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# Pediatric Nutrition in Practice

2nd, revised edition

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Co-Editors

**J. Bhatia**

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**Berthold Koletzko** Munich

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# **Pediatric Nutrition in Practice**

2nd, revised edition

Volume Editor

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## Preface

There is no other time in life when the provision of adequate and balanced nutrition is of greater importance than during infancy and childhood. During this dynamic phase of life characterized by rapid growth, development and developmental plasticity, a sufficient amount and appropriate composition of substrates both in health and disease are of key importance for growth, functional outcomes such as cognition and immune response, and the metabolic programming of long-term health and well-being. While a number of excellent textbooks on pediatric nutrition are available that provide detailed accounts on the scientific and physiologic basis of nutrition as well as its application in clinical practice, busy physicians and other health care professionals often find it difficult to devote sufficient time to the elaborate and extensive study of books on just one aspect of their practice. Therefore, we developed this compact reference book with the aim to provide concise information to readers who seek quick guidance on practically relevant issues in the nutrition of infants, children and adolescents.

The first edition was a great success, with more than 50,000 copies sold in English, Chinese, Russian and Spanish editions. Therefore, we prepared a thoroughly revised and updated second edition with a truly international perspective to address demanding issues in both affluent and economically challenged populations around the world. This could only be achieved with the enthusiastic input of a global editorial board. I wish to thank my co-editors very much indeed for their dedicated help and support in developing this project as

well as for the great and very enjoyable collaboration. I am also most grateful to the authors from all parts of the world, who are widely recognized experts in their fields, for dedicating their time, effort, knowledge and experience in preparing their chapters. It has been a great pleasure to work closely with the team at Karger publishers, including Stephanie König, Tanja Sebuk, Peter Roth and others, who did a fantastic and truly professional job in producing a book of outstanding quality. Finally, I wish to express my thanks to the Nestlé Nutrition Institute and its representatives Dr. Natalia Wagemans and Dr. Jose Saavedra for providing financial support to the publisher to facilitate the wide dissemination of this book. I am particularly grateful to the Nestlé Nutrition Institute as it supported the editors and authors in making their fully independent choices with regard to the content and course of the book and its chapters.

It is the sincere hope of the editors that the second edition of this book will again be useful to many health care professionals around the world, and that it will contribute to further enhancing the quality of feeding for healthy infants and children as well as improving the standards of nutritional care for sick children. We are keen to obtain feedback on this book from you, the readers and users, including suggestions on which aspects could be improved even further in future editions. Please do not hesitate to contact the publisher or the editors with your comments and suggestions. Thank you very much, and enjoy reading the book!

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# 1.1 Child Growth

Kim F. Michaelsen

1

### Key Words

Weight · Height · Body mass index · Obesity · Stunting · Wasting · Growth monitoring · Insulin-like growth factor 1

### Key Messages

- Growth is a sensitive marker of health and nutritional status throughout childhood
- Growth monitoring is important both for children with disease conditions and for healthy children
- Early growth is associated with long-term development, health and well-being
- Breastfed infants have a slower growth velocity during infancy, which is likely to have beneficial long-term effects

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### Introduction

Growth is a typical characteristic of childhood; it is also a sensitive indicator of a child's nutritional status. Deviations in growth, especially growth restriction, but also excess fat accumulation typical of obesity, are associated with greater risk of disease both in the short and the long run. Monitoring growth is therefore an important tool for assessing the health and well-being of children, especially in

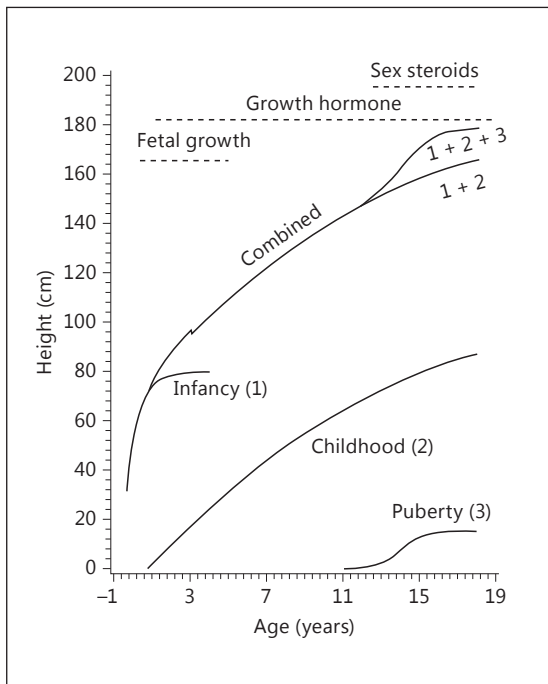
countries with limited access to other diagnostic tools. It is also important in more advanced clinical settings, but is often neglected, favouring more expensive, sophisticated examinations.

### Growth of the Healthy Child

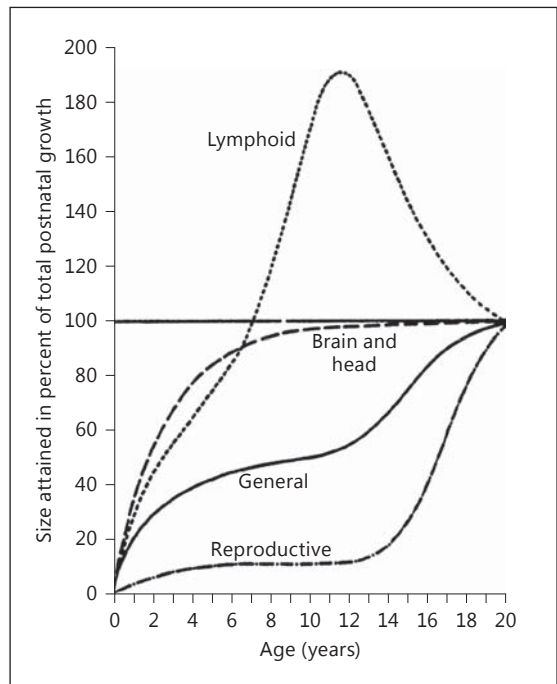
Growth during early life can be divided into periods: intrauterine, infancy, childhood and adolescence. Each period has a characteristic pattern and specific mechanisms that regulate growth (fig. 1) [1]. Nutrition, both in terms of energy and specific essential nutrients, exerts a strong regulatory effect during early life, growth hormone secretion plays a critical role throughout childhood and, finally, growth is modified by sex hormones during puberty.

Insulin-like growth factor 1 mediates the effect of growth hormone on growth, but insulin-like growth factor 1 release can also be influenced directly by nutrients. Insulin, which has a potent anabolic effect on fat and lean tissue gain, is also positively associated with childhood growth. Length and weight gain velocity is very high during the first 2 months after birth, with median monthly increments of about 4 cm and

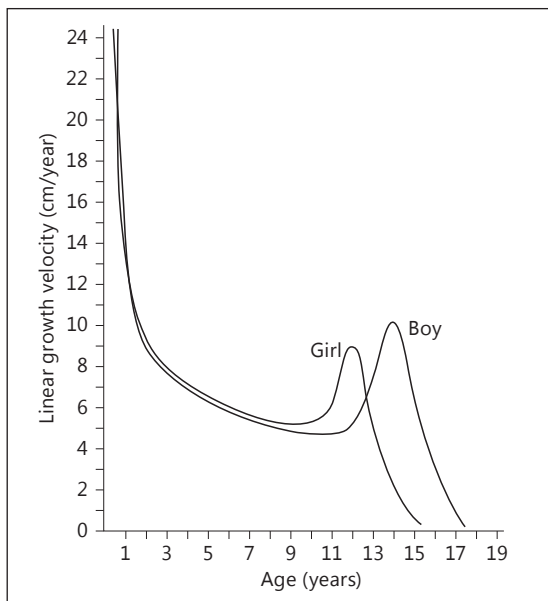




**Fig. 1.** The infancy-childhood-puberty growth model by Karlberg [1].



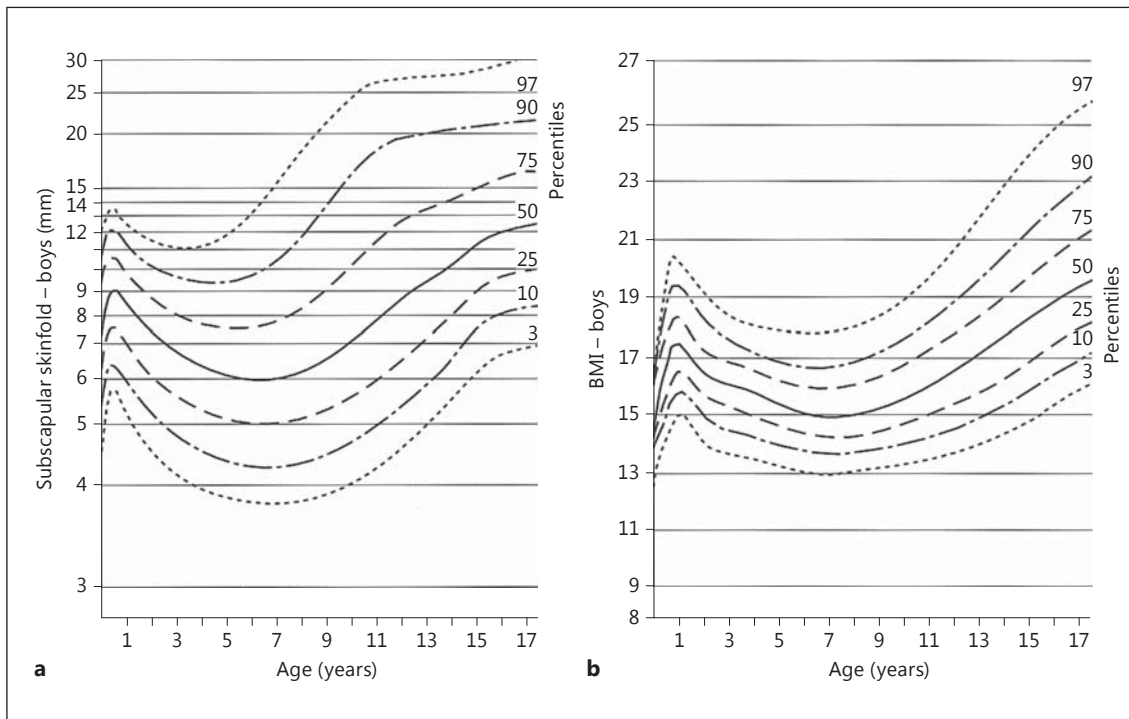
**Fig. 3.** Relative growth of different organ systems. From Tanner [13], with permission.



**Fig. 2.** Linear growth velocity according to age in girls and boys. Modified after Tanner et al. [11, 12].

0.9–1.1 kg, respectively. Then, growth velocity declines until the pubertal growth spurt, which is earlier in girls than in boys (fig. 2).

Different organs grow at very various rates (fig. 3). The relative weight of lymphoid tissue is greater in children than in adults and the size of the thymus peaks by 4–6 months of age and then decreases [2]. The brain, and thereby head circumference, grows mainly during the first 2 years of life, with the head circumference reaching about 80% of the adult values by 2 years. Body fat mass, expressed as percent total body mass, increases from birth to the age of about 6–9 months, then decreases until the age of about 5–6 years, followed by an increase (so-called ‘adiposity rebound’). These changes are reflected in reference curves for both BMI and skinfolds (fig. 4). The adiposity rebound typically occurs by 5–6 years of age. If this happens earlier, the risk of developing obesity is increased [3].



**Fig. 4.** Reference charts (percentiles) for subscapular skinfold (boy) and BMI. Modified after Tanner and Whitehouse [14] and Nysom et al. [15].

### Regulation of Growth

Many factors influence growth. Genetic influences are strong, but these can be modified by multiple environmental factors. Ethnic differences are likely to be caused more by the environment than by genetic factors. The new WHO growth standards obtained for 0- to 5-year-old children from different parts of the world show a similar growth potential. Basically, under optimal nutritional and socioeconomic conditions, the growth pattern was the same, independent of geographic and ethnic diversity (see Chapter 4.1). Other studies show that with children of families moving to a country with very different dietary and socioeconomic conditions, the growth pattern can change over time (secular trend); within one generation the growth pattern becomes more like

that in the adopted country. Adult height has increased over the last decades in many populations. This secular change came to a halt in Northern Europe around the mid-1980s, while it continues to increase in other countries [4]. The age of puberty differs considerably between populations, with later onset of puberty in populations with poor nutritional status.

Nutrition has a central influence on growth, especially during the first years of life. Breastfed infants grow faster in their first months and are slightly shorter at 12 months of age, they weigh less and are leaner than formula-fed infants [5]. Breastfeeding also influences body composition. Breastfed infants gain more fat during the first 6 months and gain more lean mass from 6 to 12 months of age than formula-fed infants [6]. The growth pattern of breastfed infants is likely to

play a role in the effects of breastfeeding on long-term health. Differences in protein intake (quality and quantity) between breast- and formula-fed infants are likely responsible for some of the differences in growth pattern between breastfed and formula-fed infants. This is in line with evidence suggesting that cow's milk promotes linear growth, even in well-nourished populations [7]. There is some evidence suggesting that high protein intake during the first years of life is associated with an increased risk of developing overweight and obesity later in life [8, 9]. Other aspects of nutrition are also important in development of overweight and obesity, as discussed in Chapter 3.5.

### **Nutritional Problems Affecting Growth**

Globally, the most common cause of growth failure is inadequate dietary quality and, in some cases, insufficient energy intake. Growth-related nutrients, e.g. zinc, magnesium, phosphorus and essential amino acids, are important. Overall, protein deficiency is seldom a problem, but if the protein quality is low (typically in diets based on cereals or tubers), essential amino acids such as lysine may be low in the diet, and this can have a negative effect on growth. Undernutrition, i.e. low weight-for-age, can be caused by low height-for-age (stunting), low weight-for-height (wasting or thinness) or a combination. In populations with poor nutrition, stunting is regarded as a result of chronic malnutrition and wasting a result of acute malnutrition. However, both forms can coexist in a given individual; thus this nomenclature is often an oversimplification. Many acute and chronic diseases result in poor appetite and eating difficulties, and thus lead to malnutrition. Infections and diseases with inflammation, such as autoimmune diseases and cancers, are associated with anorexia. Psychological problems can cause non-organic failure to thrive and eating disorders with anorexia can cause severe malnutrition.

Obesity is characterised by an increased body fat mass, but as fat mass is too complicated to measure routinely, BMI [weight (kg)/height (m)<sup>2</sup>] is commonly used to describe overweight and obesity. Children with overweight are often taller than children with normal weight until puberty, which they typically reach earlier than normal-weight children. Thus, differences in height after puberty tend to diminish.

### **Growth and Long-Term Health**

There is strong evidence that deviations from the average growth pattern, especially during early life, are associated with impaired mental development and increased risk of many non-communicable diseases later in life. Examples are increased risk of cardiovascular disease in individuals with low birth weight, and increased risk of type 2 diabetes and obesity in individuals with a high growth velocity during early life. Height as an adult is also associated with several diseases, with a low stature being associated with cardiovascular disease and a tall stature being associated with some types of cancer. Early nutrition affects both early growth and long-term health, as described in Chapter 1.5. However, the mechanisms are not clear and there is limited information on the extent to which either deviations in growth by themselves or the factors responsible for these deviations in growth are the 'real' cause of increased disease risk in later life.

### **Growth Monitoring**

Regular measurements of weight and height and plotting of weight curves during infancy and childhood are important tools in monitoring the health of children in both the primary health care system and in hospital settings. Weight-for-age curves are not sufficient, as it is not possible to determine whether the reason a child has a low

weight-for-age is shortness or thinness. There is a need for both height-for-age and either weight-for-height or BMI curves and assessment of recent growth velocity to make a comprehensive nutrition/growth evaluation. Definitions of abnormal values are often provided on the basis of standard deviations (SD), where stunting and wasting are defined as values below  $-2$  SD and severe wasting and severe stunting as values below  $-3$  SD. For a definition of overweight and obesity, the International Obesity Task Force values are often used [10]. Based on data from several countries, age-specific BMI values were identified based on the percentiles which, at 18 years, meet the male adult values of 25 for overweight and 30 for obesity.

With the development of software, easily available on the Internet (e.g. [www.who.int/childgrowth/software/en/](http://www.who.int/childgrowth/software/en/)), it has become easy to enter weight and length data, to calculate percentiles and SD scores and to plot the curves on a

graph. This is a valuable tool for surveillance, following trends of malnutrition and overweight and obesity in populations. It is also an important public health tool for monitoring the nutritional status of populations. It is often relevant to perform such surveillance on local, regional and national levels.

## Conclusions

- Regular measurements of weight and length/height as well as plotting on growth charts, including weight-for-height or BMI, are important tools in monitoring health and nutritional status of both sick and healthy children
- Regular monitoring of growth of healthy children should be conducted via the primary health care system, including school health services

## References

- 1 Karlberg J: A biologically-oriented mathematical model (ICP) for human growth. *Acta Paediatr Scand Suppl* 1989; 350:70–94.
- 2 Yekeler E, Tambag A, Tunaci A, Genchellac H, Dursun M, Gokcay G, Acunas G: Analysis of the thymus in 151 healthy infants from 0 to 2 years of age. *J Ultrasound Med* 2004;23:1321–1326.
- 3 Rolland Cachera MF, Deheeger M, Maillet M, Bellisle F: Early adiposity rebound: causes and consequences for obesity in children and adults. *Int J Obes (Lond)* 2006;30(suppl 4):S11–S17.
- 4 Larnkjær A, Schröder SA, Schmidt IM, Jørgensen MH, Michaelsen KF: Secular change in adult stature has come to a halt in northern Europe and Italy. *Acta Paediatr* 2006;95:754–755.
- 5 Dewey KG, Peerson JM, Brown KH, Krebs NF, Michaelsen KF, Persson LA, Salmenpera L, Whitehead RG, Yeung DL: Growth of breast-fed infants deviates from current reference data: a pooled analysis of US, Canadian, and European data sets. *World Health Organization Working Group on Infant Growth*. *Pediatrics* 1995;96:495–503.
- 6 Gale C, Logan KM, Santhakumaran S, Parkinson JR, Hyde MJ, Modi N: Effect of breastfeeding compared with formula feeding on infant body composition: a systematic review and meta-analysis. *Am J Clin Nutr* 2012;95:656–669.
- 7 Hoppe C, Mølgaard C, Michaelsen KF: Cow's milk and linear growth in industrialized and developing countries. *Annu Rev Nutr* 2006;26:131–173.
- 8 Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, Beyrer J, Demmelmair H, Gruszfeld D, Dobrzanska A, Sengier A, Langhendries JP, Rolland Cachera MF, Grote V; European Childhood Obesity Trial Study Group: Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. *Am J Clin Nutr* 2009;89:1836–1845.
- 9 Michaelsen KF, Greer F: Protein needs early in life and long-term health. *Am J Clin Nutr* 2014, Epub ahead of print.
- 10 Cole TJ, Bellizzi MC, Flegal KM, Dietz WH: Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320:1240–1243.
- 11 Tanner JM, Whitehouse RH, Takaishi M: Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. I. *Arch Dis Child* 1966;41:454–471.
- 12 Tanner JM, Whitehouse RH, Takaishi M: Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. II. *Arch Dis Child* 1966;41:613–635.
- 13 Tanner JM: *Growth at Adolescence*. Oxford, Blackwell, 1962.
- 14 Tanner JM, Whitehouse RH: Revised standards for triceps and subscapular skinfolds in British children. *Arch Dis Child* 1975;50:142–145.
- 15 Nysom K, Mølgaard C, Hutchings B, Michaelsen KF: Body mass index of 0 to 45-y-old Danes: reference values and comparison with published European reference values. *Int J Obes Relat Metab Disord* 2001;25:177–184.

### 1.2 Nutritional Assessment

## 1.2.1 Clinical Evaluation and Anthropometry

John W.L. Puntis

#### Key Words

Nutritional assessment · Feeding history · Anthropometry · Growth · Malnutrition

#### Key Messages

- Nutritional assessment includes feeding history, clinical examination and anthropometry; basic haematological and biochemical indices should also be included if possible, in order to identify specific nutrient deficiencies
- Careful measurement of growth status and reference to standard growth charts is essential in order to identify those children who are malnourished
- Addition of skinfold thickness measurements and mid-upper-arm circumference allows estimation of body composition; however, this is not often calculated in routine clinical practice
- There are a number of different ways of defining malnutrition, and no definition is universally agreed on
- Short-term malnutrition affects weight so that the child becomes thin ('wasting'; weight-for-height and BMI below normal reference values)
- Long-term malnutrition leads to poor linear growth so that the child will have a low height-for-age ('stunting')

- The point at which deteriorating nutritional status demands invasive intervention (tube feeding) in order to prevent adverse outcomes is unclear and will depend on the underlying disease and the overall clinical status of the individual child
- Serial measurements are required to monitor the effectiveness of nutritional intervention

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#### Nutritional Assessment

Malnutrition impairs growth, in time leading to multisystem disease. Nutritional status reflects the balance between supply and demand and the consequences of any imbalance. Nutritional assessment is therefore the foundation of nutritional care for children [1]. When judging the need for nutritional support, an assessment must be made both of the underlying reasons for any feeding difficulties, and of current nutritional status. This process includes a detailed dietary history, physical examination, anthropometry (weight, length; head circumference in younger children) using appropriate reference standards, e.g. the

WHO standard growth charts [2] (see Chapter 4.1), and basic laboratory indices (see Chapter 1.2.4) if possible. In addition, skinfold thickness and mid-upper-arm circumference measurements provide a simple method for estimating body composition [3].

### Nutritional Intake

Questions regarding mealtimes, food intake and difficulties with eating should be part of routine history taking and give a rapid qualitative impression of nutritional intake (see Chapter 1.2.2). For a more quantitative assessment, a detailed dietary history must be taken which involves recording a food diary or (less commonly) a weighed food intake. This would usually be undertaken in conjunction with an expert paediatric dietician. Use of compositional food tables or a computer software programme allows these data to be analysed so that a more accurate assessment of intake of energy and specific nutrients can be made. When considering whether such intakes are sufficient, dietary reference values provide estimates of the range of energy and nutrient requirements in groups of individuals [4]. Many countries have their own values and international values have been published by the Food and Agriculture Organization/WHO/United Nations University. Dietary reference values are based on the assumption that individual requirements for a nutrient within a population group are normally distributed and that 95% of the population will have requirements within 2 standard deviations (SD) of the mean (see Chapter 1.3.1). In a particular individual, intakes above the reference nutrient intake are almost certainly adequate, unless there are very high disease-induced requirements for specific nutrients, while intakes below the lower reference nutrient intake are almost certainly inadequate.

### Taking a Feeding History

A careful history is an important component of nutritional assessment. Listed below are some of the questions and 'cross-checks' that are integral to an accurate feeding/diet history:

Infant: is the baby being breastfed or formula fed?

*For breastfed infants:*

- How often is the baby being fed and for how long on each breast? Check positioning and technique
- Are supplementary bottles or other foods offered?

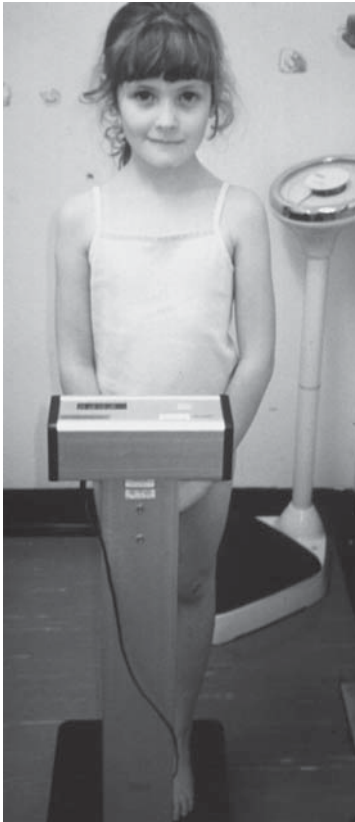
*For formula-fed infants:*

- What type of formula? How is the feed made up? i.e. establish the final energy content/100 ml
- Is each feed freshly prepared?
- How many feeds are taken over 24 h?
- How often are feeds offered: every 2, 3 or 4 h?
- What is the volume of feed offered each time?
- How much feed is taken?
- How long does this take?
- Is anything else being added to the bottle?

*For older children:*

- How many meals and snacks are eaten each day?
- What does your child eat at each meal and snack (obtain 1- or 2-day sample meal pattern)
- How do the parents describe their child's appetite?
- Where does the child eat meals?
- Are there family mealtimes?
- Are these happy and enjoyable situations?
- How much milk does the child drink?
- How much juice does the child drink?
- How often are snacks/snack foods eaten?

(Further details are provided in Chapter 1.2.2.)



**Fig. 1.** Weigh older children only in light clothing using regularly maintained and calibrated scales.

### **Basic Anthropometry: Assessment of Body Form**

Accurate measurement and charting of weight and height ('length' in children <85 cm, or unable to stand) is essential if malnutrition is to be identified; clinical examination without charting anthropometric measurements ('eye-balling') has been shown to be very inaccurate [5]. For premature infants up to 2 years of age, it is essential to deduct the number of weeks born early from actual ('chronological') age in order to derive the 'corrected' age for plotting on growth charts. Head circumference should be routinely measured and plotted in children less than 2



**Fig. 2.** An infant measuring board; two people are required for accurate determination of length.

years old. Measurements should be made as follows:

#### *Weight:*

- Weigh infants less than 2 years old naked
- Weigh older children only in light clothing (fig. 1)
- Use self-calibrating or regularly calibrated scales

#### *Length:*

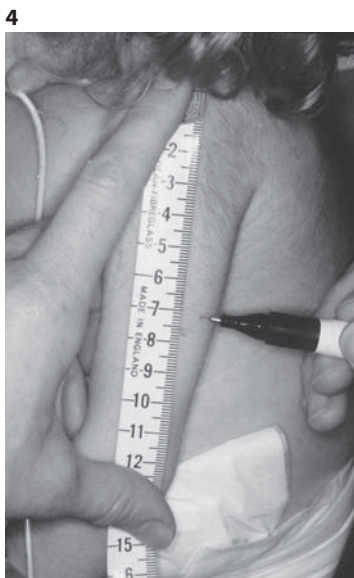
- If possible, use an infant measuring board, measuring mat (easily rolled and transported) or a measuring rod ([www.gosh.nhs.uk/health-professionals/clinical-guidelines/height-measuring-a-child/#Rationale](http://www.gosh.nhs.uk/health-professionals/clinical-guidelines/height-measuring-a-child/#Rationale))
- Two people are required to use the measuring board: one person holds the head against the headboard while the other straightens the knees and holds the feet flat against the moveable footboard (fig. 2)

#### *Height:*

- Use a stadiometer if possible (fig. 3), a device for standing height measurement comprising a vertical scale with a sliding horizontal board or arm that is adjusted to rest on top of the head
- Remove the child's shoes
- Ask the child to look straight ahead
- Ensure that the heels, buttocks and shoulder blades make contact with the wall



**Fig. 3.** A stadiometer should be used for accurate assessment of height.



**Fig. 4.** The mid upper arm is the point halfway between the acromion of the shoulder and the olecranon of the elbow (marked with a pen).

**Fig. 5.** To determine mid-upper-arm circumference, take the average of 3 readings made with a non-stretch tape measure at the mid-upper-arm point.

*Head circumference:*

- Use a tape measure that does not stretch
- Find the largest measurement around the mid forehead and occipital prominence

*Mid-upper-arm circumference:*

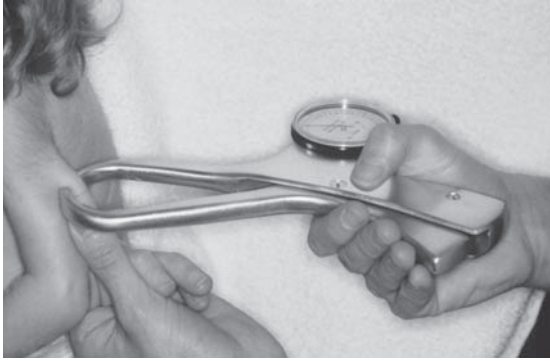
- Mark the mid upper arm (halfway between the acromion of the shoulder and the olecranon of

the elbow; fig. 4), then use a non-stretch tape measure and take the average of 3 readings at the midpoint of the upper arm (fig. 5)

*Skinfold thickness:*

- Pinch the skin between two fingers and apply specialised skinfold callipers (fig. 6); experience is needed to produce accurate and repeat-





**Fig. 6.** Triceps skinfold thickness taken with Harpenden callipers at the mid upper arm allows estimation of fat energy stores and is useful for serial monitoring.

able measurements ([http://healthsciences.qmuc.ac.uk/labweb/Equipment/skin\\_fold\\_calipers.htm](http://healthsciences.qmuc.ac.uk/labweb/Equipment/skin_fold_calipers.htm)); take triceps skinfold thickness readings at the mid upper arm using the relaxed non-dominant arm; the layer of skin and subcutaneous tissue is pulled away from the underlying muscle, and readings are taken to 0.5 mm, 3 s after the application of the callipers; measurements can also be taken at other sites ([www.cdc.gov/nchs/data/nnfyfs/Body\\_Measures.pdf](http://www.cdc.gov/nchs/data/nnfyfs/Body_Measures.pdf))

## Growth

Growth rate in infancy is a continuation of the intrauterine growth curve, and is rapidly decelerating up to 3 years of age. Growth in childhood is along a steady and slowly decelerating growth curve that continues until puberty, a phase of growth lasting from adolescence onwards. During puberty, the major sex differences in height are established, with a final height difference of around 12.5 cm between males and females. Growth charts are derived from measurements of many different children at different ages (cross-sectional data). Data on growth of children are distributed 'normally' (i.e. they form a 'bell-

shaped' curve). These data can be expressed mathematically as mean and SD from the mean. The centile lines delineate data into percentages: the 50th centile represents the mean (average); 25% of children are below the 25th centile. The normal range (approx.  $\pm 2$  SD from the mean) lies between the 3rd and the 97th centile.

## Normal Growth: Simple Rules of Thumb

Approximate average expected *weight* gain for a healthy term infant:

- 200 g/week in the first 3 months
- 130 g/week in the second 3 months
- 85 g/week in the third 3 months
- 75 g/week in the fourth 3 months
- Birth weight usually doubles by 4 months and triples by 12 months

*Length:*

- Increases by 25 cm in the first year
- Increases by 12 cm in the second year
- By 2 years, roughly half the adult height is attained

*Head circumference:*

- Increases by 1 cm/month in the first year
- Increases by 2 cm in the whole of the second year
- Will be 80% of adult size by 2 years

(N.B.: growth rates vary considerably between children; these figures should be used in conjunction with growth charts.)

## Patterns of Growth

Birth weight/centile is not always a good guide to genetic potential; some infants cross centile lines in the first few months of life ('catch down'), but from then on continue to follow along a lower centile. The maximum weight centile achieved between 4 and 8 weeks is the best predictor of weight centile at 12 months. Infants born below the 10th centile for gestational age may either

**Table 1.** Criteria for malnutrition

	Obese	Overweight	Normal	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Height-for-age, %				90–95	85–90	<85
Weight-for-height, %	>120	110–120	90–100	80–90	70–80	<70
BMI	>30	>25				

have intrauterine growth retardation (IUGR) or be within the normal 10% of the population who fall below this line. Long-standing IUGR results in low weight, head circumference and length ('symmetrically' small); catch-up growth is unlikely. Infants with late IUGR are thin but may have head circumference and length on a higher centile, and subsequently show catch-up in weight. It should be noted that rates of growth vary in young children, and assessments should be based on serial measurements. A short-term energy deficit will make a child thin (low weight-for-height = wasting). A long-term energy deficit limits height gain (and head/brain growth), causing stunting. Children who are chronically undernourished may be both thin and short.

Assessment of linear growth potential:

- Plot the height of both parents at the 18-year-old end of the centile chart
- Add together parental heights and divide by 2
- Add 7 cm (male child) or subtract 7 cm (female) = mid parental height; mid parental height  $\pm$  8.5 cm (girl) or  $\pm$  10 cm (boy) = target height centile range

### Anthropometric Indices and Definitions of Malnutrition

Weight-for-height compares a child's weight with the average weight of children of the same height, i.e. the actual weight/weight-for-height at the 50th centile – for example, a 2.5-year-old girl with height = 88 cm and weight = 9 kg: the 50th-

**Table 2.** Wellcome classification of malnutrition

Marasmus	<60% expected weight-for-age, no oedema
Marasmic kwashiorkor	<60% expected weight-for-age, oedema present
Kwashiorkor	<60–80% expected weight-for-age, oedema present
Underweight	<60–80% expected weight-for-age, no oedema

centile weight of a child who, at 88 cm, is on the 50th centile for height = 12 kg; therefore, weight-for-height =  $9/12 = 75\%$  ('moderate' malnutrition).

Weight-for-height can be expressed either as percent expected weight or as z score. The z score is commonly used when statistical comparisons are made as it enables children of different sexes and ages to be compared. A value on the 50th centile would have a z score of 0, whereas values on the 3rd and 97th centiles would be  $-2$  and  $+2$  SD, respectively. Mid-upper-arm circumference (MUAC) provides a quick population screening tool for malnutrition; reference charts are available [6]. MUAC may also be more appropriate for some children in whom body weight is misleading (e.g. childhood cancer with large tumour mass, liver disease with oedema). WHO standards show that in a well-nourished population there are very few children aged 6–60 months with an MUAC <115 mm; children below this

cut-off have a highly elevated risk of death [7]. BMI is derived from weight in kilograms divided by the square of the height in metres ( $\text{kg}/\text{m}^2$ ); it is an alternative to 'weight-for-height' as an assessment of nutritional status [8]. In a mixed population of hospital inpatients there will be only a slight difference in malnutrition prevalence using the SD score for either BMI or weight-for-height.

### Classifications of Malnutrition

There is no single, universally agreed definition of malnutrition in children [9, 10], but the criteria shown in table 1 are commonly used. The classification does not define a specific disease, but rather clinical signs that may have different aetiologies. Other nutrients such as iron, zinc and copper may be deficient in addition to protein and energy.

The Wellcome classification of malnutrition is based on the presence or absence of oedema and the body weight deficit (table 2). Severe acute malnutrition in children aged 6–60 months is now defined by the WHO as weight-for-height below  $-3$  SD or MUAC below 115 mm [7].

### When to Intervene

Malnutrition is a continuum that starts with a nutrient intake inadequate to meet physiological requirements, followed by metabolic and functional alterations and, in due course, by impairment of body composition. Malnutrition is difficult to define and assess because of insensitive assessment tools and the challenges of separating the impact of malnutrition from that of the underlying disease on markers of malnutrition (e.g. hypoalbuminemia is a marker of both malnutrition and severe inflammation) and on outcome. Nutritional intervention may be indicated both to prevent and to reverse malnutrition. In general,

the simplest intervention should be followed, if necessary, by those of increasing complexity. For example, energy-dense foods and calorie supplements before progressing to tube feeding (see Chapter 3.3). Parenteral nutrition should be reserved for children whose nutrient needs cannot be met by enteral feeding (see Chapter 3.4). When simple measures aimed at increasing energy intake by mouth are ineffective, tube feeding should be considered [11]; the following are suggested criteria [12]:

- Inadequate growth or weight gain over  $>1$  month in a child aged  $<2$  years
- Weight loss or no weight gain for  $>3$  months in a child aged  $>2$  years
- Change in weight-for-age of more than  $-1$  SD within 3 months for children aged  $<1$  year
- Change in weight-for-height of more than  $-1$  SD within 3 months for children aged  $>1$  year
- Decrease in height velocity of  $0.5-1$  SD/year at an age  $<4$  years, and of  $0.25$  SD/year at an age  $>4$  years
- Decrease in height velocity of  $>2$  cm from the preceding year during midpuberty

### Conclusions

- A detailed feeding history should be part of routine nutritional assessment
- Expert dietetic assistance is required for more objective assessment of nutritional intake, and for appropriate further management
- Accurate assessment of growth by careful measurement and reference to standard growth charts is essential to define and monitor nutritional status
- Malnutrition is a dynamic and complex process, without clearly agreed definitions
- The clinical status and particular needs of each individual child require careful evaluation when planning nutritional support

## References

- 1 Olsen IE, Mascarenhas MR, Stallings VA: Clinical assessment of nutritional status; in Walker WA, Watkins JB, Duggan C (eds): *Nutrition in Pediatrics*. London, Decker, 2005, pp 6–16.
- 2 Wright CM: The use and interpretation of growth charts. *Curr Paediatr* 2002;12: 279–282.
- 3 Brook C: Determination of body composition of children from skinfold measurements. *Arch Dis Child* 1971;46:182–184.
- 4 British Nutrition Foundation: Nutrient requirements. 2014. [www.nutrition.org.uk/nutritionscience/nutrients/nutrient-requirements](http://www.nutrition.org.uk/nutritionscience/nutrients/nutrient-requirements).
- 5 Cross JH, Holden C, MacDonald A, Pearmain G, Stevens MC, Booth IW: Clinical examination compared with anthropometry in evaluating nutritional status. *Arch Dis Child* 1995;72:60–61.
- 6 Frisancho AR: New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr* 1981; 34:2540–2545.
- 7 WHO: The WHO child growth standards. 2006. [www.who.int/childgrowth/standards](http://www.who.int/childgrowth/standards).
- 8 Hall DMB, Cole TJ: What use is the BMI? *Arch Dis Child* 2006;91:283–286.
- 9 Raynor P, Rudolf MCJ: Anthropometric indices of failure to thrive. *Arch Dis Child* 2000;82:364–365.
- 10 Puntis JWL: Malnutrition and growth. *J Pediatr Gastroenterol Nutr* 2010; 51:S125–S126.
- 11 Braegger C, Decsi T, Dias JA, et al: Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2010;51:110–122.
- 12 Joosten KFM, Hulst JM: Malnutrition in pediatric hospital patients: current issues. *Nutrition* 2011;27:133–137.

### 1.2 Nutritional Assessment

## 1.2.2 Diet History and Dietary Intake Assessment

Pauline Emmett

#### Key Words

Assessment of an individual child · Barriers to intake · Barriers to absorption · Detailed diet history · Tailored advice · Monitoring

#### Key Messages

- Assessment of dietary intake is essential in understanding the nutritional status of an individual child
  - Assessment of the barriers to intake and absorption is integral to this process
  - Assess food and drink intake in the individual child by taking a detailed dietary history, usually from the parent and child together
  - Use information gained to tailor treatment and advice
  - This is a skilled job requiring training to perform and expertise to interpret; use a dietician or experienced clinician, if possible
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#### Introduction

This chapter will deal with methods to use for the assessment of an individual child who has presented with a problem that may have a dietary origin. The fact that we are dealing with an individual child in need of diagnosis and treatment

or advice dictates the methods to be used. In assessing the nutritional status of a child, it is important to ascertain whether their likely needs are being covered by their dietary intake. This will include the assessment of any barriers to intake or absorption of nutrients from the foods consumed.

For children below the age of 8–10 years (depending on the individual child's maturity), parents or caregivers will be the main source of reliable information. Children below this age do not have the cognitive skills necessary to answer questions about foods eaten accurately enough for assessment [1]. Even with older children, it is best to obtain corroboration and expansion of child-supplied information from parents, although this process needs careful handling. Interviewing the child and parent together in a collaborative way is probably the way to start. If conflict arises at this stage, this may be an important indicator of the source of any dietary problems found.

To carry out this process is a skilled job requiring a high level of expertise to achieve the desired result of discovering the presence of likely dietary problems and to formulate recommendations for improvement. If available, a dietician will have the training and expertise to carry out

**Table 1.** Dietary assessment of an individual child

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*Assess barriers to obtaining an adequate dietary intake*

Physical problems – chewing, swallowing, use of utensils, consistency of food, etc.

Psychological problems – will only eat certain foods, in particular places, using particular plates, etc.

Parental or socio-economic problems – not enough/too much food available, parents not able to provide correct food for a particular reason (financial, illness), conflict between child and parent over food

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*Assess barriers to absorption of nutrients*

Physical – diarrhoea, vomiting, regurgitation, use of purgatives, etc.

Dietary – types of foods eaten in combination (this will be assessed after the diet history has been taken – see below)

Physical activity – is the child very inactive compared to peers, does the child exercise excessively or compulsively

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*Assess foods and drinks consumed*

Talk through and record (as the interview proceeds) a normal day's meals with the child/parent; use prompt questions and follow-up questions about foods mentioned. The examples given at breakfast below need to be tailored to the foods/drinks taken at each meal as the day progresses. Expand to cover a week for complex meals

What do you have for breakfast usually?

Bread – type? – how many slices? – Is anything normally spread on the bread, etc.

Breakfast cereal – type? – milk added? Etc.

What do you usually have to drink?

Do you usually have anything else at this time of the day?

Do you usually have anything before breakfast?

Do you usually have anything in mid-morning?

Do you usually have anything at mid-day?

Do you usually have anything in mid-afternoon?

Do you usually have anything in late afternoon?

Do you usually have anything in early evening?

Do you usually have anything in late evening?

Do you usually take any food or drink to bed?

Do you usually get up in the night to eat or drink anything?

Do you take any vitamins or other food supplements? How often do you take these?

---

and interpret this type of assessment; otherwise, a clinician who is an expert in these procedures should be used.

### **Assessment of Barriers**

The main dietary problem may be a barrier to intake or absorption which has led to the dietary deficiency. It is important, therefore, to ask some straightforward questions about the possible barriers. The most likely barriers to intake are listed in table 1, and an affirmative answer to any of these should lead to a tailored course of action

with a view to improving intake. This may involve other professionals with particular expertise to deal with the problem, such as speech therapists, psychiatrists, child feeding behaviour specialists, social workers, etc. These barriers may not be easy to resolve, but dietary intake is unlikely to improve if they are ignored.

Dealing with the barriers to absorption may also lead to referral to other professionals; however, if the barrier is due to the combinations of foods consumed, this will need to be assessed during the taking of the dietary history. During this process, it should be possible to formulate the advice necessary to correct the problem.

## Dietary History Method

The diet history method aims to find out what is being eaten or drunk by the subject over the course of a usual day [2]. For some eating occasions and meals, this is a relatively simple task, because some basic foods are eaten at similar times almost every day. For the more complex meals, the usual day needs to be expanded: for the purposes of this type of assessment, covering a usual week will provide enough information in the first instance. The questioning should be systematic with standard prompts and follow-up questions, as listed in table 1; however, some responses may be unexpected and should be probed with further questions at the time. Always return to the basic plan of the interview after a diversion in order to cover the whole day. A record should be kept during the interview of what is being said; this could be a voice or video recording if the child/parent is happy to allow it.

It is important to keep in mind the length of the interview because if the interview is very long, the child/parent may become bored or stressed and give less accurate answers. It may be possible to split the interview into sections carried out at different times. A simple diet history would typically take 45 min to complete, but if the usual foods consumed are complex, it may take much longer.

It is imperative not to show surprise or to comment on what is being consumed during the assessment, because it is important not to influence the answers given by the child/parent. The aim is to obtain as accurate a picture as possible of the child's normal diet. This should give a reasonable understanding of the type of foods usually eaten and should allow a basic assessment of whether there is likely to be a dietary problem. This information will also help to tailor any dietary advice needed to the individual situation.

## Diet Records

As a helpful adjunct to the main method, the parent/child could be asked to keep a record of all the foods and drinks consumed by the child over a period of time [3]. Typically, this would be for at least 24 h but may be between 3 and 7 days. In some circumstances, it could be helpful to request that diet records are kept for a few days prior to the initial interview; they could then be used to speed up the gaining of the detailed diet history. Another area where they could be extremely helpful is in monitoring the child's diet over time, either to understand further the dietary problem that has presented or to assess the degree to which advice is being followed. In the latter case, asking the child/parent to record the child's food and drink intake once or twice a week over the period between consultations may be more helpful than asking for more continuous recording. When the diet records are received, they should be used as a basis for follow-up questions to clarify any parts that are not explicit. They can then be used to reinforce and adapt the dietary advice that has been prescribed. If the parent/child is unable to keep a record, then asking them at the follow-up consultation about foods/drinks consumed by the child over the previous 24 h could be helpful in informing the next stage of the consultation.

## Interpretation and Advice

Table 2 lists some of the key aspects to consider in interpreting a dietary assessment of a particular child. As suggested, the interpretation is driven by the problems with which the child has presented, and examples are given for the most common diseases related to diet. The type of health professional most likely to be of help in each situation is also suggested.

The main usefulness of the dietary information collected is to get an understanding of the balance of the foods consumed, of any obvious

**Table 2.** Key aspects to consider in interpreting a dietary assessment

This will depend on the problem that the individual child presents with:

*Slow weight gain/weight loss/eating behaviour problems*

Barriers to intake or absorption are likely to be the main problem

Diet history is likely to show a limited food intake either in amount or range of foods consumed

Consider involving a child feeding behaviour specialist

*Anaemia or low blood concentrations of other key nutrients*

Barriers less likely to be the main problem

Diet history is likely to show a poor balance of foods consumed

e.g. for anaemia – check

enhancers: meat, fruit, vegetables, vitamin C [5]

inhibitors: cow's milk, tea, calcium [5]

Consider involving a dietician

*Overweight, obesity and diabetes*

Barriers less likely to be the main problem

Inactivity may be a factor

Diet history is likely to show a poor balance of foods consumed

e.g. for all three morbidities – check

promoters: snack foods, sweet foods, soft drinks [6]

inhibitors: fruits, vegetables, wholegrain cereals [6]

Consider involving a dietician

nutrient deficiencies or excesses and of any barriers to intake or to following the advice given. Advice should then be tailored accordingly. It is essential to involve both the child and the parent(s) (and any significant other carers) in understanding any dietary advice prescribed. Nutrient analysis of the diet history or food records collected can be used as a summary of the diet, but the figures obtained are not accurate at the level of the individual and thus should only be used as a rough indicator of dietary adequacy.

After the initial dietary history, if the child is thought to have an inadequate diet, advice may be given about incorporating dietary sources of the relevant nutrients into the child's diet or about the addition of suitable supplements. Wherever possible, dietary solutions should be encouraged, since, once established, they tend to be more sustainable than supplement use. Furthermore, foods tend to provide a mixture of nutrients, fibre and different textures, and it is not always understood which is providing the beneficial effect; indeed, it may be that it is the combination that is important rather than one constituent alone.

If, during the monitoring phase of working with the child, more than 7 days of reasonably complete food records have been accumulated, then nutrient analysis may be informative. This requires a suitable dietary analysis programme which can accommodate all the foods eaten and provide up-to-date nutrient contents for all the nutrients of interest [4]. Obtaining this type of analysis package needs careful thought, since foods change over time and off-the-shelf versions of packages do not always cover culturally specific foods, new foods on the market or some specific nutrients. Again, it is best to involve an expert dietician in this process.

## Conclusions

- Assessment of diet in a clinical setting with an individual child requires a different set of considerations than assessing diet in groups of children. The aim should be to diagnose the particular dietary problem and provide suitable treatment or advice to alleviate the problem



- Individualised assessment of diet and barriers to dietary intake or absorption is required before diagnosis, followed by the formulation of tailored treatment and advice and the monitoring of how that advice is being worked out over time
- Dietary assessment requires particular expertise in understanding how a balanced diet is likely to work and how to obtain and interpret information about foods and drinks consumed. An experienced dietician or clinician should preferably carry out the dietary assessment
- It is important to involve the child and the parents or caregivers at all stages of the process

## References

- 1 Livingstone MBE, Robson PJ, Wallace JMW: Issues in dietary intake assessment of children and adolescents. *Br J Nutr* 2004;92(suppl 2):S213–S222.
- 2 Livingstone MBE, Prentice AM, Coward WA, Strain JJ, Black AE, Davies PSW, Stewart CM, McKenna PG, Whitehead RG: Validation of estimates of energy intake by weighed dietary record and diet history in children and adolescents. *Am J Clin Nutr* 1992;56:29–35.
- 3 Bingham SA, Cassidy A, Cole TJ, Welch A, Runswick SA, Black AE, et al: Validation of weighed records and other methods of dietary assessment using the 24 h urine nitrogen technique and other biological markers. *Br J Nutr* 1995;73:531–550.
- 4 Price GM, Paul AA, Key FB, Harter AC, Cole TJ, Day KC, et al: Measurement of diet in a large national survey: comparison of computerized and manual coding of records in household measures. *J Hum Nutr Diet* 1995;8:417–428.
- 5 Cowin I, Emond A, Emmett P; ALSPAC Study Team: Association between composition of the diet and haemoglobin and ferritin levels in 18-month-old children. *Eur J Clin Nutr* 2001;55:278–286.
- 6 Ambrosini G, Emmett P, Northstone K, Howe L, Tilling K, Jebb S: Identification of a dietary pattern prospectively associated with increased adiposity during childhood and adolescence. *Int J Obes (Lond)* 2012;36:1299–1305.

### 1.2 Nutritional Assessment

## 1.2.3 Use of Technical Measurements in Nutritional Assessment

Babette S. Zemel · Virginia A. Stallings

#### Key Words

Resting energy expenditure · Dual-energy X-ray absorptiometry · Indirect calorimetry · Body composition

#### Key Messages

- Accurate nutritional assessment should be an integral part of pediatric care and may require technical measurements
  - The measurement of resting energy expenditure using indirect calorimetry is the best available method to accurately estimate a child's caloric needs to promote weight gain or maintenance
  - In addition to anthropometry, the most commonly used clinical method of body composition assessment is dual-energy X-ray absorptiometry (DXA). DXA-based bone density measurements are increasingly being used to assess bone health in children with chronic diseases
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#### Introduction

Accurate nutritional assessment should be an integral part of pediatric care. Children at risk of malnutrition or who are chronically ill should undergo a detailed nutritional assessment, which

sometimes requires technical measurements. An important aspect of nutritional assessment is estimating daily energy needs for optimal growth and development. This is especially important in children with health conditions causing under-nutrition or obesity. However, the energy needs of such children can be difficult to estimate [1]. Resting energy expenditure (REE) represents a large portion of the energy needed each day. The measurement of REE using indirect calorimetry is the best available method to accurately estimate an individual child's caloric needs to promote weight gain or maintenance.

Growth evaluation by measuring length or stature and weight is the first step in nutritional assessment, but measurement of body composition provides more detailed information about nutritional status than anthropometry alone. The relative and absolute amounts of muscle, fat and bone change during growth [2]. In addition to anthropometry, the most commonly used clinical method of body composition assessment is dual-energy X-ray absorptiometry (DXA). Although mainly used to assess bone health, whole-body DXA scans also provide measurements of three compartments: bone, fat and lean body mass. DXA-based bone density measurements

are increasingly being used to assess bone health in children with chronic diseases. Other methods of body composition and bone density measurement are mainly research tools that are not readily applicable to the clinical setting.

### **Resting Energy Expenditure**

Estimating daily energy needs is particularly important in caring for children with varying pediatric diagnoses that result in undernutrition or obesity. Their energy needs are difficult to estimate because of variations in metabolic demands of illness and physical activity as well as the proportion of the body composed of lean tissue. REE accounts for 60–70% of total daily expenditure and is used to estimate total energy needs in order to achieve a specific clinical goal: weight maintenance, loss or gain.

Prediction equations based on age, sex, weight and length/height have been developed to estimate REE when direct measurement is not possible. Unfortunately, these equations, derived from measurements of healthy children, do not perform well for children with serious health conditions or altered body composition. The optimal approach is to measure REE using an indirect calorimeter or metabolic cart that measures oxygen consumption and carbon dioxide production.

Accurate REE measurement by indirect calorimetry requires standardized conditions such as early-morning testing after a night of restful sleep and an 8- to 12-hour (or age- or disease-appropriate) fast. A 40- to 60-min test enables initial environmental adjustment and exclusion of measurements during episodes of movement. During the test, the patient should be in a quiet, awake and calm state, be in a supine position and not have performed any physical activity or received any medications known to change heart rate (such as bronchodilators). Developmentally normal children who are at least 5 years of age

typically do well while watching a movie. Infants are evaluated while sleeping. Children with developmental delay often require sedation with a short-acting oral agent.

Energy needed for growth or physical activity or to support therapeutic growth acceleration must be added to the REE to estimate total energy requirements. Table 1 shows the dietary reference intake prediction equations for estimated energy requirements (kcal/day) and physical activity factors for healthy infants and children [3]. For hospitalized or ill children with less spontaneous physical activity, a factor of 1.3–1.5 × REE is a better estimate of energy needs. Additional corrections are made for disease severity (such as in children with cystic fibrosis) or malabsorption. In patients who require ‘catch-up’ growth, additional energy may need to be factored into the energy requirement estimation to achieve the desired rate of growth.

### **Dual-Energy X-Ray Absorptiometry**

DXA is a low-energy X-ray technique (radiation exposure less than a day’s background exposure) that measures body composition and regional bone mass and density. DXA-based bone mineral content (BMC; g) and density (BMD; g/cm<sup>2</sup>) measurements are important in clinical care for identifying children at risk of poor bone accrual and osteoporosis [4]. Risk factors for pediatric bone disease include immobility, malabsorption, inflammation, endocrine disturbances and use of medications known to affect bone health, such as chronic glucocorticoid therapy.

BMC or BMD values of the lumbar spine and total body (excluding the head) should be compared with reference values for healthy children of the same age and sex and expressed as a z-score or standard deviation (SD) score. Adjustment for height is recommended for children with altered growth [5]. A z-score of 0 is equal to the median value for the reference population of children of



**Table 1.** Prediction equations for estimated energy requirements (kcal/day) and physical activity coefficients for healthy children

Infants	Prediction equations				
0–3 months	$89 \cdot \text{weight (kg)} - 100 + 175$				
3–6 months	$89 \cdot \text{weight (kg)} - 100 + 56$				
6–12 months	$89 \cdot \text{weight (kg)} - 100 + 22$				
12–24 months	$89 \cdot \text{weight (kg)} - 100 + 20$				
Males	General prediction equation <sup>1</sup>	Sedentary PA coefficient	Low active PA coefficient	Active PA coefficient	Very active PA coefficient
3–8 years	$88.5 - 61.9 \cdot \text{age} + \text{PAL} \cdot [(26.7 \cdot \text{weight}) + 903 \cdot (\text{height})] + 20$	1.00	1.13	1.26	1.42
9–18 years	$88.5 - 61.9 \cdot \text{age} + \text{PAL} \cdot [(26.7 \cdot \text{weight}) + 903 \cdot (\text{height})] + 25$	1.00	1.13	1.26	1.42
>18 years	$662 - 9.53 \cdot \text{age} + \text{PAL} \cdot [(15.91 \cdot \text{weight}) + 539.6 \cdot (\text{height})]$	1.00	1.11	1.25	1.48
Overweight 3–18 years	$114 - 50.9 \cdot \text{age} + \text{PAL} \cdot [(19.5 \cdot \text{weight}) + 1,161.4 \cdot (\text{height})]$	1.00	1.12	1.24	1.45
Females	General prediction equation <sup>1</sup>	Sedentary PA coefficient	Low active PA coefficient	Active PA coefficient	Very active PA coefficient
3–8 years	$135.3 - 30.8 \cdot \text{age} + \text{PAL} \cdot [(10 \cdot \text{weight}) + 934 \cdot (\text{height})] + 20$	1.00	1.16	1.31	1.56
9–18 years	$135.3 - 30.8 \cdot \text{age} + \text{PAL} \cdot [(10 \cdot \text{weight}) + 934 \cdot (\text{height})] + 25$	1.00	1.16	1.31	1.56
>18 years	$354 - 6.91 \cdot \text{age} + \text{PAL} \cdot [(9.36 \cdot \text{weight}) + 726 \cdot (\text{height})]$	1.00	1.12	1.27	1.45
Overweight 3–18 years	$389 - 41.2 \cdot \text{age} + \text{PAL} \cdot [(15 \cdot \text{weight}) + 701.6 \cdot (\text{height})]$	1.00	1.18	1.35	1.60

PA = Physical activity; PAL = PA level.

<sup>1</sup> Each prediction equation uses weight (kg) and height (m) and requires that a PA coefficient be included in the calculation of the estimated energy requirement. The PA categories, based on PAL (calculated as the ratio of total energy expenditure to REE), are as follows: sedentary = PAL is estimated to be  $\geq 1.0$  and  $< 1.4$ ; low active = PAL is estimated to be  $\geq 1.4$  and  $< 1.6$ ; active = PAL is estimated to be  $\geq 1.6$  and  $< 1.9$ ; very active = PAL is estimated to be  $\geq 1.9$  and  $< 2.5$ . Adapted from Food and Nutrition Board and Institute of Medicine [3].

the same age and sex; a z-score of  $-1$  means the patient's value is 1 SD below the median value for the reference population. In clinical practice, BMC or BMD z-scores between  $-2$  and  $+2$  are considered to be in the normal range; a BMC or BMD z-score of less than  $-2$  is considered low for chronological age. Based on these findings and the patient's clinical needs, the practitioner decides how best to increase bone accretion. Options may include optimizing calcium and vitamin D in the diet, supplementing with calcium

and/or vitamin D and prescribing weight-bearing physical activity.

Whole-body DXA scans estimate lean body mass, fat mass and percent body fat in less than 5 min. Pediatric reference ranges are now available for percent body fat [6] as well as lean body mass index [lean body mass (kg)/height (m)<sup>2</sup>] and fat mass index (kg/m<sup>2</sup>) [7]. DXA body composition assessment is not regularly used in the clinical setting, but it may prove to be useful in the diagnosis and treatment of obesity. In cases where it is dif-

difficult to distinguish whether children with a high body mass index have excess adiposity, skinfold assessment can be used to make this distinction. However, skinfold measurements by less experienced anthropometrists are subject to measurement error, and DXA assessments are more accurate. As DXA-based cutoff points are established for the level of body fat associated with the health risks of obesity, DXA could become a commonly used tool in the diagnosis and treatment of obesity.

### Other Techniques for Assessing Body Composition

Other body composition measurement techniques include air displacement plethysmography (Bod Pod and Pea Pod) and bioelectrical methods such as bioelectrical impedance analyzers (BIA). Bod Pod, Pea Pod and BIA are currently not used in the clinical care of individual patients who have illnesses that influence body composition and hydration. However, these methods are used in research settings to describe important changes in body composition in groups of subjects. With further research experience and the necessary healthy infant and child reference data, body composition assessment will likely move into the clinical care setting.

More advanced imaging technologies (CT and MRI) are particularly useful for measuring the composition of specific body compartments such as visceral adipose as well as intramuscular, intramyocellular and brown adipose tissue [2]. However, their radiation risk (CT only), availability and cost do not make them useful in clinical practice. Peripheral quantitative CT measures cross-sectional areas for fat and muscle as well as muscle density in addition to volumetric BMD of cortical and trabecular bones. However, peripheral quantitative CT generally is not available for clinical purposes.

### Conclusions

Technical measures in nutritional assessment in the clinical setting:

- include indirect calorimetry to directly measure REE; the REE is used to estimate total energy needs in order to achieve weight maintenance or gain in children;
- include DXA to measure bone mass and density in children at risk of bone disease and body composition for the diagnosis and treatment of obesity in some settings;
- do not include Bod Pod, BIA, CT and MRI, as these are primarily research tools

### References

- 1 Kaplan AS, Zemel BS, Neiswender KM, Stallings VA: Resting energy expenditure in clinical pediatrics: measured versus prediction equations. *J Pediatr* 1995; 127:200–205.
- 2 Zemel B: Body composition during growth and development; in Cameron N, Bogin B (eds): *Human Growth and Development*. Burlington, Elsevier Science, 2012, pp 462–486.
- 3 Food and Nutrition Board, Institute of Medicine: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. Washington, National Academies, 2002.
- 4 Bishop N, Braillon P, Burnham J, Cimaz R, Davies J, Fewtrell M, Hogler W, Kennedy K, Makitie O, Mughal Z, Shaw N, Vogiatzi M, Ward K, Bianchi ML: Dual-energy X-ray absorptiometry assessment in children and adolescents with diseases that may affect the skeleton: the 2007 ISCD Pediatric Official Positions. *J Clin Densitom* 2008; 11:29–42.
- 5 Gordon CM, Bachrach LK, Carpenter TO, Crabtree N, El-Hajj Fuleihan G, Kutilek S, Lorenc RS, Tosi LL, Ward KA, Ward LM, Kalkwarf HJ: Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. *J Clin Densitom* 2008; 11:43–58.
- 6 Ogden CL, Li Y, Freedman DS, Borrud LG, Flegal KM: Smoothed percentage body fat percentiles for US children and adolescents, 1999–2004. *Natl Health Stat Rep* 2011; 43:1–7.
- 7 Weber DR, Moore RH, Leonard MB, Zemel BS: Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. *Am J Clin Nutr* 2013; 98:49–56.

## 1.2 Nutritional Assessment

# 1.2.4 Use of Laboratory Measurements in Nutritional Assessment

Ryan W. Himes · Robert J. Shulman

### Key Words

Protein · Vitamin · Laboratory test · Malabsorption · Deficiency

### Key Messages

- Identification and prevention of malnutrition is crucial in the ill child
  - An understanding of the relationship between measures of visceral protein status and inflammatory responses and changes in fluid status is key to avoid misinterpretation
  - The approach to evaluating vitamin deficiency should be determined by an understanding of predisposing conditions
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### Introduction

Laboratory tests may aid in the diagnosis of primary childhood malnutrition (resulting from inadequate intake) and are invaluable in guiding therapeutic decisions in secondary malnutrition (resulting from conditions of increased need for or losses of substrate). Because nutritional status is an independent predictor of outcome in the sick child, strict attention to indicators of visceral

protein stores and vitamin or mineral deficiencies is imperative.

Although signs and symptoms of specific nutrient deficiencies commonly overlap and multiple deficiencies are frequently encountered, a judicious approach to ordering laboratory tests is recommended. While a rather comprehensive list of laboratory tests is presented here, clinical suspicion should guide the selection of specific investigations. Depending on the clinical laboratory facilities, turnaround time on certain tests may preclude their usefulness in the acute setting. Familiarity with these limitations will help to avoid ordering tests that do not contribute meaningfully to the management of a child. Table 1 provides a summary of the laboratory tests discussed here, including their normal values, signs and symptoms of the deficiency state, and pitfalls to avoid in their interpretation.

### Protein

Assessment of visceral protein stores is commonly made by measuring serum proteins (table 2), most commonly albumin, prealbumin (transthyretin) and retinol-binding protein. Interpretation of

**Table 1.** Frequently used laboratory tests in the assessment of childhood nutrition

Test (specimen)	Normal range <sup>1</sup>	Function/description	Deficiency	Pitfalls to avoid
Albumin (serum)	Infant: 29–55 g/l Child: 37–55 g/l [2]	Most abundant serum protein, half-life 20 days		Negative acute-phase reactant ↓ with hepatic synthetic dysfunction Changes with hydration status and fluid shifts
Alkaline phosphatase (serum)	Infant: 150–420 U/l 2–10 years: 100–320 U/l Adolescent boy: 100–390 U/l Adolescent girl: 100–320 U/l Adult: 30–120 U/l	Zinc-dependent metallo-enzyme found in liver, bone, biliary epithelium, kidney and intestine	Low alkaline phosphatase warrants consideration of zinc deficiency	
α <sub>1</sub> -Antitrypsin (stool)	<6 months: <4.5 mg/g of stool >6 months: <3 mg/g of stool [3]	Measure of protein loss from the gut		Unstable at pH <3, unsuitable to assess gastric protein loss [4]
Biotin (serum)	214–246 pmol/l [5]	Water-soluble vitamin, cofactor for carboxylases	Dermatitis, glossitis, alopecia, poor growth, ataxia, weakness, depression and seizures	Anticonvulsants, hemodialysis and parenteral nutrition may give rise to deficiency
Calcium (serum)	Preterm: 1.6–2.8 mmol/l Term to 10 days: 1.9–2.6 mmol/l 10 days to 2 years: 2.3–2.8 mmol/l 2–12 years: 2.2–2.7 mmol/l Adult: 2.2–2.5 mmol/l	Skeletal integrity, cofactor in clotting cascade and neuromuscular function	Fatigue, muscular irritability, tetany and seizures	Factitious hypocalcemia caused by low albumin (50% is bound to albumin)
Ceruloplasmin (serum)	Birth to 3 months: 40–160 mg/l 3–12 months: 290–380 mg/l 1–15 years: 230–490 mg/l [3]	Carries 90% of serum copper		Positive acute-phase reactant
Copper (serum)	11–22 μmol/l [2]	Mineral cofactor for superoxide dismutase and enzymes of connective tissue synthesis	Anemia, neutropenia, depigmentation, characteristic hair changes, weakened bone and connective tissue [5]	Supraphysiologic doses of iron or zinc may impair absorption of copper [5]
Creatinine (serum)	Neonate: 27–88 μmol/l Infant: 18–35 μmol/l Child: 27–62 μmol/l Adolescent: 44–88 μmol/l Adult male: 80–115 μmol/l Adult female: 53–97 μmol/l	Product of muscle creatinine-phosphate metabolism; level parallels muscle mass		Diminished glomerular filtration rate, cimetidine, cephalosporins and trimethoprim may increase serum creatinine [6]
Elastase (stool)	>200 μg/g of stool	Indicator of exocrine pancreas sufficiency		Sensitivity and specificity in mild insufficiency unclear [8]
Fat (stool)	<3 years: >85% >3 years: >95% (expressed as coefficient of absorption)	Indicator of fat malabsorption		Classically, a 72-hour stool collection with diet diary and adequate fat intake
Ferritin (serum)	Neonate: 25–200 μg/l 1 months: 200–600 μg/l 2–5 months: 50–200 μg/l 6 months to 15 years: 7–140 μg/l Adult male: 20–250 μg/l Adult female: 10–120 μg/l	Major storage form of iron; levels mirror body reserves Early and sensitive indicator of iron deficiency anemia		Positive acute-phase reactant
Folate (serum)	Neonate: 16–72 nmol/l Child: 4–20 nmol/l Adult: 10–63 nmol/l	Water-soluble vitamin, role in DNA/RNA synthesis and amino acid metabolism	Macrocytic anemia, hypersegmented neutrophils, glossitis, stomatitis, poor growth and fetal neural tube defects	Deficiency may be clinically indistinguishable from that of B <sub>12</sub> , but the latter has neurological signs Methotrexate, phenytoin and sulfasalazine antagonize folate utilization

**Table 1** (continued)

Test (specimen)	Normal range <sup>1</sup>	Function/description	Deficiency	Pitfalls to avoid
Hemoglobin (whole blood)	0–8 days: 2.06–3.79 mmol/l 9 days: 1.66–3.33 mmol/l 3 months: 1.53–2.25 mmol/l 1 year: 1.38–2.14 mmol/l 3 years: 1.58–2.31 mmol/l 11 years: 1.72–2.43 mmol/l Adult male: 1.86–2.48 mmol/l Adult female: 2.17–2.79 mmol/l	Oxygen-carrying moiety in RBC	<i>Microcytic</i> Iron deficiency, chronic disease <i>Normocytic</i> Chronic disease, acute bleeding <i>Macrocytic</i> B <sub>12</sub> , folate deficiency	Influenced by hydration status, nutrition and pregnancy
Iron (serum)	Neonate: 17.9–44.8 μmol/l Infant: 7.2–17.9 μmol/l Child: 9–21.5 μmol/l Adult male: 11.6–31.3 μmol/l Adult female: 9–30.4 μmol/l	Component in heme and cytochrome proteins	Microcytic anemia, pallor, weakness and dyspnea	Transferrin is a sensitive measure of body iron stores; however, it is a negative acute-phase protein
Lymphocytes (whole blood)	>1,500/mm <sup>3</sup>	Total lymphocyte count is inversely correlated to degree of malnutrition [6]		
Magnesium (serum)	0.63–1.00 mmol/l	Important for neuromuscular conduction; enzyme cofactor	Arrhythmia, tetany, hypocalcemia and hypokalemia	↓ by low serum albumin ↑ by hemolyzed specimens
pH (stool)	>5.5 [7]	Low fecal pH usually implies carbohydrate malabsorption		Improper specimen processing may lead to falsely low values
Phosphorus (serum)	Neonate: 1.45–2.91 mmol/l 10 days to 2 years: 1.29–2.1 mmol/l 3–9 years: 1.03–1.87 mmol/l 10–15 years: 1.07–1.74 mmol/l >15 years: 0.78–1.42 mmol/l	Vital for energy transfer at cellular level	Confusion, respiratory distress, tissue hypoxia, bone abnormalities and ↑ alkaline phosphatase	'Refeeding syndrome' is hypophosphatemia and hypokalemia complicating nutritional rehabilitation of the severely malnourished patient
Prealbumin (serum)	Neonate: 70–390 mg/l 1–6 months: 80–340 mg/l 6 months to 4 years: 120–360 mg/l 4–6 years: 120–300 mg/l 6–19 years: 120–420 mg/l	Gauge of visceral protein stores; half-life of 2 days		Negative acute-phase reactant
Prothrombin time (plasma)	11–15 s [2]	Used to assess vitamin K sufficiency, although better assessed with undercarboxylated prothrombin (PIVKA-II)		Also prolonged in liver dysfunction, malabsorption syndromes, prolonged antibiotic use and warfarin therapy
Reducing substances (stool)	Negative	Presence suggests carbohydrate malabsorption		Improper specimen processing may lead to falsely normal values
Retinol-binding protein (serum)	<9 years: 10–78 mg/l >9 years: 13–99 mg/l [2]	Gauge of visceral protein stores; half-life of 12 h		Negative acute-phase reactant ↓ in vitamin A deficiency, hepatic dysfunction ↑ in renal failure
Selenium (serum)	Preterm: 0.6–1 μmol/l Term: 0.8–1.1 μmol/l 1–5 years: 1.4–1.7 μmol/l 6–9 years: 1.4–1.8 μmol/l >10 years: 1.6–2.1 μmol/l [5]	Trace mineral essential for glutathione peroxidase	Cardiomyopathy (Keshan disease), myositis and nail dystrophy	
Urea nitrogen (serum)	Preterm (1st week): 1.1–8.9 mmol/l Neonate: 0.7–6.7 mmol/l Infant/child: 1.8–6.4 mmol/l Adult: 2.1–7.1 mmol/l	Produced in liver from protein degradation and excreted renally		↓ in low-protein-intake states ↑ in high-protein diets, but also kidney disease





**Table 1** (continued)

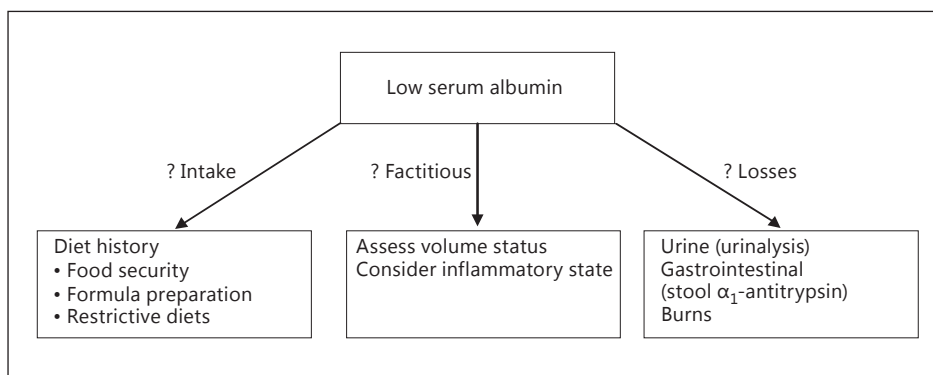
Test (specimen)	Normal range <sup>1</sup>	Function/description	Deficiency	Pitfalls to avoid
Vitamin A (serum)	Preterm: 0.46–1.6 µmol/l Term: 0.63–1.75 µmol/l 1–6 years: 0.7–1.5 µmol/l 7–12 years: 0.9–1.7 µmol/l 13–19 years: 0.9–2.5 µmol/l	Fat-soluble vitamin that functions in vision, maintenance of epithelial tissue and immunity; 90% stored in liver	Reversible night blindness (1st clinical manifestation), which, uncorrected, can progress to corneal scarring	↓ in liver disease, zinc deficiency [5] ↑ with oral contraceptive pill use
Vitamin B <sub>1</sub> – thiamine (whole blood)	Measure RBC transketolase activity <15% [2]	Water-soluble vitamin with role in oxidative phosphorylation and pentose phosphate pathway	Beriberi: cardiac failure, peripheral neuropathy ± edema Wernicke encephalopathy, Korsakoff syndrome	
Vitamin B <sub>2</sub> – riboflavin (whole blood)	Measure RBC glutathione reductase activity <20% [2]	Water-soluble vitamin that facilitates redox reactions	Dermatitis, cheilitis, glossitis and visual impairment	
Vitamin B <sub>6</sub> – pyridoxine (plasma)	Measure pyridoxal 5'-phosphate concentration 14.6–72.8 nmol/l [3]	Cofactor for enzymes in aminotransferase reactions including δ-aminolevulinic acid and the manufacture of serotonin [5]	Microcytic, hypochromic anemia, dermatitis, cheilosis, stomatitis, peripheral neuropathy, seizures and ↓ AST and ALT	↓ level with isoniazid treatment
Vitamin B <sub>12</sub> – cobalamin (serum)	Neonate: 118–959 pmol/l Infant/child: 148–616 pmol/l	Water-soluble vitamin active in DNA synthesis and branched-chain amino acid metabolism	Megaloblastic anemia, hypersegmented neutrophils and glossitis, stomatitis, weakness, elevated homocysteine and methylmalonic acid	↓ by phenytoin, proton-pump inhibitors, neomycin and folate deficiency
Vitamin C – ascorbate (plasma)	23–114 µmol/l	Water-soluble antioxidant vitamin important in collagen synthesis	Scurvy: petechial and gingival hemorrhage, gingivitis and poor wound healing	
Vitamin D – 25-hydroxy (plasma)	Summer: 15–80 µg/l Winter: 14–42 µg/l [3]	Fat-soluble vitamin involved in calcium and phosphorus homeostasis	Deficiency primarily affects bone and is called 'rickets'; ↓ serum calcium and phosphate, ↑ alkaline phosphatase	↓ with anticonvulsant therapy and cholestyramine
Vitamin E (serum)	Preterm: 1–8 µmol/l Term: 2–8 µmol/l 1–12 years: 7–21 µmol/l 13–19 years: 14–23 µmol/l	Fat-soluble antioxidant that protects cell membranes	Diminished deep tendon reflexes, impaired balance and gait	Carried in serum bound to lipid; therefore, hyperlipidemia may mask deficiency; vitamin E/lipid ratio useful in these circumstances
Zinc (plasma)	10.7–18.4 µmol/l	Cofactor for >200 enzymes, notably alkaline phosphatase, RNA/DNA polymerase and superoxide dismutase [5]	Acrodermatitis enteropathica, also delayed wound healing, impaired taste, growth failure, delayed puberty and diarrhea	↑ in hemolyzed specimens ↓ in sickle cell patients, hypoalbuminemia

<sup>1</sup> All reference ranges from Tschudy and Arcara [1] unless otherwise noted.

total protein is predicated on normal globulin levels, limiting its clinical usefulness. Generally, serial measurements of protein status are more meaningful than single values and an understanding of their biological half-lives will dictate the

frequency of assessment (table 2). A framework for the investigation of hypoalbuminemia is shown in figure 1.

The most important limitation to interpreting serum protein levels is their function in the acute-



**Fig. 1.** A suggested framework for investigating hypoalbuminemia in children.

phase response (table 3). Appreciating the positive and negative acute-phase reactants will help avoid misinterpretation of data. Another limitation of measuring serum proteins is that their manufacture is tied to hepatic synthetic function. Therefore, in a child with advanced liver disease, low serum protein may not necessarily reflect a lack of substrate but rather a lack of synthetic function. Finally, their concentrations are also susceptible to changes in hydration status and fluid shifts, and these changes may occur rapidly (e.g. increased vascular permeability associated with sepsis or trauma).

### Vitamins and Minerals

The decision to evaluate vitamin and mineral stores should take into account the suspected underlying pathophysiology (e.g. measurement of fat-soluble vitamins in conditions associated with fat malabsorption, such as celiac disease or cystic fibrosis). Frequently, signs and symptoms of nutrient deficiency overlap with one another, underscoring the importance of an informed approach to laboratory investigation. An often overlooked class of patients prone to malnutrition are those with absent (surgically resected) or diseased (Crohn’s disease, small-bowel bacterial

**Table 2.** Serum proteins used in the assessment of visceral protein stores

Protein	Half-life
Albumin	20 days
Prealbumin (transthyretin)	2 days
Retinol-binding protein	12 h

**Table 3.** Serum proteins in the acute-phase response

Positive acute-phase reactants	Negative acute-phase reactants
α <sub>1</sub> -Antitrypsin	Albumin
C3 complement	Prealbumin (transthyretin)
C-reactive protein	Retinol-binding protein
Ceruloplasmin	Transferrin
Fibrinogen	Thyroxin-binding globulin

overgrowth syndrome) terminal ilea. Deficiencies of vitamin B<sub>12</sub>, vitamin K and zinc are prevalent in these patients.

Finally, the potential effects of therapeutic drugs are important considerations. An exhaustive list of these interactions is beyond the scope of this text; however, some important nutrient-specific examples are shown in table 1.

## Tests of Maldigestion/Malabsorption/Enteric Protein Loss

Analysis of the stool is a logical starting point for the investigation of malabsorption.

- (1) Fat malabsorption: fecal fat as assessed by 72-hour collection with diet record is an accurate, albeit cumbersome tool (for patients and laboratory technicians) to quantify fat malabsorption. A fecal smear with Sudan staining gives a rough qualitative estimate of steatorrhea and may be useful for screening purposes
- (2) Pancreatic insufficiency: in addition to fecal fat measurement, determination of fecal elastase can be used as a measure of exocrine pancreas sufficiency. Its level is not affected by pancreatic enzyme supplementation. Although reliable for detecting severe pancreatic insufficiency, it is less so for mild-to-moderate pancreatic insufficiency; it will not identify other isolated enzyme deficiencies (e.g. lipase) and gives falsely low values in the presence of watery stools unless they are lyophilized [8]
- (3) Carbohydrate malabsorption: a low fecal pH and the presence of reducing substances are indicators of unabsorbed carbohydrate in stool. Testing should be done on the most liquid portion of the stool and can be done at the bedside using the same test strips used to measure pH and glucose in urine
- (4) Hydrogen breath testing: this test detects the passage of carbohydrate into the colon. Breath hydrogen is measured at baseline and after the child is given an oral load of the carbohydrate of interest (e.g. lactose); a rise in hydrogen above baseline (dependent on the sugar of interest) is diagnostic. False-negative tests may be seen in patients recently administered antibiotics. Additionally, a positive test does not always correlate with symptoms of intolerance
- (5) Small-bowel bacterial overgrowth syndrome may be assessed in an analogous manner using lactulose or glucose. A breath hydrogen peak that occurs within 15–30 min of ingestion is suggestive of overgrowth
- (6) Stool  $\alpha_1$ -antitrypsin: unlike albumin,  $\alpha_1$ -antitrypsin passes into the stool undegraded and reflects enteric protein loss but does not define etiology (can be increased in gut graft-versus-host disease, lymphangiectasia, severe heart failure, etc.)

## References

- 1 Tschudy M, Arcara K (ed): The Harriet Lane Handbook, ed 19. Philadelphia, Mosby, 2012, pp 639–647.
- 2 Kleinman R (ed): Pediatric Nutrition Handbook, ed 6. Elk Grove Village, American Academy of Pediatrics, 2009, pp 573–575.
- 3 Benedict A, Gilger M, Klish W, Motil K, Phillips S, Shulman R, Terrazas N, Thomas J: The Baylor Pediatric Nutrition Handbook, ed 4. Houston, Baylor College of Medicine, 2004, pp 34–43.
- 4 Walker A, Goulet O, Kleinman R, Sherman P, Shneider B, Sanderson I (ed): Pediatric Gastrointestinal Disease, ed 4. Hamilton, BC Decker, 2004, p 195.
- 5 Sauberlich H: Laboratory Tests for the Assessment of Nutritional Status, ed 2. Boca Raton, CRC Press, 1999.
- 6 Ravel R: Clinical Laboratory Medicine, ed 6. St Louis, Mosby, 1995, pp 655, 433.
- 7 Guandalini S: Essential Pediatric Gastroenterology, Hepatology, and Nutrition. New York, McGraw-Hill, 2005, pp 133–134.
- 8 Leeds JS, Oppong K, Sanders DS: The role of fecal elastase-1 in detecting exocrine pancreatic disease. *Nat Rev Gastroenterol Hepatol* 2011;8:405–415.

### 1.3 Nutritional Needs

## 1.3.1. Nutrient Intake Values: Concepts and Applications

Berthold Koletzko

#### Key Words

Nutrient recommendations · Nutrient requirements · Upper safe levels of intake · Extrapolation · Interpolation

#### Key Messages

- Nutrient intake values (NIV) provide estimates on appropriate dietary substrate supply for populations of healthy people
- The average nutrient requirement is the estimated median requirement for a particular age- and sex-specific group
- The population reference intake is the intake that meets the nutrient needs of practically all healthy individuals in a particular population
- Major uncertainties exist in the establishment of NIV for infants, children and adolescents due to limited scientific data. Deriving NIV from observed nutrient intakes (e.g. the nutrient supply provided by human milk) or extrapolation from other age groups has considerable limitations

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#### Introduction

Nutrient intake values (NIV) comprise a set of recommendations on dietary substrate supply for populations of healthy people. NIV are used to

assess intake data from dietary surveys and food statistics; to provide guidance on appropriate dietary composition, meal provision and food-based dietary guidelines, they serve as the basis for national or regional nutrition policies, nutritional education programmes and food regulations and provide reference points for the labelling of food products if nutrient contents are expressed as a percentage of an NIV [1, 2]. The term NIV has been agreed upon by an expert consultation convened by the United Nations University's Food and Nutrition Programme in collaboration with the FAO, WHO and UNICEF [3], rather than the terms 'nutrient reference values' (previously used in Australia and New Zealand), 'reference values for nutrient supply' (in Germany/Austria/Switzerland), 'dietary reference values' (in the UK), 'dietary reference intakes' or, previously, 'recommended dietary allowances' (RDA; in the USA and Canada) [3].

Conceptually, NIV are based on physiological requirements, which are defined as the amounts and chemical forms of nutrients needed systematically to maintain normal health and development without disturbance of the metabolism of any other nutrient and without extreme homeostatic processes, excessive depletion and/or surplus in bodily depots [1, 4–6]. The dietary re-

quirement of a nutrient is the intake sufficient to meet the physiological requirement, considering nutrient bioavailability from foodstuffs. NIV reflect the estimated distributions of nutrient intakes required to achieve a specific outcome in a defined population considered healthy, but for many nutrients, this distribution of requirements and the modifying biological and environmental factors are not well known, which results in considerable uncertainty regarding NIV. Therefore, NIV should be considered approximations that reflect the often limited data available. NIV are even more uncertain for infants and young children, on whom original data are particularly scarce, and, hence, NIV are often derived from the interpolation of data from other age groups, which must be expected to yield inaccurate values. It is important to remember that NIV refer to populations but not to individuals. NIV do not allow us to determine an insufficient nutrient intake or a nutrient deficiency in an individual, or to accurately determine nutrient needs in disease states.

## Definitions of NIV

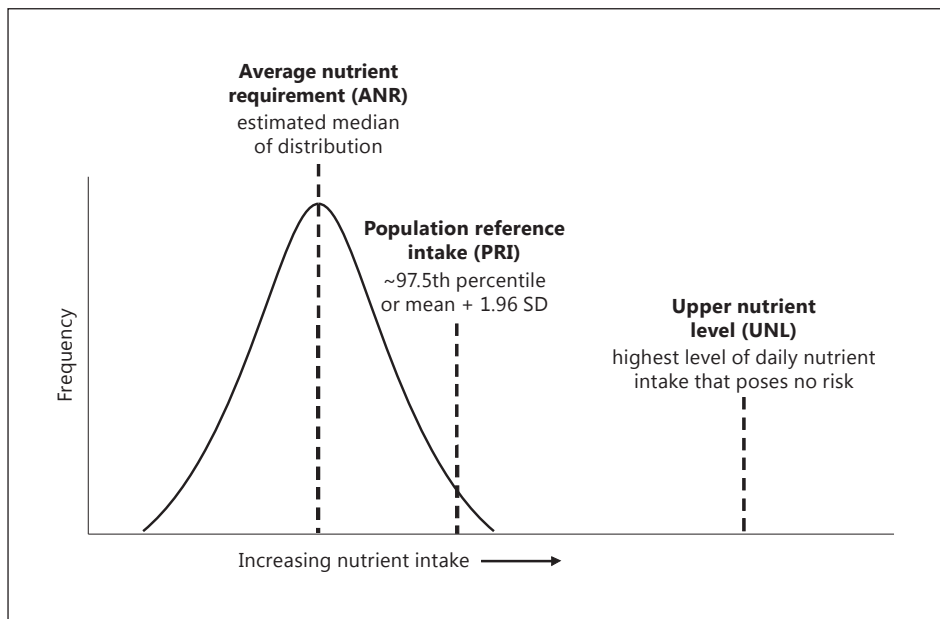
NIV for populations are generally estimated based on the concept that individual requirements follow a statistically normal distribution (bell-shaped curve in fig. 1). The average nutrient requirement (ANR; also called ‘estimated average requirement’) is the estimated average of the median requirement of a specific nutrient in the population derived from a statistical distribution of requirement criterion and for a particular age- and sex-specific group based on a specific biological end point or biochemical measure. The population reference intake (PRI; also called ‘individual nutrient level 97%’, ‘reference nutrient intake’ or RDA) is the nutrient intake considered adequate to meet the known nutrient needs of practically all healthy individuals in a particular age- and sex-specific group. Based on the assumed sta-

tistical distribution of requirements, the PRI is set at a level of intake that meets the needs of 97% of the population (mean + 2 SD) (fig. 1). The PRI value is generally used as the target for provision of essential nutrients to populations and as the reference point for the nutrient labelling of foods, with the exception of energy, where the ANR is used because the provision of energy equivalent to the PRI would result in overfeeding and induction of obesity in about one half of the population. The upper nutrient level (UNL; or upper tolerable intake level) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals of a particular age- and sex-specific group. Ideally, the UNL is based on an analysis of the statistical distribution of risk for high nutrient intakes. The UNL is generally set at a level where the risk of excessive intake is practically non-existent. A nutrient intake equal to or higher than the UNL should be avoided on a chronic basis.

Examples of NIV for children and adolescents are provided in Annex 4.3.

## Limitations to the Estimation of NIV

The concept of a near-normal, symmetrical distribution of nutrient requirements (fig. 1) is known not to be correct for a number of nutrients. Examples are the nutrient needs for iron, vitamin D and polyunsaturated fatty acids. Iron requirements are not normally distributed, with high needs in menstruating women, particularly in those with substantial blood losses. Vitamin D requirements depend on endogenous synthesis in the skin and hence on variation of UV light exposure with geographic location and the time of the year, as well as on biological determinants such as the degree of skin pigmentation and genetic variations in the vitamin D receptor. The dietary needs of essential fatty acids vary considerably with genetic polymorphisms for the fatty acid desaturation enzymes  $\Delta^6$  and  $\Delta^5$  desaturases that



**Fig. 1.** Conceptual basis for NIV.

determine the relative turnover of polyunsaturated fatty acids [7].

The establishment of NIV for infants, children and adolescents is further hampered by severe limitations to the available scientific data obtained from healthy children [8]. This is unfortunate because infants, children and adolescents have relatively large nutrient needs due to their growth and development, and adequate substrate supply is of utmost importance to support their short- and long-term health, well-being and performance [5]. Current reference values for nutrient intakes vary considerably (see Annex 4.3), partly due to the limitations to the available scientific database and partly due to major differences in underlying concepts, definitions and terminology [8].

Due to a lack of adequate scientific studies, NIV for children are often based on observed nutrient intakes of groups of children in apparent good health. However, this approach is weak, because it assumes that the subjects are in good

health and are achieving their full genetic potential and that their diets are quantitatively and qualitatively appropriate and free from adverse long-term effects. The concerns with respect to this approach are strengthened by the recent evidence on the long-term effects of early nutrition on metabolic programming and the subsequent risk of hypertension, obesity, diabetes mellitus and cardiovascular disease in adult life [9–11].

The derivation of NIV from observed intakes is a standard approach for infants during the first 6 months of life, when the intakes of breastfed babies are considered an appropriate guide to optimal nutritional supply. However, this approach has major limitations because the actual metabolizable substrate intakes of breastfed infants are not well determined. The volume of milk consumed varies between about 550 and 1,100 ml/day, and milk composition differs between women and with changes during the course of lactation, during the day and even during a single feeding. Moreover, the bioavailability of sub-



strates and their metabolism differs between infants fed human milk and those fed infant formula and complementary feeds, which can result in differences in dietary requirements. Therefore, human milk composition and the nutrient supply to breastfed infants may not always provide useful guidance for infants that are not exclusively breastfed.

Due to the paucity of original research data for estimating nutrient requirements in the paediatric age group, very often NIV are extrapolated from data for other age groups. Frequently, this involves extrapolation from adults to children and adolescents. Examples of extrapolation methods that are used include body size (weight or metabolic weight), energy intakes for age, or factorial estimates of requirements for growth [8]. However, there is no truly correct method for extrapolation that would result in physiologically adequate NIV for infants, children and adolescents. It is important that the rationale or scientific basis for the method chosen should be completely transparent and thoroughly described for each nutrient and life stage group. Extrapolation is always the second choice, and the use of innovative, non-invasive methods or of existing methods (e.g. stable isotopes) is encouraged to determine nutrient requirements of infants, children and adolescents [8].

## References

- 1 Aggett PJ, Bresson J, Haschke F, Hernell O, Koletzko B, Lafeber HN, Michaelsen KF, Micheli J, Ormiston A, Rey J, Salazar de Sousa J, Weaver L: Recommended dietary allowances (RDAs), recommended dietary intakes (RDIs), recommended nutrient intakes (RNIs), and population reference intakes (PRIs) are not 'recommended intakes'. *J Pediatr Gastroenterol Nutr* 1997;25:236–241.
- 2 Koletzko B, Poindexter B, Uauy R: Recommended nutrient intake levels for stable, fully enterally fed very low birth

- weight infants; in Koletzko B, Poindexter B, Uauy R (eds): *Nutritional Care of Preterm Infants*. Basel, Karger, 2014, pp 300–305.
- 3 King JC, Garza C: Harmonization of nutrient intake values. *Food Nutr Bull* 2007;28:S3–S12.
- 4 Hermoso M, Vollhardt C, Bergmann K, Koletzko B: Critical micronutrients in pregnancy, lactation, and infancy: considerations on vitamin D, folic acid, and iron, and priorities for future research. *Ann Nutr Metab* 2011;59:5–9.
- 5 Iglesia I, Doets EL, Bel-Serrat S, Roman

- B, Hermoso M, Pena Quintana L, Garcia-Luzardo MR, Santana-Salguero B, Garcia-Santos Y, Vucic V, Andersen LF, Perez-Rodrigo C, Aranceta J, Cavelaars A, Decsi T, Serra-Majem L, Gurinovic M, Cetin I, Koletzko B, Moreno LA: Physiological and public health basis for assessing micronutrient requirements in children and adolescents. The EURRECA network. *Matern Child Nutr* 2010;6(suppl 2):84–99.
- 6 Uauy R, Koletzko B: Defining the nutritional needs of preterm infants. *World Rev Nutr Diet* 2014;110:4–10.

## Conclusions

- NIV provide an estimate for adequate nutrient provision to populations considered healthy, but they do not determine the optimal nutrient supply for an individual
- PRI (also called reference nutrient intakes or RDA) are the levels of intake that meet the needs of almost all healthy individuals of a given age and sex group
- The diet for healthy children should generally provide nutrient intakes matching the PRI, except for energy, where ANR provide guidance on appropriate intakes for groups
- Children affected by disease or malnutrition, or those in whom catch-up growth is desired, may have nutrient needs that differ markedly from PRI

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- 7 Koletzko B, Lattka E, Zeilinger S, Illig T, Steer C: Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. *Am J Clin Nutr* 2011;93:211–219.
- 8 Atkinson SA, Koletzko B: Determining life-stage groups and extrapolating nutrient intake values (NIVs). *Food Nutr Bull* 2007;28:S61–S76.
- 9 Brands B, Demmelmair H, Koletzko B; EarlyNutrition Project: How growth due to infant nutrition influences obesity and later disease risk. *Acta Paediatr* 2014;103:578–585.
- 10 Berti C, Cetin I, Agostoni C, Desoye G, Devlieger R, Emmett PM, Ensenauer R, Hauner H, Herrera E, Hoesli I, Krauss-Etschmann S, Olsen SF, Schaefer-Graf U, Schiessl B, Symonds ME, Koletzko B: Pregnancy and infants' outcome: nutritional and metabolic implications. *Crit Rev Food Sci Nutr* 2014, Epub ahead of print.
- 11 Koletzko B, Brands B, Chourdakis M, Cramer S, Grote V, Hellmuth C, Kirshberg F, Prell C, Rzehak P, Uhl U, Weber M: The power of programming and the early nutrition project: opportunities for health promotion by nutrition during the first thousand days of life and beyond. *Ann Nutr Metab* 2014;64:141–150.





### 1.3 Nutritional Needs

## 1.3.2 Energy Requirements of Infants, Children and Adolescents

Nancy F. Butte

#### Key Words

Energy needs, requirements · Basal metabolic rate · Physical activity level · Energy cost of growth

#### Key Messages

- Energy requirements of infants, children and adolescents are defined as the amount of energy needed to balance total energy expenditure at a desirable level of physical activity, and to support optimal growth and development consistent with long-term health
- Recommendations for energy intake are based on the average requirement of the population to avoid energy intakes that exceed the requirements
- Recommendations for energy intake to support a moderately active lifestyle are encouraged to maintain fitness and health and to reduce the risk of overnutrition

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#### Introduction

Energy requirements of infants, children and adolescents are defined as the amount of energy needed to balance total energy expenditure (TEE) at a

desirable level of physical activity, and to support optimal growth and development consistent with long-term health [1]. Unlike recommendations for other nutrients, which meet or exceed the requirements of practically all individuals in the population, recommendations for energy intake are based on the average requirement of the population to avoid energy intakes that exceed requirements. Recommendations for energy intake and physical activity are intended to support and maintain the growth and development of well-nourished and healthy infants, children and adolescents. The 2004 Food and Agriculture Organization (FAO)/WHO/United Nations University (UNU) recommendations for energy intake are based upon estimates of TEE and an allowance for growth [1]. For infants, TEE is predicted from measurements of TEE by the stable isotope method of doubly labeled water (DLW). For children and adolescents, heart rate monitoring and the DLW method were used to predict TEE. The energy cost of growth was derived from average growth velocities and the composition of weight gain.

Energy requirements during growth and development can be partitioned into compo-

**Table 1.** Schofield equations for estimating BMR from weight (kilograms) [3] in children

Under 3 years		
Males	BMR (MJ/day) = 0.249 weight – 0.127	SEE = 0.293
Females	BMR (MJ/day) = 0.244 weight – 0.130	SEE = 0.246
Males	BMR (kcal/day) = 59.5 weight – 30.4	SEE = 70
Females	BMR (kcal/day) = 58.3 weight – 31.1	SEE = 59
3–10 years		
Males	BMR (MJ/day) = 0.095 weight + 2.110	SEE = 0.280
Females	BMR (MJ/day) = 0.085 weight + 2.033	SEE = 0.292
Males	BMR (kcal/day) = 22.7 weight + 504.3	SEE = 67
Females	BMR (kcal/day) = 20.3 weight + 485.9	SEE = 70
10–18 years		
Males	BMR (MJ/day) = 0.074 weight + 2.754	SEE = 0.440
Females	BMR (MJ/day) = 0.056 weight + 2.898	SEE = 0.466
Males	BMR (kcal/day) = 17.7 weight + 658.2	SEE = 105
Females	BMR (kcal/day) = 13.4 weight + 692.6	SEE = 111
SEE = Standard error of estimation.		

nents of basal metabolism, thermogenesis, physical activity and energy cost of growth [2]. Basal metabolism is defined as that energy expended to maintain cellular and tissue processes fundamental to the organism. The Schofield equations [3] to predict basal metabolic rate (BMR) are presented in table 1. Thermic effect of feeding refers to the energy required for the ingestion and digestion of food and for the absorption, transport and utilization of nutrients. The thermic effect of feeding amounts to about 10% of daily energy expenditure. Thermoregulation can constitute an additional energy cost when exposed to temperatures below and above thermoneutrality; however, clothing and behavior usually counteract such environmental influences. Physical activity is the most variable component of energy requirements, and entails both obligatory and discretionary physical activities. The energy cost of growth as a percentage of total energy requirements decreases from around 35% at 1 month to 3% at 12 months of age, and remains low until the pubertal growth spurt, at which time it increases to about 4% [2].

## Approaches to Estimating Energy Requirements

Energy requirements can be derived from TEE based on the factorial approach, measurements using the DLW method or heart rate monitoring. DLW is a stable (nonradioactive) isotope method that provides an estimate of TEE in free-living individuals [4]. By the heart rate method, TEE is predicted from the heart rate based on the nearly linear relationship between heart rate and oxygen consumption during submaximal muscular work [5].

## Energy Requirements of Infants

In the recent FAO/WHO/UNU recommendations [1], the average energy requirements of infants were based upon the TEE and growth rates of healthy, well-nourished infants (tables 2, 3; fig. 1, 2). In the FAO/WHO/UNU report, the median weight-for-age and monthly rates of weight gain of the WHO pooled breastfed data set were used to calculate energy requirements [6]. A prediction equation (1) for TEE was developed, based on

**Table 2.** Energy requirements of boys during the first year of life

Age, months	2002 Institute of Medicine [15]		2004 FAO/WHO/UNU [1]			
	MJ/day	kcal/day	MJ/day	kcal/day	kJ/kg/day	kcal/kg/day
0–1	1.975	472	2.166	518	473	113
1–2	2.372	567	2.387	570	434	104
2–3	2.393	572	2.494	596	397	95
3–4	2.293	548	2.380	569	343	82
4–5	2.494	596	2.546	608	340	81
5–6	2.699	645	2.674	639	337	81
6–7	2.795	668	2.730	653	329	79
7–8	2.971	710	2.845	680	330	79
8–9	3.121	746	2.936	702	330	79
9–10	3.318	793	3.058	731	335	80
10–11	3.418	817	3.145	752	336	80
11–12	3.531	844	3.243	775	337	81

**Table 3.** Energy requirements of girls during the first year of life

Age, months	2002 Institute of Medicine [15]		2004 FAO/WHO/UNU [1]			
	MJ/day	kcal/day	MJ/day	kcal/day	kJ/kg/day	kcal/kg/day
0–1	1.833	438	1.942	464	447	107
1–2	2.092	500	2.162	517	421	101
2–3	2.180	521	2.301	550	395	94
3–4	2.125	508	2.245	537	350	84
4–5	2.314	553	2.389	571	345	83
5–6	2.481	593	2.507	599	341	82
6–7	2.544	608	2.525	604	328	78
7–8	2.690	643	2.630	629	328	78
8–9	2.837	678	2.728	652	328	78
9–10	3.000	717	2.828	676	331	79
10–11	3.105	742	2.902	694	331	79
11–12	3.213	768	2.981	712	331	79

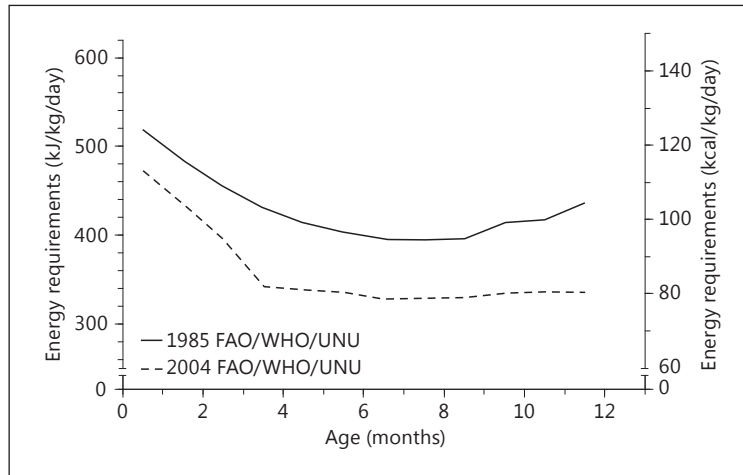
longitudinal data on 76 healthy infants studied at 3-month intervals for the first 2 years of life [2, 7]:

$$\begin{aligned}
 \text{TEE (MJ/day)} &= \\
 &-0.416 + 0.371 \text{ weight (kg)} \text{ SEE} = 0.456 \\
 \text{TEE (kcal/day)} &= \\
 &-99.4 + 88.6 \text{ weight (kg)} \text{ SEE} = 109, \quad (1)
 \end{aligned}$$

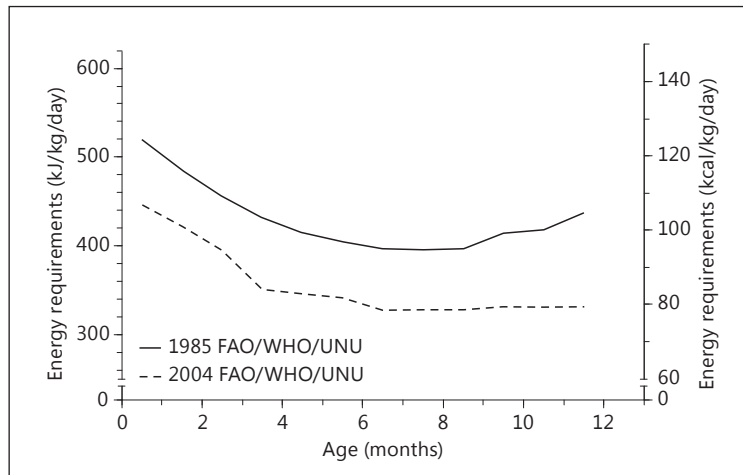
in which SEE is the standard error of estimation.

