER. It may be necessary to increase protein intake temporarily when the child is well to compensate for this

Instructions for parents

Management of intercurrent infections can be an anxious and difficult time for parents, knowing their child is at greater risk of metabolic decompensation and/or hypoglycaemia. To make this easier, parents can be taught a three-staged action plan to help with decision making [1]. Parents are asked to phone the

metabolic team (doctor, dietitian, clinical nurse specialist) for advice at an early stage and also to consult their primary care team for assessment and treatment of common childhood illnesses. One or more of the metabolic team will make contact with the parents throughout an episode of illness:

1. If the parents are unsure whether their child is showing the first signs of impending illness (pallor, dark eyes, lethargy, irritability, loss of appetite, fever, headache, aches and pain, cough, sore throat or ears), then a single ER drink is given as a precaution. Clinical observations are reported to be generally better than biochemical measurements for detecting decompensation; subtle changes in behaviour are usually the earliest signs of this and are most easily detected by parents [9]. The child's clinical state is then reviewed regularly within 1–2 hours.
2. If on reassessment their child has improved, the normal diet is resumed; if, however, their child has deteriorated or shown no signs of improvement, the full ER is commenced for a period of 24 to a maximum of 48 hours, always alert for signs of improvement or deteriorations. Once their child is recovering, parents are instructed how to reintroduce the usual diet.
3. If the child is not tolerating the ER (i.e. refusing ER drinks, vomiting, persistently high temperature, not responding or becoming encephalopathic), they should be taken to their local hospital for assessment. Parents should take all ER information and products with them.

Parents are taught to recognise signs of encephalopathy such as disorientation and poor responsiveness, accompanied by a glazed look. Measurement of blood glucose is helpful if there is a risk of hypoglycaemia, e.g. glycogen storage disorders, but is not appropriate in disorders of fatty acid oxidation where hypoglycaemia is a late finding and the child may already be very unwell before this develops. Blood glucose tests can be inaccurate at low levels. Therefore, if there are clinical signs suggesting hypoglycaemia, this should always be treated immediately. Blood ketones may be present during illness and used as a marker of catabolism (and, therefore, a possible surrogate marker of metabolic stability) in some disorders such as MSUD and OAA. Some parents are taught to monitor ketones at home. Ketone monitoring in MSUD is described on p. 540. Monitoring of temperature is important and should be treated in the normal way.

It is essential that there is close liaison and good communication between the metabolic centre, the local hospital team and parents to help with management. It is also useful to organise open access to the local hospital's paediatric ward. Parents should be given written instructions on implementation of the ER including recipes, suggested fluid volumes for increases with age or weight, feeding frequency, contact telephone numbers, an initial and provision for ongoing supply of glucose polymer and a copy of the British Inherited Metabolic Diseases Group (BIMDG) emergency protocol as a 'parent-held guideline'. Use and understanding of ER, instructions and recipes need to be regularly reviewed with parents in outpatient clinics and updated in accordance with the child's current dietary treatment, age and clinical condition. If a child is reported to be frequently on their ER, this warrants further investigation. A MedicAlert bracelet may be useful for some children.

Holiday and travelling overseas

Families can travel abroad, but it is best they go to countries that have expertise in the management of metabolic disease, should their child become unwell. This needs to be discussed with the metabolic team at an early stage of planning a trip. Parents must take all ER products and up-to-date medical and dietetic management information and have details for a hospital and consultant to go to in the event of an emergency. Sensible precautions need to be taken on holidays abroad, particularly in hot countries, to reduce the risk of dehydration and infections. ORS is essential because of an increased risk of gastroenteritis.