Assuming energy equivalents of protein (23.6 kJ/g or 5.65 kcal/g) and fat (38.7 kJ/g or 9.25 kcal/g), and body composition changes during infancy [8, 9], energy deposition decreases substantially during the first year of life from approximately 730 kJ/day (175 kcal/day) at 0–3 months to 250 kJ/day (60 kcal/day) at 4–6 months and 85 kJ/day (20 kcal/day) at 7–12 months of age.

**Fig. 1.** 2004 FAO/WHO/UNU energy requirements for boys 0–12 months of age.



**Fig. 2.** 2004 FAO/WHO/UNU energy requirements for girls 0–12 months of age.



### Energy Requirements of Children and Adolescents

In the 2004 FAO/WHO/UNU report [1], DLW and heart rate monitoring were used to predict the TEE of children and adolescents. TEE data on 801 boys and 808 girls aged 1–18 years were compiled from Canada, Denmark, Italy, Sweden, The Netherlands, Brazil, Chile, Columbia, Guatemala and Mexico, from which prediction equations for TEE were developed for boys and girls [10]:

*For boys:*

$$\begin{aligned} \text{TEE (MJ/day)} &= 1.298 + 0.265 \text{ weight (kg)} - 0.0011 \text{ weight}^2 \text{ (kg}^2\text{)} \text{ SEE} = 0.518 \\ \text{TEE (kcal/day)} &= 310.2 + 63.3 \text{ weight (kg)} - 0.263 \text{ weight}^2 \text{ (kg}^2\text{)} \text{ SEE} = 124 \end{aligned} \quad (2)$$

*For girls:*

$$\begin{aligned} \text{TEE (MJ/day)} &= 1.102 + 0.273 \text{ weight (kg)} - 0.0019 \text{ weight}^2 \text{ (kg}^2\text{)} \text{ SEE} = 0.650 \\ \text{TEE (kcal/day)} &= 263.4 + 65.3 \text{ weight (kg)} - 0.454 \text{ weight}^2 \text{ (kg}^2\text{)} \text{ SEE} = 155 \end{aligned} \quad (3)$$

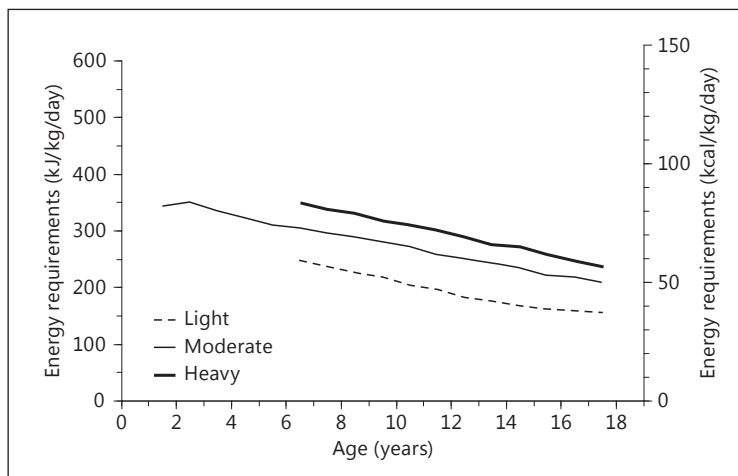
**Table 4.** Energy requirements of boys 0–18 years of age, computed for active (Institute of Medicine) or moderate (FAO/WHO/UNU) physical activity level

Age, years	2002 Institute of Medicine [15]		2004 FAO/WHO/UNU [1]			
	MJ/day	kcal/day	MJ/day	kcal/day	kJ/kg/day	kcal/kg/day
1–2	3.9	930	4.0	950	345	82
2–3	4.7	1,120	4.7	1,125	350	84
3–4	6.2	1,485	5.2	1,250	334	80
4–5	6.6	1,566	5.7	1,350	322	77
5–6	6.9	1,658	6.1	1,475	312	74
6–7	7.3	1,742	6.6	1,575	303	73
7–8	7.7	1,840	7.1	1,700	295	71
8–9	8.1	1,931	7.7	1,825	287	69
9–10	8.5	2,043	8.3	1,975	279	67
10–11	9.0	2,149	9.0	2,150	270	65
11–12	9.5	2,279	9.8	2,350	261	62
12–13	10.2	2,428	10.7	2,550	252	60
13–14	11.0	2,618	11.6	2,775	242	58
14–15	11.8	2,829	12.5	3,000	233	56
15–16	12.6	3,013	13.3	3,175	224	53
16–17	13.2	3,152	13.9	3,325	216	52
17–18	13.5	3,226	14.3	3,400	210	50

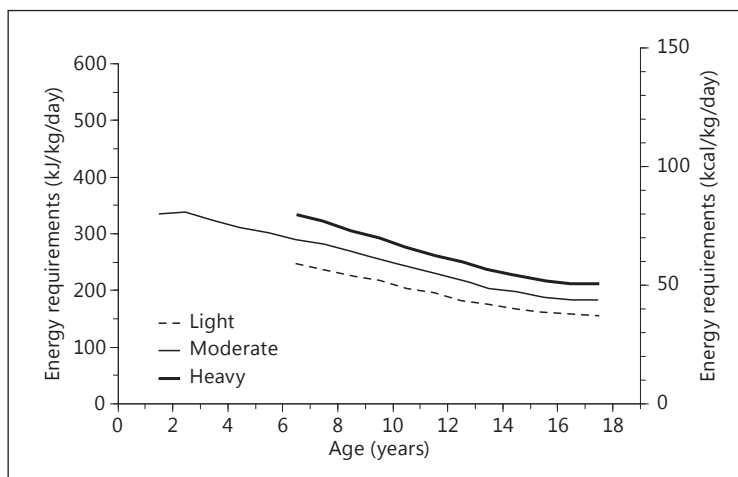
**Table 5.** Energy requirements of girls 0–18 years of age, computed for active (Institute of Medicine) or moderate (FAO/WHO/UNU) physical activity level

Age, years	2002 Institute of Medicine [15]		2004 FAO/WHO/UNU [1]			
	MJ/day	kcal/day	MJ/day	kcal/day	kJ/kg/day	kcal/kg/day
1–2	3.6	864	3.6	850	335	80
2–3	4.5	1,072	4.4	1,050	339	81
3–4	5.8	1,395	4.8	1,150	322	77
4–5	6.2	1,475	5.2	1,250	310	74
5–6	6.5	1,557	5.6	1,325	301	72
6–7	6.9	1,642	6.0	1,425	289	69
7–8	7.2	1,719	6.5	1,550	280	67
8–9	7.6	1,810	7.1	1,700	268	64
9–10	7.9	1,890	7.7	1,850	255	61
10–11	8.3	1,972	8.4	2,000	243	58
11–12	8.7	2,071	9.0	2,150	230	55
12–13	9.1	2,183	9.5	2,275	218	52
13–14	9.5	2,281	10.0	2,375	205	49
14–15	9.8	2,334	10.2	2,450	197	47
15–16	9.9	2,362	10.4	2,500	188	45
16–17	9.9	2,368	10.5	2,500	184	44
17–18	9.8	2,336	10.5	2,500	184	44

**Fig. 3.** 2004 FAO/WHO/UNU energy requirements of boys 1–18 years of age at 3 levels of habitual physical activity.



**Fig. 4.** 2004 FAO/WHO/UNU energy requirement of girls 1–18 years of age at 3 levels of habitual physical activity.



During adolescence, sex differences in body size and composition are accentuated [11]. The energy cost of growth was based on mean rates of weight gain calculated from the WHO weight-for-age standards [12]. The composition of weight gained was assumed to be 10% fat with an energy content of 38.7 kJ/g (9.25 kcal/g), 20% protein with an energy content of 23.6 kJ/g (5.65 kcal/g), or equivalent to 8.6 kJ/g (2.1 kcal/g). The energy requirements of boys and girls aged 0–18 years are summarized in tables 4 and 5 and figures 3 and 4.

### Recommendations for Physical Activity

A minimum of 60 min/day of moderate-intensity physical activity is recommended for children and adolescents [1], although there is no direct experimental or epidemiological evidence on the minimal or optimal frequency, duration or intensity of exercise that promotes health and well-being of children and adolescents [13]. Regular physical activity is often associated with decreased body fat in both sexes and, sometimes, increased fat-free mass at least in males. Physical activity is

associated with greater skeletal mineralization, bone density and bone mass.

Energy requirements must be adjusted in accordance with habitual physical activity. Torun [14] compiled 42 studies on the activity patterns of 6,400 children living in urban, rural, industrialized and developing settings from around the world. The TEE of rural boys and girls was 10, 15 and 25% higher at 5–9, 10–14 and 15–19 years of age, respectively, than that of their urban counterparts. As part of the compilation of TEE values described above, physical activity level (PAL) values were estimated by using measured or predicted BMR [10]. The Schofield equations for BMR [3] were used to predict PAL for children and adolescents if not provided in the original publication. The average PAL (1.7) from these studies reflects a moderate level of activity. To estimate the energy requirements of children with different levels of habitual physical activity, a 15% allow-

ance was subtracted or added to the average PAL to estimate light (PAL = 1.5) and vigorous (PAL = 2.0) levels of activity in the 2004 FAO/WHO/UNU report.

## Conclusions

- Energy requirements of infants, children and adolescents are defined as the amount of energy needed to balance TEE at a desirable level of physical activity, and to support optimal growth and development consistent with long-term health [1]
- Even though energy requirements are also presented for varying levels of physical activity, moderately active lifestyles are strongly encouraged for children and adolescents to maintain fitness and health and to reduce the risk of overnutrition

## References

- 1 FAO/WHO/UNU Expert Consultation. Human energy requirements. Rome, World Health Organization, 2004.
- 2 Butte NF: Energy requirements of infants. *Public Health Nutr* 2005;8:953–967.
- 3 Schofield WN, Schofield C, James WPT: Basal metabolic rate: review and prediction, together with an annotated bibliography of source material. *Hum Nutr Clin Nutr* 1985;39C:1–96.
- 4 Schoeller DA, van Santen E: Measurement of energy expenditure in humans by doubly labeled water method. *J Appl Physiol* 1982;53:955–959.
- 5 Berggren G, Christensen EH: Heart rate and body temperature as indices of metabolic rate during work. *Arbeitsphysiologie* 1950;14:255–260.
- 6 WHO Working Group on Infant Growth: An evaluation of infant growth. Geneva, Nutrition Unit, World Health Organization, 1994, vol 94, pp 1–83.
- 7 Butte NF, Wong WW, Hopkinson JM, Heinz CJ, Mehta NR, Smith EO: Energy requirements derived from total energy expenditure and energy deposition during the first 2 years of life. *Am J Clin Nutr* 2000;72:1558–1569.
- 8 Butte NF, Hopkinson JM, Wong WW, Smith EO, Ellis KJ: Body composition during the first two years of life: an updated reference. *Pediatr Res* 2000;47:578–585.
- 9 de Bruin NC, Degenhart HJ, Gál S, Westertep KR, Stijnen T, Visser HKA: Energy utilization and growth in breast-fed and formula-fed infants measured prospectively during the first year of life. *Am J Clin Nutr* 1998;67:885–896.
- 10 Torun B: Energy requirements of children and adolescents. *Public Health Nutr* 2005;8:968–993.
- 11 Forbes GB: Human Body Composition: Growth, Aging, Nutrition, and Activity. New York, Springer, 1987.
- 12 World Health Organization: Measuring change in nutritional status. Geneva, World Health Organization, 1983.
- 13 Boreham C, Riddoch C: The physical activity, fitness and health of children. *J Sports Sci* 2001;19:915–929.
- 14 Torun B: Energy cost of various physical activities in healthy children: activity, energy expenditure and energy requirements of infants and children. Lausanne, International Dietary Energy Consultancy Group, 1990, pp 139–183.
- 15 Institute of Medicine: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, National Academies Press, 2002.

### 1.3 Nutritional Needs

## 1.3.3 Protein

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#### Key Words

Protein · Amino acids · Requirement · Infants · Children

#### Key Messages

- A diet must contain a balanced mixture of all amino acids
- This can most easily be achieved by daily ingestion of animal protein; an alternative is a complementary mixture of plant proteins

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#### Introduction

Protein, derived from the Greek word *proteos*, which means 'primary' or 'taking first place', is the major structural component of all cells in the body. Proteins also function as enzymes, transport carriers and hormones, and their component amino acids are required for the synthesis of nucleic acids, hormones, vitamins and other important molecules.

The 20  $\alpha$ -amino acids which are part of proteins are classified based on their nutritional im-

portance into indispensable (essential) amino acids, conditionally indispensable (conditionally essential) amino acids and dispensable (nonessential) amino acids (table 1).

Protein in the body is in a dynamic state referred to as protein turnover, which involves continuous degradation to free amino acids and re-synthesis of new proteins. The free amino acids are also constantly degraded and oxidized to carbon dioxide and nitrogenous end products, principally urea and ammonia. Oxidation is an irreversible step and leads to so-called obligatory losses. Dietary protein is necessary to replenish these losses of amino acids to maintain protein homeostasis. Furthermore, in children, there is an increased need for dietary protein to allow new tissue growth.

The requirement of dietary protein is therefore composed of two components: maintenance and growth. The requirement of protein in children and adults has earlier been analyzed in detail [1–3], and that of individual amino acids is currently investigated but has not yet been defined by the WHO/FAO.



## Protein Requirement

The protein requirement is defined as the minimum intake of high-quality dietary protein (see Protein Quality) that will provide the means for maintaining an appropriate body composition and will permit growth at a normal rate for age, assuming an energy balance and normal physical activity.

## Expression of Requirement

The protein requirement is expressed as the estimated average requirement (EAR) or the average requirement of the population. Due to lack of conclusive data from empirical studies, the EAR is calculated by a factorial method which includes (1) the requirement for maintenance, estimated from nitrogen balance studies in children, and (2) the requirement for growth, estimated from rates of protein deposition which are derived from body composition analysis [4, 5] and the efficiency of protein utilization for each age group.

The recommended dietary allowance (RDA) is the safe level of intake which will satisfy the protein needs of nearly all individuals (97.5%) in the population. The RDA for protein is the EAR + 2 times the standard deviation of the EAR of each age group.

## Protein Requirements for Infants and Children

### *Infants: 0–6 Months*

Human milk is the optimal source of nutrients for normal, full-term infants throughout the first year of life and is recommended as the sole nutritional source for infants during the first 4–6 months of life. The recommended intakes of protein are based on an adequate intake (AI) that reflects the mean protein intake of infants fed human milk. For infants 0–6 months of age,

**Table 1.** Indispensable, conditionally indispensable and dispensable amino acids for humans

Indispensable	Conditionally indispensable	Dispensable
Histidine	Arginine	Alanine
Isoleucine	Cysteine	Aspartic acid
Leucine	Glutamine	Asparagine
Lysine	Glycine	Glutamic acid
Methionine	Proline	Serine
Phenylalanine	Tyrosine	
Threonine		
Tryptophan		
Valine		

the average milk intake is 0.78 liters per day and the average protein content of human milk is 11.7 g/l. Therefore, the AI of protein for infants 0–6 months of age is 9.1 g/day or 1.52 g/kg per day.

### *Infants: 7–12 Months*

During the second 6 months of life, solid foods become a more important part of the diet of infants and add a significant amount of protein to the diet. The recommendation is for continued feeding of human milk for infants through 9–12 months of age with appropriate introduction of solid foods. The EAR and RDA are 1.0 and 1.2 g protein/kg body weight per day, respectively (table 2).

### *Children: 1–18 Years*

Protein requirements for older children are calculated and recommended based on life stage groups representing different velocities of growth and endocrine status: toddlers (1–3 years), early childhood (4–8 years), puberty (9–13 years) and adolescence (14–18 years; table 2). During these stages, there is a continuing but slow decline in protein needs relative to weight. The EAR determined by the factorial method is set at the average for boys and girls in each age group except adolescence (table 2).

**Table 2.** Protein requirement for infants, children and adolescents

Age	Average requirement (EAR) <sup>a</sup> , g protein/kg body weight per day	Safe level of intake (RDA) <sup>b</sup> , g protein/kg body weight per day	Intake per day, g
7–12 months	1.0	1.2	11
1–3 years	0.87	1.05	13
4–8 years	0.76	0.95	19
9–13 years	0.76	0.95	34
14–18 years (boys)	0.73	0.85	52
14–18 years (girls)	0.71	0.85	46

Data from Dietary Reference Intakes 2002/2005 [3]. <sup>a</sup>Calculated from maintenance + growth (rate of protein deposition × efficiency of protein utilization). <sup>b</sup>Calculated from EAR + 2 × SD of EAR.

### Amino Acid Requirement for Infants and Children

The 9 indispensable amino acids (IAA; table 1) need to be obtained from the diet, and, therefore, requirements have been defined for them. The amino acid requirements (AI) for young infants (0–6 months) are based on an average human milk intake of 0.78 liters per day and the mean content of each IAA in human milk (table 3).

The EAR of IAA in older infants (7–12 months) and children (1–18 years) are calculated using the factorial method (table 4). The method assumes that the maintenance requirement of each IAA is similar to that of adults and the requirements differ in children only by their growth needs. The requirement for growth is estimated from the rate of protein deposition, the amino acid composition of whole-body protein and the efficiency of protein utilization.

Recently, it was shown that the maintenance requirements for adults and children are similar [6–8]. For a detailed review on the methods to determine amino acid requirements, refer to Pencharz and Ball [9]. Of late, neonatal amino acid requirements became available for some essential amino acids [10, 11].

The conditionally IAA (table 1) are those that the infant or child is unable to produce in suffi-

**Table 3.** IAA requirements for young infants 0–6 months of age

IAA	AI <sup>a</sup> , mg/kg per day	Intake per day, mg
Histidine	36	214
Isoleucine	88	529
Leucine	156	938
Lysine	107	640
Methionine + cysteine	59	353
Phenylalanine + tyrosine	135	807
Threonine	73	436
Tryptophan	28	167
Valine	87	519

Data from Dietary Reference Intakes 2002/2005 [3]. <sup>a</sup>Calculated from the average volume of human milk intake and the mean IAA content of human milk.

cient amounts and, hence, all or part of the daily needs for that amino acid must be provided by the diet.

### Protein Quality

The requirement of protein is affected not only by the quantity but also by the quality of the protein source. Different sources of protein vary widely in their chemical composition and nutritional value.

**Table 4.** IAA requirements for older infants, children and adolescents

Age	Average requirement (EAR) <sup>a</sup> , mg/kg per day	Safe level of intake (RDA) <sup>b</sup> , mg/kg per day	Age	Average requirement (EAR) <sup>a</sup> , mg/kg per day	Safe level of intake (RDA) <sup>b</sup> , mg/kg per day
<i>7–12 months</i>			<i>9–13 years (girls)</i>		
Histidine	22	32	Histidine	12	15
Isoleucine	30	43	Isoleucine	17	21
Leucine	65	93	Leucine	38	47
Lysine	62	89	Lysine	35	43
Methionine + cysteine	30	43	Methionine + cysteine	17	21
Phenylalanine + tyrosine	58	84	Phenylalanine + tyrosine	31	38
Threonine	34	49	Threonine	18	22
Tryptophan	9	13	Tryptophan	5	6
Valine	39	58	Valine	22	27
<i>1–3 years</i>			<i>14–18 years (boys)</i>		
Histidine	16	21	Histidine	12	15
Isoleucine	22	28	Isoleucine	17	21
Leucine	48	63	Leucine	38	47
Lysine	45	58	Lysine	35	43
Methionine + cysteine	22	28	Methionine + cysteine	17	21
Phenylalanine + tyrosine	41	54	Phenylalanine + tyrosine	31	38
Threonine	24	32	Threonine	18	22
Tryptophan	6	8	Tryptophan	5	6
Valine	28	37	Valine	22	27
<i>4–8 years</i>			<i>14–18 years (girls)</i>		
Histidine	13	16	Histidine	12	14
Isoleucine	18	22	Isoleucine	16	19
Leucine	40	49	Leucine	35	44
Lysine	37	46	Lysine	32	40
Methionine + cysteine	18	22	Methionine + cysteine	16	19
Phenylalanine + tyrosine	33	41	Phenylalanine + tyrosine	28	35
Threonine	19	24	Threonine	17	21
Tryptophan	5	6	Tryptophan	4	5
Valine	23	28	Valine	20	24
<i>9–13 years (boys)</i>			Data from Dietary Reference Intakes 2002/2005 [3]. <sup>a</sup> Calculated from maintenance + growth (rate of protein deposition × efficiency of protein utilization). <sup>b</sup> Calculated from EAR + 2 × SD of EAR.		
Histidine	13	17			
Isoleucine	18	22			
Leucine	40	49			
Lysine	37	46			
Methionine + cysteine	18	22			
Phenylalanine + tyrosine	33	41			
Threonine	19	24			
Tryptophan	5	6			
Valine	23	28			



The protein quality is principally determined by digestibility and the amino acid composition of the protein. The more important factor of the two is the relative content and metabolic availability of the individual IAA.

If the content of a single IAA in the diet is less than the individual's requirements, then it will limit the utilization of other amino acids and thus prevent normal rates of protein synthesis even when the total nitrogen intake is adequate. Thus, the 'limiting amino acid' will determine the nutritional value of the total nitrogen or protein in the diet.

### Protein Sources

Protein from animal sources such as meat, poultry, fish, eggs, milk, cheese and yogurt provide all 9 IAA and are called 'high-quality' or 'complete proteins'. Protein from plants, legumes, grains, nuts, seeds and vegetables tend to be deficient in one or more of the IAA and are called 'incomplete proteins'. Specifically, cereal grains are deficient in lysine and legumes are deficient in methionine.

Thus, for children who are actively growing, it is recommended to ensure sufficient intake of 'high-quality' protein. Children who restrict their diet to plant proteins should consume a varied diet containing complementary mixtures of protein (e.g. rice with beans) to ensure adequate protein intake.

### Conclusions

- For infants 0–6 months of age, human milk is considered the ideal food and the protein intake to be sufficient to maintain growth and to meet other needs
- The protein requirement for children is affected by both the quantity and quality of the protein source
- All IAA requirements must be met by the diet to ensure normal rates of protein synthesis in healthy children
- Therefore, consumption of 'high-quality' protein rich in the 9 IAA, principally animal sources such as meat, poultry, eggs, milk products and complementary mixtures of plant protein, is recommended

### References

- 1 WHO/FAO/UNU: Protein and amino acid requirements in human nutrition. World Health Organ Tech Rep Ser 2007; 935:1–265.
- 2 Dewey KG, Beaton G, Fjeld C, Lonnerdal B, Reeds P: Protein requirements of infants and children. *Eur J Clin Nutr* 1996; 50(suppl 1):S119–S147.
- 3 Institute of Medicine, Food and Nutrition Board: Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids. Washington, National Academies, 2002/2005.
- 4 Butte NF, Hopkinson JM, Wong WW, Smith EO, Ellis KJ: Body composition during the first 2 years of life: an updated reference. *Pediatr Res* 2000;47:578–585.
- 5 Ellis KJ, Shypailo RJ, Abrams SA, Wong WW: The reference child and adolescent models of body composition. A contemporary comparison. *Ann NY Acad Sci* 2000;904:374–382.
- 6 Mager DR, Wykes LJ, Ball RO, Pencharz PB: Branched-chain amino acid requirements in school-aged children determined by indicator amino acid oxidation (IAAO). *J Nutr* 2003;133: 3540–3545.
- 7 Turner JM, Humayun MA, Elango R, Rafii M, Langos V, Ball RO, Pencharz PB: Total sulfur amino acid requirement of healthy school-aged children as determined by indicator amino acid oxidation technique. *Am J Clin Nutr* 2006;83: 619–623.
- 8 Humayun MA, Turner JM, Elango R, Rafii M, Langos V, Ball RO, Pencharz PB: Minimum methionine requirement and cysteine sparing of methionine in healthy school-age children. *Am J Clin Nutr* 2006;84: 1080–1085.
- 9 Pencharz PB, Ball RO: Different approaches to define individual amino acid requirements. *Annu Rev Nutr* 2003; 23:101–116.
- 10 de Groof F, Huang L, van Vliet I, Voortman GJ, Schierbeek H, Roksnoer LC, Vermes A, Chen C, Huang Y, van Goudoever JB: Branched-chain amino acid requirements for enterally fed term neonates in the first month of life. *Am J Clin Nutr* 2014;99:62–70.
- 11 Huang L, Hogewind-Schoonenboom JE, van Dongen MJ, de Groof F, Voortman GJ, Schierbeek H, Twisk JW, Vermes A, Chen C, Huang Y, van Goudoever JB: Methionine requirement of the enterally fed term infant in the first month of life in the presence of cysteine. *Am J Clin Nutr* 2012;95:1048–1054.

### 1.3 Nutritional Needs

## 1.3.4 Digestible and Non-Digestible Carbohydrates

Iva Hojsak

#### Key Words

Carbohydrate · Fibre · Glycaemic carbohydrate · Prebiotics

#### Key Messages

- A diet rich in slowly absorbed carbohydrates should be promoted while limiting the supply of rapidly absorbed carbohydrates and simple sugars
- Recommended intake of carbohydrates should be 45–60% of total energy
- Avoidance of frequent consumption of juice or other sugar-containing drinks should be recommended
- Fibres, especially insoluble, can significantly increase stool mass and improve its consistency. Intake of 2 g per 1 MJ of energy is considered adequate
- Prebiotic carbohydrates alter the balance of the gut microflora towards a healthier one.

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#### Introduction

An appropriate diet containing sufficient energy is essential during the period of infancy and childhood due to rapid growth and development. Digestible dietary carbohydrates are the main source of energy – primarily lactose during infancy, and

starch and sugars later in life [1]. Based on their chemical structure, carbohydrates are classified as sugars, oligosaccharides and polysaccharides (table 1) [2]. Another classification is based on metabolic pathways and physiological effects. Carbohydrates which provide the body with monosaccharides are defined as ‘digestible’ (available or glycaemic) and carbohydrates that resist digestion in the small intestine or are poorly absorbed are called ‘resistant’ (unavailable or non-glycaemic) [3]. However, although resistant to digestion in the small intestine, non-glycaemic carbohydrates are also able to provide the body with energy through fermentation in the colon and absorption of short-chain fatty acids (SCFA) [2].

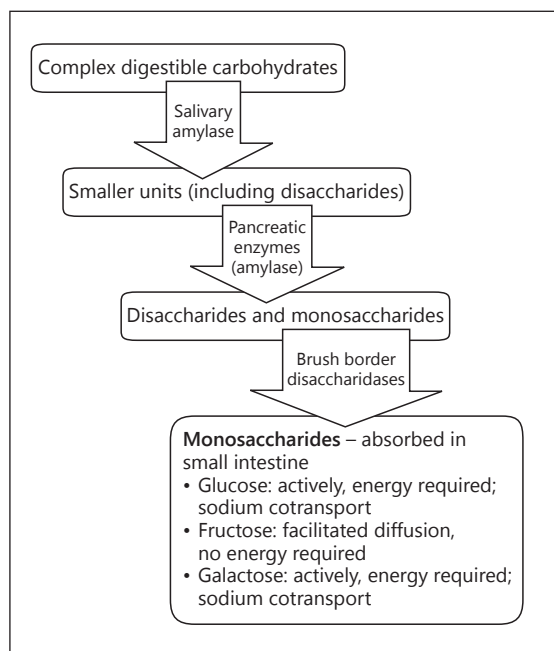
#### Digestible Carbohydrates

Digestible carbohydrates are a diverse group of substances with the primary function of serving as an energy source for all body cells. Their digestion starts in the mouth and ends in the intestinal brush border enzymes (fig. 1). Chronic low carbohydrate intake results in ketosis, which could cause long-term nutritional deficiencies. Carbohydrates are the main energy source and a recom-

**Table 1.** The main types of carbohydrates

Class	Subgroup	Components
Sugars	Monosaccharides	Glucose, galactose, fructose
	Disaccharides	Sucrose, lactose, trehalose, maltose
	Polyols	Sorbitol, mannitol
Oligosaccharides	Maltooligosaccharides	Maltodextrins
	Other oligosaccharides	GOS, FOS, polydextrose
Polysaccharides	Starch	Amylose, amylopectin, modified starches, resistant starch, inulin
	Non-starch	Cellulose, hemicellulose, pectins, hydrocolloids

GOS = Galactooligosaccharides; FOS = fructooligosaccharides. Adapted from FAO/WHO report [5] and Cummings and Stephen [2].

**Fig. 1.** Digestion and absorption of glycaemic carbohydrates.

mended intake level has been proposed by different authorities. The European Food Safety Authority (EFSA) panel recommends that 45–60% of energy should be provided as carbohydrates [4]; however, the data concerning infants and

young children are limited. For infants, human milk can be used as a model, meaning that the minimum carbohydrate intake should be 40% of total energy, and lactose should be the main digestible carbohydrate [1]. After early infancy, the intake of digestible carbohydrates should increase until reaching the recommended amounts for adults [1]. However, it should be taken into account that not only quantity but also carbohydrate type, carbohydrate origin and food processing can influence the rate of carbohydrate release; this glycaemic potential of the different carbohydrates can be valorised by the glycaemic index (GI). The GI is defined as the area under the glucose response curve after consumption of a 50-gram carbohydrate portion of a test food, and expressed as the percentage of response to the same amount of carbohydrate from a standard food taken by the same subject [5]. It was proposed that a diet with a low GI increases satiety and, consequently, reduces voluntary energy intake due to slower glucose and insulin release, which could have a preventive effect with regard to overweight and obesity; however, data on children and adolescents are limited and have yielded inconsistent findings [6]. On the contrary, higher consumption of added sugars (which have a high GI) can displace other macronutrients, increase

the risk of nutrient deficiency and significantly increase energy intake. The best evidence exists for sugar-sweetened beverages, due to the lower satiety potential of energy supplied in liquid compared with solid form [7]. Moreover, there is evidence that energy-dense food consumption can also influence insulin resistance, but there is no clear answer to whether this is caused solely by energy-rich food or influenced by overweight and increased fat mass [8].

Most paediatric authorities recommend limiting sugar-containing foods for infants and children in order to reduce the likelihood of high consumption later in life [1, 9]. Children should receive healthy food rich in slowly absorbed carbohydrates and with a limited amount of rapidly absorbed carbohydrates and simple sugars [9]. Frequent consumption of sugar-containing foods can also increase the risk of dental caries, especially when oral hygiene and fluoride prophylaxis are insufficient. Therefore, avoidance of frequent consumption of juices or other sugar-containing drinks and 'sleeping with a bottle' should be recommended, as well as maintenance of good oral hygiene [10].

In recent years there has been a growing interest in the role of fructose in obesity and metabolic disease. Fructose ingestion induces significantly more lipogenesis than isocaloric glucose ingestion, which could have an effect on obesity, the metabolic syndrome and non-alcoholic steatohepatitis [11]. Sugar-sweetened beverages and other sources of dietary fructose have been suggested to promote an increase in serum lipids and their deposition mainly in the liver, but not all published studies were able to confirm this association [7].

## **Non-Digestible (Resistant) Carbohydrates**

### *Dietary Fibres*

Dietary fibres are non-digestible carbohydrates mostly derived from plant sources that reach the colon nearly intact. These compounds can be fur-

ther classified into soluble types of fibre, like pectins, and insoluble components such as cellulose. Fibres that are added to the food and have beneficial physiological effects on humans are called 'functional fibres'.

It is not completely accurate to name fibres as non-digestible, because bacteria in the large intestine ferment mostly soluble fibres. Fermented products include gases (carbon dioxide and methane), oligofructoses as well as SCFA including acetic acid, butyric acid and propionic acid. These fermentation products derive energy for certain colonic bacteria and colonic epithelial cells which use butyrate as an energy source, even when competing substrates such as glucose are available [12]. SCFA are absorbed into the blood stream, where they can also be used as an energy source; some, like acetate, can be metabolized in brain cells, muscles and tissues, and others, like propionate, are used in the liver and can interfere with cholesterol synthesis [12].

### Fibres: Clinical Importance

The effect of dietary fibres on chronic diseases has been explored mostly in adults. The importance of fibres to children's health remains poorly investigated. Their most significant and widely studied role is in influencing bowel movement: fibres, especially insoluble ones, increase stool mass and improve its consistency; lack of dietary fibres, on the other hand, is associated with constipation and diverticulosis in adults. Yet, the exact fibre type and amount needed to elicit a positive effect have not been determined [13, 14]. Importantly, increasing dietary fibres up to the recommended levels has not been associated with any adverse events in children, and there is sufficient evidence that fibres could help in the prevention and treatment of constipation [14].

Other positive effects of increased intake of dietary fibres include body weight control and diabetes risk reduction [12]. However, the evidence is mostly limited to studies on adults, and data on children are scarce and conflicting, with

no possibility of formulating any clear recommendation; only few studies showed an association of dietary intake with fasting blood glucose concentrations and weight gain [13, 15]. Current recommendations for fibre intake in children vary among organisations; the EFSA concluded that a fibre intake of 2 g per 1 MJ of energy is adequate for normal laxation in children from the age of 1 year [4].

### Prebiotics

Prebiotics are a non-digestible food ingredients that selectively stimulate the growth and/or activity of intestinal bacteria associated with health and wellbeing [16]. Those beneficial bacteria are mostly bifidobacteria and lactobacilli. Prebiotics typically consist of  $\leq 10$  sugar molecules, and the most widely used types are fructooligosaccharides, inulin and galactooligosaccharides. The beneficial prebiotic effect proposed can be seen via improved gut barrier function and host immunity, reduction in potentially pathogenic bacterial subpopulations and enhancement of SCFA production. The most important prebiotics for infants are human milk oligosaccharides, which are very complex carbohydrates that significantly stimulate the growth of specific commensal bacteria in a breastfed infant. Although many studies demonstrated a bifidogenic effect of prebiotics and their addition to infant formulae seems rea-

sonable, there is a lack of strong evidence that their addition could improve growth or clinical outcomes in term infants [17]. Prebiotics have been shown to increase calcium absorption and bone mineral density in adolescents by lowering stool pH and increasing the amount of soluble calcium available for absorption, but this effect has not been confirmed in infants [18].

### Conclusions

- Carbohydrates may be classified into carbohydrates that provide the body with monosaccharides and are called 'digestible' (available or glycaemic) and carbohydrates that resist digestion in the small intestine and are called 'resistant' (unavailable or non-glycaemic)
- Dietary recommendations for infants and children should propose the intake of slowly absorbed carbohydrates and avoidance of added sugars and sweet drinks
- Fibres have a positive effect on laxation by increasing the amount of stool and influencing stool consistency
- Prebiotics promote the growth of beneficial bacteria, mostly bifidobacteria and lactobacilli
- For infants, the most important carbohydrates with a prebiotic effect are human milk oligosaccharides

### References

- 1 Stephen A, Alles M, de Graaf C, et al: The role and requirements of digestible dietary carbohydrates in infants and toddlers. *Eur J Clin Nutr* 2012;66:765–779.
- 2 Cummings JH, Stephen AM: Carbohydrate terminology and classification. *Eur J Clin Nutr* 2007;61(suppl 1):S5–S18.
- 3 Englyst KN, Liu S, Englyst HN: Nutritional characterization and measurement of dietary carbohydrates. *Eur J Clin Nutr* 2007;61(suppl 1):S19–S39.
- 4 EFSA Panel on Dietetic Products, Nutrition and Allergies: Scientific opinion on dietary reference values for carbohydrates and dietary fibre. *EFSA J* 2010;8:1462.
- 5 FAO/WHO: Carbohydrates in human nutrition. Report of a Joint FAO/WHO expert consultation. FAO Food and Nutrition Paper, vol 66. Rome, FAO/WHO, 1998.
- 6 Murakami K, McCaffrey TA, Livingstone MB: Dietary glycaemic index and glycaemic load in relation to food and nutrient intake and indices of body fatness in British children and adolescents. *Br J Nutr* 2013;110:1512–1523.
- 7 Te Morenga L, Mallard S, Mann J: Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* 2013;346:e7492.
- 8 Cañete R, Gil-Campos M, Aguilera CM, et al: Development of insulin resistance and its relation to diet in the obese child. *Eur J Nutr* 2007;46:181–187.



- 9 Agostoni C, Braegger C, Decsi T, et al: Role of dietary factors and food habits in the development of childhood obesity: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2011;52:662–669.
- 10 Agostoni C, Decsi T, Fewtrell M, et al: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008; 46:99–110.
- 11 Perito ER, Rodriguez LA, Lustig RH: Dietary treatment of nonalcoholic steatohepatitis. *Curr Opin Gastroenterol* 2013;29:170–176.
- 12 Slavin J: Fiber and prebiotics: mechanisms and health benefits. *Nutrients* 2013;5:1417–1435.
- 13 Kranz S, Brauchla M, Slavin JL, et al: What do we know about dietary fiber intake in children and health? The effects of fiber intake on constipation, obesity, and diabetes in children. *Adv Nutr* 2012;3:47–53.
- 14 Stewart ML, Schroeder NM: Dietary treatments for childhood constipation: efficacy of dietary fiber and whole grains. *Nutr Rev* 2013;71:98–109.
- 15 Moreno LA, Tresaco B, Bueno G, et al: Psyllium fibre and the metabolic control of obese children and adolescents. *J Physiol Biochem* 2003;59:235–242.
- 16 Gibson GR, Probert HM, Loo JV, et al: Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutr Res Rev* 2004;17:259–275.
- 17 Mugambi MN, Musekiwa A, Lombard M, et al: Synbiotics, probiotics or prebiotics in infant formula for full term infants: a systematic review. *Nutr J* 2012; 11:81.
- 18 Hicks PD, Hawthorne KM, Berseth CL, et al: Total calcium absorption is similar from infant formulas with and without prebiotics and exceeds that in human milk-fed infants. *BMC Pediatr* 2012;12: 118.

### 1.3 Nutritional Needs

## 1.3.5 Fats

Patricia Mena · Ricardo Uauy

1

#### Key Words

Lipids · Essential fatty acids · Linoleic acid ·  $\alpha$ -Linolenic acid · Long-chain polyunsaturated fatty acids · Arachidonic acid · Docosahexaenoic acid · Saturated fatty acid · *Trans* fatty acid

#### Key Messages

- Optimal lipid nutrition begins in fetal life with adequate n-3 to n-6 fatty acid and preformed long-chain polyunsaturated fatty acid (LCPUFA) supply through the maternal diet and PUFA metabolism
- Breast milk from mothers consuming a balanced diet provides the best source of bioavailable lipids for term neonates
- Linoleic and  $\alpha$ -linolenic acids are essential fatty acids; in addition, LCPUFA are important for lifelong health
- LCPUFA in the diet and the mother's genetic control of metabolism are important for visual and cognitive development in the first months of life, after which they contribute to lifelong health
- *Trans* fatty acids interfere with LCPUFA metabolism, affect lipoprotein cholesterol regulation and promote cardiovascular disease
- The balance between dietary n-3 and n-6 fatty acids is important to promote lifelong health, reducing the disease risk linked to allergic and inflammatory responses

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#### Introduction

Fats are the main source of energy for infants and young children, and n-6 and n-3 fatty acids are essential for normal growth and development. Fat-soluble vitamins (A, D, E and K) require dietary lipids for absorption. Fats provide flavor and texture to foods, and thus affect taste and acceptability of diets as well as gastric emptying and satiety. Membrane lipid composition in part defines the functional properties of membranes (fluidity, transport properties, receptor activity, uptake and release of substances, signal transduction and conduction, and ion flows). Fatty acids can also affect gene expression directly or by regulating transcription factors that affect the expression of multiple other genes (i.e. peroxisome proliferator-activated receptors). Dietary lipids provide structural components for brain and retinal structures, cell membranes and transport of lipid components in plasma, and they form the only true energy store of the body (adipose tissue). Fats and oils are key dietary factors affecting cardiovascular risk, obesity and diabetes. Linoleic acid (LA; C18:2n-6) and  $\alpha$ -linolenic acid (LNA; C18:3n-3) are essential; they serve as precursors of the long-chain polyunsaturated fatty acids (LCPUFA) such

as arachidonic acid (AA; C20:4n-6) and docosahexaenoic acid (DHA; C22:6n-3). Dietary lipids and mother and child genetic variation in fatty acid desaturase and elongase enzymes determine the balance between n-3 and n-6 effects. Neural cell phospholipids in the retina and cerebral cortex are rich in DHA, while vascular endothelia are rich in AA. LCPUFA are precursors of eicosanoids (C20) and docosanoids (C22), which act as local and systemic mediators for clotting, immune, allergic and inflammatory responses; they also affect blood pressure as well as vessel and bronchial relaxation and constriction. The dietary balance of n-6 and n-3 fatty acids can have profound influences on these responses, modulating the onset and severity of multiple disease conditions (allergy, atherosclerosis, hypertension and diabetes).

Lipids have long been considered as part of the exchangeable energy supply for infants and young children; thus, of primary concern has been the degree to which dietary fat is absorbed as an important contribution to the energy supply during early life.

### **Fats in the First Year of Life**

High-fat formulas (40–60% of energy), characteristic of infant feeding, contribute to the energy density of the diet required to support rapid weight gain, and especially to the fat accumulation observed over the first year of life. This has been traditionally considered a desirable trait, considering the increased risk of infection and potential dietary inadequacy after 6 months of life. However, the need for this fat gain for survival has been reexamined as we presently face an environment that promotes energy excess and thus increases the risk of obesity and chronic diseases later in life [1, 2]. The 2006 WHO Growth Standards, based on predominant breastfeeding for the first 6 months of life, suggest a leaner model of growth for the 2nd semester of life (see Chapter 4.1). In addition, the 2010 Food and Agricul-

ture Organization/WHO recommendation on fat has reduced amounts of total fat after 6 months and even more after 2 years of life [3].

### **Essentiality of PUFA and LCPUFA**

The essentiality of LA for human nutrition was identified about 70 years ago. In the 1980s, n-3 fatty acids were found to be essential for humans, considering the altered visual function in children receiving parenteral lipids high in n-6, which was reversed by provision of LNA, the n-3 precursor found in soy oil. Studies on preterm infants postnatally fed LCPUFA revealed that those receiving no DHA had altered electric responses to light and significant delays in maturation of visual acuity, which were only partially improved by LNA [4, 5]. These studies served to establish a need for LNA and suggested that, at least in preterm infants, DHA was also needed. Further studies have established a need for n-3 fatty acids in term infants, with some but not all studies demonstrating a benefit from receiving preformed DHA. Several stable isotope studies using labeled LA and LNA have demonstrated a limited and highly variable capacity to convert these precursors into the corresponding LCPUFA, i.e. AA and DHA, supporting the view that the latter may be considered conditionally essential during early life [2]. Preterm and term formulas are now supplemented with AA and DHA. Higher levels of DHA in formulas and breast milk should be needed for extremely preterm infants [6, 7].

LCPUFA can affect adipogenesis, but findings on their short- and long-term effects on body composition among trials using varied supplemented n-3 LCPUFA formulas are contradictory [8]. DHA should be considered essential for the treatment of certain chronic diseases, such as aminoacidopathies, and other inborn metabolic disorders because of dietary restrictions in some diseases, or because metabolism of LCPUFA is affected, as in peroxisomal diseases [9].



**Table 1.** Composition of commonly used vegetable oils

Source of oil	Fat, g	Saturates	Mono-unsaturates	Poly-unsaturates	n-6 PUFA	n-3 PUFA	Cholesterol, mg
Canola	100.0	7	59	30	20	9.3	0
Corn	100.0	13	24	59	58	0	0
Sunflower	100.0	10	19	66	66	0	0
Rapeseed	100.0	7	56	33	22	11.1	0
Soya	100.0	15	43	38	35	2.6	0
Olive	100.0	14	74	8	8	0.6	0
Vegetable solid fat	100.0	25	45	26	3	1.6	0
Animal fat lard	100.0	39	45	11	10	1	95
Milk fat	81	50	23	3	21	1.2	219

**Table 2.** Recommended fish as a source of eicosapentaenoic acid and DHA

High levels of eicosapentaenoic acid and DHA (>1,000 mg per 100 g fish)	Herring Mackerel Salmon Tuna – bluefin Greenland halibut
Medium level (500–1,000 mg per 100 g fish)	Flounder Halibut Tuna – canned white
Low level (≤300 mg per 100 g fish)	Tuna – skipjack Tuna – canned light Cod Catfish Haddock

**Table 3.** Contribution of various foods to *trans* fats consumed

Food group	% of total
Cakes, cookies, crackers, pies, bread, doughnuts, fast-fried chicken, etc. <sup>a, b</sup>	40
Animal products	21
Stick margarine	17
Fried potatoes	8
Potato chips, corn chips, popcorn	5
Household shortening	4
Breakfast cereals, candy	5
Soy oil	2

United States Department of Agriculture analysis reported 0 g of *trans* fats in salad dressing.

<sup>a</sup> Includes breakfast cereals and candy.

<sup>b</sup> Unless specifically modified and labeled.

Artificial infant formulas based on mixes of vegetable oils (coconut, palm, corn, soy, sunflower and safflower) provide LA- or oleic acid-rich contents, and some LNA from soy oil, attempting to mimic the composition of human milk (table 1). Coconut oil fractions rich in medium-chain triglycerides are used in an effort to promote absorption, especially in the feeding of preterm infants and those with fat malabsorption syndromes, since C8–10 fatty acids are absorbed directly from the intestinal mucosa passing to the portal vein [9]. Over recent years DHA or DHA + AA have been added to many infant formulas. However, it

is nearly impossible to fully replicate the unique fat composition and structure of human milk lipids. Human milk lipase activity further contributes to the improved fat digestibility of human milk. After 6 months, with the introduction of solid complementary foods, egg yolk, liver and fish can provide preformed DHA and AA (table 2) [2].

#### *Lipids in Human Milk*

Breast milk provides a ready source of both precursors and long-chain n-6 and n-3 derivatives, and is considered sufficient in these nutrients, provided mothers consume a nonrestrictive diet. The ac-

**Table 4.** Fat supply for children older than 2 years for the prevention of nutrition-related chronic diseases (based on Food and Agriculture Organization references)

Dietary component	Amount
Total dietary fat intake	25–35% of energy, depending on activity
Saturated fatty acids	<8% of energy (mainly C12, C14 and C16)
PUFA	5–15% of energy
n–6 PUFA	4–11% of energy
n–3 PUFA	<3% of energy
Eicosapentaenoic acid + DHA	100–300 mg, depending on age
n–6:n–3 ratio	5:1 to 10:1
Monounsaturated fatty acids	No restriction within limits of total fat
Cholesterol	<300 mg/day
Antioxidant vitamins	Generous intake desirable
Potentially toxic factors <sup>1</sup>	
<i>Trans</i> fatty acids	<1% of total energy
Erucic acid <sup>2</sup>	<1% of total fat
Lauric and myristic acids	<8% of total fat
Cyclopropenoids	Traces
Hydroperoxides	Traces

<sup>1</sup> Limit processed foods, hard fats and hard margarine as a practical way to limit intake of saturated and *trans* fatty acids.

<sup>2</sup> Use only rapeseed oil derived from genetic varieties low in erucic acid (canola).

tual amount of essential fatty acids and LCPUFA present in human milk varies depending on the maternal diet, being low in occidental diets, and also on maternal genetic variants in the desaturase-encoding genes [10]. Recently, an intake of at least 300 mg/day of eicosapentaenoic acid plus DHA, of which 200 mg/day are DHA, has been recommended during pregnancy and lactation [3].

Human milk provides close to 50% of the energy as lipids. Oleic acid is the predominant fatty acid, while palmitic acid is provided in the sn-2 position of the triglyceride, enhancing its absorption. Preformed cholesterol in breast milk (100–150 mg/dl) provides most of what is needed for tissue synthesis, thus downregulating endogenous cholesterol synthesis in the initial months of life.

*Trans* fatty acids are the product of hydrogenation of vegetable oils (soy) with the object of making these less susceptible to peroxidation (rancidity); thus the processed foods prepared with *trans* fatty acids have a longer shelf life, which is in the interest of producers and retailers. However, the ef-

fect of these fats on lipoprotein metabolism is indeed more harmful than that of saturated fats (C14, C16), since they not only increase LDL cholesterol (the cholesterol-rich atherogenic lipoprotein) but also lower HDL cholesterol (the protective lipoprotein responsible for reverse cholesterol transport). The net effect is that these fats contribute substantially to raising the risk of cardiovascular disease, as seen in table 3. *Trans* fatty acids during pregnancy and lactation have been associated with several negative outcomes related to conception, fetal loss and growth. The vulnerability of the mother-fetus/infant pair suggests that the diet of pregnant and lactating women should be as low in industrially derived *trans* fatty acids as practical [3].

### Fats in the Second Year of Life and Beyond

After 2 years of life, recommendations on fat intake need to consider the level of habitual physical activity, since the need for energy-dense food



sources such as fat should be adjusted to the energy required to promote healthy weight and active living; the energy needs for growth after 2 years represents 2–3% of the daily needs. Sedentary children will meet their energy needs easily with fat energy of around 30% of the total, while active children may benefit from higher fat energy (see table 4 for full details). In terms of cardiovascular disease prevention, the key aspect is the quality of the fat; decreasing saturated fats (especially C14 myristic and C16 palmitic acids) is crucial, even if C18 stearic acid is neutral in terms of cholesterol, since most of it is converted to oleic acid by the liver. Thus, a mild elevation in LDL cholesterol is offset by a rise in HDL. The key issue in the prevention of obesity is keeping energy intake and expenditure in balance at a healthy weight. Reducing fat intake is one way of achieving this, but it may not be the most sustainable way [3, 11].

DHA supply in children shows no evidence of an effect on cognitive function. There is some evidence of a benefit to behavioral changes in atten-

tion deficit syndrome, but not enough evidence for an effect on cystic fibrosis, asthma or modifying body composition [12].

## Conclusions

- According to the breast milk model, the intake of lipids in the first 6 months of life should provide 40–60% of total energy, have an n–6: n–3 ratio of 5–10:1 and <1% *trans* fats, and should be free from erucic acid
- Total fat should be gradually reduced to 35% at 24 months
- After the age of 2 years, dietary fat should provide 25–35% energy; n–6 PUFA should provide 4–10% energy, n–3 1–2% energy, saturated fat <8% energy and *trans* fats <1% energy
- n–6 fatty acids should be limited to <8% and total PUFA to <11% of total energy; n–9 oleic acid can bridge the difference
- The quality of the fat, more than its quantity, is important for lifelong health

## References

- 1 Aranceta J, Pérez-Rodrigo C: Recommended dietary reference intakes, nutritional goals and dietary guidelines for fat and fatty acids: a systematic review. *Br J Nutr* 2012;107(suppl 2):S8–S22.
- 2 Uauy R, Dangour A: Fat and fatty acid requirements and recommendations for infants of 0–2 years and children of 2–18 years. *Ann Nutr Metab* 2009;55:76–96.
- 3 FAO/WHO: Report of an Expert Consultation on fats and fatty acids in human nutrition. FAO Food and Nutrition Paper 91. Rome, FAO, 2010, pp 63–85.
- 4 Lewin GA, Schachter HM, Yuen D, Merchant P, Mamaladze V, Tsertsvadze A: 118. Effects of omega-3 fatty acids on child and maternal health. Evidence Report/Technology Assessment. Rockville, Agency for Healthcare Research and Quality, 2005.
- 5 Gould J, Smithers L, Makrides M: The effect of maternal omega-3 (n–3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2013;97:531–544.
- 6 Lapillonne A, Groh-Wargo S, Lozano Gonzalez C, Uauy R: Lipid needs of preterm infants: updated recommendations. *J Pediatr* 2013;162(suppl):S37–S47.
- 7 Lapillonne A: Enteral and parenteral lipid requirements of preterm infants. *World Rev Nutr Diet* 2014;110:82–98.
- 8 Rodríguez G, Iglesia I, Bel-Serrat S, Moreno LA: Effect of n–3 long chain polyunsaturated fatty acids during the perinatal period on later body composition. *Br J Nutr* 2012;107(suppl 2):S117–S128.
- 9 Gil-Campos M, Sanjurjo Crespo P: Omega 3 fatty acids and inborn errors of metabolism. *Br J Nutr* 2012;107(suppl 2):S129–S136.
- 10 Koletzko B, Lattka E, Zeilinger S, Illig T, Steer C: Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. *Am J Clin Nutr* 2011;93:211–219.
- 11 Koletzko B, et al: Current information and Asian perspectives on long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy. Systematic review and practice recommendations from an Early Nutrition Academy workshop. *Ann Nutr Metab* 2014;65:49–80.
- 12 Agostoni C, Braegger C, Decsi T, Kolacek S, et al: Supplementation of n–3 LCPUFA to the diet of children older than 2 years: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2011;53:2–10.

### 1.3 Nutritional Needs

## 1.3.6 Fluid and Electrolytes

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#### Key Words

Fluids · Electrolytes · Rehydration

#### Key Messages

- Maintenance of body water is principally governed by the kidney, except in pathologic states such as diarrheal disease
- Intestinal transportation of water and electrolytes is a finely tuned phenomenon regulated by complex interaction between endocrine, paracrine, immune, and enteric nervous systems
- Cotransportation of Na<sup>+</sup> with glucose by SGLT-1 is preserved in most diarrheal diseases and forms the basis for the oral rehydration solution
- Breastfed infants, including low-birth-weight infants, in hot climates do not require supplemental water
- An oral rehydration solution should be used for rehydration and accomplished rapidly over 3–4 h, except in severe dehydration or intolerance of enteral fluids

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#### Introduction

Maintenance of body water and electrolytes is a tightly regulated balance of intakes and outputs mediated by elaborate physiologic mechanisms.

Sodium (Na<sup>+</sup>) retention causes volume expansion, and Na<sup>+</sup> depletion causes volume contraction. A net negative sodium balance results in a clinical state of extracellular fluid (ECF) volume contraction, the most common cause worldwide being infectious diarrheal disease resulting in dehydration.

Unlike sodium, whose distribution in the body is uneven because of active transport of the ion, water movement is passively determined in response to osmotic gradients. Body water, being freely diffusible, is therefore in equilibrium in relation to the distribution of its nondiffusible solutes.

Maintenance of body water involves the control of intake/absorption governed by the gastrointestinal tract and excretion, but principally by excretion controlled by the kidney. Under normal conditions, losses via the gastrointestinal tract are small but can greatly increase in pathologic states such as diarrheal disease.

Over 1.7 billion episodes of diarrhea occur annually, accounting for 700,000 deaths of children younger than 5 years, with most deaths in developing countries and from dehydration [1]. The severity of dehydration is graded by clinical signs and symptoms that reflect fluid loss and that determine the treatment regimen to correspond to the degree of severity. Regardless of the etiology, more than 90% of dehydration can be safely and

effectively managed with oral rehydration therapy, using a prescribed fluid and electrolyte oral rehydration solution (ORS). Because malnutrition increases the frequency, severity, and duration of diarrhea, fluid and electrolyte replacement and nutritional therapy are critical elements for recovery [2].

## Regulation of Sodium Balance

Sodium absorption occurs in the gastrointestinal tract and excretion primarily by the kidney, with small amounts excreted in sweat and feces. In pathologic conditions, especially diarrheal disease, normal gastrointestinal mechanisms of homeostasis become disturbed and can result in large, sometimes life-threatening fluid and electrolyte losses. Systems regulating renal sodium chloride (NaCl) and water excretion operate by a negative feedback loop consisting of an afferent (sensory) component, an efferent (messenger) component, and an effector organ [3]. The renal response aims at reconstituting the ECF volume by decreasing the glomerular filtration rate and thus the filtered load of Na<sup>+</sup> and, even more critically, by promoting tubular reabsorption of Na<sup>+</sup> utilizing the various mechanisms of Na<sup>+</sup> transport including exchangers, channels, and cotransporters. Receptors located in the renal juxtaglomerular apparatus detect a reduced ECF volume and Na<sup>+</sup> concentration and stimulate renal Na<sup>+</sup> retention via the renin-angiotensin cascade.

## Regulation of Body Water

Plasma osmolality is the primary driver for thirst and, therefore, water intake, although under conditions of a reduced ECF volume such as severe dehydration, a low blood volume assumes a greater role and will override tonicity [4]. Arginine vasopressin secreted from pituitary neuronal cells in response to signals from osmoreceptors binds

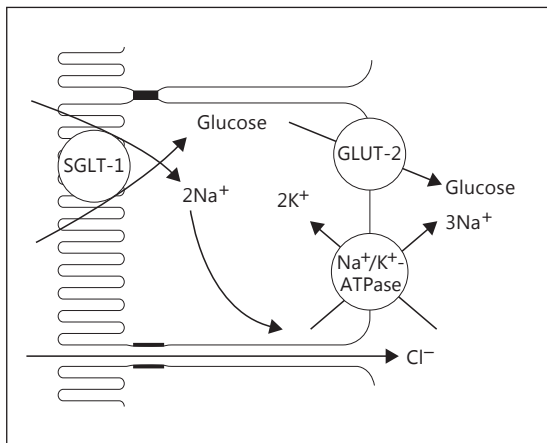
to epithelial-cell basolateral receptors of the otherwise water-impermeable collecting tubule of the nephron, stimulating the insertion of water channels (aquapores) into the apical cell surface and subsequent extraordinary movement of water from the lumen to the cell interior.

## Gastrointestinal Regulation of Fluids and Electrolytes

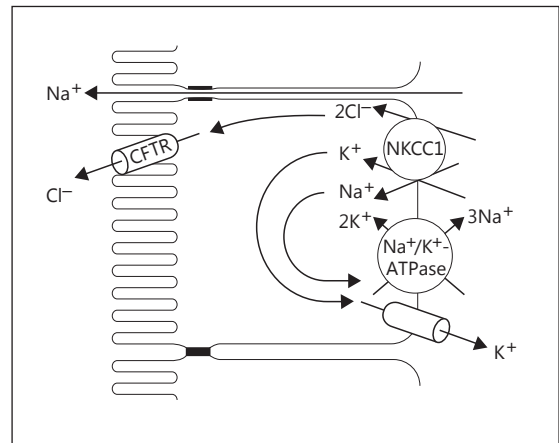
The permeability of the tight junction between epithelial cells decreases distally so that the jejunum is the most and the distal colon and rectum the least permeable to the passive movement of electrolytes and water [5]. Ions traverse the epithelium via the transcellular or paracellular routes throughout the length of the bowel by passive or active transport mechanisms. Passive movement of fluids follows, with paracellular transport being the main mechanism of flow in the small bowel and transcellular flow predominating where the epithelia are tightly aligned and less permeable, as in the distal colon. Cotransportation of Na<sup>+</sup> with certain nutrients including glucose and amino acids at the apical surface of the upper villus in the small intestine is responsible for most Na<sup>+</sup> and water absorption following a meal or ingestion of an ORS (fig. 1). The carrier specific for Na-glucose cotransportation, SGLT-1, is preserved in most diarrheal diseases and forms the basis for oral rehydration therapy [6]. In fasted states or between meals, most NaCl is transported from the lumen via exchange (Na<sup>+</sup>/H<sup>-</sup> and Cl<sup>-</sup>/HCO<sub>3</sub>).

While sodium transport drives fluid absorption, Cl<sup>-</sup> excretion is the driving force for fluid secretion. Cl<sup>-</sup> is taken up along the basolateral membrane of the epithelial cell by the electroneutral Na<sup>+</sup>/K<sup>+</sup>/2Cl<sup>-</sup> cotransporter and accumulates within the cell above its electrochemical equilibrium (fig. 2). Once within the cell, Cl<sup>-</sup> exits into the intestinal lumen via Cl<sup>-</sup> channels that open in response to regulatory agonists that invoke second messenger systems.

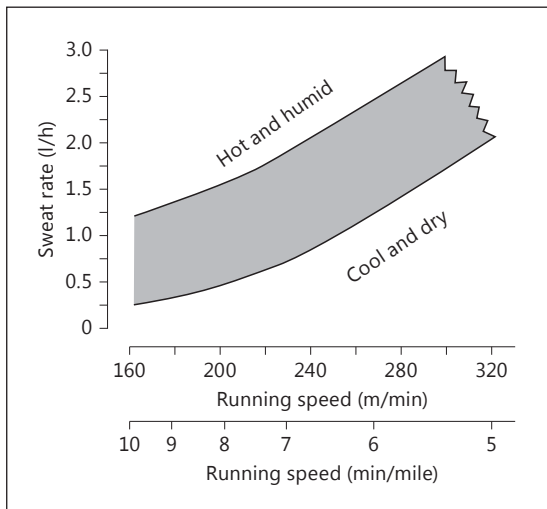




**Fig. 1.** Cotransportation of sodium and glucose.



**Fig. 2.** Chloride excretion and fluid secretion.



**Fig. 3.** The effect of ambient temperature, humidity, and exertion (running speed) on the approximate rate of sweating in adults. From Sawka and Montain [8].

### Intracellular Regulators of Ion Flux

Various hormones, neurotransmitters, and secretagogues bind to receptors along the epithelial cell membrane to initiate the intracellular cascade involving second messenger molecules of cyclic nu-

cleotides (including cyclic adenosine monophosphate and cyclic guanosine monophosphate) and ionized cytosolic calcium ( $\text{Ca}^{2+}$ ). These in turn activate protein kinases that exert direct control of ion channels to increase the efflux of Cl through Cl channels down their electrochemical gradients and the inhibition of electroneutral NaCl-coupled influx.

### Intercellular Regulators of Ion Flux

Under normal conditions, the intestinal transport of water and electrolytes is a finely tuned transcellular and paracellular phenomenon regulated by complex interactions between the endocrine, paracrine, immune, and enteric nervous systems. In reality, these systems do not function as isolated units; their borders are indistinct and overlap [4]. Examples include serotonin and vasoactive intestinal peptide, which function as hormones or neurotransmitters or both depending on the precise physiologic situation. Certain bacterial enterotoxins such as cholera and cytotoxins simultaneously stimulate paracrine, neural, and immune responses, all of which may alter ion and water flux [7].

## Other Regulatory Factors

Other factors influence fluid and electrolyte transport indirectly, including acid-base homeostasis, gut motility, luminal flow rates, intestinal permeability, blood oncotic pressure and plasma volume, venous and arterial pressure, and physical and psychological stress.

## Effects of Environment and Physical Activity

Thermoregulation is essential to the body's proper functioning. The body's core temperature is carefully regulated and maintained. Accordingly, there are multiple mechanisms to dissipate excess heat, which include sweat evaporation, radiation, convection, and conduction, with evaporation being the most effective. These same mechanisms essential for thermoregulation may also lead to fluid loss and electrolyte abnormalities. In hot climates, a considerable volume of water may be lost through perspiration for evaporative cooling and is further increased with increased humidity and during periods of physical exertion (fig. 3) [8].

Compared to adults, children have a greater surface area/body mass ratio and rely more on dry heat dissipation than evaporative heat loss. However, older children and adolescents do not have inferior thermoregulatory ability or physical exertion tolerance with higher heat injury rates than adults, even during extreme heat. Poor hydration status and excess physical exertion, especially in a hot environment, are the main determinants of exertional heat illness; modifiable risk factors include extreme exertion, inadequate recovery from repeated periods of exercise, and excessive clothing or sports equipment, among others [9].

Breastfed infants, including low-birth-weight infants, in hot climates can be adequately maintained on breast milk exclusively and do not require supplemental water. In developing coun-

tries, supplementation is associated with greater infant morbidity and mortality from diarrhea and respiratory illness, decreased milk intake, and early cessation of breastfeeding which synergistically promotes the development of malnutrition [10].

## Principles of Rehydration and Fluid Maintenance

The degree of dehydration as graded by clinical characteristics determines the fluid and electrolyte regimen to be used, regardless of the specific etiology. Except for severe dehydration or if the child cannot tolerate enteral fluids, oral ORS ( $\text{Na}^+$ ) should be used for rehydration and accomplished rapidly over 3–4 h (table 1) [11]. The WHO and UNICEF recommend a 245-mmol/l ORS of NaCl 2.6 g (75 mmol/l), glucose 13.5 g (75 mmol/l), KCl 1.5 g (20 mmol/l), and citrate 2.9 g (10 mmol/l). Breastfeeding should continue during and immediately following rehydration; in nonbreastfed infants, an unrestricted age-appropriate diet should be provided immediately following initial rehydration. If formula food is being used, it should not be diluted and does not need to be specialized, since lactose-containing formulas are usually well tolerated. Ongoing stool losses should be replaced with ORS.

Severely dehydrated children usually require initial rehydration with intravenous fluids, after which hydration can usually be maintained orally with ORS (table 1). Ringer's lactate ( $\text{Na}^+$  130 mmol/l,  $\text{K}^+$  4 mmol/l,  $\text{Cl}^-$  109 mmol/l, and lactate 28 mmol/l) with or without 5% dextrose is the preferred intravenous solution, while normal saline (0.9% NaCl;  $\text{Na}^+$  154 mmol/l) is an acceptable alternative. In extreme situations or if the child is unable to keep up with ongoing stool losses, intravenous fluids are needed beyond the initial rehydration period (table 2) [2].

In developing countries where diarrheal disease is most prevalent and associated with the

**Table 1.** Treatment of acute watery diarrhea, modified from King et al. [11]

Degree of dehydration	Signs	Rehydration therapy (within 4 h)	Replacement of losses	Nutrition
Minimal (<3%)	Well, alert	Not applicable	For each diarrheal stool or vomiting episode give 60–120 ml ORS if <10 kg body weight and 120–240 ml ORS if >10 kg body weight	Continue breastfeeding or resume age-appropriate diet after initial rehydration
Mild to moderate (3–9%)	Sunken eyes, sunken fontanelle, loss of skin turgor, dry buccal mucous membranes	ORS 50–100 ml/kg over 3–4 h	Same as above	Same as above
Severe (10%)	Signs of moderate dehydration with one of the following: rapid thready pulse, cyanosis, cold extremities, deep breathing, lethargy, unconsciousness	Intravenous fluids 30 ml/h until pulse, perfusion, and mental status improve; then, ORS 100 ml/kg over 4 h	Same as above; if unable to drink, give by nasogastric tube	

**Table 2.** Guidelines for intravenous fluids for severe dehydration

Age	First give	Then give
	30 ml/kg over <sup>a</sup>	70 ml/kg over <sup>b</sup>
Infants (<12 months)	1 h	5 h
Older children and adults	30 min	2.5 h

Modified from the WHO manual [2]. Preferably start intravenous Ringer's lactate (with or without 5% dextrose; normal saline is acceptable) immediately; give an oral rehydration solution until the intravenous line is started if the child can drink.

<sup>a</sup>Repeat once if the radial pulse remains weak or not detectable.

<sup>b</sup>If the child is able to drink and keep up with stool losses, introduce the ORS as described in table 1.

greatest mortality and morbidity, many affected children have concomitant malnutrition. Malnutrition results in an increased incidence, severity, and duration of diarrhea and is an underlying cause of much of the diarrheal disease-related mortality. Optimal prevention and management of diarrheal disease, therefore, requires attention to nutritional therapy including continued breastfeeding in breastfed infants and early refeeding during a diarrheal disease episode. Zinc supplementation promotes recovery from acute and persistent diarrhea; as well as decreas-

ing postdiarrheal disease morbidity, it is now universally recommended as adjunctive treatment for children with diarrhea older than 6 months of age. Severely malnourished children with diarrhea have unique, stereotypical clinical abnormalities and require a specific, protocolized regimen to ensure safe, efficacious fluid and electrolyte reconstitution. Due to the limited data, a potential role for zinc in the treatment of acute diarrhea in developed countries has not been identified [12].

## Conclusions

- Maintenance of body water and electrolytes is a tightly regulated balance of intakes and outputs
- Certain conditions such as gastrointestinal pathology, malnutrition, physical exertion, and environmental stress such as excessive ambient heat result in unique fluid and electrolyte losses and requirements
- In developing countries, where childhood malnutrition is often superimposed on diarrheal disease states, nutritional repletion including zinc supplementation is an additional therapeutic requirement

## References

- 1 Walker CL, Rudan I, Liu L, Nair H, Theodoratu E, Bhutta ZA, O'Brien KL, Campbell H, Black RE: Global burden of childhood pneumonia and diarrhoea. *Lancet* 2013;381:1405–1416.
- 2 WHO: The treatment of diarrhoea: a manual for physicians and other senior health workers. Geneva, WHO, 2005. <http://whqlibdoc.who.int/publications/2005/9241593180.pdf>.
- 3 Trachtman H: Sodium and water homeostasis. *Pediatr Clin North Am* 1995; 42:1343–1363.
- 4 Sterns RH, Spital A, Clark EC: Disorders of water balance; in Kokko JP, Tannen RL (eds): *Fluids and Electrolytes*. Philadelphia, Saunders, 1996, pp 63–109.
- 5 Venkatasubramanian J, Rao MC, Sellin JH: Intestinal electrolyte absorption and secretion; in Feldman M, Friedman LS, Brandt LJ (eds): *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management*. Philadelphia, Saunders, 2010.
- 6 Hirschhorn N, Greenough I: Progress in oral rehydration therapy. *Sci Am* 1991; 264:50–56.
- 7 Cho JH, Chang EB: Intracellular mediators and mechanisms of pathogen-induced alterations in intestinal electrolyte transport; in Blaser MJ, Smith PD, Ravdin JI, et al (eds): *Infections of the Gastrointestinal Tract*. New York, Raven, 1995.
- 8 Sawka MN, Montain S: Fluid and electrolyte supplementation for exercise heat stress. *Am J Clin Nutr* 2000; 72(suppl):564S–572S.
- 9 Cohen RJ, Brown KH, Rivera LL, Dewey KG: Exclusively breastfed, low birth-weight term infants do not need supplemental water. *Acta Paediatr* 2000;89: 550–552.
- 10 Council on Sports Medicine and Fitness, Council on School Health; Bergeron MF, Devore C, Rice SG; American Academy of Pediatrics: Policy statement – climatic heat stress and exercising children and adolescents. *Pediatrics* 2011;128:e741–e747.
- 11 King CK, Glass R, Breese JS, Duggan C: Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 2003;52:1–16. [www.cdc.gov/mmwr/preview/mmwrhtml/rr5216a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5216a1.htm).
- 12 Pieścik-Lech M, Shamir R, Guarino A, Szajewska H: Review article: the management of acute gastroenteritis in children. *Aliment Pharmacol Ther* 2013;37: 289–303.

### 1.3 Nutritional Needs

## 1.3.7 Vitamins and Trace Elements

Noel W. Solomons

#### Key Words

Vitamins · Trace elements · Deficiency · Excess · Growth · Complementary food

#### Key Messages

- There are 22 essential micronutrients – 13 vitamins (4 fat soluble and 9 water soluble) and 9 trace elements – to be obtained from a diet to satisfy nutrient requirements
- In addition to insufficient intake from the diet, inhibition of intestinal uptake, impairment of nutrient utilization, enhanced destruction of vitamins and increased nutrient wastage can produce micronutrient deficiencies, alone or in combination
- Biofortification, consisting of developing improved varieties of staple foods, fruits and vegetables, is an emerging approach to increasing the micronutrient supply in at-risk populations in developing countries
- The weaning period presents an enhanced risk of inadequate micronutrient intake and deficiency, and fortification of complementary feeding is a practical and important option
- However, the balancing and monitoring of micronutrient fortification in food supply is essential as the risk of overconsumption of selected micronutrients such as iron, vitamin A and folic acid is latent when public health and commercial fortification efforts combine in a given setting

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#### Introduction

From infancy through late adolescence, a series of 13 organic compounds (the vitamins, 4 soluble in lipids and 9 soluble in water) are essential for nutrition and health. Likewise, there is relative consensus that 9 inorganic elements found at low concentrations in the body (the trace elements) are beneficial or essential for the maintenance of the structure and function of the human body. The amounts to be consumed with the diet on a day-to-day basis by healthy juveniles have been established in relation to their age and gender. Diseases can lead to an additional demand for these so-called micronutrients. Deficiencies in vitamins and trace elements occur because of insufficient dietary intake or through environmental or pathological challenges. A list of the vitamins and trace elements of interest in this discussion is provided in table 1.

#### Sources of Micronutrients for Human Consumption

The vitamins and minerals needed by the body can come from three basic sources: the first is fundamentally based on the primary production of

**Table 1.** List of vitamins and beneficial and essential trace elements

Vitamins	Synopsis of role and function
<b>Fat-soluble group</b>	
Vitamin A	Retinal light receptors in vision, genetic transcription
Vitamin D	Calcium absorption, bone mineralization, cell signaling
Vitamin E	Cell membrane antioxidant protection, cell signaling
Vitamin K	Blood clotting, bone matrix formation
<b>Water-soluble group</b>	
Vitamin C	Antioxidant protection in regeneration of reduced vitamin E
Thiamin	As thiamine pyrophosphate coenzyme in metabolism
Riboflavin	As cofactors FAD and FNM in flavoproteins
Niacin	As cofactors NAD and NADP in dehydrogenases
Vitamin B <sub>6</sub>	Cofactor in transamination and carboxylation of amino acids
Pantothenic acid	Component of coenzyme A for mitochondrial energy
Biotin	Cofactor in carboxylases for fats, protein and carbohydrates
Folate	One-carbon transfer reactions in metabolism
Vitamin B <sub>12</sub>	Cofactor in one-carbon transfer reaction, specifically for 5-methyltetrahydrofolate
<b>Trace elements</b>	
Iron	Oxygen transfer, oxygen-mediated redox reactions
Zinc	Metalloenzymes, zinc-finger protein transcription factors
Copper	Diverse metalloenzymes
Iodine	Thyroid hormone structure
Fluoride	Dental and skeletal mineralization
Selenium	Glutathione peroxidase antioxidant system
Manganese	Mitochondrial superoxide dismutase
Chromium	Enhances the cellular action of insulin
Molybdenum	In molybdenum cofactor in metabolism of organic acids

FAD = Flavin adenine dinucleotide; FNM = flavin mononucleotide; NAD = nicotinamide adenine dinucleotide; NADP = nicotinamide adenine dinucleotide phosphate.

foods, and the other two are related to the mobilization of synthetic (vitamins) or isolated (trace elements) sources for consumption. These sources are outlined in table 2.

#### *Vitamins and Trace Elements Intrinsic to Foods*

It takes a wide variety of different foods in combination to obtain the entire range of necessary micronutrients in adequate amounts [1]. Micronutrients tend to be less varied, less dense and less available in foods of plant origin than in those of animal origin [2]. To the extent that plants are rich sources of vitamins E, C and K and folate, children should be encouraged to consume whole

grains and green, orange and yellow vegetables and fruits. However, for calcium and riboflavin, milk and dairy products are the richest sources, and iron and vitamins A and B<sub>12</sub> are most densely concentrated in animal foods (meat, organ meat and fish). Cooking, processing and storage destroy or elute nutrients in foods.

An emerging new strategy is biofortification, primarily for public health purposes. This involves enhancing the content of specific nutrients during the cultivation of edible plants. It can involve nutrient-enhanced fertilization, cross-breeding/hybridization or genetic modification [3]. One can variously enhance the concentration

**Table 2.** Sources of micronutrients for human consumption

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*Intrinsic micronutrients*

Nutrients contained within the tissue matrix and fluid of edible items from the animal and plant kingdoms

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*Extrinsic (added) micronutrients*

Nutrients are added to foods as enrichment, in mass fortification by public health mandate and/or with discretionary fortification, as in commercial foods or with nutrient mixes added to complementary foods in the home

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*Supplemental micronutrients*

Nutrients taken in pharmaceutical preparations (chewable candies, tablets, elixirs) in individual or combined forms

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of a nutrient (e.g. the provitamin A  $\beta$ -carotene) already in the plant (such as in orange-fleshed sweet potatoes) or introduce the same nutrient where it never existed before (as in rice or cassava).

*Vitamins and Trace Elements Added to Foods*

Extrinsic addition of micronutrients usually occurs in processing or, occasionally, in the home just prior to consumption. It includes three domains: (1) enrichment (returning the nutrients lost in processing); (2) public health-directed fortification (adding a nutrient or nutrients to a widely consumed item such as salt, sugar, oil or flour to counter a population-level deficit), and (3) market-driven fortification (adding nutrients to commercial products to enhance their appeal, such as adding vitamin C to soda beverages) [4].

Fortification is a legitimate and effective public health measure [5]. The major focus in the publication arena had traditionally been iodine in salt, but this has recently shifted to iron, specifically in wheat flours and corn meals (Flour Fortification Initiative), and other nutrients such as retinol in cooking oils and condiments. A creative avenue for young children with nutritionally precarious diets has been home fortification

in which multimicronutrient-fortified powders (sprinkles) or spreads are combined with traditional foods to support nutrient intake. The Central American republics have a several-decade history of vitamin A fortification of sugar, but increased sugar consumption is now leading to excessive consumption of the vitamin.

*Micronutrient Supplements*

The advances in pharmaceutical chemistry from the second half of the 20th century allowed high concentrations of vitamins and trace elements to be formulated as capsules, tablets and syrups. In a public health context, various forms of micronutrient supplementation are used – generally when 40% of the child population shows evidence of nutrient deficiency. This is exemplified by the periodic distribution of high-dose vitamin A capsules [6] and intensive courses of daily dosing of iron and folic acid [7].

Beyond the prevention of micronutrient deficiencies, some parents may be motivated to supplement themselves and their children with the motivation to decrease the risk of occurrence of chronic diseases such as cancer, cardiovascular diseases and cognitive decline; an analysis of the current scientific evidence does not support such an effect [8]. In fact, adverse outcomes from chronic multimicronutrient supplementation have been documented.

**Factors Affecting Vitamin and Trace Element Nutrition**

Primary vitamin and trace element undernutrition is the result of the oral intake of nutrients from any combination of the aforementioned sources not meeting the recommended amounts. This is seen not only with poverty, famine and disaster but also widely in cases where the nutrient density of the diet does not sustain nutrient requirements when energy needs are fulfilled. This is an especial concern with regard to complemen-

**Table 3.** Factors conditioning the absorption and utilization of dietary micronutrients

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*Inhibition of intestinal uptake*

Environmental enteropathy under unsanitary conditions  
Dietary constituents that interfere with nutrient absorption, such as dietary fibers and phytic acid  
Intestinal parasites (*Helicobacter pylori*, protozoa and helminths)  
Active acute, recurrent or chronic persistent gastroenteritis

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*Impairment of nutrient utilization*

Lead exposure interferes with the incorporation of iron into hemoglobin, leading to anemia  
Inflammation, chronic illness and, specifically, renal disease disrupt the mobilization of diverse nutrients to the red cells, leading to anemia  
Menkes disease impairs the cellular utilization of copper

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*Enhanced destruction of vitamins*

As organic compounds, vitamins can be denatured or metabolized, as happens with vitamin E in the presence of oxidants  
Tobacco smoking destroys vitamin C  
Note: inorganic substances (trace elements) cannot be destroyed

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*Increased nutrient wastage*

The metabolic consequences of a systemic inflammatory response leads to excessive urinary excretion of nitrogen, zinc and vitamin A  
Abuse of cathartic laxatives induces excessive losses of water, sodium, potassium, magnesium and calcium

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tary foods during the weaning process [9]. Of course, in individuals receiving part or all of their nutrition via the intravenous parenteral route, attention must be paid to perfuse micronutrients as well to avoid deficiency [10].

Secondary micronutrient undernutrition is related to the failure to absorb, to utilize or to retain the nutrient in the body once ingested with the diet or a supplement. Table 3 classifies and illustrates the factors affecting micronutrient disposition. These factors come into interplay in severe diseases commonly seen in pediatric practice, such as repeated or chronic diarrhea, Crohn's disease [11], untreated celiac disease or cystic fibrosis.

There is a narrow spectrum of situations in which there is excessive absorption or retention of certain trace elements, leading to progressive accumulation and eventual overload. This occurs with iron in conditions called hemochromatosis and hemosiderosis due to disruption of the intestinal regulation of its uptake. It also occurs with copper in that the absorbed metal cannot be normally exported from the cells after its uptake due to a genetic mutation. In both instances, these metals accumulate in selected organs, producing oxidative and degenerative damage.

### **Theoretical and Practical Precautions and Caveats regarding Vitamin and Trace Element Nutrition**

On the one hand, considerations based on climate, environmental conditions and endemic infectious diseases may modify the conventional requirements of certain micronutrients, usually increasing the demand to support nutrition and growth. Even ethnic origin can be seen as an emerging factor, as genetic polymorphisms that influence micronutrient handling are increasingly being recognized [12].

On the other hand, pathogenic viruses, bacteria, protozoa and fungi have their own specific requirements of certain trace elements such as iron, zinc and manganese. The malarial organism (*Plasmodium*) and pathogenic amoeba (e.g. *Entamoeba histolytica*) and their influence on the iron status of the host are cases in point. In situations in which sanitary or antimicrobial control cannot stem parasitic transmission, individuals having lower reserves of iron may be relatively protected against the proliferation of these pathogens.

The overall balance between micronutrients, both in the diet (on the plate) and in the body (in tissues and organs), has implications because a series of recognized nutrient-nutrient interac-



**Table 4.** A listing of some pertinent paradoxical associations and precautions related to dietary exposure to micronutrients

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The tolerable upper intake levels for zinc in toddlers and preschool children may be too low, as they are lower than the average amounts of zinc consumed by apparently healthy children in the USA

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The traditional ideal is that all members of a family unit share the majority of meals as a family. In this regard, the tolerable upper intake level of preformed vitamin A for children under 6 years is lower than the recommended daily intake of total vitamin A for pregnant or lactating women in the same household

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The currently recommended intake levels for vitamin D, especially for adolescents and for individuals from darkly pigmented ethnic groups living in temperate latitudes such as Europe, North America and southern Australia, may not be sufficient to maintain protective circulating levels of the vitamin. Pediatric dermatologists and nutritionists are at odds about the value of sun exposure. The dermatological community advocates maximal sunscreen protection to avoid skin damage and malignancy risk, whereas pediatric nutritionists realize that maximizing vitamin D formation in skin in temperate latitudes requires some relaxation of solar exposure avoidance measures

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An upward spiral of market-driven fortification, with multiple manufacturers adding micronutrients to make their products more attractive and 'nutritious', runs the risk of providing child consumers with several times the daily recommended amounts of some vitamins and minerals

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Folic acid is a synthetic and totally oxidized form of folate. Folic acid fortification is mandated in many countries for the prevention of neural tube defects in the pregnancies of susceptible women. These higher folic acid intakes may have additional benefits for adults through the prevention of stroke and vascular disease. However, in adults with established dysplastic changes in the large bowel mucosa, higher folic acid exposure accelerates the progression to colorectal cancer. Limited evidence for a similar scenario exists for prostatic neoplasia. We have little understanding of these beneficial versus harmful effects for the pediatric population

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Epidemiological evidence is accumulating that the consumption of preformed vitamin A from animal sources and food fortification weakens bone mineralization. The extent and importance of such a process in childhood merit research attention

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tions between vitamins, between trace elements and between vitamins and trace elements are recognized. These are quite common for vitamin A with its interactions with vitamins D and E and assorted elements such as iodine and iron [13]. The competition between iron and zinc is notable for its potential consequences in public health interventions [14].

Excessive exposure to certain vitamins and virtually all of the trace elements can have adverse effects on children. For 7 of the vitamins and all of the inorganic elements, certain daily dietary amounts pose the risk of the adverse con-

sequences of overload and even toxicity if exceeded. These so-called upper tolerable intake levels have been established by agencies such as the Food and Nutrition Board of the USA and the European Food Safety Authority. The interplay between essential risks of dietary deficiency and public health interventions to enhance the micronutritional status can lead to paradoxical situations. Increasingly, this also takes place at the interface of the low nutrient content of the diet selected and the sum of fortification and self-supplementation sources. Table 4 illustrates a selection of these paradoxes.

## Conclusions

- Vitamins and trace elements get into the child via natural foods and beverages, fortified products and oral micronutrient supplements; sometimes a combination is needed to achieve an adequate diet
- The weaning period for infants and toddlers is a challenging period in which to satisfy micronutrient nutriture
- In the community setting, antinutrient substances in the diet and recurrent gastrointestinal infections can interfere with micronutrient adequacy
- Overconsumption of certain vitamins and trace elements is an emerging problem due to the overlapping of self-supplementation and market-driven fortification in the pediatric context

## References

- 1 Steyn NP, Nel JH, Nantel G, Kennedy G, Labadarios D: Food variety and dietary diversity scores in children: are they good indicators of dietary adequacy? *Public Health Nutr* 2006;9:644–650.
- 2 Dwyer J: Convergence of plant-rich and plant-only diets. *Am J Clin Nutr* 1999; 70(suppl):620S–622S.
- 3 Hirschi KD: Nutrient biofortification of food crops. *Annu Rev Nutr* 2009;29: 401–421.
- 4 Allen LH, de Benoist B, Dary O, Hurrell R: Guidelines for Food Fortification with Micronutrients. Geneva, WHO, 1996.
- 5 Solomons NW: National food fortification: a dialogue with reference to Asia – balanced advocacy. *Asia Pac J Clin Nutr* 2008;17(suppl 1):20–23.
- 6 Palmer AC, West KP Jr, Dalmiya N, Schultink W: The use and interpretation of serum retinol distributions in evaluating the public health impact of vitamin A programmes. *Public Health Nutr* 2012;15:1201–1215.
- 7 Stoltzfus R, Dreyfuss ML: Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia. International Nutritional Anemia Consultancy Group. Washington, ILSI, 1998.
- 8 Huang HY, Caballero B, Chang S, Alberg A, Semba R, Schneyer C, Wilson RF, Cheng TY, Prokopowicz G, Barnes GJ 2nd, Vassy J, Bass EB: Multivitamin/mineral supplements and prevention of chronic disease. *Evid Rep Technol Assess (Full Rep)* 2006;139:1–117.
- 9 Solomons NW, Vossenaar M: Nutrient density in complementary feeding of infants and toddlers. *Eur J Clin Nutr* 2013;67:501–506.
- 10 Wong T: Parenteral trace elements in children: clinical aspects and dosage recommendations. *Curr Opin Clin Nutr Metab Care* 2012;15:649–656.
- 11 Alkhoury RH, Hashmi H, Baker RD, Gelfond D, Baker SS: Vitamin and mineral status in patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2013;56:89–92.
- 12 Leung WC, Hessel S, Méplan C, Flint J, Oberhauser V, Tourniaire F, Hesketh JE, von Lintig J, Lietz G: Two common single nucleotide polymorphisms in the gene encoding  $\beta$ -carotene 15,15'-monooxygenase alter  $\beta$ -carotene metabolism in female volunteers. *FASEB J* 2009;23: 1041–1053.
- 13 McLaren DS, Kraemer K: Interaction of vitamin A and other micronutrients. *World Rev Nutr Diet* 2012;103:101–105.
- 14 Fischer Walker C, Kordas K, Stoltzfus RJ, Black RE: Interactive effects of iron and zinc on biochemical and functional outcomes in supplementation trials. *Am J Clin Nutr* 2005;82:5–12.

## 1.4 Physical Activity, Health and Nutrition

Robert M. Malina

### Key Words

Adiposity · Bone mineral accrual · Metabolic syndrome · Fitness · Strength · Weight status

### Key Messages

- Physical activity (PA) is a behavior that changes with growth and maturation
- Regular PA favorably influences bone mineral accrual, cardiorespiratory fitness, and muscular strength and endurance
- PA has relatively small effects on lipids and adiposity and blood pressures in normal-weight and normotensive youth, respectively
- PA interventions favorably influence adiposity in the obese, blood pressures in the hypertensive, and components of the cardiometabolic profile in obese youth
- Many indicators of health and fitness, especially metabolic risk, are affected by obesity. A key issue is the prevention of unhealthy weight gain early in childhood and the potential role of PA

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From a public health perspective, PA is a behavior with important implications for health promotion and disease prevention during childhood, adolescence and adulthood. Emphasis is largely placed on the level of PA associated with health benefits. The role of PA as a medium for learning, enjoyment and social interactions is often overlooked.

Correlates of PA among children and adolescents include biological and cultural factors and their interactions. Physical fitness, specifically cardiorespiratory fitness (CRF), is both a correlate and outcome of PA. Movement skills are also an important correlate of PA. Types and settings (contexts) of PA are often overlooked, and include play, physical education, exercise, sport, transport and chores, among others. Contexts per se and meanings attached to them vary with age and also between and among different cultural groups [1]. Sport is a major context of PA for youth, but regular PA is not equivalent to training for sport.

### Introduction

Physical activity (PA) is a behavior. It is the most variable component of energy expenditure. On average, PA declines from late childhood through adolescence, and boys are more active than girls.

### Outcomes

Two questions, among others, are central to discussions of PA and health of school-age youth:  
(1) What are the health and fitness benefits of regular PA?



**Table 1.** Summary of trends in studies on relationships of habitual PA to selected indicators of health status and of the effects of specific PA programs (experimental, interventional) on indicators of health status

Health indicator	Relationships to PA	Effects of specific PA programs
Adiposity	Normal weight: less adiposity in habitually active youth	Normal weight: minimal effect Overweight/obese: reduction in overall and central adiposity with PA interventions
Bone	Increased bone mineral content in active youth	Variety of PA programs: increased bone mineral content and bone strength
Lipids and lipoproteins	Habitual PA: weak associations with TC, HDL-C, LDL-C and triglycerides	Weak beneficial effect of MVPA on HDL-C and triglycerides; no effect on TC and LDL-C
Blood pressures	Normotensive youth: no clear association between habitual PA and blood pressures	Hypertensive youth: aerobic PA programs favorably influence blood pressures Mild essential hypertension: suggestive beneficial effect
Cardiovascular health	Habitual PA: weak associations with levels of fibrinogen and C-reactive protein; inconclusive for endothelial function	Obese youth: aerobic PA programs improve resting vagal tone (heart rate variability)
Metabolic syndrome – cardiometabolic complications	High PA and CRF: better metabolic profile; association stronger for CRF than for PA	Overweight/obese youth: improved metabolic profile with PA intervention
CRF	Habitual PA associated with higher CRF	Experimental PA programs: favorable influence on CRF; gains of approx. 10% (3–4 ml/kg/min)
Muscular strength and endurance	Habitual PA: not consistently related to muscular strength and endurance	Experimental PA programs: significant gains, which vary with protocol – larger gains in strength with high resistance and low repetitions, larger gains in endurance with low resistance and high repetitions

Collated from several sources [2–4, 7–15]. TC = Total cholesterol; HDL-C/LDL-C = HDL/LDL cholesterol; MVPA = moderate-to-vigorous PA.

(2) What type and amount (frequency, intensity and duration) of PA is needed to bring about these benefits?

Allowing for variation among and limitations of studies, health benefits of PA are summarized in table 1. Data addressing the first question are largely derived from comparisons of active with less active youth and from studies of specific PA programs. Data addressing the second question are derived from experimental and intervention-

al programs which varied to some extent in setting (schools, recreation centers, etc.) and in duration, type and amount of PA. In general, the majority involved protocols of moderate-to-vigorous PA for 30–45 min, 3–5 days per week. Durations of programs varied to a greater extent. Programs in studies on bone health were more variable: moderate-to-vigorous PA 2–3 days per week, 45–60 min of weight-bearing activities and/or 10 min of high-impact activities [2].

Activity protocols in studies on CRF and muscular strength and endurance approximated systematic training. Allowing for variation among studies, protocols for CRF involved continuous PA (approx. 80% of maximal heart rate) for 30–45 min, 3 days per week for 12–16 weeks in youth 8 years of age through adolescence [2]. Protocols for muscular strength and endurance involved progressive resistance activities incorporating reciprocal and large muscle groups for 30–45 min, 2–3 days per week, with a rest day between sessions, over 8–12 weeks in youth 6 years of age through adolescence [3].

Individual differences in growth and maturation are confounding factors in evaluating effects of PA on health. Indicators of interest change with normal growth and maturation, and several (bone mineral accrual, CRF, strength, HDL cholesterol and adiposity) have growth patterns which are variable during adolescence [4]. Several studies highlight an important role for PA during the interval of maximal adolescent growth that includes peak height velocity. Longitudinal data suggest enhanced effects of PA on bone mineral accrual [5] and maximal aerobic power [6] during the interval of maximal growth in both sexes.

Data dealing with bone health are largely on prepubertal children (both sexes) and early pubertal youth (primarily girls). Among older adolescents, the influence of PA is more variable but generally positive.

Indicators of cardiometabolic health are currently of major interest: low HDL cholesterol, high triglycerides, elevated blood pressures, impaired glucose metabolism, insulin resistance, obesity and abdominal obesity, among others. The indicators tend to cluster within individuals and compose the metabolic syndrome. Higher levels of PA and CRF are independently associated with favorable metabolic profiles. Adiposity is an additional independent risk factor; leaner youth with low central adiposity (waist circumference) have a more favorable profile [7]. Rela-

tionships are stronger for CRF than for PA [8], but interactions of PA and CRF affect profiles [9]. PA interventions favorably alter risk profiles of overweight/obese youth, but not all individuals respond in the same manner [10–12]. Beneficial effects may be reduced or reversed after program cessation [13].

The preceding is derived from studies on normal-weight and overweight/obese youth in developed countries. Obesity is a consequence of an imbalance between energy intake and expenditure. Evidence dealing with PA of obese youth is equivocal, but the obese tend to have deficient movement skills and physical fitness [4]. The results highlight a need for critical evaluation of correlates of food intake, PA and physical inactivity among obese youth. Physical inactivity is a behavior independent of PA [1].

Chronic undernutrition, which is common in many developing countries, is associated with reduced PA and physical working capacity in school-age youth [4]. Conditions in many countries are changing as they experience the transition from high chronic undernutrition and associated mortality from infectious and diarrheal diseases to increasing prevalence of overweight/obesity and of morbidity and mortality from noncommunicable, degenerative diseases associated with dietary change and reduced habitual PA.

## Conclusions

- Regular PA favorably influences bone mineral accrual, CRF and muscular strength and endurance
- PA has relatively small effects on lipids, and on adiposity and blood pressures in normal-weight and normotensive youth, respectively. A greater amount of PA may be necessary in healthy youth
- Beneficial effects of PA are more apparent among ‘unhealthy’ youth – on adiposity in the

obese, on blood pressures in the hypertensive, and on insulin, triglycerides and adiposity in obese youth with the metabolic syndrome

- Many indicators of health and fitness, especially metabolic risk, are affected by obesity. A key issue is the prevention of unhealthy weight gain early in childhood and the potential role of PA [14]
- Interventional/experimental PA studies generally focus on outcomes. There is a need to consider the level of PA needed to *maintain* beneficial outcomes, as it may differ from that needed to *trigger* beneficial outcomes
- Most interventional/experimental protocols use continuous PA, except for studies of bone

health and muscular strength and endurance. Activities of children, especially young children, are largely intermittent. Potential health benefits of high-intensity, intermittent protocols need study

- Activity needs vary with age during childhood and adolescence: young children need variety in PA with opportunities to develop and refine movement skills in the context of free play; children more proficient in motor skills tend to be more physically active; with the transition into puberty and adolescence, the capacity for continuous activities increases and activity can be more prescriptive with emphasis on health and fitness

## References

- 1 Malina RM: Biocultural factors in developing physical activity levels; in Smith AL, Biddle SJH (eds): Youth Physical Activity and Inactivity: Challenges and Solutions. Champaign, Human Kinetics, 2008, pp 141–166.
- 2 Strong WB, Malina RM, Blimkie CJR, Daniels SR, Dishman RK, et al: Evidence based physical activity for school-age youth. *J Pediatr* 2005;146:732–737.
- 3 Malina RM: Weight training in youth: growth, maturation, and safety – an evidence-based review. *Clin J Sport Med* 2006;16:478–487.
- 4 Malina, RM, Bouchard C, Bar-Or O: Growth, Maturation, and Physical Activity, ed 2. Champaign, Human Kinetics, 2004.
- 5 Bailey DA, McKay HA, Mirwald RL, Crocker PRE, Faulkner RA: A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the University of Saskatchewan Bone Mineral Accrual Study. *J Bone Miner Res* 1999;14:1672–1679.
- 6 Mirwald RL, Bailey DA: Maximal Aerobic Power. London, Sport Dynamics, 1986.
- 7 Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S: Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European Youth Heart Study. *Diabetologia* 2007;50:1832–1840.
- 8 Rizzo NS, Ruiz JR, Hurtig-Wennlöf A, Ortega FB, Sjöström M: Relationship of physical activity, fitness, and fatness with clustered metabolic risk in children and adolescents: The European Youth Heart Study. *J Pediatr* 2007;150:388–394.
- 9 Brage S, Wedderkopp N, Ekelund U, Franks PA, Wareham NJ, et al: Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). *Diabetes Care* 2004;27:2141–2148.
- 10 Gutin B, Barbeau P, Litaker MS, Ferguson M, Owens S: Heart rate variability in obese children: relations to total body and visceral adiposity, and changes with physical training and detraining. *Obes Res* 2000;8:12–19.
- 11 Gutin B, Yin Z, Johnson M, Barbeau P: Preliminary findings of the effect of a 3-year after-school physical activity intervention on fitness and body fat: the Medical College of Georgia Fitkid Project. *Int J Pediatr Obes* 2008;3(suppl 1): 3–9.
- 12 Nassiss GP, Papantakou K, Skenderi K, Triandafilopoulou M, Kavouras SA, et al: Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metab Clin Exp* 2005;54: 1472–1479.
- 13 Carrel AL, Clark RR, Peterson S, Eickhoff J, Allen DB: School-based fitness changes are lost during the summer vacation. *Arch Pediatr Adolesc Med* 2007; 161:561–564.
- 14 Malina RM: Childhood and adolescent physical activity and risk of obesity in adulthood; in Bouchard C, Katzmarzyk PT (eds): Advances in Physical Activity and Obesity. Champaign, Human Kinetics, 2010, pp 111–113, 376–377.
- 15 Physical Activity Guidelines Advisory Committee: Physical activity guidelines advisory committee report 2008, part G, section 9: youth. Washington, US Department of Health and Human Services, 2008. [www.health.gov/paguidelines](http://www.health.gov/paguidelines).

## 1.5 Early Nutrition and Long-Term Health

Berthold Koletzko

### Key Words

Metabolic programming of long-term health ·  
Developmental origins of adult health ·  
Breastfeeding and obesity · Perinatal nutrition ·  
Disease risk prevention

### Key Messages

- Nutritional and metabolic factors during sensitive, limited periods of early human development have a long-term programming effect on health, well-being and performance in later age, extending into adulthood and old age
- Evidence for early programming effects arises from in vitro experiments, animal models, retro- and prospective epidemiological studies and controlled intervention trials
- Obstetric and paediatric medicine are expected to achieve a much greater role for the prevention of long-term disease risks in the population
- The important effects on health of early nutrition programming justify major investments into research and improvement of practice

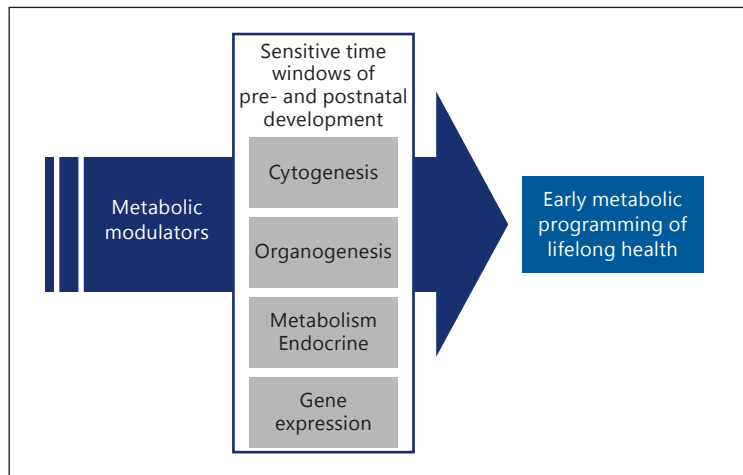
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### Introduction

Epidemiological studies, numerous animal models and clinical intervention trials provide ample evidence that nutritional and metabolic factors

during sensitive, limited periods of early human development have a long-term programming effect on health, well-being and performance in later age, extending into adulthood and old age [1–3]. Biological programming is defined as lasting effects on physiology, function, health and disease risks induced by environmental cues during limited time periods of early development and plasticity. While the term ‘programming’ was introduced into the scientific literature by Dörner [4] already in 1974, the concept has received broad attention primarily due to retrospective epidemiological studies published by Barker and others documenting inverse relationships between body weight at birth and at 1 year of age, respectively, and the risks of hypertension, diabetes and coronary heart disease (fig. 1) in adulthood [5, 6]. These observations stimulated intensive research that demonstrated powerful long-term effects of nutrition and growth before and after birth on later health, performance and disease risk. The exploration of underlying mechanisms and the resulting effects of metabolic programming offers tremendous opportunities for the early prevention of major health risks already during pregnancy and infancy, and they could provide both obstetric and paediatric medicine with a markedly increased role in promoting the long-term health of the population. It is likely that

**Fig. 1.** Nutritional and metabolic factors during sensitive time periods of developmental plasticity before and after childbirth modulate cytogenesis, organogenesis and metabolic and endocrine response as well as the epigenetic regulation of gene expression; thereby, they can induce metabolic programming of lifelong health and disease risk. Reproduced from Koletzko et al. [3], with permission.



preventive medicine will be redefined based on the evidence arising from the early origins of the adult disease hypothesis. This includes the major present causes of global death and disability [obesity, diabetes, hypertension, coronary heart disease, cerebrovascular disease and several forms of cancer (related to rates and timing of growth and hormonal maturation as well as to obesity)].

The concept of early metabolic programming of long-term health is supported by physiological, epidemiological and clinical research [1–3]. Nutritional and metabolic factors acting during sensitive time periods of developmental plasticity before and after childbirth have been shown to modulate cytogenesis, organogenesis and metabolic and endocrine response as well as the epigenetic regulation of gene expression; thereby, they can induce metabolic programming of lifelong health and disease risk (fig. 1). Specific mechanisms by which later disease is programmed are explored and the precise nutritional conditions that contribute to these processes are being established. The current key hypotheses (fig. 2) on the early nutritional programming of later adiposity, diabetes and associated non-communicable diseases include

(1) the fuel-mediated in utero hypothesis,

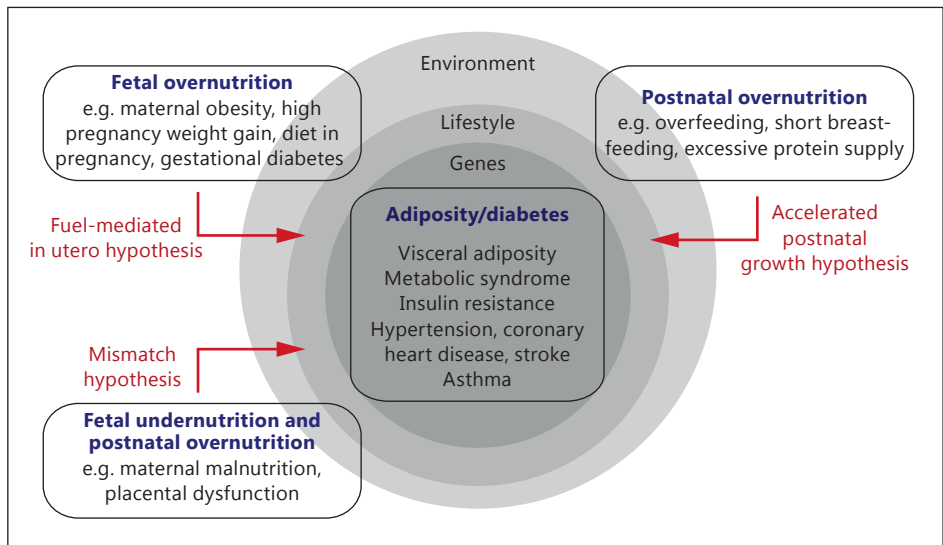
(2) the accelerated postnatal growth hypothesis and

(3) the mismatch hypothesis.

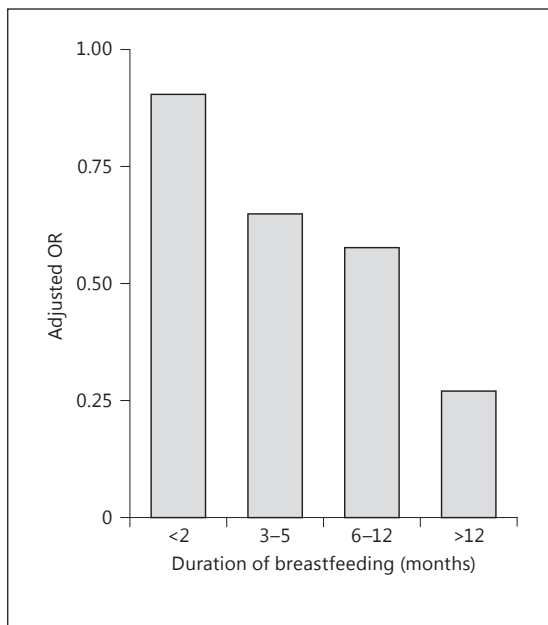
Randomized controlled trials in pregnancy and infancy now provide strong evidence for relevant programming effects of early nutrition in humans. For example, in the LIMIT randomized controlled trial, 2,212 pregnant overweight women (BMI  $\geq 25$ ) in South Australia were randomized to standard care in pregnancy or to targeted counselling with 3 face-to-face meetings and 3 telephone contacts to consolidate the messages [7]. The key focus was on encouraging a balanced diet with limited intakes of refined carbohydrates and saturated fatty acids as well as increased physical activity. While there was no significant effect on the primary outcome, infants born large for gestational age (RR 0.90), there was a marked reduction in the risk of a high birth weight  $>4,000$  g (RR 0.81;  $p = 0.03$ ; number needed to treat: 28). This is important because the systematic review of data from observational studies demonstrated that a birth weight  $>4,000$  g predicts a 2-fold increase in the risk of obesity in adulthood [8]. These findings demonstrate the large preventive potential of interventions in pregnancy and should stimulate further research in this area.







**Fig. 2.** Key hypotheses on the early nutritional programming of adiposity, diabetes and associated non-communicable diseases. Reproduced from Koletzko et al. [3], with permission.



**Fig. 3.** Longer duration of breastfeeding is linked to a lower adjusted OR of obesity at the early school age. Data from a cross-sectional study on >9,000 children in Bavaria, Germany. Reproduced from Koletzko et al. [3], with permission.

Infant feeding has also been shown to have lasting programming effects on later obesity risk. We evaluated the potential long-term impact of breastfeeding on later body weight in a large cross-sectional survey of >9,000 children participating in the obligatory school health examination in Bavaria, Germany [9]. An assessment of early feeding, diet and lifestyle factors revealed a clearly higher prevalence of obesity in children who had never been breastfed (4.5%) than in breastfed children (2.8%), with an inverse dose-response effect between the duration of breastfeeding and the prevalence of later obesity. The protective effect of breastfeeding was not attributable to differences in social class or lifestyle. After adjusting for potential confounding factors, breastfeeding remained a significant protective factor against the development of obesity (OR 0.75; 95% CI: 0.57–0.98) and overweight (OR 0.79; 95% CI: 0.68–0.93), with a dose-response relation between breastfeeding duration and later risk of overweight and obesity, respectively (fig. 3).

**Table 1.** Obesity prevalence and RR at 6 years of age in children randomized to receive formula with lower or higher protein content in infancy as well as the prevalence in a non-randomized reference group of children breastfed in infancy

Low protein content	High protein content	Unadjusted RR, OR (95% CI)	p	Adjusted RR, OR (95% CI)	p	Breastfed group
4.4%	10%	2.43 (1.12–5.27)	0.064	2.87 (1.22–6.75)	0.016	2.9%

From Weber et al. [14].

A protective effect of breastfeeding was also found in a number of studies in other populations, whereas others found no benefit. Systematic reviews and meta-analyses of cohort, case-control or cross-sectional studies concluded that breastfeeding provides a modest but consistent protective effect [10]. However, these conclusions are only based on observational data, because healthy infants cannot be assigned to breastfeeding on a randomized basis, and, hence, residual confounding cannot be excluded with certainty. The only published cluster randomized trial on breastfeeding promotion found no effects on later obesity, but basically all infants participating in this trial in Belarus had been breastfed, and the intervention only influenced the duration of breastfeeding [11]. Thus, this study does not provide sufficient statistical power to allow conclusions on the effects of early breastfeeding versus formula feeding on later obesity [12].

Various hypotheses have been raised on potential causes for a protective effect of breastfeeding. The establishment of a biological plausibility and the elucidation of mechanisms which mediate the protective effect of breastfeeding would lend support to a causal effect of breastfeeding. We proposed that its protective effect is at least in part due to lower growth rates in the first year as compared to formula-fed infants and is mediated by a lower protein content of human milk relative to formula.

Populations of breastfed infants show higher weight and length gains during the first year of

life than formula-fed infants, and more rapid weight gain in infancy and the second year of life predisposes to childhood overweight and obesity [10]. These growth differences between breastfed and formula-fed populations are most likely due to differences in metabolizable substrate intakes. Infants at ages of 3–12 months have a 10–18% higher energy intake per kilogram body weight if fed formula as compared to breastfed infants. Even larger is the difference in protein intake per kilogram body weight, which is 55–80% higher in formula-fed than in breastfed infants. In epidemiological studies, high protein intakes in early childhood, but not the intakes of energy, fat or carbohydrate, were significantly related to an early adiposity rebound and to a high childhood BMI, corrected for parental BMI. Thus, a high protein intake with infant formula in excess of metabolic requirements might predispose to an increased obesity risk in later life, a concept referred to as the ‘early protein hypothesis’. This issue has been studied in a large randomized clinical trial with allocation of healthy term infants to formulae with higher and lower protein contents (the European Childhood Obesity Project). The study showed that a lowering of the protein supply from infant and follow-on formulae closer to levels provided with breast milk normalizes growth up to the age of 2 years relative to the growth of breastfed populations [13]. Further follow-up of the participating children at the age of 6 years demonstrated a very marked, lasting effect of reducing the protein content of infant and



follow-on formulae on obesity risk at school age (table 1). These data indicate that improving infant feeding can have very large effects on later health.

These examples point to the numerous opportunities that should arise from a better understanding of early metabolic programming and its underlying mechanisms. Further elucidation of the impact of early nutrition on long-term health is expected to contribute greatly to providing improved policies of nutrition both for women during pregnancy and lactation and for their infants, as well as to enhancing standards of practice.

## Conclusions

- Optimal nutrition during pregnancy, lactation and infancy not only is important for immediate outcomes such as fetal and infant weight gain and body composition but also has long-term effects on child health, well-being and performance, extending into adulthood and old age
- Improved nutrition and physical activity in pregnancy has the potential to reduce the long-term obesity risk in the offspring

## References

- 1 Brands B, Demmelmair H, Koletzko B; EarlyNutrition Project: How growth due to infant nutrition influences obesity and later disease risk. *Acta Paediatr* 2014;103:578–585.
- 2 Berti C, Cetin I, Agostoni C, Desoye G, Devlieger R, Emmett PM, Ensenaer R, Hauner H, Herrera E, Hoesli I, Krauss-Etschmann S, Olsen SF, Schaefer-Graf U, Schiessl B, Symonds ME, Koletzko B: Pregnancy and infants' outcome: nutritional and metabolic implications. *Crit Rev Food Sci Nutr* 2014, Epub ahead of print.
- 3 Koletzko B, Brands B, Chourdakis M, Cramer S, Grote V, Hellmuth C, Kirshberg F, Prell C, Rzehak P, Uhl U, Weber M: The power of programming and the early nutrition project: opportunities for health promotion by nutrition during the first thousand days of life and beyond. *Ann Nutr Metab* 2014;64:141–150.
- 4 Dörner G: Perinatal hormone levels and brain organization; in Stumpf WE, Grant LD (eds): *Anatomical Neuroendocrinology*. Basel, Karger, 1975, pp 245–252.
- 5 Barker DJ: The origins of the developmental origins theory. *J Intern Med* 2007;261:412–417.
- 6 Gillman MW, Jaddoe VW: Appreciating David Barker (1938–2013). *Ann Nutr Metab* 2013;63:291–292.
- 7 Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, Crowther CA, Wittert G, Owens JA, Robinson JS: Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *BMJ* 2014; 348:g1285.
- 8 Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, Guo XR: Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obes Rev* 2011;12:525–542.

- Breastfeeding, compared to formula feeding, is associated with a small but consistent risk reduction for overweight and obesity at later ages, which is of considerable public health relevance on a population basis
- Overfeeding protein and/or energy in early life can have long-term adverse consequences in terms of common diet-related chronic diseases (obesity, diabetes and cardiovascular diseases)
- Reducing protein content in infant and follow-on formula to levels more similar to those found in breast milk was shown to markedly reduce obesity risk at early school age

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- 9 von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, von Voss H: Breast feeding and obesity: cross sectional study. *BMJ* 1999;319:147–150.
- 10 Koletzko B, Chourdakis M, Grote V, Hellmuth C, Prell C, Rzehak P, Uhl H, Weber M: Regulation of early human growth: impact on long-term health. *Ann Nutr Metab* 2014, in press.
- 11 Martin RM, Patel R, Kramer MS, Guthrie L, Vilchuck K, Bogdanovich N, Sergeichick N, Gusina N, Foo Y, Palmer T, Rifas-Shiman SL, Gillman MW, Smith GD, Oken E: Effects of promoting longer-term and exclusive breastfeeding on adiposity and insulin-like growth factor-I at age 11.5 years: a randomized trial. *JAMA* 2013;309:1005–1013.
- 12 Ruckinger S, von Kries R: Breastfeeding and reduced risk of childhood obesity: will randomized trials on breastfeeding promotion give the definite answer? *Am J Clin Nutr* 2009;89:653–655, author reply 655.
- 13 Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, Beyer J, Demmelmair H, Gruszfeld D, Dobrzanska A, Sengier A, Langhendries JP, Rolland Cachera MF, Grote V: Lower protein in infant formula is associated with lower weight up to age 2 years: a randomized clinical trial. *Am J Clin Nutr* 2009;89:1836–1845.
- 14 Weber M, Grote V, Closa-Monasterolo R, Escribano J, Langhendries JP, Dain E, Giovannini M, Verduci E, Gruszfeld D, Socha P, Koletzko B; European Childhood Obesity Trial Study Group: Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. *Am J Clin Nutr* 2014;99:1041–1051.



## 1.6 Food Safety

Hildegard Przyrembel

### Key Words

Food safety · Food hygiene · Residues · Contaminants · Production · Processing · Preparation · Storage · Standards · Code of practice

### Key Messages

- Nutritional safety of foods for infants and young children can be assessed by clinical studies, while microbial and chemical safety must be defined by risk analysis, regulated by law and monitored by controls
- Young and immature infants are particularly susceptible to microbial and chemical hazards from food
- Safe water, both chemically and microbially, is needed for the preparation of food for infants and young children particularly
- Safe food products can become unsafe in the course of inappropriate handling, preparation and storage

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### Introduction

While nutritional safety is the outcome tested in appropriate clinical studies by nutrition science [1, 2], chemical and microbial safety of food is not tested in humans but is the object of regulations, standards and codes of practice developed on a

global basis, e.g. by the Codex Alimentarius established in 1961 by the FAO (Food and Agriculture Organization of the United Nations) and the WHO, which are to be implemented by national legislation. Numerous scientific bodies consisting of independent experts advise on limits for residues, contaminants, naturally occurring toxins, food additives and infectious agents based on toxicological and microbial risk assessment to minimize the risk of foodborne diseases, while the FAO has established an Emergency Prevention System for Food Safety (EMPRES Food Safety) to serve as a key international system to assist in the prevention and management of global food safety emergencies, including the three pillars of early warning, emergency prevention and rapid response [3].

Foodborne diseases are caused by agents that enter the body through the ingestion of food and water and are a growing public health problem. Food and waterborne diseases kill approximately 3 million people annually, most of whom are children. In industrialized countries, the percentage of people suffering from foodborne diseases each year has been reported to be up to 30%. They are caused most often by microorganisms such as bacteria, viruses, protozoa and parasites, by naturally occurring toxins such as mycotoxins, by

persistent organic pollutants such as dioxins and PCB, and by heavy metals such as lead, cadmium and mercury.

The production of safe foods – by ensuring plant and animal health, by applying HACCP (Hazard Analysis and Critical Control Point) principles and observing hygiene [4] – must, however, be complemented by appropriate and hygienic handling of food by consumers.

## Residues

Residues in foods derive from deliberately applied substances, food additives, pesticides and veterinary drugs. For these substances, maximal residue levels (MRL) based on good practice (i.e. application at levels to achieve the desired effect but not higher) are defined. MRL must be compatible with acceptable daily intake (ADI) levels, which are the amounts of a chemical that can be ingested daily over a lifetime without producing appreciable health risks. ADI levels do not apply to infants below 3 months of age. Because infants and young children have food patterns with less variety than adults and they consume more food per unit of body mass, lower MRL are required for some pesticides in foods for infants and young children [5] – or, for instance in the European Community, the use of certain pesticides on crops intended for infants and young children is forbidden [6]. On an international level, residue levels are to be ‘reduced to the maximum extent possible’ for example in infant formulae, follow-on formulae and cereal-based complementary foods for infants and young children [7–9].

## Contaminants

Contaminants from the environment in food are unintended and often unavoidable – e.g. dioxins, PCB and heavy metals – or are introduced during processing. Naturally occurring contaminants

are fungal mycotoxins, particularly in cereals, nuts and fruit juices. They are quite stable to normal cooking temperatures and toxic to the liver and/or the kidney, and some are carcinogenic in rodents. Maximum levels for different mycotoxins in various categories of food and animal feed have been set in the majority of countries worldwide [10, 11]. For all other mycotoxins which cannot be completely eliminated in food and feed, levels must be as low as reasonably achievable.

Nitrate, which is accumulated by some plants and can occur in water wells, is considered a contaminant, and maximum levels have been set for ready-to-eat vegetable meals for infants. Nitrate, by itself not very toxic, is partially converted into nitrite, which can form carcinogenic nitrosamines with secondary amines from food and which can induce methemoglobinemia in young infants at intakes of >7 mg nitrate/kg per day, particularly in infants with still high levels of fetal hemoglobin and/or concomitant gastrointestinal or urinary tract infection. Home-prepared meals containing vegetables potentially high in nitrate (radish, beetroot, fennel, lettuce, kohlrabi and spinach) should therefore not be stored and rewarmed.

For other contaminants, both the Joint Expert Committee on Food Additives and Contaminants (JECFA) and the European Food Safety Authority (EFSA) have defined provisional tolerable weekly intake (PTWI) levels (table 1).

Heavy metals – particularly methylmercury in seafood products, cadmium taken up from the soil by plants, and lead mostly derived from industrial waste in plants and via feed in animal food – are of particular concern for children because of their long half-life and because of neurobehavioral, neurotoxic and nephrotoxic adverse effects, respectively.

Organohalogen compounds, e.g. dioxins and PCB, accumulate and persist for many years in body fat. They have adverse effects on development, reproduction and the immune and endo-

**Table 1.** Toxicological data on some relevant contaminants in food

Substance	Most recent assessment	Species	Relevant endpoint	LOAEL per kg body weight per day	(P)TWI per kg body weight per week
Methylmercury	JECFA, 2003 NRC, 2000 EFSA, 2012	Prenatal exposure of children	Neurobehavioral development		PTWI 1.6 µg PTWI 0.7 µg TWI 1.3 µg
Lead	JECFA, 2000; retracted in 2010 by EFSA and JECFA	Human	Neurotoxicity		PTWI 25 µg No threshold
Cadmium	JECFA, 2010 EFSA, 2011	Human	Renal toxicity		PTWI 5.8 µg TWI 2.5 µg
Dioxins and dioxin-like PCB	SCF, 2001	Rat	Development, reproduction		TWI 14 pg WHO-TEQ
Ochratoxin A	JECFA, 2001 EFSA, 2006, 2010	Pig	Renal toxicity	8 µg 8 µg	TWI 100 ng TWI 120 ng

LOAEL = Lowest observed adverse effect level; NRC = National Research Council (USA); SCF = Scientific Committee on Food of the European Commission; TEQ = toxicity equivalent.

crine systems. Both for heavy metals and organo-halogen compounds, maximum levels in food are recommended by the Codex Alimentarius and stipulated in national food law.

### Food Toxicology

The risk assessment of compounds used deliberately in the production of foods differs from that of contaminants, but the procedure is similar. For deliberately added compounds, ADI levels are set based on identified 'no observed adverse effect levels' (NOAEL) from the most sensitive study in the most sensitive species, and by dividing the NOAEL by a safety factor (most often of 100) to account for interspecies and intraspecies variability in sensitivity. Safety factors can be modified according to the quantity and quality of available data and by taking into account the severity or irreversibility of an effect. The result of the same procedure applied to contaminants is a tolerable

daily intake, or in the case of contaminants with long half-lives, a TWI (or PTWI if awaiting more data to become available). Dividing the NOAEL by the actual exposure of consumers permits an estimation of the margin of safety.

Compounds with genotoxic and/or carcinogenic activity presumably have no threshold for effects. Instead the margin of exposure can be estimated, that is, the ratio between a defined point on the dose-response curve in an animal carcinogenicity study and the human intake. A margin of exposure of 10,000 or higher is considered to be of low health concern [12].

Short-term intakes of a residue/contaminant in excess of ADI/tolerable daily intake levels do not necessarily entail adverse health effects. However, children may be particularly susceptible, and their expected lifespan and, therefore, the available time for the manifestation of adverse effects are longer. Table 1 lists toxicological data on some important contaminants.

**Table 2.** Recommendations for safe handling, preparation and storage of foods

- 
- Wash hands before preparing and feeding
  - Wash hands after going to toilet
  - Use safe water or treat it to make it safe
  - Wash and clean surfaces and equipment used for food preparation
  - Use clean utensils to prepare and serve food
  - Wash fruits and vegetables, especially if eaten raw
  - Separate raw and cooked food and use separate utensils for preparing them
  - Cook fresh, unpasteurized milk
  - Cook food thoroughly, particularly meat, poultry, eggs and seafood (internal temperature at least 70° C)
  - Serve foods immediately after preparation
  - Keep cooked food hot (>60° C) prior to serving
  - Do not leave cooked food for more than 2 h at room temperature
  - Discard uneaten prepared food or refrigerate, preferably <5° C
  - Refrigerate all cooked and perishable food immediately (preferably <5° C)
  - Store raw and cooked food in separate containers
  - Store food preferably dry
  - Do not store food too long (even in refrigerator) and do not use beyond expiry date
  - Do not thaw frozen food at room temperature
  - Heat stored prepared food thoroughly (>70° C)
- 

### Infectious Foodborne Diseases

Microbial contamination of food can occur throughout the chain of food production, processing and storage. Microbial diseases which can be transferred from animals to man are zoonoses, the most important agents being salmonellae, mycobacteria, brucellae, campylobacter, listeria, toxoplasma, yersiniae and parasites like trichinella and echinococci.

Foodborne viral illnesses, e.g. noroviruses and hepatitis A, are on the increase. They relate predominantly to fresh produce rather than to

industrially produced foods, and/or are linked to contamination of the food by an infected food handler.

The impact of infectious diseases on mortality of children under 5 years of age is more than 2 times greater in malnourished children. Apart from attempts to improve both the quality and the quantity of food, continued frequent breastfeeding or, when possible, relactation are important measures [13] to minimize the risk from pathogens in foods or fluids and to profit from the protective factors provided by breast milk.

### Infant Formulae

Feeding breast milk substitutes requires the availability of clean and safe water and cooking facilities [14]. A typical example of the importance of HACCP principles in the production of foods and of sanitary measures to be applied by the consumer is the case of *Enterobacter sakazakii* (*Cronobacter* spp.) in powdered infant formulae. This microorganism has caused outbreaks of sepsis, meningitis or necrotizing enterocolitis especially in premature infants and those less than 2 months old. Although the overall incidence seems to be low, mortality rates between 20–50% were reported. Powdered infant formula is not sterile, and even when manufactured under strict hygiene, the occurrence of low counts (1–3/g) of coliform bacteria cannot be prevented. *E. sakazakii* does not grow in the dry powder but starts to replicate after preparation with water and at temperatures >5°C. It can be destroyed by temperatures >60°C. Measures to reduce the risk of infection include preparation in a sterile environment with boiled water (>70°C), feeding immediately after appropriate cooling, limitation of feeding duration and of infusion via feeding tubes at room temperature to less than 4 h, and discarding uneaten residues [15–17].

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## Conclusions

- Practical recommendations for the safe handling of food at home and elsewhere are given in table 2
- Toxicological safety of food is primarily the responsibility of the manufacturer
- Microbial safety of food is both the responsibility of the manufacturer and of the person preparing and serving it

## References

- 1 Aggett PJ, Agostoni C, Goulet O, Hernell O, Koletzko B, Lafeber HL, Michaelsen KF, Rigo J, Weaver LT: The nutritional and safety assessment of breast milk substitutes and other dietary products for infants: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2001;32: 256–258.
- 2 Aggett P, Agostoni C, Axelsson I, Goulet O, Hernell O, Koletzko B, Lafeber HN, Michaelsen KF, Morley R, Rigo J, Szajewska H, Weaver LT; ESPGHAN Committee on Nutrition: Core data for nutrition trials in infants: a discussion document – a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2003;36:338–342.
- 3 FAO: EMPRES Food Safety: Emergency Prevention System for Food Safety. Strategic plan. Rome, FAO, 2010. <http://www.fao.org/docrep/012/i1646e/i1646e00.htm>.
- 4 FAO: Food Quality and Safety Systems: a training manual on food hygiene and the Hazard Analysis and Critical Control Point (HACCP) System. Rome, FAO, 1998. <http://www.fao.org/docrep/W8088E/W8088E00.htm>.
- 5 Schilter B, Renwick AG, Huggett AC: Limits for pesticide residues in infant foods: a safety-based approach. *Regul Toxicol Pharmacol* 1996;24:126–140.
- 6 Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and Amending Directive 1999/21/EC. *Offic J Eur Union* 30.12.2006:L 401/1–33.
- 7 FAO/WHO: Standard for infant formula and formulas for special medical purposes intended for infants. CODEX STAN 72 – 1981, amended 1983, 1985, 1987, 2007, 2011.
- 8 FAO/WHO: Standard for follow-up formula. CODEX STAN 156 – 1987, amended 1989, 2011.
- 9 FAO/WHO: Codex standard for processed cereal-based foods for infants and young children. CODEX STAN 074 – 1981, rev 2006.
- 10 FAO: Worldwide regulations for mycotoxins in food and feed 2003. Food and Nutrition Paper, vol 81. Rome, FAO, 2004. <http://www.fao.org/docrep/007/y5499e/y5499e04.htm>.
- 11 FAO/WHO: Codex standard for contaminants and toxins in food and feed. CODEX STAN 193 – 1995, rev 1997, 2006, 2008, 2009, amended 2010, 2012.
- 12 Larsen JC: Risk assessment of chemicals in European traditional foods. *Trends Food Sci Technol* 2006;17:471–481.
- 13 WHO: Guiding principles for feeding infants and young children during emergencies. Geneva, WHO, 2004.
- 14 Howard G, Bartram L: Domestic water quantity, service level and health. Geneva, WHO, 2003. WHO/SDE/WSH/3.02.
- 15 FAO/WHO: *Enterobacter sakazakii* and other microorganisms in powdered infant formula. Rome/Geneva, FAO/WHO, 2004. <http://www.who.int/foodsafety/publications/micro/es.pdf>.
- 16 FAO/WHO: *Enterobacter sakazakii* and *Salmonella* in powdered infant formula. Rome/Geneva, FAO/WHO, 2006. <ftp://ftp.fao.org/docrep/fao/O9/a0707e/a0707e00.pdf>.
- 17 FAO/WHO: *Enterobacter sakazakii* (*Cronobacter* spp.) in powdered follow-up formula. Rome/Geneva, FAO/WHO, 2008. <ftp://ftp.fao.org/docrep/fao/011/i0453e/i0453e00.pdf>.

## 1.7 Gastrointestinal Development, Nutrient Digestion and Absorption

Michael J. Lentze

1

### Key Words

Nutrient digestion · Absorption · Fetal intestinal development · Motility

### Key Messages

- The fetal human gut is prepared for the digestion and absorption of nutrients already at the 24th week of gestation
- Macronutrients can be digested and absorbed even by premature babies
- The rate-limiting factor during fetal life, particularly for premature infants, is the development of motility

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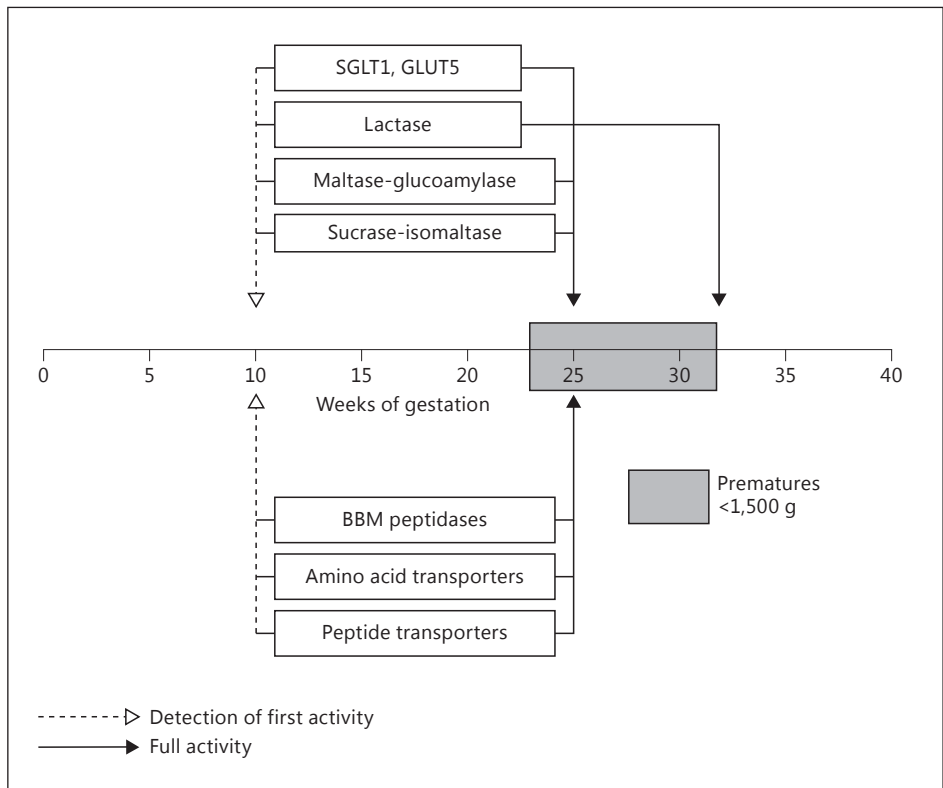
### Introduction

Development of the gastrointestinal tract during intrauterine life is the prerequisite for survival in external life for a human fetus. The digestive and absorptive capacity of the intestinal organs as well as the contact of foreign pathogens with an active immune system guarantees the normal growth and wellbeing of an infant in early life. As the number of premature babies below 1,000 g is increasing, knowledge of digestive and absorptive functions of the gastrointestinal tract is of vital

interest to neonatologists feeding these very-low-birth-weight (VLBW) infants.

The gastrointestinal tract has digestive, absorptive, secretory and barrier functions. In addition it produces a large number of gut hormones (e.g. the hormones ghrelin, peptide YY and oxyntomodulin, regulating satiety; cholecystokinin, regulating bile and pancreatic secretions and motility; and glucagon-like peptides 1 and 2) and hosts the majority of immune-competent cells of the body, including about 80% of the body's immunoglobulin producing cells. The interaction between various organs and the complex structure and function of the gastrointestinal tract is developing during fetal life in order to provide the newborn baby with a functional gastrointestinal system to survive in the external world. This includes the digestion and absorptions of nutrients, transport through the gut as well as a barrier function to a large number of microbiota and symbiotic life with them. Antigens need to be identified and taken care of without involving the whole body in an illness.

The human gut is formed from the endodermal layer of the embryo by the incorporation of the dorsal part of the yolk sac during infolding of the embryonic disk. At the 4th week of gestation,



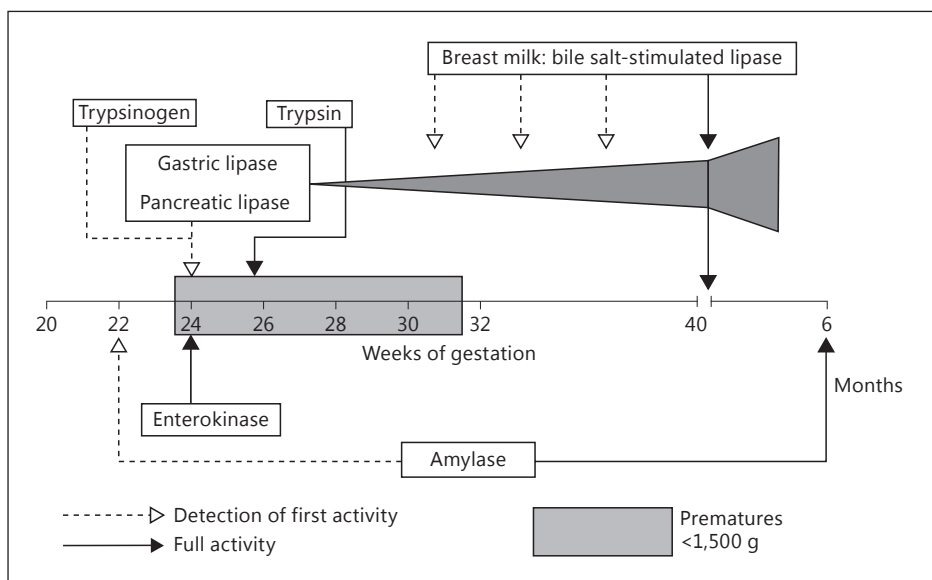
**Fig. 1.** Development of brush border enzymes and transporters during fetal life. BBM = Brush border membrane; SGLT1 = sodium-dependent glucose transporter 1; GLUT5 = glucose transporter 5.

the first tube has a length of 4 mm from the mouth to the cloaca. During pregnancy, it elongates about 1,000-fold until full term. The stomach at term has a volume of about 30 ml, the small intestine a length of 250–300 cm, the large intestine a length of 30–40 cm. Between the 9th week of gestation and birth, the small intestine undergoes extraordinary changes from a primitive stratified epithelium of undifferentiated epithelial cells into a fully differentiated organ with villi and crypts [1]. The formation of Peyer’s patches starts at 16–18 weeks of gestation when the first lymphocytes are seen in the lamina propria [2].

Parallel to the morphological changes during fetal development, the digestive and absorptive functions of the gastrointestinal tract begin to

appear at the 10th week of gestation and fully express their activities between the 26th week of gestation and term, or within the first month of life.

The brush border enzymes lactase, maltase-glucoamylase and sucrase-isomaltase are first determined at the 10th week of gestation (fig. 1). Whereas sucrase-isomaltase reaches its full activity already by the 25th week of gestation, lactase activity is fully developed by the 32nd week of gestation [3, 4]. As lactose is the predominant sugar in breast milk, the possibility exists that premature babies born before the 32nd week of gestation might lack full lactase activity when fed breast milk or a lactose-containing premature formula. However, the overall lactase activity



**Fig. 2.** Development of pancreatic enzymes, gastric lipase and enterokinase during fetal life.

along the small intestine even in VLBW infants is sufficient to hydrolyze lactose into glucose and galactose.

The transport system responsible for the uptake of glucose and galactose, the sodium-dependent glucose transporter 1, is already fully active by the 25th week of gestation, as is glucose transporter 5 [5]. For the digestion of proteins, the pancreatic enzymes trypsin, chymotrypsin and carboxypeptidase are first detected in the 24th week of gestation (fig. 2). Full activity is reached by the 26th week of gestation. Trypsinogen is activated by enterokinase in the 24th week of gestation. The brush border peptidases, the amino acid transporters as well as peptide transporters start their transport activities at the 10th week of gestation and reach their full activity by 25th week of gestation [6]. The digestion of proteins and the absorption of amino acids and dipeptides are effective already in VLBW infants. Fat digestion depends on various lipases and the formation of micelles. The responsible lipases,

such as gastric and pancreatic lipases, show their first measurable activities at the 24th week of gestation. Full enzyme activity develops steadily toward term and after birth. Depending on the type of food, breast milk lipase given to infants by breastfeeding supplements fat digestion during the first weeks of life [7]. The digestion of starch is the last to develop during pregnancy and after birth. Pancreatic amylase is first detected in the 22nd week of gestation, but reaches its full activity as late as the 6th month after birth. Premature or term infants cannot easily digest large amounts of starch. Small amounts of starch, however, can be given to premature and term infants without difficulty because amylose and amylopectin are also hydrolyzed by the action of sucrase-isomaltase and maltase-glucoamylase [8].

Although the digestive and absorptive capacity of the gastrointestinal tract is well prepared for external life after birth even in premature babies, immature motility is the limiting system

particularly in premature infants coping with external feeding. Here, the response of the intestine to a bolus feed depends on the maturity of the gut. In small infants before 31 weeks of postconceptional age, who usually receive low volumes of continuous enteral feed, ordinary postprandial activity does not occur [9]. Between 31 and 35 weeks of postconceptional age, postprandial activity is induced in infants by giving them larger volumes of feed. However, the activity remains in a fasting pattern with superimposed, more random postprandial activity. Finally, in infants over 35 weeks of postconceptional age who receive large volumes of bolus feed, there is a disruption in cyclical fasting activity and replacement by continuous activity. Whether this motility pattern can be advanced by pharmacological measures such as the administration of cortisol remains to be seen [10, 11].

## Conclusions

Feeding of premature infants below 35 weeks of gestation requires knowledge of physiological functions at this time. Whereas digestive and absorptive functions are mostly developed from the 24th week of postconceptional age, gastrointestinal motility is still not very active. Premature formulas or fortified breast milk can be given to VLBW infants or extremely LBW infants in small quantities. From the 31st postconceptional week onward, the quantity of enteral feeds becomes less of a problem. As far as macronutrients are concerned, protein is digested and absorbed well. Carbohydrates, in form of lactose, are also digested and absorbed well. Starch can only be digested in small quantities. The digestion of fat increases quickly from the 26th week of gestation and can be enhanced by administration of milk lipase via breast milk.

## References

- 1 Moxey PC, Trier JS: Development of villous absorptive cells in the human fetal small intestine: a morphological and morphometric study. *Anat Rec* 1979;195:463–482.
- 2 Owen WL, Jone AL: Epithelial cell specialisation within human Peyer's patches: an ultrastructural study of intestinal lymphoid follicles. *Gastroenterology* 1974;66:189–203.
- 3 Lentze MJ: Die Ernährung von Frühgeborenen unter 1,500 g: Enterale Voraussetzungen. *Monatsschr Kinderheilkd* 1986;134:502–507.
- 4 Menard D: Development of human intestinal and gastric enzymes. *Acta Paediatr Suppl* 1994;405:1–6.
- 5 Davidson NO, Hausman AM, Ifkovits CA, Buse JB, Gould GW, Burant CF, Bell GI: Human intestinal glucose transporter expression and localization of GLUT5. *Am J Physiol* 1992;262:C795–C800.
- 6 Adibi SA: Regulation of expression of the intestinal oligopeptide transporter (Pept-1) in health and disease. *Am J Physiol Gastrointest Liver Physiol* 2003; 285:G779–G788.
- 7 Boehm G, Bierbach U, Senger H, Jakobson I, Minoli I, Moro G, Rähä NC: Activities of lipase and trypsin in duodenal juice of infants small for gestational age. *J Pediatr Gastroenterol Nutr* 1991;12: 324–327.
- 8 Terada T, Nakanuma Y: Expression of pancreatic enzymes ( $\alpha$ -amylase, trypsinogen, and lipase) during human liver development and maturation. *Gastroenterology* 1995;108:1236–1245.
- 9 Bisset WM, Watt J, Rivers RP, Milla PJ: Postprandial motor response of the small intestine to enteral feeds in preterm infants. *Arch Dis Child* 1989;64: 1356–1361.
- 10 Bisset WM, Watt JB, Rivers RP, Milla PJ: Ontogeny of fasting small intestinal motor activity in the human infant. *Gut* 1988;29:483–488.
- 11 Bisset WM, Watt JB, Rivers RP, Milla PJ: Measurement of small-intestinal motor activity in the preterm infant. *J Biomed Eng* 1988;10:155–158.

## 1.8 Gut Microbiota in Infants

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1

### Key Words

Microbiota · Probiotics · Prebiotics · Health

### Key Messages

- A healthy microbiota preserves and promotes host wellbeing and absence of disease in general – not only in the gastrointestinal tract
- Colonization of the infant by microbes is initiated during pregnancy
- Initial colonization by ‘pioneer bacteria’ is enhanced by both naturally occurring bacteria and oligosaccharides in breast milk
- These pioneer bacteria direct later microbiota succession, forming a basis for a healthy gut microbiota throughout one’s lifetime
- The microbiota resembles that of adults by 2–3 years of age
- Disturbed microbiota succession during early infancy has been linked to increased risk of infectious, inflammatory and allergic diseases later in life
- Intestinal microbial colonization and its modulation by dietary means are important considerations during the first years of life

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### Initial Establishment of Microbiota

#### *Source of Original Microbiota*

The microbiota of a newborn is acquired from the mother before and after birth and develops rapidly following delivery. It is initially strongly dependent on the mother’s microbiota, the mode of delivery and the birth environment [1, 2]. The microbiota of the mother is determined by genetic and environmental factors. Stress and dietary habits during later pregnancy have a significant impact on the microbiota. Even in healthy pregnancy, the maternal microbiota changes considerably between the 1st and the 3rd trimester [3]. Such changes influence the quality and quantity of the initial colonizers of the newborn. Subsequently, feeding practices (formula or human milk) and the infant’s home environment influence microbiota succession at the genus and species level, as well as species composition and numbers of bacteria.

#### *Succession of Microbial Communities*

Establishment of the microbiota in the newborn occurs in a stepwise fashion. Studies on mice have shown that the first bacteria to colonize the intestine, even prior to delivery and during the perinatal period (‘pioneer bacteria’), can modulate gene expression in host intestinal epithelial cells. This

results in an altered intestinal microenvironment, which influences the nature of subsequent intestinal colonization.

In the newborn, initial colonization with facultative anaerobes, enterobacteria, coliforms, proteobacteria, lactobacilli and streptococci is rapidly followed by colonization with anaerobic genera such as *Bifidobacterium*, *Bacteroides*, *Clostridium* and lactic acid bacteria. Although recent research indicates that the interhost differences are much less marked than previously thought, molecular analyses demonstrate differences between the microbiota of formula-fed and breastfed infants with respect to bifidobacterial numbers and species composition. In breastfed infants, bifidobacteria constitute 60–90% of the total fecal microbiota, while lactobacilli comprise less than 1% [1, 4]. The most common bifidobacterial species in breastfed infants are *B. longum*, *B. breve* and *B. infantis* [5]. In formula-fed infants, the microbiota is more complex and influenced by the formula composition – for instance, by reported overrepresentation of *Clostridium difficile* and a higher richness in species. Lactic acid bacteria composition in breastfed and formula-fed infants is similar (with some geographic differences), with *Lactobacillus casei* group microorganisms such as *L. paracasei* and *L. rhamnosus* being common [unpubl. results]. Differences in microbiota between breastfed and formula-fed infants have lessened with improved infant formulae.

### **Gut Microbiota in the First Six Months of Life**

Breastfeeding for 4–6 months will assist in the development of healthy gut microbiota by providing bifidobacteria and lactic acid bacteria, which reinforce colonization, and by supplying human milk oligosaccharides, which promote a healthy microbiota composition. Breastfeeding also facilitates the exchange of microbes between mother and infant, since breast milk itself is a rich source of bacteria. Of note, the breast milk microbiota in

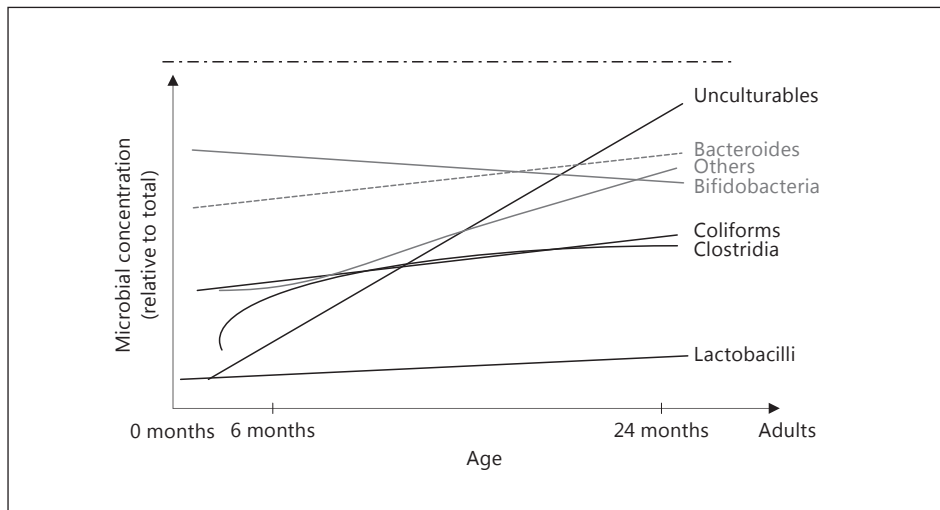
mothers having a cesarian section differs from that of mothers having a vaginal delivery [6]. Microbes are also exchanged via skin contact and exposure to the microbiota in the immediate environment. Every individual has a unique, characteristic microbiota during later phases of breastfeeding that comprises a dynamic mixture of microbes typical to each individual. Weaning, introduction of solid foods, and antimicrobial drug treatment will break the constant supply of oligosaccharides and microbes from the mother, thus affecting intestinal microbiota development.

Molecular analysis of bacterial communities in healthy babies during the first 10 months of life demonstrates progression from a simple profile in the first days of life to a more complex, diverse profile with members of the genera *Bifidobacterium*, *Ruminococcus*, *Enterococcus*, *Clostridium* and *Enterobacter* identified by 6 months of age [1–4]. *Bifidobacterium* and *Ruminococcus* species dominate the intestinal microbiota with high-level, stable expression over time. A Canadian study on 4-month-old infants reported higher bifidobacterial levels and lower clostridial numbers in breastfed infants than in infants receiving formula [14]. Ongoing improvements in formulae have lessened these differences [7].

The healthy intestinal microbiota in infancy is characterized by a large Gram-positive bacterial population which contains significant numbers of bifidobacteria, mainly *B. longum*, *B. breve* and *B. infantis*. Lactic acid bacteria may play a role in providing the right intestinal environment for bifidobacteria to dominate. A healthy microbiota during infancy is particularly important as this establishes the basis for healthy gut microbiota later in life.

### **Gut Microbiota in Infants from Six Months Onward**

After the first 6 months of life, the microbiota becomes more diverse [1, 6, 9]. Several studies have examined the progression of microbiota from birth



**Fig. 1.** Relative changes in gut microbiota composition suggested by culture-dependent and culture-independent studies. The numbers of bifidobacteria can be influenced by diet, probiotics and prebiotics.

through the first years of life (summarized in fig. 1). Weaning is associated with changes including increased levels of *Escherichia coli*, enterococci, bacteroides and anaerobic gram-positive cocci and decreased enterobacteria. Differences between breast-fed and formula-fed infants seem to disappear.

By 1–2 years of age, the microbiota resembles that of adults, although levels of bifidobacteria and enterobacteria in children (16 months to 7 years) remain higher than in adults. Early change of the microbiota to the adult type may be linked with development of eczema [9]. The intestinal microbiota is crucial for normal development of the gut-associated lymphoid tissue and has important effects on intestinal mucosal barrier function and other aspects of intestinal function.

### Immune Development

Microbial colonization of the newborn intestine is required for normal immune development, which in turn is important for regulation of gut

inflammatory responses and oral tolerance induction. The mucosal immune system of the gastrointestinal tract is constantly challenged by diverse antigens, such as microbial and food antigens. Such priming of the gut-associated lymphoid tissue is important for two opposing functions: mounting a response to pathogens and maintaining hyporesponsiveness to innocuous antigens. Mice raised in a germ-free environment fail to develop oral tolerance and have a persistent Th2-dependent antibody response [11]. This immune deviation can be corrected by reconstitution of intestinal microbiota, but only if this occurs during the neonatal period [11]. Prenatal exposure to companion animals is linked with changes in microbiota and infantile pet exposure is negatively associated with wheezy bronchitis at 24 months of age [10].

An important question is how the microbiota is altered by the significant changes in diet during the first years of life, and how this affects intestinal immune development; the host-microbe crosstalk during and after breastfeeding is criti-





cal in this regard. The strains of healthy gut microbiota are likely to stimulate local and systemic immune responses via pattern recognition molecules such as Toll-like receptors, providing the host with an anti-inflammatory stimulus and directing the host-microbe interaction toward immune tolerance. The bifidobacteria-dominated environment in childhood in particular may provide more of an anti-inflammatory stimulus than bacteria from adults, which have been shown to be more proinflammatory. A complex microbial community is required to achieve a healthy microbiota that exhibits powerful antipathogenic and anti-inflammatory capabilities.

### **Intestinal Function**

An absent or inadequate intestinal microbiota has been shown to cause defects in intestinal barrier function. The microbiota may also influence other intestinal functions. Before weaning, formula-fed infants have a greater ability to ferment complex carbohydrates than breastfed infants, probably due to the presence of a more complex microbiota. Following weaning, these differences disappear. Breastfed infants have delayed establishment of mucin-degrading microbiota, but this increases in both groups between 6 and 9 months. Conversion of cholesterol to coprostanol commences after 6 months of age, and levels of ammonia, phenol,  $\beta$ -glucosidase and  $\beta$ -glucuronidase activity increase after weaning.

### **Maintenance and Modulation of the Individually Optimized Healthy Microbiota**

The healthy gut microbiota created during early life must be maintained throughout life. Deviations in microbiota associated with disease can be redirected to a healthy balance by dietary means, for instance by using probiotics or prebiotics. Probiotics are defined as viable microbes which

through oral administration produce health benefits to the host. Probiotics are members of the healthy gut microbiota that mimic the healthy microbiota of a healthy infant, and are generally regarded as safe [12]. Prebiotics are oligosaccharides that promote expansion of specific microbes with potential to maintain health. A prerequisite for the efficacy of prebiotics is that such strains are already present in the gut. Carefully designed combinations of probiotics and prebiotics may offer an optimal means of creating and maintaining a healthy microbiota as this would mimic the mother-infant relationship of offering both microbes and oligosaccharides to the newborn infant.

It is important to recognize that individual probiotic bacterial strains can have distinct and specific effects. Therefore, the effects of one probiotic strain cannot be generalized to another, and the individual properties of a probiotic strain must be evaluated prior to clinical application. Furthermore, in addition to species/strain-specific effects of probiotics, the timing of probiotic administration may also be important. Meta-analysis of randomized controlled trials of probiotic interventions for allergic disease prevention show beneficial effects when probiotic supplementation is commenced during the prenatal period, and not when probiotics are solely administered to the infant postnatally [13]. This suggests that prenatal administration may be a requisite for efficacy in the prevention of allergic disease. These results highlight the different effects of specific probiotics, which are further supported by genomic studies.

Similarly, prebiotic oligosaccharides have different microbiota-modifying properties. Although most prebiotic components have been shown to enhance the bifidobacterial microbiota, detailed investigation of specific effects is required. A wide variety of oligosaccharides (human milk oligosaccharides) is found in breast milk and has documented bifidogenic and health-promoting effects on the infant gut. Combina-

tions of galactooligosaccharides and fructooligosaccharides have been used in infant formulae in specified conditions. Some fructooligosaccharides have been reported to enhance levels of unknown microbes in the human gut, thus potentially facilitating untoward effects in infants. Therefore, when evaluating a probiotic or prebiotic for clinical use, the safety and clinical benefit of that specific product must be documented before it can be recommended for clinical application.

## Conclusions

- The healthy human microbiota is metabolically active and provides an important defense mechanism for the host. Deviations in its composition are related to multiple disease states

promoting the bifidogenic environment via prebiotic galactooligosaccharides and microbes in breast milk and introducing environmental bacteria through contact with the infant

- Both the succession of microbial communities during the first years of life and the sequelae of these events need to be clarified in more detail
- The first colonization steps have a crucial role in the infant microbiota and later health. Bifidobacteria play a key role in this process
- The mother-infant contact has an important impact on initial microbiota development, providing the critical first inoculum already prior to birth, followed by another inoculum at delivery, and then progressing with breastfeeding
- The potential application of specific probiotics and/or prebiotics to influence microbiota development for the treatment and prevention of disease also warrants further evaluation

## References

- 1 Rautava S, Luoto R, Salminen S, Isolauri E: Microbial contact during pregnancy, intestinal colonization and human disease. *Nat Rev Gastroenterol Hepatol* 2012;9:565–576.
- 2 Jost T, Lacroix C, Braegger CP, Chassard C: New insights in gut microbiota establishment in healthy breast fed neonates. *PLoS One* 2012;7:e44595.
- 3 Koren O, Goodrich JK, Cullender TC, Spor A, Laitinen K, Bäckhed HK, Gonzalez A, Werner JJ, Angenent LT, Knight R, Bäckhed F, Isolauri E, Salminen S, Ley RE: Host remodeling of the gut microbiome and metabolic changes during pregnancy. *Cell* 2012;150:470–480.
- 4 Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, Angenent LT, Ley RE: Succession of microbial consortia in the developing infant gut microbiome. *Proc Natl Acad Sci USA* 2011;108(suppl 1):4578–4585.
- 5 Favier CF, Vaughan EE, de Vos WM, Akkermans AD: Molecular monitoring of succession of bacterial communities in human neonates. *Appl Environ Microbiol* 2002;68:219–226.
- 6 Cabrera-Rubio R, Collado MC, Laitinen K, Salminen S, Isolauri E, Mira A: The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery. *Am J Clin Nutr* 2012;96:544–551.
- 7 Rinne MM, Gueimonde M, Kalliomäki M, Hoppu U, Salminen SJ, Isolauri E: Similar bifidogenic effects of prebiotic-supplemented partially hydrolyzed infant formula and breastfeeding on infant gut microbiota. *FEMS Immunol Med Microbiol* 2005;43:59–65.
- 8 Jost T, Lacroix C, Braegger C, Chassard C: Assessment of bacterial diversity in breast milk using culture-dependent and culture-independent approaches. *Br J Nutr* 2013;110:1253–1262.
- 9 Nylund L, Satokari R, Nikkilä J, Rajilić-Stojanović M, Kalliomäki M, Isolauri E, Salminen S, de Vos WM: Microarray analysis reveals marked intestinal microbiota aberrancy in infants having eczema compared to healthy children in at-risk for atopic disease. *BMC Microbiol* 2013;13:12.
- 10 Nermes M, Niinivirta K, Nylund L, Laitinen K, Matomäki J, Salminen S, Isolauri E: Perinatal pet exposure, faecal microbiota, and wheezy bronchitis: is there a connection? *ISRN Allergy* 2013; 2013:827934.
- 11 Sudo N, Sawamura S, Tanaka K, et al: The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1995; 159:1739–1745.
- 12 van Loveren H, Sanz Y, Salminen S: Health claims in Europe: probiotics and prebiotics as case examples. *Annu Rev Food Sci Technol* 2012;3:247–261.
- 13 Tang ML, Lahtinen SJ, Boyle RJ: Probiotics and prebiotics: clinical effects in allergic disease. *Curr Opin Pediatr* 2010; 22:626–634.
- 14 Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, Sears MR, Becker AB, Scott JA, Kozyrskyj AL; CHILD Study Investigators: Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ* 2013;185:385–394.

## 2.1 Breastfeeding

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### Key Words

Breastfeeding · Human milk · Lactation · Health benefits · Preterm infants · HIV, mother-to-child transmission

### Key Messages

- Breastfeeding provides optimal nutrition for infants
- Breastfeeding has significant positive effects on infant health, growth and development and decreases the risk of diseases later in life
- Infants should preferably be exclusively breastfed for about 6 months and should continually be breastfed up to the age of 12 months or beyond
- In most populations, the duration of breastfeeding is considerably shorter than recommended. The health profession has therefore an important role in protecting, promoting and supporting breastfeeding

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aim for exclusive breastfeeding of infants for about 6 months [1, 2]. In industrialized countries, continued partial breastfeeding up to the age of 12 months or beyond is the general recommendation. In populations with high rates of infectious diseases, breastfeeding during the 2nd year of life or longer has been shown to reduce morbidity and mortality, and therefore the recommendation by the WHO has been to continue breastfeeding until the age of 24 months or beyond. In most populations, the duration of both exclusive breastfeeding and continued breastfeeding is considerably shorter, emphasizing the need to protect, promote and support breastfeeding via broad public health initiatives and support from the health care systems. It has been estimated that, globally, suboptimal breastfeeding may result in more than 800,000 deaths annually [5].

### Introduction

Breastfeeding provides optimal nutrition for the infant and also has many important nonnutritional benefits for the child and the mother [1–5]. Therefore, it has been recommended by the WHO and pediatric societies that one should

### Content of Human Milk

Human milk has about the same energy content as cow's milk, while many nutrients important for growth such as protein, sodium, potassium, magnesium and zinc are present in much lower quan-

**Table 1.** Mean macronutrient and energy contents in mature human milk and in cow's milk

Component	Mature human milk ( $\geq 14$ days)	% of energy	Cow's milk	% of energy
Protein	1.0 g/100 g	6	3.4 g/100g	21
Of which caseins	0.4 g/100 g (40% of protein)	2.4	2.8 g/100 g (80% of protein)	17
Fat	3.8 g/100 g	52	3.7 g/100 g	51
Lactose	7.0 g/100 g	42	4.6 g/100 g	28
Minerals	0.2 g/100 g	–	0.8 g/100 g	–
Energy	66 kcal/100 g	100	65 kcal/100 g	100

Adapted from Koletzko [13].

ties, typically one third to half of the content found in cow's milk (table 1). This is a reflection of the much slower growth velocity in infants than in calves, and thereby a lower requirement for growth nutrients. The fat content is at the same level as in cow's milk, while the content of lactose is considerably higher. Human milk also contains many other substances apart from nutrients with specific important functions. These include hormones, growth factors, oligosaccharides, and immune-related compounds such as antibodies (sIgA), leukocytes (B and T lymphocytes, neutrophils and macrophages), nucleotides and cytokines. These nonnutritional substances are involved in many of the short- and long-term effects breastfeeding has on the infant.

### Positive Effects on the Infant and Mother

Breastfeeding has significant positive effects on health and development during infancy, with some effects reaching into childhood and adulthood [1, 2, 6]. Most studies, however, are observational, and confounding can therefore be difficult to rule out; mothers who choose to breastfeed in industrialized countries, for example, are typically better educated and their children also have a lower risk of developing some diseases. Nevertheless, for many of the effects there is convincing evidence.

The most evident effect of breastfeeding is protection against infectious diseases, especially diarrhea and respiratory tract infections [1]. This is the main reason that mortality in low-income countries is several times higher among those not being breastfed. In high-income countries, the risk of diarrhea in breastfed infants is only about one third of the risk in infants not breastfed [2]. These differences could be explained by passive protection of mucous membranes provided by the antibodies and other immune components in human milk, but there is also evidence that the child's own immune system is positively influenced by breastfeeding. There is also convincing evidence that breastfeeding has positive effects on long-term health and development [1, 2, 6]. The influence of breastfeeding on the development of the immune system could be the reason for the fact that some immune-related diseases, e.g. asthma, type 1 diabetes, inflammatory bowel diseases and some childhood cancers, are less common among children who have been breastfed than among children who are predominantly formula fed. A consistent finding throughout many studies from both industrial and low-income countries is a small but significant advantage of breastfeeding to later cognitive function [6]. This effect is likely to be related to an optimal ratio between n-3 and n-6 fatty acids and the content of the long-chain polyunsaturated fatty acid docosa-

hexanoic acid in human milk. Breastfeeding has also an effect on growth. Breastfed infants gain weight faster during the first months of life and are leaner and slightly shorter than formula-fed infants at the age of 12 months [7; Chapter 1.1]. This was the main reason why the WHO developed a new global growth standard based on breastfed infants [8, 9; Chapter 4.1]. It has been suggested that the difference in growth pattern could be one of the reasons why breastfed infants have a lower risk of some noncommunicable diseases, including obesity, later in life.

Breastfeeding also affects maternal physiology and health. From a global perspective, the most important byproduct is the inhibitory effect on ovulation, i.e. lactational amenorrhea, which in populations with low use of contraceptives enhances child spacing, and thereby has a positive effect on infant and young child health. Breastfeeding also has a positive effect on maternal health. Breastfeeding induces utilization of maternal body fat stores and thus can help to decrease excessive body fat depots. Cumulative duration of breastfeeding for more than 12 months is in some studies associated with substantial reductions in the risk of breast and ovarian cancer, type 2 diabetes and rheumatoid arthritis [2].

## **Potential Untoward Effects of Breastfeeding**

### *Transmission of HIV*

Breastfeeding can cause mother-to-child transmission of HIV. Therefore, breastfeeding by HIV-positive mothers is not recommended in high-income countries. In low-income countries with a high prevalence of infectious diseases and high infant mortality, mothers are recommended to breastfeed until 12 months of age if they receive antiretroviral drugs. In these settings, replacement feeding should only be used if it is acceptable, feasible, affordable, sustainable and safe. The UN agency guidelines on HIV and infant feeding were updated 2010 [10].

### *Hypernatremic Dehydration*

If there are problems with initiation of milk production during the first 1–2 weeks after delivery and no other fluids are given, there is a risk that the infant develops hypernatremic dehydration. In severe cases this can cause convulsions and brain damage, and in rare cases death [11]. This can be prevented by supervision and support during initiation of breastfeeding, monitoring weight loss and urine production, and provision of other fluids if there are signs of dehydration.

### *Environmental Contaminants*

The content of environmental contaminants is higher in breast milk than in cow's milk or infant formulae because of the accumulation particularly of lipid-soluble contaminants in maternal tissues [1]. Some studies have shown an association between high levels of contaminants in the mother's blood and negative effects on health and development of the infant. However, it is difficult to disentangle intrauterine exposure from exposure through breast milk. There is general agreement that the positive effects of breastfeeding are far more important than the potential negative effects, but also that it is important to reduce the level of contaminants in the environment and in the diet of pregnant and lactating mothers.

### *Maternal Medication*

Most drugs given to a breastfeeding mother are excreted in her milk. However, there are only a few drugs with an absolute contraindication. A mother should not breastfeed if she receives chemotherapy, ergotamines, amphetamines or statins [2]. Information on the safety of maternal medication is given on the LactMed website [12].

## **Support of Breastfeeding**

Many factors influence the initiation and duration of breastfeeding: cultural patterns, the mother's perception, and the attitudes of friends and

**Table 2.** WHO/UNICEF: Ten steps to successful breastfeeding

- 
- Have a written breastfeeding policy that is routinely communicated to all health care staff
  - Train all health care staff in skills necessary to implement this policy
  - Inform all pregnant women about the benefits and management of breastfeeding
  - Help mothers initiate breastfeeding within 0.5 h of birth
  - Show mothers how to breastfeed and maintain lactation, even if they should be separated from their infants
  - Give newborn infants no food or drink other than breast milk, unless medically indicated
  - Practice rooming in – that is, allow mothers and infants to remain together 24 h a day
  - Encourage breastfeeding on demand
  - Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants
  - Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic
- 

family. The health profession has an important role in educating and supporting the mother in breastfeeding. Traditional hospital routines with separation of the mother and the infant, scheduled feeding intervals and provision of other drinks have a negative impact on the prevalence of breastfeeding. This is the reason why the UNICEF and WHO launched the Baby-Friendly Hospital Initiative in 1992. By training hospital staff in the 10 steps to successful breastfeeding (table 2) it has been possible to increase breastfeeding rates in many settings. Health professionals should also be trained in solving common problems during the first days after delivery, like positioning of the infant, sore nipples and sucking difficulties. To stop the negative influence of marketing of infant formulae, the World Health Assembly has adopted the International Code of Marketing of Breast-Milk Substitutes (Chapter 2.3).

### **Breastfeeding of Preterm Infants**

Breastfeeding is especially important for preterm infants because human milk appears to have a protective effect on the immature gut and reduces the risk of necrotizing enterocolitis. Preterm infants have a higher protein need, which should be

covered by adding an appropriate human milk fortifier (Chapter 3.14). If the mother cannot supply milk for her infant, provision of donor milk should be considered. This could be provided by individual donors or from a human milk bank. If donor milk is used, there are a number of procedures regarding testing, storage and pasteurization that have to be followed [3].

### **Conclusions**

- Populations of breastfed infants have fewer infections, and most likely fewer immune-related diseases such as asthma, diabetes and inflammatory bowel diseases, a small advantage in cognitive development and some protection against noncommunicable diseases (e.g. obesity)
- For the mother, breastfeeding results in lactational amenorrhea, child spacing – which is important in populations with low use of contraceptives – and a reduced risk of breast and ovarian cancer and type 2 diabetes
- Feeding of human milk to preterm infants protects the immature gut and decreases the risk of necrotizing enterocolitis. If the mother cannot provide breast milk, provision of donor milk should be considered

## References

- 1 Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, Mihatsch W, Moreno LA, Puntis J, Shamir R, Szajewska H, Turck D, van Goudoever J: Breast-feeding: a Commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2009;49:112–125.
- 2 Section on Breastfeeding: Breastfeeding and the use of human milk. *Pediatrics* 2012;129:e827–e841.
- 3 Lawrence RA, Lawrence RM (eds): *Breastfeeding: A Guide for the Medical Profession*, ed 7. Philadelphia, Elsevier Mosby, 2011.
- 4 Hale TW, Hartmann PE: *Textbook of Human Lactation*, ed 1. Amarillo, Hale Publishing, 2007.
- 5 Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, Uauy R; Maternal and Child Nutrition Study Group: Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013; 382:427–451.
- 6 Horta BL, Victora C: Long-term effects of breastfeeding: a systematic review. Geneva, WHO, 2013. [http://apps.who.int/iris/bitstream/10665/79198/1/9789241505307\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/79198/1/9789241505307_eng.pdf).
- 7 Dewey KG, Peerson JM, Brown KH, Krebs NF, Michaelsen KF, Persson LA, Salmenpera L, Whitehead RG, Yeung DL: Growth of breast-fed infants deviates from current reference data: a pooled analysis of US, Canadian, and European data sets. WHO Working Group on Infant Growth. *Pediatrics* 1995;96:495–503.
- 8 WHO: Child growth standards. 2014. <http://www.who.int/childgrowth/en/>.
- 9 Turck D, Michaelsen KF, Shamir R, Braegger C, Campoy C, Colomb V, Decsi T, Domellöf M, Fewtrell M, Kolacek S, Mihatsch W, Moreno LA, van Goudoever J: World Health Organization 2006 child growth standards and 2007 growth reference charts: a discussion paper by the Committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2013; 57:258–264.
- 10 WHO: Guidelines on HIV and infant feeding. Geneva, WHO, 2010. [http://whqlibdoc.who.int/publications/2010/9789241599535\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf).
- 11 Pelleboer RA, Bontemps ST, Verkerk PH, van Dommelen P, Pereira RR, van Wouwe JP: A nationwide study on hospital admissions due to dehydration in exclusively breastfed infants in the Netherlands: its incidence, clinical characteristics, treatment and outcome. *Acta Paediatr* 2009;98:807–811.
- 12 Drugs and Lactation Database (LactMed). <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>.
- 13 Koletzko B (ed): *Kinder- und Jugendmedizin*, ed 13. Berlin, Springer, 2007.

## 2.2 Formula Feeding

Berthold Koletzko

### Key Words

Infant formula · Follow-up formula · Soy protein formula · Protein hydrolysate formula · Thickened formula

### Key Messages

- Infant formula is required as a substitute for breast milk for infants who are not fully breastfed
  - Infant formula must satisfy all the nutritional needs of an infant from one food product and needs to meet high quality and safety standards
  - The suitability of infant formula should be determined by comparing its effects on outcomes with those in healthy, exclusively breastfed infants
  - Powdered formula is not a sterile product and may contain pathogenic bacteria (e.g. *Cronobacter* spp.). Powdered formula should always be freshly prepared prior to feeding
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### Infant Formula

Breastfeeding is the best choice for infant feeding and provides multiple benefits for children's health [1]. Therefore, breastfeeding should be actively promoted, protected and supported. Infants who cannot be breastfed (or should not receive breast milk, or for whom breast milk is not available) should receive an infant formula with a

composition based on current scientific knowledge [2, 3]. Infant formula must satisfy all the nutritional needs of an infant from one food product, and it provides a high intake per kilogram body weight during a very sensitive period of life. Therefore, particularly high quality and safety standards are applied to infant formulae [4]. The composition of infant formulae should serve to meet the particular nutritional requirements, and promote the normal growth and development, of healthy infants. While the composition of human milk of well-nourished women provides some guidance for the composition of infant formulae, gross compositional similarity is not an adequate determinant or indicator of the safety and nutritional adequacy of infant formulae [3]. Rather, the suitability of infant formula should be determined by a comparison of its effects on physiological (e.g. growth patterns), biochemical (e.g. plasma markers) and functional outcomes (e.g. immune responses) in formula-fed infants with those found in populations of healthy, exclusively breastfed infants [3].

Revised global recommendations on the composition of infant formulae have been adopted in the Codex Alimentarius of the Food and Agriculture Organization of the United Nations (FAO) and the WHO [5], which to a large extent followed recommendations by an International Ex-



pert Group co-ordinated by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [3] (table 1).

### **Optional Ingredients in Infant Formula**

The addition of a variety of optional ingredients is generally accepted if there are adequate evidence of their safety and indications of a benefit.

While the Codex Alimentarius considered the addition of the long-chain polyunsaturated fatty acids docosahexaenoic acid (DHA) and arachidonic acid to infant formula an option, recent expert recommendations considered it advisable to always provide DHA and arachidonic acid to infants [6, 7], and recent European Food Safety Authority (EFSA) recommendations for infant formula in Europe advised that all formulae should contain 20–50 mg DHA/100 kcal [8].

In recent years, many infant formulae have been marketed with the addition of live bacteria with proposed beneficial health effects for the recipient infant (probiotic effects), non-digestible oligosaccharides with proposed beneficial (prebiotic) health effects and the combination of probiotic and prebiotic (synbiotic) ingredients. Based on a systematic review, the ESPGHAN concluded that the use of currently used formula with added probiotics and/or prebiotics in healthy infants does not raise safety concerns with regard to growth and reported adverse effects [9]. However, the available data were considered insufficient to recommend the routine use of probiotic or prebiotic supplemented formulae. It was emphasized that there are considerable differences amongst various probiotic or prebiotic components. Therefore, the safety and clinical effects of each formula concept should be individually assessed and not be extrapolated from data on other products.

Thickening agents such as starch or carob bean gum have been added to infant formulae marketed as ‘antireflux’ or ‘antiregurgitation’ formulae. The ESPGHAN advised that there are only limited in-

dications for thickened formulae, which are not needed for most infants with moderate spitting and regurgitation who thrive well [10]. However, the use of thickened formula can be beneficial to reduce the loss of energy and nutrients in infants with marked spitting and growth faltering.

### **Infant Formula Based on Soy Protein Isolate**

Infant formula can be based on the milk of cows or other animals as well as other ingredients suitable for infant feeding, including soy protein isolate [5]. The digestibility and biological value of soy protein is lower as compared to cow’s milk protein, and infant formulae based on soy protein generally require the addition of some free amino acids. A higher protein content is required for infant formula based on soy protein compared to cow’s milk protein (table 1). There is concern on further potential disadvantages due to high contents of phytate, which reduces the bioavailability of some nutrients, phytoestrogens (isoflavones), which induce alterations to immune effects in animals, and aluminium, although the long-term effects of these components are not known [11]. Soy protein formulae have no benefit for the prevention of allergy and food intolerance [12]. It is recommended that soy formula should only be used with a specific indication, such as complete lactose intolerance (galactosaemia), cow’s milk allergy in infants older than 6 months, or family convictions such as the wish to follow a vegan or kosher diet [11].

### **Infant Formula Based on Protein Hydrolysates**

Therapeutic formulae for infants with cow’s milk protein allergy that are based on extensive protein hydrolysates, or crystalline amino acid mixtures, are considered foods for special medical purposes and are not intended for use in healthy children. However, infant formulae for healthy infants with

**Table 1.** Compositional requirements of infant formulae proposed by an international expert group co-ordinated by the ESPGHAN

Component/unit	Minimum	Maximum
Energy, kcal/100 ml	60	70
Proteins, g/100 kcal		
Cow's milk protein	1.8 <sup>a</sup>	3
Soy protein isolates	2.25	3
Hydrolysed cow's milk protein	1.8 <sup>b</sup>	3
Lipids		
Total fat, g/100 kcal	4.4	6.0
Linoleic acid, g/100 kcal	0.3	1.2
$\alpha$ -Linolenic acid, mg/100 kcal	50	n.s.
Ratio linoleic/ $\alpha$ -linolenic acids	5:1	15:1
Lauric + myristic acids, % of fat	n.s.	20
<i>Trans</i> fatty acids, % of fat	n.s.	3
Erucic acid, % of fat	n.s.	1
Carbohydrates, g/100 kcal		
Total carbohydrates <sup>c</sup>	9.0	14.0
Vitamins		
Vitamin A, $\mu$ g RE/100 kcal <sup>d</sup>	60	180
Vitamin D <sub>3</sub> , $\mu$ g/100 kcal	1	2.5
Vitamin E, mg $\alpha$ -TE/100 kcal <sup>e</sup>	0.5	5
Vitamin K, $\mu$ g/100 kcal	4	25
Thiamin, $\mu$ g/100 kcal	60	300
Riboflavin, $\mu$ g/100 kcal	80	400
Niacin <sup>f</sup> , $\mu$ g/100 kcal	300	1,500
Vitamin B <sub>6</sub> , $\mu$ g/100 kcal	35	175
Vitamin B <sub>12</sub> , $\mu$ g/100 kcal	0.1	0.5
Pantothenic acid, $\mu$ g/100 kcal	400	2,000
Folic acid, $\mu$ g/100 kcal	10	50
Vitamin C, mg/100 kcal	10	30
Biotin, $\mu$ g/100 kcal	1.5	7.5
Minerals and trace elements		
Iron (formula based on cow's milk protein and protein hydrolysate), mg/100 kcal	0.3 <sup>g</sup>	1.3
Iron (formula based on soy protein isolate), mg/100 kcal	0.45	2.0
Calcium, mg/100 kcal	50	140
Phosphorus (formula based on cow's milk protein and protein hydrolysate), mg/100 kcal	25	90
Phosphorus (formula based on soy protein isolate), mg/100 kcal	30	100
Ratio calcium/phosphorus, mg/mg	1:1	2:1
Magnesium, mg/100 kcal	5	15
Sodium, mg/100 kcal	20	60
Chloride, mg/100 kcal	50	160
Potassium, mg/100 kcal	60	160
Manganese, $\mu$ g/100 kcal	1	50
Fluoride, $\mu$ g/100 kcal	n.s.	60
Iodine, $\mu$ g/100 kcal	10	50
Selenium, $\mu$ g/100 kcal	1	9
Copper, $\mu$ g/100 kcal	35	80
Zinc, mg/100 kcal	0.5	1.5



**Table 1** (continued)

Component/unit	Minimum	Maximum
Other substances		
Choline, mg/100 kcal	7	50
Myo-inositol, mg/100 kcal	4	40
L-Carnitine, mg/100 kcal	1.2	n.s.

n.s. = Not specified.

<sup>a</sup> The determination of the protein content of formulae based on non-hydrolysed cow's milk protein with a protein content between 1.8 and 2.0 g/100 kcal should be based on the measurement of true protein [(total N – NPN) × 6.25].

<sup>b</sup> Formula based on hydrolysed milk protein with a protein content <2.25 g/100 kcal should be clinically tested.

<sup>c</sup> Sucrose (saccharose) and fructose should not be added to infant formula.

<sup>d</sup> 1 mg RE (retinol equivalent) = 1 mg all-*trans* retinol = 3.33 IU vitamin A. Retinol contents shall be provided by preformed retinol, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A activity.

<sup>e</sup> 1 mg α-TE (α-tocopherol equivalent) = 1 mg D-α-tocopherol. The vitamin E content shall be at least 0.5 mg α-TE/g polyunsaturated fatty acid, using the following factors of equivalence to adapt the minimal vitamin E content to the number of fatty acid double bonds in the formula: 0.5 mg α-TE/g linoleic acid (18:2n–6); 0.75 mg α-TE/g α-linolenic acid (18:3n–3); 1.0 mg α-TE/g arachidonic acid (20:4n–6); 1.25 mg α-TE/g eicosapentaenoic acid (20:5n–3); 1.5 mg α-TE/g DHA (22:6n–3).

<sup>f</sup> Niacin refers to preformed niacin.

<sup>g</sup> In populations where infants are at risk of iron deficiency, iron contents higher than the minimum level of 0.3 mg/100 kcal may be appropriate and recommended at a national level.

a family history of allergy or atopic dermatitis that are based mostly on partially (moderately) hydrolysed protein and in part on extensively hydrolysed protein have been developed for allergy prevention. Some of these formulations were shown to be effective for the long-term prevention of allergic manifestations, in particular of atopic dermatitis [13]. Therefore, infant formulae based on protein hydrolysates are accepted [5] and recommended for use during the first 4–6 months of life in infants with a family history of allergy or atopy who are not fully breastfed [14].

### Preparation, Storage and Handling of Infant Formula

Powdered formula is sterile and may contain pathogenic bacteria such as *Cronobacter* spp. which, if sufficiently multiplied once the formula

is prepared, may cause invasive infections, particularly in preterm and term neonates [15]. Therefore, it is recommended that powdered formula should be freshly prepared for each feed and be fed within a period of 2 h after preparation. Unused prepared formula should be discarded. Hospitals, day care centres and other institutions should follow strict hygienic standards as well as written guidelines for the preparation and handling of formula. For neonatal wards, the use of ready-to-feed liquid formula is encouraged where feasible and affordable.

### Follow-Up Formula for Infants

Follow-up formula (also called follow-on formula) has been defined in the Codex Alimentarius as a liquid food that contributes part of the increasingly diversified weaning diet for infants from the

**Table 2.** Compositional requirements of follow-up formula proposed by an international expert group co-ordinated by the Early Nutrition Academy [17]

Component/unit	Minimum	Maximum	Guidance upper level
Energy, kcal/100 ml	60	70	
Proteins, g/100 kcal			
Cow's milk protein	1.7 <sup>a</sup>	2.5 <sup>a</sup>	
Soy protein isolates	2.1 <sup>a</sup>	2.5 <sup>a</sup>	
Lipids			
Total fat, g/100 kcal	4.4	6.0	
Linoleic acid, g/100 kcal	0.3		1.4
$\alpha$ -Linolenic acid, mg/100 kcal	50	n.s.	
Ratio linoleic/ $\alpha$ -linolenic acids	5:1	15:1	
Lauric + myristic acids, % of fat	n.s.	20	
<i>Trans</i> fatty acids, % of fat	n.s.	3	
DHA, % of fat <sup>b</sup>	n.s.	1.0 <sup>a</sup>	
Erucic acid, % of fat	n.s.	1	
Phospholipids, mg/100 kcal			550
Carbohydrates, g/100 kcal			
Total carbohydrates	9.0	14.0	
Vitamins			
Vitamin A, $\mu$ g RE/100 kcal <sup>c</sup>	60	180	
Vitamin D <sub>3</sub> , $\mu$ g/100 kcal	1	4.5 <sup>a</sup>	
Vitamin E, mg $\alpha$ -TE/100 kcal <sup>d</sup>	0.5 <sup>e</sup>		5
Vitamin K, $\mu$ g/100 kcal	4		27
Thiamin, $\mu$ g/100 kcal	60		300
Riboflavin, $\mu$ g/100 kcal	80		500
Niacin <sup>f</sup> , $\mu$ g/100 kcal	300		1,500
Vitamin B <sub>6</sub> , $\mu$ g/100 kcal	35		175
Vitamin B <sub>12</sub> , $\mu$ g/100 kcal	0.1		1.5
Pantothenic acid, $\mu$ g/100 kcal	400		2,000
Folic acid, $\mu$ g/100 kcal	10		50
Vitamin C, mg/100 kcal	10		70
Biotin, $\mu$ g/100 kcal	1.5		10

n.s. = Not specified.

<sup>a</sup> Levels different from those in the Codex standard for infant formula and formulas for special medical purposes intended for infants (CODEX STAN 72/1981) [5].

<sup>b</sup> The content of DHA (22:6n-3) shall be at least as high as the content of eicosapentaenoic acid (20:5n-3).

<sup>c</sup> 1  $\mu$ g RE (retinol equivalent) = 1  $\mu$ g all-*trans* retinol = 3.33 IU vitamin A. Retinol contents shall be provided by preformed retinol, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A activity.

<sup>d</sup> The vitamin E content shall be at least 0.5 mg  $\alpha$ -TE ( $\alpha$ -tocopherol equivalent)/g polyunsaturated fatty acid, using the following factors of equivalence to adapt the minimal vitamin E content to the number of fatty acid double bonds in the formula: 0.5 mg  $\alpha$ -TE/g linoleic acid (18:2n-6); 0.75 mg  $\alpha$ -TE/g  $\alpha$ -linolenic acid (18:3n-3); 1.0 mg  $\alpha$ -TE/g arachidonic acid (20:4n-6); 1.25 mg  $\alpha$ -TE/g eicosapentaenoic acid (20:5n-3); 1.5 mg  $\alpha$ -TE/g DHA (22:6n-3).

<sup>e</sup> 1 mg  $\alpha$ -TE = 1 mg D- $\alpha$ -tocopherol.

<sup>f</sup> Niacin refers to preformed niacin.

6th month on and for young children [16]. The concept of follow-up formula offers the potential to adapt the product composition to the changing needs with increasing age, e.g. by increasing iron and decreasing protein contents. The current Codex standard for follow-up formula was adopted in 1987 and does not reflect current scientific knowledge. Therefore, an international expert group recently reviewed the available evidence from studies addressing the specific nutrient needs of infants aged 6–12 months and provided recommendations on the composition requirements of follow-up formulas for older infants [17] (table 2).

### Follow-Up Formula for Young Children

While follow-up formula for infants may be fed after the age of 1 year without harm, special formula products for young children aged 1–3 years have been widely marketed. Such products are not necessary to meet the nutritional needs of young children who receive a balanced, quality diet. However, many young children have a less than satisfactory intake of critical nutrients such as iron, iodine, vitamin D,  $\alpha$ -linolenic acid and DHA [7]. Nutrient-enriched follow-up formulae for young children that serve as a substitute for cow's milk may help to improve nutrient supply but should be composed in such a way that they are not inferior to cow's milk, e.g. provide at least a similar supply of calcium and avoid a high con-

tent of sugars and flavouring that may interfere with the desirable development of taste preferences [18].

### Conclusions

- Infant formulae serve as substitutes for breast-feeding and must meet very high quality and safety standards
- The composition of infant formula should follow current science-based recommendations
- Special infant formulae such as soy protein-based and thickened formulae should be used according to specific indications
- Some formulae based on protein hydrolysates were shown to reduce the long-term risk of food allergy and atopic dermatitis and are recommended during the first 4–6 months of life in infants with a family history of allergy who are not fully breastfed
- Follow-up formulae for infants offer the potential to provide an age-adapted nutrient content, e.g. a higher iron and a lower protein concentration
- Follow-up formulae for young children aged 1–3 years are not necessary to meet the nutritional needs of young children who receive a balanced, quality diet, but they may contribute to improving the supply of critical nutrients. If used, they should not be inferior in their composition to cow's milk, while a high content of sugars and flavouring should be avoided

### References

- 1 ESPGHAN Committee on Nutrition; Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, Mihatsch W, Moreno LA, Puntis J, Shamir R, Szajewska H, Turck D, van Goudoever J: Breast-feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2009;49:112–125.
- 2 WHO: Global strategy for infant and young child feeding. Geneva, WHO, 2003.
- 3 Koletzko B, Baker S, Cleghorn G, Neto UF, Gopalan S, Hernell O, Hock QS, Jirapinyo P, Lonnerdal B, Pencharz P, Pzyrembel H, Ramirez-Mayans J, Shamir R, Turck D, Yamashiro Y, Zong-Yi D: Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group. *J Pediatr Gastroenterol Nutr* 2005;41:584–599.

- 4 Koletzko B, Shamir R, Ashwell M: Quality and safety aspects of infant nutrition. *Ann Nutr Metab* 2012;60:179–184.
- 5 Codex Alimentarius Commission: Standard for infant formula and formulas for special medical purposes intended for infants. CODEX STAN 72/1981. Rome, Codex Alimentarius Commission, 2007, pp 1–21.
- 6 Koletzko B, Boey CCM, Campoy C, Carlson SE, Chang N, Guillermo-Tuazon MA, Joshi S, Prell C, Quak SH, Rusli Sjarif D, Supapannachart S, Yamashiro Y, Osendarp S: Current information and Asian perspectives on long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy. Systematic review and practice recommendations from an Early Nutrition Academy workshop. *Ann Nutr Metab* 2014;65:49–80.
- 7 EFSA Panel on Dietetic Products, Nutrition and Allergy: Scientific opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. *EFSA J* 2013;11:3408.
- 8 EFSA Panel on Dietetic Products, Nutrition and Allergy: Scientific opinion on the essential composition of infant and follow-on formulae. Parma, EFSA, 2014.
- 9 Braegger C, Chmielewska A, Decsi T, Kolacek S, Mihatsch W, Moreno L, Piescik M, Puntis J, Shamir R, Szajewska H, Turck D, van Goudoever J: Supplementation of infant formula with probiotics and/or prebiotics: a systematic review and comment by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2011;52:238–250.
- 10 Aggett PJ, Agostoni C, Goulet O, Hernell O, Koletzko B, Lafeber HL, Michaelsen KF, Milla P, Rigo J, Weaver LT: Antireflux or antiregurgitation milk products for infants and young children: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2002;34:496–498.
- 11 Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, Puntis J, Rieu D, Rigo J, Shamir R, Szajewska H, Turck D: Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2006;42:352–361.
- 12 Osborn DA, Sinn J: Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;4:CD003741.
- 13 von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, Hoffmann U, Reinhardt D, Grubl A, Heinrich J, Wichmann HE, Bauer CP, Koletzko S, Berdel D: Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol* 2013;131:1565–1573.
- 14 Koletzko B, Bauer CP, Brönstrup A, Cremer M, Flothkötter M, Hellmers C, Kersting M, Krawinkel M, Przyrembel H, Schäfer T, Vetter K, Wahn U, Weissenborn A: Säuglingsernährung und Ernährung der stillenden Mutter. Aktualisierte Handlungsempfehlungen des Netzwerks Gesund ins Leben – Netzwerk Junge Familie, ein Projekt von IN FORM. *Monatsschr Kinderheilkd* 2013;161:237–246.
- 15 Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, Puntis JW, Rigo J, Shamir R, Szajewska H, Turck D, Vandenplas Y, Weaver LT: Preparation and handling of powdered infant formula: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2004;39:320–322.
- 16 Codex Alimentarius Commission: Codex standard for follow-up formula. CODEX STAN 156/1987. Rome, Codex Alimentarius Commission, 1987, pp 1–9.
- 17 Koletzko B, Bhutta ZA, Cai W, Cruchet S, El Guindi M, Fuchs GJ, Goddard EA, van Goudoever JB, Quak SH, Kulkarni B, Makrides M, Ribeiro H, Walker A: Compositional requirements of follow-up formula for use in infancy: recommendations of an international expert group coordinated by the Early Nutrition Academy. *Ann Nutr Metab* 2013;62:44–54.
- 18 Ernährungskommission der Deutschen Gesellschaft für Kinder und Jugendmedizin (DGKJ); Böhles HJ, Fusch C, Genzel-Boroviczeny O, Jochum F, Kauth T, Kersting M, Koletzko B, Lentze MJ, Mihatsch WA, Przyrembel H, Wabitsch M: Zusammensetzung und Gebrauch von Milchgetränken für Kleinkinder. *Monatsschr Kinderheilkd* 2011;159:981–984.

## 2.3 Marketing of Breast Milk Substitutes

Neelam Kler · Naveen Gupta · Anup Thakur

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### Key Words

Breast milk · Infant milk substitutes · International Code of Marketing of Breast-Milk Substitutes · Marketing, formula · Millennium Development Goals

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### Key Messages

- Breast milk is best for optimal growth and development of a baby; breast milk substitutes are an alternative where breast milk is not available
- Particularly in poor populations, a reduction in child mortality [Millennium Development Goal (MDG) 4] and improved maternal health (MDG 5) can be achieved through exclusive breastfeeding during the first 6 months and continued breastfeeding as appropriate for most mothers
- The International Code of Marketing of Breast-Milk Substitutes was developed to enhance breastfeeding practices and to prevent uninterrupted marketing of formulae
- Governments and nongovernmental organizations need to monitor the implementation of the code and report violations
- Health care workers should promote breastfeeding by providing counseling and lactation support before and after the birth of a child

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### Introduction

An estimate by the WHO suggests that 1.5 million babies could be prevented from dying each year if women breastfed their infants (exclusively up to the age of 6 months, and then until the infants are 2 years old) [1]. Breastfeeding was almost universal in the 19th century until the first commercial breast milk substitutes came out [2]. Thereafter, substitute feeding became available as an alternative to breastfeeding. Soon, in various countries breastfeeding rates decreased significantly, and this had an impact in the form of increased mortality because of diarrhea and infections in developing countries. One main reason behind the drastic fall in breastfeeding to low rates in the late 19th century and in the 20th century was widespread advertising by formula companies. During the 1970s and 1980s, breastfeeding rates picked up again, especially with older and educated mothers in industrialized countries. Formula companies responded by vigorously seeking new markets in the developing world. Companies started giving gifts and other incentives to health workers for promoting formulae. Due to improper preparation of formulae

**Table 1.** International Code of Marketing of Breast-Milk Substitutes [4]

Summary of articles

- There should be no advertising or other forms of promotion of the products
- Manufacturers or distributors should not provide free product samples to mothers
- Manufacturers or distributors should not distribute any gifts or articles to mothers
- Marketing personnel should not seek direct or indirect contact with mothers
- Facilities of the health care system should not be used for display of products
- No health care services should use professional service representatives provided or paid by manufacturers or distributors
- Health workers should encourage and protect breastfeeding
- Health professionals should be provided with scientific and factual information about the product
- No information to health workers should imply or create a belief that bottle feeding is superior to breastfeeding
- No material or financial inducements to promote products should be offered to health workers or members of their families
- Health workers should not give samples of infant formula to mothers or members of their families
- Labels should provide the necessary information about a product
- Labels should state the superiority of breastfeeding and provide information on appropriate preparation of a product
- Labels or the container should not have any picture or text that idealizes the use of infant formulae
- Labels should indicate the ingredients used, the composition, storage conditions required, batch number and date before which the product is to be consumed
- Monitoring the application of the code lies with the government, acting individually and collectively through the WHO

in developing countries, mortality from malnutrition, diarrhea and pneumonia increased significantly [3].

### The International Code

On May 21, 1981, the 34th meeting of the World Health Assembly adopted the fourth draft of the International Code of Marketing of Breast-Milk Substitutes as a minimum requirement to protect and promote appropriate feeding of infants and young children [4]. This code was developed by the WHO and the UNICEF in partnership with governments, nongovernmental organizations and the infant food industry. It was developed to protect mothers and health workers

from commercial pressure by manufacturers of breast milk substitutes. It forbids provision of free samples to mothers or health facilities (except for professional research), because of their negative impact on breastfeeding. It also forbids inducements to health workers, because recipients are more likely to promote a particular product and remain passive in promoting breastfeeding (table 1). The code was passed by 118 votes to 1 (USA); 3 countries abstained (Argentina, Japan and Korea). By the 1996 World Health Assembly meeting, all 191 member states had affirmed their support for the code, its implementation and the implementation of relevant resolutions. By 1997, 17 countries had adopted all or substantially all of the code's provisions as legal requirements. Adoption of the



code represents the development of an international consensus. The code also covers ethical considerations and regulations for the marketing of feeding bottles and teats. Even after 3 decades of implementation of the code there are continuing issues of implementation, monitoring and compliance, which predominantly reflect weak governance [5].

### **Violations of the Code**

Since 1981, when the code was formulated, numerous violations have been reported both from the developing and the developed world. In developing nations, multistage, random sampling of pregnant mothers and mothers of infants less than 6 months old was carried out in 4 cities (Dhaka, Durban, Bangkok and Warsaw) with disappointing results: 26% of mothers in Bangkok received free samples of breast milk substitutes from companies [6]. Many violations were reported in Uganda in a survey of mothers and health workers. In 2008, 70% of 427 health professionals in Pakistan were unaware of their own breastfeeding laws, and 80% unaware of the code; 12% had received sponsorship from pharmaceutical companies for training sessions or attendance at conferences [7]. In countries with weak regulations, sales of formula were noticed to be higher. Differences were seen, for example, between the Philippines and India. In India, where advertising is strictly controlled by the Infant Milk Substitutes Act [8], breastfeeding rates are 46% at 5 months of age. In contrast, the Philippines, with much weaker regulations, have 3 times lower breastfeeding rates [9]. In the developed world, marketing tends to be more subtle than in developing countries [10]. Among the industrialized nations, the lowest breastfeeding rates (7% at 4 months) were seen in the UK, where companies spend 10 times more on advertising than the Department of Health spends on promoting breastfeeding. Interestingly, 20% of moth-

ers in the UK who were weaning their babies at 4–6 months of age thought formula was better and more nutritious than breast milk.

### **Monitoring the Code**

Information provided by monitoring helps the WHO, UNICEF, governments and nongovernmental organizations to imply the code and monitor violations. The reports on violations demonstrate the need for transparent, independent and effective controls in the marketing of baby food and bottles. Governments should ensure a consistent strategy of monitoring, involving investigation, observation and recording of information. The basics of monitoring include: familiarization with the main points of the International Code and with national measures; obtaining information on the breast milk substitutes locally used; recording details about the company and brand names and the hospitals/clinics where infant formula is used; description of posters, displays, etc.; and reporting of violations to the appropriate body.

It is now recognized that voluntary initiatives alone are inadequate for implementation of the International Code of Marketing of Breast-Milk Substitutes. Health professionals and breastfeeding organizations call for enforcement of stricter rules. Under the international code, information provided by the manufacturers should not imply or create a belief that bottle feeding is equivalent or superior to breastfeeding.

### **Impact on Mortality and Morbidity**

In developing countries, numerous studies have reported an increased mortality and morbidity with the use of breast milk substitutes. A recent meta-analysis showed excess risk of diarrhea mortality in nonbreastfed babies in comparison with exclusive breastfeeding among infants 0–5 months of age (relative risk: 10.52) and with any breast-

feeding among children aged 6–23 months (relative risk: 2.18) [11]. Early initiation of breastfeeding is critical. In a Ghanaian study, neonatal mortality of babies fed after the first 24 h was more than twice that of those fed within the first hour. In the developed world, exclusive breastfeeding has no detectable effect on mortality, but significant reductions in both short-term and long-term morbidity were noted. Failure to breastfeed increases the risk of gastrointestinal disease, acute otitis media and acute lower respiratory tract infection in infancy. In older children, the likelihood of obesity, elevated cholesterol levels, hypertension as well as type 1 and type 2 diabetes is increased. In a recent meta-analysis, negative emotions such as guilt, anger, uncertainty and sense of failure were found more often in mothers of bottle-fed babies [12]. Term small-for-gestational-age babies are at risk of obesity and metabolic problems like hypertension and diabetes. Breastfeeding is protective by preventing accelerated growth in these subsets of babies [13].

### Situations in Which Breast Milk Substitutes Can Be Used

Formula feeding is clearly essential in certain circumstances, such as when the mother is on cytotoxic drugs or is unwilling to breastfeed. Since

HIV can be transmitted with breast milk, infected mothers were advised to use breast milk substitutes in 1985. This practice led to an increase in infant mortality in resource-poor countries where safe formula feeding was not feasible. Therefore, the WHO guidelines of 2010 recommend exclusive breastfeeding for the first 6 months with antiretroviral treatment of the mother unless substitute feeding is acceptable, feasible, affordable, sustainable and safe [14].

### Conclusions

- Breastfeeding is the best source of nutrition for infants less than 6 months of age
- Formula feeding can lead to increased infant mortality, especially in developing countries, due to poor hygiene and sanitation facilities
- The risks of short- and long-term morbidities such as infections, allergies, obesity and lifestyle diseases increase with formula feeding
- The International Code of Marketing of Breast-Milk Substitutes must be monitored and implemented in all countries. Health care professionals can play a very important role by explaining the benefits of breastfeeding to pregnant women and by promoting early initiation of breastfeeding after birth

### References

- 1 WHO: Infant and young child nutrition. Geneva, WHO, 1993. EB93/17.
- 2 Palmer G: The industrial revolution in Britain: the era of progress? In Palmer G (ed): *The Politics of Breastfeeding*. London, Pinter & Martin, 2009, pp 205–207.
- 3 Jelliffe DB, Jelliffe EF: Feeding young infants in developing countries: comments on the current situation and future needs. *Stud Fam Plann* 1978;9: 227–229.
- 4 World Health Assembly: Resolutions of the Executive Board at its sixty-seventh session and of the thirty-fourth World Health Assembly on the International Code of Marketing of Breast-Milk Substitutes. Resolution EB67.R12 Draft International Code of Marketing of Breast-Milk Substitutes. Geneva, WHO, 1981.
- 5 Forsyth S: Three decades of the WHO code and marketing of infant formulas. *Curr Opin Clin Nutr Metab Care* 2012; 15:273–277.
- 6 Taylor A: Violations of the international code of marketing of breast milk substitutes: prevalence in four countries. *BMJ* 1998;316:1117–1122.
- 7 Salasibew M, Kiani A, Faragher B, et al: Awareness and reported violations of the WHO International Code and Pakistan's national breastfeeding legislation: a descriptive cross-sectional survey. *Int Breastfeed J* 2008;3:24.

- 8 The Infant Milk Substitutes, Feeding Bottles and Infant Foods (Regulation of Production, Supply and Distribution) Act, 1992, as Amended in 2003 (IMS Act). <http://www.gujhealth.gov.in/images/pdf/infant-milk-substitution2003.pdf> (accessed July 30, 2013).
- 9 Sobel HL, Iellamo A, Raya RR, et al: Is unimpeded marketing for breast milk substitutes responsible for the decline in breastfeeding in the Philippines? An exploratory survey and focus group analysis. *Soc Sci Med* 2011;73:1445–1448.
- 10 Coutsoudis A, Coovadia HM, King J: The breastmilk brand: promotion of child survival in the face of formula-milk marketing. *Lancet* 2009;374:423–425.
- 11 Lamberti LM, Fischer Walker CL, Noiman A, et al: Breastfeeding and the risk for diarrhea morbidity and mortality. *BMC Public Health* 2011;11(suppl 3): S15–S27.
- 12 Lakshman R, Ogilvie D, Ong KK: Mothers' experiences of bottle-feeding: a systematic review of qualitative and quantitative studies. *Arch Dis Child* 2009;94: 596–601.
- 13 Singhal A, Lucas A: Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet* 2004;363:1642–1645.
- 14 Ip S, Chung M, Raman G, et al: A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries. *Breastfeed Med* 2009;4(suppl 1):S17–S30.

## 2.4 Complementary Foods

Mary Fewtrell

### Key Words

Complementary feeding · Infant · Breastfeeding

### Key Messages

- Complementary foods are defined by the WHO as any food or liquid other than breast milk. However, since many infants receive human milk substitutes from the first weeks of life, other authorities have suggested that the term 'complementary foods' should be applied to foods and liquids other than breast milk or infant formulas
- Complementary foods are required for nutritional and developmental reasons. They should not be introduced before 17 weeks of age, but all infants should start complementary foods by 26 weeks of age
- It is important to ensure that complementary foods provide adequate energy density (minimum 25% fat), and that the diet includes good sources of protein, iron and zinc. Strategies used to achieve this will vary in different environments

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### Introduction

Complementary foods are defined by the WHO as any food or liquid other than breast milk. This definition means that infant formulas and

follow-on formulas (human milk substitutes, HMS) are regarded as complementary foods, which can be confusing, since many infants receive HMS from the first weeks of life. Other authorities (European Society for Paediatric Gastroenterology, Hepatology and Nutrition, ESPGHAN [1]) have suggested that the term complementary food should be applied to foods and liquids other than breast milk or infant formulas.

Complementary foods are required during the second part of the first year of life for both nutritional and developmental reasons, and to enable the transition from milk feeding to family foods. From a nutritional point of view, the ability of breast milk to continue to meet macro- and micronutrient requirements becomes limited, whereas from a developmental perspective, infants develop the ability to chew and start to show an interest in foods other than milk.

Current WHO recommendations on the age at which complementary foods should be introduced are based on consideration of the optimal duration of exclusive breastfeeding. However, since HMS are defined by the WHO as complementary food, it is difficult to translate this recommendation to formula-fed infants. Following a systematic review [2] and expert consultation

in 2001 [3], the WHO recommended that infants should be exclusively breastfed for 6 months, although this contrasts with current practice in many countries, where complementary foods may be introduced as early as 3–4 months of age.