Learning points: emergency regimens

- *ER should be used during episodes of illness to prevent metabolic decompensation and or hypoglycaemia*
- *The standard ER is suitable for most disorders, but some require additional specific ER instructions*
- *Emergency guidelines (IV and enteral) can be accessed from www.bimdg.org*
- *Good daily communication is needed between parents, metabolic team and local paediatric hospital team to optimise management*

Idiopathic ketotic hypoglycaemia

IKH is the most common cause of hypoglycaemia beyond infancy. Children typically present between 18 months and 7 years of age with an episode of hypoglycaemia accompanied by high levels of ketones in plasma and urine, precipitated by a period of prolonged fasting often associated with intercurrent illness. Seizures may occur, but neurological sequelae are rare [10]. IKH improves with age and rarely manifests beyond about 8 years of age [11]. The prognosis is generally good, and some children never experience a second episode. IKH is considered to be due to a failure to sustain sufficient hepatic glucose production [10, 12]. This may, however, just represent the 'lowest percentile of normative distribution of fasting tolerance in children', and, as such, IKH should not be classified as a pathological condition; diagnosis is only made after exclusion of any specific endocrine or metabolic disorder that can cause a ketotic hypoglycaemia [12].

Presentation and management

The clinical history is characteristic. Normally the child will present acutely to their local hospital A&E department with a history of being unwell, having gone to bed with a poor food intake the day/evening before, and the next morning is pale, floppy and unrousable. On arrival at hospital they are found to be hypoglycaemic. This is treated immediately with either IV glucose, or oral glucose such as Glucogel (a 40% dextrose gel) rubbed into the buccal cavity, or a sugary drink. The child usually responds promptly to glucose. A short stay in hospital on IV fluids and for observation may be needed until the child recovers and begins to eat and drink normally again. Before discharge parents should be advised on the use of the standard ER and their child referred to a specialist metabolic centre for a diagnosis of IKH to be made or excluded.

Dietetic management: advice to parents

- Implement standard ER during episodes of illness to prevent fasting and risk of hypoglycaemia
- Provide written ER instructions and supplies of glucose polymer powder
- Recognise the early warning signs of hypoglycaemia such as irritability, sweatiness, dizziness, confusion, pallor and drowsiness
- Specialist nurses/doctors to advise on use of dextrose gel to treat the semi-conscious or uncooperative child
- In the well child healthy eating with regular meals (three main meals) including starchy foods
- Avoidance of prolonged overnight fasts by giving a bedtime snack and not to miss breakfast (this may change with results of fasting studies, see below)
- Give more frequent feeding if the appetite is poor and during illness
- Management of hypoglycaemia: give 10–20 g CHO of oral glucose from glucose polymer or equivalent CHO drink followed by a starch snack

Fasting tests and management

Fasting tests are commonly used to help establish the cause of hypoglycaemia and fasting tolerance [13, 14]. Tests are performed under controlled conditions in hospital, usually by a specialist metabolic or endocrine team. Younger children have a faster decrease in blood glucose levels and faster increase in ketone body levels than older children; thus fasting tolerance improves with age [15]. The results can help establish the diagnosis and determine the maximum safe fasting time for the child at that age. Most children with IKH will not develop hypoglycaemia during the fasting test. If on fasting the child does become hypoglycaemic, further dietary intervention is necessary, usually at night, by either:

- reducing the length of the overnight fast and giving a starch-rich bedtime snack and early breakfast
- giving the above plus provision of a high CHO drink (at least 10% concentration) or milk drink in the middle of the night
- giving a dose of 1.0–1.5 g/kg of uncooked cornstarch (UCCS) before bed. Practical aspects of giving UCCS are described on p. 613

A small number of children with IKH complain of hypoglycaemic symptoms even when completely well. Parents often just treat these symptoms with a high CHO drink or food, without knowing the actual blood glucose level. McSweeney *et al*. [16] reported that a continuous glucose monitoring system (CGMS) over several days at home provided more real-time information and helped identify the true incidence of hypoglycaemia in children with IKH, despite them having a normal fasting test in hospital. CGMS enabled a more individualised treatment plan to be given. The use and understanding of ER, instructions and recipes need to be regularly reviewed in outpatient clinics and updated in accordance with age and clinical condition. Follow-up also allows identification of further possible hypoglycaemic episodes necessitating repeat investigation or further dietary manipulation.

References, further reading, guidelines, support groups and other useful links are on the companion website: **www.wiley.com/go/shaw/paediatricdietetics-5e**

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