### **Timing of Complementary Feeding**

Complementary feeding recommendations and practices are generally not evidence based and vary between countries. Gastrointestinal and renal functions are likely to be sufficiently mature by around 4 months of age to enable infants to process some complementary foods, whereas the age at which infants attain the necessary motor skills is likely to fall within the 4- to 6-month period. There is general consensus that complementary foods should not be given before 17 weeks of age as this may be associated with increased later fatness, respiratory symptoms and eczema. The WHO recommends that infants should be exclusively breastfed for 6 months before the introduction of complementary foods [3], based on a systematic review of the optimal duration of exclusive breastfeeding [2] comparing mother and infant outcomes with exclusive breastfeeding for 6 months versus 3–4 months (updated in 2012 [4]). While there is agreement that exclusive breastfeeding for 6 months is desirable in situations where there is a lack of clean drinking water or of safe nutritious complementary foods, there is less consensus regarding infants in higher-income settings. Although many countries have adopted the new WHO recommendation, other countries still recommend 4–6 months of breastfeeding. The ESPGHAN Committee on Nutrition concluded that complementary foods should not be introduced before 17 weeks of age, but that all infants should start by 26 weeks of age [1]. A review by an expert panel of the European Food Safety Authority also concluded that the introduction of complementary

food to healthy term infants in the EU between 4 and 6 months is safe and does not pose a risk for adverse health effects [5].

### **Content of the Diet**

Most current guidelines on the gradual introduction of different foods during complementary feeding are based on cultural factors and food availability rather than scientific evidence. In developing countries, the focus is still on providing adequate nutrients to support growth and development, whereas in more affluent environments, achieving a better balance of nutrients and avoiding excess may be more important. Recommendations are based on the concept that breast milk cannot meet the full requirements for energy, protein and micronutrients beyond about 6 months of age.

#### *Energy*

Energy requirements remain high during the first year of life. The fat content of the diet is an important determinant of its energy density and should not be less than 25% of energy intake. A higher proportion might be required if the infant's appetite is poor or if the infant has recurrent infections or is fed infrequently. Reduced-fat cow's milk reduces the energy density of the diet, and consideration should be given to the rest of the infant's diet and to its growth when deciding to introduce this. However, in countries with high rates of childhood obesity, it may be advantageous to accustom children to low-fat products from a fairly early age.

#### *Iron and Zinc*

More than 90% of iron requirements during the complementary feeding period of a breastfed infant must be provided by complementary foods. Strategies for achieving adequate iron and zinc intakes include the use of fortified weaning foods, iron-fortified infant formulas, foods rich in bio-

available iron such as meat, or supplements. The most suitable strategy will vary with the circumstances; cow's milk is a very poor source of iron, and it is generally recommended that it should not be used as the main drink before 12 months of age.

### *Salt and Sugar*

High intakes of salt in infancy may be associated with later higher blood pressure [6]. Furthermore, infants may become accustomed to a salty taste, which could affect subsequent food preferences. Hence, salt should not be added to complementary foods. Sugar is associated with the development of dental caries. Its use should be restricted, and good dental hygiene practices introduced early.

### *Gluten*

In contrast to data from previous observational studies, the findings from two recent randomised trials have shown that the age at introduction of gluten does not influence the risk of developing coeliac disease. Both trials also concluded that the risk was not influenced by breastfeeding at the time of introduction of gluten [7, 8].

### *Vegetarian Diets*

If infants receive a vegetarian diet, it is important that the diet includes a sufficient amount of milk (about 500 ml/day) and dairy products. Vegan diets should be discouraged in infancy, particularly because of the risk of vitamin B<sub>12</sub> deficiency, which can affect neurodevelopment.

### *Allergy*

Certain foods, including egg, fish, nuts and seafood, are potentially allergenic. However, the evidence that delaying the introduction of such foods reduces the risk of developing food allergy is not convincing. Allergy may be increased if solids are introduced before 3–4 months of age, but also by delayed introduction of certain allergens [9]. Furthermore, the exclusion of fish and eggs

from the diet could itself have undesirable nutritional consequences.

### *Taste and Food Acceptance*

Children are predisposed to like high-energy foods, to prefer sweet and salty tastes and to reject new foods, but these predispositions may be modified by early dietary experience and feeding practices. A feeding style typified by emotional warmth and responsiveness but high expectations for children's dietary adequacy and behaviour – accompanied by practices such as parents leading by example, making fruit and vegetables available within the home, moderately restricting unhealthy alternative snack foods and encouraging children to try vegetables and fruits – is associated with better consumption in the childhood years [10]. Hence, parents play an important role in establishing good dietary habits.

## **Conclusions**

- Complementary foods should not be introduced before 17 weeks of age, but all infants should start complementary foods by 26 weeks of age
- It is important to ensure that complementary foods provide adequate energy density (minimum 25% fat), and that the diet includes good sources of protein, iron and zinc. Strategies used to achieve this will vary with the environment
- The complementary feeding period is important for establishing good eating habits and food preferences. Sugar and salt should not be added to complementary foods

## References

- 1 Agostoni C, Decsi T, Fewtrell MS, et al; ESPGHAN Committee on Nutrition: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008; 46:99–110.
- 2 Kramer MS, Kakuma R: Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* 2002;1: CD003517.
- 3 WHO: The optimal duration of exclusive breastfeeding. Report of an Expert Consultation. Geneva, WHO, 2001.
- 4 Kramer MS, Kakuma R: Optimal duration of exclusive breastfeeding. *Cochrane Database of Syst Rev* 2012;8: CD003517.
- 5 EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA): Scientific opinion on the appropriate age for introduction of complementary feeding of infants. *EFSA J* 2009;7:1423. <http://www.efsa.europa.eu/de/efsajournal/doc/1423.pdf>.
- 6 Geleijnse JM, Hofman A, Witteman JC, Hazebroek AA, Vankenburg HA, Grobbee DE: Long-term effects of neonatal sodium restriction on blood pressure. *Hypertension* 1997;29:913–917.
- 7 Vriezinga SL, Auricchio R, Bravi E, et al: Randomized feeding intervention in infants at high risk for celiac disease. *N Engl J Med* 2014;371:1304–1315.
- 8 Lionetti E, Castellaneta S, Francavilla R, et al: Introduction of gluten, HLA status, and the risk of celiac disease in children. *N Engl J Med* 2014;371:1295–1303.
- 9 Prescott SL, Smith P, Tang M, Palmer DJ, Huntley SJ, Cormack B, Heine RG, Gibson RA, Makrides M: The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. *Pediatr Allerg Immunol* 2008;19:375–380.
- 10 Blissett J: Relationships between parenting style, feeding style and feeding practices and fruit and vegetable consumption in early childhood. *Appetite* 2011; 57:826–831.

## 2.5 Allergy Prevention through Early Nutrition

Sibylle Koletzko

### Key Words

Tolerance induction · Sensitization · Allergen avoidance · Breastfeeding · Atopic dermatitis

### Key Messages

- Allergen contact during the first months of life modulates the induction of tolerance and sensitization to food antigens
- Nutritional intervention can reduce the risk of allergic manifestations, particularly of atopic dermatitis and cow's milk protein allergy, during the first year of life in children with a positive family history of allergy
- Exclusive breastfeeding for the first 4 months of life, with gradual introduction of solid foods with a high diversity during continuous breastfeeding from the 5th month onward, is strongly recommended for all healthy infants, regardless of allergy risk
- Maternal exclusion diets during pregnancy and/or lactation do not reduce allergy risks for the offspring and are not recommended. Fish in the maternal diet seems to reduce the risk of allergic diseases in the offspring
- Delaying the introduction of certain allergens beyond the 7th month of life has no preventive effect and is not recommended. Fish should be introduced during the second half-year of life
- There is some evidence that certain probiotics given to the mother and/or infant and some prebiotic mixtures as supplements to infant formulae may reduce the risk of allergy, and particularly of eczema,

in children. Due to the heterogeneity of products, study designs, target groups, applications and the timing and duration of supplementation, no general recommendations can be made

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### Introduction

Contact with food allergens in early infancy modulates the development of tolerance to food allergens, but also of sensitization and allergic manifestations. Nutritional intervention aiming at a reduction in allergy risk should be started early in infancy, and potentially even with the maternal diet during the last weeks of pregnancy. Data on alimentary allergy prevention were obtained in observational cohort studies, which describe associations and can generate hypotheses, and in controlled intervention studies, which can demonstrate causal relationships. The available data do not support the conclusion that maternal elimination diets during pregnancy and lactation provide a benefit for allergy risk reduction in the infant. Data on breastfeeding effects on allergy point to a beneficial impact of exclusive breastfeeding during the first 4 months of life, with continued breastfeeding while solid foods are being



introduced. In infants with a positive family history of allergy who are not exclusively breastfed, the use of infant formulae based on hydrolyzed cow's milk proteins reduces the risk of atopic eczema. Delayed introduction of complementary feeding has no proven benefit.

### **Maternal Diet and Avoidance of Allergenic Foods during Pregnancy and Lactation**

Maternal dietary allergen exclusion during pregnancy has been proposed as a potential strategy for reducing allergy risk in the offspring, but the available data do not support any beneficial effects [1]. In human milk, food antigens derived from cow's milk, egg, wheat and other foods can be detected a few hours after maternal consumption of the respective foods. The concentration of cow's milk protein in breast milk is found to be 100,000 times lower than that in cow's milk and does not correlate with the amount of antigen ingested by the mother. Whether these low amounts of antigen in breast milk induce sensitization or tolerance is not clear. In a randomized controlled trial, no beneficial effect of avoidance of egg and milk consumption by lactating women was found with regard to the development of allergic disease in children up to 5 years of age [2]. Maternal exclusion diets bear the risk of inadequate supply of certain nutrients. In the absence of beneficial evidence, maternal exclusion diets during pregnancy and lactation for allergy prevention are not recommended. However, there is some evidence that consumption of oily fish by the mother during pregnancy and breastfeeding reduces the risk of allergic diseases in the offspring [3].

### **Breastfeeding**

Breastfeeding is preferred for infants because of its nutritional, immunological and psychological benefits. The potential allergy-preventive effect of

exclusive or partial breastfeeding has not been properly assessed because randomization of breastfeeding is not possible for ethical reasons. Mothers who breastfeed exclusively differ markedly from those who feed formula with regard to education, socioeconomic factors, smoking, keeping pets at home, introduction of other foods, and many other factors which may influence the incidence of allergy. Inverse causality may occur in nonrandomized studies, i.e. mothers of infants with the highest degree of heredity or signs of atopy within the first months of life may tend to prolong exclusive and total breastfeeding.

However, evidence from a cluster randomized trial of the promotion of breastfeeding in the Republic of Belarus [4] and from a recent meta-analysis of the effect of breastfeeding on allergy in the offspring support that exclusive breastfeeding for 3 months or longer confers a protective effect against atopic dermatitis during infancy [5].

### **Feeding Hydrolyzed Infant Formulae**

Several intervention trials evaluated infant formulae based on partially or extensively hydrolyzed proteins compared with standard cow's milk formula, often with nonrandomized breastfed reference groups. All randomized trials published were performed on infants with an increased atopy risk, based on one parent or sibling affected by allergy, both parents affected, elevated cord blood IgE or other criteria. Therefore, the results cannot be generalized to infants with non-atopic parents. Some of the studies included additional cointerventions such as maternal dietary or environmental restrictions, or delayed introduction of complementary feeding.

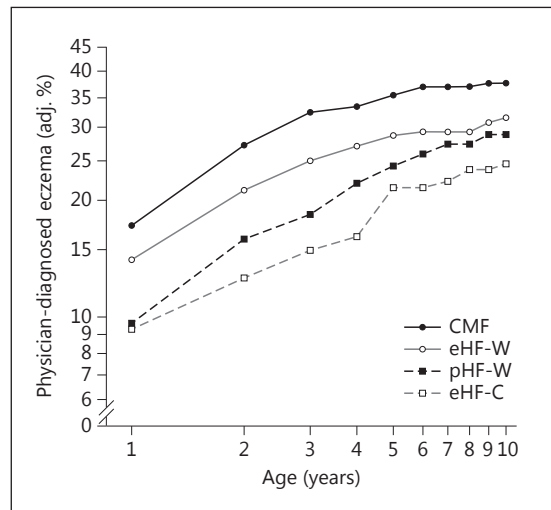
A recent Cochrane review on these studies concluded that there is limited evidence that the use of hydrolyzed formulae reduces the risk of infant and childhood allergy and infant cow's milk allergy when compared with using a standard cow's milk formula [6]. In this analysis, many

studies even of high quality were excluded because of dropout rates of more than 20%. For this and other reasons, the Cochrane review has been criticized, and the conclusions were challenged by an international panel of allergy experts [7].

The German Infant Nutritional Intervention study is by far the largest double-blind, randomized, controlled intervention trial in this area, and the only trial sponsored by a governmental grant rather than by industry funds [8, 9]. The trial evaluated allergy-preventive effects of three hydrolyzed formulae compared with a cow's milk formula in high-risk infants provided during the first 4 months of life. Among different atopic manifestations (atopic dermatitis, asthma, gastrointestinal manifestations, allergic rhinitis and urticaria), only the risk of atopic dermatitis was reduced by the hydrolyzed formulae. Compared with the cow's milk formula, both an extensively hydrolyzed casein formula and a partly hydrolyzed whey formula significantly reduced atopic dermatitis. In contrast, the risk reduction with the extensively hydrolyzed whey formula did not reach significance. The effect developed in the first year of life and persisted until the age of 10 years (fig. 1). No significant effect was observed on asthma, allergic rhinitis or sensitization pattern.

### Protein Sources other than Cow's Milk in Infant Feeding

The use of unmodified mammalian milk protein, including unmodified sheep, buffalo, mare or goat's milk, or unmodified soy or rice milk, is not recommended for infants because their composition is inadequate to serve as the sole food source for infants. Moreover, these milks are not recommended for infants with suspected or proven cow's milk protein allergy because of the risk of possible allergenic cross-reactivity. A Cochrane review concluded that infant formulae based on soy protein do not reduce allergy risk, including food allergy [10]. There is no evidence to support



**Fig. 1.** Cumulative incidence of parent-reported, physician-diagnosed atopic dermatitis in 988 infants who were fed 1 of 4 study formulae during the first 4 months of life and were followed until 10 years of age (per-protocol analysis). Results are adjusted (adj.) for sex, BMI at birth, parental education, biological siblings at birth, study region, maternal smoking during pregnancy and/or during the child's first 4 months, smoking in the presence of the child during the child's first 4 months, furry pets in the home during the child's first year of life, and age of mother at birth. CMF = Cow's milk formula; pHF-W = partially hydrolyzed whey formula; eHF-W = extensively hydrolyzed whey formula; eHF-C = extensively hydrolyzed casein formula [9].

allergy-preventive effects of infant formulae based on protein sources other than hydrolyzed cow's milk proteins.

### Complementary Foods

Most available data originate from large cohort studies. Very early introduction of solid food within the first 3 months of life seems to increase the risk of eczema, and possibly also of food allergy. However, delaying the introduction of solid foods beyond the 6th month of life has no protective effect and may even increase the risk of dif-



ferent allergic diseases [11]. This effect was also found for allergenic foods such as hen's egg, cow's milk, fish and wheat [12–14]. A high diversity of complementary foods seems to decrease the risk of allergies [15]. Thus it is recommended that complementary foods should not be introduced before the 17th week of life or later than the 26th week of life, regardless of the familial risk of allergy [16, 17].

### Probiotics and Prebiotics

The impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood was investigated by a recent meta-analysis including 7 randomized, double-blind, placebo-controlled trials [18]. The authors conclude that there is some evidence for lactobacilli – but not for different mixtures of probiotics – to reduce the risk of eczema in the offspring.

Several studies investigated the effect of probiotics given to infants either as a supplement or as a component of the infant formula. A recent position paper of the World Allergy Organization reviewed the evidence and concluded that with the current knowledge, probiotics have no established role in the prevention or treatment of allergy [19].

Similarly, a Cochrane review on the addition of prebiotics to infant formulae concluded that certain prebiotic mixtures of galacto- and fruc-

tooligosaccharides have shown some beneficial effect in reducing eczema in infants [20]. However, the heterogeneity of these studies with regard to their design and target groups does not allow any generalized recommendations on supplementation for reducing the risk of allergy.

### Conclusions

- Maternal exclusion diet during pregnancy and lactation has no allergy-preventive effect and is not recommended
- Exclusive breastfeeding for the first 4 months of life and continuous breastfeeding while gradually introducing solid foods is recommended for all infants
- In populations with low infection risks, solid foods should not be introduced before the 17th or after the 26th week of life, regardless of the hereditary risk of allergy
- If infant formulae are given during the first 4 months of life to infants with a family history of allergy, a protein hydrolysate formula should be used
- Formulae based on other milk proteins (sheep, buffalo, mare or goat's milk), as well as soy or rice protein, have no demonstrated allergy-preventive effect and are not recommended
- Probiotics and prebiotics do not have an established role in the prevention of allergy

### References

- 1 Kramer MS, Kakuma R: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2006; 3:CD000133.
- 2 Björkstén B: Allergy prevention: interventions during pregnancy and early infancy. *Clin Rev Allergy Immunol* 2004;26:129–138.
- 3 Dotterud CK, Storro O, Simpson MR, Johnsen R, Øien T: The impact of pre- and postnatal exposures on allergy related diseases in childhood: a controlled multicentre intervention study in primary health care. *BMC Public Health* 2013;13:123.
- 4 Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, et al: Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA* 2001;285:413–420.
- 5 Kramer MS: Breastfeeding and allergy: the evidence. *Ann Nutr Metab* 2011; 59(suppl 1):20–26.

- 6 Osborn DA, Sinn J: Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;4: CD003664.
- 7 Høst A, Halken S, Muraro A, Dreborg S, Niggemann B, Aalberse R, et al: Dietary prevention of allergic diseases in infants and small children. *Pediatr Allergy Immunol* 2008;19:1–4.
- 8 von Berg A, Koletzko S, Grühl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP, et al: The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol* 2003;111:533–540.
- 9 von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, et al: Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol* 2013;131:1565–1573.
- 10 Osborn DA, Sinn J: Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2004;3:CD003741.
- 11 Zutavern A, Brockow I, Schaaf B, von Berg A, Diez U, Borte M, et al: Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics* 2008;121:e44–e52.
- 12 Nwaru BI, Takkinen HM, Niemelä O, Kaila M, Erkkola M, Ahonen S, et al: Timing of infant feeding in relation to childhood asthma and allergic diseases. *J Allergy Clin Immunol* 2013;131:78–86.
- 13 Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al: Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010;126:807–813.
- 14 Kull I, Bergström A, Lilja G, Pershagen G, Wickman M: Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy* 2006;61:1009–1015.
- 15 Nwaru BI, Takkinen HM, Kaila M, Erkkola M, Ahonen S, Pekkanen J, et al: Food diversity in infancy and the risk of childhood asthma and allergies. *J Allergy Clin Immunol* 2014, Epub ahead of print.
- 16 Agostoni C, Decsi T, Fewtrell M, Goulet O, Kolacek S, Koletzko B, et al: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:99–110.
- 17 Greer FR, Sicherer SH, Burks AW: Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121:183–191.
- 18 Doege K, Grajecki D, Zyriax BC, Detinkina E, zu Eulenburg C, Buhling KJ: Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood: a meta-analysis. *Br J Nutr* 2012;107:1–6.
- 19 Fiocchi A, Burks W, Bahna SL, Bielory L, Boyle RJ, Cocco R, et al: Clinical Use of Probiotics in Pediatric Allergy (CUPPA): a World Allergy Organization Position Paper. *World Allergy Organ J* 2012;5:148–167.
- 20 Osborn DA, Sinn JK: Prebiotics in infants for prevention of allergy. *Cochrane Database Syst Rev* 2013;3:CD006474.

## 2.6 Toddlers, Preschool and School Children

Hildegard Przyrembel

### Key Words

Dietary guidelines, food-based · Dietary habits · Food preference · Food choice · Feeding skills · Meals

### Key Messages

- Toddlers and children should participate in family meals
- Toddlers do not need specially prepared commercial foods for particular nutritional uses. The use of such meals is determined by convenience
- Food-based dietary guidelines for children should name basic food groups, give approximate amounts to be consumed and provide exemplary recipes according to local habits
- Nutrient supplements and fortified foods should be used only when indicated
- Beverages of no or low energy content should accompany meals

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### Introduction

The age range of 1 to approximately 12 years includes very different phases of development. With increasing motor skills, toddlers – some of which are still partly breastfed – will feed themselves with an increasing variety of foods as part

of the family diet. Food preferences developed in the first year of life tend to persist but are modified under the influence of parents, siblings and playmates. Preschool and school children increase both the frequency and variety of social contacts outside the home, and thereby food and meal choices [1].

A healthy diet for children should be devised on the basis of both scientific and practical considerations. Scientific criteria are adequacy of intake in comparison with recommendations on energy and nutrient intake to support normal growth and development, taking into account the preventive effects of an adequate diet on chronic diseases in adulthood [2]. Practical criteria are regional or national dietary habits, availability and cost of foods, and taste preferences of children.

Food-based dietary guidelines for children have been devised. As an example, the so-called ‘optimized mixed diet’ [3, 4] developed in Germany is described. Such guidelines can be easily adapted to different typical eating habits, meal schedules and differences in locally available basic foods. They are based on commonly available foods to be prepared at home, but leave room for the integration of ready-to-eat products and foods preferred by many children, such as ‘fast foods’ and sweets.

**Table 1.** Example of adequate amounts of foods to be consumed per day at different ages

Age, years	1	2–3	4–6	7–9	10–12
Total energy, kcal/day	850	950	1,250	1,600	1,900
<i>Recommended foods (≥90% of total energy)</i>					
Generously					
Beverages, ml/day	600	700	800	900	1,000
Vegetables, g/day	120	150	200	220	250
Fruit, g/day	120	150	200	220	250
Potatoes, pasta, flakes, rice, etc., g/day	100	120	150	180	220
Moderately					
Milk, milk products, ml or g/day	300	330	350	400	420
Meat, meat products, g/day	30	35	40	50	60
Eggs, n/week	1–2	1–2	2	2	2–3
Fish, g/week	25	35	50	75	90
Sparingly					
Oil, butter, margarine, g/day	15	20	25	30	35
<i>Tolerated foods (≤10% of total energy)</i>					
Cake, sweets, jam, sugar, etc., max. kcal/day	85	95	125	160	190
Modified 2013 from Kersting et al. [3] and Alexy et al. [4] according to the most recent dietary reference values.					

## Principles of Children's Diets and Eating

Food-based dietary guidelines based on the energy and nutrient needs of children, on children's preferences as well as on health aspects provide advice on food selection, meal composition and meal patterns, including recipes. The main food groups included are of high nutrient density: cereals and other starchy foods (bread, pasta, potatoes, etc.); vegetables, legumes and fruits; milk and dairy products; meat, poultry, eggs and (oily) fish; and fats and oils.

A list of reference amounts of the main food groups, which provide ≥90% of the appropriate energy intake and 100% of practically all micro-nutrients, is part of OptimiX (table 1) [3, 4]. In addition, <10% of the energy intake is provided by 'tolerated' food groups, often of low nutrient but high energy density. These foods are not prohibited but permitted to meet, for instance, the preferences for sweets of some children and

to permit flexibility in the composition of meals. The amounts of foods are guidance values, with the possibility of choosing within a food group – e.g. instead of milk and milk products, cheese can be consumed, based on their equivalency in calcium content (100 ml of milk correspond to about 15 g of hard or 30 g of soft cheese). The amounts shown in table 1 need not to be consumed every day; the aim should be the average amount consumed per week. Variability in daily intake is normal; in children, the variability in daily energy intake can be 50% around the average. Moreover, small and inactive children will eat smaller amounts than active and big children, and boys will consume more than girls of the same age. From the start, children should be allowed to determine the amounts they wish to eat and not be forced to empty their plates. This will permit them to eat to satiety and help to avoid overnutrition and overweight.

## Recommended Diet Composition

OptimiX provides about 53% of the energy intake mostly from complex carbohydrates, 33% of the energy from fat mostly of plant origin (saturated fatty acids: 10%; monounsaturated fatty acids: 15%; polyunsaturated fatty acids: 7% of total energy) and 14% of the energy from protein, half of animal and half of plant origin. The energy density is about 70 kcal/100 g, the fiber density 17 g/1,000 kcal and the water density about 1.2 g/kcal. The most suitable fat intake for toddlers is not known; it should not be <25% of the energy [2, 5, 6]. Protein sources will reflect country- and culture-specific dietary habits, and plant protein can provide the majority of protein intake. In that case, a variety of plant foods should be consumed, which compensate for each other's deficiencies in certain indispensable amino acids. A vegan diet with no animal-derived food is not suitable for toddlers.

## Meals and Meal Patterns

Whenever possible, meals should be consumed in the company of others and at regular times, while snacking should be avoided. The distribution of basic and tolerated foods over different meals can vary, but all meals together should add up to provide an adequate intake of all nutrients and energy. Toddlers will need more frequent meals than older children. The types of meal, both hot and cold, and the time of day at which they are consumed will vary between countries and families. Both cold and hot meals should be accompanied by a beverage. Cold meals will mostly consist of bread and cereals, dairy products, and raw fruit and vegetables, and thus provide the majority of the daily carbohydrate, fiber and calcium intake besides significant percentages of vitamin C and folate intake. Hot meals are based on potatoes, rice or pasta, vegetables and salads, while meat or fish serves as a supplement and therefore need

not be eaten every day of the week. Hot meals thus contribute significantly to the intake of numerous vitamins and minerals such as vitamins B<sub>6</sub> and B<sub>12</sub>, magnesium, phosphorus and iodine.

## Choice of Foods

Foods particularly manufactured and specially fortified with nutrients are not a necessary part of a healthy toddler's diet, although a wide variety of such foods is available and is convenient to use. In circumstances where nutrient-dense foods are scarce, fortification or supplementation can, however, become necessary, particularly with regard to iron, iodine, zinc and calcium. Self-prepared food for toddlers should not be salted. Low-salt varieties of processed foods should be chosen.

*Bread and cereals*, but also rice and pasta, should preferably be wholegrain products, which contain B vitamins, magnesium, iron, fiber, protein and unsaturated fatty acids. A mixture of wholegrain and more refined products may be better accepted by young children.

*Vegetables and fruits*, if not served raw, should be boiled as briefly and in as little water as possible to reduce inevitable losses of vitamins, minerals and secondary plant substances such as carotenoids, phytosterins and polyphenols. While the primary choice of fruit, legumes and vegetables should be those which are in season, it may be necessary to be more flexible in the case of strong dislikes. Fruit juices can substitute for fruit in exceptional cases.

*Milk and dairy products* are indispensable in all children's diets as sources of calcium and other minerals as well as of vitamins. From the age of about 2 years, whole milk and milk products can be replaced by reduced-fat products.

*Meat and meat products* are important because of well-available iron and zinc, particularly for toddlers and young children. Moreover, they provide high-quality protein and important B vitamins. Products low in fat should be preferred.

Heme iron also increases the absorption of iron from plant food.

*Fish* is an important source of iodine and long-chain n-3 fatty acids and should be eaten at least once a week. Many children only accept braised and fried fish, which might be high in fat.

To increase the quality of the *fat* consumed, at least half of the total fat intake – both ‘hidden’ and visible – should come from plant oils, preferably those with a high content of mono- and polyunsaturated fatty acids and which contain some  $\alpha$ -linolenic acid (rapeseed, soy, flaxseed) and sufficient vitamin E. These oils are practically free of *trans*-fatty acids. An overall low fat use will further reduce the total intake of saturated and *trans*-fatty acids.

*Beverages* should preferably be offered to toddlers from a cup and should be free of or low in energy (water or unsweetened herbal or fruit teas). Milk is not to be regarded as a beverage but as a food. Fruit juices can contain valuable vita-

mins and minerals but, if undiluted, are high in sugars (>10% of weight). Fruit-based beverages, lemonades and cola beverages often contain large amounts of sugar and are unsuitable for relief of thirst. Sugar-sweetened beverages tend to be overconsumed, which can result in a positive energy balance and overweight [7–9].

## Conclusions

- Dietary recommendations for toddlers (1–3 years of age) gradually approach those for children, adolescents and adults; the percentage of energy derived from fat should decrease from >40% to around 30%
- Children should be permitted (within reasonable limits) to determine the amount of food they consume from a range of basic food groups
- Preferences for taste should be respected to a certain degree

## References

- 1 Young EM, Fors SW, Hayes DM: Associations between perceived parent behaviors and middle school student fruit and vegetable consumption. *J Nutr Educ Behav* 2004;36:2–8.
- 2 Gidding SS, Dennison BA, Birch LL, Daniels SR, Gilman MW, Lichtenstein AH, Rattay KT, Steinberger J, Stettler N, van Horn L; American Heart Association: Dietary recommendations for children and adolescents: a guide for practitioners. *Pediatrics* 2006;117:544–559.
- 3 Kersting M, Alexy U, Clausen K: Using the concept of Food Based Dietary Guidelines to develop an Optimized Mixed Diet (OMD) for German children and adolescents. *J Pediatr Gastroenterol Nutr* 2005;40:301–308.
- 4 Alexy U, Clausen K, Kersting M: Nutrition of healthy children and adolescents according to the Optimised Mixed Diet concept. *Ernährungsumschau* 2008;3:169–177.
- 5 Agostoni C, Decsi T, Fewtrell M, Goulet O, Kolacek S, Koletzko B, Michaelsen KF, Moreno L, Puntis J, Rigo J, Shamir R, Szajewska H, Turck D, van Goudoever J; ESPGHAN Committee on Nutrition: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:99–110.
- 6 Hilbig A, Kersting M: Effects of age and time on energy and macronutrient intake in German infants and young children: results of the DONALD study. *J Pediatr Gastroenterol Nutr* 2006;43:518–524.
- 7 Kranz S, Smiciklas-Wright H, Siega-Riz AM, Mitchell AD: Adverse effect of high added sugar consumption on dietary intake in American preschoolers. *J Pediatr* 2005;146:105–111.
- 8 Ludwig DS, Peterson KE, Gortmaker SL: Relation between consumption of sugar-sweetened drinks and childhood obesity. *Lancet* 2001;357:505–508.
- 9 Welsh JA, Cogswell ME, Rogers S, Rockett H, Mei Z, Grummer-Strawn LM: Overweight among low-income preschool children associated with the consumption of sweet drinks: Missouri, 1999–2002. *Pediatrics* 2005;115:e223–e229.



# 2.7 Adolescent Nutrition

Rehana A. Salam · Zulfiqar A. Bhutta

### Key Words

Adolescence · Nutrition · Adolescent health

### Key Messages

- Adolescents (10–19 years of age) represent one fifth of the global population and are considered a healthy age group who will eventually enter the work force and raise the economic productivity of any country
- It is a critical period marking phenomenal changes including rapid physical, psychosocial, sexual and cognitive maturation, and hence the nutrient needs are higher in adolescence than at any other time in the life cycle
- Nutritional interventions for adolescents need to be tailored to the developmental level of each individual adolescent to respond to their needs and should be delivered on a platform where they can be reached
- Adolescent nutrition research must move towards identifying how effective intervention components can be embedded within health, education and care systems and achieve a long-term sustainable impact

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### Introduction

Adolescents (10–19 years of age) represent one fifth of the global population and are considered a healthy age group who will eventually enter the work force and raise the economic productivity of any country. There are 1.2 billion adolescents in the world, 90% of whom live in low- and middle-income countries (LMICs), and they make up 12% of the population in industrialized countries compared with 19% in LMICs [1].

Adolescence is a critical period marking phenomenal changes including rapid physical, psychosocial, sexual and cognitive maturation, and hence the nutrient needs are higher in adolescence than at any other time in the life cycle. Healthy eating in childhood and adolescence is important for proper growth and development, as optimal nutrition is a prerequisite for achieving the full growth potential and failure to achieve optimal nutrition may lead to delayed and stunted linear growth. Furthermore, healthy nutrition can also help prevent diet-related chronic diseases such as obesity, type 2 diabetes, cardiovascular diseases, pulmonary, hepatic and renal diseases, cancer and osteoporosis [2, 3]. It has been highlighted that nutrition interventions for adoles-

cents need to be tailored to the developmental level of each individual adolescent to respond to their needs and should be delivered on a platform where they can be reached.

This chapter will review the trends for childhood and adolescent malnutrition, adolescent eating behaviors and factors influencing them as well as interventions and platforms to promote healthy nutrition habits among adolescents and to prevent obesity.

### Adolescent Nutrition Trends

Over the last two decades, increasing prevalence rates of overweight and obesity among children and adolescents have been seen in many countries. Many of the LMICs now bear the double burden of malnutrition due to the emerging issue of overweight and obesity along with the existing high rates of stunting and other micronutrient deficiencies. In 2011, an estimated 43 million children under 5 years of age were overweight, marking a 54% increase from an estimated 28 million in 1990. In Africa, the estimated prevalence increased from 4% in 1990 to 7% in 2011, while it is a little lower in Asia (5% in 2011), with the number of affected children being higher than in Africa (17 and 12 million, respectively) [4]. Globally, childhood obesity rates continue to rise in developing countries, while in the developed part of the world, they are gradually plateauing [5, 6]. These figures are alarming and require immediate attention, as childhood overweight is associated with multiple immediate and long-term risks including raised cholesterol, triglycerides and glucose, type 2 diabetes, high blood pressure as well as adult obesity and its associated consequences [7, 8]. Primary prevention remains pivotal as there is strong evidence that obesity is difficult to reverse and continues through to adulthood. Adolescent nutrition is also important with regard to maternal nutrition, as pregnant adolescents are

at risk for adverse outcomes including low birth weight, preterm delivery, anemia and excessive postpartum weight retention due to a combination of physiological, socioeconomic and behavioral factors [9, 10]. Nutrition among pregnant teens is crucial as they tend to give low priority to nutrition despite having an enhanced need for nutrients due to their pregnant state. Recently, there has been a growing interest in adolescent nutrition in developing countries as a means of improving the health of women and children, as interventions targeted at adolescents allow time for the interventions to have the maximum impact on optimizing health in the years ahead.

Eating patterns and behaviors are influenced by many factors during adolescence including peer influences, parental modeling, food availability, food preferences, costs, convenience, personal and cultural beliefs, mass media and body image. These could be broadly classified as follows: (1) personal factors including attitudes, beliefs, food preferences, self-efficacy and biological changes; (2) environmental factors including family, friends, peer networks, school, fast food outlets and social and cultural norms, and (3) macrosystemic factors including food availability, food production, distribution systems, the mass media and advertising.

### Interventions

Various interventions including education, health promotion as well as behavioral and psychological counseling could be implemented either at the individual level or combined with family/parent support with a focus on diet, physical activity or lifestyle. These interventions could be school based, health care center based or delivered at the community level. Evidence suggests that educational, health promotional, psychological and behavioral counseling interventions focusing on diet, physical activity or

lifestyle support are effective at lowering BMI and reducing adiposity among children and adolescents, although not all interventions are effective at individual levels as it is difficult to differentiate individual intervention from a multicomponent intervention program [11]. School-based nutrition education interventions to prevent and reduce obesity in children and adolescents are effective in reducing the rates of overweight and obesity and in increasing fruit and vegetable consumption [12, 13]. Evidence also suggests that combining an educational and an environmental component might be more preferable for school-based nutrition and physical activity interventions in some populations [12, 13]. Parental involvement in school-based obesity prevention interventions is often advocated as important and has shown some positive effects on children's behaviors and behavioral determinants. Various parental modules addressing several home-related determinants and parenting practices related to eating and physical activity are more likely to be effective; however, the added value of parent involvement remains inconclusive [14]. Weight-related health interventions involving parent participation can more effectively reduce BMIs of children and adolescents, and longer interventions that include parent participation appear to have greater success [15]. Energy intake and food choices are more likely to be addressed in family-targeted interventions [16]. The effect of aerobic exercise on non-high-density lipoprotein cholesterol in children and adolescents is not yet established; however, it can decrease the percentage of body fat and increase aerobic capacity among children and adolescents [17].

Nutrition interventions for pregnant adolescents mainly involve education regarding balanced diet and consuming adequate amounts of iron, folate, calcium and zinc along with food provision for low-income teens to ensure appropriate gestational weight gain and adequate nutritional intake. Nutrition intervention pro-

grams for pregnant adolescents can have positive effects on birth outcomes due to multidisciplinary teams, individualized education and counseling, home visits as well as support/discussion groups [18].

### **Intervention Delivery and Challenges**

Evidence exists in various adolescent health domains including nutrition that points towards potential benefits of these strategies; however, their implementation, scaling up and sustainability may be difficult to achieve and need careful consideration. The most commonly evaluated delivery platforms for targeting children and adolescents have by far been school-based delivery of nutrition interventions followed by home- and community-based delivery. Very few evaluations have been carried out to assess interventions delivered in care settings tailored for adolescent needs. Efforts should be made to utilize health sector interfaces to cater to the adolescent health and nutrition needs. It is vital that health care providers who provide nutrition education and counseling have a thorough understanding of adolescent physical and psychosocial growth and development. Health professionals should be trained to allow adequate time to determine an adolescent's degree of biological maturity and level of cognitive development in order to determine his/her individual nutritional needs and the type of educational messages that are given when counseling the adolescent. Other sectors, including civil society bodies, faith-based institutions and the community at large, should also make efforts to constructively impact adolescent health and nutrition and respond to the needs of their adolescents.

In 1995, the World Health Organization (WHO) organized a study group on programming for adolescent health and development along with the United Nations International Children's Emergency Fund (UNICEF) and the

United Nations Framework for Population Activities (UNFPA), and since then, efforts have been made to identify various interventions and their effectiveness to improve access to primary health care and commodities for adolescents. It has become increasingly more important to target this vulnerable group as today's adolescents are exposed to nutritional risks, harmful alcohol consumption, sexually transmitted diseases and other risks more than in the past, and they face other new challenges such as social media [19–22].

## Conclusions

- Promising policies and strategies for delivering adolescent nutrition interventions include the school curriculum (focusing on healthy

eating practices, physical activity and body image), improvements in the nutritional quality of the food supply in schools and training and involvement of parents and teachers to successfully implement health promotion strategies and activities

- At the national level, governments should conduct a situation analysis of adolescent health and nutrition and develop an appropriate strategy to strengthen the response of the health sector for scale-up and implementation
- Adolescent nutrition research must move towards identifying how effective intervention components can be embedded within health, education and care systems and achieve a long-term sustainable impact

## References

- 1 Cappa C, Wardlaw T, Langevin-Falcon C, Diers J: Progress for children: a report card on adolescents. *Lancet* 2012;379: 2323–2325.
- 2 Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GLA, Saaddine J, Gregg EW, Williamson DF: Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 2000; 136:664–672.
- 3 Freedman DS, Dietz WH, Srinivasan SR, Berenson GS: The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics* 1999;103:1175–1182.
- 4 UNICEF, WHO, World Bank: Levels and trends in child malnutrition. Joint child malnutrition estimates. New York, UNICEF; Geneva, WHO; Washington, World Bank; 2012.
- 5 Rokholm B, Baker JL, Sørensen TI: The levelling off of the obesity epidemic since the year 1999: a review of evidence and perspectives. *Obes Rev* 2010;11: 835–846.
- 6 Nichols MS, de Silva-Sanigorski AM, Cleary JE, Goldfeld SR, Colahan A, Swinburn BA: Decreasing trends in overweight and obesity among an Australian population of preschool children. *Int J Obes* 2011;35:916–924.
- 7 Koplan JP, Liverman CT, Kraak VI: Preventing childhood obesity: health in the balance – executive summary. *J Am Diet Assoc* 2005;105:131–138.
- 8 Lloyd LJ, Langley-Evans SC, McMullen S: Childhood obesity and risk of the adult metabolic syndrome: a systematic review. *Int J Obes* 2012;36:1–11.
- 9 Hediger ML, Scholl TO, Schall JE: Implications of the Camden Study of adolescent pregnancy: interactions among maternal growth, nutritional status, and body composition. *Ann NY Acad Sci* 1997;817:281–291.
- 10 Strobino DM, Ensminger ME, Kim YJ, Nanda J: Mechanisms for maternal age differences in birth weight. *Am J Epidemiol* 1995;142:504–514.
- 11 Waters E, de Silva-Sanigorski A, Hall BJ, Brown T, Campbell KJ, Gao Y, Armstrong R, Prosser L, Summerbell CD: Interventions for preventing obesity in children. *Cochrane Database Syst Rev* 2011;12:CD001871.
- 12 Silveira JA, Taddei JA, Guerra PH, Nobre MR: Effectiveness of school-based nutrition education interventions to prevent and reduce excessive weight gain in children and adolescents: a systematic review (in English, Portuguese). *J Pediatr (Rio J)* 2011;87:382–392.
- 13 Van Cauwenbergh E, Maes L, Spittaels H, van Lenthe FJ, Brug J, Oppert JM, De Bourdeaudhuij I: Effectiveness of school-based interventions in Europe to promote healthy nutrition in children and adolescents: systematic review of published and 'grey' literature. *Br J Nutr* 2010;103:781–797.

- 14 Van Lippevelde W, Verloigne Mt, De Bourdeaudhuij I, Brug J, Bjelland M, Lien N, Maes L: Does parental involvement make a difference in school-based nutrition and physical activity interventions? A systematic review of randomized controlled trials. *Int J Public Health* 2012;57:673–678.
- 15 Niemeier BS, Hektner JM, Enger KB: Parent participation in weight-related health interventions for children and adolescents: a systematic review and meta-analysis. *Prev Med* 2012;55:3–13.
- 16 Golley RK, Hendrie GA, Slater A, Corsini N: Interventions that involve parents to improve children's weight-related nutrition intake and activity patterns – what nutrition and activity targets and behaviour change techniques are associated with intervention effectiveness? *Obes Rev* 2011;12:114–130.
- 17 Kelley GA, Kelley KS: Effects of aerobic exercise on non-high-density lipoprotein cholesterol in children and adolescents: a meta-analysis of randomized controlled trials. *Prog Cardiovasc Nurs* 2008;23:128–132.
- 18 Nielsen JN, Gittelsohn J, Anliker J, O'Brien K: Interventions to improve diet and weight gain among pregnant adolescents and recommendations for future research. *J Am Diet Assoc* 2006;106:1825–1840.
- 19 Sawyer SM, Afifi RA, Bearinger LH, Blakemore S-J, Dick B, Ezech AC, Patton GC: Adolescence: a foundation for future health. *Lancet* 2012;379:1630–1640.
- 20 Viner RM, Ozer EM, Denny S, Marmot M, Resnick M, Fatusi A, Currie C: Adolescence and the social determinants of health. *Lancet* 2012;379:1641–1652.
- 21 Catalano RF, Fagan AA, Gavin LE, Greenberg MT, Irwin CE Jr, Ross DA, Shek DT: Worldwide application of prevention science in adolescent health. *Lancet* 2012;379:1653–1664.
- 22 Patton GC, Coffey C, Cappa C, Currie D, Riley L, Gore F, Degenhardt L, Richardson D, Astone N, Sangowawa AO, et al: Health of the world's adolescents: a synthesis of internationally comparable data. *Lancet* 2012;379:1665–1675.

## 2.8 Nutrition in Pregnancy and Lactation

Lenka Malek · Maria Makrides

### Key Words

Pregnancy · Lactation · Gestational weight gain · Nutrient requirements, during pregnancy, lactation · Supplements

### Key Messages

- Appropriate gestational weight gain is determined by the pre-pregnancy body mass index
- Most nutritional requirements of most pregnant and lactating women can be met by consuming a variety of foods according to government-endorsed guidelines
- There are almost universal recommendations for periconceptional folic acid supplementation to prevent neural tube defects. Supplementation with iodine during pregnancy and lactation, and with iron during pregnancy, is also recommended in different countries. Additional nutrient supplementation may be required for vegetarians, women having multifetal pregnancies and women diagnosed with deficiencies
- High-listeria-risk foods and alcohol should be avoided during pregnancy, and caffeine intake should be limited

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### Introduction

Maternal nutrition from preconception through to lactation has both short- and long-term health effects on the offspring [1]. While requirements

for many nutrients increase in pregnancy and lactation, and some dietary changes are required, hormonal changes lead to physiological adaptations which help the body balance maternal and fetal demands, making ‘eating for two’ largely unnecessary.

There is a negligible increase in energy requirements in the first trimester, followed by an average extra requirement of 1.4 MJ/day (335 kcal/day) in the second trimester, of 1.9 MJ/day (450 kcal/day) in the third trimester and of 2.0–2.1 MJ/day (275–500 kcal/day) during lactation for women with a normal pre-pregnancy body mass index (BMI). Energy requirements vary according to the pre-pregnancy BMI, with lower requirements for overweight and obese women and higher requirements for underweight women.

Healthy weight gain targets for pregnancy are also based on the pre-pregnancy BMI and are shown in table 1 [2]. Weight gain should be monitored throughout pregnancy to achieve the appropriate weight gain goal. Dieting to prevent weight gain or achieve weight loss is not recommended during pregnancy as it may result in inadequate intake of essential nutrients, which could adversely affect fetal growth and development. In the post-partum period, return to pre-pregnancy weight is faster in lactating women as fat stores laid down in pregnancy are mobilised to support lactation.

**Table 1.** The 2009 Institute of Medicine gestational weight gain recommendations for singleton and twin pregnancies [2]

Pre-pregnancy BMI category	Singleton pregnancy		Twin pregnancy total weight gain
	total weight gain	mean rate (range) of weight gain in the second and third trimesters	
Underweight (<18.5)	28–40 lb	1.0 (1.0–1.3) lb/week	–
	12.5–18 kg	0.51 (0.44–0.58) kg/week	–
Normal weight (18.5–24.9)	25–35 lb	1.0 (0.8–1.0) lb/week	37–54 lb
	11.5–16 kg	0.42 (0.35–0.50) kg/week	17–25 kg
Overweight (25.0–29.9)	15–25 lb	0.6 (0.5–0.7) lb/week	31–50 lb
	7–11.5 kg	0.28 (0.23–0.33) kg/week	14–23 kg
Obese (≥30.0)	11–20 lb	0.5 (0.4–0.6) lb/week	25–42 lb
	5–9 kg	0.22 (0.17–0.27) kg/week	11–19 kg

Pregnant and lactating women can largely meet their nutritional needs by following the government-endorsed dietary guidelines available in most countries and adding some extra daily servings of some core food groups [3, 4]. An example is provided in table 2.

The remainder of the chapter outlines the cases of specific nutrients and special conditions in pregnancy and lactation.

### Folic Acid

Periconceptual folic acid supplementation has been shown to reduce the first-time occurrence of neural tube defects (NTD) by up to 72% and recurrence by 68% [5]. The critical window for increasing folate intake for the prevention of NTDs is before neural tube closure, which normally occurs by day 28 after conception. Given it can take 3 weeks to increase serum folate towards adequacy, supplementation should commence at least 1 month before conception and continue until at least 1 month after conception, although up to 3 months is often advised. A daily folic acid dose of 400–500 µg is recommended for low-risk women (i.e. no family history of NTDs, not on anticon-

vulsants) and 4,000–5,000 µg for women with a personal or close family history of NTDs. See table 3 for natural and fortified sources of folate.

### Iodine

Iodine is required for the production of thyroid hormones, which are essential for normal fetal and infant growth and brain development. Major fetal effects of severe iodine deficiency (ID) include abortions, stillbirths, congenital abnormalities, increased perinatal and infant mortality and cretinism [6]. In an effort to prevent ID, salt iodisation has been implemented in nearly all countries worldwide, and in countries where <20% of households have access to iodised salt, the WHO and UNICEF recommend iodine supplementation for pregnant and lactating women.

Mild-to-moderate ID also occurs in many countries. Although its functional consequences are not well established, many countries recommend a daily supplement containing 150 µg of iodine in preconception, pregnancy and lactation.

Iodine-fortified foods, including bread, are available in some countries. While iodine is also found naturally in certain foods (table 3), the io-

**Table 2.** Minimum recommended number of serves per day from core food groups for adult women as well as additional requirements for pregnant and lactating women

Food group	Example serves	Women	Pregnant women	Lactating women
Grain (cereal) foods, mostly wholegrain and/or high-cereal-fibre varieties	<ul style="list-style-type: none"> <li>- 1 slice bread</li> <li>- 1/2 medium roll or flat bread</li> <li>- 1/2 cup cooked rice, pasta, noodles or other grains</li> <li>- 2/3 cup wheat cereal flakes</li> <li>- 1/2 cup cooked porridge</li> <li>- 1/4 cup muesli</li> <li>- 3 (35 g) crisp breads</li> <li>- 1 crumpet, small English muffin or scone</li> </ul>	6	+2.5	+3
Vegetables and legumes/beans	<ul style="list-style-type: none"> <li>- 1/2 cup cooked green or orange vegetables</li> <li>- 1/2 cup cooked dried or canned legumes/beans</li> <li>- 1 cup green leafy or raw salad vegetables</li> <li>- 1/2 cup sweet corn</li> <li>- 1/2 medium potato or other starchy vegetable</li> <li>- 1 medium tomato</li> </ul>	5	No change	+2.5
Fruit	<ul style="list-style-type: none"> <li>- 1 medium piece (e.g. apple, banana)</li> <li>- 2 small pieces (e.g. apricots, kiwi fruit)</li> <li>- 1 cup diced or canned fruit (no added sugar)</li> </ul> <p><i>Or only occasionally:</i></p> <ul style="list-style-type: none"> <li>- 1/2 cup fruit juice (no added sugar)</li> <li>- 30 g dried fruit (e.g. 4 dried apricot halves, 1.5 tablespoons of sultanas)</li> </ul>	2	No change	No change
Milk, yoghurt, cheese and/or their alternatives, mostly reduced fat	<ul style="list-style-type: none"> <li>- 1 cup (250ml) milk</li> <li>- 1/2 cup evaporated unsweetened milk</li> <li>- 40 g (2 slices or 4 small cubes) hard cheese, such as cheddar</li> <li>- 1/2 cup ricotta cheese</li> <li>- 3/4 cup (200 g) yoghurt</li> <li>- 1 cup soy, rice or other cereal drink with at least 100 mg of added calcium per 100 ml</li> </ul> <p><i>The following alternatives contain about the same amount of calcium as a serve of milk, yoghurt or cheese:</i></p> <ul style="list-style-type: none"> <li>- 100 g almonds with skin</li> <li>- 60 g sardines, canned in water</li> <li>- 1/2 cup (100 g) canned pink salmon with bones</li> <li>- 100 g firm tofu (check label as calcium levels vary)</li> </ul>	2.5	+1	+1
Lean meat and poultry, fish, eggs, nuts and seeds as well as legumes/beans	<ul style="list-style-type: none"> <li>- 65 g cooked lean red meats (~90 – 100 g raw)</li> <li>- 80 g cooked lean poultry (~100 g raw)</li> <li>- 100 g cooked fish fillet (~115 g raw) or 1 small can of fish</li> <li>- 2 large eggs</li> <li>- 1 cup (150 g) cooked or canned legumes/beans (preferably with no added salt)</li> <li>- 170 g tofu</li> <li>- 30 g nuts, seeds, peanut or almond butter or tahini, or other nut or seed paste</li> </ul>	2.5	+1	No change

Values are given for women aged 19 – 50 years. Adapted from the *Australian Dietary Guidelines* [3].





**Table 3.** Animal-derived, plant-derived and fortified sources of key nutrients

	Animal-derived sources	Plant-derived sources	Fortified sources (available in some countries)
Folate	Boiled egg yolk	Green leafy vegetables, oranges, orange juice, grapefruit, strawberries, raspberries, blackberries, sultanas, yeast spread (Marmite, Vegemite), legumes, peanuts, sesame seeds, tahini, sunflower seeds	Bread, breakfast cereals, flavoured beverage bases (e.g. Milo), milk, soy beverages, fruit juice
Iodine	Fish/seafood, milk, yogurt, cheese, eggs	Seaweed; minimal amounts in other sources	Bread, iodised salt
Iron	Meat, poultry, fish/seafood (haem-iron) Eggs (non-haem iron)	Cooked legumes (chickpeas, lentils, kidney and lima beans), wholegrain breads and cereals, nuts, seeds, dried fruit and green leafy vegetables (non-haem iron)	Breakfast cereals, flavoured beverage bases (e.g. Milo; non-haem iron)
Calcium	Milk, cheese, yogurt, fish with bones (e.g. salmon, sardines), fish paste/spread, crab meat	Amaranth, grain-based foods, green leafy vegetables, almonds, Brazil nuts, sesame seeds, tahini, soybeans, firm tofu, dried fruit	Soy/oat/rice/nut beverages, soy yogurt, tofu, breakfast cereals, fruit/vegetable juice, flavoured beverage bases (e.g. Milo), bread, edible oil spreads
Vitamin D	Oily fish, egg yolks	Mushrooms	Margarines, milk, powdered milk, soy beverages, yogurt, cheese, eggs, breakfast cereals, orange juice
Vitamin B <sub>12</sub>	Meat, poultry, fish/seafood, milk, cheese, yogurt, eggs	None	Soy beverages, veggie burgers, soy-based meat analogues and yeast extracts (e.g. Marmite)
Zinc	Meat, poultry, eggs, milk, cheese, yogurt, cooked seafood (especially oysters)	Legumes, wholegrain breads and cereals, brown rice, soy products (e.g. tofu and tempeh), nuts, seeds	Breakfast cereals

dine content can vary widely due to a number of factors including geographical location and environmental factors such as the iodine concentration in the soil. Kelp and seaweed-based products should be avoided during pregnancy and lactation due to their large variability in iodine content.

## Iron

Iron requirements increase in the second and third trimesters to support fetal growth, placental tissue development and expansion of the red cell mass. Intestinal iron absorption increases to meet

increased iron requirements, and reaches peak efficiency during the third trimester, when the majority of iron transfer occurs. In iron-sufficient pregnancies, enough iron is transferred to meet the infant's iron requirements for the first 6 months of life. Maternal iron requirements are reduced during lactation and increase to pre-pregnancy levels when menstruation resumes.

Haem iron from animal sources is better absorbed than non-haem iron from plant sources (table 3). Iron absorption from plant foods can be increased by consuming meat proteins or a source of vitamin C (e.g. citrus fruits/juices, strawberries, kiwi fruit, tomatoes and broccoli) at the same meal. Dietary components which can in-

hibit the absorption of both haem and non-haem iron include calcium, zinc and phytates found in legumes and whole grains. Polyphenols found in tea and coffee can also inhibit non-haem iron absorption. This may have special significance for vegetarians who also consume tea and coffee as part of their daily diets.

While routine iron supplementation during pregnancy is not common practice in all countries, the WHO recommends daily oral iron supplementation (30–60 mg of elemental iron) as part of antenatal care to reduce the risk of low birth weight, maternal anaemia and iron deficiency. A daily dose of 60 mg of elemental iron is recommended in settings where the prevalence of anaemia in pregnancy is  $\geq 40\%$ , and 120 mg is recommended when there is a clinical diagnosis of anaemia [7].

## Calcium

Calcium is required for fetal and infant bone development and mineralisation, as well as for breast milk production. Maternal bone turnover and the intestinal absorption of calcium increase during pregnancy to help meet fetal calcium requirements. The majority of calcium is transferred to the fetus in the third trimester. During lactation, calcium from the mother's bones is transferred to the infant via breast milk. This bone resorption is independent of the calcium intake and is completely reversible, with the bone density being restored 6–12 months after the cessation of breastfeeding.

The recommended daily intake of calcium during pregnancy and lactation is 1000 mg for adults and 1,300 mg for adolescents. This can be provided by 3–4 serves of calcium-rich foods (each serve providing approx. 300 mg of calcium). Dietary sources of calcium are shown in table 3. Calcium supplements should be taken if dairy intake is low or if the intake from other sources is inadequate.

## Vitamin D

Vitamin D is important for regulating calcium and phosphorus metabolism. A deficiency during pregnancy has been associated with impaired calcium and skeletal homeostasis, congenital rickets and fractures in the newborn. Vitamin D<sub>3</sub> (cholecalciferol) is synthesised in skin cells upon exposure to UVB radiation from sunlight, and adequate exposure to sunlight can provide most people with their daily vitamin D requirement. Vitamin D can also be obtained through the diet from a limited range of natural sources and variably fortified foods available in some countries (table 3).

Darker-skinned women and those with limited exposure to sunlight are less likely to synthesise sufficient vitamin D. Women at risk of deficiency should be screened for low serum 25-hydroxyvitamin D levels and supplemented as required.

## Multifetal Pregnancies

In addition to the usual maternal physiological adaptations that occur with singleton pregnancies, in multifetal pregnancies there is an additional increase in plasma volume, basal metabolic rate and resistance to carbohydrate metabolism [8]. Higher intakes of protein, calcium, iron and folate are required to support fetal and placental growth and increased maternal metabolism.

## Vegetarian Diets

Vegetarian diets vary, and identifying which foods are excluded will help determine which nutrients are likely to be inadequately supplied. Vitamin B<sub>12</sub> is an essential nutrient which only occurs naturally in animal-derived foods. Therefore, diets low in or excluding animal products can be low in vitamin B<sub>12</sub>. Vitamin B<sub>12</sub> deficiency during pregnancy and lactation can cause megaloblastic anaemia and neurological damage in the

infant. To avoid a deficiency, some animal-derived foods or vitamin B<sub>12</sub>-fortified foods should be consumed or a vitamin B<sub>12</sub> supplement taken.

An adequate intake of iron, zinc, calcium and protein should also be ensured. Vegetarian sources of protein include dairy foods, legumes, cereals and grains as well as nuts and seeds. Vegetarian sources of iron, zinc and calcium are shown in table 3.

### **Mercury in Fish**

Fish is an important part of a healthy diet. It provides long-chain omega-3 fatty acids and is a good source of protein and minerals including iodine. Mercury is a neurotoxin which occurs naturally in the environment and accumulates in fish. The consumption of fish during pregnancy and lactation should be guided by national, government-endorsed recommendations, which generally advise eating 2–3 meals per week of fish/shellfish with low mercury levels and avoiding or limiting the consumption of fish high in mercury (predatory deep-sea fish) [9, 10]. Canned fish generally has lower levels of mercury, as smaller species and younger fish are used for canning.

### **Herbal Teas and Herbal Supplements**

There is insufficient evidence to support the consumption of herbal teas or herbal supplements during pregnancy or lactation. Most herbal preparations have not been tested to establish their efficacy and safety, and some may be dangerous to the developing fetus or infant.

### **Listeriosis**

Listeriosis is a rare but serious infection caused by eating food contaminated with the bacterium *Listeria monocytogenes*. The transmission of lis-

teria to the fetus can cause miscarriage, premature labour or stillbirth. The risk of listeriosis can be reduced by avoiding high-risk foods and taking simple food hygiene and food safety steps. Foods to avoid include chilled, ready-to-eat foods such as cold cooked chicken, cold processed meats, pre-prepared or pre-packed cold salads, raw seafood, soft-serve ice cream, unpasteurised dairy products, pâté as well as soft and semi-soft cheese.

### **Caffeine (Coffee, Tea and Caffeine Soft Drinks)**

Some caffeine is transferred to the fetus via the placenta and to the infant via breast milk. A daily intake of 200–300 mg caffeine, equivalent to 2–3 cups of coffee, is considered to have no adverse effect. Energy drinks are not recommended as they can contain high levels of caffeine.

### **Alcohol**

Alcohol is transferred to the fetus via the placenta and to the infant via breast milk. There is no safe limit for alcohol intake, and it is recommended that alcohol consumption be avoided during pregnancy. During lactation, the alcohol content of breast milk reflects maternal blood alcohol levels. As a general rule, it takes an average-sized woman 2 h for blood alcohol levels to return to zero after consuming 10 g of alcohol (1 standard drink). Therefore, women who plan to consume alcohol should breastfeed or express breast milk before drinking.

### **Conclusions**

- Nutrition in pregnancy can exert important short- and long-term effects on the mother and baby

- The increased nutritional requirements during pregnancy can generally be met by eating a wide variety of foods according to the relevant government guidelines
- Specific supplementation for folate to prevent NTD is widely recommended
- Recommendations for other nutrients like iodine and iron are more country and region specific

## References

- 1 Osmond C, Barker DJP: Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environ Health Perspect* 2000;108:545–553.
- 2 Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines; Rasmussen K, Yaktine A (eds): *Weight Gain during Pregnancy: Reexamining the Guidelines*. Washington, National Academies Press, 2009.
- 3 National Health and Medical Research Council: *Australian Dietary Guidelines*. Canberra, National Health and Medical Research Council, 2013.
- 4 US Department of Agriculture, US Department of Health and Human Services: *Dietary Guidelines for Americans*, 2010, ed 7. Washington, US Government Printing Office, 2010.
- 5 De-Regil LM, Fernández-Gaxiola AC, Dowswell T, Peña-Rosas JP: Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochrane Database Syst Rev* 2010; 10:CD007950.
- 6 Hetzel BS: Iodine deficiency disorders (IDD) and their eradication. *Lancet* 1983;2:1126–1129.
- 7 WHO: *Guideline: daily iron and folic acid supplementation in pregnant women*. Geneva, WHO, 2012.
- 8 Goodnight W, Newman R; Society of Maternal-Fetal Medicine: Optimal nutrition for improved twin pregnancy outcome. *Obstet Gynecol* 2009;114:1121–1134.
- 9 Food Standards Australia New Zealand: *Mercury in fish*. 2011. [www.foodstandards.gov.au/consumer/chemicals/mercury/Pages/default.aspx](http://www.foodstandards.gov.au/consumer/chemicals/mercury/Pages/default.aspx).
- 10 US Food and Drug Administration, US Environmental Protection Agency: *What you need to know about mercury in fish and shellfish: advice for women who might become pregnant, women who are pregnant, nursing mothers, young children*. 2004. [www.fda.gov/food/resourcesforyou/consumers/ucm110591.htm](http://www.fda.gov/food/resourcesforyou/consumers/ucm110591.htm).



## 2.9 Vegetarian Diets

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### Key Words

Vegetarian diet · Vegan diet · Nutrient deficiencies

### Key Messages

- Carefully planned mixed vegetarian diets (with milk and eggs) can provide sufficient energy, protein and nutrients for all stages of childhood growth and development
- Very restrictive or unbalanced vegetarian diets can result in failure to thrive and serious nutrient deficiencies in infants and children
- Vegan diets pose the highest risk for nutrient deficiencies in childhood, particularly for energy, protein, essential fatty acids, vitamin B<sub>12</sub>, vitamin D, iron, calcium and zinc
- Practical dietary advice should include alternative dietary sources of nutrients and supplementation of the diet where clinically indicated

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### Introduction

Guidance on nutrient intakes to support optimal growth and development in vegetarian infants, children and adolescents is identical to that for non-vegetarians (see Annex 4.3). Vegetarian chil-

dren can meet all nutritional needs for growth and development, provided the diet is well designed, balanced and appropriate to the stage of development. Vegetarianism is used to describe a range of highly diverse eating patterns, broadly characterised by the degree of restriction of animal products, as shown in table 1. Semi- and lacto-(ovo-)vegetarian diets containing milk products, eggs and/or fish can easily provide adequate nutrients throughout all life stages. However, there is a greater risk for nutritional deficiencies, especially for energy, protein, n-3 fatty acids, vitamin B<sub>12</sub>, vitamin D, calcium, iron and zinc, in children eating more restrictive vegan diets.

Vegetarians tend to consume less saturated fat and a higher amount of fibre and micronutrients compared to omnivores [1]. Health benefits, such as low rates of obesity and reduced risk of coronary heart disease and diabetes, have been associated with a vegetarian diet in adults [2] but are less established in children, although vegan children do tend to be leaner than their omnivorous peers [3].

The main challenges for paediatric care clinicians are to assess the quality of the vegetarian diet, to determine the likely risk for nutritional deficiency and to offer dietary education and family

**Table 1.** Types of vegetarian diets practiced as well as associated nutrients of concern for children

Vegetarian diet	Description	Main nutritional concerns in children
Semi- or demi-	Excludes red meat; may exclude poultry; fish is usually eaten	Iron
Pescatarian	Excludes red meat and poultry but eats fish and possibly shellfish	Iron, zinc
Lacto-ovo-	Excludes all meat, fish and poultry; milk, milk products and eggs are usually eaten	Iron, zinc, n-3 fatty acids
Vegan	Consumes no foods of animal origin; emphasis on plant foods, grains, legumes, nuts, seeds and vegetable oils	Energy, protein, vitamin B <sub>12</sub> , zinc, vitamin D, calcium, n-3 fatty acids
Raw food	An extreme form of veganism with the emphasis on organic, home-grown or wild foods in their raw or natural state; usually comprises 80% by weight raw plants	Not suitable for children
Fruitarian	An extreme form of veganism which excludes all foods of animal origin and also living plants; the diet is mainly raw: 70–80% fruit with small amounts of beans, bread, tofu, nuts and seeds	Not suitable for children
Macrobiotic	Extreme diet progressing through 10 levels becoming increasingly restrictive; foods are gradually eliminated through the 10 levels; at the final level, only cereal (brown rice) is eaten	Not suitable for children

counselling to ensure the child's nutritional needs for growth and development are met. A referral to a qualified dietitian and supplementation of the diet may be indicated for vegan children. This chapter will outline the most common nutritional considerations for vegetarian children.

### Growth and Development

Breastfed infants obtain nutrients exclusively from breast milk, and its composition will be determined by the maternal diet. For non-breastfed vegetarian infants, soy-based infant formula is

available. This tends to be higher in phyto-oestrogens than human breast milk, but there is currently no conclusive evidence of any adverse effects of increased phyto-oestrogen intake on human development, reproduction or endocrine function, and soy formula appears safe for use, when clinically indicated, in term babies with normal renal function [4]. Clinicians should be aware that most commercial soy formula will contain vitamin D<sub>3</sub> from animal sources, which can be unacceptable for vegans but may represent the best option if breastfeeding is contraindicated. Homemade milk preparations (soy milk, rice milk and nut milk) are not suitable in the first

year, owing to low iron bioavailability, insufficient vitamins and inappropriately high concentrations of minerals [5].

Weaning guidelines are similar to that for non-vegetarian infants. Regular monitoring of weight is paramount to ensure sufficient energy and protein intake for normal growth. Vegetarian diets can be lower in energy and higher in dietary fibre compared to omnivore diets and can result in early satiety in infants when small quantities of foods are consumed [5]. Good sources of nutrient-dense foods for vegetarian weaning diets include: full-fat dairy products, mashed or pureed beans/tofu, soy yogurts, mashed avocado and mashed vegetables with added fats/oils. Smooth nut butters, which are calorific, can be introduced after 1 year.

Cow's milk, if acceptable, can be started at 1 year of age. Vegan infants can commence fortified full-fat soy milk at this time, which should continue to be supplemented with human milk or soy-based formula and other sources of adequate protein and calories.

For vegetarian toddlers and older children, the main challenge is to ensure adequate intake of energy, protein, vitamins and minerals for optimum growth and development. In vegetarian children, growth rates have been found to be similar to those of omnivores, whereas vegans tend to be smaller and leaner [6]. However, height measurements for vegan children may still reside within normal limits, and catch-up growth usually occurs by the age of 10 years [1].

Vegetarian diets that are adequate in energy are also likely to provide sufficient protein to support optimum growth in children. However, plant proteins tend to have lower biological values than animal protein, and vegan children are estimated to require a 1.3 times higher protein intake than omnivores to meet all essential amino acid requirements [1, 6]. This is best achieved when a wide range of plant proteins is consumed (soy protein, textured vegetable protein, legumes, nuts, seeds and grains) within the diet [1].

## Special Nutrient Considerations in Vegetarian Diets

### *Essential Fatty Acids*

Essential long-chain (n-3) fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are derived largely from marine dietary sources and are important for immune, cognitive and retina development in children. Lower levels of DHA have been demonstrated in milk from vegan mothers compared to omnivore mothers [7]. Vegetarian or vegan breastfeeding mothers and children should aim for adequate plant-derived  $\alpha$ -linolenic acid such as flaxseed and canola oils, as shown in table 2, which can be converted to DHA/EPA in vivo, although conversion rates are low. A vegan DHA supplement (for example algal oil) may be indicated in vegan children with insufficient dietary intake and/or low serum DHA levels.

### *Vitamin B<sub>12</sub>*

Vitamin B<sub>12</sub> is only derived from animal sources and important for infant neuronal, cognitive and brain development. Deficiency can result in megaloblastic anaemia, neurodevelopmental delay and, in severe cases, irreversible brain damage. Breastfed infants whose mothers have inadequate vitamin B<sub>12</sub> intake or status should receive a supplement (0.4–0.5  $\mu$ g/day) due to their limited body reserves at birth [5, 6]. The risk of vitamin B<sub>12</sub> deficiency in vegan children is increased if the diet is not supplemented with fortified foods, as shown in table 2.

### *Vitamin D*

Children with dark skin pigmentation, those living in northern latitudes (with less sunlight exposure) and those exclusively breastfed are especially at risk of vitamin D deficiency [5, 8]. Good dietary sources of vitamin D<sub>3</sub> include oily fish, egg yolks and fortified food products (shown in table 2). Vegan foods are fortified with vitamin D<sub>2</sub> from yeast, although this may not be as well ab-

**Table 2.** Vegetarian (includes semi- and lacto-vegetarian and vegan) food sources for main nutrient concerns in children

Nutrient	Main food source	Points to note
n-3 fatty acids	Oily fish (EPA/DHA); ground flaxseed; flaxseed/linseed oil; canola/rapeseed oil; cooked soybeans; tofu; walnuts; walnut oil	Supplement may be required in vegans
Vitamin B <sub>12</sub>	Dairy products; eggs; poultry; fish; fortified cereal; fortified yeast; fortified soy milk	Supplement may be required in vegans
Vitamin D	Fortified dairy products; egg yolks; oily fish; fortified soy products (milk, yogurts, tofu, tempeh); fortified vegan margarines	Supplement is required in infants; supplement may be required in vegan children/adolescents
Calcium	Dairy products; green vegetables (broccoli, cabbage, collard greens, bok choy, turnip greens, kale); fortified soy products (milk, yogurts, tofu, tempeh); fortified cereals; dried figs; almonds; sesame tahini	Oxalate/phytate reduces bioavailability; intestinal absorption increases when intake is reduced; supplement may be required in vegans
Iron	Animal products (dairy, fish, poultry); cooked soybeans, tofu, tempeh; cooked legumes (lentils, chickpeas, adzuki, kidney); dried pumpkin/squash seeds, cashews, sunflower seeds, tahini; fortified cereals; baked potatoes (including skin)	Non-haem iron absorption enhanced by vitamin C, vitamin A (retinol) and carotenes, inhibited by phytates, tannins/polyphenols and soy protein
Zinc	Soybeans (cooked/roasted), tofu, fortified vegetarian meats; baked beans, lentils, navy beans; dried pumpkin/squash seeds, cashews, toasted sunflower seeds; fortified cereals; wheat germ; cooked peas	Phytate reduces bioavailability

sorbed as the vitamin D<sub>3</sub> derivative from lanolin (sheep's wool) more commonly found in fortified foods [9].

### Calcium

Calcium intakes tend to be adequate in lacto-vegetarian children but can be lower than recommended in vegan children. Good sources of calcium in vegetarian diets are shown in table 2. Calcium bioavailability is inhibited by phytate (found in high-fibre cereals, legumes and seeds) and oxalate (found in fruit, vegetables, legumes and grains) content of food. In addition to consuming calcium-fortified soy products, low-oxalate green

vegetables such as cabbage, spring greens and kale have higher calcium bioavailability (49–61%) and should be consumed regularly by vegans [10].

### Iron

The clinical incidence of iron deficiency anaemia is no greater in vegetarian children than in omnivores, although iron stores tend to be lower [11]. It is recommended that iron intakes are 1.8 times higher in vegetarians [10] as plant sources of iron (non-haem) are less bioavailable. Phytate, soy protein and polyphenols/tannins can inhibit iron absorption, while several nutrients, including vitamin C, retinol and carotenes, can enhance the



absorption of non-haem iron. Dietary advice should encourage a variety of non-haem iron sources (as shown in table 2) and vitamin C with meals to aid iron absorption. Food preparation methods such as soaking beans prior to cooking and fermenting soy protein (e.g. miso and tempeh) can reduce the phytate content of these foods and improve iron availability [10].

### Zinc

Zinc deficiency can cause failure to thrive and impaired taste acuity in children [11, 12]. The main sources of zinc in vegetarian diets include cereals and grains, which are also high in phytate and reduce zinc bioavailability [10]. Differences in zinc intake between vegetarian and omnivorous children are negligible [11]. However, the ratio of phytate to zinc intake is much greater in vegetarian children, which can increase the risk of suboptimal zinc status especially during periods of rapid growth [11, 12]. Little is known regarding the effects of marginal zinc deficiency on childhood growth and development, although adaptation to a low intake may occur over time with increased intestinal absorption [11]. Good plant sources of zinc, as shown in table 2, should be advised.

### Conclusions

- Vegetarian diets can provide adequate nutrients for optimum growth and development in childhood. However, a broad range of vegetarian dietary patterns are often practiced, and while many parents invariably wish their offspring to share their eating pattern, some diets may be too nutritionally restrictive for infants and young children to thrive
- Variety in individual vegetarian diets is paramount to achieve the balance of nutrients to support each stage of development in childhood. If a particular food or food group is not consumed routinely, alternative nutrient sources should be encouraged, within the constraints imposed by the diet, and supplements advised when clinically indicated
- Vegan infants and children are especially at risk of energy, protein and other nutrient deficiencies. In these cases, a referral to a dietitian may be necessary for nutritional assessment and family counselling
- Further research is required to determine the health benefits and risks of vegetarian diets in childhood

### References

- 1 Messina V, Mangels AR: Considerations in planning vegan diets: children. *J Am Diet Assoc* 2001;101:661–669.
- 2 McEvoy CT, Temple N, Woodside J: Vegetarian, low-meat diets and health: a review. *Public Health Nutr* 2012;15:2287–2294.
- 3 Sabaté J, Wien M: Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr* 2010;91:1525S–1529S.
- 4 American Academy of Paediatrics: Soy protein-based formulas: recommendations for use in infant feeding (RE9806). *Paediatrics* 1998;101:148–153.
- 5 Mangels AR, Messina V: Considerations in planning vegan diets: infants. *J Am Diet Assoc* 2001;101:670–677.
- 6 Van Winckel M, Vande Velde S, De Bruyne R, Van Biervliet S: Vegetarian infant and child nutrition. *Eur J Pediatr* 2011;170:1489–1494.
- 7 Sanders TA, Reddy S: Vegetarian diets and children. *Am J Clin Nutr* 1994;59(suppl):1176S–1181S.
- 8 National Institute for Health and Clinical Excellence (NICE): Public health guidance PH11. Maternal and child nutrition. 2008. <http://www.nice.org.uk/PH11> (accessed 21 May, 2013).
- 9 Armas LAG, Hollis BW, Heaney RP: Vitamin D<sub>2</sub> is much less effective than vitamin D<sub>3</sub> in humans. *J Clin Endocrinol Metab* 2004;89:5387–5391.
- 10 American Dietetic Association, Dietitians of Canada: Position of the American Dietetic Association and Dietitians of Canada: vegetarian diets. *J Am Diet Assoc* 2003;103:748–765.
- 11 Hunt J: Bioavailability of iron, zinc and other trace minerals from vegetarian diets. *Am J Clin Nutr* 2003;78:633S–639S.
- 12 Gibson RS: content and bioavailability of trace elements in vegetarian diets. *Am J Clin Nutr* 1994;59:1223S–1232S.

### 3.1 Primary and Secondary Malnutrition

Lubaba Shahrin · Mohammod Jobayer Chisti · Tahmeed Ahmed

#### Key Words

Primary malnutrition · Secondary malnutrition ·  
Management · Prevention

#### Key Messages

- Malnutrition is responsible for almost one third of all deaths in children <5 years of age and causes impaired intellectual capabilities among those who survive
- Primary malnutrition, commonly seen in developing countries, is due to the combined effect of multiple factors including low birth weight, lack of adequate food, frequent infections and environmental enteropathy
- Secondary malnutrition results from an underlying disease that compromises growth directly or through its deleterious effect on appetite or the absorption of nutrients
- Most children with primary malnutrition can be managed at home with interventions such as counseling of parents on the proper diet to be given to the child, with emphasis on continued breastfeeding and appropriate complementary feeding, micronutrient supplementation, periodic deworming, ensuring household food security, etc.
- Children with severe acute malnutrition and complications require treatment in a hospital; those without complications can be treated at home with ready-to-use therapeutic food
- Without treating the underlying cause (malabsorption, infections, etc.), it is impossible to manage secondary malnutrition

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#### Introduction

To ensure proper physical growth and cognitive development, appropriate and adequate nutrition is essential. Malnutrition is defined as a deviation from the normal state of nutrition; it can logically be either undernutrition or overnutrition (overweight and obesity). A deficiency in proper nutritional elements due to any cause leads to undernutrition. Undernutrition is a broad term ranging from restricted intrauterine growth, low birth weight, stunting, wasting and underweight to micronutrient deficiencies. It is the outcome of sub-optimal dietary intake, metabolic stress, malabsorption and increased nutrient demands. It includes having low weight for age (underweight), being too short for one's age (stunted) or too thin for one's height (wasted) and/or being deficient in vitamins and minerals (micronutrient malnutrition). Undernutrition may develop either because people cannot access proper food or have an underlying disorder that limits eating or absorbing consumed food. In the context of low- and middle-income countries, where overnutrition is relatively less prevalent, malnutrition commonly implies stunting, wasting and/or underweight. There is no universally accepted definition of malnutrition; however, the WHO states that malnutrition is the cellular imbalance between the supply of nutrients and energy and the

body's demand for them to ensure growth, maintenance and specific functions [1].

Primary malnutrition in children is most commonly seen in low- and middle-income countries. The factors responsible for primary malnutrition include household food insecurity, poverty, poor nutrition of women during pregnancy, intrauterine growth restriction, low birth weight, poor breastfeeding and inappropriate complementary feeding, frequent infectious illnesses, poor quality of water, sanitation and hygiene, etc. Most cases of malnutrition seen across the globe are primary in nature. Although there is enough food in the world to feed all, it is sad to see hunger and malnutrition ravage through many countries primarily because of inequity and inequality affecting access to nutritious food. The problem of primary malnutrition is, therefore, mostly social rather than biomedical in origin. It is also multifactorial. For example, poor water quality, sanitation and hygiene practices are increasingly believed to be the cause of the condition called 'environmental enteropathy' that results in children becoming stunted [2]. A child who is repeatedly exposed to pathogens in the environment has bacterial colonization of the small intestine. There is an increased accumulation of inflammatory cells in the small intestinal mucosa, the intestinal villi are damaged and distorted by the inflammatory process, and, consequently, they malabsorb nutrients, which results in malnutrition. Chronic inflammatory processes also suppress the production of IGF-1, upset the growth hormone axis and lead to linear growth retardation [3].

Secondary malnutrition, in contrast, results from an underlying disease that compromises growth directly or through its deleterious effect on appetite or the absorption of nutrients. The underlying disease can cause poor appetite as a result of a release of inflammatory mediators including TNF- $\alpha$ ; the disease also affects nutritional status by inducing a catabolic state in the body. Infectious illnesses result in malnutrition by reducing the intake of nutrients and their bioavailability, by increasing nutrient and energy expen-

diture and by diverting nutrients away from growth. In patients with extensive burns, increased catabolism, anorexia and loss of plasma proteins from the exposed skin surfaces lead to malnutrition. Nutrient loss in Crohn's disease and increased energy expenditure in congenital heart disease also contribute to malnutrition. The main cause of malnutrition seen in developed countries is secondary malnutrition. If not identified early on, or if left untreated, secondary malnutrition increases the risk of infection, delayed wound or burn healing and an overall poor response to treatment of the underlying cause. Table 1 lists common conditions that can lead to secondary malnutrition, although not all of them are commonly seen in developed countries.

### **The Burden of Malnutrition**

Globally, an estimated 165 million children <5 years of age (or 26%) were stunted (height-for-age Z score  $\leq -2$  based on the WHO Child Growth Standards) in 2011 [4]. The estimated number of underweight children (weight-for-age Z score  $< -2$ ) globally is 101 million or 16%. Wasting affects 52 million children <5 years of age, which is 8% of all children of that age group. Severe wasting or severe acute malnutrition (SAM), defined as a weight-for-height Z score  $< -3$ , affects nearly 19 million children, with a global prevalence of 2.9%. Stunting is the cause of 14.7% of deaths in children <5 years old. Underweight is responsible for 14.4% of deaths, while wasting kills 12.6% of the children <5 years of age. It has been estimated that fetal growth restriction, stunting, wasting and deficiencies in vitamin A and zinc along with suboptimal breastfeeding cause 3.1 million child deaths annually or 45% of all child deaths in 2011. The overall risks of mortality from any cause (diarrhea, pneumonia, malaria or measles) for severe stunting, severe wasting and severe underweight are 4.1, 9.4 and 9.7, respectively. Among those who survive, impaired intellectual or cognitive and motor de-

**Table 1.** Diseases or conditions that can cause secondary malnutrition in children

Infectious causes	Noninfectious causes
Diarrhea, dysentery, persistent diarrhea (continuing for $\geq 14$ days)	Low birth weight
Repeated episodes of acute respiratory infection	Burns
Tuberculosis	Chromosomal disorders (e.g. trisomy 21); cleft lip/palate
Helminthiasis	Food allergy (e.g. cow's milk protein allergy)
Measles	Alimentary and hepatic diseases: inflammatory bowel disease (ulcerative colitis, Crohn's disease), celiac disease, chronic liver disease
Malaria	Respiratory disease: cystic fibrosis, bronchiectasis, bronchial asthma
Kala azar (leishmaniasis)	Cardiac diseases: congenital heart disease, rheumatic heart disease, endocarditis, heart failure due to any cause
Human immunodeficiency virus infection	Renal diseases: chronic kidney disease, renal tubular acidosis, glomerulonephritis, nephrotic syndrome Endocrine diseases: diabetes mellitus, congenital hypothyroidism, congenital adrenal hyperplasia Nervous system diseases: cerebral palsy, neuroendocrine disorder Malignancies: leukemias, lymphomas, other malignancies Metabolic diseases: inborn errors of metabolism, Wilson's disease, etc.

velopment is common. Length for age at 2 years is associated with better cognitive scores in later childhood (0.17–0.19 cognitive Z scores per unit change in length-for-age Z score) [5].

The high prevalence of stunting among children <5 years of age in Africa (36% in 2011) and Asia (27% in 2011) remains a pervasive public health problem. The prevalence of stunting is slowly decreasing globally, but the absolute number of children affected has increased in Africa. More than 80% of the world's stunted children live in only 14 countries in Asia and Africa, the top 6 countries being India, Nigeria, Pakistan, China, Indonesia and Bangladesh [6].

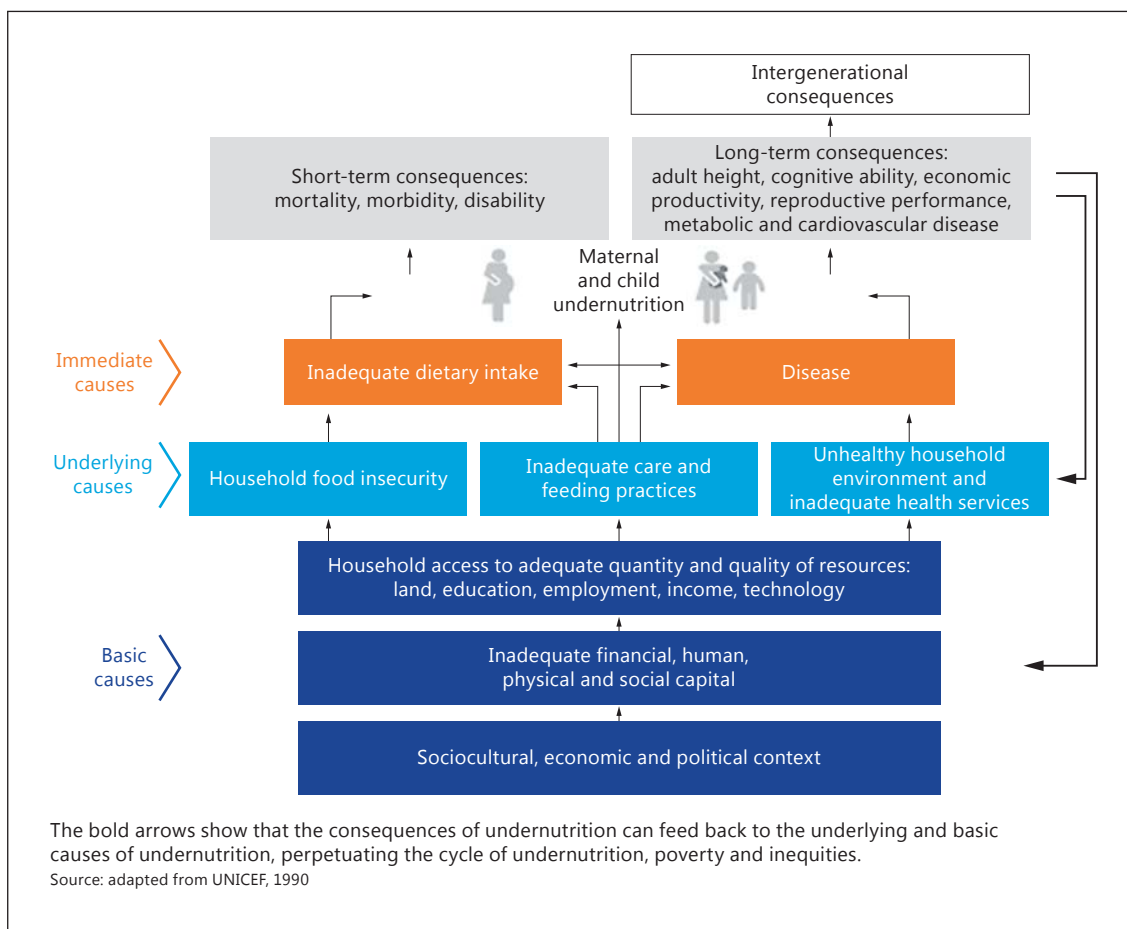
### Causes of Malnutrition

The UNICEF formulated a conceptual framework to identify the determinants or causes of malnutrition (fig. 1) [6]. In addition to these determinants, other factors such as unplanned ur-

banization, environmental degradation, time constraints of caregivers and the consumption of food contaminated with toxins (e.g. aflatoxin in food) should also be taken into consideration [7]. Poverty and food insecurity constrain the accessibility of nutritious diets that have a high protein quality, adequate micronutrient content and bioavailability, essential fatty acids, low antinutrient content and high nutrient density [8].

### Classification of Malnutrition

Based on anthropometric measurements, malnutrition can be classified as stunting, wasting and underweight. Height or length for age is useful for assessing stunting, which is the result of chronic malnutrition. Weight for height or length is used for assessing wasting, which is the result of acute malnutrition. Weight for age measures underweight, indicating the combined effect of acute and chronic malnutrition (table 2).



**Fig. 1.** Framework of the relations between poverty, food insecurity and other underlying and immediate causes of maternal and child undernutrition and their short- and long-term consequences. From UNICEF [6].

## Management

Management of malnutrition depends on the type of malnutrition, identification of its cause, if applicable, and its severity.

In primary moderate acute malnutrition, management at home is recommended. This includes nutrition-specific interventions such as counseling of parents on the proper diet to be given to the child, with emphasis on continued breastfeeding and appropriate complementary feeding, micronutrient supplementation, period-

ic deworming, etc. Ideally, these children should receive 25 kcal/kg per day of energy in excess of what their healthy peers get, and their diets should contain animal-source foods which are rich in essential fatty acids and micronutrients including vitamin A, iron and zinc [9]. Stunting cannot be addressed by nutrition-specific interventions alone. For the control of stunting, nutrition-sensitive interventions should be scaled up at the national or regional level. These include ensuring household food security, safe water, proper sanitation and adequate hygiene, female edu-

**Table 2.** New terms recommended for childhood malnutrition

Moderate acute malnutrition (MAM)	Weight-for-height Z score <-2 but >-3
Severe acute malnutrition (SAM)	Mid-upper-arm circumference <115 mm Weight-for-height Z score <-3 Bilateral pitting edema Marasmic kwashiorkor
Global acute malnutrition (GAM)	The sum of the prevalence of SAM plus MAM at a population level

cation and empowerment, creating proper livelihoods, social protection schemes, etc. The effects of stunting on the developing brain may be irreversible after the age of 3–4 years. Efforts should therefore be taken to implement the nutrition interventions at an early age so that stunting and its negative effects on cognition are reversed. Growth monitoring and promotion programs should be implemented at the community level, where the nutritional status of infants and young children is assessed every 1–3 months and their growth is promoted through counseling of the parents.

Since SAM is associated with an almost 10-fold increase in risk of death, this condition requires special attention. Children with SAM and complications should be treated in a hospital until they are fit to continue management at home. Complications include severe diarrhea, dysentery, hypoglycemia, hypothermia, pneumonia, urinary tract infection, septic illness or any danger sign as per the Integrated Management of Childhood Illness guidelines [unable to drink or breastfeed, vomits everything, has had convulsions (>1 or prolonged for >15 min), lethargy or unconsciousness or currently convulsing]. The line of management for this stabilization phase of treatment of complications is as follows [10]:

- Treat hypoglycemia, which is common in these children, with oral or intravenous glucose if the child is lethargic, unconscious or convulsing
- Treat and prevent hypothermia by keeping the child warm
- Treat shock, if present, with oxygen therapy, intravenous fluids and glucose and broad-spectrum antibiotics
- Treat and prevent dehydration. The WHO oral rehydration solution (75 mmol sodium/l) contains too much sodium and too little potassium for severely malnourished children. They should be given the special rehydration solution for malnutrition (ReSoMal). It is difficult to estimate the dehydration status of a severely malnourished child. All children with watery diarrhea should be assumed to have dehydration and given the following: every 30 min for the first 2 h, ReSoMal at 5 ml/kg body weight orally or by nasogastric tube; then, in alternate hours for up to 10 h, ReSoMal at 5–10 ml/kg/h (the amount to be given should be determined by how much the child wants as well as by stool loss and vomiting). The liquid food, F-75, is given in alternate hours during this period until the child is rehydrated. If the diarrhea is severe, then WHO oral rehydration solution may be used, because the loss of sodium in stool is high and symptomatic hyponatremia can occur with ReSoMal. Severe diarrhea can be due to cholera or rotavirus infection and is usually defined as stool output >5 ml/kg/h
- Treat and prevent infection. If the child appears to have no complications, give oral amoxicillin at 15 mg/kg 8-hourly for 5 days.



If the child is sick looking or has complications, give ampicillin at 50 mg/kg i.m./i.v. 6-hourly for 2 days, then oral amoxicillin at 15 mg/kg 8-hourly for 5 days and gentamicin at 7.5 mg/kg i.m./i.v. once daily for 7 days. If the child fails to improve clinically by 48 h or deteriorates after 24 h, a third-generation cephalosporin (e.g. ceftriaxone at 50–75 mg/kg i.v. or i.m. once daily) may be started with gentamicin. Where specific infections are identified, add specific antimicrobials as appropriate

- Start careful feeding. During the stabilization phase, a cautious approach is required because of the child's fragile physiological state and reduced capacity to handle large feeds. Feeding should be started as soon as possible after admission with the WHO-recommended milk-based starter formula F-75, which contains 75 kcal/100 ml and 0.9 g protein/100 ml. The feeding frequency is gradually decreased (table 3). If the child is anorexic and oral intake does not reach 80 kcal/kg/day, give the remaining feed by a nasogastric tube
- Achieve catch-up growth, which starts when the energy intake is >150 kcal/kg/day. In settings where a program for the community-based management of SAM with ready-to-use therapeutic food (RUTF) is not available, F-100 is used. During the nutritional rehabilitation phase, feeding is gradually increased to achieve a rapid weight gain of >10 g/kg/day. The WHO recommends the milk-based diet for nutritional rehabilitation F-100, which contains 100 kcal and 2.9 g protein/100 ml. Modified porridges or family foods can be used, provided they have comparable energy and protein concentrations. Readiness to enter the nutritional rehabilitation phase is signaled by a return of appetite, usually about 1 week after admission. A gradual transition is recommended to avoid the risk of heart failure, which can occur if children suddenly consume huge amounts. In case of infants with SAM <6

**Table 3.** Feeding of children with SAM

Days	Frequency	Volume/kg per feed, ml	Volume/kg per day, ml
1 and 2	2-hourly	11	130
3–5	3-hourly	16	130
6 and 7	4-hourly	22	130

months old, feeding should be initiated with F-75. During the nutritional rehabilitation phase, F-75 can be continued, and, if possible, relactation should be done

### Community-Based Management of SAM

Children with SAM without any complications can be managed in the community with RUTF. Children who have been treated for complications can also be treated in the hospital with RUTF if they have appetite. In general, most children with SAM can be treated in the community. The requirements for a community-based program for SAM are: a cadre of trained health workers who can screen children for SAM, a referral mechanism for the stabilization of children with complications, a functional stabilization center with adequate staff, F-75, F-100, medicines and RUTF. RUTF has the nutrient composition of F-100 but is more energy dense and does not contain any water. Bacterial contamination, therefore, does not occur, and the food is safe for use also in home conditions. The prototype RUTF is made of peanut paste, milk powder, vegetable oil and a mineral and vitamin mix as per WHO recommendations. It is available as a paste in a sachet; thus, it does not require any cooking, and children can eat directly from the sachet. The production of RUTF from locally available food ingredients has recently commenced in some countries; such RUTF can make programs more cost-effective and sustainable.

## Management of Secondary Malnutrition

For the management of secondary malnutrition, it is crucial to identify the underlying disease by proper history taking, examination and suggestive laboratory investigations. Without treating the underlying cause, it is impossible to manage secondary malnutrition. Preterm and low-birth-weight infants are at risk of necrotizing enterocolitis if aggressive enteral feeding is done. Exclusive breastfeeding for the first 6 months along with iron supplementation is a safe way to ensure optimal nutrition for such infants.

In mild inflammatory bowel disease or disease in remission, encouraging the intake of a normal diet is important to prevent or treat malnutrition. Commercial, specially prepared liquid formulas are helpful for some patients with inflammatory bowel disease. Partial or total parenteral nutrition can be administered to patients who cannot tolerate enteral feeding.

Children with chronic liver disease (CLD) become malnourished due to vomiting, poor appetite, infection, gastroesophageal reflux and the compressive effects of ascites or hepatosplenomegaly. In advanced CLD, the diet may need to be protein sparing for the prevention hyperammonemia. A combination of lipids and carbohydrates with a minimal amount of protein should be used. Another important feature in CLD is decreased excretion of bile salts into the small intestine, which can cause malabsorption of fats and fat-soluble vitamins. This can be countered by using medium-chain triglycerides as the source of dietary fat, since they do not depend upon bile acids for absorption. Water-soluble forms of the usually fat-soluble vitamins (A, D, E and K) should be used when available.

More than one third of children with chronic renal disease suffer from impaired linear growth. This can be prevented by providing high-energy as well as high-quality protein in quantities that will not induce or aggravate uremia.

Children with congenital heart disease have reduced food intake due to fatigue, breathlessness and frequent lung infections. The heart failure and increased breathing efforts induce a hypermetabolic state that further increases the demand for more nutrients. The challenge is to provide sufficient energy and protein without increasing the fluid volume too much.

While TNF- $\alpha$  and tumor metabolites are responsible for the cachexia observed in children with cancer, chemotherapy, radiation, surgery and infections also substantially contribute to malnutrition in these children. The diet has to be modified to cater to the increased energy demands. Elemental diets sometimes have to be provided through nasogastric tubes. Total parenteral nutrition, if available, can be used to improve nutrition in children who cannot tolerate large amounts of food enterally.

The principles of management of severe malnutrition resulting from the underlying diseases mentioned above are similar to those for primary SAM. Nutritional support for a child with secondary malnutrition is as imperative as it is for a child with primary malnutrition [11].

## Prevention

Reducing malnutrition through prevention and treatment can reduce the incidence of infectious diseases, most commonly diarrhea and pneumonia. It is now imperative to scale up both nutrition-specific and nutrition-sensitive interventions in countries that are burdened with childhood malnutrition. Scaling up essential nutrition-specific interventions alone can reduce 15% of deaths among <5-year-old children, control 20% of stunting and reduce wasting by >60% [12]. To prevent malnutrition, care should be taken prior to conception. There is a narrow window of opportunity in utero when the fetus is increasing in length and weight maximally. Proper antenatal care along with iron-folic acid supplementation is required to



achieve the optimal in utero growth. National immunization programs, vitamin A supplementation campaigns, zinc as part of the treatment of diarrhea and periodic deworming programs have immense roles in preventing malnutrition.

## Conclusions

- Primary malnutrition is mainly a concern in developing countries, and the contributing factors are found to be food insecurity, pov-

erty, maternal malnutrition, malfeeding practice and environmental enteropathy

- Community-based screening and management should be emphasized in preventing and managing primary malnutrition
- Secondary malnutrition is more prevalent in developed countries and is difficult to treat without alleviation of the underlying causes
- Secondary malnutrition should be managed in a facility as an adjunct to the management of the underlying cause

## References

- 1 WHO: Malnutrition: the global picture. Geneva, WHO, 2000.
- 2 Ahmed T, Michaelsen KF, Frem JC, Tumvine J: Malnutrition: report of the FISPUGHAN Working Group. *J Pediatr Gastroenterol Nutr* 2012;55:626–631.
- 3 Prendergast AJ, Rukobo S, Chasekwa B, Mutasa K, Ntozini R, et al: Stunting is characterized by chronic inflammation in Zimbabwean infants. *PLoS One* 2014; 9:e86928.
- 4 Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, et al: Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013;382:427–451.
- 5 Fischer Walker CL, Lamberti L, Adair L, et al: Does childhood diarrhea influence cognition beyond the diarrhea-stunting pathway? *PLoS One* 2012;7:e47908.
- 6 UNICEF: Improving child nutrition. The achievable imperative for global progress. New York, UNICEF, 2013.
- 7 Jamison DT, Feachem RG, Makgoba MW, et al (eds): *Disease and Mortality in Sub-Saharan Africa*, ed 2. Washington, World Bank, 2006. <http://www.ncbi.nlm.nih.gov/books/NBK2279/>.
- 8 Liu L, Johnson HL, Cousens S, Perin J, Scott S, et al: Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012;379: 2151–2161.
- 9 WHO: Report of Second Nutrition Guidance Expert Advisory Group (NUGAG) meeting of the Subgroup of Nutrition in the Life Course and Undernutrition – Area Acute Malnutrition. WHO, Geneva, 2011.
- 10 WHO: Guideline: updates on the management of severe acute malnutrition in infants and children. Geneva, WHO, 2013.
- 11 Fuchs GJ: Secondary malnutrition in children; in Suskind RM, Lewinter-Suskind L (eds): *The Malnourished Child*. New York, Vevey/Raven, 1990.
- 12 Bhutta ZA, Das JK, Rizvi A, Gaffey MF, et al.; Lancet Nutrition Interventions Review Group; Maternal and Child Nutrition Study Group: Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *Lancet* 2013;382: 452–477.

## 3.2 Micronutrient Deficiencies in Children

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### Key Words

Chronic malnutrition · Micronutrient deficiency · Iron deficiency anemia · Developing world

### Key Messages

- Micronutrient insufficiency is associated with an increasing prevalence of stunting among children in developing countries
- Four micronutrients (vitamin A, zinc, iron and iodine) have been directly or indirectly associated with about 12% of deaths among <5-year-old children globally
- In resource-poor settings, along with iron deficiency anemia, low levels of other micronutrients (vitamin A, zinc, calcium, riboflavin and vitamin B<sub>12</sub>) can also contribute to anemia
- Vitamin A supplementation reduces all-cause mortality by 24% and diarrhea-related mortality by 28% in children aged 6–59 months
- Zinc supplementation in children aged 1–4 years is associated with approximately a 9–18% reduction in all-cause mortality
- In resource-poor settings, multiple micronutrient supplementation improves growth and motor development, reduces anemia and improves the zinc and vitamin A status of infants as well as preschool and school children

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### Introduction

Global undernutrition estimates suggest that approximately 178 million children worldwide are stunted, while 55 million are wasted. The majority lives in developing countries [1, 2]. Multiple micronutrient (MMN) deficiencies continue to account for a substantial number of maternal and child deaths, low birth weight, maternal and child undernutrition, wasting and stunting as well as delayed child development globally [3]. It is well established that about 12% of the global deaths of children <5 years of age can be attributed to deficiencies in five common micronutrients (vitamins A and D, iron, zinc and iodine) singly or in combination. Maternal micronutrient deficiencies are widespread and have major public health implications in developing countries [4, 5].

There has been considerable progress in global health. However, factors such as poor breastfeeding, poverty, food insecurity, inappropriate feeding practices for infants and young children, maternal micronutrient deficiencies, poor hygiene and sanitation as well as a high burden of pneumonia and gastroenteritis with tropical enteropathy in children continue to contribute to child undernutrition in developing countries [1, 2]. Despite efforts to combat and reduce the factors mentioned above, there is very little progress.

**Table 1.** Global deaths attributed to micronutrient deficiencies as well as disability-adjusted life years (DALYs) of children <5 years of age [23]

	Deaths	% of deaths in children <5 years	Disease burden, 1,000 DALYs	% of DALYs in children <5 years
Vitamin A deficiency	667,771	6.5	22,668	5.3
Zinc deficiency	453,207	4.4	16,342	3.8
Iron deficiency	20,854	0.2	2,156	0.5
Iodine deficiency	3,619	0.03	2,614	0.6

### Global Micronutrient Deficiencies: Perspective of Developing Countries

Women of child-bearing age, infants and children are at high risk of micronutrient deficiencies or malnutrition in developing countries. Four micronutrients (vitamin A, zinc, iron and iodine) have been directly or indirectly associated with about 12% of deaths among <5-year-old children globally [1, 2]. Other manifestations associated with micronutrient deficiencies (i.e., iron and zinc) not only affect birth weight and lead to birth defects but also impact child growth as well as later cognitive and reproductive performance. Vitamin A deficiency (VAD) is associated with xerophthalmia, corneal xerosis, ulceration and keratomalacia, and vitamin D deficiency leads to rickets and osteomalacia. Micronutrient deficiencies directly and/or indirectly affect learning and adult productivity, thus impacting economic growth in terms of premature deaths and loss of healthy lives as expressed in disability-adjusted life years (table 1).

A need to strengthen our efforts and sharpen our focus, concentrating efforts on the crucial period of pregnancy and the first 2 years of life – the 1,000 days from conception to a child's second birthday – has gained wide acceptance. This is the time period in which good nutrition and healthy growth not only can have lasting benefits for individuals but also may be important for the economic productivity of a society [1].

### Iron and Anemia

Iron deficiency anemia (IDA) is the most prevalent form of nutritional anemia. It accounts for approximately half of the global anemia cases and poses an increased risk of maternal and child mortality [2, 6]. Multiple risk factors including poor dietary intake of iron, high intake of fibers from cereal and legumes, low birth weight, infections and poverty contribute to IDA. A Cochrane review of daily iron supplementation to women during pregnancy reported a 19% reduction in the incidence of low birth weight [7, 8].

The cognition of children aged  $\geq 5$  years with IDA generally benefited from iron supplementation, but studies of children <3 years of age have had mostly negative findings, except for delayed brain maturation [1, 9, 10]. The role of iron supplementation on mental development has been questioned in the past. Black et al. [1] reviewed 7 double-blind randomized controlled trials of iron supplementation lasting  $\geq 8$  weeks to children <4 years of age. Five trials showed benefits in motor development, 1 showed a benefit in language; however, there is no convincing evidence that iron treatment had an effect on mental development in children <27 months of age [8].

It is also important to note that in resource-poor settings, low levels of other micronutrients (vitamin A, zinc, calcium, riboflavin and vitamin

B<sub>12</sub>) can also contribute to anemia. Thus, supplementing only with iron may not be effective in correcting nutritional anemia. Therefore, MMN supplementation in poverty settings may better address the issue of anemia [5, 11].

### **Vitamin A Deficiency**

An estimated 0.9% or 5.2 million of the world's preschool-age population suffers from night blindness, and approximately 90 million have subclinical VAD. The prevalence is higher in Africa than elsewhere [1]. Clinical assessment of eye symptoms (night blindness and xerophthalmia) and biochemical assessment of serum retinol are the two commonest methods for the estimation of VAD prevalence in communities [1, 2]. VAD is most common during childhood. The reasons are multiple; they include widespread maternal undernutrition, poor dietary quality and losses during diarrhea [12, 13]. A Cochrane review of 43 randomized trials showed that vitamin A supplementation reduced all-cause mortality by 24% and diarrhea-related mortality by 28% in children aged 6–59 months [14]. The corresponding Cochrane review on vitamin A supplementation to neonates showed a 14% reduction in the risk of infant death at 6 months in neonates supplemented with vitamin A compared to controls [15]. The prevalence of VAD has declined over time because of large-scale vitamin A supplementation programs in many developing countries.

### **Zinc Deficiency**

More than half of the populations of developing countries are at an increased risk of low dietary zinc intake [16]. Zinc is a key micronutrient and essential for normal functioning of the body. The biological functions affected by a zinc deficit include protein synthesis, cell replication and nu-

cleic acid metabolism [1, 16, 17]. Preventive zinc supplementation is associated with a reduction in morbidity from childhood diarrhea and decreases the severity of lower respiratory infection; it may also contribute to an improved linear growth and weight gain in infants and young children in populations where diarrhea is prevalent and the risk of zinc deficiency is higher [18, 19].

A systematic review showed that zinc supplementation resulted in a 9% reduction (RR 0.91, 95% CI 0.82–1.01) in all-cause child mortality [20]. Another analysis showed a significant 18% reduction (RR 0.82, 95% CI 0.70–0.96) in all-cause mortality in children aged 1–4 years [19]. However, there is no convincing evidence that zinc supplementation to infants and children results in improved motor or mental development [8, 21].

### **Iodine Deficiency**

Global estimates suggest that approximately 1.9 billion individuals are iodine deficient [1, 22]. A large part only suffers from a mild deficiency, but even a subclinical maternal iodine deficiency is associated with impaired motor and mental development in the fetus and increases the risk of miscarriage and fetal growth faltering [2, 23]. It also causes cretinism if the deficiency is severe. The full extent of mild or moderate iodine deficiency on infant brain development is not fully established. Iodine fortification is a cost-effective way of reducing the prevalence of iodine deficiency worldwide.

### **Provision of MMN rather than Two or Fewer Micronutrients to Micronutrient-Deficient Children**

Deficiencies in MMN usually co-occur in developing country settings and are generally associated with poor-quality diets. Most national sup-

plementation programs commonly focus on 1 or 2 micronutrients at a time. Previously, research has been even more reductionist, focusing on a single micronutrient; however, in the last decade, the effect of MMN interventions on the health and development of infants and children has been promoted. A Cochrane review assessed 23 trials of MMN supplementation and reported an 11–13% reduction in low-birth-weight and small-for-gestational-age infants without any impact on anemia and IDA [8, 24]. A meta-analysis comparing MMN interventions for children from HIV/AIDS-affected populations [25] resulted in small but significantly greater improvements in length (or height) and weight as well as hemoglobin levels and motor development in these children. MMN induced a significant reduction in the prevalence of respiratory infections (26%), diarrhea (11–18%) and fever (7%). However, to date, their role in reducing child mortality is not well established [25–27]. In conclusion, providing MMN, compared to 0–2 micronutrients at a time, reduces anemia and improves growth and motor development among young children [25].

### **Provision of MMN during Pregnancy and Fetal Outcome**

MMN during pregnancy result in a significant reduction in the incidence of low-birth-weight (pooled RR 0.86, 95% CI 0.81–0.91) and small-for-gestational-age infants (pooled RR 0.83, 95% CI 0.73–0.95) and an increase in mean birth weight (mean difference 52.6 g, 95% CI 43.2–62). However, there was no significant difference in the overall risk of preterm birth, stillbirth and maternal or neonatal mortality in mothers who had received a lower amount of micronutrients [11].

### **Interventions to Combat Micronutrient Deficiencies in Children**

Dietary or micronutrient supplementation interventions in micronutrient-deficient populations are supported by the best evidence, as recently reported by Bhutta et al. [8]. Breastfeeding promotion is not only associated with decreased morbidity but also with a 44–45% reduction in all-cause and infection-related neonatal mortality [1, 8]. Vitamin A supplementation to young children has shown promising results, namely a reduction of 24% in all-cause mortality, as published in a recent Cochrane review [14]. In a systemic review, iron supplementation also showed marked decrease in anemia and some improvement in cognitive development in young children [8, 28]. Preventive zinc supplementation has been associated with a reduction in the prevalence of diarrhea and pneumonia in young children but has no significant effect on mortality [21].

### **Conclusion**

- Four micronutrients (vitamin A, zinc, iron and iodine) are essential for child development
- Their sufficiency helps in improving linear growth and motor development, along with reducing anemia and the functional status of infants as well as preschool and school children

### **References**

- 1 Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al: Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013;382:427–451.
- 2 Ahmed T, Hossain M, Sanin KI: Global burden of maternal and child undernutrition and micronutrient deficiencies. *Ann Nutr Metab* 2012;61(suppl 1):8–17.

- 3 Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, et al: What works? Interventions for maternal and child undernutrition and survival. *Lancet* 2008;371:417–440.
- 4 Bhutta ZA, Rizvi A, Raza F, Hotwani S, Zaidi S, Moazzam Hossain S, et al: A comparative evaluation of multiple micronutrient and iron-folic acid supplementation during pregnancy in Pakistan: impact on pregnancy outcomes. *Food Nutr Bull* 2009;30(4 suppl):S496–S505.
- 5 Bhutta ZA, Haider BA: Maternal micronutrient deficiencies in developing countries. *Lancet* 2008;371:186–187.
- 6 WHO: Guideline: use of multiple micronutrient powders for home fortification of foods consumed by infants and children 6–23 months of age. Geneva, WHO, 2011.
- 7 Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE: Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 12;12:CD004736.
- 8 Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, et al: Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *Lancet* 2013; 382:452–477.
- 9 Szajewska H, Ruszczyński M, Chmielewska A: Effects of iron supplementation in nonanemic pregnant women, infants, and young children on the mental performance and psychomotor development of children: a systematic review of randomized controlled trials. *Am J Clin Nutr* 2010;91:1684–1690.
- 10 Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, Huffman SL, et al: Inequality in early childhood: risk and protective factors for early child development. *Lancet* 2011;378:1325–1338.
- 11 Ramakrishnan U, Grant FK, Goldenberg T, Bui V, Imdad A, Bhutta ZA: Effect of multiple micronutrient supplementation on pregnancy and infant outcomes: a systematic review. *Paediatr Perinat Epidemiol* 2012;26(suppl 1):153–167.
- 12 Bhutta ZA: Effect of infections and environmental factors on growth and nutritional status in developing countries. *J Pediatr Gastroenterol Nutr* 2006; 43(suppl 3):S13–S21.
- 13 Mayo-Wilson E, Imdad A, Herzer K, Yakoob MY, Bhutta ZA: Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis. *BMJ* 2011;343:d5094.
- 14 Imdad A, Herzer K, Mayo-Wilson E, Yakoob MY, Bhutta ZA: Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age. *Cochrane Database Syst Rev* 2010;12:CD008524.
- 15 Haider BA, Bhutta ZA: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries. *Cochrane Database Syst Rev* 2011;10:CD006980.
- 16 Akhtar S: Zinc status in South Asian populations – an update. *J Health Popul Nutr* 2013;31:139–149.
- 17 Brown KH, Rivera JA, Bhutta Z, Gibson RS, King JC, Lonnerdal B, et al: International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. *Food Nutr Bull* 2004;25(1 suppl 2): S99–S203.
- 18 Imdad A, Bhutta ZA: Effect of preventive zinc supplementation on linear growth in children under 5 years of age in developing countries: a meta-analysis of studies for input to the lives saved tool. *BMC Public Health* 2011; 11(suppl 3):S22.
- 19 Brown KH, Pearson JM, Baker SK, Hess SY: Preventive zinc supplementation among infants, preschoolers, and older prepubertal children. *Food Nutr Bull* 2009;30(1 suppl):S12–S40.
- 20 Yakoob MY, Theodoratou E, Jabeen A, Imdad A, Eisele TP, Ferguson J, et al: Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria. *BMC Public Health* 2011;11(suppl 3):S23.
- 21 Gogia S, Sachdev HS: Zinc supplementation for mental and motor development in children. *Cochrane Database Syst Rev* 2012;12:CD007991.
- 22 Andersson M, Karumbunathan V, Zimmermann MB: Global iodine status in 2011 and trends over the past decade. *J Nutr* 2012;142:744–750.
- 23 Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, et al: Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008;371:243–260.
- 24 Haider BA, Bhutta ZA: Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2012;11:CD004905.
- 25 Allen LH, Pearson JM, Olney DK: Provision of multiple rather than two or fewer micronutrients more effectively improves growth and other outcomes in micronutrient-deficient children and adults. *J Nutr* 2009;139:1022–1030.
- 26 Sazawal S, Dhingra U, Dhingra P, Hiremath G, Kumar J, Sarkar A, et al: Effects of fortified milk on morbidity in young children in north India: community based, randomised, double masked placebo controlled trial. *BMJ* 2007;334:140.
- 27 Sharieff W, Bhutta Z, Schauer C, Tomlinson G, Zlotkin S: Micronutrients (including zinc) reduce diarrhoea in children: the Pakistan Sprinkles Diarrhoea Study. *Arch Dis Child* 2006;91:573–579.
- 28 De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T: Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. *Cochrane Database Syst Rev* 2011;12:CD009085.

## 3.3 Enteral Nutritional Support

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### Key Words

Enteral nutrition · Indications · Formulations · Administration · Tube feeding

### Key Messages

- Enteral nutrition (EN) should be provided to a patient with a functioning gut whose energy and nutrient requirements cannot be met by regular food intake via the normal oral route
- A standard age-appropriate isocaloric (1 kcal/1 ml) and iso-osmolar (300–350 mOsm/kg) polymeric enteral formula is adequate and cost-effective for the majority of patients
- The stomach is the preferred delivery site, due to better tolerance and fewer complications. When long-term tube feeding (>6–12 weeks) is anticipated, endoscopic stoma placement is the preferred method
- Close monitoring and strict adherence to established protocols are important as different complications may occur
- EN can be stopped when oral intake satisfies nutritional requirements and growth continues to be age appropriate

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### Introduction

Enteral nutrition (EN) is defined as oral feeding using special formulae, or delivery of food beyond the esophagus via a feeding tube/stoma. In gen-

eral, it should be provided to a child with a sufficient level of gastrointestinal function preserved but who is unable to meet energy and nutrient requirements by regular food intake via the normal oral route. It is also indicated whenever a liquid diet is used for the treatment of a disease and when the feeding time is excessively prolonged (>4–6 h/day) [1]. Suggested criteria for nutritional support are presented in table 1 [1, 2], and specific clinical indications are listed in table 2. When compared with parenteral feeding, EN has numerous advantages, such as preservation of gastrointestinal function, lower costs, better manageability and increased safety. However, in some clinical settings such as intensive care units, reliance on EN alone may result in severe underfeeding despite a functional gut, mostly due to fluid restriction, diagnostic procedures and inadequate prescription and/or delivery [3]. In those patients a combination of enteral and parenteral nutrition is recommended [1]. There are only few absolute contraindications to EN, such as necrotizing enterocolitis, intestinal perforation, gastrointestinal obstruction and major intra-abdominal sepsis.

When the clinical condition of a patient is stable, home EN should be considered. Although a dedicated team approach is required whenever EN is provided [4], its role is particularly important in teaching parents and children techniques required before being discharged, such as naso-

**Table 1.** Suggested criteria for EN support for children with sufficiently preserved gut function [1, 2]

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Insufficient oral intake
Inability to meet 60–80% of individual requirements for >10 days
Total time of feeding a disabled child of >4–6 h/day
Wasting and stunting
Inadequate growth or weight gain for >1 month below the age of 2 years
Weight loss/no weight gain for >3 months above the age of 2 years
Change in weight-for-age or weight-for-height over 2 growth channels
Triceps skinfolds consistently at <5th percentile for age
Treatment of disease
Metabolic diseases (galactosemia, primary lactose intolerance, etc.)
Food allergy in infants (cow's milk protein allergy, multiple food allergy, etc.)
Crohn's disease

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**Table 2.** Clinical indications for pediatric EN

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1	Inadequate oral intake
	Disorders of sucking and swallowing: prematurity, cleft lip and palate, neuromuscular impairment (e.g. cerebral palsy, myopathies)
	Congenital abnormalities of the upper gastrointestinal tract: tracheoesophageal fistula
	Tumors of oral cavity, head and neck cancer
	Trauma and extensive facial burns
	Critical illness: coma, mechanical ventilation
	Severe gastroesophageal reflux
	Psychiatric disorders: food aversion, anorexia, depression
2	Disorders of digestion and absorption
	Cystic fibrosis
	Short bowel syndrome
	Inflammatory bowel disease
	Malabsorption syndrome due to food intolerances and allergy
	Enteritis due to chronic infection ( <i>Giardia lamblia</i> , protozoa, etc.)
	Protracted diarrhea in infancy
	Pancreatic insufficiencies
	Severe primary or acquired immunodeficiency
	Chronic liver disease
	Graft-versus-host disease
	Intestinal fistulae
	Disorders of gastrointestinal motility with pseudo-obstruction
3	Increased nutritional requirements and losses
	Cystic fibrosis
	Chronic solid organ diseases: renal, heart, liver, lungs
	Multiple trauma, extensive burns
4	Growth failure or chronic malnutrition (in addition to the above)
	Nonorganic failure
	Food deprivation
5	Altered metabolism and metabolic inborn errors
6	Primary disease management (e.g. Crohn's disease)

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**Table 3.** Comparison of different enteral formulae for children and adults

	Polymeric formulae	Oligomeric formulae	Monomeric formulae
Protein content, g/l	30–80	20–50	19.5–25
Nitrogen source	polypeptides	small peptides	amino acids
Carbohydrate content, g/l	90–200	100–200	81–146
Fat content, g/l	20–90	5–20	35
Caloric density, kcal/ml	1–2	0.67–1.7	0.67–1
Osmolarity, mOsm/l	300	300–500	300–600
Advantages	palatable, cheap	hypoallergenic, easily absorbed	nonallergenic
Disadvantages	requires intact gut, allergenic	bitter taste, expensive	hyperosmolar, expensive

gastric (NG) tube placement and maintenance, sterile feed preparation and administration, enteral pump management, as well as prevention, recognition and management of the most common complications.

Transition to normal oral feed needs to be gradual, and EN can be stopped when oral intake satisfies caloric and nutrient requirements while growth continues to be age appropriate.

### Enteral Formula Properties and Selection Criteria

Enteral formulae should supply a balanced intake of energy and nutrients to support age-appropriate growth and development. The content of all essential nutrients should provide at least 100% of the reference intake for healthy individuals of the relevant age group. Standard (polymeric) pediatric enteral formulae are recommended as the adequate and cost-effective form of EN for the majority of patients [1]; this implies an energy density of 1 kcal/ml (or 0.67 kcal/ml for infants), iso-osmolality (300–350 mOsm/kg), whole proteins as a nitrogen source, and a nutrient content adapted to the requirements of children under the age of 10 years. In addition, it is generally lactose and gluten free. More concentrated enteral for-

mulae are also available (1.3–2.0 kcal/ml) for patients with increased energy requirements or limited fluid intake. Since recently, standard formulations also contain nondigestible carbohydrates (fibers), which have benefits in reducing gastrointestinal side effects such as diarrhea and constipation [5]. If pediatric formulae are not available, an adult formulation can be used only after the age of 8–10 years [1]. In polymeric formulae, macronutrients are provided in an intact form. If proteins are hydrolyzed to an extent that can be tolerated by at least 90% of patients with verified allergy to the nitrogen source, the formula is called ‘semi-elemental’ or ‘oligomeric’ [6]. Monomeric/elemental formulae are nutritionally complete solutions containing amino acids, carbohydrates and fats, often as a mixture of long- and medium-chain triglycerides. A comparison of different formulae is presented in table 3.

In contrast to standard EN formulae there are disease-specific formulations which were first developed for infants and children with intolerances such as food allergy or inborn errors of metabolism and who required elimination of one or more food components. The next step entailed different modifications aiming to be beneficial against specific disorders. Examples are formulae with a high fat content, which may be of value to patients with insulin resistance and to hypercapnic patients

with pulmonary disease due to lower CO<sub>2</sub> production, formulae with reduced protein content for patients with renal disease, or formulae with a specific amino acid profile that may benefit patients with hepatic encephalopathy. The most recent research topics in enteral formula design are contents of anti-inflammatory cytokines (transforming growth factor- $\beta$ ) or nutrients (e.g. glutamine, arginine and n-3 fatty acids), which, if provided in high doses, may exert immune-regulating effects. However, for all of these there are very few controlled studies of sufficient quality on pediatric patients and, therefore, claims of beneficial effects should be evaluated critically [7].

In formula selection, the following should be considered: (a) nutrients and energy requirements adjusted for age and clinical condition of the patient; (b) history of food intolerances or allergy; (c) level of intestinal function; (d) site and route of formula delivery; (e) formula characteristics such as osmolality, viscosity and nutrient density; (f) taste preference; and (g) cost.

## Administration of EN

### *Sites of Delivery*

EN can be administered either into the stomach or into the proximal small intestine. Among the two sites, intragastric feeding is associated with a more flexible feeding schedule, antimicrobial properties, larger volume and higher osmotic tolerance, and lower frequency of diarrhea and of dumping syndrome because (a) of stimulation of normal digestive and hormonal responses, (b) of a preserved acid barrier, (c) tubes are more easily placed, and (d) the stomach serves as a reservoir gradually releasing nutrients. Postpyloric access is reserved for clinical conditions in which tracheal aspiration, gastroparesis and gastric outlet obstruction preclude gastric feeding. However, results of studies comparing both sites are conflicting, often not showing benefits either in adults or in children [8, 9].

### *Routes of Delivery*

If the expected duration of EN is short (<6–12 weeks), it is preferentially delivered by NG or nasoenteric tube, but if the expected duration is longer, a feeding gastrojejunostomy is recommended, placed by endoscopy, which is the quickest and cheapest procedure with only a low rate of complications [10, 11].

Among different tubes, those made of PVC are the least desirable, because of the potential release of toxic phthalate esters into the lipid-containing feeds – and if left in place for >4 to 6 days, they may become rigid and cause lesions of the upper gastrointestinal tract. Silicon and polyurethane tubes are more convenient and can be safely kept in place for several weeks. Considering the required length of the tube, it equals the distance from the nose over the ear lobe to the xiphoid in children, and from the nose over the ear lobe to the mid-umbilicus in neonates. Placement into the stomach is confirmed by measuring the pH of the aspirate, which should be <4 in children and  $\leq 5$  in neonates. Radiologic confirmation must be obtained if (a) the pH is >5, (b) an aspirate cannot be obtained, or (c) the patient's condition changes during NG tube insertion, with prolonged coughing, restlessness and discomfort or hoarseness [8, 12, 13].

### *Modes to Deliver EN*

EN delivery modes are intermittent, continuous or combined. Intermittent/bolus delivery is physiological, provides a cyclical hormone surge and regular gallbladder emptying, and, if delivered orally, supports the development of age-appropriate feeding habits and oromotor skills. Continuous formula infusion is often recommended for malnourished children with severe chronic diarrhea and intestinal failure because reduced surface and transport proteins can be more efficiently used and the osmotic load is better tolerated [1, 14]. An appropriate and constant flow is ensured by the use of a peristaltic enteral pump. When the child can eat, both methods of feed delivery can

**Table 4.** Enteral feeding complications as well as preventive and therapeutic measures [1]

Complications	Prevention and treatment
Gastrointestinal Diarrhea, nausea, vomiting, bloating, abdominal distension	Formula selection Polymeric vs. predigested Disease specific
Technical Occlusion, migration	Feeding techniques Bolus vs. continuous Gradual initiation of EN
Metabolic Fluid, glucose and electrolyte imbalance	EN administration
Infective Gastroenteritis, septicemia	Delivery site (stomach vs. jejunum) Delivery route (tube vs. stoma)
Psychological Oral aversion, altered body self-image	Monitoring Growth (weight, height/length, skinfolds) Hematology, biochemistry Multidisciplinary team approach Protocol application and quality control
	Others Tube selection (PVC vs. silicon), maintenance

be combined, with tube feeding overnight for 10–12 h and oral intake during the day.

#### *Initiation of EN*

Initiation of EN should be gradual, depending on: (a) age; (b) clinical condition and gut status; (c) formula choice (polymeric vs. elemental); and (d) route of delivery (stomach vs. jejunum). A slow, stepwise increase in volume and concentration is particularly important for patients with grossly impaired intestinal function and when the feed is delivered postpylorically.

#### **Monitoring and Complications**

Patients receiving EN should be monitored regularly for growth, fluid, energy and nutrient intake, therapeutic efficacy, and hematologic and biochemical changes.

Possible complications and preventive measures are listed in table 4 [1]. Their occurrence can be minimized by: (a) avoidance of drip feed-

ing and of blenderized feeds; (b) using silicon and polyurethane NG tubes; (c) gradual initiation and stepwise increase in volume and concentration; (d) regular monitoring of residual gastric volumes; (e) strict adherence to management protocols, particularly with respect to bacteriological safety; and (f) close supervision by a dedicated multidisciplinary team [1, 4, 15].

Despite the broad range of potential complications, EN is a well-established, safe and effective method of improving a patient's clinical condition, nutritional status and growth, particularly if procedural protocols are followed and regular quality control is applied [1].

#### **Areas for Future Developments and Research**

- Defining the criteria for initiation of EN support more precisely
- The suitability and benefits of disease-specific formulations should be evaluated in pediatric patients by controlled clinical studies

- Determination of the role of transpyloric feeding, and establishment of a practical and safe bedside method of checking the position of the feeding tube tip
- Identifying risk factors for complications, and developing protocols that minimize them, particularly with respect to bacterial contamination
- EN should be provided when oral feeds cannot sustain normal growth in a child with reasonably preserved gastrointestinal function
- Selection of an enteral formula depends on the patient's age and clinical condition, but for the majority of patients, a standard age-adapted polymeric formula is the appropriate choice, with the best cost-benefit ratio

## Conclusions

- EN is a safe and effective method of nutritional therapy
- Technical, metabolic, gastrointestinal, infective and psychological complications may occur; close monitoring by a multidisciplinary team, application of procedural protocols and regular quality control are therefore required

## References

- 1 Braegger C, Decsi T, Dias JA, Hartmann C, Kolaček S, et al: Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2010; 51:110–122.
- 2 Axelrod D, Kazmerski K, Iyer K: Pediatric enteral nutrition. *JPEN J Parenter Enteral Nutr* 2006;30(suppl):S21–S26.
- 3 Mehta NM, Bechard LJ, Cahill N, et al: Nutritional practices and their relationship to clinical outcomes in critically ill children: an international cohort study. *Crit Care Med* 2012;40:2204–2011.
- 4 Agostoni C, Axelson I, Colomb V, Goulet O, Koletzko B, Michaelsen KF, Puntis J, Rigo J, Shamir R, Szajewska H, Turck D: The need for nutrition support teams in pediatric units: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2005;41: 8–11.
- 5 Elia M, Engfer MB, Green CJ, Silk DB: Systematic review and meta-analysis: the clinical and physiological effects of fibre-containing enteral formulae. *Aliment Pharmacol Ther* 2008;27:120–145.
- 6 American Academy of Pediatrics Committee on Nutrition: Hypoallergenic infant formulas. *Pediatrics* 2000;106: 346–349.
- 7 Koletzko S: Progress of enteral feeding practice over time: moving from energy supply to patient and disease-adapted formulations; in Koletzko B, Koletzko S, Rummelle F (eds): *Drivers in Innovation in Pediatric Nutrition*. Nestle Nutr Inst Workshop Ser Pediatr Program. Basel, Karger, 2010, vol 66, pp 41–54.
- 8 Kolaček S: Enteral nutrition; in Szajewska H, Shamir R (eds): *Evidence-Based Approaches in Human Nutrition*. World Rev Nutr Diet. Basel, Karger, 2013, vol 108, pp 86–90.
- 9 Rosen R, Hart K, Warlaumont M: Incidence of gastroesophageal reflux during transpyloric feeds. *J Pediatr Gastroenterol Nutr* 2011;52:532–535.
- 10 ASGE Standards of Practice Committee, Jain R, Maple JT, Anderson MA, Appalaneni V, Ben-Menachem T, Decker GA, Fanelli RD, Fisher L, Fukami N, Ikenberry SO, Jue T, Khan K, Krinsky ML, Malpas P, Sharaf RN, Dominitz JA: The role of endoscopy in enteral feeding. *Gastrointest Endosc* 2011;74:7–12.
- 11 SENPE's Standardization Group, Pedrón Giner C, Martínez-Costa C, Navas-López VM, et al: Consensus on paediatric enteral nutrition access: a document approved by SENPE/SEGHNP/ANECIPN/SECP (in English/Spanish). *Nutr Hosp* 2011;26:1–15.
- 12 Koletzko B, Goulet O: Nutritional support to infants, children and adolescents; in Sobotka L (ed): *Basics in Clinical Nutrition*, ed 4. Prague, Galen, 2011, pp 625–653.
- 13 Gilbertson HR, Rogers EJ, Ukoumunne OC: Determination of practical pH cut-off level for reliable confirmation of nasogastric tube placement. *JPEN J Parenter Enteral Nutr* 2011;35:540–544.
- 14 Olieman JF, Penning C, Ijsselstijn H, et al: Enteral nutrition in children with short-bowel syndrome: current evidence and recommendations for the clinician. *J Am Diet Assoc* 2010;110:420–426.
- 15 Bankhead R, Boullata J, Brantley C, Corkins M, et al; ASPEN Board of Directors: Enteral nutrition practice recommendations. *JPEN J Parenter Enteral Nutr* 2009;33:122–167.

## 3.4 Parenteral Nutritional Support

Berthold Koletzko

### Key Words

Parenteral feeding · Intravenous alimentation · Substrate requirements, parenteral · Infant · Child

### Key Messages

- Parenteral nutrition (PN) is indicated when adequate nutrition cannot be provided orally or enterally
  - PN is not indicated in patients with adequate small intestinal function who can be enterally (tube) fed
  - Ordering and monitoring of PN should follow agreed algorithms to improve the quality of care
  - Patients receiving PN should be evaluated 2–3 times/week (e.g. clinical examination, weight, anthropometry, laboratory values and dietary intake as appropriate)
  - The available evidence-based guidelines on paediatric PN should guide practice, including the dosage of substrate supply
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### Introduction

Parenteral nutrition (PN) is generally indicated when adequate nutrition cannot be provided orally or enterally, to prevent or correct malnutrition, and to sustain appropriate growth. It should be avoided whenever possible by use of adequate care, specialized enteral nutrition (EN) and artifi-

cial feeding devices as appropriate, because PN is more costly and carries higher risks than oral nutrition or EN. PN is not indicated in patients with adequate small intestinal function in whom oral tube or gastrostomy feeding can be used. The time when PN should be initiated depends both on individual circumstances and the patient's age and size. In small preterm infants, starvation for just 1 day may be detrimental, and PN must be instituted shortly after birth if it is obvious that adequate amounts of EN will not be tolerated soon. In older children and in adolescence, longer periods of inadequate nutrition (up to 7 days) may be tolerated, depending on the age, nutritional status and disease of the patient as well as on the type of intervention (surgery or medical). Whenever possible, PN should be combined with some (at least minimal) EN. Establishing a multidisciplinary paediatric nutrition support team for the supervision of PN can improve the quality of care and save costs; hence, it is highly recommended [1]. Ordering and monitoring PN should follow agreed algorithms to improve the quality of care. Patients receiving PN should be evaluated 2–3 times/week (e.g. clinical examination, weight, anthropometry, laboratory values and dietary intake as appropriate). The recommendations provided here are based on the recent evidence-based guidelines for paediatric PN [2, 3].

The recommendations on parenteral substrate supply to stable patients are summarized in table 1. In individual patients, other dosages may be required, depending on the patients' condition.

## Water

Fluid needs vary markedly and must be adapted to the individual patient's condition. For example, some renal or cardiac disorders require lower water intakes, whereas higher intakes are needed with enhanced fluid losses (e.g. due to fever, hyperventilation or diarrhoea, or from wounds or fistulae). Monitoring of the fluid status is necessary, considering the patient's clinical status, body weight and possibly water intake and excretion, blood electrolytes, acid base status, haematocrit, urine-specific gravity and urine electrolytes. The postnatal fluid supply should be gradually increased (table 2).

## Energy

Energy needs vary with physical activity, growth and the possible need to correct malnutrition. The energy supply can be adjusted based on formulae for energy expenditure (see Chapter 1.3.2) and during weight changes. Low energy supplies induce failure to thrive, but excessive energy intake ('hyperalimentation') must also be avoided because it may induce metabolic imbalances, liver damage and a serious refeeding syndrome particularly in severely malnourished patients [4].

## Amino Acids

Parenteral amino acid requirements are lower than enteral needs because PN bypasses intestinal amino acid uptake and utilization. Amino acid

**Table 1.** Recommended dosages for parenteral substrate supply to stable patients by age

Age group	Water, ml/kg	Energy, kcal/kg	Amino acids, g/kg	Glucose, g/kg	Lipids, g triglycerides/kg	Sodium, mmol/kg	Potassium, mmol/kg	Calcium, mmol/kg	Phosphorus, mmol/kg	Magnesium, mmol/kg
Preterm	140–160	110–120	1.5–4	18	up to 3–4	3–5 (–7)	2–5			
Neonate (1st month)	140–160	90–100	1.5–3	18	up to 3–4	2–3	1.5–3			
0–1 years	120–150 (max. 180)	90–100	1–2.5	16–18	up to 3–4	2–3	1–3	0–6 months: 0.8 7–12 months: 0.5	0.5	0.2
1–2 years	80–120 (max. 150)	75–90	1–2	1–3	up to 2–3	1–3	1–3	0.2	0.2	0.1
3–6 years	80–100	75–90	1–2	1–3	up to 2–3	1–3	1–3	0.2	0.2	0.1
7–12 years	60–80	60–75	1–2	1–3	up to 2–3	1–3	1–3	0.2	0.2	0.1
13–18 years	50–70	30–60	1–2	1–3	up to 2–3	1–3	1–3	0.2	0.2	0.1

Depending on the condition of the individual patient, different dosages may be required. Adapted from Koletzko et al. [3]. K<sup>+</sup> supplementation should usually start after onset of diuresis. Chloride supply usually equals the sum of sodium and potassium supply.



**Table 2.** Recommended standard parenteral fluid supply (in ml)

	Time after birth					
	1 day	2 days	3 days	4 days	5 days	6 days
Term neonate	60–120	80–120	100–130	120–150	140–160	140–180
Preterm neonate						
>1,500 g	60–80	80–100	100–120	120–150	140–160	140–160
<1,500 g	80–90	100–110	120–130	130–150	140–160	160–180

In neonates, parenteral fluid supply should be gradually increased over the first days of life. Adapted from Koletzko et al. [3].

utilization requires an energy supply of ~30–40 kcal/g of amino acid to prevent excessive amino acid oxidation. In very-low-birth-weight infants (VLBWI) requiring PN, amino acid supply should start on the first day of life with a dose of  $\geq 2$  g/kg per day [5]. Infants and young children should receive paediatric amino acid solutions with adequate amounts of cysteine, taurine and tyrosine (conditionally essential amino acids; see Chapter 1.3.3).

## Glucose

Glucose is the only carbohydrate recommended for PN and should provide 60–75% of non-protein calorie intake. During the first days on PN, the glucose supply should be gradually increased. In preterm infants, the glucose intake should begin with 4–8 mg/kg per minute (5.8–11.5 g/kg per day) and increase gradually. In critically ill children, the glucose intake should be  $\leq 5$  mg/kg per minute (7.2 g/kg per day). Glucose infusion for term neonates and children  $\leq 2$  years should not exceed 18 g/kg per day (13 mg/kg per minute). Glucose intake should be adapted to the administration of drugs that impair glucose metabolism (e.g. steroids, somatostatin analogues and tacrolimus). Very high glucose intakes and marked hyperglycaemia should be avoided because they

may induce increased lipogenesis and tissue fat deposition, liver steatosis, enhanced CO<sub>2</sub> production, impaired protein metabolism and possibly increased infection-related morbidity and mortality [3]. In critically ill and unstable patients, the glucose dosage should be lower and increased according to the patient's condition and blood glucose levels.

## Lipids

Lipid emulsions supply essential fatty acids and energy at iso-osmolarity. Lipids should generally provide 25–40% of non-protein PN calories. Parenteral lipid intake is usually limited to 3–4 g/kg per day (0.13–0.17 g/kg per hour) in infants and 2–3 g/kg per day (0.08–0.13 g/kg per hour) in children. In VLBWI requiring PN, the supply of lipid emulsions should start on the first day with a dose of at least 2 g/kg per day [5]. A stepwise increase of lipid infusion rates by 0.5–1 g/kg per day has not been shown to improve tolerance, but it allows monitoring for hypertriglyceridaemia. Regular plasma triglyceride measurements are recommended, particularly in critically ill or infected patients during PN. A dosage reduction should be considered at triglyceride concentrations during infusion  $>250$  mg/dl in infants or  $>400$  mg/dl in children, but there

should always be a minimum linoleic acid intake to prevent essential fatty acid deficiency (pre-term infants:  $\geq 0.25$  g linoleic acid/kg per day; term infants/children:  $\geq 0.1$  g/kg per day). In neonates requiring PN, lipids can start on day 1 of life and should start no later than day 3. In young infants, lipids should be administered continuously over  $\sim 24$  h.

During phototherapy, validated light-protected tubing for lipid emulsions is recommended to decrease hydroperoxide formation. Lipid emulsions have no demonstrable effect on hyperbilirubinaemia. There is no firm evidence on adverse effects in severe acute respiratory failure, but avoiding high lipid dosages in these patients appears prudent. In severe, progressive PN-associated cholestasis, a decrease in or transient interruption of intravenous lipids should be considered.

Commercial lipid emulsions based on soybean oil, or mixtures of olive and soybean oils or of medium-chain triglycerides and soybean oil, as well as mixed emulsions with fish oil are considered safe and are registered for paediatric patients in many countries around the world. In a meta-analysis of randomized controlled trials in VLBWI, the use of mixed emulsions without and with fish oil showed a 25% lower risk of sepsis than the use of 100% soybean oil emulsions [6]. In view of these data and concerns on an imbalanced fatty acid composition and an apparently high risk of liver damage, the use of lipid emulsions based only on soybean oil has been discouraged in young infants, and these emulsions are not preferred for use in paediatric patients [2].

### Other Aspects

Vitamins and minerals should be supplied with all PN and provided over several days. Cyclical PN (over  $\sim 8$ – $14$  h/day) should be considered from the age of 3–6 months onwards [2, 4].

Individualized prescriptions of paediatric PN are widely used, but standard PN solutions are suitable for many paediatric patients with adequate monitoring and the possible addition of electrolytes/nutrients. They can improve the quality and safety of PN and reduce costs [7].

The risks of PN are best reduced by limiting its amount and duration combined with persistent attempts to increase the amount of enteral feedings as tolerated. Rather than enteral starvation, minimal enteral feeds should be given whenever possible, and experienced paediatricians and dietitians should be involved.

### Conclusions

- PN is an essential and often life-saving treatment for infants and children who cannot be adequately fed orally or enterally
- PN should only be used when all alternative options have been explored, including adequate care, specialized EN and artificial feeding devices
- PN can induce severe adverse effects. The risk is reduced by a meticulous approach, establishment of a multidisciplinary nutrition support team, avoidance of unbalanced or excessive substrate supplies, strict hygiene measures to reduce catheter infections, concomitant minimal enteral feeding and forceful enhancement of enteral feeding where possible to limit the amount and duration of PN

### References

- 1 Agostoni C, Axelson I, Colomb V, Goulet O, Koletzko B, Michaelsen KF, Puntis JW, Rigo J, Shamir R, Szajewska H, Turk D: The need for nutrition support teams in pediatric units: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2005; 41:8–11.



- 2 Jochum F, Krohn K, Kohl M, Loui A, Nomayo A, Koletzko B; DGEM Steering Committee: Parenterale Ernährung in der Kinder- und Jugendmedizin. S3-Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin. *Akt Ernährungsmed* 2014;39:233–255.
- 3 Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R: Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005;41(suppl 2):S1–S87.
- 4 Koletzko B, Goulet O: Nutritional support in infants, children and adolescents; in Sobotka L (ed): *Basics in Clinical Nutrition*. Prague, Galén, 2011, pp 625–653.
- 5 Koletzko B, Poindexter B, Uauy R (eds): *Nutritional Care of Preterm Infants*. Basel, Karger, 2014, vol 110, p 314.
- 6 Vlaardingerbroek H, Veldhorst MA, Spronk S, van den Akker CH, van Goudoever JB: Parenteral lipid administration to very-low-birth-weight infants – early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis. *Am J Clin Nutr* 2012;96:255–268.
- 7 Krohn K, Babl J, Reiter K, Koletzko B: Parenteral nutrition with standard solutions in paediatric intensive care patients. *Clin Nutr* 2005;24:274–280.

## 3.5 Management of Child and Adolescent Obesity

Louise A. Baur

### Key Words

Obesity · Children · Adolescents · Assessment · Management

### Key Messages

- The BMI [weight (kg)/height (m)<sup>2</sup>] should be plotted routinely on a BMI-for-age chart
- The principles of obesity management include: management of comorbidities; family involvement; a developmentally appropriate approach; the use of a range of behavior change techniques; long-term dietary change; increased physical activity, and decreased sedentary behaviors
- Orlistat may be useful as an adjunct to lifestyle change for more severely obese adolescents, and metformin for adolescents with clinical insulin resistance
- Bariatric surgery should be considered with severely obese adolescents
- Coordinated models of care for health service delivery are needed for the management of pediatric obesity

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### Introduction

Child and adolescent obesity is a prevalent problem in most westernized and rapidly westernizing countries and is associated with both immediate and longer-term complications. Effective treatment of those affected by obesity is vital.

### Clinical Assessment

Clinical history should aid in assessing current and potential future comorbidities as well as modifiable lifestyle practices (table 1) [1–4]. The BMI [weight (kg)/height (m)<sup>2</sup>], a clinically useful measure of body fatness in those aged >2 years, should be plotted on nationally recommended BMI-for-age charts [5], e.g. the WHO Child Growth Standards. However, the cutoff points used to define overweight and obesity are somewhat arbitrary and may vary between countries. For example, in the UK the cutoff points for overweight and obesity are the 91st and 98th percentiles, respectively, compared with the 85th and 95th in the USA. Hence, local recommendations should be checked. A waist circumference-to-height ratio of >0.5 is associated with increased cardiometabolic risk in school-aged children [6]. Waist circumference-for-age charts are available for some countries.

Physical examination is used to assess obesity-associated comorbidities as well as signs of underlying genetic or endocrine disorders (table 2). The level of investigation is dependent on the patient's severity of obesity and age, the clinical findings and associated familial risk factors. Baseline investigations may include fasting lipid screening, glucose, liver function tests and, possibly, insulin [1–4]. Second-line investigations

**Table 1.** Elements of history-taking in obese children and adolescents

General history	Prenatal and birth – history of gestational diabetes and birth weight Infant feeding – duration of breastfeeding Current medications – glucocorticoids, some antiepileptics and antipsychotics
Weight history	Onset of obesity and duration of parental and child concerns about their weight Previous weight management interventions Previous and current dieting behaviors
Complications history	Psychological – bullying, poor self-esteem, depression Sleep – snoring, symptoms suggestive of sleep apnea Exercise tolerance Specific symptoms related to gastroesophageal reflux, gallstones, benign intracranial hypertension, orthopedic complications, enuresis, constipation Menstrual history (girls)
Family history	Ethnicity Family members with a history of: obesity, type 2 diabetes, gestational diabetes, cardiovascular disease, dyslipidemia, obstructive sleep apnea, polycystic ovary syndrome, bariatric surgery, eating disorders
Lifestyle history	Diet and eating behaviors – breakfast consumption, snacking, fast-food intake, beverage consumption, family routines around food, binge eating, sneaking food Sedentary behavior – daily screen time; numbers of televisions, gaming consoles, computers and smart phones in the bedroom and home; pattern of screen time Physical activity – after school and weekend recreation, sports participation, transport to and from school, family activities Sleep – duration and routines

may include liver ultrasound, an oral glucose tolerance test, more detailed endocrine assessment and polysomnography.

### Treatment Strategies

Systematic reviews of pediatric obesity treatment show that lifestyle interventions can lead to improvements in weight and cardiometabolic outcomes [7, 8]. While there is no evidence to support one specific treatment program over another, meta-analyses show that family-targeted behavioral lifestyle interventions can lead to a

mean BMI reduction of 1.25 to 1.30 when compared with no treatment or usual care [8]. The longer the duration of treatment, the greater the weight loss observed [8]. Lifestyle interventions also lead to improvements in low-density lipoprotein cholesterol, triglycerides, fasting insulin and blood pressure up to 1 year from baseline [8].

Some of the challenges of treatment are that ‘real-world’ obesity clinics are often more poorly resourced than in clinical trials, and clinic patients may be more socially disadvantaged, or have a broader range of comorbidities, than those who take part in trials, making treatment adherence more difficult.

**Table 2.** Physical examination of obese children or adolescents and important physical findings [9, 11]

Organ system	Physical findings
Skin/subcutaneous tissues	Acanthosis nigricans, skin tags, hirsutism, acne, striae, pseudogynecomastia (males), intertrigo, xanthelasma (hypercholesterolemia)
Neurological	Papilledema and/or reduced venous pulsations on funduscopy (pseudotumor cerebri)
Head and neck	Tonsillar size, obstructed breathing
Cardiovascular	Hypertension, heart rate (cardiorespiratory fitness)
Respiratory	Exercise intolerance, wheeze (asthma)
Gastrointestinal	Hepatomegaly and hepatic tenderness (nonalcoholic fatty liver disease), abdominal tenderness (secondary to gallstones or gastroesophageal reflux)
Musculoskeletal	Pes planus, groin pain, and painful or waddling gait (slipped capital femoral epiphysis), tibia vara (Blount disease), lower-limb arthralgia and restriction of joint movement
Endocrine	Goiter, extensive striae, hypertension, dorsocervical fat pad, pubertal staging, reduced growth velocity
Psychosocial	Flat affect and low mood, poor self-esteem, social isolation
Other – evidence of a possible underlying genetic syndrome	Short stature, disproportion, dysmorphism, developmental delay

However, the broad principles of management are well recognized [1–4, 7, 8]: management of obesity-associated comorbidities; family involvement; a developmentally appropriate approach; long-term behavior modification; dietary change; increased physical activity; decreased sedentary behaviors; a plan for longer-term weight maintenance strategies; and consideration of the use of pharmacotherapy and other nonconventional therapies.

## Elements of Treatment

### *Family Focus*

Many clinical trials show that family-based interventions can lead to long-term relative weight loss, i.e. from 2 to 10 years. Parental involvement when managing obese preadolescent children appears vital, although there are more limited data on management of adolescents.

### *A Developmentally Appropriate Approach*

For preadolescent children, weight outcomes may be improved with a parent-focused intervention, without direct engagement of the child [9]. There are more limited data on the treatment of adolescent obesity than on younger children, and especially on interventions that would be sustainable in most health care settings. Generally, provision of at least some separate therapist session time with the adolescent seems appropriate.

### *Behavior Modification*

Weight outcomes are improved with the use of a broader range of behavior change techniques [1–4]. One such technique, goal-setting, can include performance goals (such as changing eating or activity behaviors) or outcome goals (such as specific weight loss). Examples of the former include not buying cookies, or reducing television time to 3 h per day. Another technique, stimulus control, refers to modifying or restricting environmental

influences in order to aid weight control, with examples including not eating in front of the television, or using smaller plates and bowls within the home. A third commonly used technique, self-monitoring, involves the recording of a specific behavior or outcome, such as the use of a food diary, daily pedometer measurement of physical activity, or weekly weighing.

#### *Dietary Change and Eating Behaviors*

Treatment programs incorporating a dietary component can be effective in achieving relative weight loss in children and adolescents, although no one dietary prescription appears superior to another [8]. However, dietary interventions are usually part of a broader lifestyle change program, and are rarely evaluated on their own. The two most commonly reported diets are: (a) the modified stop/traffic light approach, where foods are color-coded on the basis of nutritional value and energy content to indicate those to be eaten freely (green) or more cautiously (amber, red), and (b) a calorie restriction/hypocaloric diet approach. Both diets can lead to sustained weight loss across different settings and age groups [8]. The role of dietary macronutrient modification in the management of obese children and adolescents remains unclear.

In general, dietary interventions should follow national nutritional guidelines and have an emphasis on the following [1–3]:

- Regular meals
- Eating together as a family
- Choosing nutrient-rich foods which are lower in energy and glycemic index
- Increased vegetable and fruit intake
- Healthier snack food options
- Decreased portion sizes
- Drinking water as the main beverage
- Reduction in sugary drink intake
- Involvement of the entire family in making sustainable dietary changes

In advising patients and families on dietary changes, is there a risk of an eating disorder developing?

While most people with obesity do not have a binge eating disorder, the latter is more common in people with severe obesity. Further, overweight adolescents are more likely to binge-eat, and childhood obesity is a risk factor for later bulimia. However, professionally run pediatric obesity programs do not increase the risk of disordered eating and may improve psychological wellbeing [10].

#### *Physical Activity and Sedentary Behaviors*

In clinical practice, increased physical activity may best result from a change in incidental, or unplanned, activity, such as by walking or cycling for transport, undertaking household chores and playing. Organized exercise programs have a role, with children and adolescents being encouraged to choose activities that they enjoy and which are sustainable. Limiting television and other small-screen recreation to less than 2 h per day is particularly strategic, but may be challenging [11]. Parental involvement is vital and may include monitoring and limiting television use, role-modeling of healthy behaviors, and providing access to recreation areas or recreational equipment.

#### *Long-Term Weight Maintenance*

In those who undergo an initial weight management intervention, a period of further therapeutic contact appears to slow weight regain [12]. At present, there is limited evidence to guide the nature and type of long-term weight maintenance interventions.

### **Nonconventional Therapies**

There is relatively limited evidence to guide the use of less orthodox treatment approaches such as very-low-energy diets, pharmacological therapy or bariatric surgery in treating severe pediatric obesity. Such therapies should occur on the background of a behavioral weight management program and be restricted to specialist centers with expertise in managing severe obesity.

Existing recommendations on management of pediatric obesity suggest that drug therapy (largely orlistat, a gastrointestinal and pancreatic lipase inhibitor) can be used in the treatment of severely obese adolescents, in the context of a tertiary care protocol provided by a multidisciplinary care team and incorporating continued diet and activity counseling [1–4]. For obese, insulin-resistant adolescents there may be a role for the use of metformin, an insulin-sensitizing agent [13].

The few consensus guidelines for bariatric surgery in adolescents have highlighted its use in severely obese adolescents, with consideration of the adolescent's decisional capacity and attainment of physical maturity, as well as the presence of a supportive family environment [1, 3, 4, 14, 15]. The need for management in centers with multidisciplinary weight management teams, for the surgery to be performed in tertiary institutions experienced in bariatric surgery and for long-term multidisciplinary follow-up has been emphasized.

## Health Service Delivery Issues

Given the high prevalence and chronicity of pediatric obesity, there is a need for coordinated models of care for health service delivery. One potential approach, the chronic disease care model, is based upon a tiered level of service delivery relating to disease severity [16]. Thus, while most people affected by the problem of obesity can be managed via self-care or family-based care, with support from primary care or community-based health service providers, there is a need for treatment by multidisciplinary care teams, and possibly tertiary care clinics, for those who are more severely affected. Individual clinicians should be aware of the presence of other services within their geographic region, and the capacity of these to take referrals or to comanage patients.

## References

- 1 Barlow SE; Expert Committee: Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007;120(suppl 4):S164–S192.
- 2 National Health and Medical Research Council: Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. 2013. <http://www.nhmrc.gov.au/guidelines/publications/n57>.
- 3 Scottish Intercollegiate Guidelines Network: Management of obesity: a national clinical guideline. 2010. <http://www.sign.ac.uk/pdf/sign115.pdf>.
- 4 National Institute for Health and Clinical Excellence: Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. 2006. <http://guidance.nice.org.uk/CG43/NICEGuidance/pdf/English>.
- 5 Freedman DS, Wang J, Thornton JC, et al: Classification of body fatness by body mass index-for-age categories among children. *Arch Pediatr Adolesc Med* 2009;163:805–811.
- 6 Garnett SP, Baur LA, Cowell CT: Waist-to-height ratio: a simple option for determining excess central adiposity in young people. *Int J Obes (Lond)* 2008;32:1028–1030.
- 7 Oude Luttikhuis H, Baur L, Jansen H, et al: Interventions for treating obesity in children. *Cochrane Database Syst Rev* 2009;1:CD001872.
- 8 Ho M, Garnett SP, Baur LA, et al: Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. *Pediatrics* 2012;130:e1647–e1671.
- 9 Golan M, Crow S: Targeting parents exclusively in the treatment of childhood obesity: long-term results. *Obesity Res* 2004;12:357–361.
- 10 Hill AJ: Obesity and eating disorders. *Obes Rev* 2007;8(suppl 1):151–155.
- 11 Whitaker RC: Obesity prevention in pediatric primary care: four behaviors to target. *Arch Pediatr Adolesc Med* 2003;157:725–727.
- 12 Wilfley DE, Stein RI, Saelens BE, et al: Efficacy of maintenance treatment approaches for childhood overweight: a randomized controlled trial. *JAMA* 2007;298:1661–1673.
- 13 Quinn SM, Baur LA, Garnett SP, Cowell CT: Treatment of clinical insulin resistance in children: a systematic review. *Obes Rev* 2010;11:722–730.
- 14 Baur LA, Fitzgerald DA: Recommendations for bariatric surgery in adolescents in Australia and New Zealand. *J Paediatr Child Health* 2010;46:704–707.
- 15 Inge TH, Krebs NF, Garcia VF, et al: Bariatric surgery for severely overweight adolescents: concerns and recommendations. *Pediatrics* 2004;114:217–223.
- 16 Department of Health: Supporting people with long term health conditions. 2007. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/Browsable/DH\\_4100317](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/Browsable/DH_4100317).

## 3.6 Reducing the Burden of Acute and Prolonged Childhood Diarrhea

Jai K. Das · Zulfiqar A. Bhutta

### Key Words

Diarrhea · Nutrition · Children

### Key Messages

- Diarrhea remains one of the leading causes of mortality among children under 5 years of age
- Risk factors for diarrhea include those related to poverty, undernutrition, poor hygiene, and underprivileged household conditions making children more at risk of developing infectious diarrhea
- Recent evidence suggests that if a range of existing interventions are scaled up, diarrhea burden can be significantly reduced

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### Introduction

In 2011, 6.9 million children under 5 years of age died; 4.4 million (58%) of these deaths were attributable to infectious diseases, of which pneumonia and diarrhea were the leading ones [1]. The incidence of diarrhea has decreased from 3.4 episodes per child-year in 1990 to 2.9 episodes per child-year in 2010; however, it still remains one of the most common reasons for hospital admission, with an estimated 1,731 million episodes of childhood diarrhea reported in 2011 [2]. There

are three clinical types of diarrhea: (1) acute watery diarrhea that lasts several hours or days and includes cholera; (2) acute bloody diarrhea, also called dysentery, and (3) persistent diarrhea that lasts 14 days or longer. Risk factors for diarrhea include those related to poverty, undernutrition, poor hygiene, and underprivileged household conditions making children more at risk of developing infectious diarrhea. Lack of breastfeeding is a single independent risk factor for diarrhea, and it is estimated that not breastfeeding is associated with a 165% increase in diarrhea incidence among 0- to 5-month-olds, a 47% increase in diarrhea-related mortality among 6- to 11-month-olds, and a 157% increase among 12- to 23-month-olds. Overall, lack of breastfeeding is found to be associated with a 566% increase in all-cause mortality among children aged 6–11 months and a 223% increase in mortality among those aged 12–23 months [3]. Despite these figures, the rates of exclusive breastfeeding (EBF) remain unacceptably low worldwide, especially in low- and middle-income countries. In this chapter, we will discuss the preventive and therapeutic strategies and nutrition interventions pertaining to acute and persistent diarrhea among children along with the delivery strategies to increase access to these interventions.

## Interventions for Diarrhea Prevention and Management

Recent evidence suggests that if a range of existing interventions are scaled up, diarrhea burden can be significantly reduced. These include EBF up to 6 months of age, the promotion of complementary feeding, rotavirus vaccinations, use of oral rehydration solution (ORS) and zinc in diarrhea, improved case management, antibiotics for dysentery, as well as water, sanitation and hygiene (WASH) strategies. Table 1 summarizes the effects of the preventive and therapeutic interventions for diarrhea.

Among the diarrhea prevention interventions, breastfeeding promotion interventions in developing countries can significantly increase EBF rates by 43% at day 1, 30% at <1 month, and 90% at 1–5 months, with reductions in rates of no breastfeeding by 32% at 1 day, 30% at <1 month, and 18% at 1–5 months [4]. Vaccinations for rotavirus and cholera can reduce rotavirus-specific mortality by 74% and the cholera incidence by 52%, respectively [5]. WASH strategies are pivotal for the prevention of diarrheal diseases, as interventions for water quality, sanitation, and hygiene can reduce diarrhea morbidity in children by 42, 37, and 31%, respectively [6].

Since the immediate cause of death in most cases of diarrhea is dehydration, deaths are almost entirely preventable if dehydration is prevented or treated. ORS, zinc, and continued feeding are the recommended treatments for acute diarrhea among young children. The use of ORS in developing-country settings can reduce diarrhea-specific mortality by 69% and results in a treatment failure rate of 0.2% [7]. Since 2004, the WHO and United Nations International Children's Emergency Fund (UNICEF) have recommended zinc for the treatment of diarrhea, which can reduce all-cause mortality by 46% and diarrhea-related hospital admissions by 23% [8]. Although the WHO program for the control of

diarrheal disease began in 1978, the global ORS use has remained stagnant. Interventions pertaining to ORS promotion, including co-promotion of zinc and ORS, social marketing, and mass media strategies, are effective in improving ORS usage and should be utilized to improve coverage of this lifesaving and simple intervention. There is evidence to recommend antibiotics use for the reduction of morbidity and mortality due to cholera, *Shigella*, and *Cryptosporidium*. However, this area requires more clinical trials to evaluate the efficacy and safety of the drugs currently in use for the treatment of diarrhea and dysentery in both developing and developed countries [9]. Another major challenge in diarrhea treatment is the vomiting associated with acute gastroenteritis, which limits the success of ORS, leading to an increased use of intravenous rehydration, prolonged emergency department stay, and hospitalization. Although, antiemetics are not routinely recommended, recent evidence suggests that their use can significantly reduce the incidence of vomiting, hospitalization, and intravenous fluid requirements and may have the potential to decrease morbidity and mortality burden due to diarrhea; however, further evidence is required before universal recommendation [10].

These preventive and therapeutic interventions, if implemented at current coverage rates in the 75 low- and middle-income countries (Countdown countries), could avert 54% of diarrhea deaths by 2025 at a cost of USD 3.8 billion. However, if the coverage of these key evidence-based interventions were scaled up to at least 80%, and that of immunizations to at least 90%, virtually all diarrhea deaths in children younger than 5 years could be averted by 2025 at a cost of USD 6.715 billion [11]. In their recent report [12], the Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN) working group prioritized interventions that could contribute greatly to achieving Millennium Development



**Table 1.** Key interventions for diarrhea and potential effects

Intervention	Effect estimate
WASH	48, 17, and 36% risk reductions for diarrhea with hand washing with soap, improved water quality, and excreta disposal, respectively
Breastfeeding education and effects on breastfeeding rates	EBF rates increase by 43% at 1 day, 30% till 1 month, and 90% from 1–6 months; rates of no breastfeeding decrease by 32% at 1 day, 30% till 1 month, and 18% from 1–6 months
Preventive zinc supplementation	18% reduction in diarrhea-related mortality
Vaccines for rotavirus	74% reduction in very severe rotavirus infections and 47% reduction in rotavirus hospitalizations
Vaccines for cholera	52% effective against cholera infection; vibriocidal antibodies increase by 124%
Vaccines for <i>Shigella</i>	28% effective against <i>S. flexneri</i> infection and 53% against <i>S. sonnei</i>
Vaccines for enterotoxigenic <i>Escherichia coli</i>	Increase in serum IgA and IgG seroconversion rates by 170 and 500%, respectively
ORS and recommended home fluids	69% reduction in diarrhea-specific mortality
Dietary management of diarrhea	Lactose-free diets reduce the duration of diarrhea treatment failure significantly by 47%
Probiotics	14% reduction in diarrhea duration, 11% reduction in stool frequency on day 2, and 19% reduction in hospitalizations, although statistically nonsignificant
Therapeutic zinc supplementation	66% reduction in diarrhea-specific mortality, 23% reduction in diarrhea hospitalizations, and 19% reduction in diarrhea prevalence
Antiemetics for gastroenteritis	54% reduction in the incidence of vomiting and hospitalizations and 60% reduction in intravenous fluid requirement rates
Antibiotics for cholera	63% reduction in clinical failure rates and 75% reduction in bacteriological failure rates
Antibiotics for <i>Shigella</i>	82% reduction in clinical failure rates and 96% reduction in bacteriological failure rates
Antibiotics for cryptosporidiosis	52% reduction in clinical failure rates and 38% reduction in parasitological failure rates
Community-based interventions	153% increase in the use of ORS and manifold rise in the use of zinc in diarrhea; 76% decline in the use of antibiotics for diarrhea
Community case management	63% reduction in diarrhea-related mortality
Financial schemes	Conditional transfer programs: 14% increase in preventive health care use, 22% increase in the percentage of newborns receiving colostrum, and 16% increase in the coverage of vitamin A supplementation

Goal 4 by impacting diarrhea-related mortality; these, according to the priority ratings, included rotavirus immunization, the promotion of ORS and a reduction in inappropriate medical interventions (hospitalizations, microbiological investigations, dietary modifications, and unnecessary drug administration).

### Nutrition in Acute and Persistent Diarrhea

There is some debate about the optimum diet or dietary components for quick recovery in children with diarrhea; however, the current WHO guidelines strongly recommend continued feeding alongside the administration of ORS and zinc therapy. Recent evidence suggests that among

children with acute diarrhea, lactose-free liquid feeds can reduce the duration and the risk of treatment failure compared to lactose-containing liquid feeds, with only limited evidence assessing either of these two approaches in persistent diarrhea. Home-available lactose-free diets impact weight gain in children with acute diarrhea compared to those fed with a commercial diet. For children in low- and middle-income countries, where diarrhea and malnutrition co-exist, it is suggested to use locally available age-appropriate foods in the majority of acute diarrhea cases, but the evidence remains limited for the dietary management of children with persistent diarrhea [13]. Probiotics are becoming increasingly popular treatments for diarrhea in some countries and have been shown to reduce diarrhea duration and stool frequency on the second day of treatment with no effect on the risk of diarrhea hospitalizations. However, evidence is still needed to understand the effect of probiotics as adjunct therapy for diarrhea among children in developing countries [14].

### **Intervention Delivery Strategies**

No new innovations are required, just improving the coverage of the above-mentioned existing proven interventions could help achieve the goal of reducing diarrhea burden. Most of the interventions exist within present health systems, although their coverage and availability to poor and marginalized populations vary greatly. Improving the coverage of these key, effective, and affordable interventions requires alternate strategies or platforms to accelerate their uptake and scale-up. Given the shortage of human resources in some of the poorest areas of the world, one such strategy is reaching out through community health workers, which offers an opportunity to reach the population with only minimal health care access [15]. Recent evidence suggests that community-delivered interventions for diarrhea

prevention and management can improve care-seeking behaviors and the use of ORS, and they are also associated with a decline in the unnecessary use of antibiotics for diarrhea [16]. Such delivery platforms also offer a unique opportunity for integrating services at the point of service delivery and enabling an implementation strategy in poor and difficult-to-reach populations. Financial incentives are also being widely used to alleviate poverty, reduce barriers to health care access, promote care seeking, and improve health. Financial incentives in the form of vouchers and conditional and unconditional cash transfers could promote increased coverage of several important child health interventions, with the most pronounced effects achieved by the mechanisms that directly removed user fees for access to health services [17].

### **Way Forward**

Implementing these interventions and utilizing the delivery platforms could be made possible by engaging policy makers and civil society when assessing the overall progress in coverage at the country level. Political will and partnerships are imperative to implement evidence-based interventions at scale. With an increasing number of countries deploying community health worker programs to reach the unreached, real opportunities exist to scale up community advocacy and education programs and early case detection and management strategies. Bangladesh provides an example of how targeting the poorest for key diarrhea interventions could result in far more lives saved. Nearly 6 times more lives could be saved in the poorest households when compared to the richest by scaling up key diarrhea interventions to near universal levels [18]. Similar attention needs to be paid to countries contributing considerably to the diarrhea burden, including India, Nigeria, Pakistan, the Democratic Republic of the Congo, and China.

## Conclusions

- A high level of coverage must be ensured for proven and effective interventions in the 75 Countdown countries, where more than 95% of all child deaths occur
- Tangible progress can be made if the prevention and treatment of diarrhea becomes an international priority and the global health community commits to a number of key actions as laid out in the 2009 UNICEF/WHO report [19] and, more recently, in the Global Action Plan for Diarrhea and Pneumonia [18]
- Promising indications show that such scaling up is beginning to happen and is being recommended as a strategy to reduce inequities in child survival in high-burden countries
- In a broader context, poverty alleviation, safety and security, economic development, food security, improved education, and basic human rights are imperative for long-term success and sustainability

## References

- 1 UNICEF: Levels and trends in child mortality. Report 2012. Estimates developed by the UN Inter-Agency Group for Child Mortality Estimation. New York, UNICEF, 2012.
- 2 Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, O'Brien KL, Campbell H, Black RE: Global burden of childhood pneumonia and diarrhoea. *Lancet* 2013;381:1405–1416.
- 3 Lamberti LM, Fischer Walker CL, Noiman A, Victora C, Black RE: Breastfeeding and the risk for diarrhea morbidity and mortality. *BMC Public Health* 2011; 11(suppl 3):S15.
- 4 Haroon S, Das JK, Salam RA, Imdad A, Bhutta ZA: Breastfeeding promotion interventions and breastfeeding practices: a systematic review. *BMC Public Health* 2013;13:1–18.
- 5 Das JK, Tripathi A, Ali A, Hassan A, Dojosoandy C, Bhutta ZA: Vaccines for the prevention of diarrhea due to cholera, shigella, ETEC and rotavirus. *BMC Public Health* 2013;13(suppl 3):S11.
- 6 Waddington H, Snilstveit B, White H, Fewtrell L: Water, sanitation and hygiene interventions to combat childhood diarrhoea in developing countries. Delhi, International Initiative for Impact Evaluation, 2009, vol 31.
- 7 Munos MK, Walker CL, Black RE: The effect of oral rehydration solution and recommended home fluids on diarrhoea mortality. *Int J Epidemiol* 2010;39(suppl 1):i75–i87.
- 8 Walker CL, Black RE: Zinc for the treatment of diarrhoea: effect on diarrhoea morbidity, mortality and incidence of future episodes. *Int J Epidemiol* 2010; 39(suppl 1):i63–i69.
- 9 Das JK, Ali A, Salam RA, Bhutta ZA: Antibiotics for the treatment of cholera, *Shigella* and *Cryptosporidium* in children. *BMC Public Health* 2013;13(suppl 3):S10.
- 10 Das JK, Kumar R, Salam RA, Freedman S, Bhutta ZA: The effect of antiemetics in childhood gastroenteritis. *BMC Public Health* 2013;13(suppl 3):S9.
- 11 Bhutta ZA, Das JK, Walker N, Rizvi A, Campbell H, Rudan I, Black RE: Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* 2013;381:1417–1429.
- 12 Guarino A, Winter H, Sandhu B, Quak SH, Lanata C: Acute gastroenteritis disease: report of the FISPUGHAN Working Group. *J Pediatr Gastroenterol Nutr* 2012;55:621–626.
- 13 Gaffey MF, Wazny K, Bassani DG, Bhutta ZA: Dietary management of childhood diarrhea in low- and middle-income countries: a systematic review. *BMC Public Health* 2013;13(suppl 3): S17.
- 14 Applegate JA, Walker CLF, Ambikapathi R, Black RE: Systematic review of probiotics for the treatment of community-acquired acute diarrhea in children. *BMC Public Health* 2013;13(suppl 3): S16.
- 15 Bhutta ZA, Lassi ZS, Pariyo G, Huicho L: Global experience of community health workers for delivery of health related Millennium Development Goals: a systematic review, country case studies, and recommendations for integration into national health systems. Geneva, WHO/Global Health Workforce Alliance, 2010.
- 16 Das JK, Lassi ZS, Salam RA, Bhutta ZA: Effect of community based interventions on childhood diarrhea and pneumonia: uptake of treatment modalities and impact on mortality. *BMC Public Health* 2013;13(suppl 3):S29.
- 17 Chopra M, Sharkey A, Dalmiya N, Anthony D, Binkin N: Strategies to improve health coverage and narrow the equity gap in child survival, health, and nutrition. *Lancet* 2012;380:1331–1340.
- 18 UNICEF: Pneumonia and diarrhoea: tackling the deadliest diseases for the world's poorest children. New York, UNICEF, 2012.
- 19 UNICEF, WHO: Diarrhoea: why children are still dying and what can be done. Geneva, WHO, 2009.

### 3.7 HIV and AIDS

Haroon Saloojee · Peter Cooper

#### Key Words

HIV · AIDS · Nutrition · Breastfeeding ·  
Complementary feeding · Malnutrition ·  
Micronutrients · Antiretroviral therapy

#### Key Messages

- HIV infection has greater nutritional consequences for children than for adults, mainly because children have the additional nutritional demands of growth and development
- The WHO recommends exclusive breastfeeding for the first 6 months of life followed by complementary foods and continued breastfeeding through 12 months of age, accompanied by postnatal infant or maternal antiretroviral prophylaxis, for HIV-exposed infants (or antiretroviral therapy, ART, for infected infants)
- The focus of nutritional activity has moved from supporting undernourished HIV-infected infants and children to ensuring that infected children on ART are adequately nourished
- ART is associated with improvements in weight, weight-for-height, mid-arm circumference and lean body mass in HIV-infected children

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#### Introduction

The field of postnatal and child HIV/AIDS has experienced a number of exciting breakthroughs in the past 5 years. Prevention of mother-to-child transmission strategies are now more widely available, even in resource-poor settings. Access to antiretroviral therapy (ART) has also increased and is now commenced earlier in HIV-infected children, i.e. at first diagnosis, ideally in the first 2–3 months of life.

Transmission through breastfeeding remains a problem. In the absence of antiretroviral prophylaxis, postnatal transmission appears to be highest in the first 4–6 weeks of life, ranging from 0.7 to 1% per week. However, the risk continues for the duration of breastfeeding and is constant throughout this period. Efforts have moved in support of safer feeding by promoting exclusive breastfeeding for 6 months coupled with concomitant antiretroviral prophylaxis delivered to breastfeeding mothers or the infant.

Two essential tenets underpin the approach to HIV: ART is essential to save and prolong lives, and good nutrition is vital to ensure children's overall health. Thus, the focus of nutrition-related activities has moved from supporting under-

**Table 1.** Definition of commonly used infant feeding terms

Exclusive breastfeeding	Receipt of no other substance than human breast milk; medications such as oral rehydration therapy, antibiotics or multivitamin syrups are permitted; breast milk can include the mother's expressed milk or milk from a wet nurse
Replacement feeding	Receipt of no breast milk, but of suitable breast milk substitutes in the form of commercial infant formulae
Mixed feeding	Receipt of both breast milk and other liquids or solids, including water and commercial infant formulae, before the age of 6 months
Complementary feeding	Addition of solids, semi-solids and liquids to a breastfeeding diet after the age of 6 months; at this age an infant needs more vitamins, minerals, proteins, fats and carbohydrates than are available from breast milk alone

nourished HIV-infected infants and children to ensuring that infected children on ART are well nourished.

This chapter reflects this transition, focusing less on the anthropometric effects and nutritional management of HIV-infected children, and more on evolving issues in the management of HIV-exposed infants and the nutritional support of HIV-infected children and adolescents receiving ART. Nevertheless, achievement of food and nutrition security and management of nutrition-related complications of HIV infection remain significant challenges in resource-poor environments.

### Feeding the HIV-Exposed Uninfected Infant

#### *Breastfeeding*

HIV-positive women living in resource-poor settings must balance opposing risks – breast milk can transmit HIV, but lack of breastfeeding increases the risk of infections, malnutrition and death. In 2010, the WHO revised its position by recommending exclusive breastfeeding (see table 1 for definitions used) for the first 6 months of life followed by complementary foods and continued breastfeeding through 12 months of age, accompanied by postnatal infant or maternal antiretroviral prophylaxis [1].

Breastfeeding should only be stopped once nutritionally adequate and safe food intake is assured to the child. Abrupt weaning from breast milk should be avoided; breastfeeding should stop gradually over a 1-month period. Mothers or infants who have been receiving antiretroviral prophylaxis should continue prophylaxis for 1 week after breastfeeding has been fully stopped [1]. Maintaining exclusive breastfeeding for 6 months remains a practical challenge in many settings where early introduction of other foods or liquids is an established cultural norm. Maintaining exclusivity may be less important in the face of concomitant antiretroviral prophylaxis [2].

#### *Replacement Feeding*

In contrast to the WHO, the American Academy of Pediatrics recommends that HIV-infected mothers not breastfeed their infants, regardless of maternal disease status, viral load or ART [3]. The British HIV Association and Children's HIV Association both concur [4]. Safely prepared exclusive commercial infant formulae can meet all the nutrient needs of HIV-exposed infants if fed in amounts calculated to meet the infants' energy requirements. Women with suspected acute HIV infection, or those not on ART with low CD4 counts or who have progressed to AIDS, are encouraged to consider replacement

**Table 2.** Conditions needed to safely replacement feed

Mothers known to be HIV infected should only give commercial infant formula milk as a replacement feed to their HIV-uninfected infants or infants who are of unknown HIV status if specific conditions are met. The mother or caregiver:

- has access to safe water and sanitation in the home and in the community;
- can reliably provide sufficient infant formula milk to support normal growth and development of the infant;
- can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhea and malnutrition;
- can, in the first 6 months, exclusively give infant formula milk;
- obtains the family's support for the practice, and
- can access health care that offers comprehensive child health services.

Source: WHO [1].

feeding (to reduce the high transmission risk). In resource-limited settings, the conditions under which replacement feeding is preferred are commonly referred to as AFASS – affordable, feasible, acceptable, sustainable and safe. The acronym is now described in everyday language in the 2010 WHO recommendations (table 2) [1].

#### *Other Measures*

The WHO recommends home pasteurization of breast milk only as an 'interim' strategy, e.g. if ART is temporarily unavailable or the mother or infant is too ill to breastfeed [1]. Adequately heat treated, expressed milk from HIV-positive mothers does not transmit HIV and remains nutritionally and immunologically superior to infant formula. Wet-nursing may be considered in communities where this option is accepted. The wet nurse needs to have a negative HIV test before and 6 weeks after starting. Experience with breast milk banks in Latin America, particularly Brazil, has been positive, although limited by the extent of coverage of the at-risk population. HIV-infected caregivers should be warned against the common practice of providing children with pre-masticated (pre-chewed) food as this practice has been implicated in HIV transmission [5].

#### **Feeding the HIV-Infected Child Not on ART**

Nine of 10 studies on HIV-infected children, conducted in resource-constrained countries, reported low height-for-age (stunting), and all 10 described poor weight gain [6]. Untreated HIV infection is characterized by increased resting energy expenditure, and decreased appetite, digestion of food and absorption of nutrients. HIV-infected children often have a range of micronutrient deficiencies.

At their first contact with a health care professional, children with HIV should have their anthropometric status (e.g. weight, height, head circumference and arm circumference) measured, and nutritional problems screened for. A dietary history should be obtained and compared with estimated needs to assess adequacy of intake.

Women who have an HIV-infected child should be strongly encouraged to breastfeed. Since it is difficult to calculate the precise caloric needs of an HIV-infected child, the energy intakes for HIV-infected children experiencing weight loss need to be increased by 50–100% over established requirements for otherwise healthy uninfected children [7].

After 4–6 months, complementary foods should be increased to as much as can be tolerated. If the child is eating solids, adding a high-fat supplement

such as oil or margarine may be helpful. Commercial nutritional supplements are an acceptable alternative. Supplementation with specific macronutrients such as amino acids, whey protein concentration or other dietary supplements (such as spirulina) does not significantly alter clinical, anthropometric or immunological outcomes compared with placebo in HIV-infected children [8].

Adequate micronutrient intake is best achieved via an adequate diet. In keeping with WHO recommendations, children younger than 5 years born to HIV-infected mothers living in resource-limited settings should receive periodic (6-monthly) vitamin A supplements in the same dose as for other children. There are no evidence-based guidelines on the appropriate prescription of micronutrient supplements for HIV-infected children.

### **Feeding the HIV-Infected Child on ART**

Initiation of ART therapy is associated with improvements in many growth parameters for HIV-infected children. Immediate gains first manifest in weight and arm muscle circumference. Lean body mass improves as well, while a height response occurs more slowly and variably. Energy expenditure in children on ART has not been studied.

Gains in weight correlate with treatment response. Underlying malnutrition does not adversely affect growth, immunologic or virologic response to ART in HIV-infected children. Underweight children exhibit an equally robust response to ART as their well-nourished peers [9]. The BMI does not increase in all children, but improvements are greatest in children with the lowest baseline BMI and who have more advanced HIV disease.

Children are not spared from the metabolic effects of ART, particularly protease inhibitors, and they too have a significant (up to 33%) risk of lipodystrophy syndrome, hyperlipidemia and peripheral insulin resistance. No therapeutic strategies to diminish the clinical and biochemical fea-

tures of the fat redistribution syndrome have yet been described for children.

Adolescents who acquired HIV infection in early life have a unique development profile that includes stunting, delayed puberty and the complications of prolonged ART exposure. Dietary goals for HIV-infected adolescents are similar to those for their noninfected peers, including consumption of a high-quality, nutrient-dense diet, establishing good eating habits and avoiding obesity.

The integration of nutritional support for HIV-infected children on ART is a recognized need; however, the evidence for effective programmatic solutions is weak. Limited data exist regarding the role of macro- or micronutrients in children on ART.

The WHO has previously endorsed the use of ready-to-use therapeutic foods to reduce case fatality and undernutrition among community-based, ART-naïve, HIV-positive children [10]. In Tanzania, among HIV-positive children on ART, the provision of ready-to-use therapeutic foods for at least 4 months was associated with less underweight, wasting and stunting [11].

### **Conclusions**

- Nutritional advice and support should be a priority component of the continuum of care and support services for HIV-infected women and children
- A focus on the growth and nutrition of the HIV-infected child at each visit is warranted. An adequate diet, prevention of opportunistic infections and ART all contribute to ensuring satisfactory growth
- There is limited evidence for routine macro- and micronutrient supplementation in both untreated and ART-treated HIV-infected children
- The special nutritional needs of adolescents need to be considered as more children on ART survive to this age

## References

- 1 WHO: Guidelines on HIV and infant feeding 2010: principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva, WHO, 2010. [http://www.who.int/maternal\\_child\\_adolescent/documents/9789241599535/en/](http://www.who.int/maternal_child_adolescent/documents/9789241599535/en/) (accessed July 3, 2013).
- 2 Bulterys M, Ellington S, Kourtis AP: HIV-1 and breastfeeding: biology of transmission and advances in prevention. *Clin Perinatol* 2010;37:807–824.
- 3 Committee on Pediatric Aids: Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics* 2013;131:391–396.
- 4 Taylor GP, Anderson J, Clayden P, Gazzard BG, Fortin J, et al: British HIV Association and Children's HIV Association position statement on infant feeding in the UK 2011. *HIV Med* 2011;12:389–393.
- 5 Ivy W 3rd, Dominguez KL, Rakhmanina NY, Iuliano AD, Danner SP, Borkowf CB, et al: Premastication as a route of pediatric HIV transmission: case-control and cross-sectional investigations. *J Acquir Immune Defic Syndr* 2012;59:207–212.
- 6 Isanaka S, Duggan C, Fawzi WW: Patterns of postnatal growth in HIV-infected and HIV-exposed children. *Nutr Rev* 2009;67:343–359.
- 7 WHO: Nutrient requirements for people living with HIV/AIDS: report of a technical consultation. Geneva, WHO, 2003.
- 8 Grobler L, Siegfried N, Visser ME, Mahlungulu SS, Volmink J: Nutritional interventions for reducing morbidity and mortality in people with HIV. *Cochrane Database Syst Rev* 2013;2:CD004536.
- 9 Naidoo R, Rennert W, Lung A, Naidoo K, McKerrow N: The influence of nutritional status on the response to HAART in HIV-infected children in South Africa. *Pediatr Infect Dis J* 2010;29:511–513.
- 10 WHO: Community-based management of severe acute malnutrition. Geneva, WHO, 2007.
- 11 Sunguya BF, Poudel KC, Mlunde LB, Otsuka K, Yasuoka J, Urassa DP, et al: Ready-to-Use Therapeutic Foods (RUTF) improves undernutrition among ART-treated, HIV-positive children in Dar es Salaam, Tanzania. *Nutr J* 2012;11:60.



## 3.8 Nutritional Management in Cholestatic Liver Disease

Bram P. Raphael

### Key Words

Cholestasis · Cirrhosis · Biliary atresia · Vitamins

### Key Messages

- Nutritional issues are common in children with cholestatic liver disease
- Patients need special attention to prevent fat-soluble vitamin deficiencies
- Cirrhosis and ascites require fluid and electrolyte management
- Liver transplantation is associated with improvement in growth and development

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The most common types of cholestatic liver disease in children include extrahepatic biliary atresia, Alagille's syndrome,  $\alpha_1$ -antitrypsin deficiency, cystic fibrosis and intestinal failure-associated liver disease. Other causes include primary sclerosing cholangitis and drug-induced liver injury. Nutritional issues are common in children with all types of cholestatic liver disease.

Causes of malnutrition are inadequate energy intake, intestinal malabsorption and increased energy needs (table 1). The underlying mecha-

nisms are multifactorial, including gastric dysmotility, ascites, bacterial overgrowth, hepatomegaly and secondary effects from medications. There may be problems with malabsorption. Decreased hepatic bile salt excretion leads to inadequate micelle formation and impaired lipid and fat-soluble vitamin uptake. Triglyceride clearance may also be impaired. Moreover, infants and children with chronic liver disease may have increased energy needs. For example, resting energy expenditure is increased by 30% in extrahepatic biliary atresia [1]. Factors contributing to hypermetabolism include ascites, infection and portal hypertension.

Nutritional assessment begins with a careful dietary history and review of growth records. Special attention should be devoted to sodium and fluid intake. Over time, ascites and edema may lead to changes in weight deceptively similar to weight gain. In addition, hypoalbuminemia may reflect impaired hepatic synthetic function as opposed to protein energy malnutrition. Interpretation of certain micronutrient levels requires simultaneous measurement of carrier proteins. Because calcium and magnesium are bound to albumin, serum levels may appear falsely low in the setting of hypoalbuminemia. Ionized calci-

**Table 1.** Clinical manifestations and etiologies of common nutritional problems in liver disease

Nutrient affected	Manifestation	Etiology
Protein	Stunting, muscle wasting, motor developmental delay Ascites or peripheral edema	Protein energy malnutrition, decreased insulin-like growth factor 1 synthesis Decreased albumin synthesis leading to decreased oncotic pressure
	Coagulopathy Hepatic encephalopathy	Alteration of synthesis in clotting factors Decreased aromatic amino acid metabolism
Fat	Steatorrhea, essential fatty acid deficiency (rash), fat-soluble vitamin deficiencies (see below)	Impaired intestinal absorption, decreased intake of essential fatty acids
	Hypercholesterolemia, hypertriglyceridemia (xanthomas)	Impaired hepatic lipid clearance
Carbohydrate	Hyperglycemia	Insulin resistance leading to impaired muscle and liver glycogen synthesis
	Fasting hypoglycemia	Decreased glycogen stores with hepatocellular dysfunction
Vitamin A	Night blindness, degeneration of retina, xerophthalmia, poor growth, hyperkeratosis	Impaired intestinal absorption
Vitamin D	Rickets, osteoporosis, cranial bossing, epiphyseal enlargement, persistently open fontanelle in infants	Impaired intestinal absorption, and decreased hepatic 25-hydroxylation
Vitamin E	Peripheral neuropathy, ataxia, hemolytic anemia	Impaired intestinal absorption
Vitamin K	Coagulopathy, hemorrhagic manifestations such as bruising, bone disease	Impaired intestinal absorption
Minerals	Low iron, copper, zinc, selenium, calcium	Impaired intestinal absorption

um may be helpful in this setting. Similarly, the retinol-to-retinol-binding protein ratio (retinol divided by retinol-binding protein, both in micromoles per liter) is a preferred method of interpreting vitamin A status. Possible toxicity is suggested by a ratio of >1, and deficiency is suggested by a ratio of <0.8. Similarly, vitamins E status should be interpreted by the ratio of vitamin E to the total lipid concentration. Vitamin E deficiency is suggested by a ratio of <0.6 mg/g in children under the age of 1 year, and <0.8 mg/g in older children.

To compensate for increased energy needs and anorexia, supplemental nasogastric tube feeds

may be helpful. Hepatosplenomegaly, ascites or varices may limit the feasibility of placing a permanent feeding tube. Parenteral nutrition should be reserved for those incapable of receiving enteral feeds by mouth or feeding tube, or for those unwilling to do so. Although there is unease surrounding parenteral nutrition due to possible hepatotoxicity, it may be used safely for short intervals without problems. Standard parenteral amino acid solutions are adequate in nearly all situations. In studies on adults, the use of branched-chain amino acids may have shown beneficial effects on uncontrolled encephalopathy. At this time, the use of branched-chain ami-

**Table 2.** Maintenance recommendations on vitamin and mineral supplementation for patients with cholestasis

	Product	Dose
Vitamin A [3]	Liquid vitamin A	5,000–25,000 IU/day
Vitamin D [4]	Vitamin D	200–1,000 IU/day
Vitamin E [5, 6]	Liquid vitamin E (preferably water-soluble preparation)	15–25 IU/kg/day
Vitamin K [7]	Vitamin K <sub>1</sub> (Mephyton)	2.5–5 mg/day, every 2–3 days
Zinc [4]	Zinc sulfate	1 mg/kg/day
Calcium [4]	Elemental calcium	25–100 mg/kg/day
Phosphorus [4]	Elemental phosphorus	25–50 mg/kg/day

no acid formulae in children with chronic liver disease is only investigational.

With coexisting cirrhosis there are added nutritional challenges such as anorexia, impaired glucose tolerance and salt-fluid balance. Patients with cirrhosis can have impaired glucose tolerance with hyperinsulinemia and insulin resistance. Protein energy malnutrition is present in 20% of patients with well-compensated cirrhosis and in 60% of patients with severe liver dysfunction [2]. On the other hand, decreased glycogen stores and decreased glucose production in all types of end-stage liver disease may result in fasting hypoglycemia. Protein turnover is usually normal or increased.

Where the cholestasis is attributed primarily to chronic parenteral nutritional exposure, restricting the dose of intravenous lipid emulsion may be considered, typically 1–2 g/kg/day. The use of alternative lipid emulsions should be considered because components of soybean-based lipids have been suspected for their possible role in intestinal failure-associated liver disease, including plant sterols, high intakes of precursor polyunsaturated fatty acids, low-bioactivity vitamin E content, and others. Restricting enteral fat intake is not indicated. Alternative intravenous lipid emulsions containing fish oil show promise, and further studies are anticipated.

In choosing enteral formulae, standard products may be adequate. With intestinal malabsorption, patients may benefit from formulae rich

in medium-chain triglycerides or formulae supplemented with medium-chain triglyceride oil. When using specialized formulae chronically, long-chain triglycerides are also needed to prevent essential fatty acid deficiency. Restrictive diets are not necessary, and may be dangerous. Protein should be provided according to the recommended daily allowance in order to prevent protein catabolism. It may be appropriate to temper sodium intake for ascites or edema. Table 2 lists recommendations on vitamin and mineral supplementation for chronic liver disease.

Successful liver transplantation is usually associated with improved growth and developmental outcomes. Following liver transplantation, enteral feeds should be started as soon as possible, but short-term parenteral nutrition may be safely used while awaiting return of bowel function. Tube feeds may be helpful in postoperative anorexia. Mild sodium restriction may be necessary to minimize edema with steroids.

## Conclusions

- Children with cholestatic liver disease have special nutritional needs
- Treatment is aimed at reversing consequences of anorexia, increased energy needs, associated intestinal malabsorption as well as altered carbohydrate and protein metabolism

## References

- 1 Pierro A, Koletzko B, Carnielli V, et al: Resting energy expenditure is increased in infants and children with extrahepatic biliary atresia. *J Pediatr Surg* 1989;24:534–538.
- 2 Nutritional status in cirrhosis. Italian Multicentre Cooperative Project on Nutrition in Liver Cirrhosis. *J Hepatol* 1994;21:317–325.
- 3 Erlichman J, Hohlweg K, Haber BA: Biliary atresia: how medical complications and therapies impact outcome. *Expert Rev Gastroenterol Hepatol* 2009;3:425–434.
- 4 Ramirez RO, Sokol KI: Medical management of cholestasis; in Suchy FJ (ed): *Liver Disease in Children*. St Louis, Mosby, 1994.
- 5 Sathe MN, Patel AS: Update in pediatrics: focus on fat-soluble vitamins. *Nutr Clin Pract* 2010;25:340–346.
- 6 Kelly DA, Davenport M: Current management of biliary atresia. *Arch Dis Child* 2007;92:1132–1135.
- 7 Duggan C, Watkins JB, Walker WA: *Nutrition in Pediatrics: Basic Science, Clinical Application*, ed 4. Hamilton, BC Decker, 2008.

## 3.9 Malabsorptive Disorders and Short Bowel Syndrome

Olivier Goulet

### Key Words

Short bowel syndrome · Intestinal adaptation · Protracted diarrhea of infancy · Parenteral nutrition · Feeding, oral, enteral · Breast milk · Long-chain fatty acid-containing formulas · Medium-chain triglycerides · Hydrolyzed protein formulas · Amino acid formulas · Small intestinal bacterial overgrowth · Feeding aversion

### Key Messages

- Protracted diarrhea of infancy or short bowel syndrome (SBS) requires parenteral nutrition together with oral feeding (OF) or enteral feeding (EF). The use of the gastrointestinal (GI) tract as early and as much as possible, according to clinical tolerance, should be promoted and feeding aversion prevented
- Adaptation – the physical and physiological processes by which the intestine compensates for loss of intestinal length or function – is optimized with the provision of OF or EF
- Direct mucosal contact with nutrients, pancreaticobiliary secretions and neurohormonal factors explains how the use of the GI tract promotes physiological intestinal adaptation. It may also contribute to preventing cholestasis and liver disease
- The intestinal microbiota has both positive (short-chain fatty acid production) and deleterious effects (intraluminal bacterial overgrowth)

- The types of diet regarding breast milk, protein hydrolysates and formulas containing amino acids or long- or medium-chain fatty acids remain controversial. The routes (oral, gastric and transpyloric) and the modes (bolus, continuous or both) of feeding are also debated. Very few randomized trials have been performed

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### Introduction

The so-called protracted diarrhea of infancy (PDI), which has become a rare condition in developed countries, is caused by severe malabsorption secondary to an acquired intestinal mucosal injury due to infection, inflammation or allergic reaction. ‘Intractable diarrhea of infancy’ refers to congenital enteropathies involving the development or renewal of intestinal mucosa that lead to very long-lasting or often irreversible intestinal failure (IF) [1]. Short bowel syndrome (SBS) is the leading cause of IF and is a state of malabsorption following extensive small intestinal resection. The functional consequences as well as the prognosis of SBS depend on the age-adjusted small bowel length, site of resection, presence or absence of the ileocecal valve (ICV) and occurrence

of cholestasis [2]. The cause of resection and the age of a patient also influence the functional capacity of the remnant gut and its potential for adaptation [2, 3]. Management of SBS involves measures aimed at promoting small bowel adaptation and villous hyperplasia by enteral (oral or tube) feeding, by providing normal somatic growth with parenteral nutrition (PN), and by optimizing the bowel's absorptive surface via nontransplant surgical techniques. PN is the cornerstone of management, but as much enteral feeding (EF) as possible should be provided to the patient to improve the physiological processes of small bowel adaptation. Moreover, in infants or children, oral feeding (OF) skills have to be acquired or maintained. Different concepts exist with respect to what the composition of feeds (elemental, semi-elemental or polymeric) and their mode of delivery (OF or gastric tube feeding) should be. Current studies do not provide evidence-based data for establishing recommendations for SBS patients.

### Rationale for EF

The use of the gastrointestinal (GI) tract is vital for preserving or restoring normal intestinal structure and function [3]. Functional intestinal adaptation refers to the gross anatomic and histologic changes that occur after extensive intestinal resection. Following bowel enlargement and lengthening of villi, the intestinal absorptive surface area increases, and absorptive function gradually improves. Changes in intestinal motility, commensal microbiota and barrier function are associated with the anatomic and histologic changes. The use of the intestinal tract has a critical role in the process of intestinal adaptation, based on the effects of direct nutrient contact with the mucosa, pancreatic and hepatobiliary secretions, and circulating hormones. OF promotes the release of epidermal growth factor (EGF) from salivary glands, increases GI secretion of

trophic factors and helps prevent feeding disorders. Only few clinical trials have been performed on patients with PDI or SBS, but they support that EF maintains and/or promotes intestinal function [4–6]. The choice of diet as well the mode of delivery remain debated (tables 1, 2).

### Which Diet Should Be Used

*Breast milk* contains lactose and theoretically is considered to be not well tolerated by patients with a reduced intestinal surface area. However, breast milk contains many factors that may promote intestinal adaptation and has been shown to improve immune function as well as the genesis of a fecal microbiota rich in lactobacilli and bifidobacteria. With infants with SBS, the percentage of days that they received breast milk was correlated with fewer days of PN use [7]. To patients with neonatal SBS, breast milk should be given as often as possible – by breastfeeding or, if necessary, by tube feeding.

*The choice of enteral formula* is controversial. A limited mucosal absorptive surface area can lead to lactose, long-chain fatty acid and protein malabsorption. In PDI, electrolyte and metabolic balance can be difficult to achieve. In SBS patients, complex nutrients may promote mucosal cell proliferation via direct contact with disaccharides [8]. Additionally, colonic exposure to luminal nutrients promotes the release of trophic factors that enhance small bowel mucosal trophicity.

*Oligo- and polysaccharides* are poorly tolerated by these patients, being broken down into osmotically active organic acids that can present a major osmotic load to the distal small intestine and colon. For patients with intractable diarrhea of infancy, the carbohydrate content should not exceed 40% of calories, and be lactose free.

*Fiber supplementation*, by promoting the production of short-chain fatty acids such as butyrate, has trophic effects on the small intestine. Short-

**Table 1.** Which type of diet should be used*Breast milk*

- Contains lactose, growth factors, nucleotides, long-chain fatty acids, glutamine and other amino acids that promote intestinal adaptation
- Promotes microbiota rich in lactobacilli and bifidobacteria
- In infants with SBS, it reduces the duration of PN
- Should be used as much as possible in neonatal SBS

*Enteral formulas*

## Carbohydrates

## Oligo- and polysaccharides

- Poorly tolerated by patients with limited mucosal absorptive surface area
- Broken down in small intestinal lumen into osmotically active organic acids
- Should not exceed 40% of calories, and be lactose free for patients with intractable diarrhea of infancy

## Fiber supplementation

- Helpful in older children with SBS with intact colon
- Promotes colonic bacterial production of short-chain fatty acids

## Lipids

## Long-chain triglycerides

- Poorly digested in case of small intestinal bacterial overgrowth because of bile acid changes
- Poorly absorbed in patients with severe malabsorption
- Have trophic effects on small intestinal mucosa
- Supplementation with n-3 or n-6 polyunsaturated fatty acids may enhance mucosal growth

## MCT

- Rapidly hydrolyzed by pancreatic lipase
- Do not provide essential fatty acids
- Less dependent on an extensive absorptive surface for adequate absorption
- Water soluble, and absorbed intact directly into the portal circulation
- As part of lipid supply appropriate for most infants with SBS
- Excessive intake can cause diarrhea
- Recommended use of formulas containing no more than 60% MCT as fat

## Nitrogen

## HPF

- Have changed the incidence and outcome of PDI
- No demonstrated advantages in comparison with intact protein infant formulas
- Lactose free and containing MCT
- Recommended for SBS patients

## Elemental amino acid-based formulas

- Not yet established whether this type of formula can influence the outcome of SBS
- Contain lower amounts of MCT than HPF

## Glutamine

- Currently no benefit demonstrated

MCT = Medium-chain triglycerides; HPF = hydrolyzed protein formulas.

**Table 2.** Management and outcome of neonatal SBS according to anatomic characteristics

SBS is a very variable condition, which can be as mild as that following terminal ileal resection and also very debilitating following total jejunoileal and colonic resection. Management and outcome vary according to the cause, extent and site of resection and the degree of adaptation of the remaining bowel. Patients with dilated, poorly motile segments of small bowel (gastroschisis, atresia and necrotizing enterocolitis) should benefit from an approach aiming to reduce bowel dilatation and SIBO, since they may develop progressive liver disease. PN should be delivered, as soon as tolerance permits, by cyclical infusion. Early OF should be promoted, while the benefits of continuous EF should be balanced in combination with PN, the risk of 'intestinal overload' with subsequent SIBO, and tube feeding-induced food aversion and eating disorders

*SBS with SBL of <40 cm with loss of the ICV and associated partial or large colectomy*

Patients need home PN over a very long period of time. Indications for reducing PN are appropriate weight gain and tolerance to other feeds. However, digestive outcome for patients with SBL <40 cm and loss of the colon is poor; they will mostly remain dependent on permanent PN or intestinal transplantation

*SBS with SBL of <40 cm or only duodenum, with totally or largely intact colon*

Patients need long-term home PN. However, many infants and children may have a degree of adaptation and require less PN and benefit from orally and/or enterally administered nutrients. Some of them may be progressively weaned from PN. Infants with duodeno-right colon anastomosis have little chance of being weaned from PN and should receive OF to promote optimal psychological behavior. These patients are at risk of developing D-lactic acidosis

*SBS with SBL of 40 – 100 cm with loss of the ICV and associated partial or large colectomy*

Patients require midterm home PN and can immediately be fed orally. Combination of continuous EF and OF may help in reducing PN duration. Bile salt-induced diarrhea may impede rapid weaning from PN

*SBS with SBL of 40 – 100 cm with terminal ileum and the entire colon*

Patients require very short-term PN and can immediately be fed orally. EF in combination with OF may help in reducing PN duration. These patients are at risk of developing D-lactic acidosis

*SBS with terminal ileum resection*

Patients have bile salt-induced diarrhea and benefit from the administration of 1 – 2 g of cholestyramine 3 times a day to bind bile salts left unabsorbed by the resected ileum. Vitamin B<sub>12</sub> plasma levels should be measured, and if low, supplemental vitamin B<sub>12</sub> should be provided by intramuscular injection at a dose of 100 – 150 µg per month or 1,000 µg every 6 months

SIBO = Small intestinal bacterial overgrowth; SBL = small bowel length.

**Table 3.** Small intestinal bacterial overgrowth

*General remarks*

- Several factors intrinsic to SBS predispose to SIBO and explain its high prevalence in this patient population
- Poorly motile segments of the small bowel in close proximity to the colon are common in patients with SBS and dysmotility, and the intestinal stasis and contamination that results promotes abnormal growth of bacteria in the small intestine
- The link between SIBO, translocation, cholestasis, portal fibrosis and cirrhosis is now clearly established
- SIBO may significantly compromise digestive and absorptive functions and may delay or prevent weaning from PN
- Traditional clinical tests for overgrowth may be unreliable
- Management may include surgery if advocated; antibiotic therapy should be carefully selected to avoid resistance
- The intestinal microbiota plays an important role in intestinal adaptation and should be preserved as much as possible
- The use of probiotics might offer potential based on experimental evidence, but there is a lack of sufficient data from human studies. The use of D-lactate producing probiotics should be avoided
- D-Lactic acidosis is secondary to bacterial hypermetabolism, especially in the colon, as a consequence of intestinal malabsorption

*Definition*

- CFU per milliliter of bacteria in the proximal small bowel
- Overgrowth of  $>10^5$  CFU/ml
  - Overgrowth of  $>10^3$  CFU/ml provided that the species of bacteria isolated from the jejunal aspirate are those that normally colonize the large bowel or provided that those same species are absent from the saliva and gastric juice
  - Breath hydrogen testing

*Caused by small intestine stasis from:*

- Intestinal obstruction (e.g. stenosis, narrowed anastomosis)
- Blind loop from terminolateral anastomosis
- Dilated and poorly motile segments of the small bowel in close proximity to the colon

*Consequences*

- Small intestinal mucosal injury with villous atrophy and subsequent malabsorption
- Increased small intestinal mucosal permeability
- IgE-mediated sensitization and allergic enteritis
- Gram-negative sepsis from bacterial translocation
- Portal inflammation, cholestasis, fibrosis and end-stage liver disease (cirrhosis)

*Management*

Reversal or removal of any predisposing condition(s)

- Redo anastomosis
- Enteroplasty
  - Small intestinal tapering and lengthening (Bianchi procedure)
  - Serial transverse enteroplasty (STEP procedure)

Appropriate nutritional support/replacement

Suppression or eradication of the contaminating bacterial flora

- Intermittent bowel decontamination with antibiotics
- Use of probiotics (*Lactobacillus rhamnosus* GG, *Saccharomyces boulardii*, etc.)

CFU = Colony-forming unit.

chain fatty acids, especially butyrate, are known to promote glucagon-like peptide-2 release.

*Long-chain triglycerides* are poorly absorbed by patients with a reduced absorptive surface. In case of small intestinal bacterial overgrowth (SIBO), bacteria metabolize and inactivate bile acids, preventing the solubilization necessary for long-chain triglyceride digestion.

*Medium-chain triglycerides* (MCT) are rapidly hydrolyzed by pancreatic lipase and are less dependent on an extensive absorptive surface for adequate absorption. They are water soluble, and can be absorbed intact directly into the portal circulation [9]. Excessive intake of MCT can cause diarrhea and ketosis, while MCT do not provide essential fatty acids. Current clinical practice is based on formulas containing no more than 60% MCT as fat.

*Whether the molecular form of the nitrogen* taken up might influence PN duration and/or the occurrence of non-IgE-mediated sensitization and allergic enteritis remains debated. A link between SIBO, abnormal mucosal permeability and protein sensitization is possible, but the use of elemental diets (amino acid-based formulas) is not clinically established (table 3). Patients with dilated, poorly motile segments of the small bowel should benefit first from an approach aiming to reduce bowel dilatation and SIBO, with subsequent bacterial translocation [10].

*Hydrolyzed protein formulas* (HPF) have been used for many years and have changed the incidence and outcome of PDI during the last decades. HPF have been evaluated by comparison with intact protein infant formulas in a crossover study of 60 days duration on 10 infants with SBS [11]. No effect of formula type was observed on growth, nitrogen absorption or mucosal permeability. In general, HPF are lactose free and contain MCT [11, 12].

*Elemental amino acid-based formulas* (EAABF) have been introduced more recently for infants suffering from severe allergic diseases. It is not yet established whether this type of formula may influence the outcome of SBS. A ben-



**Table 4.** Different routes of feeding

Devices	Indications	Contraindications	Advantages	Disadvantages or risks
<i>OF</i> None	To be used systematically	Artificial ventilation Orofacial malformation	Discontinuous physiologic mode of feeding Self-regulation of intake EGF release by salivary glands Promotes bowel adaptation Psychological behavior	Insufficient intake
<i>Gastric feeding</i>				
Nasogastric	Nutritional support <3 months	Severe GE reflux Slow gastric emptying	Easy to place even at home	Frequent dislodgements Nasal symptoms
Percutaneous endoscopic gastrostomy	Nutritional support >3 months	Repeated abdominal surgery Abnormal gastric anatomy	Fewer occlusions with larger bore, one-step low-profile devices available	Skin injury at abdominal exit site
Surgical gastrostomy	Nutritional support >3 months	Poor candidate for surgery	Immediate placement of low-profile device, direct visualization of stomach	Open surgery
<i>Duodenal or jejunal feeding</i>				
Nasojejunal	Short term for patients with severe GERD, gastric dysmotility	Recent proximal surgical anastomosis	Radiologic or bedside placement techniques Noninvasive	Frequent dislodgements Risk of intussusception Nasal symptoms Intestinal contamination
Gastrojejunal	Longer-term EF for patients with severe GERD, gastric dysmotility or need for gastric decompression	Recent proximal surgical anastomosis	Endoscopic or radiologic placement through existing gastrostomy tube	Requires healing of gastrostomy tract prior to placement Skin injury at abdominal exit site Frequent occlusions of jejunal port Intestinal contamination
Jejunal	Long-term EF for patients with severe GERD and upper intestinal dysmotility	Dysmotility	Direct surgical access to small intestine	Open surgical procedure Mechanical problems Intestinal contamination

GE = Gastroesophageal; GERD = gastroesophageal reflux disease.

eficial effect of EAABF was reported in an open case study involving only 4 SBS patients with persistent feeding intolerance [13]. A retrospective study found a shorter duration of PN dependency with the use of EAABF [14]. Current data are insufficient to recommend such expensive formulas with often increased osmolality for infants and children with SBS.

*Glutamine (Gln)*, a nonessential amino acid, plays an important role in energy metabolism of the intestinal mucosa and other rapid-turnover tissues. A randomized controlled pilot study of Gln-supplemented EF in infants with IF failed to show any advantages [15]. Gln cannot be recommended unless larger multicenter trials on infants with IF provide evidence for beneficial effects.

**Table 5.** Modes and management of feeding

*Modes*

OF is the most physiological and most stimulates intestinal adaptation

Continuous EF is beneficial to patients with SBS or intractable diarrhea of infancy by improving saturation of carrier transport proteins, thus taking full advantage of the available absorptive surface area as compared with intermittent feeding

Oropharyngeal shunting suppresses direct stimulation of the salivary glands, resulting in lower release of EGF, an important intestinal mucosal trophic factor

Continuous infusion leads to a loss of self-regulation of intake with vomiting, or to intestinal stasis with an increased risk of SIBO and subsequent mucosal injury, sepsis, liver disease, etc.

In the case of full EF, a small extent of OF should be introduced in infants 2 or 3 times a day, to stimulate sucking and swallowing and to minimize the chances of eating disorders in the future

A nasogastric tube may impair normal acquisition of oral behavior and induces eating disorders

Percutaneous gastrostomy is indicated with children who require EF for >3 months

*Jejunal feeding*

- Whatever the device (nasojejunal, gastrojejunal or jejunal), it should be limited to very special situations
- Exposes to the risk of intestinal contamination with subsequent SIBO and sepsis
- Excessive infusion rate may be responsible for severe diarrhea and dehydration

*Progression and monitoring of feeding program*

Intestinal transit must be well established by coloanal transit or ostomy

*Absence of contraindications*

- Patient's general condition (sepsis, bleeding, respiratory distress syndrome, etc.)
- Bloody stools
- High ostomy or stool output of >3 ml/kg/h
- Bilious and/or persistent vomiting
- Electrolyte imbalance

*Quantify feeding tolerance*

- Stool or ostomy output
- Reducing substances in stools or ostomy output
- Recurrent vomiting and abdominal distension

*Ultimate goals*

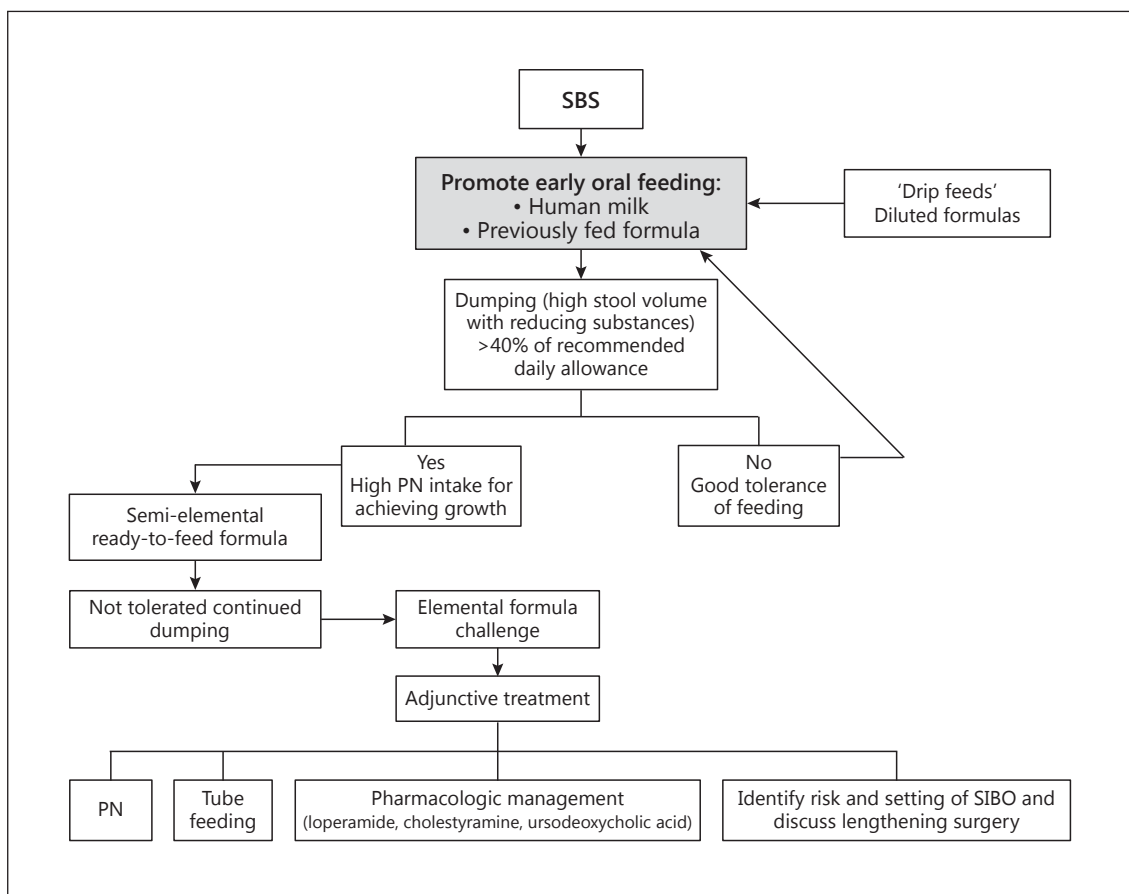
- Provide 150 – 200 ml/kg/day or 100 – 140 kcal/kg/day
- If ostomy/stool output precludes advancement at 20 cal/oz for 7 days
- Increasing caloric density of the formula can be performed
- Isocaloric reductions in PN support simultaneously with feeding advancement

*Warnings*

- EF can induce severe adverse effects related to intestinal overload and/or bacterial contamination with subsequent SIBO
- A meticulous approach, avoidance of excessive enteral formula supply, strict hygiene measures
- Concomitant OF prevents psychological disorders and eating aversion

*Water electrolyte losses from persistent diarrhea or end jejunostomies* should be replaced parenterally, based on the electrolyte concentration of the lost fluids. Monitoring urine sodium concentration provides guidance for correcting or preventing Na depletion (<10 mEq/l), even if serum sodium is near normal. Magnesium and

trace element losses can occur with high stoma output. Zinc supplements are often used empirically, given that serum values do not reliably reflect body stores. Ileal resection or diversion leads to fat-soluble vitamin and vitamin B<sub>12</sub> deficiency requiring monitoring and (parenteral) supplementation.



**Fig. 1.** Algorithm for management of feeding.

### Advancement of Feeding

Whatever the route of feeding (table 4), EF advancement can occur as long as fluid and electrolyte balance is maintained and nutritional goals are achieved (table 5). EF may eventually be transitioned to oral/bolus feeding, or oral/bolus and nocturnal feeding, in order to allow more freedom from the feeding pump. The transition from IF to adequate intestinal function can take weeks, months and sometimes years. The bowel function of infants with SBS improves over time due to the opportunity for further intestinal growth. Provi-

sion of EF plays a major role in the management of any child with IF, even of those for whom complete weaning from PN seems unlikely (fig. 1).

### Conclusions

- Intestinal adaptation following resection is a physiological process best enhanced by early use of the GI tract, especially by OF, which is more physiological, furthers oral skills and promotes the release of trophic factors such as EGF from the salivary glands

- Continuous EF has advantages for digestion/absorption of nutrients but should be used carefully to avoid 'intestinal overload' of poorly motile segments of the small bowel and development of eating disorders
- Breastfeeding may be used, and may be complemented with HPF containing up to 60% MCT. Current data are not sufficient to recommend EAABF for infants and children with SBS
- SIBO may significantly compromise digestive and absorptive functions, promotes liver disease and may delay or prevent weaning from PN

## References

- 1 D'Antiga L, Goulet O: Intestinal failure in children: the European view. *J Pediatr Gastroenterol Nutr* 2013;56:118–126.
- 2 Goulet O, Olieman J, Ksiazek J, Spolidoro J, Tibboe D, Köhler H, Yagci RV, Falconer J, Grimble G, Beattie RM: Neonatal short bowel syndrome as a model of intestinal failure: physiological background for enteral feeding. *Clin Nutr* 2013;32:162–171.
- 3 American Gastroenterological Association: American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. *Gastroenterology* 2003; 124:1105–1110.
- 4 Greene HL, McCabe DR, Merenstein GB: Protracted diarrhea and malnutrition in infancy: changes in intestinal morphology and disaccharidase activities during treatment with total intravenous nutrition or oral elemental diets. *J Pediatr* 1975;87:695–704.
- 5 Orenstein SR: Enteral versus parenteral therapy for intractable diarrhea of infancy: a prospective, randomized trial. *J Pediatr* 1986;109:277–286.
- 6 Sondheimer JM, Cadnapaphornchai M, Sontag M, Zerbe GO: Predicting the duration of dependence on parenteral nutrition after neonatal intestinal resection. *J Pediatr* 1998;132:80–84.
- 7 Andorsky DJ, Lund DP, Lillehei CW, Jaksic T, Dicanzio J, Richardson DS, Collier SB, Lo C, Duggan C: Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. *J Pediatr* 2001;139:27–33.
- 8 Bines JE, Taylor RG, Justice F, Paris MC, Sourial M, Nagy E, et al: Influence of diet complexity on intestinal adaptation following massive small bowel resection in a preclinical model. *J Gastroenterol Hepatol* 2002;17:1170–1179.
- 9 Bach AC, Babayan VK: Medium-chain triglycerides: an update. *Am J Clin Nutr* 1982;36:950–962.
- 10 Miyake Y, Yamamoto K: Role of gut microbiota in liver diseases. *Hepatal Res* 2013;43:139–146.
- 11 Ksiazek J, Piena M, Kierkus J, Lyszkowska M: Hydrolyzed versus nonhydrolyzed protein diet in short bowel syndrome in children. *J Pediatr Gastroenterol Nutr* 2002;35:615–618.
- 12 Bines J, Francis D, Hill D: Reducing parenteral requirement in children with short bowel syndrome: impact of an amino acid-based complete infant formula. *J Pediatr Gastroenterol Nutr* 1998; 26:123–128.
- 13 Andorsky DJ, Lund DP, Lillehei CW, et al: Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. *J Pediatr* 2001;139:27–33.
- 14 Vanderhoof JA, Young RJ: Hydrolyzed versus nonhydrolyzed protein diet in short bowel syndrome in children. *J Pediatr Gastroenterol Nutr* 2004;38:107.
- 15 Duggan C, Stark AR, Auestad N, et al: Glutamine supplementation in infants with gastrointestinal disease: a randomized, placebo-controlled pilot trial. *Nutrition* 2004;20:752–756.



## 3.10 Celiac Disease

Riccardo Troncone · Marco Sarno

### Key Words

Celiac disease · Gluten-free diet · Oats · Prevention · Gluten-related disorders

### Key Messages

- Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals
- CD offers a wide range of clinical presentations from severe gastrointestinal symptoms (diarrhea, vomiting and failure to thrive) and extraintestinal symptoms (iron deficiency anemia, neurological problems, alterations in liver function tests, enamel defects and osteoporosis) to asymptomatic cases. The nutrition status at diagnosis depends mostly on the extent of the intestinal damage
- All CD patients should be treated with lifelong gluten-free diet (GFD) irrespective of symptoms
- An experienced dietician should be involved in order to evaluate the patient's current nutritional status, to assess macronutrient and/or micronutrient intake, to detect deficiencies, to educate patients to the GFD and to monitor dietary compliance
- Alternative therapies and strategies of prevention can now be envisaged

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### Introduction

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines (from wheat, barley and rye) in genetically susceptible individuals. It is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies [antibodies to endomysium (EMA), tissue transglutaminase 2 (TG2) and deamidated gliadin peptides (DGP)], HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy [1].

The accuracy of identifying and estimating the real prevalence of CD has been improved in recent years by the introduction of serological screening tests: 0.6–1.0% of the European general population is affected, with some regional differences (0.3% in Germany, 0.9% in Italy and 2.4% in Finland) [2]. CD is also common in North and South America, North Africa and the Middle East. The prevalence of CD is increasing because of a westernization of diets, changes in wheat production and increased awareness of the disease.

CD offers a wide range of clinical presentations from severe gastrointestinal symptoms (diarrhea, vomiting and failure to thrive) and

**Table 1.** Fundamentals of the GFD

Grains that should be avoided	Wheat (including spelt, Kamut, semolina and triticale), rye and barley (including malt)
Safe grains (gluten free)	Rice, amaranth, buckwheat, corn, millet, quinoa, sorghum, teff (an Ethiopian cereal grain) and oats (?)
Sources of gluten-free starches that can be used as flour alternatives	Cereal grains: rice, amaranth, buckwheat, corn, millet, quinoa, sorghum and teff Tubers: potato, arrowroot, jicama, taro and tapioca Legumes: chickpeas, lentils, kidney beans, navy beans, pea beans, peanuts and soybeans Nuts: almonds, walnuts, chestnuts, hazelnuts and cashews Seeds: sunflower, flax and pumpkin

extraintestinal symptoms (iron deficiency anemia, neurological problems, alterations in liver function tests, enamel defects and osteoporosis) to asymptomatic cases [3]. Also, the small intestinal lesions may range from epithelial lymphocyte infiltration with preserved villous architecture to severe villous atrophy [4]. The nutrition status at diagnosis depends mostly on the extent of the intestinal damage. The classic presentation is accompanied by steatorrhea and fat-soluble vitamin deficiency. Malabsorption of iron, calcium and folic acid is also frequent, as these are absorbed in the proximal small intestine [5].

The diagnostic approach has recently been revised [1]. Children found positive for CD-specific antibodies (anti-TG2, EMA and anti-DGP) should undergo duodenal biopsies unless certain conditions are fulfilled which allow the option to omit the confirmatory biopsies. In children and adolescents with signs or symptoms suggestive of CD and very high anti-TG2 (or anti-DGP) titers with levels exceeding 10 times the upper limit of normal, the likelihood for villous atrophy (Marsh score 3) is high. In this situation, the pediatric gastroenterologist may discuss with the parents and patient (as appropriate for the patient's age) the option of performing further laboratory testing (EMA, HLA) in order to make the diagnosis of CD without biopsies. In the case of an asymptomatic

child or adolescent with CD-associated conditions, duodenal biopsies are still advocated in all cases.

### Gluten-Free Diet

The only treatment for CD is lifelong strict adherence to a gluten-free diet (GFD; table 1). GFD consist of the dietary exclusion of grains containing gluten (wheat, rye, barley, triticale, couscous, spelt and Kamut). Rice, corn and buckwheat do not contain gluten and can be eaten. Potato, chestnut, tapioca, sorghum, quinoa and amaranth are also tolerated. Although there is now a large body of clinical evidence suggesting oats lacking toxicity for CD patients, there are still some important aspects to consider [6]. There are documented cases of oat-dependent villous atrophy in patients with oat-specific mucosal T cell reactivity. Furthermore, there is also the possibility that symptoms are related to wheat proteins contaminating oats during the harvesting and milling process. Another issue that warrants further investigation is related to the great heterogeneity of oat cultivars. On the other hand, the incorporation of oats into a GFD provides high fiber and vitamin B content, increased palatability and beneficial effects on cardiovascular health. However, it seems wise to add oats only when the



GFD is well established, so that possible adverse reactions can be readily identified by a strict clinical follow-up.

There is a general consensus that all CD patients should be treated with a GFD irrespective of the presence of symptoms. However, while it is relatively easy to assess the health improvement after treatment of CD in patients with clinical symptoms of the disease, it proves difficult in persons with asymptomatic CD. A high rate of osteoporosis/osteopenia (60%) was observed in asymptomatic patients with villous atrophy; this finding suggests that, in CD, clinical tolerance does not reflect tolerance to gluten and that, in silent cases, the increased risk of osteoporosis substantiates the need for a GFD. There are no guidelines concerning the need for a GFD in subjects with 'potential' CD (patients with positive CD-associated serology but without enteropathy). Most of the 'potential' cases are left on gluten-containing diet and strictly monitored for the appearance of complications. While a risk of osteoporosis also for this group of patients has been reported in the past [7], no significant differences have recently been found between CD patients on a long-term GFD and 'latent' patients (patients with a clear previous diagnosis of CD and no clinical/histological relapse after a long period of GFD) as far as biological tests of malabsorption and the overall nutritional status, including bone mass density, are concerned. Similarly, we did not observe any major nutritional problem in our cohort of potential CD subjects [8].

#### *Compliance with GFD*

It is important that an experienced dietician with specific expertise in CD counseling educates the family and the child about dietary restrictions. An expert dietician should be consulted in order to evaluate the patient's current nutritional status, to assess macronutrient and/or micronutrient intake, to detect deficiencies, to educate the patient to the GFD and to monitor dietary compliance. Compliance with a GFD can be difficult, especial-

ly in adolescents [9]. It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical status and adherence to GFD. Periodic measurements of tissue TG antibody levels to document reductions in antibody titers can be helpful as indirect evidence of adherence to a GFD, although they are inaccurate in detecting slight dietary transgressions. Recently, methods based on the detection of a 33-mer gliadin peptide in feces have been proposed to assess compliance with the GFD [10].

#### *Limits*

More information is needed on the daily gluten amount that may be tolerated by CD patients. The data available so far seem to suggest that, although individual variability makes it difficult to set a universal threshold, this should be set below 50 mg/day, a level unlikely to cause significant histological abnormalities. The regulations on the composition and labeling of food suitable for CD patients have recently changed. In 2008, the Codex Alimentarius revised the previous standard indicating 2 thresholds: 20 ppm for products to be labeled gluten free and 100 ppm for products with very low gluten content. The 20-ppm threshold is considered a safe option for CD patients, considering the overall consumption of gluten-free products [11].

#### **Alternative Therapies**

Breeding programs and transgenic technology may lead to the production of wheat that is devoid of biologically active peptide sequences. Recently, new, alternative approaches to GFD have been investigated (table 2) [12]. As gliadin peptides are highly resistant to digestive processing, prolyl endopeptidase produced by probiotic microorganisms has been shown to promote digestion of gliadin. Clinical trials have already started. Other approaches include restoring intestinal permea-

**Table 2.** Alternative therapies for CD

1. Intraluminal therapies
Wheat varieties
(Ancient) wheat variants with low immunogenicity
Genetically modified wheat variants or deletion lines of common wheat with lower immunogenicity
Flour/dough treatment
Pretreatment with lactobacilli
Transamidation of gliadin
Ingested gliadin peptide modifications
Prolyl endopeptidases from <i>Aspergillus niger</i> or <i>Sphingomonas capsulata</i>
Intraluminal gliadin binding by polymers
2. Transepithelial uptake
Epithelial tight junctions
ZOT receptor antagonist AT1001
3. Adaptive immune response
TG2
TG inhibitors
HLA-DQ2
Blocking DQ2 analogs
4. Immune modulators
Gluten vaccination
5. Biologicals (T cell or cytokine blockers)

bility with anti-zonulin antibodies, preventing gliadin presentation to T cells by blocking HLA binding sites and the use of tissue TG inhibitors. The efficacy of these approaches needs to be assessed in more in vivo studies.

## Prevention

Evidence suggests that the first months of life are crucial for CD development; breastfeeding has a protective role, and indeed there is a negative correlation between its duration and the development of CD. Moreover, the age at introduction of gluten to the diet is important: exposure to gluten in the first 3 months significantly increases the risk of CD in genetically susceptible individuals.

One study has suggested the existence of a window of opportunity as the late introduction of gluten to the diet (after the 7th month of life) has been found to be associated with a higher risk. On the basis of the present evidence, breastfeeding should be strongly encouraged and gluten should not be introduced before the 4th month of life, preferably while the baby is still breastfed [13]. Finally, increasing attention is being devoted to the possible role of viruses, which could trigger CD autoimmunity in genetically susceptible children by increasing intestinal permeability and activating innate immune pathways linked to CD pathophysiology.

## Other Conditions Requiring GFD

The spectrum of gluten-related disorders also includes wheat allergy (WA) and nonceliac gluten sensitivity (NCGS). WA is defined as an adverse immunologic reaction to wheat proteins. Depending on the allergen exposure and the immunologic mechanisms, WA is classified into (1) classic food allergy affecting the skin, gastrointestinal tract or respiratory tract, (2) wheat-dependent, exercise-induced anaphylaxis, (3) occupational asthma (baker's asthma) and rhinitis as well as (4) contact urticaria. IgE antibodies play a central role in the pathogenesis of these diseases. WA is treated by GFD, and the same limits as discussed for CD seem to apply to WA [14].

NCGS refers to individuals who show distress when eating gluten and improvement when following a GFD. CD autoantibodies are absent, the small intestine is usually normal, and allergy tests are negative. Thus, NCGS is a diagnosis by exclusion criteria. However, many suggest caution, as there is a noticeable lack of controlled studies unequivocally demonstrating the role of gluten. Other food components (fermentable oligo-, di- and monosaccharides and polyols or FODMAPs) have been suspected to be responsible for symptoms attributed to NCGS. Further caution is required due



to the fact that unmotivated GFD is dangerous not only because of the costs imposed upon the community but also because it may affect the health of incorrectly classified patients [15].

## Conclusions

- CD patients should be treated with GFD irrespective of the presence of symptoms. There is still uncertainty as to whether to treat 'potential' CD or not

- It is important that an experienced dietician with specific expertise educates the family and the child about dietary restrictions
- It seems wise to add oats only when the GFD is well established, so that possible adverse reactions can be readily identified
- The 20-ppm threshold is considered a safe option for CD patients
- To prevent CD, breastfeeding should be strongly encouraged; gluten should not be introduced before the 4th month of life, preferably while the baby is still breastfed

## References

- 1 Husby S, Koletzko S, Korponay-Szabó IR, et al; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition: European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54:136–160.
- 2 Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, Murray L, Metzger MH, Gasparin M, Bravi E, Mäki M; Coeliac EU Cluster, Project Epidemiology: The prevalence of coeliac disease in Europe: results of a centralized, international mass screening project. *Ann Med* 2010;42:587–595.
- 3 Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C: The Oslo definitions for coeliac disease and related terms. *Gut* 2013;62:43–52.
- 4 Oberhuber G, Granditsch G, Vogelsang H: The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol* 1999;11:1185–1194.
- 5 Garcia-Manzanares A, Lucendo JA: Nutritional and dietary aspects of celiac disease. *Nutr Clin Pract* 2011;26:163–173.
- 6 Pulido O, Gillespie Z, Zarkadas M, et al: Introduction of oats in the diet of individuals with celiac disease: a systematic review. *Adv Food Nutr Res* 2009;57:235–285.
- 7 Kaukinen K, Mäki M, Partanen J, Sievänen H, Collin P: Celiac disease without villous atrophy: revision of criteria called for. *Dig Dis Sci* 2001;46:879–887.
- 8 Tosco A, Salvati VM, Auricchio R, Maglio M, Borrelli M, Coruzzo A, Paparo F, Boffardi M, Esposito A, D'Adamo G, Malamisura B, Greco L, Troncone R: Natural history of potential celiac disease in children. *Clin Gastroenterol Hepatol* 2011;9:320–325.
- 9 Errichiello S, Esposito O, Di Mase R, Camarca ME, Natale C, Limongelli MG, Marano C, Coruzzo A, Lombardo M, Strisciuglio P, Greco L: Celiac disease: predictors of compliance with a gluten-free diet in adolescents and young adults. *J Pediatr Gastroenterol Nutr* 2010;50:54–60.
- 10 Comino I, Real A, Vivas S, Siglez MÁ, Caminero A, Nistal E, Casqueiro J, Rodríguez-Herrera A, Cebolla A, Sousa C: Monitoring of gluten-free diet compliance in celiac patients by assessment of gliadin 33-mer equivalent epitopes in feces. *Am J Clin Nutr* 2012;95:670–677.
- 11 Gilbert A, Kruijzinga AG, Neuhold S, Haoben GF, Canela MA, Fasano A, Cattassi C: Might gluten traces in wheat substitutes pose a risk in patients with celiac disease? A population-based probabilistic approach to risk estimation. *Am J Clin Nutr* 2013;97:109–116.
- 12 Gianfrani C, Auricchio S, Troncone R: Possible drug targets for celiac disease. *Expert Opin Ther Targets* 2006;10:601–611.
- 13 Szajewska H, Chmielewska A, Pieścik-Lech M, Ivarsson A, Kolacek S, Koletzko S, Mearin ML, Shamir R, Auricchio R, Troncone R; PREVENTCD Study Group: Systematic review: early infant feeding and the prevention of coeliac disease. *Aliment Pharmacol Ther* 2012;36:607–618.
- 14 Hischenhuber C, Crevel R, Jarry B, Mäki M, Moneret-Vautrin DA, Romano A, Troncone R, Ward R: Review article: safe amounts of gluten for patients with wheat allergy or coeliac disease. *Aliment Pharmacol Ther* 2006;23:559–575.
- 15 Di Sabatino A, Giuffrida P, Corazza GR: Still waiting for a definition of nonceliac gluten sensitivity. *J Clin Gastroenterol* 2013;47:567–569.

## 3.11 Food Intolerance and Allergy

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### Key Words

Food allergy · Lactose intolerance · Enteropathy, food protein-induced · Enterocolitis syndrome, food protein-induced · Proctocolitis, food protein-induced · Elimination diet · Hypoallergenic formula · Amino acid-based formula · Hydrolyzed formula · Soy formula

### Key Messages

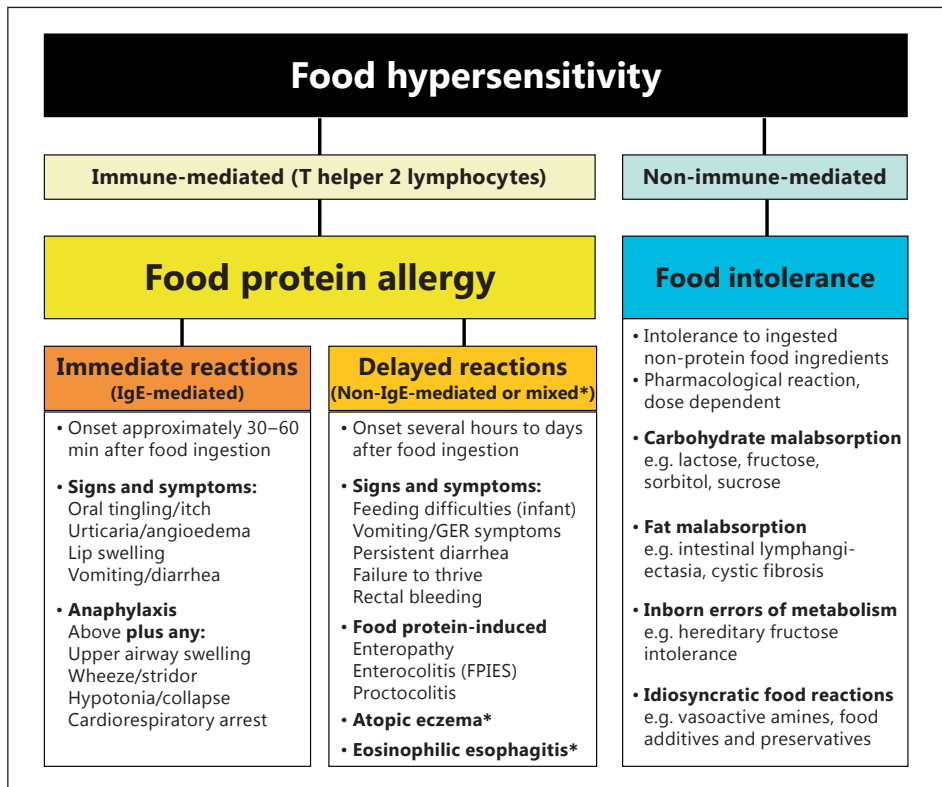
- *Food allergy* is an immune-mediated reaction against food proteins, whereas *food intolerances* can be caused by any food constituent and do not involve immunological mechanisms
- Treatment of food allergies involves strict avoidance of the offending food allergen, either by use of a hypoallergenic infant formula or a specific elimination diet. By contrast, patients with food intolerances generally tolerate small quantities of the offending food ingredient (dose-response relationship)
- Infants and young children with gastrointestinal food allergies and persistent vomiting or diarrhea are at high risk of failure to thrive, particularly if there are associated feeding difficulties
- Correct identification of food allergies and intolerances in infancy and childhood is important in order to prevent growth impairment and nutritional deficiency states

- Close monitoring of dietary intake and growth parameters, regular reassessment of persistent allergies and dietary introduction of tolerated food proteins are essential steps in the nutritional management of children with food allergies

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### Introduction

Food allergy is defined as a reproducible, T helper lymphocyte type 2-mediated reaction to food proteins. Over the past decades, the prevalence of food allergy has increased dramatically in many developed countries. Cow's milk, egg, soy, wheat, peanuts, tree nuts, fish and shellfish cause more than 90% of food allergies [1]. A recent population-based study in Australia demonstrated challenge-proven, immunoglobulin E (IgE)-mediated food allergy in more than 10% of 12-month-old infants [2]. Possible reasons for the increased prevalence of food allergy in children include genetic factors, epigenetic dysregulation of gene expression, exposure to toxins and pollutants (e.g. tobacco smoke), dietary factors, reduced environmental microbial exposure and reduced fecal microbial diversity [3, 4].



**Fig. 1.** Classification of adverse reactions to foods. GER = Gastroesophageal reflux; FPIES = food protein-induced enterocolitis syndrome.

Food allergy needs to be distinguished from food intolerance, which is a non-immune-mediated adverse reaction to food constituents [2]. Examples of food intolerance include lactose malabsorption, fructose malabsorption as well as idiosyncratic reactions to food additives or naturally occurring vasoactive compounds in foods. Lactose malabsorption is the most common food intolerance in non-Caucasian individuals. About 70% of adults worldwide suffer from lactose intolerance due to a genetically determined decline in lactase activity (adult-onset hypolactasia) [5]. In children, food intolerances may indicate the presence of an underlying gastrointestinal condition such as celiac disease or other enteropathies [6]. Due to considerable

overlap between the symptoms of gastrointestinal food allergy and intolerances, the diagnostic process can be complex and confusing. For example, cow's milk may cause diarrhea due to non-IgE-mediated gastrointestinal allergy to cow's milk protein, or due to malabsorption of lactose (lactose intolerance).

### Pathophysiology

There are two main types of allergic reactions to food, differentiated by the timing of onset in relation to food ingestion (fig. 1). Immediate-onset reactions occur within minutes after ingestion. In these patients, the reaction is mediated by food-

specific serum IgE antibodies [1]. Delayed-onset reactions occur within several hours to days after ingestion and may involve the gut, skin or respiratory tract. These reactions are cell mediated (lymphocytes, eosinophils and mast cells), and individuals lack evidence of systemic IgE sensitization (skin prick testing, SPT, and food-specific serum IgE antibodies negative). Finally, some allergic conditions (e.g. atopic eczema or eosinophilic esophagitis) display mixed features of IgE-mediated and non-IgE-mediated immune mechanisms.

An increasing number of major food allergens have been characterized at the molecular level, e.g.  $\beta$ -lactoglobulin in cow's milk, ovomucin in hen's egg or Ara h2 in peanut. On each of these proteins, specific epitope regions have been mapped that interact with either specific IgE antibodies or T cell receptors. Conformational epitopes (with a three-dimensional structure) may be inactivated by heating or acidification, while linear epitopes are more resistant to degradation. For example, egg-allergic patients may tolerate baked egg in cakes, while still reacting to uncooked egg [7]. By contrast, boiling of cow's milk or roasting of nuts generally does not reduce their allergenicity.

### Clinical Manifestations of Food Allergy

Food allergy may present with a diverse range of clinical manifestations (table 1) [1]. Immediate reactions consist of urticaria, angioedema, oral tingling/itch, vomiting or diarrhea within 30–60 min of allergen ingestion. Atopic dermatitis with onset in the first months of life is closely associated with IgE-mediated food allergy [1]. The term 'anaphylaxis' is reserved for severe immediate-type reactions with either respiratory compromise (wheeze, stridor, cough) or systemic hypotension [8]. Anaphylaxis may occur in response to small allergen doses and can be fatal, particularly in adolescents and young adults with unstable asthma.

Delayed-onset reactions (non-IgE-mediated food allergy) typically involve the gastrointestinal tract or skin. While gastrointestinal food allergy is thought to be relatively common in the first 2–3 years of life, population-based prevalence estimates are scarce. In infants and young children, gastrointestinal food allergies may cause growth failure due to persistent vomiting/regurgitation, diarrhea and/or poor feeding [6]. The gastrointestinal allergy syndromes can be divided into food protein-induced (1) enteropathy, (2) enterocolitis syndrome (FPIES) and (3) proctocolitis (table 1) [6]. Enteropathy and proctocolitis may occur in exclusively breastfed infants [9], whereas FPIES seems to require direct ingestion of the allergen by the infant [10]. Recently, eosinophilic esophagitis has been recognized as a condition associated with food allergy that often responds to dietary elimination of food allergens [11].

### Lactose Intolerance

Lactose is the main disaccharide in mammalian milk. It can only be absorbed after digestion into glucose and galactose by the small intestinal brush border enzyme lactase. Failure to absorb lactase results in bacterial fermentation in the colon, presenting as flatulence, diarrhea, acidic stools and perianal skin excoriation [5]. The abundance of lactase activity is genetically regulated and slowly drops after infancy (lactase nonpersistence). This often leads to symptomatic hypolactasia by adult age, particularly in non-Caucasian individuals. Primary lactose intolerance (congenital absence of lactase) in infants is rare [5]. Secondary forms of lactose intolerance may be transient and resolve after the underlying gastrointestinal condition (e.g. viral gastroenteritis or celiac disease) has remitted.

Lactase malabsorption can be confused with cow's milk allergy, and both conditions may co-exist in cow's milk enteropathy (table 2) [6].

**Table 1.** Gastrointestinal food allergy

Diagnosis	Clinical features	Investigations	Complications	Treatment
Food protein-induced enteropathy	Mainly affects formula-fed infants (cow's milk or soy formula) Persistent diarrhea Occasional vomiting Failure to thrive	SPT/serum-specific IgE (ImmunoCAP®) negative Intestinal biopsy: evidence of small intestinal villus shortening and crypt hyperplasia Duodenal disaccharidases: secondary lactase deficiency	Growth failure Secondary lactose malabsorption Protein-losing enteropathy Hypoproteinemia and edema Iron deficiency anemia Hypogammaglobulinemia in severe cases	Strict cow's milk- and soy-free diet Extensively hydrolyzed formula as first-line treatment If not tolerated, change to amino acid-based formula
FPIES	Profuse vomiting about 2 h after ingestion of food allergen Does not occur in breastfed infants Common allergens are cow's milk, soy, grains (rice, oats) and poultry meat (chicken, turkey) Low-grade rectal bleeding may occur after reaction	SPT/serum-specific IgE (ImmunoCAP) negative Negative atopy patch test may predict tolerance on subsequent food challenge, but its clinical usefulness is controversial FPIES food challenge generally not performed before 2 years of age	Acute dehydration and hypovolemic shock occur in about 20% of first presentations May be mistaken for sepsis, gastroenteritis or intestinal obstruction	Strict avoidance of offending food item Requires hypoallergenic formula if previous reaction to cow's milk or soy (extensively hydrolyzed formula considered first-line treatment)
Food protein-induced proctocolitis	May occur in breast- or formula-fed infants within the first weeks of life Low-grade rectal bleeding, often mixed in with mucus Infants otherwise well and thriving	SPT/serum-specific IgE (ImmunoCAP) negative Sigmoidoscopy and biopsy not always required, particularly if responding to cow's milk protein elimination Rectal biopsy: increased lymphocytes and eosinophils, with focal epithelial erosion	Iron deficiency anemia uncommon	Breastfed infants often respond to maternal elimination diet In formula-fed infants, use extensively hydrolyzed formula If ongoing rectal bleeding, change to amino acid-based formula (rare)

FPIES = Food protein-induced enterocolitis syndrome.

Breath hydrogen testing may be used to confirm the diagnosis of lactose malabsorption; however, its correlation with diet response varies [5]. Dietary avoidance of fresh cow's milk and dairy products is usually sufficient to control gastrointestinal symptoms in lactose-intolerant individuals, and small amounts of lactose are generally tolerated. In formula-fed infants, a lactose-reduced formula or soy formula can be used if symptoms are significant. In breastfed infants, low-grade lactose malabsorption is physiological. In cases of postenteritic lactose malabsorp-

tion, breastfeeding should be continued. Incubation of expressed breast milk with lactase drops may be effective if symptoms are severe [5].

### Diagnostic Evaluation

The diagnosis of IgE-mediated food allergy requires a typical immediate-type clinical reaction to a food, in conjunction with demonstration of IgE antibodies by either SPT or measurement of

**Table 2.** Lactose malabsorption and its management

Type of lactose intolerance	Differential diagnosis	Treatment	Comments
Primary	Congenital (rare)	Lactose restriction (long-term)	Extremely rare
	'Adult-onset' hypolactasia	Lactose restriction (long-term)	Common Genetic polymorphism Lactase decline may commence in childhood
Secondary	Acute gastroenteritis/postenteritic lactose malabsorption	Short-term lactose restriction (lactose-free formula) In breastfed infants, continue breastfeeding If not tolerated, incubation of expressed breast milk with lactase may be successful	Mainly occurs in infancy Typically resolves within 1–2 weeks In very young infants, recovery may be delayed
	Celiac disease (untreated)	Ongoing strict gluten-free diet Lactose restriction until intestinal mucosa has been restored on gluten-free diet	Beware of false diagnostic labeling as 'lactose intolerance' or 'irritable bowel syndrome'
	Food protein-induced enteropathy (non-IgE-mediated cow's milk or soy allergy)	Extensively hydrolyzed (first-line treatment) or amino acid-based formula (if intolerant to extensively hydrolyzed formula)	Cow's milk-based, lactose-free formula may control the malabsorptive symptoms but does not allow mucosal repair (due to ongoing exposure to cow's milk protein)
	Intestinal dysplasia syndromes (e.g. microvillus inclusion disease, tufting enteropathy)	Depends on severity of disease May require parenteral nutrition Lactose restriction generally required	Rare Presents with intestinal failure
	Intestinal mucosal transporter defects (e.g. glucose-galactose malabsorption)	Strict avoidance of lactose-, glucose-, galactose- and sucrose-containing foods Fructose is tolerated	Rare defect of sodium-glucose transporter 1 Presents with profuse osmotic diarrhea and severe dehydration in first weeks of life

food-specific serum IgE antibodies (ImmunoCAP®) [12]. Detection of specific IgE antibodies (sensitization) on its own, in the absence of clinical symptoms, is not diagnostic (table 3). A negative SPT or specific IgE test has a high negative predictive value and makes IgE-mediated food allergy unlikely [12, 13]. Conversely, high SPT levels or specific IgE concentrations beyond a defined cutoff (95% predictive decision point) are considered diagnostic [12, 13]. In patients with equivocal results, the diagnosis of IgE-mediated food allergy needs to be assessed by formal food challenge in hospital (due to the potential risk of anaphylaxis) [8]. No useful in vitro

markers for non-IgE-mediated food allergy are currently available. The diagnosis of non-IgE-mediated food allergy relies on recognition of the clinical presentation, demonstration of improvement after a 2- to 4-week period of food allergen elimination, and relapse of symptoms after a food challenge. The investigation of possible food intolerances follows the same principles. In addition, breath hydrogen testing (lactose and fructose) and measurement of disaccharidase levels in duodenal biopsies may be useful in patients with suspected carbohydrate malabsorption syndromes (lactase or sucrase-isomaltase deficiency).

**Table 3.** Investigation of food allergy

Clinical presentation	Diagnostic test	Comments
<i>Immediate-onset reaction (IgE-mediated)</i> Urticaria/angioedema Oral allergy syndrome Anaphylaxis	Food-specific serum IgE antibody (ImmunoCAP) or SPT demonstrate evidence of sensitization	Diagnosis of IgE-mediated food allergy likely if food-specific serum IgE levels or SPT diameter above 95% predictive diagnostic decision points If inconclusive, food challenges in controlled environment (hospital) are required to confirm allergy or tolerance Home challenges may be indicated if SPT or serum food-specific IgE is negative (requires supervision by trained allergist)
<i>Delayed-onset reaction (non-IgE-mediated)</i> FPIES or proctocolitis	Diagnosis based on symptomatic improvement within 2–4 weeks after allergen elimination and relapse on subsequent food challenge FPIES food challenge generally not performed before 2 years of age Gastrointestinal biopsy, as clinically indicated (mainly for enteropathy; sometimes required in infantile allergic proctocolitis if atypical presentation)	Food-specific serum IgE antibody and SPT negative Histological appearance of allergic enteropathy similar to celiac disease
<i>Mixed reaction (IgE-/non-IgE-mediated)</i> Atopic dermatitis Eosinophilic esophagitis	Food-specific serum IgE antibody (ImmunoCAP) or SPT Esophageal biopsy in patients with suspected eosinophilic esophagitis (severe feeding refusal in infants; gastroesophageal reflux symptoms, dysphagia or food impaction in older children)	Elimination diet, as guided by history and SPT/specific IgE testing, and empirical elimination of non-IgE food allergens (followed by challenge) Esophageal biopsy reveals increased tissue eosinophils (>15 eosinophils per high-power field in upper and lower esophagus)

### Dietary Management of Food Allergy

Treatment of food allergies is based on strict elimination of specific food proteins until tolerance has developed [1]. As allergens are commonly disguised in manufactured food products, this involves education of parents and careful reading of ingredient labels [14]. In non-IgE-mediated food allergy, due to the diverse spectrum and underlying mechanisms and the absence of clear diagnostic markers, it may be difficult to define an exact diagnosis. In these children, empirical treatment with dietary manipulations is common practice. Elimination diets avoiding multiple food allergens should be monitored by a pediatric dietician to safeguard the nutritional adequacy of the diet, and growth parameters should be carefully monitored.

In breastfed infants, a maternal elimination diet may be effective as intact food antigens in

breast milk can elicit allergic manifestations in the infant [9]. The maternal diet should be normalized as soon as tolerated by the infant. An adequate maternal intake of protein and micronutrients needs to be maintained. The maternal calcium intake recommended for breastfeeding mothers is 1.2 g per day (provided as separate portions throughout the day).

Several hypoallergenic formulas are available for the treatment of infants with cow's milk and/or soy allergy who are not breastfed (table 4). These hypoallergenic formulas are tolerated by at least 90% of infants with cow's milk allergy [15]. There are two main types of hydrolyzed formula, partially and extensively hydrolyzed formulas. Partially hydrolyzed formulas may have a role in allergy prevention but are not suitable for infants with established clinical signs of cow's milk allergy [16]. Extensively hydrolyzed formulas are

**Table 4.** Formulas used in the treatment of infants with food allergies or intolerances

Type of formula	Features and indications
Partially hydrolyzed cow's milk-based formula	Contains relatively large cow's milk protein fragments/peptides Not suitable for treatment of cow's milk allergy May have a role in allergy prevention in high-risk infants in the first 6 months of life
Extensively hydrolyzed cow's milk-based formula (whey-predominant or casein-predominant)	Treatment of choice for formula-fed infants with cow's milk allergy Contains small cow's milk peptides Residual allergenicity due to trace amounts of cow's milk proteins Infants with previous cow's milk anaphylaxis require introduction of extensively hydrolyzed formula under medical observation Not tolerated by approximately 10–20% of infants with cow's milk allergy
Amino acid-based formula	Synthetic formula containing mixture of free amino acids Nutritionally complete formula Treatment of choice for infants with intolerance to extensively hydrolyzed formula, multiple food allergy of infancy or history of cow's milk anaphylaxis
Soy formula	Generally not considered first-line treatment formula for infants with cow's milk allergy under 6 months of age Has a role in the treatment of cow's milk allergy in older infants who are tolerant to soy protein Treatment of lactose malabsorption or galactosemia
Lactose-free cow's milk-based formula	Contains intact cow's milk protein (same as in standard cow's milk-based formula) Useful for infants with transient lactose intolerance (e.g. after acute gastroenteritis) Not suitable for infants with secondary lactose malabsorption due to cow's milk protein-induced enteropathy

the first-line treatment for infants with cow's milk allergy. Infants with ongoing symptoms while on an extensively hydrolyzed formula, and those with a history of cow's milk anaphylaxis, require an amino acid-based formula [15, 17]. The role of soy formulas in the treatment of young infants with cow's milk allergy is controversial. Concomitant soy allergy occurs in about 15% of infants with IgE-mediated cow's milk allergy [18]. Because of the risk of soy allergy and concerns regarding the phytoestrogen and phytate content of soy formulas, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition has advised against using soy formulas with infants with cow's milk allergy under 6 months of age [15, 19]. However, for older infants, soy is a suitable treatment option for cow's milk allergy, provided tolerance to soy has been established [19].

## Conclusions

- Hypoallergenic formulas (extensively hydrolyzed formulas or amino acid-based formulas) are used in the treatment of cow's milk allergy in formula-fed infants. Soy formulas are also suitable for infants over 6 months of age without concomitant soy allergy
- In breastfed infants with food-allergic manifestations, a maternal elimination diet may control symptoms in the infant. Prolonged maternal elimination diets should be supervised by a dietician
- Lactose intolerance is the most common food intolerance and is treated with a low-lactose diet. Causes of secondary lactose intolerance, such as celiac disease, should be considered in the differential diagnosis



## References

- 1 Allen KJ, Hill DJ, Heine RG: 4. Food allergy in childhood. *Med J Aust* 2006; 185:394–400.
- 2 Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, Ponsonby AL, Wake M, Tang ML, Dharmage SC, Allen KJ; HealthNuts Investigators: Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and pre-determined challenge criteria in infants. *J Allergy Clin Immunol* 2011;127:668–676e2.
- 3 Prescott S, Saffery R: The role of epigenetic dysregulation in the epidemic of allergic disease. *Clin Epigenetics* 2011;2: 223–232.
- 4 Heederik D, von Mutius E: Does diversity of environmental microbial exposure matter for the occurrence of allergy and asthma? *J Allergy Clin Immunol* 2012;130:44–50.
- 5 Heyman MB; Committee on Nutrition: Lactose intolerance in infants, children, and adolescents. *Pediatrics* 2006;118: 1279–1286.
- 6 Heine RG: Pathophysiology, diagnosis and treatment of food protein-induced gastrointestinal diseases. *Curr Opin Allergy Clin Immunol* 2004;4:221–229.
- 7 Leonard SA, Sampson HA, Sicherer SH, Noone S, Moshier EL, Godbold J, Nowak-Wegrzyn A: Dietary baked egg accelerates resolution of egg allergy in children. *J Allergy Clin Immunol* 2012; 130:473–480e1.
- 8 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW: Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–397.
- 9 Järvinen KM, Mäkinen-Kiljunen S, Suomalainen H: Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. *J Pediatr* 1999;135:506–512.
- 10 Leonard SA, Nowak-Wegrzyn A: Clinical diagnosis and management of food protein-induced enterocolitis syndrome. *Curr Opin Pediatr* 2012;24:739–745.
- 11 Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS: Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20e6.
- 12 Hill DJ, Heine RG, Hosking CS: The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol* 2004;15:435–441.
- 13 Sampson HA: Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891–896.
- 14 Mofidi S: Nutritional management of pediatric food hypersensitivity. *Pediatrics* 2003;111:1645–1653.
- 15 Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, Bozzola M, Bradsher J, Compalati E, Ebisawa M, Guzman MA, Li H, Heine RG, Keith P, Lack G, Landi M, Martelli A, Rance F, Sampson H, Stein A, Terracciano L, Vieths S; World Allergy Organization Special Committee on Food Allergy: World Allergy Organization (WAO): Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. *Pediatr Allergy Immunol* 2010;21(suppl 21):1–125.
- 16 Osborn DA, Sinn J: Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2003;4: CD003664.
- 17 de Boissieu D, Dupont C: Allergy to extensively hydrolyzed cow's milk proteins in infants: safety and duration of amino acid-based formula. *J Pediatr* 2002;141: 271–273.
- 18 Zeiger RS, Sampson HA, Bock SA, Burks AW Jr, Harden K, Noone S, Martin D, Leung S, Wilson G: Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr* 1999;134:614–622.
- 19 Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, Puntis J, Rieu D, Rigo J, Shamir R, Szajewska H, Turck D: Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2006;42: 352–361.

## 3.12 Regurgitation and Gastroesophageal Reflux

Noam Zevit · Raanan Shamir

### Key Words

Gastroesophageal reflux · Gastroesophageal reflux disease · Regurgitation · Nutrition treatment · Food allergy

### Key Messages

- In infants, gastroesophageal reflux (GER) and regurgitation are most commonly self-resolving conditions that do not require treatment or ancillary testing
- GER disease (GERD) in infants may be indistinguishable from milk protein allergy; therefore, if troublesome symptoms persist in an infant, the possibility of allergy should be considered
- Assessment of nutritional status must be undertaken concomitantly with the investigation and treatment of GERD in order to refrain from either suboptimal or excessive intake
- If prolonged medical treatment is deemed necessary, proton pump inhibitors are the treatment of choice, whereas conservative measures are adequate to treat mild GERD symptoms

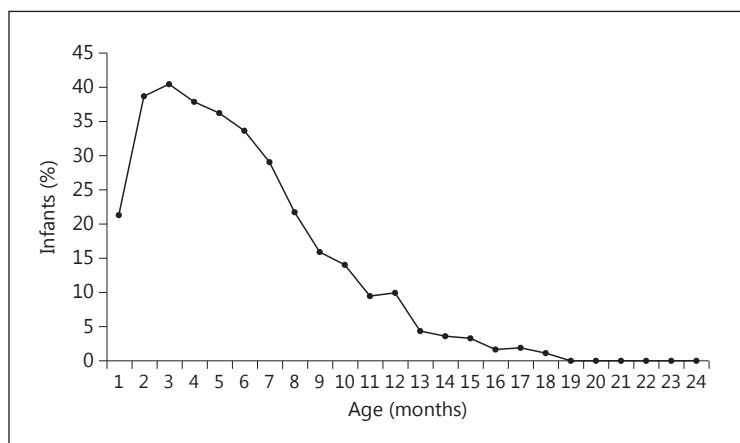
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### Introduction

Gastroesophageal reflux (GER) is defined as the passage of contents from the stomach into the esophagus, and may be associated with regurgitation or vomiting. GER is a common phenome-

non, especially in infants, and is considered a physiologic occurrence [1]. If GER is associated with troublesome signs or symptoms, however, GER disease (GERD) is diagnosed, a condition which may justify diagnostic or therapeutic interventions. Most cases of GER and GERD occur without any predisposing factors, with reflux occurring during transient lower esophageal sphincter relaxations (TLESR) [2, 3]. These relaxations occur physiologically in all people, are more common after meals, in the sitting position, and following high-osmolarity meals. They allow the release of gases swallowed or produced in the stomach; however, when TLESR is associated with the efflux of food retrograde through the lower esophageal sphincter, it produces GER. Almost 100% of GER and nonerosive GERD, and an estimated 70% of erosive GERD, occur during TLESR [4]. There are several predisposing factors which increase the incidence of GER. These include a dysfunctional lower esophageal sphincter (hiatal hernia, after repair of esophageal atresia, after Heller myotomy), increased intra-abdominal pressure (peritoneal dialysis, abdominal mass), cystic fibrosis, psychomotor delay, obesity, prematurity and others. Several hormones, drugs and nutrients have been implicated in influencing tone of the lower esophageal sphincter, but the clinical significance of most of these have not yet been rigorously studied.

**Fig. 1.** Proportion of infants regurgitating most feeds. Reproduced and adapted with permission from Martin et al. [5].



In infancy, regurgitation may not appear immediately after birth and becomes more common in the first months of life, peaking at approximately 4–5 months, at which time nearly 40% of infants regurgitate more than once daily (fig. 1) [5]. Thereafter there is a gradual decrease in prevalence, such that by around 18 months of age, reflux has resolved in the vast majority of cases. The remaining patients generally warrant investigation even if the regurgitation remains asymptomatic.

### Signs and Symptoms

The clinical presentation of GER and GERD ranges across a spectrum of signs and symptoms which may vary with age and can include both esophageal and extraesophageal symptoms (table 1) [1]. In infants, the most common presentation is that of a well-thriving, regurgitating baby (the ‘happy spitter’). In most cases of GER, the child has no symptoms or distress. GER may at times be associated with a vomiting reflex. As GER in infants and young children progresses to GERD, fussiness at times of eating or following meals, food refusal with subsequent poor weight gain, arching of the back with turning of the head, coined Sandifer syndrome (which at times can

appear seizure-like or be mistaken for torticollis), and excessive crying may be seen, though none of these are specific. Apnea and bradycardia are rare.

Older children and adolescents may present with frank regurgitation, and heartburn, noncardiac chest pain and epigastric abdominal pain may be present [6]. Chronic iron deficiency anemia may indicate erosive esophagitis. Extraesophageal manifestations (table 1) become more prevalent in older children and adolescents. Longstanding reflux may lead to peptic strictures inducing dysphagia and even food impaction. Furthermore, chronic reflux is associated with Barrett’s esophagus.

### Diagnosis

Currently, no diagnostic test exists which can be considered a gold standard for the diagnosis of GERD and which can adequately differentiate between physiological and pathological signs and symptoms throughout the spectrum of presentations. As such, there are several diagnostic methods which may be utilized in an investigation.

A thorough history and physical examination can aid in the diagnosis of GERD and help to

**Table 1.** Signs and symptoms of GER and GERD

Infants	Older children	Extravesophageal signs
Recurrent spitting up/vomiting	Heartburn	Treatment-resistant asthma
Poor weight gain	Substernal pain	Dental erosion
Feeding refusal	Water brash	Recurrent pneumonia
Irritability	Nausea	Hoarseness
Back arching	Epigastric abdominal pain	Chronic cough
Apnea/bradycardia	Recurrent vomiting	

**Table 2.** Warning signs that may warrant further investigation

Persistent forceful vomiting
Bilious vomiting
Gastrointestinal bleeding
Late onset (>6 months)
Failure to thrive
Repeated choking or episode of apparent life-threatening event
Constipation
Bulging fontanel, seizures or new neurological deficits
Family history of genetic or metabolic disorder

identify ‘red flags’ which may indicate the need for a different or accelerated approach (table 2). The history should take into account the patient’s age, birth history, allergies and development, as well as the feeding history and temporal relationship of symptoms to meals. In the case of infantile and childhood reflux, however, the history is neither sensitive nor specific enough to be credibly relied on for a diagnosis of GERD. This was demonstrated by Orenstein et al. [7], who attempted to treat infants with a history suggestive of GERD with proton pump inhibitors (PPI) or placebo. Both arms of the study responded similarly. This would seem to indicate that the history alone is not able to identify which patients have GERD as a cause of their symptoms, and which have other etiologies with similar presentations (e.g. infantile colic and cow’s milk protein allergy). Furthermore, the study indicates that a PPI test in which the drug may be given for a limited time is also inaccurate.

Historically, patients were often sent to perform barium swallows to diagnose reflux; however, the test should not be used for this indication because it has both low sensitivity and specificity, not to mention the significant radiation exposure involved. Esophago-gastro-duodenoscopy allows for visualization of damage caused to the esophageal mucosa by acid reflux as well as direct tissue sampling, which may also aid in the identification of other conditions that may present diagnostic challenges (e.g. eosinophilic esophagitis, allergic gastritis and inflammatory bowel disease). However, esophago-gastro-duodenoscopy is neither able to identify nonerosive GERD nor to directly demonstrate reflux but rather only its consequences.

Prolonged esophageal pH monitoring, in which a pH-sensitive probe is placed in the lower esophagus and left for 24 h, allows for direct demonstration of esophageal acid, although it cannot differentiate swallowed from regurgitated acid.

Furthermore, since a certain degree of reflux is present in normal individuals, symptom associations are often difficult to demonstrate. In addition there is a poor correlation between acid exposure and endoscopic findings or symptoms. pH multichannel intraluminal impedance, a relatively new methodology involving a traditional pH monitor with several impedance probes located throughout the esophagus, is able to overcome some of these obstacles [8]. This technology permits direct measurement of bolus transit in the esophagus both temporally and geographically. Better symptom association calculations may be generated. Unfortunately, pediatric norms are still unavailable, and its high cost limits its use in many regions. Radionucleotide scans are now rarely used for the diagnosis of GER. Finally, extensively hydrolyzed or amino acid-based formulas may be used for infants with GERD to eliminate the possibility of food allergy (see section Treatment below).

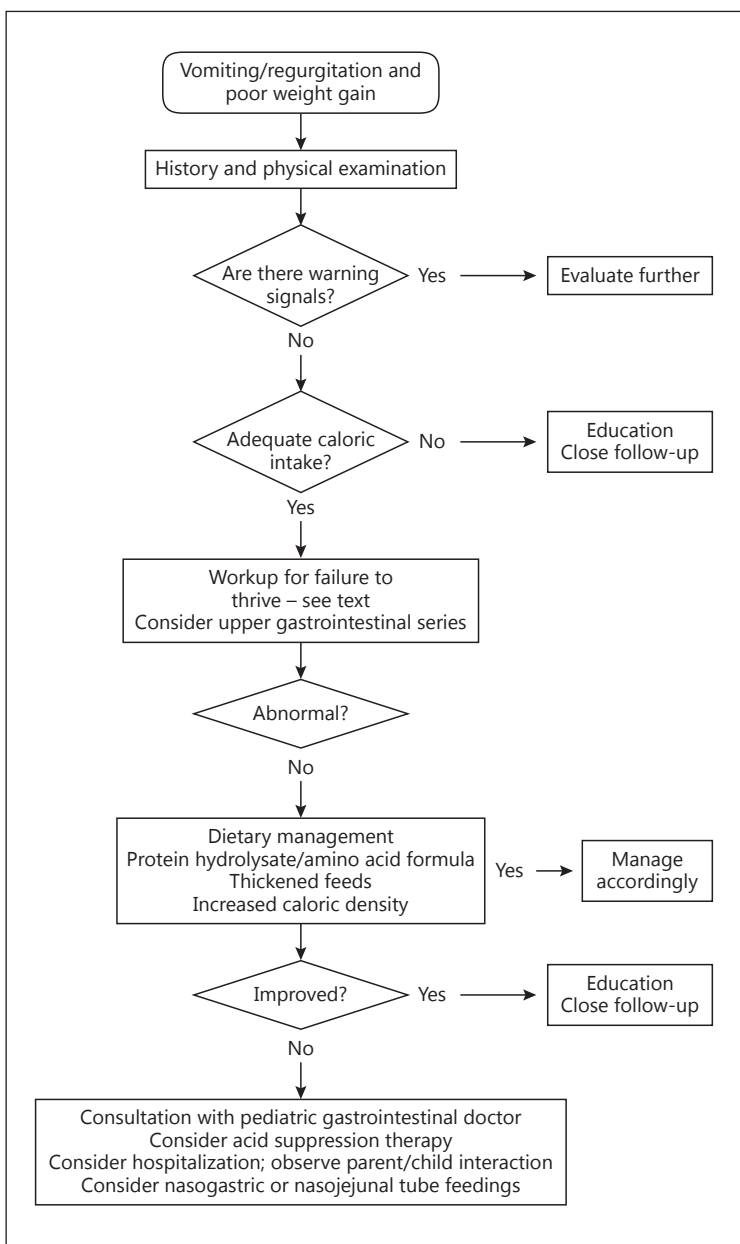
## Treatment

In most cases of GER or uncomplicated GERD in an infant, treatment involves educating the parents as to the generally benign nature of the condition and its natural history in this age group, stressing that GER is not a disease but rather a common transient state which in most cases resolves toward the end of the first year of life [1]. Coupled with continued follow-up and a trusting relationship with the pediatrician, further interventions are usually found to be unnecessary. While prone positioning of infants has been found to decrease regurgitations, this is no longer recommended – except while the infant is awake and observed by a caregiver – because of the increased risk of sudden infant death in this position [1].

However, in some infants, the irritability associated with GERD leads to decreased feeding volumes or to large fractions of the ingested food be-

ing regurgitated, with consequent poor weight gain, aspiration of refluxed content or indolent nutrient deficiency (e.g. iron). In these cases and whenever significant GERD is suspected in children, cow's milk protein allergy should be considered, because such allergy may present identically to GERD [9]. A time-limited trial of dietary exclusion of milk products from the maternal diet for breastfeeding infants, and use of extensively hydrolyzed or amino acid-based formulas with others, may be attempted. If no response is seen within 2–4 weeks, the infant may return to the previous diet. If milk allergy is found in a breastfed infant and the mother continues a milk-restricted diet, the need for calcium supplementation of the mother's diet should be assessed. If dietary restriction and rescheduling of feeds fail, other interventions such as thickening of formulas may be attempted. Thickening of formulas can be performed by caretakers by addition of thickeners such as corn, rice or potato starch to the water in which the formulas are to be prepared. Adding starch changes the nutritional composition of the feeds and increases carbohydrate calories. Alternatives are addition of locust bean gum (from the carob tree) or guar gum. Additionally, factory-made antiregurgitation formulas based on either rice or locust bean gum are available in a nutritionally balanced format. Each has its advantages and disadvantages, which are beyond the scope of this chapter. It must be noted that these antiregurgitation formulas do not cure GER or GERD but rather decrease the number of regurgitations and the height of the regurgitant column and may be nutritionally disadvantaged [10].

When these interventions fail, and GERD has been diagnosed, medical treatment may be justified. This may include histamine 2 receptor blockers, such as ranitidine, or PPI. Currently, only histamine 2 receptor blockers are approved for infants under 1 year of age. If used at appropriate doses, they produce an effective acid blockade; however, tachyphylaxis may become a problem after a few weeks use. PPI are considered the



**Fig. 2.** The infant with regurgitation and poor weight gain. Reproduced and adapted with permission from Vandenas et al. [1].

most effective mechanism of acid blockade, and while not yet approved below 1 year of age, they are broadly prescribed in this age group. Response to treatment and the need to maintain prolonged treatment should be regularly reassessed as there appear to be consequences of pro-

longed treatment with PPI. If needed, prolonged medical treatment is now generally preferred to surgical interventions for GERD, due to nonnegligible complications and failure rates of the surgical procedures and the relatively benign nature and high effectiveness of drug treatment (fig. 2).

## References

- 1 Vandenplas Y, Rudolph CD, di Lorenzo C, et al: Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49:498–547.
- 2 Kawahara H, Dent J, Davidson G: Mechanisms responsible for gastroesophageal reflux in children. *Gastroenterology* 1997;113:399–408.
- 3 Dodds WJ, Dent J, Hogan WJ, et al: Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med* 1982;307:1547–1552.
- 4 Mittal RK, Holloway RH, Penagini R, et al: Transient lower esophageal sphincter relaxation. *Gastroenterology* 1995;109:601–610.
- 5 Martin AJ, Pratt N, Kennedy JD, et al: Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics* 2002;109:1061–1067.
- 6 Nelson SP, Chen EH, Syniar GM, et al: Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. *Pediatric Practice Research Group. Arch Pediatr Adolesc Med* 2000;154:150–154.
- 7 Orenstein SR, Hassall E, Furmaga-Jablonska W, et al: Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr* 2009;154:514–520e4.
- 8 Mousa HM, Rosen R, Woodley FW, et al: Esophageal impedance monitoring for gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 2011;52:129–139.
- 9 Koletzko S, Niggemann B, Arato A, et al: Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:221–229.
- 10 Aggett PJ, Agostoni C, Goulet O, et al: Antireflux or antiregurgitation milk products for infants and young children: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2002;34:496–498.

### 3.13 Childhood Feeding Problems

Maureen M. Black

#### Key Words

Feeding problems · Food refusal · Pickiness · Responsive feeding

#### Key Messages

- Children acquire independence in feeding skills during the first 2 years of life and can start to self-feed within the first year
- Feeding problems (food refusal, pickiness, and disruptive mealtime behavior) are common and part of the normal development of children
- Feeding problems can lead to family stress with long-term negative consequences on children's growth, nutrition, and behavior
- Caregivers can promote healthy feeding behavior and prevent feeding problems by establishing healthy mealtime structure routines and responding to their child's signals of hunger and satiety, adopting principles of responsive feeding
- Feeding guidelines to caregivers should extend beyond 'what' and 'when' to feed. Guidelines to promote healthy feeding behaviors can be effective in preventing feeding problems

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#### Introduction

Feeding problems are a major concern among typically developing infants and toddlers throughout the world, with prevalence estimates that

range up to 45% in the USA [1]. Observational data on infants and toddlers from Bangladesh have shown that not only are rates of food refusal relatively high (mean of 6–7 refusals/meal), but fewer than 20% of mouthfuls are self-fed. Feeding problems tend to peak at around 2 years of age and often include food refusals, pickiness, and disruptive mealtime behavior [2]. Food refusal is a major concern because it may be both a sign of satiety [3] and a sign of feeding problems. In many cases, early feeding problems resolve over time, particularly when caregivers are sensitive to their child's signals of satiety and emerging autonomy. However, feeding problems often increase family stress [2] and can result in weight-related problems (either underweight or overweight) [4], nutrition-related health conditions, and long-term behavioral problems [5]. Deviations in children's growth during the first 2 years of life can have long-term health and developmental consequences. Early stunting has been associated with poor academic performance during schooling [6], and early obesity increases the risk for adult obesity and associated problems [7].

There is a dramatic evolution of feeding behavior over the first 2 years of life as infants acquire the oral motor, physical, digestive, and social skills to progress from a liquid diet of breast milk/formula to the texture and variety of the family diet. Based on a national sample of over



3,000 infants and toddlers in the USA, by 7–8 months of age, 96% of children can grasp food with their hands and 77% can remove food from a spoon with their lips with little spilling; by 15–18 months, 64% of children can self-feed with a spoon with little spilling [8]. In addition to the maturational changes that influence feeding behavior, caregivers play central roles in socializing children into feeding routines and managing their feeding behavior.

### Caregiver Feeding Practices

Feeding practices are the behaviors that caregivers use to feed their children and help them gain feeding skills. Caregiver feeding practices are influenced by cultural, environmental, and personal factors, along with caregivers' perceptions of their child's size, appetite, and temperament. In some cultures, children are fed separately from the family, while in others, they eat together and thus may model feeding behaviors from parents and siblings. In some households, mothers have limited time to spend feeding their children [9]. Caregivers of children with high rates of food refusal report depressive symptoms. Maternal depression has been associated with unresponsive feeding practices through caregiver report [10] and observation [11], including verbal and physical pressure along with using incentives (bargaining) to get their child to eat. These strategies may override children's internal regulatory cues [12] and lead to overemotionalizing food and eating, thus increasing the risk of children using feeding behavior as a tool for manipulation. In addition to depressive symptoms, caregivers with poor feeding behavior themselves, such as frequent intake of snacks and sugar-sweetened beverages, inconsistent meal times, and use of food as rewards, increase the likelihood of their children's feeding problems. Caregivers who are concerned about their child's feeding behavior and growth have been observed to use negative, coercive strategies

to promote eating [3], along with permissive strategies such as making food available throughout the day or providing favorite foods (e.g., sweet or salty snacks) with little regard to quality. These strategies are likely to undermine children's normal appetite development, increasing mealtime stress as children hold out for snacks. Caregivers also use food to manage children's behavior, especially children who are perceived to be temperamentally difficult. This strategy has been associated with overeating among preschoolers [13]. Early in life, children learn that food refusal can be a powerful strategy that attracts the caregiver's attention and may lead to increased access to snacks and favorite foods.

Responsive feeding is a strategy based on both control and nurturance. Caregivers provide mealtime structure by selecting the food, the timing, and the context in which feeding takes place (fig. 1). They also respond to children's signals of hunger and satiety promptly, and with developmentally appropriate and nurturing feeding practices [14]. Responsive feeding acknowledges children's feelings and allows them to determine how much they eat, while the caregiver decides what is offered and when. Embedded within the domain of responsive parenting, responsive feeding emphasizes the interactive nature of feeding, whereby caregivers set guidelines but their reactions are gaged to the signals they read from their children, ideally resulting in a respectful give-and-take (serve-and-return) around feeding, in turn resulting in healthy weight gain.

### Screening, Recommendations, and Interventions

Systematic strategies are available to screen for children's feeding problems, such as the Behavioral Pediatrics Feeding Assessment Scale (BPFAS) [15], a 35-item scale that asks caregivers to respond to the frequency of child and caregiver feeding behaviors along with an indi-

**Fig. 1.** Photo of responsive feeding (P. Caceres, Chile, 'Mutual Understanding'; [http://www.paho.org/hq/index.php?option=com\\_content&view=article&id=8371&Itemid=39899&lang=en](http://www.paho.org/hq/index.php?option=com_content&view=article&id=8371&Itemid=39899&lang=en)).



cation of whether each behavior presents a problem. The BPFAS has been validated among typically developing children and used in non-clinical samples to identify children with feeding problems [16].

Feeding recommendations often focus on what and when to feed, beginning with breastfeeding promotion and the timing of complementary feeding. Traditionally, there has been limited attention to feeding behavior. A recent review of feeding guidelines found substantial variability in recommendations with little attention to how to handle food refusal [17]. Although the UNICEF and WHO have guidelines that include responsive feeding, there are few actual recommendations on how to prevent or handle common feeding problems, such as food refusal, and limited attention to developmental changes in children's feeding behavior, such as self-feeding.

Education on strategies to promote healthy child feeding behavior is often provided through information sharing modalities such as leaflets. However, evidence has shown that to be effective, education should be provided before feeding problems occur, should include caregiver social support, and should provide opportunities to simulate the recommended practices [18]. Two recent interventions in Australia were effective in promoting caregiver-child feeding interactions.

An 8-session, group-based behavioral intervention was effective in reducing feeding problems among typically developing children, as measured by parent report and direct observation [19]. A second intervention to promote responsive feeding among caregivers of infants as a strategy to prevent childhood obesity found increases in caregiver-reported responsive feeding and decreases in controlling feeding practices, with no differences in children's growth or the prevalence of overweight/obesity [20].

Interventions have also been conducted in low-income countries. An intervention in Bangladesh that demonstrated and coached caregivers to adopt responsive feeding behaviors was successful in increasing child hand washing, self-feeding, and maternal verbal responsiveness but did not change weight gain over the study period [2]. Hand washing is a particularly relevant intervention because it promotes good hygiene and prepares the child for self-feeding. An analysis of maternal responses from the intervention identified four barriers that interfered with the adoption of self-feeding in this resource-poor setting: (1) the time required to allow the child to self-feed, (2) the potential mess as the child spilled the food, (3) food waste that occurred when the child played with the food or dropped it, and (4) a perception that the child was unable to self-feed,



**Table 1.** Strategies to promote healthy child feeding and avoid feeding problems

- 
1. Cultural beliefs: recognition that children's feeding skills increase over the first 2 years of life and that self-feeding (with fingers) can start during the first year
  2. Family support and labor-saving strategies to help caregivers devote the time necessary for responsive feeding and to promote self-feeding [9]
  3. Access: families need access to a variety of healthy food [9]
  4. Hygiene: promotion of hygienic practices such as hand washing by making soap and water accessible [2]
  5. Positioning: children who are seated in a comfortable position where they can reach the food are more likely to eat during the meal
  6. Modeling: children learn by imitation and are more likely to exhibit healthy feeding behaviors when they observe others eating
  7. Exposure: children may require multiple exposures to a new food (10 – 20) prior to tasting [21]
  8. Self-feeding: children strive for independence and will retain their focus in eating when they can self-feed, first using fingers, then using utensils; provide food that children can self-feed
  9. Recognition of satiety signals: when parents pressure children to eat after they have signaled that they have reached satiety, the meal should end
  10. Freedom from distractions: distractions such as television may interfere with self-regulation of hunger and satiety, leading to refusal to eat or overeating
  11. Routine, habits, and mealtime rules: establishing feeding habits related to healthy food can improve children's food intake [22]
  12. Food as nutrition, not as a reward: using food as a reward overvalues the 'reward' and increases the likelihood of overeating [13]
  13. Ensure hunger at meals: meal consumption is increased when children are hungry and not filling up on snacks and sugary beverages
  14. Covert restriction of high-fat, high-sugar foods: covert restriction means limiting access for all family members rather than only for the child and does not result in the restricted food becoming overvalued [23]
  15. Pleasant and stress-free interactions: children are more likely to eat and enjoy the meal when interactions are pleasant than when they are characterized by conflict or arguments
- 

leading to the possibility of hunger and associated irritability [9]. When asked about allowing children to determine how much they wanted to eat and responding to food refusal by terminating the meal, many caregivers expressed grave concerns about the child's ability to determine satiety and the health consequences that could result in 'sickness or death' without adequate food. Caregivers often reported that they had no choice other than to force-feed their children. These findings emphasize the central role that maternal beliefs, the social conditions, and local customs play in feeding behavior.

## Conclusions

- Childhood feeding problems are common among infants and young children throughout the world. They can increase family stress and lead to long-term negative nutritional and behavioral problems
- Strategies to promote healthy feeding behaviors and avoid childhood feeding problems extend from cultural recognition and support of infant developmental needs and young child feeding skills (including self-feeding) to caregiver practices such as ensuring that children

are hungry at meals and not satiated from snacks and beverages (table 1)

- Principles of responsive feeding, whereby caregivers provide mealtime structure, help children build healthy habits, and respond to

their children's signals of hunger and satiety (which may include food refusal) in a prompt and nurturing manner, form the basis of successful interventions to promote healthy feeding behavior and avoid feeding problems

## References

- 1 Lewinsohn PM, Holm-Denoma JM, Gau JM, Joiner TE Jr, Striegel-Moore R, Bear P, et al: Problematic eating and feeding behaviors of 36-month-old children. *Int J Eat Disord* 2005;38:208–219.
- 2 Aboud FE, Shafique S, Akhter S: A responsive feeding intervention increases children's self-feeding and maternal responsiveness but not weight gain. *J Nutr* 2009;139:1738–1743.
- 3 Sanders MR, Patel RK, Le Grice B, Shepherd RW: Children with persistent feeding difficulties: an observational analysis of the feeding interactions of problem and non-problem eaters. *Health Psychol* 1993;12:64–73.
- 4 Chan L, Magarey AM, Daniels LA: Maternal feeding practices and feeding behaviors of Australian children aged 12–36 months. *Matern Child Health J* 2011;15:1363–1371.
- 5 Nicklas TA, Hayes D: Position of the American Dietetic Association: nutrition guidance for healthy children ages 2 to 11 years. *J Am Diet Assoc* 2008;108:1038–1044, 1046–1047.
- 6 Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman G, Pollitt E, Carter J: Child development: risk factors for adverse outcomes in developing countries. *Lancet* 2007;369:145–157.
- 7 Baird J, Fisher D, Lucas P, Kleyne J, Roberts H, Law C: Being big or growing fast. Systematic review of size and growth in infancy and later obesity. *BMJ* 2005;331:929–931.
- 8 Carruth BR, Ziegler PJ, Gordon A, Hendricks K: Developmental milestones and self-feeding behaviors in infants and toddlers. *J Am Diet Assoc* 2004;104(suppl 1):s51–s56.
- 9 Affleck W, Pelto G: Caregivers' responses to an intervention to improve young child feeding behaviors in rural Bangladesh: a mixed method study of the facilitators and barriers to change. *Soc Sci Med* 2012;75:651–658.
- 10 Hurley KM, Black MM, Papas MA, Caulfield LE: Maternal symptoms of stress, depression, and anxiety are related to non-responsive feeding styles in a statewide sample of WIC participants. *J Nutr* 2008;138:799–805.
- 11 Haycraft E, Farrow C, Blissett J: Maternal symptoms of depression are related to observations of controlling feeding practices in mothers of young children. *J Fam Psychol* 2013;27:159–164.
- 12 Birch LL, Fisher JO: Development of eating behaviors among children and adolescents. *Pediatrics* 1998;101(pt 2):539–549.
- 13 Blissett J, Meyer C, Haycraft E: The role of parenting in the relationship between childhood eating problems and broader behaviour problems. *Child Care Health Dev* 2011;37:642–648.
- 14 Black MM, Aboud FE: Responsive feeding is embedded in a theoretical framework of responsive parenting. *J Nutr* 2011;141:490–494.
- 15 Crist W, Napier-Philips A: Mealtime behaviours of young children: a comparison of normative and clinical data. *J Dev Behav Pediatr* 2001;22:279–286.
- 16 Dovey TM, Jordan C, Aldridge VK, Martin CI: Screening for feeding disorders. Creating critical values using the Behavioural Pediatrics Feeding Assessment Scale. *Appetite* 2013;69:108–113.
- 17 Schwartz C, Scholtens PA, Lalanne A, Weenen H, Nicklaus S: Development of healthy eating habits early in life. Review of recent evidence and selected guidelines. *Appetite* 2011;57:796–807.
- 18 Mitchell GL, Farrow C, Haycraft E, Meyer C: Parental influences on children's eating behaviour and characteristics of successful parent-focussed interventions. *Appetite* 2013;60:85–94.
- 19 Adamson M, Morawska A, Sanders MR: Childhood feeding difficulties: a randomized controlled trial of a group-based parenting intervention. *J Dev Behav Pediatr* 2013;34:293–302.
- 20 Daniels LA, Mallan KM, Nicholson JM, Battistutta D, Magarey A: Outcomes of an early feeding practices intervention to prevent childhood obesity. *Pediatrics* 2013;132:e109–e118.
- 21 Wardle J, Cooke LJ, Gibson EL, Sapochnik M, Sheiham A, Lawson M: Increasing children's acceptance of vegetables: a randomized trial of parent-led exposure. *Appetite* 2003;40:155–162.
- 22 McGowan L, Cooke LJ, Gardner B, Beeken RJ, Croker H, Wardle J: Healthy feeding habits: efficacy results from a cluster-randomized, controlled exploratory trial of a novel, habit-based intervention with parents. *Am J Clin Nutr* 2013;98:769–777.
- 23 Ogden J, Reynolds R, Smith A: Expanding the concept of parental control: a role for overt and covert control in children's snacking behaviour? *Appetite* 2006;47:100–106.

## 3.14 Preterm and Low-Birth-Weight Infants

Ekhard E. Ziegler

### Key Words

Growth failure · Parenteral nutrition ·  
Gastrointestinal priming · Human milk fortification

### Key Messages

- Nutrient administration, though technically difficult, must be initiated promptly after birth to avoid adverse effects of undernutrition
- Because of immaturity of the intestinal tract, the use of parenteral nutrition is necessary until feeds can be given
- Trophic feeding (gastrointestinal priming) should be started promptly and advanced as permitted by maturation of intestinal motility
- The preferred feed is breast milk (the mother's own or donated) because of its protective effect against sepsis and necrotizing enterocolitis. Formulas for preterm infants are the second choice
- Breast milk must be fortified with nutrients to meet the high nutrient needs of preterm infants. Fortifiers raise the nutrient content to adequate levels, compensating for shortfalls

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### Introduction

Postnatal (extrauterine) growth failure is common among prematurely born infants. It used to be considered inevitable as well as innocuous. But it has become clear that far from being inevitable, it is largely if not exclusively the result of inadequate intakes of nutrients. Ehrenkranz et al. [1], among others, have shown in a landmark study that it is not innocuous. The study established that growth failure is associated with impairment of neurocognitive development in a dose-dependent fashion. The more severe the growth failure, the more severe is the neurocognitive impairment.

There are mainly two reasons for the occurrence of growth failure in premature infants. One is that there are physiological limitations that prevent the provision of nutrients in the usual way, i.e. through enteral feeding. The other reason is that the nutrient needs are exceedingly high, as summarized in table 1. These needs cannot be met by human milk alone without nutrient fortification. Thus, providing nutritional support to preterm infants presents unique challenges as failure to provide adequate nutrient intakes at all stages of development places them at risk of impaired neurodevelopment. Every effort must therefore be made to provide complete nutrition beginning from birth [2].

## Nourishing Preterm and Low-Birth-Weight Infants

Provision of nutrients has to overcome the immaturity of the intestinal tract; this is the most important physiological limitation in these infants. This necessitates the use of parenteral nutrition during the early days and often weeks of life. Although parenteral nutrition carries risks, especially that of infection, failure to provide nutrients parenterally would place these infants at high risk of impaired neurodevelopment or impaired host defenses. Immaturity of the intestinal tract is also the main reason why preterm infants are susceptible to necrotizing enterocolitis (NEC). While nutrients are provided parenterally, small trophic feedings (gastrointestinal priming) are given with the sole purpose of stimulating the intestinal tract to undergo maturation. Breast milk is the most effective and safest feed to bring about intestinal maturation. Once maturation has occurred, nutrients can be delivered enterally and parenteral nutrition may be phased out.

Nutritional support of preterm infants occurs in four distinct phases, each with its own risks and challenges. During the early phase, nutrients are almost exclusively provided via the parenteral route, while small enteral feedings (gastrointestinal priming) are used to prod the immature intestinal tract into undergoing maturation. During the subsequent transition phase, enteral feeding is slowly advanced as the intestinal tract shows evidence of maturation, and parenteral nutrition is gradually phased out. During the late phase, infants are on exclusive enteral feeding and are expected to grow normally. If provided the necessary nutrients, preterm infants may also show catch-up growth, that is, they may be making up for lost time during the early phase. Preterm infants continue to have special nutritional needs after discharge from hospital.

### *Early Phase*

During the immediate postnatal period, the objective of nutritional support is twofold: to provide an uninterrupted flow of nutrients so that the anabolic state that existed in utero can continue with minimal or no interruption, and to stimulate the immature gastrointestinal tract to undergo maturation. As gastrointestinal maturation progresses, a gradual shift occurs from exclusive parenteral nutrition to predominant, and finally exclusive, enteral nutrition. The early phase ends when enteral feedings exceed about 20 ml/kg/day.

### Parenteral Nutrition

In immature infants, parenteral nutrition must begin immediately (within 2 h of birth), and as a minimum must provide glucose, amino acids, electrolytes, Ca, P and Mg (starter parenteral nutrition) until full parenteral nutrition can be started. It is acceptable for the amount of amino acid to be less than 3.5 g/kg/day for a few days. Initiation of lipid emulsion is somewhat less urgent, and a delay of 24 h is acceptable. The initial rate should be 1.0 g lipids/kg/day. The efficacy and safety of parenteral nutrition starting immediately after birth have been established [3]. Full parenteral nutrition should be maintained until enteral feedings of 20 ml/kg/day are regularly tolerated. As the feedings are increased, the amount of parenteral nutrition is tapered, with total (parenteral plus enteral) intake of nutrients always remaining at full level.

### Enteral Nutrition

The anatomically and functionally immature intestine can undergo maturation in a relatively short time if the necessary stimulation is provided in the form of trophic feedings (gastrointestinal priming). Gastrointestinal priming should be started on the first day of life. Feeding volumes initially may be as low as 2 ml every 6 or 4 h. Stimulation of the gut is initially the sole objective of enteral feeding. Motility serves as a marker of gut maturation and is monitored clinically by assessment of gastric residuals. As gastric emptying im-

**Table 1.** Requirements for protein and energy (best estimates by factorial and empirical methods)

	Body weight			
	500–1,000 g	1,000–1,500 g	1,500–2,200 g	2,200–3,000 g
Fetal weight gain, g/kg/day	19.0	17.4	16.4	13.4
Protein, g/kg/day	4.0	3.9	3.7	3.4
Energy, kcal/kg/day	106	115	123	130
Protein/energy, g/100 kcal	3.8	3.4	3.0	2.6

proves, it is assumed that the ability to digest and absorb nutrients is also improving. Gastric emptying thus serves as an important clinical guide in early enteral feeding. The risk of NEC is quite low with trophic feedings, but it somewhat increases subsequently as feeding volumes increase.

The preferred feed for gastrointestinal priming is maternal milk or, if not available, donor milk. Donor milk is pasteurized and free of viruses such as HIV and cytomegalovirus. Although pasteurization diminishes some of the protective and trophic factors of human milk, donor milk retains its protective effect against NEC [4] and sepsis and has strong trophic effects. When human milk is not available, formulas can also be used for gastrointestinal priming.

#### *Transition Phase*

Feeding volumes are usually kept low for several days and are gradually increased as gastric residuals diminish. At each new level, the adequacy of gastric emptying (absence of gastric residuals) must be ascertained before the feeding volume is further increased. The presence of gastric residuals does not require cessation of feedings as long as there are no signs suggestive of NEC. The use of gastrointestinal priming has been shown to lead to earlier establishment of full feedings and to earlier hospital discharge without an increase in NEC [5]. In fact, earlier achievement of full feedings has been shown to decrease the risk of sepsis [6]. Feeding volumes can be increased by 20 ml/kg each day as gastric residuals permit. Al-

though more rapid increases are safe, intestinal maturation requires time and therefore more rapid increases are not necessary. When feeding volumes are 80–100 ml/kg/day, fortification of breast milk is usually initiated, although in some units fortification is started much earlier. Parenteral nutrition can be discontinued when enteral feedings are at least 90% of the full amount.

#### *Late Phase*

The late phase begins when full feedings are established and parenteral nutrition is discontinued. The objective of nutrition is to allow growth to proceed parallel to intrauterine growth. The energy and protein intakes listed in table 1 are needed to support growth at the intrauterine rate. If the infant is to catch up in growth, intakes must be increased by perhaps 10–20%. Intakes below those listed in table 1 lead to extrauterine growth failure with all its negative consequences. Feedings are fortified human milk or, when not available, special formulas.

With standard preterm formulas with a protein/energy ratio (3.0 g/100 kcal) protein intakes are marginally adequate. Formulas with higher protein content (3.3–3.6 g/100 kcal) are therefore preferable in order to achieve appropriate ‘catch up’ growth of lean body mass.

Breast milk must be fortified (supplemented) with nutrients in order to meet the preterm infant’s high needs (table 1). Fortifiers are available as powders and as liquids. Commercially available fortifiers provide the necessary nutrients in suffi-

cient amounts with the exception of protein, which is inadequate in most fortifiers. Protein intakes are therefore often inadequate. The reason why powder fortifiers, and some liquid fortifiers, are too low in protein is that they were designed at a time when the overriding consideration was the avoidance of 'high' protein intakes in the face of variable protein concentrations of expressed human milk. The inevitable consequence is that protein intakes are too low most of the time. Today the ill effects of inadequate protein intakes are better known. Fortifiers (liquid) with higher protein content are available and should be used. With their use, protein intakes are adequate most of the time, albeit being somewhat high at times when the protein content of expressed milk is relatively high.

Customizing approaches to fortification have been developed with the aim of overcoming the

inadequacy of protein intakes with powder fortifiers. A method for BUN-guided fortification has been described by Arslanoglu et al.[7]. The method is somewhat cumbersome, which may be the reason for its limited use. Approaches based on periodic analysis of expressed milk (targeted fortification) also have been shown to lead to more adequate nutrient intakes and improved growth [8].

#### *After Discharge*

When preterm infants leave the hospital their nutrient needs are still high. In addition, they often have accrued deficits in bone mineral content. This is the reason why there is a need for continued fortification of human milk. In the case of formula feeding, the use of enriched post-discharge formulas is necessary.

## References

- 1 Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK: Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics* 2006;117:1253–1261.
- 2 Ziegler EE: Meeting the nutritional needs of the low-birth-weight infant. *Ann Nutr Metab* 2011;58(suppl 1):8–18.
- 3 te Braake FWJ, van den Akker CHP, Wattimena DJL, Huijmans JGM, van Goudoever JB: Amino acid administration to premature infants directly after birth. *J Pediatr* 2005;147:457–461.
- 4 Boyd CA, Quigley MA, Brocklehurst P: Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. *Arch Dis Child Fetal Neon Ed* 2007;92:F169–F175.
- 5 Tyson JA, Kennedy KA: Trophic feedings for parenterally fed infants (Review). *Cochrane Database Syst Rev* 2005;CD000504.
- 6 Ronnestad A, Abrahamsen TG, Medbø S, Reigstad H, Lossius K, Kaaresen PI, et al: Late-onset septicemia in a Norwegian national cohort of extremely premature infants receiving very early full human milk feeding. *Pediatrics* 2005;115:e269–e276.
- 7 Arslanoglu S, Moro GE, Ziegler EE: Adjustable fortification of human milk fed to preterm infants: does it make a difference? *J Perinatol* 2006;26:1–8.
- 8 Polberger S, Riih  NCR, Juvonen P, Moro GE, Minoli I, Warm A: Individualized protein fortification of human milk for preterm infants: comparison of ultrafiltrated human milk protein and a bovine whey fortifier. *J Pediatr Gast Nut* 1999;29:332–338.





## 3.15 Nutritional Management of Diabetes in Childhood

Carmel Smart

### Key Words

Diet · Type 1 diabetes · Glycemic index · Intensive insulin therapy · Carbohydrate counting

### Key Messages

- Nutrition management is one of the fundamental elements of care and education for children with type 1 diabetes
- Medical nutrition therapy should be provided at diagnosis of diabetes and reviewed at least annually to increase dietary knowledge and adherence
- Healthy eating recommendations suitable for all children should underlie all education. Education on carbohydrate counting should be given with consideration of dietary quality and low-glycemic index food choices
- Matching of the insulin dose to carbohydrate intake is recommended for children using intensive insulin therapy. Carbohydrate counting has the potential to increase flexibility in food intake and quality of life. However, regularity in meal routines remains important for optimal metabolic outcomes
- There is increasing evidence that other macronutrients impact postprandial blood glucose levels. Recent studies have shown that it is important to consider both protein and fat in the calculation of the meal insulin dose and how it is delivered

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### Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in childhood [1]. Nutritional management is fundamental to diabetes care and education. Nutrition therapy should focus on interventions to ensure normal growth and development, promote lifelong healthy eating habits and optimize glycemic control as well as assist with prevention of the complications associated with diabetes.

Dietary recommendations for children with diabetes are based on healthy eating recommendations suitable for all children – and thus the entire family [2]. Nutrition education should be individualized and adapted to cultural, ethnic, religious and family traditions. Regular dietetic assessment is necessary to adapt nutritional advice to growth, diabetes management and lifestyle changes as well as to permit the identification and treatment of disordered eating patterns. Eating disorders and celiac disease occur more commonly in T1DM and require specialized dietetic support. All children with diabetes and their families should have access to a specialist pediatric dietitian with experience in childhood diabetes as part of the interdisciplinary diabetes

care team. However, every team member should have an understanding of the principles of nutritional management.

Advice on carbohydrate quantity, type and distribution is important as carbohydrate is the main determinant of postprandial glucose response. Education should take into account an individual's energy needs, eating and physical activity patterns and insulin regimen. Matching insulin to carbohydrate intake for those on intensive insulin therapy requires comprehensive education in carbohydrate counting. It is vital that healthy eating principles targeting an increased consumption of fruit and vegetables and a decreased saturated fat intake underlie education.

### Goals of Nutrition Therapy

The main aims of nutritional management in pediatric diabetes are to

- encourage healthy lifelong eating habits;
- achieve and maintain blood glucose levels in the normal range by a balance between food intake, energy expenditure and insulin action profiles;
- provide appropriate energy intake and nutrients for optimal growth, development and good health;
- consider personal and cultural food preferences to preserve social, cultural and psychological well-being;
- achieve and maintain an appropriate body mass index and waist circumference through healthy eating and regular physical activity;
- optimize lipid and lipoprotein profiles to reduce cardiovascular disease risk, and
- maintain the pleasure of eating by encouraging a wide variety in food choices.

Dietetic advice is required at the initial diagnosis of diabetes, with follow-up 2–4 weeks later and regular (at least annual) review to meet changes in appetite and to provide ongoing age-appropriate education [3]. Circumstances such as

changes in the insulin regimen, dyslipidemia, excessive weight gain or loss as well as the diagnosis of a comorbidity such as celiac disease require additional dietary intervention with more frequent review.

### Eating Patterns

The key dietary behaviors that have been associated with improved glycemic outcomes in people with T1DM are adherence to an individualized meal plan, particularly carbohydrate intake recommendations [4], avoidance of frequent snacking episodes or large snacks without adequate insulin coverage, regular meals and avoidance of skipping meals [5], avoidance of overtreatment of hypoglycemia and insulin boluses before meals [6]. Regularity in mealtimes and routines where the child and family sit down and eat together – helping to establish better eating practices and monitoring of food intake – has been shown to be associated with better glycemic outcomes across all insulin regimens.

The recommended meal plan should consider usual appetite, food intake and exercise patterns (including at school or preschool), activity level and insulin regimen. A key aspect of nutrition therapy is advice on the amount, type and distribution of carbohydrate over the day. Nutritional advice regarding carbohydrate distribution, including the need for snacks, differs according to the insulin regimen [7]. Recommendations for different insulin regimens are presented in table 1.

### Energy Balance

At diagnosis, appetite and energy intake are often high to compensate for catabolic weight loss. Energy intake should be reduced when an appropriate healthy weight is restored. Regular monitoring by the diabetes team should assess appropriate weight gain.

**Table 1.** Nutritional recommendations for different insulin regimens

Insulin regimen	Meal structure
<i>Twice daily mixed insulin doses</i>	Three meals and 3 snacks per day at regular times to balance the insulin action profile Consistent carbohydrate quantities at each meal and snack on a daily basis Treat hypoglycemia with short-acting carbohydrate followed by long-acting carbohydrate
<i>Multiple daily injections</i> using rapid-acting insulin premeals and long-acting insulin as the basal dose; greater flexibility in meal timing and food quantity as one is able to change the mealtime insulin dose and timing	Snacks between meals should not exceed 1–2 carbohydrate serves (e.g. 15–30 g of carbohydrate) unless an additional injection is given Requires knowledge of carbohydrate counting for insulin dose adjustment at mealtimes Treat hypoglycemia with short-acting carbohydrate only
<i>Insulin pump therapy</i> provides a continuous subcutaneous infusion of basal insulin, with bolus doses given to match the carbohydrate amount to be eaten	Offers the greatest flexibility in meal timing and quantities; hence, it is particularly helpful for toddlers to decrease parental anxiety at mealtimes Good knowledge of carbohydrate counting is essential as bolus insulin is matched to the carbohydrate eaten at all meals and snacks Insulin for food must be given prior to eating for the best glycemic outcome A missed mealtime insulin bolus is the biggest contributor to poor glycemic outcome Basal rates, insulin-to-carbohydrate ratios and correction factors are individually calculated The bolus type and dose can be adjusted to match the meal composition and, hence, better mimics the physiological absorption profile Treat hypoglycemia with short-acting carbohydrate only

With all insulin regimens, individualized advice regarding carbohydrate amount and distribution should consider usual appetite, food intake patterns, exercise and energy requirements of the person with diabetes.

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The prevention or treatment of overweight or obesity is a key strategy of care, and guidance on appropriate serving sizes, frequency of snacking and appropriate hypoglycemia treatment is important. Additionally, advice should be provided on food and insulin adjustment for exercise.

The total daily energy intake should be distributed as follows: 45–65% carbohydrate, 30–35% fat and 15–25% protein [8]. Carbohydrate should not

be restricted, as it is essential for growth. Carbohydrate intake should come predominantly from wholegrain breads and cereals, legumes, fruit, vegetables and low-fat dairy foods (except for children <2 years). Food models such as the plate food model (fig. 1) are useful in providing basic nutritional information and healthy eating concepts [9]. They also illustrate carbohydrate-containing foods in relation to other foods visually.



# Australian Guide to Healthy Eating

Enjoy a wide variety of nutritious foods from these five food groups every day.  
Drink plenty of water.

Grain (cereal) foods, mostly wholegrain and/or high cereal fibre varieties



Vegetables and legumes/beans



Lean meats and poultry, fish, eggs, tofu, nuts and seeds and legumes/beans



Milk, yoghurt, cheese and/or alternatives, mostly reduced fat



Fruit



Use small amounts



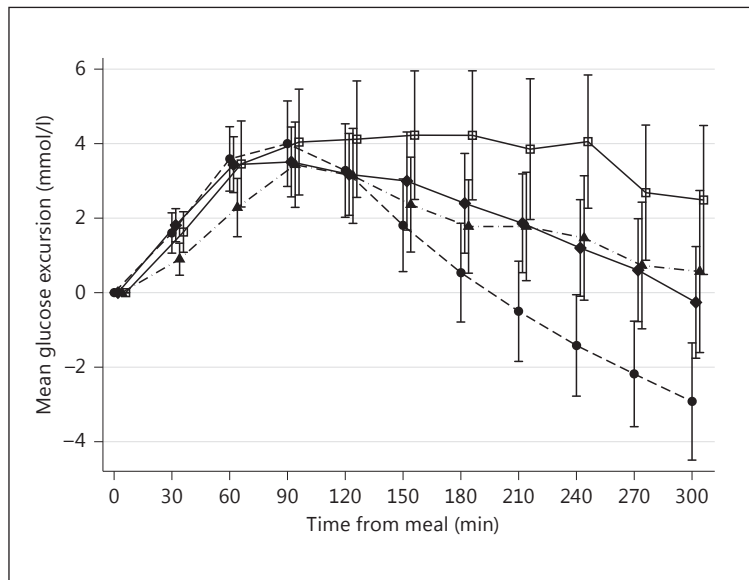
Only sometimes and in small amounts



(For legend see next page.)

**Fig. 1.** Australian guide to healthy eating. Canberra, National Health and Medical Research Council, 2013 [9].

**Fig. 2.** Mean postprandial glucose excursions from 0 to 300 min for 33 subjects after test meals of low fat/low protein (●), low fat/high protein (◆), high fat/low protein (▲) and high fat/high protein (□) content. The carbohydrate amount was the same in all meals. There were significant differences in glucose excursions between meal types from 150 to 300 min ( $p < 0.03$ ). © American Diabetes Association. Reproduced from Smart et al. [12].



2

## Carbohydrate Assessment

Children and adolescents with T1DM require education regarding the amount, type and distribution of carbohydrate over the day, taking into account their age, food intake patterns and insulin regimens (table 1). Day-to-day consistency in carbohydrate intake using serves or 15-gram carbohydrate exchanges is encouraged for those receiving fixed mealtime insulin doses. A more flexible carbohydrate intake can be achieved using an insulin-to-carbohydrate ratio for those on intensive insulin therapy.

Carbohydrate counting is a key nutritional intervention for young people using insulin pump or multiple daily injection therapy. It enables adjustment of the prandial insulin dose according to carbohydrate consumption, thus permitting carbohydrate intake to be varied. Multiple benefits have been reported when carbohydrate counting is used as an intervention, including improvements in glycemic control, diabetes-specific quality of life and coping ability [10]. Advice on carbohydrate quantification should be given

within the context of a healthy diet as focusing only on the amount of carbohydrate can lead to unhealthy food choices.

In clinical practice, a number of methods for carbohydrate quantification are commonly taught, including 1-gram increments, 10-gram carbohydrate portions and 15-gram carbohydrate exchanges. Research has demonstrated that carbohydrate counting is difficult, and repeated age-appropriate education by experienced health professionals is necessary to maintain accuracy in estimations [11]. Inaccurate carbohydrate counting has been associated with higher daily blood glucose variability.

It is becoming increasingly recognized that fat and protein also contribute to postprandial hyperglycemia. Fat and protein have been found to increase the delayed postprandial glucose rise (fig. 2) [12]. Consideration of the impact of fat and protein on glucose levels involves the application of advanced nutritional concepts that are best taught after basic carbohydrate counting skills are established. Alterations to the insulin dose and distribution at a mealtime may be necessary

**Table 2.** Common issues to consider for each age group

Age group	Issues to consider
Toddlers	<p>Encourage them to eat the usual family diet; offer finger foods to encourage self-feeding; discourage offering a bottle for 'easy' carbohydrate intake</p> <p>Decreased appetite, food refusal and food fads are common; it is important to avoid 'grazing' and excessive milk consumption</p> <p>Regular carbohydrate intake is required to prevent hypoglycemia on twice-daily insulin doses; offer routine meals and 2 small snacks over the day</p> <p>Insulin pump therapy is beneficial in managing toddler eating behaviors; it is preferable that preprandial insulin doses are given, but the dose can be split to some before and some during the meal when eating is erratic or new foods are offered; it is important that carbohydrate quantities as small as 7 g are covered by insulin</p>
School-aged children	<p>They become more independent and take on aspects of own care but always with parental supervision and support</p> <p>Blood testing during the school day is recommended for all children</p> <p>The meal and snack routine is ideally incorporated into the usual school timetable</p> <p>They need to have an understanding of carbohydrate quantities in foods to ensure an appropriate distribution over the school day; labelling the carbohydrate quantities of foods in the lunch box is recommended</p> <p>Avoid excessive eating at afternoon tea contributing to predinner hyperglycemia by either eating more during the day to spread carbohydrate more evenly or considering an additional dose of insulin in the afternoon to cover the extra carbohydrate</p> <p>Extra carbohydrate food is required only for additional strenuous activity and not needed for the child's usual active play</p>
Teenagers	<p>Challenging behaviors including smoking, drinking, staying out late, sleeping in, skipping insulin and missing meals</p> <p>Emphasis should be placed on the importance of routine meals and snacks, particularly during periods of rapid growth, to prevent excessive afternoon or evening snacking</p> <p>Disordered eating habits can be an issue that clashes with diabetes management, and they may require specialist dietetic support</p> <p>Parental supervision and support continues to be essential, particularly at mealtimes, to ensure insulin boluses are not missed</p> <p>Alcohol can cause delayed hypoglycemia, and advice needs to be given about moderate alcohol consumption and regular carbohydrate intake during drinking</p> <p>Participation in competitive sports requires appropriate insulin adjustment as well as an appropriate timing and quantity of carbohydrate intake and adequate fluid to optimize performance</p>

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for meals very rich in fat and protein. An advantage of insulin pump therapy is that it is possible to tailor prandial insulin delivery to meal composition. Combination boluses have been recommended for high-fat, high-protein meals and low-glycemic index (GI) meals.

### **Glycemic Index**

Nutrition therapy for young people with T1DM should include education regarding the GI. This is a ranking of foods based on their acute glycemic impact. The GI has been shown to provide addi-

tional benefit to glycemic control over that observed when carbohydrate amount is considered alone [13]. Low-GI foods lower the postprandial glucose excursion compared to carbohydrates with a higher GI. If possible, high-GI food choices should be substituted with lower-GI foods. Examples of low-GI food choices include wholegrain breads, pasta, many fruits, milk and yoghurt. It is important that the GI is not taught in isolation, as monitoring the amount of carbohydrate is a key strategy of care.

### **Specific Advice for Different Age Groups**

At all ages, advice should focus on decreasing the intake of sweetened drinks and saturated fat [7]. Specially labeled 'diabetic foods' are not necessary and may contain sweeteners with laxative effects. Missed meal boluses are a major cause of suboptimal glycemic control at all ages, and it is advisable to always give insulin before meals. Common dietary issues to consider at specific ages are outlined in table 2.

### **Nutritional Management of Type 2 Diabetes in Children**

Most children with type 2 diabetes are overweight or obese; therefore, nutritional advice should be focused on dietary changes and lifestyle interventions to prevent further weight gain or to achieve weight loss. The entire family should be included in the education, since caregivers influence the child's food intake and physical activity. Families should be counseled to decrease energy intake by focusing on healthy eating and strategies to decrease portion sizes of foods as well as by lowering the intake of high-energy-, high-fat- and high-sugar-containing foods. Snacks should be limited. Those on medication or insulin therapy require more in-depth teaching on carbohydrate management. Regular follow-up is essential to

monitor weight and glycemic control and to prevent the development of diabetes-related complications.

### **Conclusions**

- Nutrition therapy is one of the fundamental elements of care and education for children and adolescents with diabetes
- Individualized nutritional education should be provided at diagnosis by a dietitian with experience in childhood diabetes. Regular supportive contacts with dietetic health professionals are required to increase dietary knowledge and adherence across the life span
- Dietary recommendations should be based on healthy eating guidelines suitable for all children and families with the aim of improving diabetes outcomes and reducing cardiovascular risks
- Nutritional interventions should aim to maintain an ideal body weight, optimal growth as well as health and development. Growth monitoring is an important part of diabetes management
- The optimal macronutrient distribution varies depending on the individualized assessment of a young person. As a guide, carbohydrate should approximate 45–55%, fat <30–35% (saturated fat <10%) and protein 15–20% of the energy intake
- The use of an insulin-to-carbohydrate ratio on intensive insulin regimens allows greater flexibility in carbohydrate intake and mealtimes, with potential for improvements in glycemic control and quality of life
- Regularity in mealtimes and eating routines are important for optimal glycemic outcomes on all insulin regimens
- Fixed insulin regimens require consistency in the amount and timing of carbohydrate intake over the day

- Low-GI foods should be substituted for high-GI foods in the diets of children with diabetes to improve glycemic control
- The prevention of overweight and obesity in pediatric T1DM is a key strategy of care and should involve a family-based approach
- Individualized nutritional advice should be provided on how to manage physical activity, exercise and competitive sports
- Nutritional management of type 2 diabetes requires a family and community approach to manage issues of excessive weight gain, lack of physical activity and the increased risk of cardiovascular disease

## References

- 1 Craig ME, Hattersley A, Donaghue K: ISPAD clinical consensus guidelines 2009 compendium. Definition, epidemiology and classification of diabetes. *Pediatr Diabetes* 2009;10(suppl 12):3–12.
- 2 American Diabetes Association: Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 2005;28:186–212.
- 3 Smart CE, Aslander-van de Vliet E, Waldron S: ISPAD clinical practice consensus guidelines 2009 compendium. Nutritional management in children and adolescents with diabetes. *Pediatr Diabetes* 2009;10(suppl 12):100–117.
- 4 Mehta S, Volkening L, Anderson B, Nansel T, Weissberg-Benchell J, Wysocinski T, et al: Dietary behaviors predict glycemic control in youth with type 1 diabetes. *Diabetes Care* 2008;31:1318–1320.
- 5 Øverby N, Margeirsdottir H, Brunborg C, Andersen L, Dahl-Jørgensen K: The influence of dietary intake and meal pattern on blood glucose control in children and adolescents using intensive insulin treatment. *Diabetologia* 2007;50:2044–2051.
- 6 Scaramuzza AE, Iafusco D, Santoro L, Bosetti A, De Palma A, Spiri D, et al: Timing of bolus in children with type 1 diabetes using continuous subcutaneous insulin infusion (TiBoDi Study). *Diabetes Technol Ther* 2010;12:149–152.
- 7 Barclay A, Gilbertson H, Marsh K, Smart CE: Dietary management in diabetes. *Aust Fam Physician* 2010;39:579–583.
- 8 National Health and Medical Research Council: Australian dietary guidelines. Canberra, National Health and Medical Research Council, 2013.
- 9 National Health and Medical Research Council: Australian guide to healthy eating. Canberra, National Health and Medical Research Council, 2013.
- 10 Laurenzi A, Bolla A, Panigoni G, Doria V, Uccellatore A, Peretti E, et al: Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GIOCAR). *Diabetes Care* 2011;34:823–827.
- 11 Smart CE, Ross K, Edge JA, King BR, McElduff P, Collins CE: Can children with type 1 diabetes and their caregivers estimate the carbohydrate content of meals and snacks? *Diabet Med* 2010;27:348–353.
- 12 Smart C, Evans M, O’Connell S, McElduff P, Lopez P, Jones T, et al: Both dietary protein and fat increase postprandial glucose excursions in children with type 1 diabetes, and the effect is additive. *Diabetes Care* 2013;36:3897–3902.
- 13 Thomas D, Elliott E: Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. *Cochrane Database Syst Rev* 2009;1:CD006296.





## 3.16 Inborn Errors of Metabolism

Anita MacDonald

### Key Words

Phenylketonuria · Maple syrup urine disease · Urea cycle disorders · Organic acidaemias · Galactosaemia · Glycogen storage disease · Protein · Amino acids · Galactose · Fructose · Glucose

### Key Messages

- Common inborn errors of metabolism (IEM) treated by life-long dietary management are responsible for a collection of diverse clinical conditions
- It is essential to diagnose conditions before neurological or other toxicological damage occurs
- Treatment strategies involve avoidance or controlled intake of dietary precursors of toxic metabolites in amino acid disorders, organic acidaemias, urea cycle disorders, galactosaemia and hereditary fructose intolerance
- Other disorders need to avoid prolonged fasting (e.g. fatty acid oxidation disorders) or a regular glucose supply (e.g. glycogen storage disorders)
- In IEM where acute metabolic decompensation occurs, the use of an emergency regimen is imperative
- Attentive nutritional support with the provision of macronutrients and micronutrients to meet dietary reference values/requirements is essential
- Frequent monitoring of growth, nutritional intake, development and biochemical control is necessary

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### Introduction

Common inborn errors of metabolism (IEM) treated by life-long dietary management are responsible for a collection of diverse clinical conditions. Each condition may present at different ages with variable severity and outcome. Disorders requiring avoidance of/reduction in dietary precursors of toxic metabolites include phenylketonuria (PKU), maple syrup urine disease (MSUD), organic acidurias, urea cycle disorders (UCD) and galactosaemia. Disorders requiring glucose stabilisation include fatty acid oxidation defects and glycogen storage diseases (GSD). It is essential to diagnose conditions before neurological or other toxicological damage occurs. Many IEM are now recognised by newborn screening programmes. In some conditions, neonates may require emergency treatment such as dialysis to remove toxic organic acids or ammonia.

In IEM where acute metabolic decompensation occurs (precipitated by infections/surgery/trauma combined with poor oral intake and fasting), with risk of further irreversible damage, particularly neurological, the use of an emergency regimen is imperative. An emergency regimen provides an exogenous energy source (either

from oral glucose polymer solutions or intravenous glucose) to reduce production of potentially toxic metabolites or to prevent hypoglycaemia [1]. This is essential for a variety of conditions including MSUD, organic acidaemias, UCD, long-chain and medium-chain fatty acid oxidation disorders and GSD.

## Disorders of Amino Acid Metabolism

Deficiencies in enzymes involved in amino acid metabolism cause abnormalities in the breakdown of amino acids, resulting in the accumulation of toxic substances, e.g. phenylalanine, phenylpyruvate and phenylacetic acid in PKU, and subsequent organ damage (table 1) [2]. The brain, liver and kidney are the most frequently affected organs. Some disorders cause chronic neurological damage without acute decompensation (e.g. PKU), others cause acute symptoms associated with catabolic states leading to endogenous protein breakdown and release of amino acids (MSUD) [3]. Dietary treatment is essential for PKU, homocystinuria (HCU), MSUD and tyrosinaemia type 1 (HT1) [4].

Dietary treatment involves:

- Avoidance of foods high in natural protein to prevent excess accumulation of the 'precursor' amino acid(s); foods such as meat, fish, eggs, cheese, nuts and seeds are not permitted unless it is a very mild disorder phenotype
- A limited amount of natural protein is given to maintain 'precursor' blood amino acids within the target treatment range; natural food sources allocated for substrate amino acids are from cereal, potato, some vegetables and milk
- Provision of L-amino acids that are free of 'precursor' amino acids to meet at least safe levels of protein/nitrogen requirements with an additional amount to compensate for the inefficiency of L-amino acid utilisation
- Provision of indispensable/conditionally indispensable amino acids that may become de-

ficient as a result of the enzyme block or dietary treatment (e.g. phenylalanine in HT1, cystine in HCU)

- Maintenance of a normal energy intake by encouraging the use of foods naturally low in protein and of specially manufactured low-protein foods such as bread and pasta
- Prevention of catabolism and metabolic decompensation during illness/trauma, particularly in MSUD

Diet may be the sole form of therapy or used in combination with other treatments. In mild or moderate PKU, adjunct therapy in the form of tetrahydrobiopterin, a coenzyme in the hydroxylation reaction of phenylalanine to tyrosine, may help to enhance natural protein tolerance or improve blood phenylalanine control. It acts as a chaperone to increase the activity of the defective enzyme [4]. In HT1, the drug nitisone inhibits the accumulation of the catabolic intermediates which are converted to succinyl acetone and succinyl acetoacetate, which are responsible for liver and kidney toxicity [5].

## Organic Acidurias

Organic acidurias are a diverse group of disorders, typically in the degradative pathways of amino acids, carbohydrates and fatty acids, characterised by increased excretion of organic acids in the urine. They include the conditions affecting abnormal catabolism of branched-chain amino acids: methylmalonic aciduria (MMA), propionic aciduria (PA) and isovaleric aciduria (table 2). Clinical features frequently include encephalopathy and episodic metabolic acidosis, caused not only by the accumulation of toxic intermediates but also by disturbances of mitochondrial energy metabolism and carnitine homeostasis [3]. Symptoms commonly develop between days 2 and 5 of life, although they can commence at any age. Major goals of therapy are the reversal of catabolism, the promotion of anab-

**Table 1.** Incidence, classification and symptoms of amino acid disorders

Condition	Incidence	Classification	Symptoms in untreated patients	Treatment
PKU	Varies between populations: 1 in 4,000 to 1 in 200,000	<p><i>Classic or severe PKU</i> Plasma phenylalanine concentrations &gt;1,200 µmol/l</p> <p><i>Moderate PKU</i> Plasma phenylalanine concentrations &gt;600–1,200 µmol/l</p> <p><i>Mild PKU or hyperphenylalaninaemia</i> Phenylalanine concentrations &lt;600 µmol/l</p>	<ul style="list-style-type: none"> <li>- Severe intellectual and neurological impairment</li> <li>- Mousy odour</li> <li>- Infantile spasms</li> <li>- Lightly pigmented (hair, eyes and skin)</li> <li>- Eczema</li> <li>- Microcephaly</li> <li>- Delayed speech development</li> </ul> <p><i>Older patients</i></p> <ul style="list-style-type: none"> <li>- Hyperactivity</li> <li>- Disturbed behaviour</li> <li>- Autistic features</li> <li>- Self-injury</li> <li>- Abnormalities of gait</li> <li>- Tremor</li> <li>- Grand mal seizures</li> </ul>	<ul style="list-style-type: none"> <li>- Low phenylalanine diet (classic PKU, children: tolerate 200–500 mg daily)</li> <li>- Phenylalanine-free L-amino acid supplement</li> <li>- Tyrosine supplementations (usually already added to L-amino acid supplement)</li> <li>- Vitamins/minerals/essential and LC PUFA</li> <li>- Use of low-protein foods (special and natural) to maintain 'normal' energy requirements</li> <li>- Patients with mild/moderate PKU may respond to 5–20 mg/kg sapropterin daily</li> </ul>
MSUD	1 in 116,000	<p>Classic MSUD</p> <p>Intermediate form</p> <p>Intermittent form</p> <p>Thiamin-responsive form (a cofactor for BCKD complex)</p>	<p><i>Classic (neonatal onset)</i></p> <ul style="list-style-type: none"> <li>- Poor feeding</li> <li>- Sweet, malty, caramel-like smell</li> <li>- Episodic vomiting</li> <li>- Irritability</li> <li>- Hypoglycaemia</li> <li>- Lethargy</li> <li>- Encephalopathy</li> <li>- Cerebral oedema</li> <li>- Seizures</li> <li>- Delay in diagnosis may result in neurological damage or death</li> </ul> <p><i>Intermediate form</i></p> <ul style="list-style-type: none"> <li>- Presents at any age (infancy to adulthood)</li> <li>- Failure to thrive</li> <li>- Hypotonia</li> <li>- Progressive developmental delay</li> </ul> <p><i>Intermittent form</i></p> <ul style="list-style-type: none"> <li>- Ketoacidosis</li> <li>- Episodic ataxia and ketoacidosis (often with intercurrent illness or increased protein intake)</li> </ul>	<ul style="list-style-type: none"> <li>- Diet low in BCAA (leucine, valine, isoleucine; 'classic' children with MSUD tolerate 400–600 mg daily)</li> <li>- BCAA-free L-amino acid supplement</li> <li>- Valine/isoleucine supplements if blood levels low (dosage titrated to valine/isoleucine blood concentrations)</li> <li>- Vitamin/minerals/essential and LC PUFA</li> <li>- Use of low-protein foods (special and natural) to maintain 'normal' energy requirements</li> <li>- Requires emergency regimen during illness, fasting, infection or surgery</li> </ul>
HTI	1 in 100,000	Acute or chronic form	<p><i>Acute</i></p> <ul style="list-style-type: none"> <li>- Early infancy</li> <li>- Severe liver failure</li> <li>- Cirrhosis</li> <li>- Hepatocellular carcinoma</li> <li>- Renal Fanconi syndrome</li> <li>- Glomerulosclerosis</li> <li>- Vitamin D-resistant rickets</li> <li>- Neurological crisis</li> </ul> <p><i>Chronic</i></p> <ul style="list-style-type: none"> <li>- Slight enlargement of liver</li> <li>- Mild growth retardation</li> <li>- Renal tubular dysfunction and rickets</li> <li>- Hepatosplenomegaly</li> <li>- Liver cirrhosis</li> <li>- Hepatocellular carcinoma</li> </ul>	<ul style="list-style-type: none"> <li>- Diet low in tyrosine and phenylalanine</li> <li>- May tolerate up to 0.5 g/kg natural protein daily, but amount to be titrated to tyrosine/phenylalanine concentrations</li> <li>- Tyrosine/phenylalanine-free amino acid supplement</li> <li>- Phenylalanine supplements if blood levels low (dosage titrated according to blood levels)</li> <li>- Use of low-protein foods (special and natural) to maintain 'normal' energy requirements</li> <li>- Vitamin/minerals/essential and LC PUFA</li> <li>- Nitisinone (1 mg/kg/day)</li> </ul>

**Table 1 (continued)**

Condition	Incidence	Classification	Symptoms in untreated patients	Treatment
HCU	1 in 344,000 in classic HCU (varies from 1 in 65,000 to 1 in 900,000)	Pyridoxine responsive Non-pyridoxine responsive	- Dislocation of the optic lens, myopia and glaucoma - Osteoporosis, scoliosis, thinning and lengthening of the long bones - Learning difficulties, developmental delay, psychiatric problems, EEG abnormalities and epilepsy - Thromboembolism	- Classic HCU only - Low-methionine diet (classic HCU tolerates a median of 230 mg/day) - Methionine-free L-amino acid supplement - Cystine supplements if blood levels low (dosage titrated according to blood levels) - Use of low-protein foods (special and natural) to maintain 'normal' energy requirements - Vitamin/minerals/essential and LC PUFA - Folic acid supplementation - Betaine supplementation

BCKD = Branched-chain  $\alpha$ -keto acid dehydrogenase; BCAA = branched-chain amino acids; LC PUFA = long-chain polyunsaturated fatty acids.

olism and, as a consequence, the reversal of the breakdown of endogenous protein [3].

Treatment strategies include: (1) natural protein restriction of precursor amino acids (aiming to provide safe levels of protein intake [6]); (2) maintaining an optimal energy intake; and (3) use of adjunctive compounds to dispose of toxic metabolites (e.g. carnitine) or to increase activity of deficient enzymes (e.g. vitamin B<sub>12</sub> in MMA). Some inherited metabolic disease centres prescribe precursor-free amino acids to supplement natural protein intake, although the long-term value of these supplements remains uncertain. In MMA and PA, to reduce the production of propionate, it is also necessary to avoid prolonged fasting (with the use of overnight tube feeding) in order to limit oxidation of odd-chain fatty acids liberated from triglyceride stores during lipolysis. Also in MMA/PA, metronidazole is given to reduce intestinal production of propionate. Metabolic decompensation caused by catabolic stress (e.g. from vomiting and decreased oral intake) requires prompt intervention with an emergency regimen.

### Urea Cycle Disorders

UCD are rare defects in waste nitrogen metabolism associated with the breakdown of protein and other nitrogen-containing molecules [7]. Partial deficiency or total absence of any of the enzyme activities in the urea cycle (including carbamoyl-phosphate synthetase 1, ornithine carbamoyltransferase, argininosuccinate synthetase, argininosuccinate lyase and arginase) causes accumulation of ammonia and glutamine, and normal arginine biosynthesis is interrupted. The resulting hyperammonaemia and central nervous system dysfunction is associated with high mortality and morbidity. Although symptoms mainly develop in the neonatal period, patients differ in age at presentation, in the character and severity of symptoms and in their susceptibility to meta-

**Table 2. Incidence, classification and symptoms of organic acidurias**

Condition	Prevalence	Classification	Signs and Symptoms	Treatment	Complications
PA	Uncertain Estimates: 1 in 50,000 to 1 in 500,000 High in regions of Saudi Arabia (1 in 2,000 to 1 in 5,000)	<i>Early onset</i> Presenting in neonatal period; severe illness follows introduction of protein- containing feeds <i>Late onset (&gt;6 weeks)</i> Less common, and variable clinical presentation	Life-threatening illness Poor feeding/feed refusal Faltering growth Vomiting Dehydration Dyspnoea Hypothermia Lethargy Hypotonia Hepatomegaly Developmental delay Seizures Somnolence Coma	1. Low-protein diet ± amino acid supplements free of methionine, threonine, valine and isoleucine 2. Carnitine 3. Metronidazole 4. Sodium bicarbonate for acidosis 5. Sodium benzoate for hyperammonaemia 6. Emergency regimen during intercurrent infections	Neurological damage Movement disorders and dystonia Developmental delay Poor growth Hair loss Nutritional deficiencies, e.g. selenium and zinc Acute protein malnutrition Dermatitis Candida infections Recurrent infections Osteoporosis Acute and recurrent pancreatitis Hypocalcaemia due to parathyroid hormone resistance Cardiomyopathy
MMA	Uncertain Estimates: 1 in 50,000	<i>Methylmalonyl-CoA mutase</i> <i>phenotypes:</i> Mut <sup>+</sup> (no mutase activity) Mut <sup>-</sup> (residual mutase activity) <i>Cobalamin disorders</i> cblA cblB <i>Cobalamin reduction pathway</i> <i>disorders</i> cblC cblD	Poor feeding/feed refusal Faltering growth Vomiting Candida infections Hypotonia Dehydration Dyspnoea Lethargy Progressive encephalopathy Hepatomegaly Developmental delay Seizures	1. Vitamin B <sub>12</sub> for responsive patients 2. Low-protein diet ± amino acid supplements free of methionine, threonine, valine and isoleucine 3. Carnitine 4. Metronidazole 5. Sodium bicarbonate for acidosis 6. Sodium benzoate for hyperammonaemia 7. Emergency regimen during intercurrent infections	Neurological damage Hypotonia Neurodevelopmental delay Learning difficulties Basal ganglion damage and stroke-like symptoms Poor growth Hair loss Nutritional deficiencies, e.g. selenium and zinc Acute protein malnutrition Osteoporosis Acute and recurrent pancreatitis Tubular acidosis with hyperuricaemia Chronic renal failure Cardiomyopathy
Isovaleric acidaemia	Unknown	Acute, severe neonatal form Chronic intermittent form	Episodic vomiting Poor feeding/feed refusal Hypotonia Dehydration Dyspnoea Lethargy Hypothermia Sweaty feet odour Progressive encephalopathy Psychomotor delay Seizures	1. Low-protein diet ± amino acid supplements free of leucine 2. Carnitine 3. Glycine 4. Emergency regimen during intercurrent infections	Neurological damage Natural aversion to protein-containing foods Pancreatitis Faltering growth Learning difficulties

bolic derangement depending on the affected enzyme and its residual activity [8].

Treatment for UCD involves reducing protein intake, supplementing essential amino acids and avoiding catabolic states. Drug therapy produces alternative pathways for nitrogen excretion and includes ammonia-scavenging drugs (e.g. sodium phenylbutyrate or sodium benzoate) and arginine (except in arginase deficiency), which promotes incorporation of ammonia into citrulline and arginosuccinate. L-Citrulline may be given as an alternative to arginine in ornithine carbamoyltransferase and carbamoyl-phosphate synthase deficiency [7].

### Disorders of Fatty Acid Oxidation

Mitochondrial fatty acid oxidation is required for energy during fasting, either through complete oxidation or through production of ketones in the liver that then serve as an alternative energy source for the brain. Disorders are mainly precipitated by fasting and typically present as hypoketotic hypoglycaemia, which leads to coma or convulsions. The most common fatty acid disorder in Northern Europe is medium-chain acyl-CoA dehydrogenase deficiency (MCADD) [5]. In unscreened populations, MCADD is associated with 25% mortality on presentation. Most children identified through newborn screening remain well without long-term sequelae. Precipitating factors of acute metabolic episodes in infancy include prolonged fasting caused by vomiting/diarrhoea/fever, and in teenagers/adults strenuous exercise, alcohol and drugs (with vomiting/fasting), surgery and pregnancy [9]. Treatment consists of avoidance of fasting and use of an emergency regimen with illness/surgery/trauma. See table 3 for suggested safe fasting times.

### Disorders of Carbohydrate Metabolism

The disorders of carbohydrate metabolism display a wide range of clinical features: symptoms caused by toxicity (galactosaemia and hereditary fructose intolerance, HFI) or hypoglycaemia (GSD).

#### *Disorders of Galactose and Fructose Metabolism*

Galactosaemia is a disorder of galactose metabolism causing abnormal glycosylation of glycoproteins and glycolipids [10]. In HFI, accumulation of fructose 1-phosphate causes inhibition of glycogen breakdown and glucose synthesis, thereby causing severe hypoglycaemia following fructose ingestion [11]. Both conditions are potentially life threatening on presentation. Children with galactosaemia and HFI typically develop evidence of severe damage to the liver and kidneys after dietary intake of lactose (milk, milk products) in galactosaemia or of fructose (fruits, sucrose) in HFI [5]. Treatment includes the elimination of the intake of galactose or fructose, respectively. In HFI, an aversion to fructose is common.

Children with galactosaemia often present in the first week of life. Children with HFI develop symptoms after the introduction of fruits, vegetables and particularly table sugar (the fructose-glucose disaccharide sucrose) to their diet, often between 4 and 8 months of age [12]. Long-term complications are common in galactosaemia and appear to be independent of the severity of illness, type of diet therapy or dietary adherence, and there is debate about how stringent dietary restriction should be later in life. In contrast, in HFI outcome is good, with normal growth, intelligence and life span [12].

#### *Disorders of Gluconeogenesis and Glycogen Storage*

GSD are defects of a number of different enzymes involved in glycogen synthesis and degradation [13]. Glycogen is primarily stored in the

**Table 3. Incidence, classification and symptoms of MCADD and carbohydrate disorders**

Condition	Prevalence	Classification	Signs and Symptoms	Treatment	Complications
MCADD	1 in 12,000–20,000 in the UK, USA and Australia	Common mutation is c.985A>G and is associated with clinically severe presentation Milder forms have uncertain clinical relevance	Acute 'hypoketotic' hypoglycaemic encephalopathy and liver dysfunction	Frequent regular feeds in 1st year of life >1 year: avoid fasting for >12–14 h Dietary fat restriction unnecessary Emergency protocol for intercurrent infections, surgery or other conditions requiring prolonged fasting (regular feeds from glucose polymer); if not tolerated or feasible, will require glucose-containing IV fluids	Developmental delay secondary to acute metabolic event
Galactosaemia	1 in 16,000 to 1 in 40,000 in Western Europe	Deficiency of GALT Classic galactosaemia: GALT enzyme activity <5% of controls Duarte variant: GALT activity is approx. 25% of control values	Feeding problems Faltering growth Hepatocellular damage Bleeding Liver failure Sepsis Neonatal death Cataracts Intellectual disability Developmental delay Verbal dyspraxia Abnormalities of motor function	Low-galactose diet (lactose free) Lactose-free medications	Premature ovarian dysfunction Delayed growth Osteopenia Osteoporosis
HFI	1 in 20,000 (1 in 11,000 to 1 in 100,000)	Deficiency of fructose 1-phosphate aldolase activity	Nausea Vomiting Restlessness Pallor, sweating, trembling Lethargy Hepatomegaly, jaundice Haemorrhage Proximal renal tubular syndrome Hepatic failure and death	1. Fructose-, sucrose- and sorbitol-free diet 2. Sucrose-/fructose-free multivitamin supplement 3. Fructose-, sucrose- and sorbitol-free medications	Liver and kidney dysfunction
GSD	1 in 100,000	GSD Ia (von Gierke) Glucose-6-phosphatase deficiency	Hepatomegaly Hypoglycaemia Hyperlipidaemia Lethargy Seizures Developmental delay Protuberant abdomen	1. Lactose-free ( $\pm$ sucrose-/fructose-free) formula (but breast milk not contraindicated) 2. Frequent, small daytime feedings with avoidance of fasting (high in complex carbohydrate) 3. Continuous overnight tube feedings of glucose 4. Uncooked cornstarch >1 year (starting dose of 1 g/kg/dose); titrate dose according to glucose/lactate monitoring 5. Protein (10–15% of recommended total energy intake) 6. Vitamins/minerals/essential and LC PUFA 7. Emergency protocol for intercurrent infections (continuous tube feedings from glucose polymer) 8. Xanthine-oxidase inhibitor (allopurinol) to prevent gout 9. Lipid-lowering medications	Short stature Osteoporosis Delayed puberty Gout Renal disease Pulmonary hypertension Hepatic adenomas Polycystic kidneys Pancreatitis Neurocognitive effects Menorrhagia
	1 in 8 GSD I patients have type Ib	GSD Ib (von Gierke) Glucose-6-phosphate translocase deficiency	Same as in GSD Ia Neutropenia Infections Inflammatory bowel disease		
	1 in 100,000	GSD III (Cori/Forbes) Deficiency of debranching enzyme and of subtypes GSD IIIa: 85% of all GSD III GSD IIIb: 15% of all GSD III	Hepatomegaly (Cardiomyopathy) Short stature Hypoglycaemia GSD IIIa: symptoms related to liver disease and progressive muscle (cardiac and skeletal) involvement GSD IIIb: symptoms primarily related to liver disease	1. High-protein diet 2. Uncooked cornstarch >1 year (starting dose of 1 g/kg/dose); titrate dose according to glucose/lactate monitoring; regular feeding 3. Vitamins/minerals/essential and LC PUFA 4. Emergency protocol for intercurrent infections (continuous tube feedings from glucose polymer)	Cardiomyopathy Myopathy Poor growth Osteoporosis and osteopenia Polycystic ovary disease

GALT = Galactose-1-phosphate uridylyltransferase; LC PUFA = long-chain polyunsaturated fatty acids.

liver and muscle, and disorders of glycogen degradation may affect the liver or muscle or both [14]. The liver GSD include GSD I and the hepatic presentation of GSD III [15]. Typical metabolic features are lactic acidemia and hypoglycaemia. Variable organ dysfunction, most frequently hepatomegaly, occurs. The goal of treatment is to maintain normoglycaemia, prevent hypoglycaemia and prevent secondary complications. Treatments include frequent meals, cornstarch supplementation and/or continuous overnight tube feeding to avoid hypoglycaemia. In GSD I, allopurinol reduces uric acid levels in the blood to prevent gout and kidney stones [14].

## Conclusions

- The treatment goal for all IEM is to achieve optimal development and nutritional status during childhood, and maximal independence, social integration and self-esteem in adolescence and adulthood
- All conditions require diligent care, and IEM are best managed by a multidisciplinary team led by a physician
- Attentive nutritional support with the provision of macronutrients and micronutrients to meet dietary reference values/requirements is essential
- Frequent monitoring of growth, nutritional intake, development and biochemical control is necessary

## References

- 1 Dixon M: Emergency regimens; in Shaw V, Lawson M (eds): *Clinical Paediatric Dietetics*, ed 3. Oxford, Blackwell, 2007, pp 375–389.
- 2 Hoffmann GF, Nyhan WL, Zschocke J, Kahler SG, Mayatepek E: *Inherited Metabolic Diseases: A Clinical Approach*. Philadelphia, Lippincott Williams & Wilkins, 2002.
- 3 de Baulny HO, Dionisi-Vici C, Wendel U: Branched-chain organic acidurias/acidemias; in Saudubray JM, van den Berghe G, Walter JH (eds): *Inborn Metabolic Diseases: Diagnosis and Treatment*, ed 5. Berlin, Springer, 2012, pp 278–296.
- 4 MacDonald A, White F, Dixon M: Amino acid disorders; in Shaw V (ed): *Clinical Paediatric Dietetics*, ed 4. Oxford, Blackwell, 2014, in press.
- 5 Zschocke J, Hoffmann GF: *Vademecum Metabolicum: Diagnosis and Treatment of Inborn Errors of Metabolism*, ed 3. Friedrichsdorf, Milupa Metabolics, 2011.
- 6 WHO/FAO/UNU: Protein and amino acid requirements in human nutrition: report of a joint WHO/FAO/UNU expert consultation. WHO Technical Report Series, vol 935. Geneva, WHO, 2007.
- 7 Adam S, Champion H, Daly A, Dawson S, Dixon M, Dunlop C, Eardley J, Evans S, Ferguson C, Jankowski C, Lowry S, MacDonald A, Maritz C, Micciche A, Robertson L, Stafford J, Terry A, Thom R, van Wyk K, Webster D, White FJ, Wildgoose J; British Inherited Metabolic Diseases Group (BIMDG) Dietitian's Group: Dietary management of urea cycle disorders: UK practice. *J Hum Nutr Diet* 2012;25:398–404.
- 8 Lanpher BC, Gropman A, Chapman KA, Lichter-Konecki U, Urea Cycle Disorders Consortium, Summar ML: Urea cycle disorders overview; in Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K (eds): *GeneReviews*™. Seattle, University of Washington, Seattle, 2003, updated 2011.
- 9 Lang TF: Adult presentations of medium-chain acyl-CoA dehydrogenase deficiency (MCADD). *J Inherit Metab Dis* 2009;32:675–683.
- 10 Elsas LJ: Galactosemia; in Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K (eds): *GeneReviews*™. Seattle, University of Washington, Seattle, 2000, updated 2010.
- 11 Bouteldja N, Timson DJ: The biochemical basis of hereditary fructose intolerance. *J Inherit Metab Dis* 2010;33:105–112.
- 12 Steinmann B, Santer R: Disorders of fructose metabolism; in Saudubray JM, van den Berghe G, Walter JH (eds): *Inborn Metabolic Diseases: Diagnosis and Treatment*, ed 5. Berlin, Springer, 2012, pp 157–165.
- 13 van den Berghe G: Disorders of gluconeogenesis. *J Inherit Metab Dis* 1996;19:470–477.
- 14 Laforet P, Weinstein DA, Smit PA: The glycogen storage diseases and related disorders; in Saudubray JM, van den Berghe G, Walter JH (eds): *Inborn Metabolic Diseases: Diagnosis and Treatment*, ed 5. Berlin, Springer, 2012, pp 115–116.
- 15 Kishnani PS, Austin SL, Arn P, Bali DS, Boney A, Case LE, Chung WK, Desai DM, El-Gharbawy A, Haller R, Smit GP, Smith AD, Hobson-Webb LD, Wechsler SB, Weinstein DA, Watson MS; ACMG: Glycogen storage disease type III diagnosis and management guidelines. *Genet Med* 2010;12:446–463.



## 3.17 Hypercholesterolemia

Berthold Koletzko

### Key Words

Familial hypercholesterolemia · LDL cholesterol ·  
Dietary treatment · Saturated fat · Plant sterols

### Key Messages

- Children with severe hypercholesterolemia should be diagnosed and treated early to reduce the risk for premature cardiovascular morbidity and mortality
- Dietary modification can be initiated from the age of 2–3 years onwards
- Modifying dietary fat intake with limitation of saturated fats and their replacement by monounsaturated and polyunsaturated fats are the most important factors
- Preferential consumption of complex and slowly digested carbohydrates over sugars moderately reduces plasma cholesterol levels but is often difficult to achieve in children
- Soluble (but not insoluble) dietary fiber may contribute to cholesterol lowering and may be recommended to selected, highly motivated families

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### Introduction

A large body of evidence from epidemiological and intervention studies demonstrates that high plasma concentrations of cholesterol and particularly of LDL cholesterol are risk factors for the early development of premature cardiovascular diseases such as coronary heart disease and stroke, and for the associated increased mortality [1, 2]. In children, high plasma concentrations of cholesterol and LDL cholesterol lead to enhanced early development of vascular damage in autopsy studies, and clinical studies using ultrasound techniques show increased lipid deposition in the vascular intima and decreased vascular distensibility. For the general population, including children, healthy lifestyles and dietary habits that promote cardiovascular health are advocated [3]. Children with markedly elevated cholesterol, for example due to primary genetic disorders such as familial hypercholesterolemia, should be diagnosed early and treated effectively. The basis of intervention in children with hypercholesterolemia is dietary modification, which is described here. In the subgroup of children with severe hypercholesterolemia who do not achieve a satisfactory reduction of plasma cholesterol concentrations with diet alone, the use of lipid-lowering drugs in addition to diet should be considered.

**Table 1.** Characteristics of plasma lipoproteins

	Chylomicrons	VLDL	LDL	HDL
Major lipids	Triglycerides	Triglycerides	Cholesterol	Cholesterol, phospholipids
Major apoproteins	A, B48, C	B100, C, E	B100	A, E
Formation	Gut	Gut, liver	VLDL catabolism	Gut, liver
Major function	Transport of exogenous triglycerides	Transport of endogenous triglycerides from the liver to extrahepatic tissues	Cholesterol transport to extrahepatic tissues	Cholesterol transport from extrahepatic tissues to the liver

**Table 2.** Assessment of plasma lipid, lipoprotein and apoprotein concentrations (mg/dl) in children and adolescents

Lipid	Low	Acceptable	Borderline (~75th centile)	Increased (~95th centile)
Total cholesterol	–	<170	170–199	≥200
LDL cholesterol	–	<110	110–129	≥130
Non-HDL cholesterol <sup>a</sup>	–	<123	120–144	≥145
Triglycerides				
0 <sup>b</sup> –9 years	–	<75	75–99	≥100
10–19 years	–	<90	90–129	≥130
HDL cholesterol	<35	>45	35–45	–
Apolipoprotein A-1	<115	>120	115–120	–
Apolipoprotein B	–	<90	90–109	≥110
Lipoprotein(a)		<30		>30

Modified from refs. 3, 8 and 9. Cholesterol in mg/dl  $\times$  0.0259 = mmol/l; triglycerides in mg/dl  $\times$  0.01 = mmol/l.

<sup>a</sup>Non-HDL cholesterol = total cholesterol – HDL cholesterol.

<sup>b</sup>Triglyceride concentrations above these reference values are frequently observed in infancy when dietary fat intakes are high and fasted blood samples cannot be obtained.

## Lipoproteins

Lipids are transported in the plasma by lipoproteins (table 1), which carry apoproteins that mediate their receptor binding and tissue uptake. Triglyceride-rich chylomicrons are formed in intestinal epithelial cells from absorbed dietary fats, are secreted into the lymph and consecutively transported into the blood stream. Chylomicron triglycerides are hydrolyzed by lipoprotein lipase linked to the capillary endothelium. Lipolysis products are taken up and utilized by tissues. Lipoprotein lipase also hydrolyzes triglycerides in VLDL synthesized in the gut and liver. This lipol-

ysis results in the formation of intermediate-density lipoproteins and further of LDL in the circulation. LDL are rich in cholesterol and apoprotein B100, bind to apoprotein receptors in hepatocytes and peripheral cells and transport cholesterol to tissues. High plasma concentrations of LDL lead to increased deposition of cholesterol in the vascular intima, atherosclerotic vascular damage and premature coronary artery disease. LDL cholesterol can be measured directly by using ultracentrifugation but in clinical practice is usually determined from after an overnight fast using the Friedewald formula: LDL cholesterol (mg/dl) = total cholesterol (mg/dl) – HDL cholesterol (mg/dl) –

[triglycerides (mg/dl) × 0.2]. (Cholesterol in mg/dl is converted into mmol/l by multiplication with 0.0259.) Increased plasma levels (>30 mg/dl) of lipoprotein(a), an LDL particle with added apoprotein(a), are an independent risk factor for coronary artery disease and juvenile thrombosis. The liver and gut secrete apoprotein A containing HDL low in cholesterol ('nascent HDL'), which takes up cholesterol from tissues and from VLDL and LDL and transports it back to the liver. In contrast to LDL, high plasma levels of HDL are protective against the development of atherosclerotic diseases. Reference values for plasma lipids, lipoproteins and apoproteins in children and adolescents are shown in table 2.

### Hypercholesterolemia

The heterozygous form of familial hypercholesterolemia is one of the most frequent inherited metabolic disorders, affecting about 1 in 500 newborns in Europe and North America. The underlying defect in LDL receptor function is dominantly inherited (i.e. affects ~50% of children of an affected parent). From the onset of enteral feeding, levels are markedly increased for LDL cholesterol (usually >180 mg/dl), total cholesterol (>250 mg/dl) and apoprotein B (>150 mg/dl; Frederickson hyperlipidemia type IIa). In untreated patients, coronary heart disease may manifest itself already in the third decade of life. Diagnosis is performed based on repeated measurement of plasma lipoproteins in the fasted state, family history (dominant inheritance) and, if desired, by molecular genetic analysis of the underlying mutation. The rare homozygous form of familial hypercholesterolemia is found in about 1 of 1,000,000 individuals and leads to excessive levels of cholesterol (>600 mg/dl) from infancy due to an almost complete deficiency of LDL receptor function. Affected children develop xanthomas already in the first decade of life (fig. 1) and usually die before the age of 20 years unless effectively treated with extracorporeal LDL apheresis



**Fig. 1.** Xanthomas over the patellae and elbow in a 12-year-old child with homozygous familial hypercholesterolemia.

**Table 3.** Selected secondary hyperlipidemias in children and adolescents

<i>Hypercholesterolemias</i>
Acute intermittent porphyria
Anorexia nervosa
Cholestatic liver diseases
Cushing syndrome
Hypothyreosis
Nephrotic syndrome, renal failure, dialysis
<i>Hypertriglyceridemias</i>
Obesity
Diabetes mellitus
Glycogen storage disease type 1
Pancreatitis
<i>Combined hyperlipidemias</i>
Obesity
Diabetes mellitus
Glycogen storage disease type 1
Hepatitis
Nephrotic syndrome, renal failure, dialysis
Drugs: $\beta$ -blockers, corticoids, estrogens, progesterone, thiazide diuretics
Pregnancy
Systemic lupus erythematosus

or liver transplantation. A phenotype similar to the heterozygous form of familial hypercholesterolemia is found in children with familial defective apoprotein B, which also leads to defective receptor binding of LDL. Its prevalence is almost as high as that of the LDL receptor defect. Secondary hyper-

**Table 4.** Effects of dietary fats on plasma LDL and HDL cholesterol

Dietary fats	Food sources	Cholesterol	
		LDL	HDL
Saturated fatty acid (12–16 carbons)	Fatty milk products (butter, cream), fatty meats, coconut oil	↑↑↑	↑
<i>Trans</i> -fatty acids	Hydrogenated fats (deep frying fats, hard margarine, baked goods); ruminant fats (milk, beef, lamb)	↑↑	↓
Monounsaturated fatty acids (e.g. oleic acid)	Rapeseed and olive oil, avocado	↓↓	↑
Polyunsaturated fatty acids (e.g. linoleic acid)	Most vegetable oils (e.g. corn oil, sunflower seed oil), soft margarine	↓↓	↓ (at high intakes)
Cholesterol	Eggs, offal	↑	=

lipidemias (table 3) are relatively common in children and can often be influenced by treating the underlying disorder or by elimination of causative substances. Severe and lasting secondary hyperlipidemias may necessitate treatment similar to that of primary genetic hyperlipidemias.

### Dietary Treatment of Hypercholesterolemia

Treatment should achieve a lasting lowering of cholesterol, thereby reducing the risk for premature cardiovascular morbidity and mortality while supporting a good quality of life and enjoyment of eating. At normal HDL cholesterol levels (>45 mg/dl), a targeted dietary modification is indicated at an LDL cholesterol concentration >130 mg/dl (table 2). Prerequisites for an effective dietary change are good information and motivation of the patient and family, which should be supported by repeated counselling and practical training.

Dietary modification can be initiated from the age of 2–3 years onwards. Modifying dietary fat intake is the most important factor. Saturated fatty acids with 12–16 carbon atoms (primarily animal fats and some tropical oils) and *trans*-isomeric fatty acids (primarily from hydrogenated fats) increase LDL cholesterol (table 4) and should not

exceed 8–12% of the dietary energy intake. Dietary fat should preferentially comprise monounsaturated fatty acids (>10% of energy; e.g. rapeseed and olive oils), which reduce LDL and increase HDL cholesterol (table 4), as well as moderate amounts of polyunsaturated fatty acids (7–10% of energy; e.g. corn and sunflower seed oils). Limiting the total fat intake to 30–35% of energy intake contributes to the desired limitation of saturated and *trans*-fatty acid intake. Dietary cholesterol intake should not exceed 300 mg/day.

Preferential consumption of complex and slowly digested carbohydrates over sugars (mono- and disaccharides) moderately reduces plasma cholesterol levels. Soluble dietary fiber (e.g. parts of oat bran, psyllium) may also contribute to cholesterol lowering, but not insoluble fiber (e.g. wheat bran). However, diets with strictly limited sugar and high fiber content are difficult to maintain for many children and should only be recommended to selected, highly motivated families.

Patients and their family members require intensive dietary counseling by a physician and a dietician or nutritionist. Concomitant to dietary treatment, normal weight and regular physical activity are encouraged, and smoking is strongly discouraged. Dietary records may indicate existing problems and help achieve improvements.

The effect of treatment is assessed by repeated measurements of LDL cholesterol (every ~3–6 months). Dietary fat modification may reduce LDL on average by 10–15% [4], with marked inter-individual variation partly predicted by the apo-protein E genotype: individuals with the apoprotein E4 phenotype (~10–15% of the European population) with higher mean cholesterol and lower triglyceride levels show a stronger response of plasma cholesterol to dietary cholesterol intake. In contrast, individuals with the apoprotein E3 phenotype (~75–80% of the population) show a lesser response to dietary cholesterol restriction.

The regular consumption of plant sterols or plant stanols from enriched spreads or other enriched foods (also available as granulates) can markedly reduce plasma LDL cholesterol by an additional 10–15% and is encouraged [5–7].

If dietary modification alone does not achieve a satisfactory reduction in plasma LDL, additional drug treatment with statins, ezetimibe or anion exchange resins may be considered from the age of 8–10 years onwards; however, the cholesterol-lowering diet should be continued.

## Conclusions

- At normal HDL cholesterol levels (>45 mg/dl), dietary modification should be considered for children with LDL cholesterol levels >130 mg/dl
- Dietary saturated and *trans*-fats should be limited to 8–12% of energy intake (E%), while monounsaturated fats should provide >10 E% and polyunsaturated fats 7–10 E%
- Limiting the total fat intake to 30–35% of energy intake contributes to the desired limitation of saturated and *trans*-fatty acid intake
- Dietary cholesterol intake should be <300 mg/day
- This dietary fat modification may reduce LDL by 10–15%, with marked interindividual variation
- Regular consumption of plant sterols/stanols from enriched foods can reduce plasma LDL cholesterol by an additional 10–15%
- Dietary treatment should be continued if drugs are used

## References

- 1 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486–2497.
- 2 Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syv anne M, Scholte Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Atherosclerosis* 2012; 223:1–68.
- 3 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics* 2011;128(suppl 5): S213–S256.
- 4 Koletzko B, Kupke I, Wendel U: Treatment of hypercholesterolemia in children and adolescents. *Acta Paediatr* 1992;81: 682–685.
- 5 Eussen SR, de Jong N, Rompelberg CJ, Garssen J, Verschuren WM, Klungel OH: Dose-dependent cholesterol-lowering effects of phytosterol/phytostanol-enriched margarine in statin users and statin non-users under free-living conditions. *Public Health Nutr* 2011;14:1823–1832.
- 6 Malhotra A, Shafiq N, Arora A, Singh M, Kumar R, Malhotra S: Dietary interventions (plant sterols, stanols, omega-3 fatty acids, soy protein and dietary fibers) for familial hypercholesterolaemia. *Cochrane Database Syst Rev* 2014;6:CD001918.
- 7 Amir Shaghghi M, Abumweis SS, Jones PJ: Cholesterol-lowering efficacy of plant sterols/stanols provided in capsule and tablet formats: results of a systematic review and meta-analysis. *J Acad Nutr Diet* 2013;113:1494–1503.
- 8 Braamskamp MJ, Wijburg FA, Wiegman A: Drug therapy of hypercholesterolaemia in children and adolescents. *Drugs* 2012; 72:759–772.
- 9 Daniels SR, Greer FR; Committee on Nutrition: Lipid screening and cardiovascular health in childhood. *Pediatrics* 2008; 122:198–208.

## 3.18 Enteral Nutrition for Paediatric Inflammatory Bowel Disease

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### Key Words

Enteral nutrition · Inflammatory bowel disease · Growth · Treatment

### Key Messages

- Exclusive enteral nutrition (EEN) is an alternative to drug therapy in inducing remission in active Crohn disease
- In the treatment of active Crohn disease either elemental or polymeric formulae should be provided as the sole source of nutrition for 6–8 weeks
- Supplementary enteral nutrition will facilitate weight gain and linear growth and may help maintain clinical remission
- Further research is needed to clarify the mechanisms of action of EEN as primary therapy

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### Introduction

Enteral feeding of formulated food can be used to correct or prevent malnutrition in inflammatory bowel disease [1]. Exclusive enteral nutrition (EEN) implies the use of an artificial formula for

the provision of 100% of daily energy as well as macro- and micronutrient requirements in lieu of a regular diet. EEN is an alternative to corticosteroids for active Crohn disease, employed more often in children than adults, and more widely in Europe than in North America [2]. Its efficacy is supported by data from randomized controlled trials versus corticosteroids, and from comparative trials of different formulae [3]. The mechanism of action remains conjectural but may involve alteration in the enteric microflora [4].

Treatment algorithms for Crohn disease are changing. Corticosteroids alleviate symptoms but seldom heal the intestine. In Europe, EEN is endorsed as the primary therapy of new-onset Crohn disease, with thiopurines introduced early for maintenance therapy. Recent guidelines have been put forth to enhance the use of enteral nutrition in the management of paediatric Crohn disease in North America [5]. The support of a multidisciplinary team of nurses and dieticians is essential [5, 6]. This chapter focuses on the use of EEN as the primary therapy of intestinal inflammation and aims to provide a practical guide for its implementation.

## Treatment of Active Crohn Disease

### *Evidence of Efficacy*

Most data concerning the efficacy of EEN in treating active Crohn disease relate to clinical endpoints. Response to EEN has been associated with endoscopic healing in uncontrolled studies. In a recent controlled trial among 35 children treated for active Crohn disease, clinical response was associated with endoscopic improvement in 77% with EEN, but in only 33% with steroids [7].

### *Patient Selection*

Roughly 50–60% of Crohn disease patients treated with EEN achieve clinical remission [3]. The response depends on the patient population. Recent-onset disease may be more responsive [3], perhaps contributing to the superior response rates reported in small trials conducted exclusively among children and summarized in a meta-analysis of outcomes in paediatric trials [8]. Although controversial, predominantly small intestinal inflammation is considered more likely to respond to EEN, compared with isolated Crohn colitis [6, 9]. This may be a reflection of the fact that Crohn colitis is particularly difficult to control. European and American guidelines advocate in favour of EEN use, irrespective of disease location [5, 10]. EEN is not used to treat ulcerative colitis.

### *Therapeutic Regimens*

#### Exclusive versus Supplementary Enteral Nutrition

To be successful, EEN should be the sole source of nutrition. Allowance of regular food during treatment of active disease compromises its efficacy [11] and may induce satiety and intolerance of the amounts of prescribed formula.

Screening for micronutrient deficiencies (e.g. vitamin D) should guide the need for supplementation. The micronutrient content of the formula, as well as its mucosal healing effects, is also expected to assist in the correction of nutritional imbalances [12].

### Mode of Administration

Liquid diets may be sipped orally or administered via a silastic nasogastric feeding tube (NG tube; size: 6 or 8 Fr). Most children learn to insert the NG tube and administer the formula overnight. The tube is removed each morning to facilitate daytime activities. When use over a period of months is contemplated, an indwelling gastrostomy tube may be inserted.

### Target Volume and Calories

EEN should provide 100% of the patient's estimated caloric and protein requirements. These are calculated using normal predictive equations (e.g. Schofield, WHO equation, etc.; summarized in the clinical guidelines by the NASPGHAN Committee on Inflammatory Bowel Disease) [5]. In the setting of malnutrition, ideal body weight (the weight for the patient's age that corresponds to the same percentile on the growth chart as their height percentile) should be used instead of actual weight to prevent underfeeding. An activity factor should be added for the estimation of total energy requirements. Maintenance fluid volumes do not have to be provided exclusively via EEN as consumption of clear fluids is also allowed.

When using NG feeding, infusion rates should be increased in a stepwise manner considering tolerance. The duration of infusion is gradually decreased. A sample protocol for the gradual increase to full feeds is given in table 1. Most young patients aim to complete the infusion over 10–14 h.

### Choice of Formula

Polymeric, peptide-based and amino acid-based formulae have all been used to treat active Crohn disease [3]. There is general agreement that the protein content of liquid diets does not influence their efficacy [3]. Dietary lipids, however, can modulate inflammation by a variety of mechanisms which influence cellular production of cytokines and eicosanoids [3, 13]. While the amount and type of fat may modulate inflammatory pathways, the therapeutic success achieved

**Table 1.** Proposed protocol for the initiation of EEN

Initial rate of feeds	Start with half of the target hourly volume and give continuously over 24 h
Increasing feeds	Increase by 10 ml/h every 3–6 h, depending on symptoms
Cycling feeds	Decrease the overall feed duration by 2–3 h every day; the rate is determined by the total volume to be given over the desired number of hours
Final goal of feeds	The maximum rate is usually 6–8 ml/kg/h; the final duration of feeding is 10–14 h

**Table 2.** Sample protocol for reintroduction of solid foods

Day of introduction	Type of food	Examples
1–4	Grains; low fibre	White flour bread, crackers, pasta, rice Hot cereal: cream of wheat Cold cereal (low fat, low fibre)
5–9	Meat, fish and alternatives; low fibre, low fat	Plain (not fried, not processed) lamb, veal, beef, pork, chicken, turkey Fish (low fat) Tofu Eggs
10–14	Fruits and vegetables; low fibre, low fat	Raw fruits without skin/seeds Canned fruits without skin/seeds Cooked vegetables without skin/seeds
15–17	Dairy; low fat	Milk, yogurt, cheese
18	Regular diet	Slowly increasing fat and fibre content based on tolerance

with a variety of both polymeric (usually high-fat) and elemental (usually low-fat) formulae suggests that efficacy does not depend solely on fat content.

For those determined to drink the liquid diet, a polymeric formula must be used because of its greater palatability. If the formula is to be administered by NG tube, its palatability becomes unimportant. Given the influence of fat content on efficacy, a conventional elemental liquid diet (low fat content) may offer some therapeutic advan-

tage. The treatment benefit of a low-fat compared with a conventional polymeric diet is admittedly small [3].

#### Duration of EEN

The required duration of EEN has not been well defined. Improvements in clinical and laboratory parameters occur quickly, often by 2 weeks, but the optimal time for achievement of mucosal healing has not been established. Most gastroenterologists suggest continuing the therapy for a



minimum of 6 weeks, longer if ideal weight has not been reached yet.

#### Reintroduction of Solid Food

Foods are usually reintroduced gradually. It may be prudent, particularly if there are intestinal strictures, to offer a low-fibre diet initially following completion of the enteral nutrition regimen. A sample order of food reintroduction is given in table 2.

#### Facilitation of Linear Growth

Impairment of linear growth commonly complicates Crohn disease. The major contributing factors are the direct growth-inhibiting effects of proinflammatory cytokines produced by the inflamed intestine and chronic undernutrition [14]. Inappropriate use of chronic corticosteroid therapy will also impede linear growth. Other treatment strategies, which induce mucosal healing, will be associated with reduced cytokine production and will facilitate growth as long as the control of inflammation can be sustained. Resumption of normal linear growth is a marker of therapeutic success. Conversely, if a child merely gains weight but does not grow normally in height, it can be assumed that the inflamed intestine is not healing, and that other anti-inflammatory interventions must be adopted.

#### Maintenance of Clinical Remission

Symptoms tend to recur following the cessation of enteral nutrition. In most studies, 60–70% of patients experience a symptomatic relapse within 12 months of enteral nutrition [3]. Two nutritional strategies can be considered to maintain remission: firstly, ‘cyclical EEN’, meaning administration of a liquid diet and avoidance of regular food 1 month out of 4, or, secondly, ‘supplementary enteral nutrition’. The latter, which has been employed primarily if nocturnal NG feeding is used, involves continuation of such feeding 4–5 times weekly as supplement to an unrestricted ad libitum daytime diet [15]. In Europe, the most common strategy to maintain clinical remission following EEN is institution of immunomodulatory drugs.

#### Conclusions

- Exacerbations of Crohn disease, particularly involving the small intestine, may be treated with 4–6 weeks of EEN
- Use of palatable polymeric formulae may avoid the need for nocturnal NG infusion
- Because relapse is common following cessation of enteral nutrition, strategies to maintain remission must be planned
- Sustained, normal linear growth is a marker of success of therapy

#### References

- 1 Voitk AJ, Echave V, Feller JH, et al: Experience with elemental diet in the treatment of inflammatory bowel disease: is this primary therapy? *Arch Surg* 1973; 107:329–333.
- 2 Levine A, Milo T, Buller H, Markowitz J: Consensus and controversy in the management of pediatric Crohn disease: an international survey. *J Pediatr Gastroenterol Nutr* 2003;36:464–469.
- 3 Zachos M, Tondeur M, Griffiths AM: Enteral nutritional therapy for induction of remission in Crohn’s disease. *Cochrane Database Syst Rev* 2007;1:CD000542.
- 4 Leach ST, Mitchell HM, Eng WR, Zhang L, Day AS: Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn’s disease. *Aliment Pharmacol Ther* 2008;28:724–733.
- 5 Critch J, Day AS, Otley A, et al: Use of enteral nutrition for the control of intestinal inflammation in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2012;54:298–305.
- 6 Buchanan E, Gaunt WW, Cardigan T, et al: The use of exclusive enteral nutrition for induction of remission in children with Crohn’s disease demonstrates that disease phenotype does not influence clinical remission. *Aliment Pharmacol Ther* 2009;30:501–507.

- 7 Borrelli O, Cordischi L, Cirulli M, et al: Polymeric diet alone versus corticosteroids in the treatment of active paediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol* 2006;4:744–753.
- 8 Heuschkel RB, Menache CC, Megerian JT, Baird AE: Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. *J Pediatr Gastroenterol Nutr* 2000;31:8–15.
- 9 Afzal NA, Davies S, Paintin M, Arnaud-Battandier F, Walker-Smith JA, Murch S, Heuschkel R, Fell J: Colonic Crohn's disease in children does not respond well to treatment with enteral nutrition if the ileum is not involved. *Dig Dis Sci* 2005;50:1471–1475.
- 10 Sandhu BK, Fell JM, Beattie RM, Mitton SG, Wilson DC, Jenkins H; IBD Working Group of the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition: Guidelines for the management of inflammatory bowel disease in children in the United Kingdom. *J Pediatr Gastroenterol Nutr* 2010;50(suppl 1): S1–S13.
- 11 Johnson T, Macdonald S, Hill SM, Thomas A, Murphy MS: Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: a randomized controlled trial. *Gut* 2006;55:356–361.
- 12 Gerasimidis K, Talwar D, Duncan A, Moyes P, Buchanan E, Hassan K, O'Reilly D, McGrogan P, Edwards CA: Impact of exclusive enteral nutrition on body composition and circulating micronutrients in plasma and erythrocytes of children with active Crohn's disease. *Inflamm Bowel Dis* 2012;18:1672–1681.
- 13 Gassull MA, Fernández-Bañares F, Cabré E, Papo M, Gaffer MH, Sánchez-Lombrana JL, Richart C, Malchow H, González-Huix F, Esteve M: Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohn's disease: results of a double blind randomized multicentre European trial. *Gut* 2002;51:164–168.
- 14 Walters T, Griffiths A: Mechanisms of growth impairment in pediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2009;6:513–523.
- 15 Wilschanski M, Sherman P, Pencharz P, Davis L, Corey M, Griffiths A: Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. *Gut* 1996;38:543–548.

## 3.19 Nutrition in Cystic Fibrosis

Michael Wilschanski

### Key Words

Cystic fibrosis · Nutritional status · Pancreatic enzymes · Gastrostomy

### Key Messages

- Survival from cystic fibrosis (CF) has substantially improved over the past four decades. The advance in nutritional management is one factor which has contributed to this change
- This chapter reviews the basic defect of CF and how it influences nutritional status
- Normal growth and development can be achieved in CF, and to this end, nutritional counseling is paramount at all ages. The prevention and early detection of growth failure is the key to successful nutritional counseling
- An approach to the CF patient who is not thriving and an outline of nutritional management is proposed

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### Introduction

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease in Caucasians with an incidence of 1 in 2,500 live births. The disease is caused by mutations in the *cftr* gene on chromosome 7, which codes for a cAMP-regulated chloride channel [1]. Nonfunctioning CFTR protein affects epithelial ion and water

transport in a variety of organs including the respiratory, gastrointestinal, hepatobiliary, reproductive and sweat glands. The lack of CFTR function in the pancreatic duct is responsible for obstruction and autodigestion of the pancreas in utero, leading to exocrine pancreatic insufficiency (PI) in 85% of CF infants.

The early growth of infants with PI due to CF is dependent on the age at diagnosis. Clinical diagnosis may be difficult unless meconium ileus occurs, typically in only 15% of cases. The remaining patients are diagnosed later, mainly presenting with failure to thrive with steatorrhea, accompanied in some cases with respiratory symptoms. An increasing number of countries have initiated newborn screening for CF using a serum marker of PI, and this has been shown to facilitate an earlier diagnosis with better growth and nutritional status [2]. Longer-term studies after neonatal screening are now revealing reduced pulmonary disease progression [3].

Numerous studies have shown that underweight and poor linear growth in children and malnutrition in adults are independent factors predicting mortality [4, 5]. Together with this, undernutrition has been shown to have an adverse effect on the outcome of lung transplantation [6]. These data reinforce the importance of the prevention and early detection of growth failure, leading to the aggressive management of nu-

tritional deficits at all ages. This has led to the publication of nutritional guidelines in Europe and in North America [7, 8].

## Infants

The evaluation of an infant with CF should be expedited. If PI is established by tests for steatorrhea and indirect pancreatic function tests, pancreatic enzyme replacement therapy should be initiated as soon as possible. Breast milk can provide complete nutritional support to infants with CF for the first 4–6 months of age, though supplemental energy may sometimes be required by fortifying a portion of the breast milk feeds with formula or by fortifying formulas to a more concentrated energy level for those infants on a combination of breast milk and formula or on formula alone [9]. Regular cow's milk-based infant formulas can be used if breastfeeding is not an option or if supplementation is required; there is no need for a predigested formula in most instances. Enzymes are given with all foods and milk products including predigested formulas containing medium-chain triglyceride. Infants require powder, which should be taken with fruit sauce with lubricant pretreatment to the mouth and perianal area to avoid skin excoriation. The enzymes should be administered at the beginning of and during the meal. The initial dose of enzymes should be approximately 5,000 IU lipase/kg/day. The dose may be gradually increased according to symptoms and objective assessment of growth and fat absorption. In many instances, the caloric density needs to be increased, and this may be achieved by fortifying breast milk, adding fat or carbohydrate or concentrating the formula. Once solid food is introduced, enzymes should be titrated by fat intake. The maximum dose is 10,000 IU lipase/kg/day. Fat-soluble vitamin (ADEK) supplementation should be initiated according to the current recommendations [7, 8].

New guidelines from the North American Cystic Fibrosis Foundation Committee on Vita-

**Table 1.** Recommended dietary macronutrient composition in CF and non-CF patients (% of energy intake)

	Non-CF	CF
Protein	10–15	15
Carbohydrate	55–60	35–40
Fat	30	45–50

min D advise higher supplemental amounts of vitamin D than are found in the currently available CF vitamin supplements. Additional vitamin D supplements are therefore recommended to keep the lower limit of 25-hydroxyvitamin D at 30 ng/ml (75 nmol/l) [10]. Yearly monitoring of serum vitamin levels is recommended for vitamin A, vitamin E and vitamin D. Hyponatremic alkalosis may occur in infants, especially during the summer months; supplementation with sodium chloride is recommended. Zinc supplementation may be considered in the child who is not thriving [9].

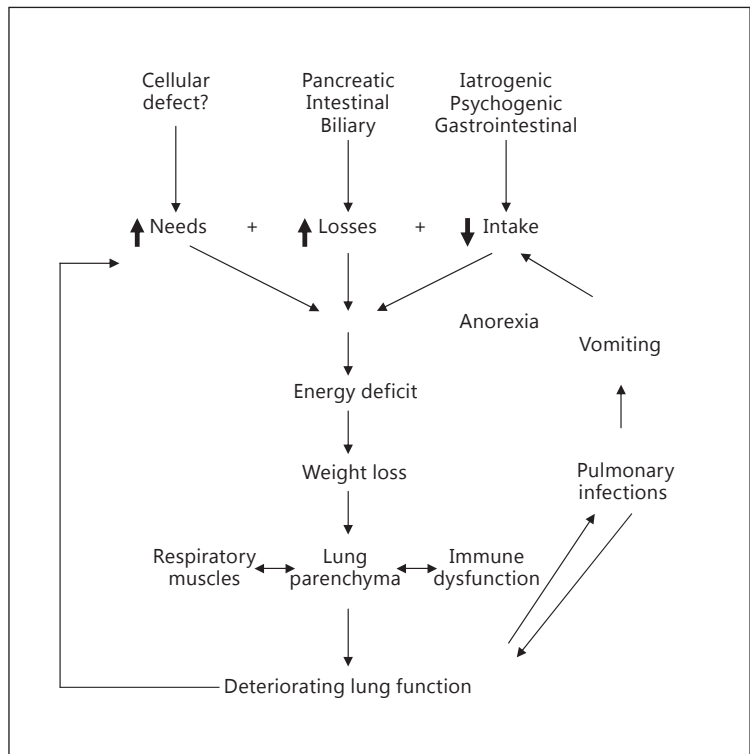
## Toddlers

As infants are introduced to table foods, it is important that the diet be balanced, with moderately increased fat and protein content (table 1). Parents need to be in control, routinely adding calories to maintain growth. The child with CF should avoid low-fat food and 'grazing'. The dietician should promote positive interactions around meals. The mealtime must not turn into a battleground which is the catalyst for poor feeding behavior.

## School-Age Children

School age is the age at which encourage the child to obtain a basic knowledge of the physiological processes, eventually leading to taking increasing responsibility for practical enzyme and nutritional management.

3



**Fig. 1.** The pathogenesis of energy imbalance in CF.

## Adolescence

This stage is associated with increased growth, puberty and increased physical activity. This adds up to markedly increased nutritional requirements which are often difficult to attain. Pulmonary infections are more common, as is the onset of CF-related diabetes and, in a small minority of cases, CF-related liver disease. Female patients are at a greater risk of nutritional failure at this age [11]. This may be partly due to dissatisfaction with weight and body shape in healthy adolescent females. Growth retardation and pubertal delay occur with increased social pressure and psychosocial stress. These factors must be considered when nutritional advice is provided to teenagers. Ideally, dietary advice should be passed on before conception as a low prepregnancy BMI is associ-

ated with reduced birth weight. Nutrition should be optimized throughout pregnancy and vitamin levels should be monitored [12].

## Bone Health

A decrease in bone mineral density (BMD) in patients with CF may begin at a young age [13]. There are many factors that influence bone health both in healthy individuals and in patients with CF; these include nutritional status, calcium, vitamins D and K, pulmonary infection, exercise, glucocorticoids and the class of *CFTR* mutation. The causes of poor BMD, a reflection of bone health, are thus multifactorial. Evidence for the efficacy of treatments for maintaining and improving bone health is lacking in CF; however, consensus

guidelines have been established. It is recommended that monitoring of BMD and ensuring factors related to bone health be addressed at routine visits.

### Follow-Up

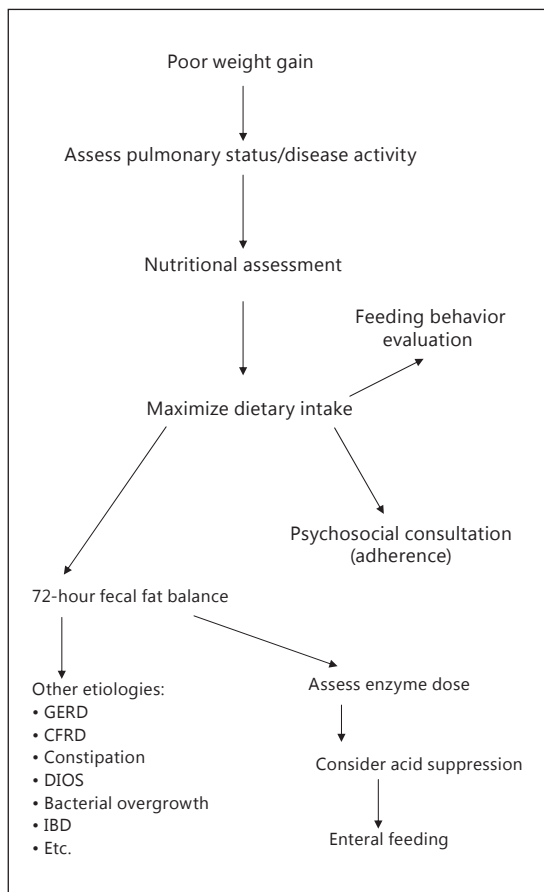
A formal dietary assessment should be undertaken annually. This should incorporate a review of nutritional intake, the enzyme dose, the timing of administration as well as vitamin supplement intake. Anthropometry should be performed regularly and at length, and BMI percentile charts should be used for the interpretation of nutritional status. Bone health is an increasing concern in CF [14]. BMD and body composition should be assessed by dual-energy X-ray absorptiometry [15].

### When Things Go Wrong

Figure 1 demonstrates the pathogenesis of malnutrition in CF [16]. As pulmonary disease worsens and resting energy expenditure increases, other factors predispose to an energy deficit. The frequency and severity of infections increase, inducing anorexia and/or vomiting, in turn reducing intake. Weight loss results in causing loss of muscle tissue; respiratory muscle wasting reduces effective coughing, further contributing to the deterioration in lung function. Malnutrition is known to cause immune dysfunction. Taken together, a vicious cycle is established, leading to further deterioration.

### Management of the Malnourished Child

Once poor growth is identified, patients must be evaluated more frequently. The visits must include medical, nutritional and behavioral input. Figure 2 shows an algorithm for the work-up.



**Fig. 2.** Plan of action for poor weight gain in CF. GERD = Gastroesophageal reflux disease; CFRD = CF-related diabetes; DIOS = distal intestinal obstruction syndrome; IBD = inflammatory bowel disease.

### Nutritional Intervention

If the reason for the poor weight gain is poor intake, the first strategy must be to gradually increase calories at mealtime. At the same time, nutritional intervention with high-calorie supplements may be made. The long-term effect of supplements is controversial and they must not take the place of meals [17]. If this fails, enteral feeding should be commenced [18]. The choice of access should be made together with the family, but, generally, nasogastric feeding is started before gastrostomy



placement. Calorically dense formulas (1.5–2.0 kcal/ml) are well tolerated, and, initially, nocturnal infusion is encouraged to promote normal eating behavior during the day. Our experience is that once families see a success after 6–8 weeks of nasogastric feeding, gastrostomy placement is welcomed. Patients with excessive nausea, bloating or vomiting may benefit from prokinetic drugs or semielemental or elemental formula.

### Growth Hormone and Appetite Stimulants

The efficacy of growth hormone therapy in CF has recently been reviewed [19]. While growth parameters and pulmonary function seem to improve in treated patients, the overall benefits to health cannot be determined from the moderate evidence available. One recent multicenter trial in which growth hormone was administered for 12 months to patients with reduced growth and bone age indicated its effectiveness in improving growth and lung volumes [20]. Larger trials with appropriate patient selection are needed in order to establish its safety and effectiveness.

Appetite stimulants (AS) are often requested by individuals with CF, or by parents of a child with CF, in anticipation of an enhanced appetite

and increased energy intake to promote weight gain [21]. While megestrol acetate is one of the most studied AS in CF, results are not conclusive on the use of AS in patients with CF at this time, and larger, controlled studies are needed.

### Conclusions

- The overall goal is that every patient with CF should achieve normal growth. This requires regular surveillance including age-specific individualized expert advice with nutritional care plans to suit each patient. Nutritional intervention should be appropriately timed to influence the evolution of the disease
- Nutritional support is an integral part of the care of patients with CF
- At diagnosis, all patients require pancreatic and nutritional assessment
- Patients must be carefully monitored and dietary counseling provided
- Nutritional evaluation and support is age related
- Patients who fail to respond require enteral supplementation
- Nutritional status impacts on the progression of CF

### References

- 1 Welsh MJ, Tsui LC, Boat TF, et al: Cystic fibrosis; in Scriver C, Beaudet AL, Valle D (eds): *The Metabolic and Molecular Basis of Inherited Disease*, ed 7. New York, McGraw-Hill, 1995, pp 3799–3876.
- 2 Farrell PM, Kosorok MR, Laxova A, et al: Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *N Engl J Med* 1997;337: 963–969.
- 3 Sims E, Clark A, McCormick J, et al: Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. *Pediatrics* 2007; 119:19–28.
- 4 Kraemer R, Rudelberg A, Hadorn B, Rossi E: Relative underweight in cystic fibrosis and its prognostic value. *Acta Paediatr Scand* 1978;67:33–37.
- 5 Sharma R, Florea VG, Bolger AP, et al: Wasting as an independent predictor of mortality in patients with cystic fibrosis. *Thorax* 2001;56:746–750.
- 6 Snell GI, Bennetts K, Bartolo J, et al: Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation. *J Heart Lung Transplant* 1998;17:1097–1103.
- 7 Sinaasappel M, Stern M, Littlewood J, et al: Nutrition in patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2002;2:51–75.
- 8 Borowitz D, Baker RD, Stallings V: Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2002;35:246–259.

- 9 Borowitz D, Robinson KA, Rosenfeld M, et al: Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr* 2009;155(suppl):S73–S93.
- 10 Tangpricha V, Kelly A, Stephenson A, et al: An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. *J Clin Endocrinol Metab* 2012;97:1082–1093.
- 11 Lai HC, Kosorok MR, Sondel SA, et al: Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: evaluation of various criteria used to identify malnutrition. *J Pediatr* 1988;132:478–485.
- 12 Edenborough FP, Borgo G, Knoop C, et al: Guidelines for the management of pregnancy in women with cystic fibrosis. *J Cyst Fibros* 2008;7(suppl 1):S2–S32.
- 13 Bianchi ML, Romano G, Saraifoger S, et al: BMD and body composition in children and young patients affected by cystic fibrosis. *J Bone Miner Res* 2006;21:388–396.
- 14 Buntain HM, Schluter PJ, Bell SC, et al: Controlled longitudinal study of bone mass accrual in children and adolescents with cystic fibrosis. *Thorax* 2006;61:146–154.
- 15 Kerem E, Conway S, Elborn S, Heijerman H; Consensus Committee: Standards of care for patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2005;4:7–26.
- 16 Durie PR, Pencharz PB: A rational approach to the nutritional care of patients with cystic fibrosis. *J R Soc Med* 1989;18(suppl 16):11–20.
- 17 Kalnins D, Corey M, Ellis L, et al: Failure of conventional strategies to improve nutritional status in malnourished adolescents and adults with cystic fibrosis. *J Pediatr* 2005;147:399–401.
- 18 Jelalian E, Stark LJ, Reynolds L, Seifer R: Nutritional intervention for weight gain in cystic fibrosis: a meta-analysis. *J Pediatr* 1988;132:486–492.
- 19 Phung OJ, Coleman CI, Baker EL, et al: Recombinant human growth hormone in the treatment of patients with cystic fibrosis. *Pediatrics* 2010;126:e1211–e1226.
- 20 Stalvey MS, Anbar RD, Konstan MW, et al: A multi-center controlled trial of growth hormone treatment in children with cystic fibrosis. *Pediatr Pulmonol* 2012;47:252–263.
- 21 Chinuck RS, Fortnum H, Baldwin DR: Appetite stimulants in cystic fibrosis: a systematic review. *J Hum Nutr Diet* 2007;20:526–537.





## 3.20 Heart Disease

Michelle M. Steltzer · Terra Lafranchi

### Key Words

Congenital heart disease · Reflux · Growth · Nutrition · Lactation consultation · Breastfeeding

### Key Messages

- Assess and maximize growth promotion in every encounter/visit
  - Utilize breast milk if available and tolerated
  - Encourage breastfeeding/nonnutritive sucking if safe
  - Treat clinical symptoms of reflux, constipation and formula/milk intolerance
  - Close communication concerning goals of growth and development
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### Introduction

Congenital heart disease (CHD) and its impact on infant growth and development has been well documented in the literature over the years. The most risky cardiac lesions are cyanotic CHD lesions, and they are outlined in table 1. The goal of this chapter is to focus on those infants with single-ventricle physiology at high risk for growth failure, such as double outlet right ventricle, tricuspid atresia and hypoplastic left heart syndrome, who have undergone stage 1 palliation (Norwood or Sano procedure). Practical guidance will be provided to those practitioners caring for fragile and at-risk neonates

between stage 1 and stage 2 palliation (Glenn procedure). However, the principles outlined can be applied to other conditions associated with poor growth listed in table 1.

Outlined here are key concepts essential for optimizing growth; they include the following: utilization of breast milk; lactation consultation; practical caloric density increases; hands-on recipe education; and promotion of normal growth and development. Speech and otolaryngology involvement in the care team is also key to promoting optimal growth and developmental milestones. Equally important is acknowledging reflux, constipation, and milk and protein intolerance, and treating these issues early, as they are essential to optimal growth success. Figure 1 demonstrates the complexity of the many common growth variables interacting in CHD.

### Impact of Home Surveillance Program on Nutrition and CHD

With the advent of home surveillance in 2000 [1], postnatal attention to nutrition following discharge from stage 1 palliation has become heightened and a main center of focus until stage 2 palliation, typically at 3–6 months of age [2–5]. In 2003 the first multicenter quality improvement collaborative within the USA, the Joint Council

**Table 1.** Cardiac lesions posing risks for growth delay

*Acyanotic CHD lesions: weight growth disturbance<sup>1</sup>*

Aortic stenosis  
Pulmonary stenosis  
Coarctation of the aorta  
Ventricular septal defect<sup>2</sup>  
Patent ductus arteriosus<sup>2</sup>  
Atrial septal defect<sup>2</sup>  
Atrioventricular valve regurgitation<sup>2</sup>  
Semilunar valve regurgitation (less common)<sup>2</sup>

*Cyanotic CHD lesions: weight and height growth disturbance<sup>3</sup>*

Double outlet right ventricle  
Transposition of the great arteries  
Tetralogy of Fallot with or without pulmonary atresia  
Tricuspid atresia  
Hypoplastic left heart syndrome

<sup>1</sup> If there is significant shunting and/or pulmonary hypertension, height disturbances may also be noted.

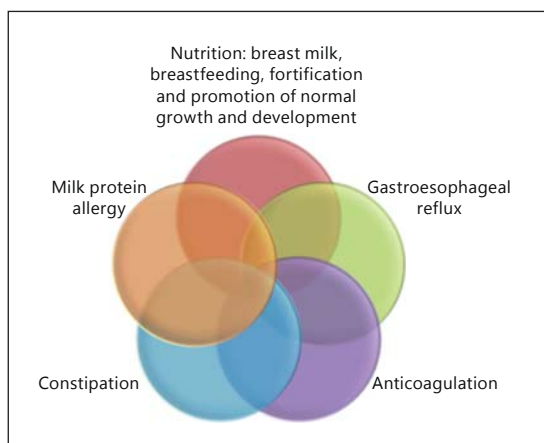
<sup>2</sup> Lesions prone to pulmonary overcirculation have a greater impact on growth.

<sup>3</sup> Hypoxemia length in years is thought to affect growth retardation. Hypoxemia accompanied by congestive heart failure has a greater impact on growth.

on CHD, was formed, and was subsequently instrumental in bringing parents and caregivers at home to the table as team members [6]. The team works in concert to optimize growth strategies for this fragile single-ventricle physiology population at every encounter/visit. Many lessons learned by the Joint Council on CHD can be shared with international centers.

### **Nutrition: Breast Milk, Breastfeeding and Fortification**

Breast milk has many known benefits: parental bonding; antibodies; being easier to digest; and often having a higher calorie content than 20-cal formulae (65–70 kcal/100 ml). Breastfeeding also provides oral motor and speech benefits [5]. Now that prenatal diagnosis is more common, parents have more time to become educated on breast



**Fig. 1.** Common growth variables in CHD.

milk and breastfeeding prior to delivery. Lactation consultants should meet with families prenatally to discuss ways to promote and establish early breast milk supply, pumping, early nonnutritive breastfeeding and maternal diet with the ultimate goal to maximize breastfeeding and utilization of available breast milk from birth. With CHD, the feeding process is often complex and dependent on the medical status of the patient. The breast milk may need to be primarily hind-milk, fortified or even supplemented with bottle or other enteral feeding methods, particularly during the initial postoperative newborn period. With the many individual confounding variables considering patients' medical intake [5, 7], ideas about sole breastfeeding in this population are inconsistent. Opportunities to promote successful breastfeeding during first hospitalization and the interstage period are present. A recent case study on a high-risk infant unable to breastfeed at time of discharge from stage 1 palliation has shown promise and successful transition to full breastfeeding by the time of stage 2 palliation [8, 9].

Caloric supplementation is common in the high-risk single-ventricle population to aid in growth. The focus on proper education by nutritionists utilizing measuring utensils is critical,

particularly for those families with language and/or educational challenges. With any fortification, some patients may not tolerate the higher caloric density and show more signs of gastrointestinal distress and less weight gain [5]. Fortification above 26–28 calories per ounce (90 kcal/100 ml) [10] commonly results in more gastrointestinal distress signs. When using breast milk for fortification, its source is an important issue, because hindmilk is higher in calories than is foremilk. This becomes particularly important with an infant failing to demonstrate growth. Some lactoengineering options are available at different institutions [9] to aid in assessment of caloric density of the breast milk being delivered. Breastfeeding has become a more acceptable practice. In some institutions, patients may be started on enteral feedings with available colostrum and/or breast milk by nasogastric, nutritive and/or nonnutritive breastfeeding before Norwood palliation, based on physiological status and recommendations by the medical care team [5, 8].

### **Normal Infant Growth and Development and Gastroesophageal Reflux**

Infants are known to have gastroesophageal reflux (GER) in the early months of infancy. GER not only comprises vomiting but may also manifest as silent reflux (pain during or after feeds and position changes, or with stooling). Promotion of normal infant developmental milestones throughout the entire feeding experience is crucial. Engaging the primary caregivers in proper positioning of the infant during and after all forms of feeding can help minimize GER. If there is intolerance of fortified formula/breast milk, as evidenced by irritability, vomiting, diarrhea and poor weight gain, consider adjusting back to 20 cal (65–70 kcal/100 ml) or to straight breast milk or formula for a few days and reassess whether the infant can make up the missed calories with increased volume. The feeding team (speech/feeding therapist and/or otolar-

ngologist) is important to facilitate the instalment of safe, positive and effective feeding strategies.

Pediatric gastroenterologists may also be team-consulting members. Although no firm, consistent recommendations, minimizing high caloric density, maximizing doses of GER medications (specifically proton pump inhibitors, PPI) and/or changing to elemental formulae [5] are encouraged and can be done simultaneously. Consultation with a pediatric gastroenterologist during the interstage period is ideal to ensure optimal titration of gastrointestinal medications and/or reassessment of the plan of care; if possible, administer medications 20–30 min before feed to let them reach the small bowel, where they work. Recognition of the safety profile with anticoagulants is important in this population. Practitioners need to weigh the benefits and risks with the team. If using these medications, adjustment for weight gain should be considered if the infant seems to have recurring symptoms, and treatment should be allowed for 7 days before declaring the intervention not to be effective.

### **Anticoagulants**

The use of anticoagulants to prevent shunt thrombosis is common in this population. Aspirin use is irritating to the stomach, and thus acid suppression is often recommended. In symptomatic patients, use a ‘top-down’ approach and start with a PPI (omeprazole or lansoprazole) rather than an H<sub>2</sub> blocker (ranitidine). Ranitidine is often less effective after several weeks of exposure; however, for infants with very difficult-to-manage reflux, ranitidine is used in conjunction with a PPI to smooth over the peaks, i.e. the periods when PPI coverage is waning (PPI twice daily and H<sub>2</sub> blocker daily halfway between the 2 PPI doses). Team members may also be gastroenterologists, and although no firm and consistent recommendations can be achieved among centers of excellence, our team at Boston Children’s Hospital focuses on

optimizing caloric density as needed to the lowest density tolerated to promote growth, maximizing GER medications and/or changing formula type [5]. Consultation with a pediatric gastroenterologist during the interstage period is also recommended to ensure optimal titration of medications and/or reassessment of the plan of care.

## Constipation

If an infant is struggling with reflux, vomiting, poor feeding, etc., consider starting to use a preparation containing polyethylene glycol 3350 given twice daily – do not wait for hard or infrequent stools. The goal is for the infant to have stool 3–4 times per day, and for the process to be easy and not painful. Consider polyethylene glycol to help with ‘sludgy’ bowel patterns that are often associated with diuretic use, high-calorie formulae or protein allergies. When the infant bears down to stool, the pressure in the chest increases, and the infant vomits or has reflux. Polyethylene glycol is a helpful stool softener for any infant who works to pass stool (e.g. grunting, crying with stooling even in the setting of soft stools, vomiting and not eating). It binds to water molecules, keeps them in the colon, and makes the stool a bit softer. Drug safety profiles typically

do not give recommendations for this population, so please consult the primary team and a gastroenterologist. The infant may initially have somewhat watery stools, but this resolves with time.

## Milk Protein Allergy

Milk, soy and egg protein allergy (or inability to digest large protein molecules) is important to consider in this population. Symptoms may include: loose or mucous stools (possibly containing blood); constipation; reflux; vomiting; gagging; refusing food; irritability or colic; and skin rashes (cradle cap, diaper rash and eczema). Breastfeeding mothers can attempt dairy, soy and egg elimination diets (read fine print of all labels). Formula-fed infants can transition to hypoallergenic amino acid-based formulae (e.g. EleCare or Neocate). A gastroenterology consult is recommended and EleCare is often preferred due to its higher medium-to-long-chain triglyceride ratio. If the infant does not like the taste, start with 1 oz (30 ml) elemental to 4 oz (120 ml) regular formula. Gradually increase by 1 oz (30 ml) every week until consistently only elemental formula is achieved. The threshold for use of elemental formulae in this patient population is often higher for the entire first year of life.



## References

- Ghanayem N, Hoffman G, Mussatto K, et al: Home surveillance program prevents interstage mortality after the Norwood procedure. *J Thorac Cardiovasc Surg* 2003;126:1367–1377.
- Steltzer M, Rudd N, Pick B: Nutrition care for newborns with congenital heart disease. *Clin Perinatol* 2005;32:1017–1030.
- Braudis J, Curley M, Beaupre E, et al: Enteral feeding algorithm for infants with hypoplastic left heart syndrome poststage 1 palliation. *Pediatr Crit Care Med* 2009;10:460–466.
- Ghanayem N, Tweddell J, Hoffman G, et al: Optimal timing of the second stage of palliation for hypoplastic left heart syndrome facilitated through home monitoring, and the results of early cavopulmonary anastomosis. *Cardiol Young* 2006;16(suppl 1):61–66.
- Slicker J, Hehir D, Horsley M, et al: Nutrition algorithms for infants with hypoplastic left heart syndrome: birth through the first interstage period. *Congenit Heart Dis* 2013;8:89–102.
- Kugler J, Beekman R 3rd, Rosenthal G, et al: Development of a pediatric cardiology quality improvement collaborative: from inception to implementation. From the Joint Council on Congenital Heart Disease Quality Improvement Task Force. *Congenit Heart Dis* 2009;4:318–328.
- Uzark K, Wang Y, Rudd N, et al: Interstage feeding and weight gain in infants following the Norwood operation: can we change the outcome? *Cardiol Young* 2012;22:520–527.
- Steltzer M, Connor J, Sussman-Karten K: Case study: transition to full breastfeeding in an infant with single ventricle heart disease in the interstage period (poster presentation). Boston Children’s Hospital, May 2013.
- Nutrition month: breastfeeding the HLHS baby – the practitioner perspective. March 7, 2013. [http://www.sisters-by-heart.org/2013/03/nutrition-month-breastfeeding-hlhs-baby\\_7.html](http://www.sisters-by-heart.org/2013/03/nutrition-month-breastfeeding-hlhs-baby_7.html).
- Boctor D, Pillo-Blocka F, McCrindle B: Nutrition after cardiac surgery for infants with congenital heart disease. *Nutr Clin Pract* 1999;14:111–115.

## 3.21 Nutritional Management in Children with Chronic Kidney Disease

Lesley Rees

### Key Words

Chronic kidney disease · Short stature · Supplements · Protein · Enteral feeding

### Key Messages

- Short stature is a common complication of chronic kidney disease. Inadequate intake to meet nutritional needs is a well-described cause of poor growth, and this worsens as the glomerular filtration rate declines
- Linear growth is particularly vulnerable during the infantile phase of growth; without early nutritional intervention, losses of as much as 2 height standard deviations may occur in the first 6 months of life
- Children with congenital abnormalities of the kidneys and urinary tract may lose salt (Na), water and bicarbonate and have chronic volume contraction and acidosis which impair growth; supplementation with sodium chloride and bicarbonate and free access to water is important in these circumstances
- Energy intakes should be maintained at a level equivalent to the estimated average requirement for the normal population of the same age, and protein intake at the recommended dietary intake for height age. Protein supplementation may be needed to compensate for dialysate losses
- Phosphate restriction is often necessary to prevent hyperparathyroidism. This may lead to calcium and vitamin D deficiency, since these nutrients are mainly found in phosphate-containing foods

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### Introduction

Children with chronic kidney disease (CKD) have a mortality that is 30 times higher than that of age-matched, healthy children. There is also a high incidence of malnutrition and short stature. These factors are interlinked: short stature at the start of dialysis is associated with a 2-fold increased mortality risk, decreased school attendance and increased hospitalisation. It is likely that malnutrition contributes to this as serum albumin correlates with morbidity and mortality [1]. Thus, strict attention to nutrition is essential to optimise linear growth, wellbeing and survival.

### Epidemiology of Growth

National and international registries all show below-average height for children with CKD. In the USA, around one third have a height standard deviation score (Ht SDS) of less than the 3rd percentile, rising to half by the time they need dialysis, and with a continuing decline thereafter. There is, however, great variation, with a mean Ht SDS for children on dialysis ranging from –1.3 in the UK to –3.5 in Brazil amongst 21 countries. The mean BMI SDS does not parallel the Ht SDS,

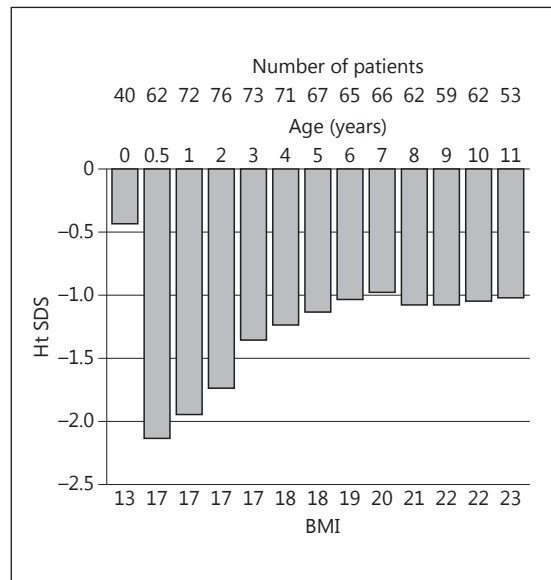
being highest in the USA at 0.8 and lowest in India at -1.4. It is likely that some of these international differences reflect limited access to adequate resources in the developing world [2]. Infants are particularly vulnerable and more severely affected. Posttransplant catch-up growth depends on graft function and use of steroid therapy, and is most likely to occur in younger children. Secular trends in recent decades show that height growth is improving for all children with CKD [3].

### Causes of Poor Growth

The best-described cause of poor growth is decreased nutritional intake. However, aetiologies are multiple and include: metabolic disturbances such as acidosis, chronic sodium depletion, and mineral and bone disorder; anaemia; and the growth hormone/insulin-like growth factor 1 axis and other hormonal derangements. Dialysis dose is another important factor affecting dietary intake, nutritional status and growth [1].

### Causes of Poor Nutritional Intake

CKD is characterised by a predisposition to anorexia and vomiting. Poor appetite may be due to abnormal taste sensation, the requirement for multiple medications, preference for water in the polyuric child, and a full abdomen in the child on peritoneal dialysis (PD). Vomiting is common, particularly with infants, and may result from gastro-oesophageal reflux and delayed gastric emptying in association with increased polypeptide hormones. The use of prokinetic, antireflux and anti-nausea drugs may be of benefit, although in infants with severe vomiting, a Nissen fundoplication may be necessary. Inadequate intake may occur during periods of sepsis and surgery, or as a result of fluid restriction in the child on dialysis. Loss of amino acids and protein occurs in



**Fig. 1.** Ht SDS of infants with CKD 5 showing the decline over the first 6 months of life. Adapted from Mekahli et al. [5].

dialysate. Acidosis and inflammation increase circulating cytokines such as leptin; levels can paradoxically be high in malnourished patients, since this hormone is excreted by the kidneys and not cleared by dialysis, thus contributing further to decreased food intake and increased energy needs [1].

### Management of Poor Nutrition

Ensuring adequate nutrition in order to promote optimum growth is the most important aspect of care of a child with CKD. The aim is to control symptoms and prevent complications, particularly uraemia and renal bone disease. There is also some evidence that ensuring normal bicarbonate and phosphate levels may slow down the progression of CKD. In 2008 the Kidney Disease Outcomes Quality Initiative, a group of experts in the field of dietary management in children with



**Table 1.** Energy and protein requirements according to age for CKD and for children on dialysis

	Energy, <sup>1</sup> kcal/kg	Protein RNI, g/kg/day	Protein for PD, g/kg/day	Protein for HD, g/kg/day
Preterm	120–180	2.5–3.0	3.0–4.0	3.0
0–3 months	115–150	2.1	≥2.4	≥2.2
4–6 months	95–150	1.6	≥1.9	≥1.7
7–12 months	95–150	1.5	≥1.8	≥1.6
1–3 years	95–125	1.1	≥1.4	≥1.2
4–6 years	90–110	1.1	≥1.3	≥1.1
7–10 years	1,740♀ – 1,970♂ kcal/day	28 g/day	≥1.2	≥1.0
11–14 years	1,845♀ – 2,220♂ kcal/day	42 g/day	3.0–4.0	3.0
15–18 years	2,110♀ – 2,755♂ kcal/day	55 g/day♂; 45 g/day♀	≥2.4	≥2.2

RNI + 0.3 g/kg/day to compensate for losses on PD; RNI + 0.1 g/kg/day to compensate for losses on HD. HD = Haemodialysis. <sup>1</sup>Estimated average requirement.

CKD, wrote guidelines covering all aspects of their nutritional care. These are used internationally [4].

#### *The Role of the Dietician*

Involvement of a paediatric renal dietician is essential for successful nutritional management. The aim is to preserve normal growth and body composition; this can be achieved by consuming appropriate amounts of calories, protein, fat, sodium, water, bicarbonate, iron, calcium, phosphate, vitamins and minerals. Nutritional assessment requires that height, weight and head circumference are plotted on centile charts at regular intervals. The most vulnerable time is infancy, and in particular the first 6 months of life, when loss of as much as 2 Ht SDS can occur (fig. 1) [5]. Frequent review is necessary for early detection of a decline in height gain velocity; prevention rather than treatment of malnutrition is the goal, so early intervention is crucial.

#### *Energy*

The diet should contain 100% of the estimated average requirement for energy for chronological

age. Inadequate energy from non-protein sources will result in the use of dietary protein for energy rather than growth, and an increase in plasma urea and potassium levels. Children on PD having glucose-containing dialysate may absorb up to 10–12 extra kilocalories per kilogram body weight per day [6].

#### *Protein*

Protein intake must provide at least 100% of the reference nutrient intake (RNI) to prevent growth failure. Serum albumin should be normal. To ensure adequate protein intake, the RNI for height age is used if the child is below the 3rd centile. On the other hand, excess protein will result in a high blood urea and toxic by-products of metabolism. The aim is for plasma urea levels to be <20 mmol/l in children under 10 years, and <30 mmol/l thereafter; nausea and anorexia increase when the urea exceeds 20 mmol/l. The blood urea level is a reflection of protein intake, unless there is a catabolic state, at which time it reflects tissue breakdown. A very low urea level suggests low protein intake and risk of protein malnutrition. Dietary protein intake is rarely inadequate in predialysis CKD, but on dialysis a

supplement is needed to replace losses in dialysate (table 1). These losses are greatest in infants and after peritonitis [6].

#### *Calcium and Phosphate*

Dietary phosphate usually should be restricted in CKD to prevent secondary hyperparathyroidism. Phosphate is principally in protein-containing foods such as meats and dairy products. Processed foods contain phosphate in significant quantities as it is a component of moisture and flavour enhancers. Foods that are a good source of calcium and vitamin D are also high in phosphate, so phosphate restriction is commonly associated with 25-hydroxyvitamin D and calcium deficiency [6].

#### *Sodium, Bicarbonate and Water*

The requirements for salt, water and bicarbonate vary with the type of renal disease. Children with congenital abnormalities of the kidneys and urinary tract, which predominantly affect the renal tubule, are usually sodium, bicarbonate and water losers. Therefore, these children need salt and bicarbonate supplementation and free access to water. Many infants on PD lose excessive amounts of sodium in dialysate, and they too need supplementation. Children with CKD predominantly due to glomerular disease may retain salt and water and develop hypertension. Such children should be managed with a 'no-added-salt' diet [3].

#### *Potassium*

CKD can be associated with potassium retention, but hyperkalaemia does not usually occur until the glomerular filtration rate is <10% of normal. Adequate control of plasma potassium can usually be achieved by improving the energy intake to prevent protein catabolism and the avoidance of foods that are very high in potassium [6].

#### *Vitamins and Minerals*

Few data are available on the micronutrient requirements for children with CKD. Vitamin sup-

plements should not be routinely prescribed as renal excretion of vitamin A metabolites is impaired in CKD. Nutritional vitamin D (25-hydroxyvitamin D) deficiency is common, and the activated form may also need replacement as the glomerular filtration rate falls to <40 ml/min/1.73 m<sup>2</sup> [6].

#### *Enteral Feeding*

Oral supplements and/or enteral feeding are necessary when spontaneous intake is inadequate to maintain growth, and should be considered as soon as the growth rate falls below normal. Percentage time with gastrostomy feeding has been shown to be an important positive predictor of longitudinal growth in under-2-year-olds on PD, being superior to provision of feed orally or by nasogastric tube [7]. Reports of whether enteral feeding can induce catch-up when started after the infantile phase of growth are conflicting, although it can improve nutritional status [3]. Supplements can be given as top-up bolus feeds, an overnight feed or an overnight continuous feed with daytime boluses, depending on the severity of the anorexia. A whey-based formula is used for children aged <2 years and a whole-protein enteral feed for those aged >2 years. These can be supplemented with fat or carbohydrate or both. Protein can be supplemented as a whey protein concentrate with amino acids [6].

#### **Obesity**

Obesity in CKD is increasing around the world, paralleling its incidence in the normal population. A high BMI increases the risk of cardiovascular disease, to which patients with CKD are already predisposed. Care must be taken not to augment energy intake above requirements, particularly in an enterally fed child [1].



## References

- 1 Rees L, Mak RH: Nutrition and growth in children with chronic kidney disease. *Nat Rev Nephrol* 2011;7:615–623.
- 2 International Pediatric Dialysis Network. <http://www.pedpd.org/index.php?id=98>.
- 3 Rees L, Jones H: Nutritional management and growth in children with chronic kidney disease. *Pediatr Nephrol* 2013;28:527–536.
- 4 KDOQI Work Group: KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update. *Am J Kidney Dis* 2009;53(suppl 2):S11–S104.
- 5 Mekahli D, Shaw V, Ledermann SE, Rees L: Long-term outcome of infants with severe chronic kidney disease. *Clin J Am Soc Nephrol* 2010;5:10–17.
- 6 Rees L, Shaw V: Nutrition in children with CRF and on dialysis. *Pediatr Nephrol* 2007;22:1689–1702.
- 7 Rees L, Azocar M, Borzych D, Watson AR, Büscher A, Edefonti A, Bilge I, Askenazi D, Leozappa G, Gonzales C, van Hoeck K, Secker D, Zurowska A, Rönnholm K, Bouts AH, Stewart H, Ariceta G, Ranchin B, Warady BA, Schaefer F; International Pediatric Peritoneal Dialysis Network (IPPN) registry: Growth in very young children undergoing chronic peritoneal dialysis. *J Am Soc Nephrol* 2011;22:2303–2312.

## 3.22 Nutrition Rehabilitation in Eating Disorders

Berthold Koletzko

### Key Words

Eating disorders · Malnutrition · Oral nutritional supplements · Nasogastric tube feeding · Refeeding syndrome

### Key Messages

- Anorexia nervosa (AN) is an eating disorder characterized by a fear of weight gain, unusual eating habits and restricted food consumption
- AN predominantly manifests in adolescent females
- AN patients tend to restrict their energy intake, avoid energy-dense and fatty foods, choose a narrow range of foods and consume vegetarian diets with a low energy density
- Severe malnutrition develops regularly, with markedly reduced body weight, BMI and body fat content as well as numerous complications (e.g. secondary amenorrhoea, osteopenia, short stature, bradycardia and a high mortality risk)

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### Introduction

Anorexia nervosa (AN) is a complex and usually chronic disorder characterized by a fear of weight gain, unusual eating habits and restricted food in-

take. AN typically manifests predominantly in adolescent females and may affect up to 0.7% of this age group [1]. AN patients tend to restrict their energy intake, avoid energy-dense and fatty foods, choose a narrow range of foods and consume vegetarian diets with a low energy density [1]. As a result, AN patients often consume no more than 10–20 kcal/kg per day and develop severe malnutrition with markedly reduced body weight, BMI and body fat content, which can result in numerous complications (e.g. secondary amenorrhoea, osteopenia, short stature, bradycardia and a high mortality risk). Treatment must address psychological and medical issues. It is based on inpatient or outpatient psychiatric treatment but regularly needs to involve several medical professions, including experts in nutritional rehabilitation [2].

### Nutritional Rehabilitation

Guidelines for nutritional rehabilitation of AN have been published by the American Psychiatric Association [3] (table 1) and the UK National Institute for Health and Clinical Excellence [4] (table 2). Both guidelines advise aiming for only a

**Table 1.** Guidelines of the American Psychiatric Association for nutritional rehabilitation in AN

The goals of nutritional rehabilitation for seriously underweight patients are to restore weight, normalize eating patterns, achieve normal perceptions of hunger and satiety, and correct biological and psychological sequelae of malnutrition.	I
In working to achieve target weights, the treatment plan should also establish expected rates of controlled weight gain. Clinical consensus suggests that realistic targets are 2–3 lb/week for hospitalized patients and 0.5–1 lb/week for individuals in outpatient programs.	II
Registered dietitians can help patients choose their own meals and can provide a structured meal plan that ensures nutritional adequacy and that none of the major food groups are avoided.	I
It is important to encourage patients with AN to expand their food choices to minimize the severely restricted range of foods initially acceptable to them.	II
Caloric intake levels should usually start at 30–40 kcal/kg per day (approx. 1,000–1,600 kcal/day). During the weight gain phase, intake may have to be advanced progressively to as high as 70–100 kcal/kg per day for some patients; many male patients require a very large number of calories to gain weight.	II
Patients who require much lower caloric intakes or are suspected of artificially increasing their weight by fluid loading should be weighed in the morning after they have voided and are wearing only a gown; their fluid intake should also be carefully monitored.	I
Urine specimens obtained at the time of a patient's weigh-in may need to be assessed for specific gravity to help ascertain the extent to which the measured weight reflects excessive water intake.	I
Regular monitoring of serum potassium levels is recommended in patients who are persistent vomiters.	I
Weight gain results in improvements in most of the physiological and psychological complications of semistarvation.	I
It is important to warn patients about the following aspects of early recovery:	I
As they start to recover and feel their bodies getting larger, especially as they approach frightening, magical numbers on the scale that represent phobic weights, they may experience a resurgence of anxious and depressive symptoms, irritability and sometimes suicidal thoughts. These mood symptoms, non-food-related obsessional thoughts, and compulsive behaviours, although often not eradicated, usually decrease with sustained weight gain and weight maintenance. Initial refeeding may be associated with mild transient fluid retention, but patients who abruptly stop taking laxatives or diuretics may experience marked rebound fluid retention for several weeks. As weight gain progresses, many patients also develop acne and breast tenderness and become unhappy and demoralized about resulting changes in body shape. Patients may experience abdominal pain and bloating with meals from the delayed gastric emptying that accompanies malnutrition. These symptoms may respond to promotility agents.	III
When life-preserving nutrition must be provided to a patient who refuses to eat, nasogastric feeding is preferable to intravenous feeding.	I
I = Recommended with substantial clinical confidence; II = recommended with moderate clinical confidence; III = may be recommended on the basis of individual circumstances. Modified from American Psychiatric Association [3].	

**Table 2.** Guidelines of the UK National Institute for Health and Clinical Excellence for nutritional rehabilitation in AN

<i>Managing weight gain in AN</i>	
In most patients with AN, an average weekly weight gain of 0.5–1 kg in inpatient settings and 0.5 kg in outpatient settings should be an aim of treatment. This requires about 3,500–7,000 extra calories a week.	C
Regular physical monitoring, and in some cases treatment with a multivitamin/multimineral supplement in oral form, is recommended for people with AN during both inpatient and outpatient weight restoration.	C
Total parenteral nutrition should not be used for people with AN, unless there is significant gastrointestinal dysfunction.	C
<i>Managing risk in AN</i>	
Health care professionals should monitor physical risks in patients with AN. If this leads to the identification of increased physical risks, the frequency and the monitoring and nature of the investigations should be adjusted accordingly.	C
People with AN and their carers should be informed if the risk to their physical health is high.	C
The involvement of a physician or paediatrician with expertise in the treatment of physically at-risk patients with AN should be considered for all individuals who are physically at risk.	C
Pregnant women with either current or remitted AN may need more intensive prenatal care to ensure adequate prenatal nutrition and fetal development.	C
Oestrogen administration should not be used to treat bone density problems in children and adolescents as this may lead to premature fusion of the epiphyses.	C
Evidence C: this grading indicates that directly applicable clinical studies of good quality are absent or not readily available. Modified from National Institute for Health and Clinical Excellence [4].	

moderate rate of weight gain up to ~1 kg/week. However, the implementation of increased nutrient intakes from foods, oral nutritional supplements or tube feedings is often made difficult by the denial of illness and resistance to treatment that is frequently found in AN patients, who tend to drop out of recommended treatment programmes.

While healthy women without an eating disorder require 20–40 kcal/kg per day to maintain their weight, the energy intake of AN patients needs to be increased stepwise to about 60–100 kcal/kg per day to achieve a sustained weight gain

[1]. This rather high energy need reflects a hyper-metabolic state, which in part may be due to excessive physical activity and exercise – a common behaviour in AN. Increasing energy and nutrient intake to achieve nutritional rehabilitation can be approached either by increased intakes of regular foods, energy-dense oral nutritional supplements with an energy density of  $\geq 1$  kcal/ml, nasogastric tube feeding or a combination thereof. There is broad agreement that parenteral nutrition should generally be avoided unless a severely impaired gut function prevents the use of oral or enteral nutrition.

**Table 3.** Benefits and disadvantages of different feeding methods in AN patients

Benefits	Disadvantages
<p><i>Only regular foods</i></p> <ul style="list-style-type: none"> <li>– It teaches skills for eating, promotes normal behaviour and challenges unhelpful coping strategies</li> <li>– Patients experience the amount of food necessary for weight gain and weight maintenance</li> <li>– Food makes hospital meal management home-like and realistic, which exposes patients to a situation which is anxiety-provoking, and gives them confidence in managing meals at home</li> </ul>	<ul style="list-style-type: none"> <li>– Less energy is delivered from food when compared with nasogastric feeding</li> </ul>
<p><i>High-energy oral nutritional supplements</i></p> <ul style="list-style-type: none"> <li>– Supplements can meet the high-energy requirements needed for weight gain in a smaller volume than food</li> <li>– They are helpful as a top-up for patients struggling with satiety and the quantities of food required to promote weight gain</li> <li>– It can be seen as a type of medicine</li> </ul>	<ul style="list-style-type: none"> <li>– The frequent use of supplements encourages patients away from the experience of food, re-enforces their avoidance of food and can foster dependency on artificial food sources</li> </ul>
<p><i>Nasogastric tube feeding</i></p> <ul style="list-style-type: none"> <li>– More comfortable for the patient with less pain, physical discomfort and abdominal distension than large amounts of food</li> <li>– A helpful strategy aiding recovery: it transfers the responsibility of weight gain from the patient to the treatment team; if placed upon admission, it ‘medicalises’ the treatment and reduces the ‘power struggle’ between the patient and clinicians</li> <li>– Opinions from patients and carers: nasogastric feeding was seen as necessary by some patients because they believed they lacked the physical or psychological capacity to eat; parents recognized it as a last resort that was required to keep their child alive; it reduces the pressure patients perceive is being placed on them to eat and temporarily relieves them from the responsibility for adopting improved eating behaviours</li> </ul>	<ul style="list-style-type: none"> <li>– It interferes with the fragile alliance between the patient and treatment team</li> <li>– The patient may feel disempowered and embittered towards the treatment team, which may have an impact on future personal and professional relationships</li> <li>– There is an emotional toll on staff treating involuntary patients</li> <li>– Not helpful for long term recovery: patients may demonstrate an inability to maintain an adequate intake and weight gain once the tube is removed; force-feeding in low-weight patients achieves little in relation to remitting illness or suffering; patients tamper with the tube by adjusting the control, decanting the feed into other containers when unobserved, biting, and removing the tube</li> <li>– Medical complications (i.e. aspiration, nasal bleeding and nasal irritation, reflux and sinusitis)</li> <li>– The tube may not be inserted properly, which is more likely when patients have it inserted against their will</li> <li>– Opinions from patients and carers: it disguises the consumption of food; patients become emotionally attached to and physically reliant on nasogastric feeding, and are anxious about the tube being removed; it is used as a form of punishment and seen as a strategy that doctors use to assert their control</li> </ul>

**Table 3** (continued)

Benefits	Disadvantages
<i>Parenteral nutrition</i> – It requires minimal patient cooperation	– It may reinforce a tendency to focus only on physical symptoms rather than the psychiatric implications of AN – Sabotage occurs by pouring solutions into the sink and removing the device – It cannot teach patients anything about eating, food choice or portion size, or about perceiving their bodies more accurately – Medical complications [i.e. infections; arterial injury; cardiac arrhythmias (from placement); changes in vascular endothelium; hyperosmolarity and hyperglycaemia; hypophosphataemia and hypokalaemia] – More medically intensive, incurring high costs

Modified from Hart et al. [5].

### Choice of Refeeding Methods

Hart et al. [5] reviewed the literature to identify which of the different feeding methods is most effective and advantageous in AN. An analysis of the published information revealed that the most common method of refeeding was by nasogastric feeding and food, followed by high-energy density oral nutritional supplements and food [5]. However, due to the limited evidence available, no conclusion could be drawn on the most effective method of nutritional rehabilitation in AN. However, the authors compiled benefits and disadvantages of the different feeding methods for AN patients (table 3). Similarly, Rocks et al. [6] concluded from their review of the available literature that a consensus on the most effective and safe treatment for weight restoration in inpatient children and adolescents with AN is not currently feasible. Nonetheless, these authors concluded that the use of tube feeding in addition to normal food intake increased energy intake and body weight, although it was associated with more frequent adverse effects.

A particular concern related to the use of nasogastric tube feeding in malnourished patients is the risk of inducing refeeding syndrome with hypophosphataemia. Adaption to starvation in malnourished children and adolescents is associated with a reduced metabolic turnover, cellular activity and organ function, low insulin secretion, and deficiencies in a variety of micronutrients, minerals and electrolytes [7]. Catabolic patients use substrates from adipose tissue and muscle as sources of energy, and the total body stores of nitrogen, phosphate, magnesium and potassium become depleted. The sudden provision of energy and nutrients reverses catabolism and leads to a surge of insulin secretion, which in turn leads to massive intracellular shifts of phosphate, magnesium and potassium with a subsequent fall in their serum concentrations. The clinical consequences of the resulting electrolyte disturbances with hypophosphataemia include haemolytic anaemia, muscle weakness and impaired cardiac function, with the risks of fluid overload, cardiac failure, arrhythmia and death.



## Refeeding Syndrome and Outcome

The risk of refeeding syndrome is highest in AN patients with severe underweight, which is a better risk predictor than total energy intake [8]. The first week after starting enteral nutrition is the time with the highest rate of refeeding syndrome manifestations. To reduce the risk, a patient's nutritional status and hydration as well as serum electrolytes, magnesium and phosphate should be assessed prior to initiating tube feeding. During the initial phase of refeeding, daily monitoring of plasma electrolytes, phosphate, magnesium, calcium, urea and creatinine as well as of cardiac status (pulse, heart failure) is advisable [8]. Initial enteral feeding should be limited to provide only about three quarters of the estimated requirements in severe cases (i.e. 11–14 years: 45 kcal/kg per day; 15–18 years: 40 kcal/kg per day). If this supply is tolerated and no imbalances are encountered, the supply may be gradually increased over 1–3 weeks towards reaching intakes that achieve a sustainable weight gain. Frequent small feeds with an energy density of 1 kcal/ml should be used in order to minimize fluid load. The following supplements may be provided: Na<sup>+</sup> at 1 mmol/kg per day, K<sup>+</sup> at 4 mmol/kg per day, Mg<sup>2+</sup> at 0.6 mmol/kg per day and phosphate at ≤100 mmol orally for children and adolescents >5 years of age [8]. An occurring hypocalcaemia must be corrected. Thiamine, riboflavin, folic acid, ascorbic acid, pyridoxine and fat-soluble vitamins should be supplemented along with trace elements. Patients with a BMI <16, weight loss of >15% within the previous 3–6 months, very little or no nutrient intake for >10 days, and low levels of potassium, phosphate or magnesium prior to any feeding are considered a high-risk group for developing refeeding syndrome and should not only have an initial restriction of their protein and energy intake but also be given thiamin and other B group vitamins, a balanced multivitamin and trace element supplement, as well as potassium, magnesium and phosphate under close monitoring of plasma concentrations.

Agostino et al. [9] reviewed the outcomes of AN patients treated with nasogastric tube feeding or a standard bolus meal treatment in one centre. The patients with nasogastric tube feeding had a significantly shorter hospital stay (33.8 vs. 50.9 days;  $p = 0.0002$ ) and an improved rate of weight gain, while the rate of complications or electrolyte abnormalities with prophylactic phosphate supplementation from admission was not different. One may conclude that even though an individualized approach to refeeding AN patients is appropriate, the available data support the option of treating undernourished AN inpatients with nasogastric tube feeding while using appropriate precautions and monitoring.

## Conclusions

- AN patients require inpatient or outpatient psychiatric treatment, but they also regularly need treatment involving experts in nutritional rehabilitation
- Nutritional rehabilitation aims at only a moderate rate of weight gain up to ~1 kg/week
- Refeeding can be achieved by increased nutrient intake from foods, oral nutritional supplements or tube feedings but is often made difficult by the denial of illness and resistance to treatment frequently found in AN patients
- A slow initiation of refeeding as well as close monitoring are needed, particularly in markedly malnourished patients, to reduce the risk of refeeding syndrome and hypophosphataemia
- The energy intake in AN patients needs to be slowly increased to ~60–100 kcal/kg per day to achieve a sustained weight gain, partly due to high energy expenditure resulting from excessive physical activity
- In addition to regular foods, the use of oral nutritional supplements and nasogastric tube feedings is a suitable option for refeeding AN patients

## References

- 1 Marzola E, Nasser JA, Hashim SA, Shih PA, Kaye WH: Nutritional rehabilitation in anorexia nervosa: review of the literature and implications for treatment. *BMC Psychiatry* 2013;13:290.
- 2 Weaver L, Sit L, Liebman R: Treatment of anorexia nervosa in children and adolescents. *Curr Psychiatry Rep* 2012;14: 96–100.
- 3 American Psychiatric Association: Treatment of patients with eating disorders, third edition. American Psychiatric Association. *Am J Psychiatry* 2006; 163(suppl):4–54.
- 4 National Institute for Health and Clinical Excellence: Eating Disorders. Manchester, National Institute for Health and Clinical Excellence, 2004.
- 5 Hart S, Franklin RC, Russell J, Abraham S: A review of feeding methods used in the treatment of anorexia nervosa. *J Eat Disord* 2013;1:36.
- 6 Rocks T, Pelly F, Wilkinson P: Nutrition therapy during initiation of refeeding in underweight children and adolescent inpatients with anorexia nervosa: a systematic review of the evidence. *J Acad Nutr Diet* 2014;114:897–907.
- 7 Koletzko B, Goulet O: Nutritional support in infants, children and adolescents; in Sobotka L (ed): *Basics in Clinical Nutrition*. Prague, Galén, 2011, pp 625–653.
- 8 O'Connor G, Nicholls D: Refeeding hypophosphatemia in adolescents with anorexia nervosa: a systematic review. *Nutr Clin Pract* 2013;28:358–364.
- 9 Agostino H, Erdstein J, Di Meglio G: Shifting paradigms: continuous nasogastric feeding with high caloric intakes in anorexia nervosa. *J Adolesc Health* 2013;53:590–594.



## 3.23 Haemato-Oncology

John W.L. Puntis

### Key Words

Malignant disease · Bone marrow/stem cell transplantation · Mucositis · Enteral tube feeding · Parenteral nutrition

### Key Messages

- Malnutrition is a common complication of malignant disease and its treatment, and is most likely to occur in advanced-stage solid tumours, acute myeloblastic leukaemia and bone marrow/stem cell transplantation
- Nutritional support is a major part of therapy; there is no evidence that extra nutrients promote tumour growth
- The aims of nutritional support are to reverse malnutrition if present at diagnosis, to prevent deterioration in nutritional status during treatment, and to promote normal growth
- Children at low nutritional risk require high-energy supplements that can be taken by mouth; they benefit from flexibility in mealtimes and menus
- When oral energy intake is inadequate, enteral tube feeding should be used; this is usually well tolerated and improves wellbeing even in children undergoing intensive chemotherapy
- Parenteral nutrition is reserved for those children with severe gastrointestinal symptoms related to underlying disease, chemotherapy or radiotherapy

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### Introduction

Nutritional status influences prognosis in children with cancer and affects treatment tolerance and susceptibility to infection. Patients often have significant difficulties with eating during long periods of treatment and recurrent admissions to hospital, and have particular nutritional needs [1]. Malnutrition is common, with estimates of prevalence ranging up to 50% depending on the type, stage and metastatic status of the disease as well as the toxicity of various cancer therapies [2]. Children with large, solid abdominal masses (e.g. neuroblastoma, hepatoblastoma, Wilms' tumour) may present with normal weight despite severe nutritional depletion, so that simple anthropometric assessment can be misleading [3]. The highest risk posed to nutritional status comes from advanced-stage solid tumours, acute myeloid leukaemia, multiple-relapse leukaemia, head and neck cancer, medulloblastoma and bone marrow or stem cell transplantation. The pathophysiology of malnutrition is multifactorial and includes complex interactions between energy and substrate metabolism, hormonal and inflammatory components, and alterations of metabolic compartments. These result in accelerated

**Table 1.** Risk factors for nutritional compromise

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Decreased food intake
Inadequate amount of food offered
Unappetising food; lack of flexibility in meeting a child's preferences
Too much food
'Forced' feeding
Reduced appetite from illness
Symptoms associated with disease or treatments, e.g. nausea, vomiting, sore mouth, pain, diarrhoea and breathlessness
Repeated fasting for treatments or procedures
Mucositis, swallowing or chewing difficulties
Difficulty self-feeding
Poor child-carer interaction at meal times
Impaired conscious level
Increased nutritional requirements
Illness/metabolic stress
Wound or fistula losses
Impaired ability to absorb or utilise nutrients
Due to disease or treatment, e.g. chemotherapy causing enteropathy or pancreatic exocrine impairment
Infection as a consequence of immunosuppression

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mobilisation, oxidation of energy substrates and loss of body protein [4].

General risk factors for malnutrition are shown in table 1. Learned food aversion associated with nausea-inducing treatment sometimes leads to anticipatory vomiting. Chemotherapy may adversely affect food intake and gastrointestinal function by causing oral or oesophageal ulceration, altered taste perception, anorexia, nausea, vomiting, and enteritis with malabsorption and diarrhoea. Serving food cold or at room temperature and covering drinks (taken through a straw) can decrease tastes and smells and make it easier for children to eat. Radiation therapy to the head and neck can cause mucositis, anorexia, nausea, vomiting, dysphagia, dry mouth and altered taste, while radiation to the abdomen may cause enteritis and bowel stricture.

Bone marrow transplantation (BMT) or stem cell transplantation is indicated in children with a range of malignant and non-malignant conditions. Chemotherapy and/or radiation therapy

are used to reduce host cells to the point that donor stem cells will engraft (allogeneic BMT), or to reduce the tumour burden and rescue the patient with his/her own stem cells (autologous BMT). Priming chemotherapy causes severe nausea, vomiting and oral ulceration, and is often associated with diarrhoea, protein losing enteropathy, and depletion of zinc and electrolytes [5, 6]. Most children undergoing BMT stop eating either as a result of these side effects or because eating becomes one of the few areas over which they can exercise some control. Impairment of gastrointestinal barrier function increases the risk of viral, bacterial and fungal infections. Episodes of sepsis are associated with protein catabolism and negative nitrogen balance. Enteral feeds should be prepared in a manner that renders them low in bacterial load ('clean feeds'); parenteral nutrition (PN) may be necessary, but enteral tube feeding (ETF), if tolerated, is associated with better nutritional response and sense of wellbeing.



## Provision of Nutritional Support

A nutritional care plan for each patient should be developed by the multidisciplinary haematology-oncology team (including an expert dietitian). The goals of nutritional support are to reduce morbidity and minimise or prevent complications such as infection and growth failure; there is no evidence that nutritional support promotes tumour growth. Baseline nutritional status should be established, including eating habits and any family perceptions of problems around eating. Weight measurement is inaccurate as an indicator of nutritional status in children with a large tumour mass, and mid-upper-arm circumference and skinfold thickness measurements are more reliable methods of assessment and monitoring [7]. Neutropenic patients must avoid food that may carry a high microbial load, such as poorly cooked meats, soft cheeses, pâté, shellfish, and raw or soft-cooked eggs; however, most infections are hospital acquired and not food borne, so over-restriction of food choices may be counterproductive. Mucositis (painful mouth ulcers ± superinfection), vomiting and anorexia often limit oral intake. Routine saline mouthwashes are used, together with adequate pain relief (opiates if necessary). Frequent small meals of appetising food are more likely to be accepted, and advice with regard to the use of high-calorie foods should be given routinely. There should be flexibility with regard to menu choice, mealtimes and parental involvement; children on the ward should be encouraged to eat together at mealtimes. Tastes may be bitter or metallic with some drugs (e.g. procarbazine and cyclophosphamide) or food may have no taste at all. Some children develop a liking for strong flavours (pickles, spices). Serving food with sauces and gravies will increase moisture and help swallowing if the mouth is dry. Food can be purchased from the shop/canteen or brought in from home if tempting meals cannot be provided in hospital. Ideally, a hospital cook should prepare meals on demand from a ward kitchen, or meals be ordered

directly from the catering service as required throughout the day and not just at mealtimes [8]. The use of a reward system (star chart) may motivate some younger children to eat, but rewards need to be appropriate to the child's age and goals must be achievable and relevant.

## ETF and PN

ETF or PN is likely to be needed when:

- the child is malnourished at diagnosis;
- there is loss of >5% body weight during treatment;
- weight-for-height is <90%;
- there is a drop in weight across 2 centiles;
- food intake is <80% of the estimated requirement;
- triceps skinfold thickness is <5th centile, or
- the child is a BMT patient.

Long-term use of ETF in infants often leads to later feeding difficulties, and early advice should be sought from a speech and language therapist. Gastrostomy may be considered if tube feeding is required for more than 4 weeks or if the nasogastric tube is not tolerated (e.g. severe mucositis; vomiting). Older children should be allowed to choose between a nasogastric tube and percutaneous endoscopic gastrostomy. Tube feeds are generally given overnight to allow for normal activities and oral intake during the daytime. Tube feeding [9] may result in a number of complications including vomiting, regurgitation/aspiration and diarrhoea (see table 2 for potential problems and solutions). Whereas the enteral route should be used for nutritional support whenever possible, PN must be considered when gut dysfunction precludes enteral feeding for more than 5 days. This may occur when there is severe mucositis and enteritis, neutropenic enterocolitis, ileus, bowel obstruction, chylous ascites following surgery, and severe graft-versus-host disease. Standard PN regimens can be used, although refeeding syndrome is a risk in malnourished patients, and careful

**Table 2.** ETF: problems and potential solutions

Symptom	Cause	Possible solution
Diarrhoea	Unsuitable feed for a child with impaired gut function	Change to hydrolysed formula or modular feed
	Excessive infusion rate	Slow rate, increase as tolerated
	Intolerance of bolus feeds	Frequent, smaller feeds, or change to continuous feeds
	High feed osmolarity	Build up strength of feed slowly and give by continuous infusion
	Microbial contamination of feed	Use sterile, commercially produced feeds if possible; prepare other feeds in a clean environment
	Drugs (e.g. antibiotics, laxatives)	Review drug prescription
Nausea/ vomiting	Excessive infusion rate	Slowly build up feed infusion
	Slow gastric emptying	Encourage lying on right side; prokinetics
	Constipation	Maintain regular bowel habit with adequate fluid intake, fibre-containing feed and/or laxatives
	Medicines given at the same time as feed	Allow time between giving medicines and giving feed, or stop continuous feeding for a short time
	Psychological factors	Review feeding behaviour; consider referral to psychologist
Regurgitation/ aspiration	Gastro-oesophageal reflux	Correct positioning; feed thickener; drugs; continuous feeds; jejunal tube (consider fundoplication)
	Dislodged tube	Secure tube adequately and regularly review position
	Excessive infusion rate	Slow infusion rate
	Intolerance of bolus feeds	Smaller, more frequent feeds, or continuous infusion

monitoring is required [10]; regimens also require modification in the light of nutritional response. It is important to consider and regularly review the objectives of nutritional support in individual patients. Monitoring will include assessment of nutritional intake, anthropometry, biochemical and haematological parameters, general clinical state, gastrointestinal function and feeding tube/central venous catheter integrity.

### Late Nutritional Complications

Survivors of common paediatric malignancies are at risk of obesity, which in turn is associated with cardiovascular and endocrine diseases. Increased BMI (>25) was found in survivors of acute lymphoblastic leukaemia <4 years of age at diagnosis receiving cranial radiation therapy, and in chil-

dren with brain tumours, especially craniopharyngioma survivors [11]. Late nutritional complications also include a reduction in lean body mass in some patients [12]. Reduced bone mineral density can result from decreased physical activity, reduced calcium intake and the effects of corticosteroid treatment; undermineralisation may persist in a small proportion of patients. Growth and nutritional status should be monitored during long-term follow-up.

### Conclusions

Always try to:

- identify a child's favourite foods – these are best avoided whilst having chemotherapy so that aversion does not develop;
- offer small, frequent meals;

- encourage dietary supplements;
- provide skilled dietetic supervision;
- manage side effects of chemotherapy effectively (nausea, vomiting);
- consider the need for tube feeding early, especially in high-nutritional-risk patients;
- remember that a child may eat better at home, and
- use parenteral nutrition when appropriate (i.e. when enteral feeds are precluded by gastrointestinal dysfunction).

## References

- 1 Capra S, Ferguson M, Ried K: Cancer: impact of nutrition intervention outcome – nutrition issues for patients. *Nutrition* 2001;17:769–772.
- 2 Bauer J, Jürgens H, Frühwald MC: Important aspects of nutrition in children with cancer. *Adv Nutr* 2011;2:67–77.
- 3 Skipworth RJ, Stewart DFG, Dejong CH, Preston T, Fearon KC: Pathophysiology of cancer cachexia: much more than host-tumour interaction? *Clin Nutr* 2007;26:667–676.
- 4 Murphy AJ, White M, Davies PSW: The validity of simple methods to detect poor nutritional status in paediatric oncology patients. *Br J Nutr* 2009;101:1388–1392.
- 5 Papadopoulou A, Williams MD, Darbyshire PJ, Booth IW: Nutritional support in children undergoing bone marrow transplantation. *Clin Nutr* 1998;17:57–63.
- 6 Papadopoulou A, MacDonald A, Williams MD, Darbyshire PJ, Booth IW: Enteral nutrition after bone marrow transplantation. *Arch Dis Child* 1997;77:131–136.
- 7 Smith DE, Stevenson MCG, Booth IW: Malnutrition at diagnosis of malignancy in childhood: common but mostly missed. *Eur J Pediatr* 1991;150:318–322.
- 8 Royal College of Nursing: Nutrition in children and young people with cancer. London, Royal College of Nursing, 2010. [http://www.rcn.org.uk/\\_data/assets/pdf\\_file/0010/338689/003805.pdf](http://www.rcn.org.uk/_data/assets/pdf_file/0010/338689/003805.pdf).
- 9 Smith DE, Handy DJ, Holden CE, et al: An investigation of supplementary naso-gastric feeding in malnourished children undergoing treatment for malignancy: results of a pilot study. *J Hum Nutr Dietet* 1992;5:85–91.
- 10 Afzal NA, Addai S, Fagbemi A, Murch S, Thomson M, Heuschkel R: Refeeding syndrome with enteral nutrition in children: a case report, literature review and clinical guidelines. *Clin Nutr* 2002;21:515–520.
- 11 Meacham LR, Gurney JG, Mertens AC, et al: Body mass index in long-term adult survivors of childhood cancer: a report of the Childhood Cancer Survival Study. *Cancer* 2005;103:1730–1739.
- 12 Oeffinger KC, Mertens AC, Sklar CA, et al: Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2003;21:1359–1365.

### 3.24 Intensive Care

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#### Key Words

Intensive care · Burn injury · Energy expenditure · Critical illness · Nutritional support

#### Key Messages

- Malnutrition leads to increased morbidity and mortality in pediatric hospital patients, with particularly severe consequences in critically ill children
- Both under- and overfeeding have negative consequences
- Nutritional support for the critically ill child is an essential aspect of clinical management and should be integrated into daily care
- Nutritional guidelines in this area are not evidence based, because little research has been conducted

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#### Introduction

During critical illness and recovery thereafter, adequate nutritional support is an essential aspect of the clinical management of pediatric intensive care patients. Adequate feeding is essential for complete recovery and normal functioning of the growing child. Thus clinicians in the pediatric intensive care unit (PICU) are challenged to pro-

vide adequate nutrition for optimal tissue synthesis and immune function while avoiding complications of under- or overfeeding.

The prevalence of malnutrition among children admitted to a PICU, including burn and trauma patients, is high [1–3]. Protein-energy malnutrition in hospital patients is associated with increased mortality and morbidity, including a higher risk of infections due to poor immune defense, wound healing problems, reduced gut function, longer dependency on mechanical ventilation and longer hospital stay [1, 4].

Studies have shown that the nutritional status of children admitted to a PICU deteriorates during hospitalization [2] as children often do not receive adequate feeding. Besides underfeeding, overfeeding also has negative consequences: it is of no benefit in maintaining lean body mass and results in the excessive synthesis of fat. This may induce hepatic steatosis and impaired liver function and increase the risk of hyperglycemia. Hyperglycemia itself results in a higher mortality and morbidity in critically ill children [5]. Nutrition delivery is generally inadequate in critically ill children. Improved adequacy of energy intake has been shown to improve mortality and morbidity [6].

**Table 1.** Schofield equations for estimating REE from weight and from weight and height in kcal/day<sup>1</sup> [9]

Age, years	Boys	Girls
0–3	$60.9 \times \text{weight} - 54$ $0.167 \times \text{weight} + 1,516.7 \times \text{height} - 617.6$	$61.0 \times \text{weight} - 51$ $16.2 \times \text{weight} + 1,022.7 \times \text{height} - 413.5$
3–10	$22.7 \times \text{weight} + 495$ $19.6 \times \text{weight} + 130.2 \times \text{height} + 414.9$	$22.5 \times \text{weight} + 499$ $17.0 \times \text{weight} + 161.7 \times \text{height} + 371.2$
10–18	$17.5 \times \text{weight} + 651$ $16.2 \times \text{weight} + 137.1 \times \text{height} + 515.5$	$12.2 \times \text{weight} + 746$ $8.4 \times \text{weight} + 465.4 \times \text{height} + 200.0$

In order to calculate total energy needs, additional factors must be taken into account: (a) illness factor of critically ill children – 1.2–1.6 with PICU patients, 1.4 with burn patients, 1.3–1.5 with trauma patients; (b) activity factor of critically ill children – 1.0–1.1; (c) growth factor of critically ill children – 1.0 in the acute phase; in convalescent phase, 1.3 if age <4 months, 1.1 if age 4–12 months, and 1.02–1.04 for older children.

<sup>1</sup> 1 kcal = 4,186 kJ; weight in kilograms, height in meters.

## Nutritional Requirements

Nutritional requirements for critically ill children range widely with altered metabolic states determined by the children's age and nutritional status. Metabolic responses may greatly vary as well, depending on the nature of the injury and the variability in the individual response to the same type of injury. Both a hypometabolic and a hypermetabolic response may occur [7]. Especially in children with burn injury there is an exaggerated catabolic response and they also show exudation of nutrients through the damaged skin. These factors together result in very high requirements for energy, protein and other nutrients in this category of patients [8].

### Energy

In practice, daily energy demands of critically ill children should be calculated individually based on one of the following methods:

- (1) Measurement of resting energy expenditure (REE) by indirect calorimetry in ventilated and nonventilated children
- (2) Estimation of REE by predictive equations based on weight (and height), age and sex

- (3) Estimation using dietary reference intakes for healthy children matched for age and sex

The preferred method is measuring the REE. The measured REE is the minimum amount of energy needed. Several factors commonly present in the ICU population might affect measured REE and must be taken into account when interpreting the outcome; fever, for example, can increase energy expenditure, while sedatives, anesthesia and muscle relaxants may decrease it in some patients. The Schofield equation [9] is a useful alternative for estimating REE and is shown in table 1.

In the recovery phase, additional factors should be taken into account to calculate energy needs, such as activity, illness, growth and absorption coefficient in case of enteral feeding. In general, infants require 10–20% more calories when fed enterally than when fed parenterally, whereas the differences are smaller in children (close to 10%), primarily because of more effective enteral absorption with older age.

### Proteins

Both protein synthesis and protein breakdown are intensified in critical illness, but the latter pre-

**Table 2.** Current nutritional recommendations for critically ill children [10]

Age	Total energy expenditure in health, kcal	REE, kcal	Parenteral amino acid, g/kg/day	Parenteral lipid, g/kg/day
0–2 months	100	50	1.5–3.0	3–5
3–12 months	100	50	1.0–2.5	3–4
1–6 years	90	45	1.0–2.0	2–3
7–12 years	70	35	1.0–2.0	2–3
>12 years	50	25	1.0–2.0	2–3

dominates. Thus, critically ill children typically manifest a net negative protein balance, which may clinically be noted by weight loss and skeletal muscle wasting which may have deleterious effects on outcome. An increased protein intake cannot reverse protein breakdown but can improve nitrogen balance by enhancing protein synthesis. There is a close interrelationship between protein and energy metabolism. A lack of energy supply will enhance an already increased protein catabolism during critical illness. However, an increase in the energy supply will not promote nitrogen retention unless the protein supply is adequate, and, conversely, an increased protein supply will be useless if energy is limited. The current guidelines on parenteral amino acid intake are shown in table 2 [10]. For enteral feeding, the same intake can be followed.

### *Carbohydrates*

Energy requirements of the body, and especially the brain, depend on glucose as the major fuel. Plasma glucose levels are the resultant of a balance between exogenous glucose intake and endogenous glucose production (glycogenolysis and gluconeogenesis) on the one hand and glucose utilization (oxidation or storage as glycogen and triglycerides) on the other. Initial screening for hypo- and hyperglycemia should be performed on all critically ill children. Both low and high blood glucose levels as well as variability in glucose levels worsen outcome and should be treated. Hyperglycemia with high plasma insulin

concentrations is the result of insulin insensitivity that occurs during stress. Both insulin resistance and (relative)  $\beta$ -cell dysfunction play a role in the occurrence of hyperglycemia in critically ill children [11].

For children <30 kg, a glucose intake of 4–6 mg/kg/min is recommended, whereas for children >30 kg this is 2–4 mg/kg/min. In case of hyperglycemia, glucose intake can be decreased, but it is recommended to start insulin therapy in an early phase [12]. Large randomized outcome studies of a tight glucose regimen with insulin therapy in the critically ill pediatric population are limited; so far one study showed an improved outcome, using tight glycemic control in a mixed PICU population [13].

### *Lipids*

Lipid metabolism is generally accelerated by illness and physiologic stress, and lipids are a prime source of energy. Infusion of lipid emulsions allows a high energy supply, facilitates the prevention of high glucose infusion rates and is indispensable for the supply of essential fatty acids. Lipid intake should usually provide 25–40% of nonprotein calories in fully parenterally fed patients (table 2). A minimum linoleic acid intake of 0.1 g/kg/day should be administered to infants and older children in order to prevent essential fatty acid deficiency. The dosage of fat should not exceed the capacity for lipid clearance, and should be adapted if marked hyperlipidemia occurs. It is recommended to decrease or stop parenteral lipid





infusion if the serum triglyceride level is >250 mg/dl (>2.9 mmol/l) in infants and >400 mg/dl (>4.6 mmol/l) in children.

### *Burn Injury*

In pediatric burn patients, several additional formulas for determining energy needs have been used, but they have been shown to either underestimate or overestimate energy expenditure [14, 15]. Therefore, measurement of energy expenditure is highly recommended in this population. In the absence of indirect calorimetry, the Schofield prediction equation based on weight and height [9] seems to be the best alternative for estimating REE (table 1).

Protein requirements are higher in burned children than in normal children. In addition to increased loss of protein across the burn wound, there is a great demand for protein for wound healing, host defense and gluconeogenesis as amino acids become a primary source of energy. Current recommendations for patients with burns of more than 10% of the body surface area are: 20% of the total kilocalories provided from protein acids (children: 3 g/kg/day), 55–60% from carbohydrates without exceeding 5 mg/kg/min, and up to 30% from fats.

## **Nutritional Support**

### *Indication and Goal*

Nutritional support is important in the management of the critically ill patient when oral food intake is inadequate or not possible. To determine the risk for deterioration of the nutritional status during admission, the use of a risk screening tool (e.g. STRONG<sub>kids</sub>) is advocated [16]. It is employed to minimize the loss of lean body mass and support the synthesis of critical visceral proteins.

### *Timing of Nutritional Support*

Nutritional support should be started within the first 24 h of admission to the PICU for children

who are hemodynamically stable and have a functioning gastrointestinal tract.

### *Route of Nutritional Support*

Enteral nutrition (EN) via tube is the preferred way of feeding the critically ill and burn patients. EN reverses the loss of gastrointestinal mucosal integrity, maintains intestinal blood flow, preserves the IgA-dependent immunity and contributes to the maintenance of the host immune response. Meta-analyses of clinical studies have reported that EN as opposed to parenteral nutrition (PN) is associated with a lower risk of infection and also results in cost savings [17]. With transpyloric feeding, it is possible to increase the delivery of EN, but it is unable to impede tracheal aspiration of gastric fluids.

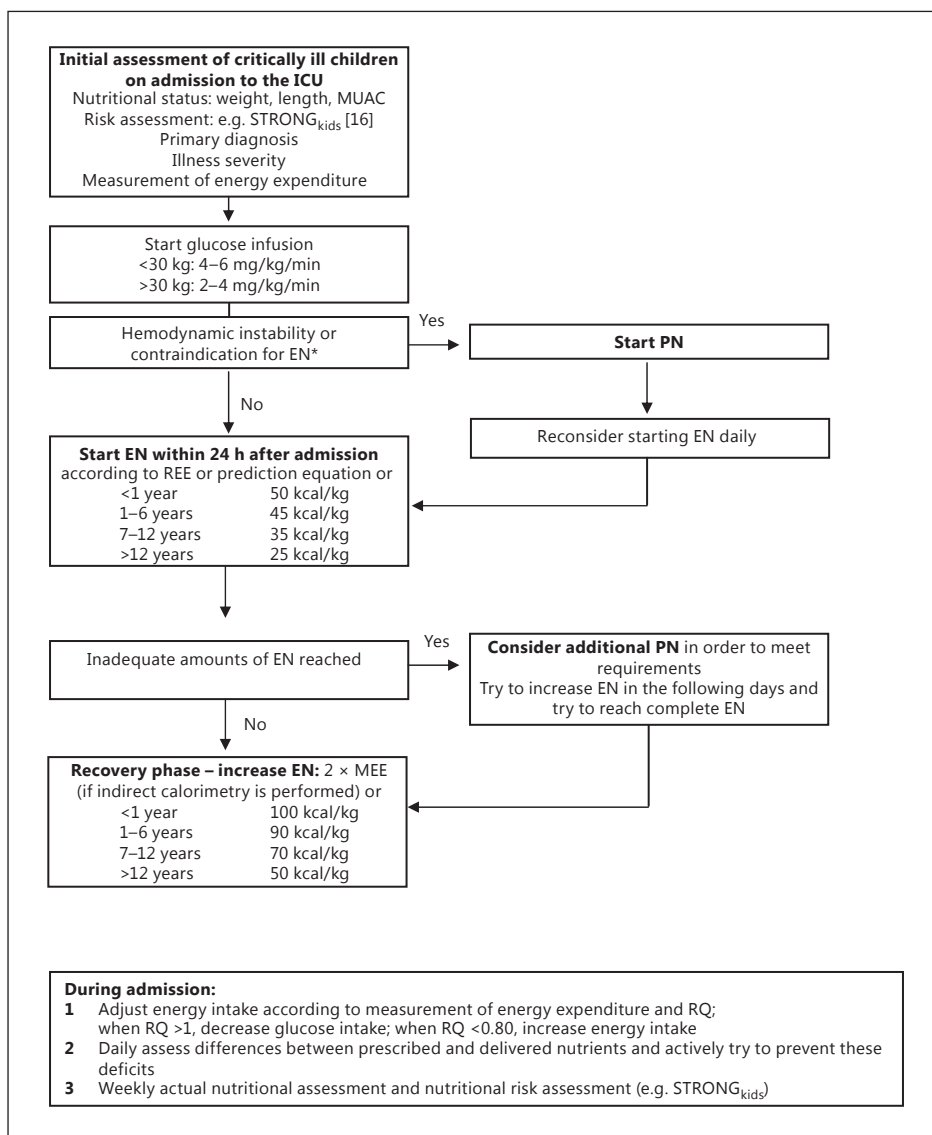
When EN is contraindicated or insufficiently tolerated, PN may be used to supplement or replace EN. Recently, in adults, a large randomized controlled study evaluated whether early PN, to supplement EN if energy goals are not met, was more beneficial than initiating supplemental PN after 1 week [18]. It appeared that late initiation resulted in reduced morbidity as compared with early initiation. No such comparisons have been done on children, but results may differ for children because they have fewer energy reserves and a shorter duration of acute stress response.

### *Type of Formula*

There are no studies available that support a clinical advantage of oligomeric formulas over polymeric formulas for critically ill children. No evidence is available yet on the use of immune-modulating formulas, e.g. formulas enriched with glutamine, arginine or nucleotides, in the critically ill child. This can be considered with burn injury and trauma patients.

### *Compliance*

It is important to realize that large discrepancies may arise between prescribed and deliv-



**Fig. 1.** Nutritional strategy in pediatric intensive care patients. MUAC = Mid-upper-arm circumference; MEE = measured energy expenditure; RQ = respiratory quotient. \* Contraindications for EN: serious gastrointestinal difficulties; congenital anomalies of the gastrointestinal tract; surgery to the gastrointestinal system; short bowel disease; hemodynamic instability; asphyxia.

ered, or prescribed and required, nutrients due to inadequate delivery or poor compliance [19]. The main reasons for inadequate delivery are interruptions to EN due to gastrointestinal dysfunction (e.g. vomiting, nausea, retention and

diarrhea) or fasting in anticipation of diagnostic or surgical procedures, delayed EN initiation, fluid restriction, patients on vasoactive drugs, and general reluctance to address nutrition delivery.



### Follow-Up of Nutritional Support

Once nutritional support is started, its adequacy may be assessed by parameters of nutritional status such as anthropometric measurements, indirect calorimetry and the inflammatory condition (C-reactive protein) of the patient. The minimum standard for nutritional assessment should include measurements of weight, mid-upper-arm circumference and possibly length, and indirect calorimetry. Biochemical markers such as prealbumin (short-term) or albumin (long-term) can be used to assess nutrition adequacy, but they are not specific. An overall practical nutritional guideline is shown in figure 1.

### Conclusions

- Critically ill children are in a catabolic state, characterized by 3 major metabolic changes: (1) increased protein turnover with enhanced hepatic protein synthesis and muscle protein

breakdown with negative protein balance; (2) increased lipolysis, and (3) insulin resistance causing hyperglycemia

- Nutritional support is an essential aspect of clinical management of the critically ill child and should be integrated into daily care
- EN is the preferred route in patients with a functional gastrointestinal tract and can be initiated within 24 h after admission in the majority of the children
- The main advantages of EN over PN include preservation of gastrointestinal function, reduced costs, manageability and safety
- The use of appropriate clinical feeding protocols that incorporate guidelines for nutritional assessment, early initiation of EN with protocolized regular advancement, monitoring energy balance with the use of indirect calorimetry, defining intolerance and minimizing interruptions to EN are desirable and can help to overcome the barriers to achieving adequate EN in critically ill children

### References

- 1 Pollack M, Ruttimann U, Wiley J: Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. *JPEN J Parenter Enteral Nutr* 1985;9:309–313.
- 2 Hulst J, Joosten K, Zimmermann L, Hop W, van Buuren S, Büller H, et al: Malnutrition in critically ill children: from admission to 6 months after discharge. *Clin Nutr* 2004;23:223–232.
- 3 Klein GL, Herndon DN: Burns. *Pediatr Rev* 2004;25:411–417.
- 4 Briassoulis G, Zavras N, Hatzis T: Malnutrition, nutritional indices, and early enteral feeding in critically ill children. *Nutrition* 2001;17:548–557.
- 5 Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V: Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. *Pediatr Crit Care Med* 2004;5:329–336.
- 6 Mehta NM, Bechara LJ, Cahill N, Wang M, Day A, Duggan CP, et al: Nutritional practices and their relationship to clinical outcomes in critically ill children: an international multicenter cohort study. *Crit Care Med* 2012;40:2204–2211.
- 7 Mehta NM, Bechara LJ, Dolan M, Ariagno K, Jiang H, Duggan C: Energy imbalance and the risk of overfeeding in critically ill children. *Pediatr Crit Care Med* 2011;12:398–405.
- 8 Jeschke MG, Gauglitz GG, Finnerty CC, Kraft R, Mlcak RP, Herndon DN: Survivors versus nonsurvivors postburn: differences in inflammatory and hypermetabolic trajectories. *Ann Surg* 2013, Epub ahead of print.
- 9 Schofield W: Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 1985; 39(suppl 1):5–41.
- 10 Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R; Parenteral Nutrition Guidelines Working Group; et al: 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005; 41(suppl 2):S1–S87.
- 11 Preissig CM, Rigby MR: Hyperglycaemia results from beta-cell dysfunction in critically ill children with respiratory and cardiovascular failure: a prospective observational study. *Crit Care* 2009; 13:R27.
- 12 Verbruggen SC, Joosten KF, Castillo L, van Goudoever JB: Insulin therapy in the pediatric intensive care unit. *Clin Nutr* 2007;26:677–690.

- 13 Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, et al: Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 2009;373:547–556.
- 14 Suman OE, Mlcak RP, Chinkes DL, Herndon DN: Resting energy expenditure in severely burned children: analysis of agreement between indirect calorimetry and prediction equations using the Bland-Altman method. *Burns* 2006; 32:335–342.
- 15 Rousseau AF, Losser MR, Ichai C, Berger MM: ESPEN endorsed recommendations: nutritional therapy in major burns. *Clin Nutr* 2013;32:497–502.
- 16 Hulst JM, Zwart H, Hop WC, Joosten KF: Dutch national survey to test the STRONG<sub>kids</sub> nutritional risk screening tool in hospitalized children. *Clin Nutr* 2010;29:106–111.
- 17 Petros S, Engelmann L: Enteral nutrition delivery and energy expenditure in medical intensive care patients. *Clin Nutr* 2006;25:51–59.
- 18 Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al: Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011;365:506–517.
- 19 Mehta NM, McAleer D, Hamilton S, Naples E, Leavitt K, Mitchell P, et al: Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. *JPEN J Parenter Enteral Nutr* 2010;34:38–45.

## 4.1 The WHO Child Growth Standards

Mercedes de Onis

### Key Words

Growth standards · Growth references · Nutritional status · Anthropometry · Nutritional assessment

### Key Messages

- Growth assessment is a key screening tool for assessing child health and nutritional wellbeing
- Anthropometry is the most universally applicable, noninvasive method of assessing the growth status of children
- Interpretation of the growth trajectory is highly dependent on the growth charts used
- The WHO Child Growth Standards, based on the physiological growth of healthy breastfed infants, are the growth charts recommended by the WHO for universal application
- Anthropometric measurements need to be accurate; adequate equipment and the use of standardized techniques are essential for reducing measurement error and minimizing bias

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### Introduction

Assessing childhood growth remains a mainstay of pediatric care in all settings, from the most advanced healthcare centers to those faced with severe resource constraints. If adequate growth is achieved, the probability is high that children will

be healthy and well-nourished. The documentation of abnormal growth, on the other hand, signals that something is not going well and flags the need for careful diagnostic follow-up and action. The value of growth assessment is thus its principal utility as a key screening tool in order to assess children's general wellbeing, to identify faltering and excessive growth, to evaluate maternal lactation performance and infant feeding practices, and to monitor children with medical conditions known to adversely affect growth, such as renal and cardiac conditions.

Growth assessment is best done by the appropriate use and interpretation of anthropometric indexes [1]. Anthropometry is the single most universally applicable, inexpensive and noninvasive method available for assessing the proportions, size and composition of the human body. The successful assessment of growth using anthropometry is founded on (a) the selection of an appropriate anthropometric indicator, (b) the accuracy and reliability of the anthropometric measures taken, and (c) the proper interpretation of the values by selecting suitable growth charts and cutoffs to assess risk or classify children according to variable degrees of undernutrition and overweight/obesity.

The WHO holds copyright of the WHO Child Growth Standards.

The growth charts presented in this Annex are a subset of the WHO Child Growth Standards [2, 3], which are based on an international sample of healthy breastfed infants and young children [4].

### **Construction of the WHO Child Growth Standards**

The origin of the WHO Child Growth Standards dates back to the early 1990s, when the WHO conducted a comprehensive review of anthropometric references. This review showed that the growth pattern of healthy breastfed infants deviated significantly from the National Center for Health Statistics/WHO international reference [5]. In particular, the reference was inadequate for assessing the growth pattern of healthy breastfed infants. The expert group recommended the development of new standards, adopting a novel approach that would describe how children should grow when free of disease and when their care follows healthy practices such as breastfeeding and nonsmoking [5]. This approach would permit the development of a standard as opposed to a reference merely describing how children grew in a particular place and time. Although standards and references both serve as a basis for comparison, each permits a different interpretation. Since a standard defines how children should grow, deviations from the pattern it describes are evidence of abnormal growth. A reference, on the other hand, does not provide as sound a basis for such value judgments, although, in practice, references often are mistakenly used as standards.

Following a resolution from the World Health Assembly in 1994 endorsing these recommendations, the WHO Multicentre Growth Reference Study (MGRS) [4] was launched in 1997 to collect primary growth data that would allow the construction of new growth charts consistent with 'best' health practices.

The goal of the MGRS was to describe the growth of healthy children. The MGRS was a population-based study conducted in 6 countries from diverse geographical regions: Brazil, Ghana, India, Norway, Oman and the USA [4]. The study combined a longitudinal follow-up from birth to 24 months with a cross-sectional component of children aged 18–71 months. In the longitudinal component, mothers and newborns were enrolled at birth and visited at home a total of 21 times at weeks 1, 2, 4 and 6, monthly from 2–12 months, and bimonthly in the second year.

The study populations lived in socioeconomic conditions favorable to growth. The individual inclusion criteria were: no known health or environmental constraints on growth; mothers willing to follow MGRS feeding recommendations (i.e. exclusive or predominant breastfeeding for at least 4 months, introduction of complementary foods by 6 months of age, and continued breastfeeding to at least 12 months of age); no maternal smoking before and after delivery; single term birth; and absence of significant morbidity. Rigorously standardized methods of data collection and procedures for data management across sites yielded high-quality data [2, 3].

The length of children was strikingly similar among the 6 sites, with only about 3% of variability in length being due to intersite differences compared with 70% for individuals within sites [6]. The striking similarity in growth during early childhood across human populations means either a recent common origin, as some suggest [7], or a strong selective advantage associated with the current pattern of growth and development across human environments. The data from all sites were pooled to construct the standards, following state-of-the-art statistical methodologies [2].

This Annex presents growth charts for weight-for-age, length/height-for-age, weight-for-length/height, BMI-for-age and head circumference-for-age, in percentile values, for boys and girls aged 0–60 months. The full set



of tables and charts is presented on the WHO website ([www.who.int/childgrowth/en](http://www.who.int/childgrowth/en)), together with tools such as software and training materials that facilitate their clinical application. The disjunction observed at 24 months in the length-/height-based charts represents the change from measuring recumbent length to standing height. Standards for other anthropometric variables (i.e. mid-upper-arm circumference, and triceps and subscapular skinfolds) are also available on the website.

### **Implications of Adopting the WHO Child Growth Standards**

The scrutiny that the WHO Standards have undergone is without precedent in the history of developing and applying growth assessment tools. Governments set up committees to scrutinize the new standards before deciding to adopt them, and professional groups conducted thorough examinations of the standards. The detailed evaluation allowed assessing the impact of the new standards and documenting their robustness and benefits for child health programs. Since their release in 2006, the WHO Growth Standards have been widely implemented globally [8]. Reasons for adoption include: (1) providing a more reliable tool for assessing growth that is consistent with the Global Strategy for Infant and Young Child Feeding; (2) protecting and promoting breastfeeding; (3) allowing monitoring of malnutrition's double burden, i.e. stunting and overweight; (4) promoting healthy growth and protecting the right of children to reach their full genetic potential; and (5) harmonizing national growth assessment systems. In adopting the WHO Growth Standards, countries have harmonized best practices in child growth assessment and established the breastfed infant as the norm against which to assess compliance with children's right to achieve their full genetic growth potential.

The detailed examination of the WHO Growth Standards by technical and scientific groups has provided a unique opportunity to validate their robustness and to improve our understanding of their broad benefits:

- The WHO Standards identify more children as severely wasted [9]; besides being more accurate in predicting mortality risk [10–12], use of the WHO Standards results in shorter duration of treatment, higher rates of recovery and fewer deaths, and it reduced loss to follow-up or the need for inpatient care [13]
- The WHO Standards confirm the dissimilar growth patterns of breastfed and formula-fed infants, and provide an improved tool for correctly assessing adequacy of growth in breastfed infants [14–16]; they thereby considerably reduce the risk of unnecessary supplementation or cessation of breastfeeding, which are major sources of morbidity and mortality in poor-hygiene settings
- In addition to confirming the importance of the first 2 years of life as a window of opportunity for promoting growth, the WHO Standards demonstrate that intrauterine retardation in linear growth is more prevalent than previously thought [17], making a strong case for the need for interventions to start early in pregnancy and before
- Another important feature of the WHO Standards is that they demonstrate that undernutrition during the first 6 months of life is a considerably more serious problem than previously detected [16–18], thereby reconciling the rates of undernutrition observed for young infants and the prevalence of low birth weight and early abandonment of exclusive breastfeeding
- The WHO Standards also improve early detection of excess weight gain among infants and young children [19, 20], showing that obesity often begins in early childhood, as should measures to tackle this global 'time bomb'

- Last but not least, the WHO Standards are an important means of ensuring the right of all children to be healthy and to achieve their full growth potential; they provide sound scientific evidence that, on average, young children everywhere experience similar growth patterns when their health and nutritional needs are met. For this reason the WHO Standards can be used to assess compliance with the UN Convention on the Rights of the Child, which recognizes the duties and obligations to children that cannot be met without attention to normal human development

## Conclusions

The WHO Child Growth Standards were derived from children who were raised in environments that minimized constraints on growth such as poor diets and infection. In addition, their mothers followed healthy practices such as breastfeeding their children and not smoking during and after pregnancy. The standards depict normal human growth under optimal environmental conditions

and can be used to assess children everywhere, regardless of ethnicity, socioeconomic status and type of feeding. They also demonstrate that healthy children from around the world who are raised in healthy environments and follow recommended feeding practices have strikingly similar patterns of growth. The International Pediatric Association has officially endorsed the use of the WHO Standards, describing them as ‘an effective tool for detecting both undernutrition and obesity’ [21].

Early recognition of growth problems, such as faltering growth and excessive weight gain relative to linear growth, should become standard clinical practice by:

- routine collection of accurate weight and height measurements to permit monitoring of childhood growth;
- interpretation of anthropometric indices such as height-for-age and BMI-for-age based on the WHO Child Growth Standards, and
- early intervention after changes to growth patterns (e.g. upward or downward crossing of percentiles) have been observed to provide parents and caregivers with appropriate guidance and support.

## References

- 1 Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1995;854:1–452.
- 2 WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva, WHO, 2006.
- 3 WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl* 2006;450:76–85.
- 4 de Onis M, Garza C, Victora CG, et al (eds): WHO Multicentre Growth Reference Study (MGRS): rationale, planning and implementation. *Food Nutr Bull* 2004;25(suppl 1):S3–S84.
- 5 Garza C, de Onis M; WHO Multicentre Growth Reference Study Group: Rationale for developing a new international growth reference. *Food Nutr Bull* 2004; 25(suppl 1):S5–S14.
- 6 WHO Multicentre Growth Reference Study Group: Assessment of differences in linear growth among populations in the WHO Multicentre Growth Reference Study. *Acta Paediatr Suppl* 2006;450:56–65.
- 7 Rosenberg NA, Pritchard JK, Weber JL, et al: Genetic structure of human populations. *Science* 2002;298:2381–2385.
- 8 de Onis M, Onyango A, Borghi E, Siyam A, Blössner M, Lutter CK; WHO Multicentre Growth Reference Study Group: Worldwide implementation of the WHO Child Growth Standards. *Public Health Nutr* 2012;15:1603–1610.
- 9 Dale NM, Grais RF, Minetti A, Miettola J, Barengo NC: Comparison of the new World Health Organization growth standards and the National Center for Health Statistics growth reference regarding mortality of malnourished children treated in a 2006 nutrition program in Niger. *Arch Pediatr Adolesc Med* 2009;163:126–130.

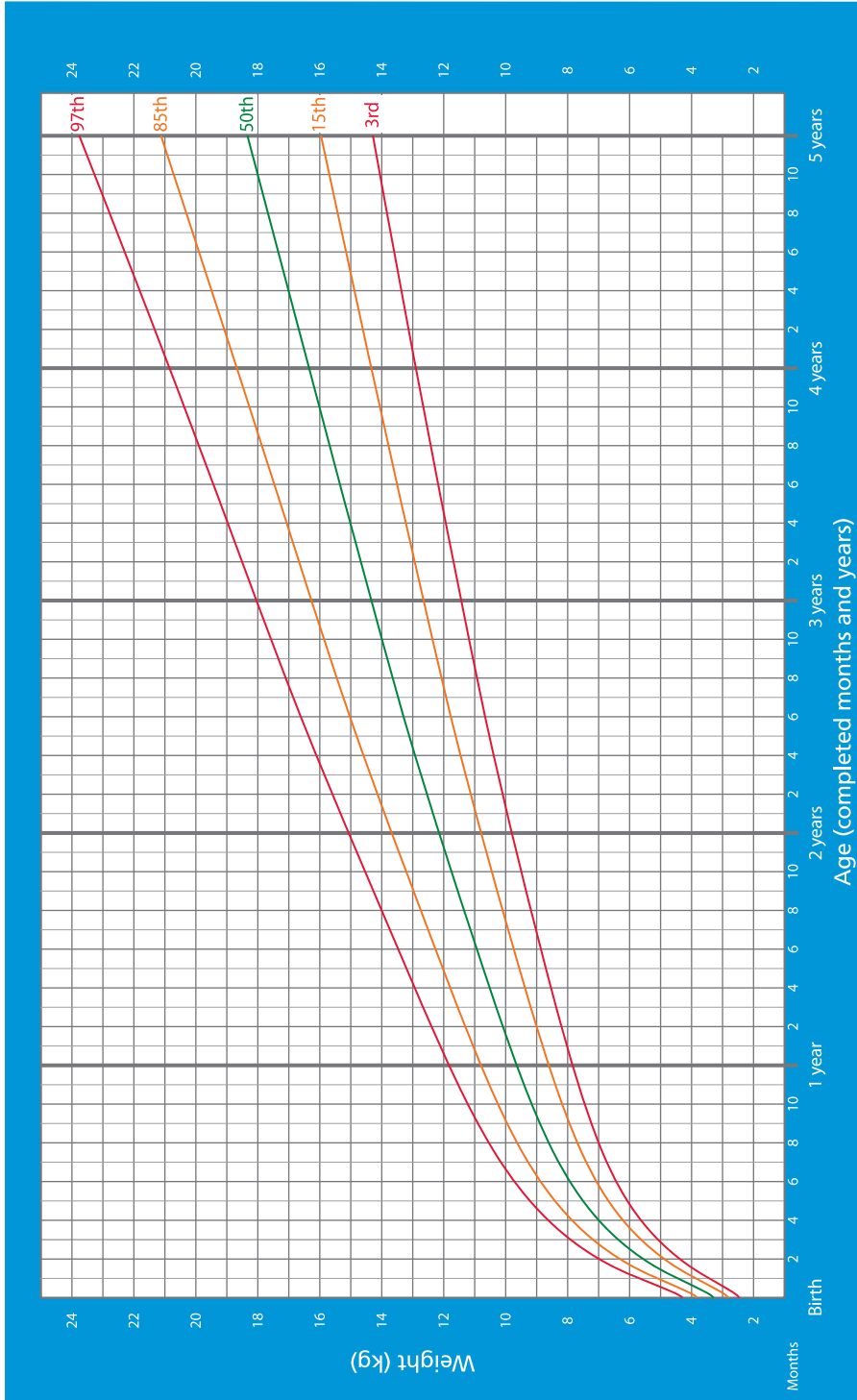




- 10 Lapidus N, Luquero FJ, Gaboulaud V, Shepherd S, Grais RF: Prognostic accuracy of WHO growth standards to predict mortality in a large-scale nutritional program in Niger. *PLoS Med* 2009;6: e1000039.
- 11 Vesel L, Bahl R, Martines J, Penny M, Bhandari N, Kirkwood BR; WHO Immunization-Linked Vitamin A Supplementation Study Group: Use of new World Health Organization child growth standards to assess how infant malnutrition relates to breastfeeding and mortality. *Bull World Health Organ* 2010;88: 39–48.
- 12 O'Neill S, Fitzgerald A, Briend A, van den Broeck J: Child mortality as predicted by nutritional status and recent weight velocity in children under two in rural Africa. *J Nutr* 2012;142:520–525.
- 13 Isanaka S, Villamor E, Shepherd S, Grais RF: Assessing the impact of the introduction of the World Health Organization growth standards and weight-for-height z-score criterion on the response to treatment of severe acute malnutrition in children: secondary data analysis. *Pediatrics* 2009;123:e54–e59.
- 14 Saha KK, Frongillo EA, Alam DS, Arifeen SE, Persson LA, Rasmussen KM: Use of the new World Health Organization child growth standards to describe longitudinal growth of breastfed rural Bangladeshi infants and young children. *Food Nutr Bull* 2009;30:137–144.
- 15 Bois C, Servolin J, Guillermet G: Usage comparé des courbes de l'Organisation mondiale de la santé et des courbes françaises dans le suivi de la croissance pondérale des jeunes nourrissons. *Arch Pediatr* 2010;17:1035–1041.
- 16 de Onis M, Onyango AW, Borghi E, Garza C, Yang H; WHO Multicentre Growth Reference Study Group: Comparison of the WHO Child Growth Standards and the NCHS/WHO international growth reference: implications for child health programmes. *Public Health Nutr* 2006; 9:942–947.
- 17 Victora CG, de Onis M, Hallal PC, Blössner M, Shrimpton R: Worldwide timing of growth faltering: revisiting implications for interventions using the World Health Organization growth standards. *Pediatrics* 2010;125:e473–e480.
- 18 Kerac M, Blencowe H, Grijalva-Eternod C, McGrath M, Shoham J, Cole TJ, Seal A: Prevalence of wasting among under 6-month-old infants in developing countries and implications of new case definitions using WHO growth standards: a secondary data analysis. *Arch Dis Child* 2011;96:1008–1013.
- 19 van Dijk CE, Innis SM: Growth-curve standards and the assessment of early excess weight gain in infancy. *Pediatrics* 2009;123:102–108.
- 20 Maalouf-Manasseh Z, Metallinos-Katsaras E, Dewey KG: Obesity in preschool children is more prevalent and identified at a younger age when WHO growth charts are used compared with CDC charts. *J Nutr* 2011;141:1154–1158.
- 21 International Pediatric Association Endorsement: the new WHO Growth Standards for infants and young children. 2006. [http://www.who.int/childgrowth/Endorsement\\_IPA.pdf](http://www.who.int/childgrowth/Endorsement_IPA.pdf).

# Weight-for-age BOYS

Birth to 5 years (percentiles)



WHO Child Growth Standards



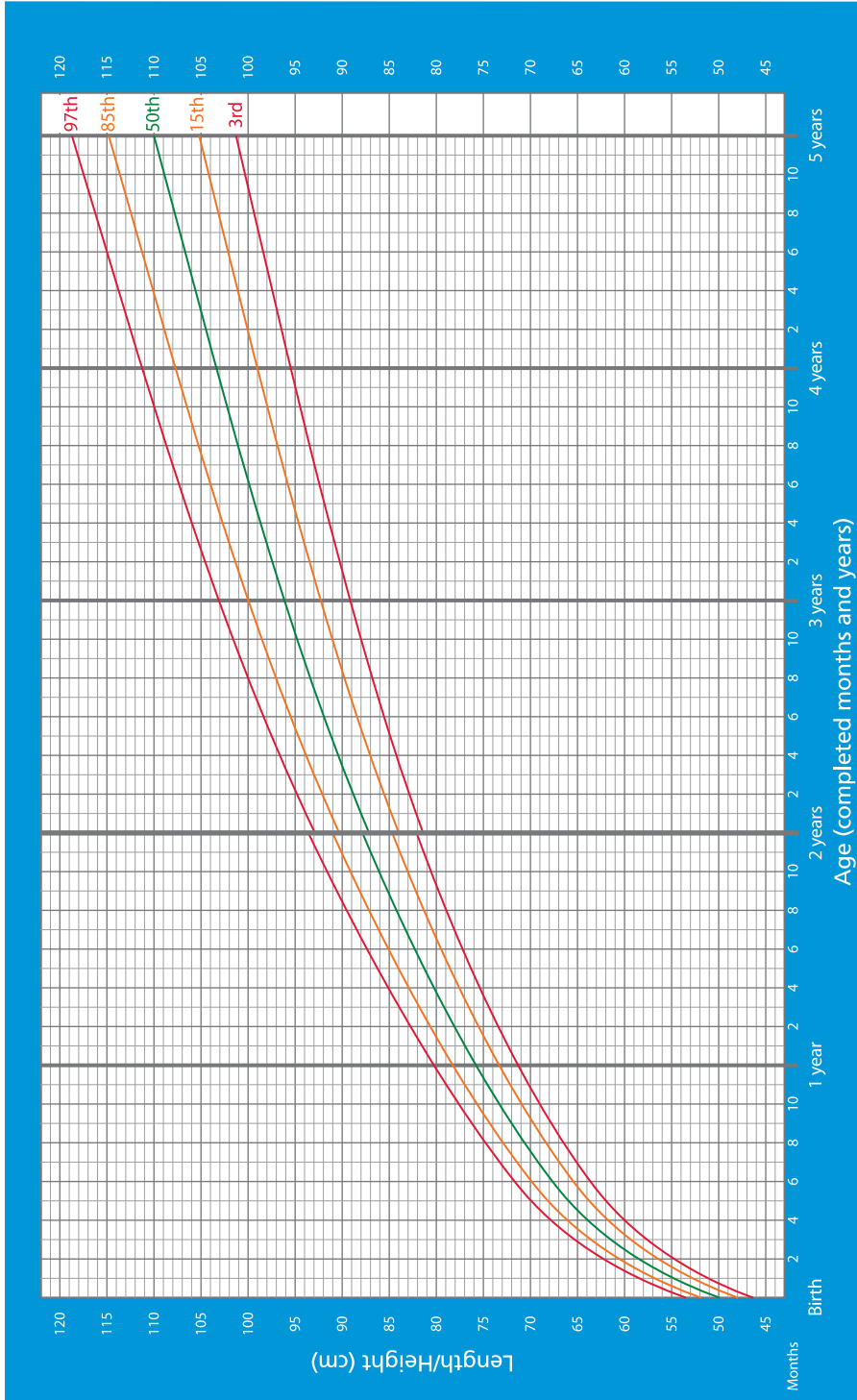
# Weight-for-age GIRLS

Birth to 5 years (percentiles)



# Length/height-for-age BOYS

Birth to 5 years (percentiles)



WHO Child Growth Standards



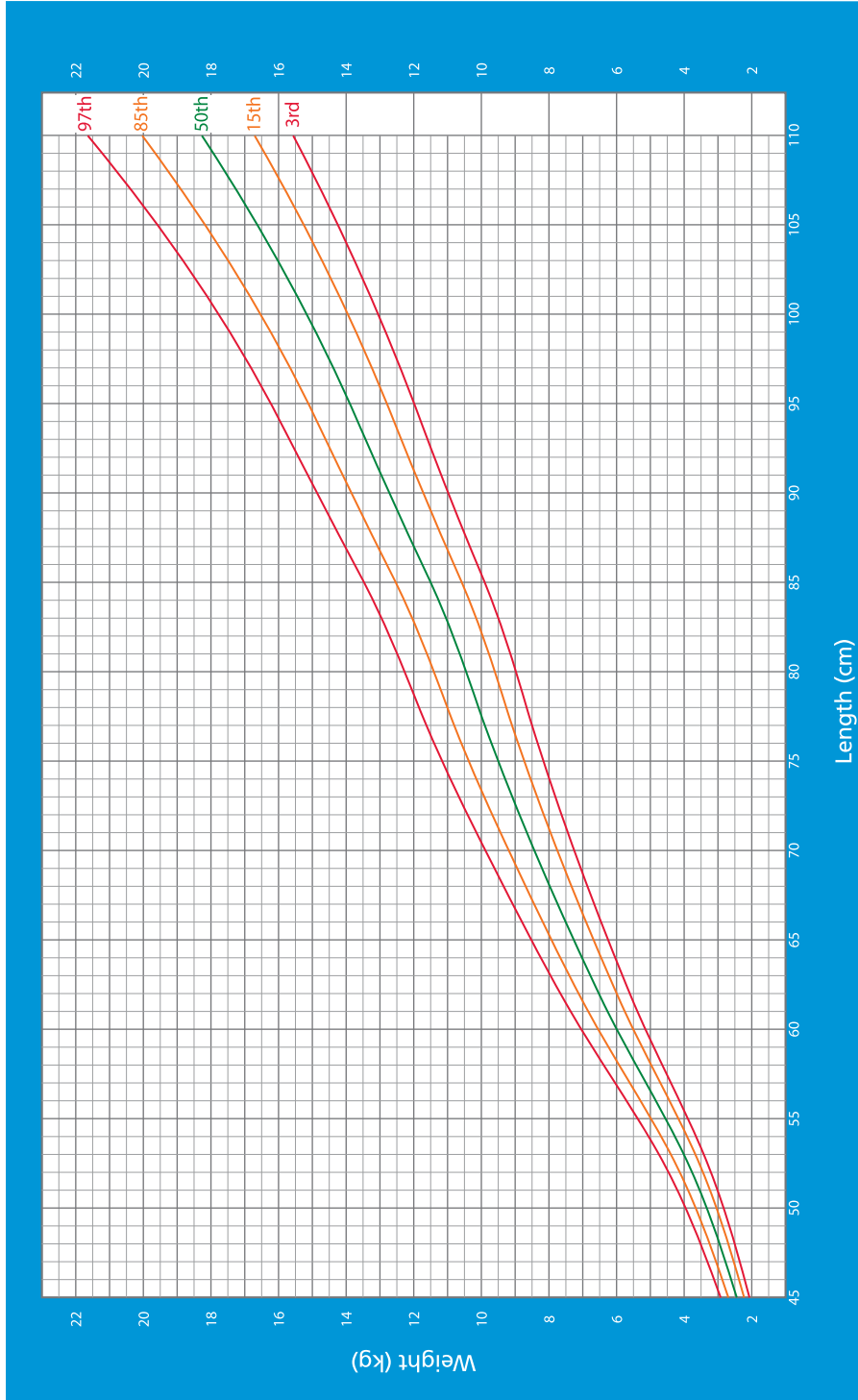
# Length/height-for-age GIRLS

Birth to 5 years (percentiles)



# Weight-for-length BOYS

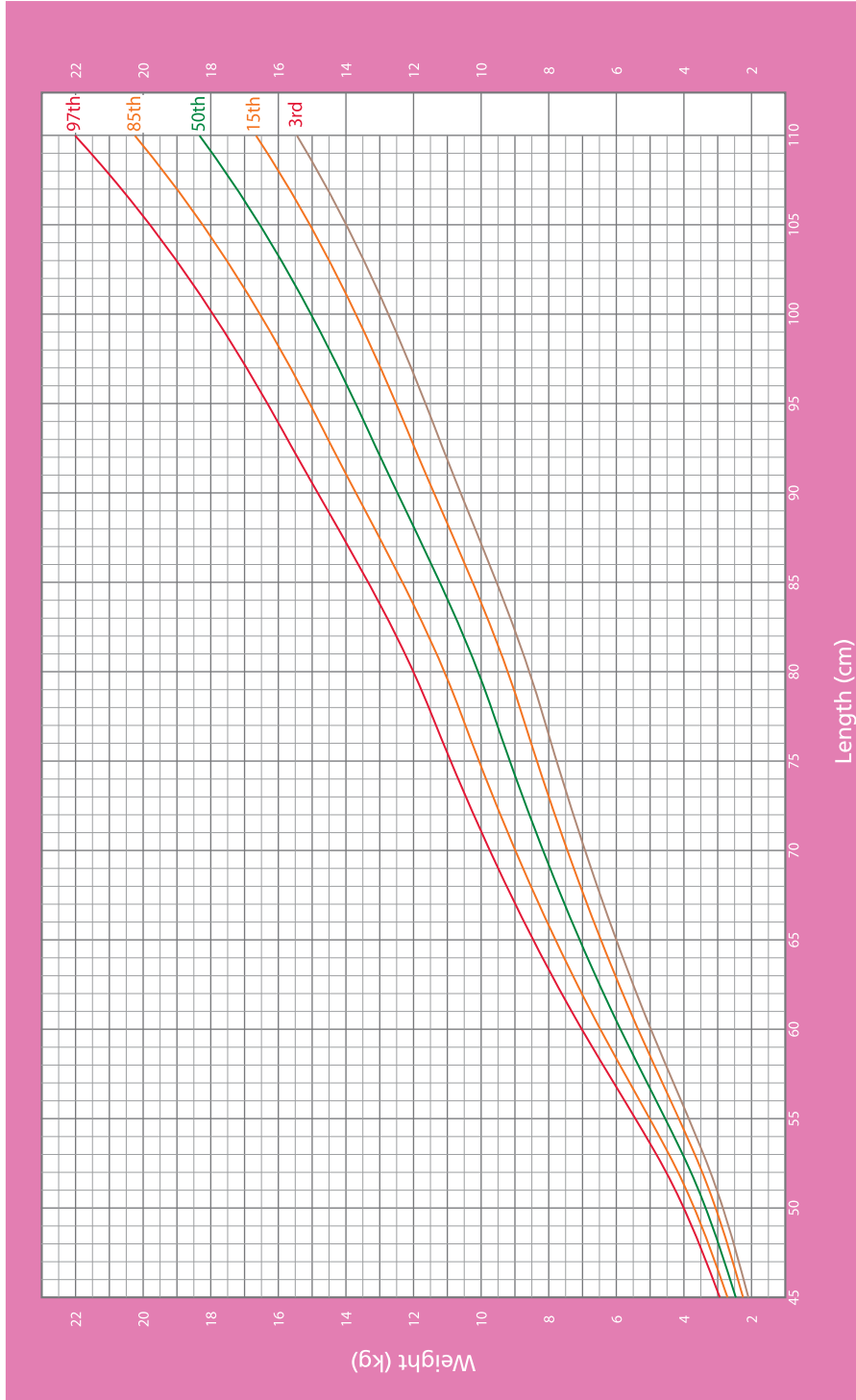
Birth to 2 years (percentiles)



WHO Child Growth Standards

# Weight-for-length GIRLS

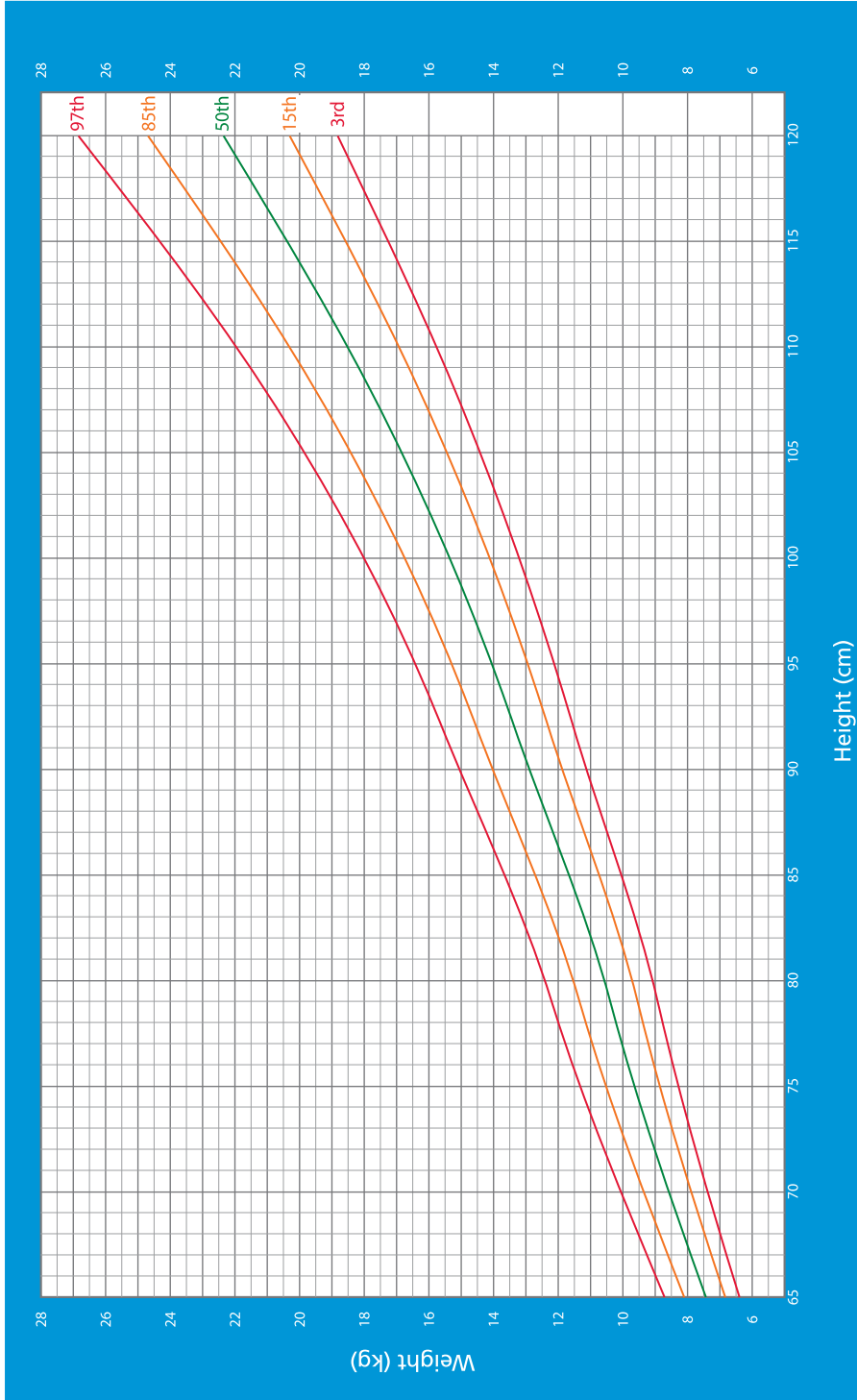
Birth to 2 years (percentiles)



WHO Child Growth Standards

# Weight-for-height BOYS

2 to 5 years (percentiles)

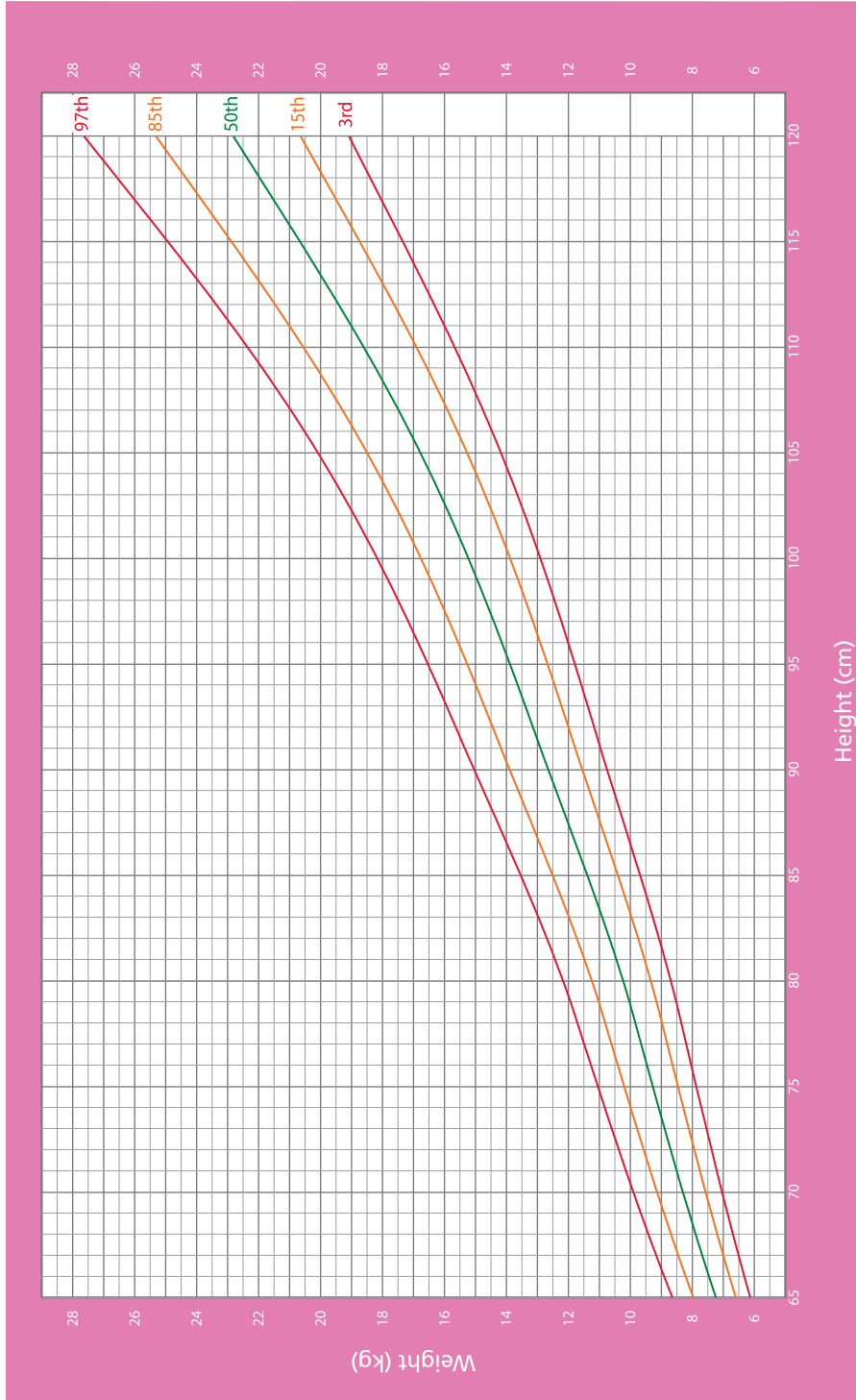


WHO Child Growth Standards



# Weight-for-height GIRLS

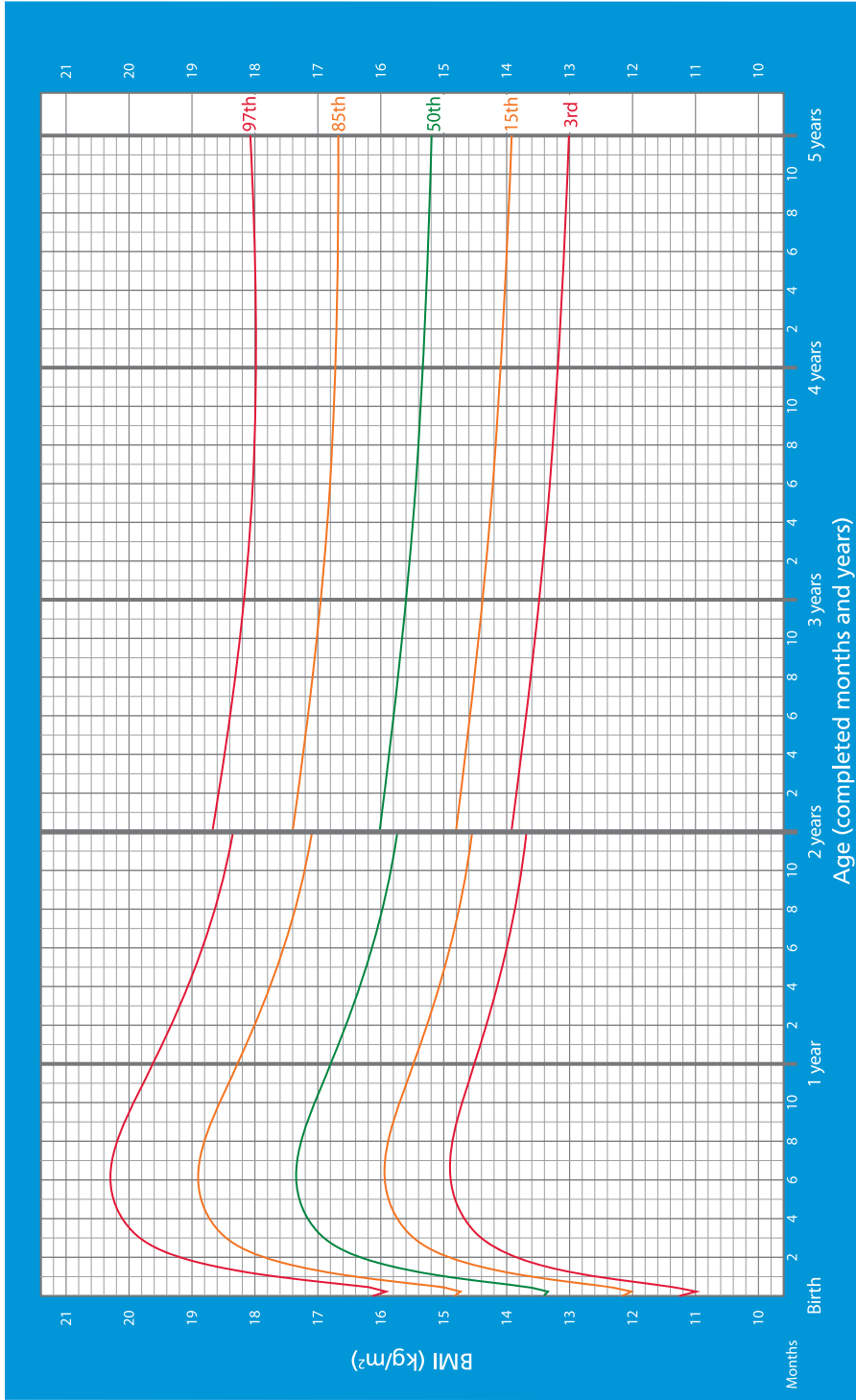
2 to 5 years (percentiles)



WHO Child Growth Standards

# BMI-for-age BOYS

Birth to 5 years (percentiles)

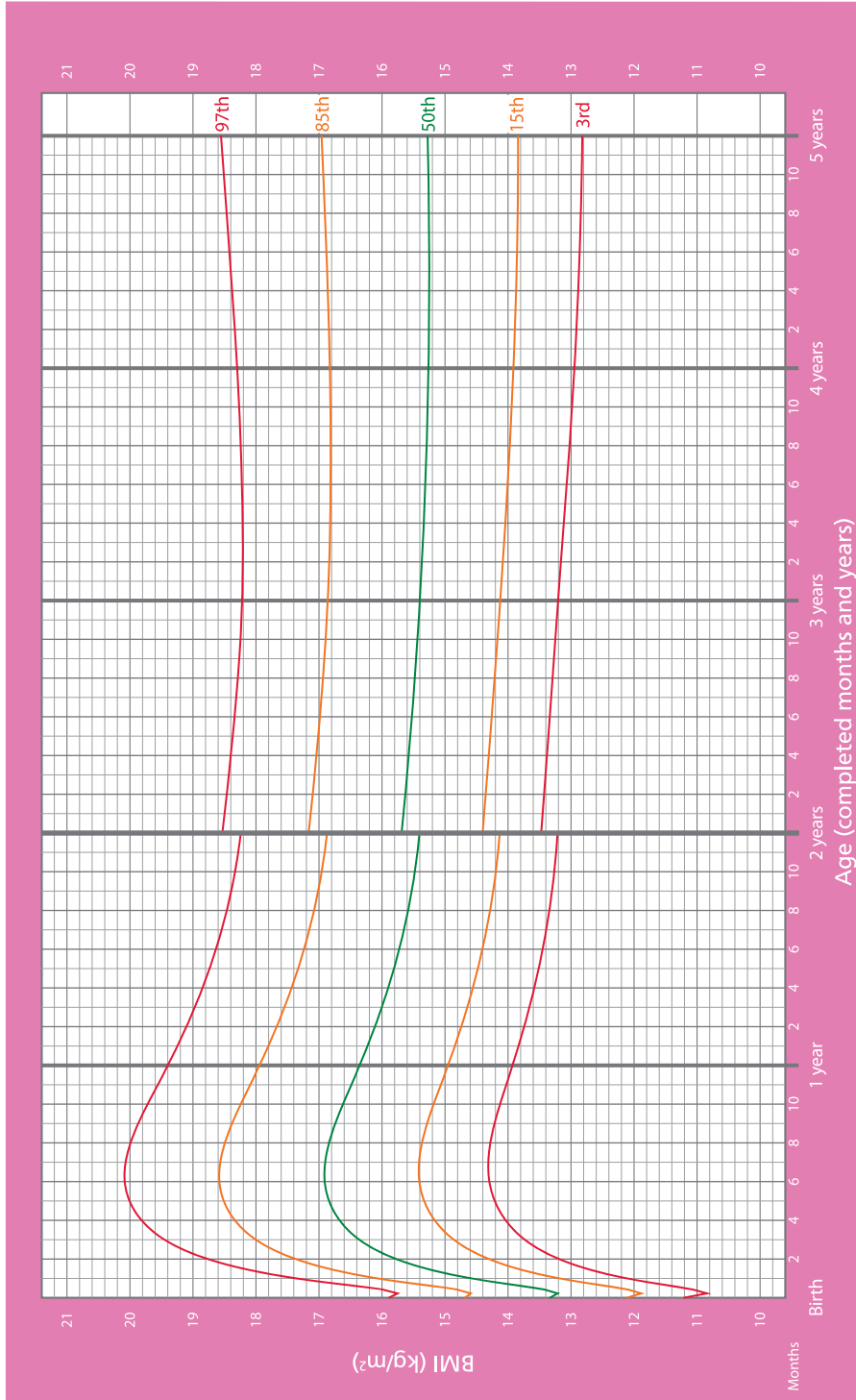


WHO Child Growth Standards



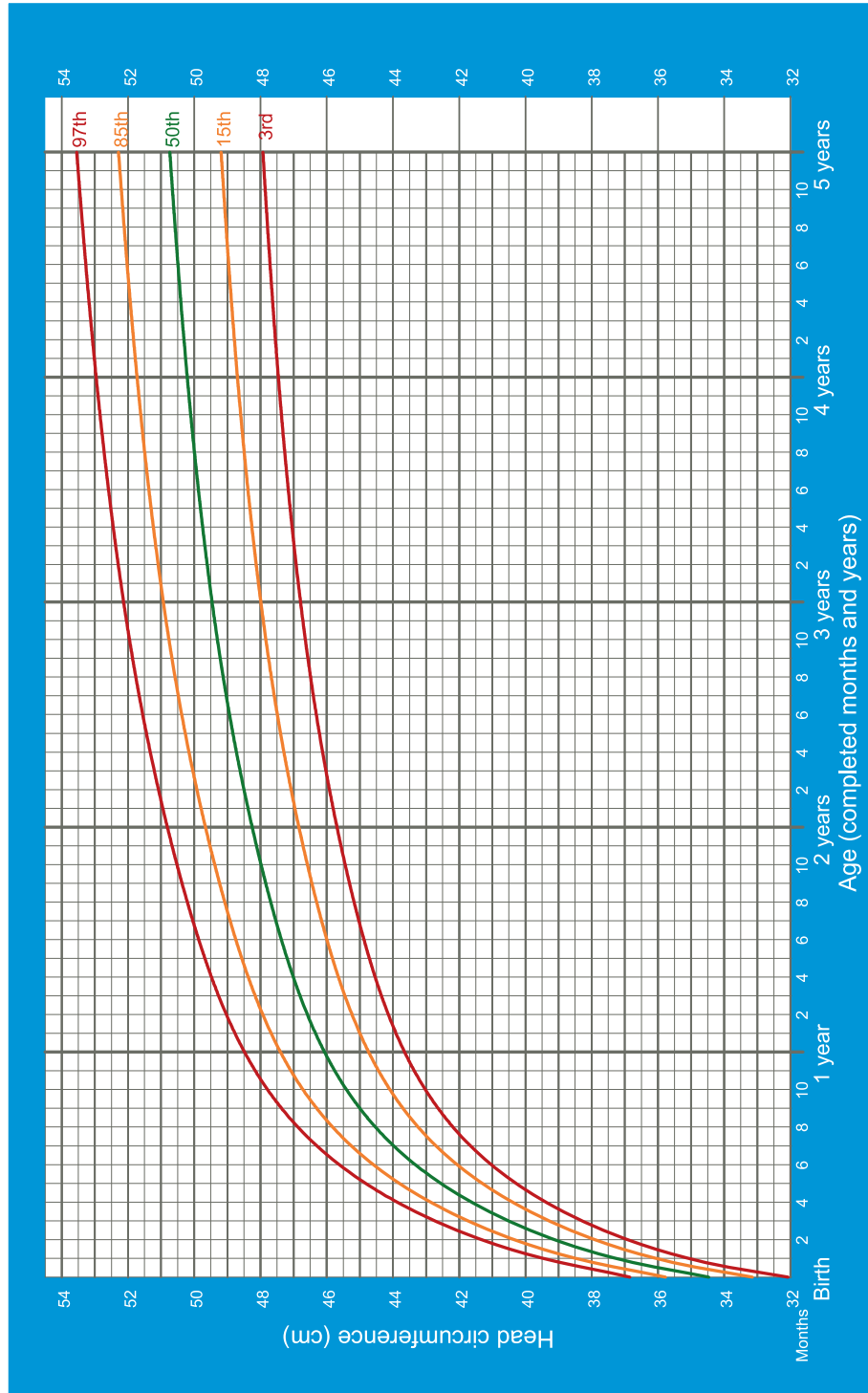
# BMI-for-age GIRLS

Birth to 5 years (percentiles)



# Head circumference-for-age BOYS

Birth to 5 years (percentiles)



WHO Child Growth Standards



# Head circumference-for-age GIRLS



Birth to 5 years (percentiles)



WHO Child Growth Standards

## 4.2 The CDC and Euro Growth Charts

Ekhard E. Ziegler

### Key Words

Growth assessment · Growth references · Anthropometry · Interpretation

### Key Messages

- Growth charts are essential tools for the interpretation of growth measurements in children
- The CDC and Euro Growth charts are growth references that describe the growth of populations of children as they exist at a given time in a given location
- Growth standards (e.g. WHO Child Growth Standards) describe the growth of children who live in favorable circumstances, receive optimal nutrition and show desirable growth characteristics
- Anthropometric measurements need to use proper techniques. Measurements of recumbent length must be interpreted against charts of recumbent length, and measurements of standing height must be interpreted against charts of standing height

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### Introduction

Growth assessment is an integral part of childhood health monitoring. For interpretation, growth measurements must be compared with appropriate norms. Such norms are provided by growth references which describe the growth of

children who are living in a defined geographic area and are deemed healthy. The relative position of a child undergoing assessment in comparison with reference data determines whether the child's growth is judged normal or abnormal. Widely used growth references are the CDC Growth Charts [1] and the Euro Growth Charts [2]. Both were released in 2000. These charts describe the growth of children living in the USA and in Europe, respectively. The WHO Growth Standards [3, 4], on the other hand, describe the growth of children worldwide; for these standards, data were obtained in Norway, the USA, Brazil, Ghana, Oman and India from children living under 'ideal' circumstances with nonsmoking mothers and from infants receiving 'optimal nutrition' (predominantly breast milk for the first 6 months), and thus they illustrate what 'normal growth' is under optimal environmental conditions.

When growth has to be assessed on the basis of a single measurement, its interpretation has to rely solely on the relative position of the measured value on the growth reference chart. The accuracy of growth assessment is greatly improved if two or more measurements are performed at different times. This not only minimizes the impact of inherent measurement errors, it also permits the assessment of time trends and thus strengthens the assessment of a child's growth vis-à-vis the growth reference chart.

## CDC Growth Charts: USA

The CDC charts [1] were created to replace the widely used National Center for Health Statistics/WHO charts of 1974 because of inadequacies identified in the latter. The CDC charts are based on a large number of nationally representative data from several national surveys conducted between 1976 and 1994. The exception are data concerning the first year of life, which, besides being few in number, were obtained mostly from infants representing lower socioeconomic strata. Also data on subjects more than 6 years of age from the survey in 1988–1994 were excluded because of the increased prevalence of high weight. All data were cross-sectional. State-of-the-art smoothing procedures were used to generate percentile curves. Charts on weight-for-age and (recumbent) length-for-age are available for the age period from birth to 3 years. For the age period from 2 to 20 years, charts for weight-for-age, height-for-age and BMI-for-age are available.

## Euro Growth Charts

The Euro Growth Charts [2] were the result of a multinational effort. Data for these charts were gathered from birth to 5 years of age in children who were born between 1990 and 1993 and lived close to 22 measurement sites in 11 European

countries. The data were gathered longitudinally, with 1,746 children being followed to the age of 1 year, and 1,071 to the age of 3 years. The data were analyzed cross-sectionally, using state-of-the-art smoothing techniques.

## Comment

In contradistinction to the WHO Growth Standards [3, 4], the CDC and Euro Growth Charts are growth references. They represent, with minor exceptions, the growth of healthy children living in the respective geographic areas. Use of references for the interpretation of growth measurements thus indicates a child's position in relation to other children living in the same area. Growth standards, on the other hand, already incorporate an element of judgment, and their use provides information on desirable (ideal) child growth derived from predominantly breastfed infants.

The importance of using proper measurement techniques cannot be overemphasized, in particular with regard to measurement of recumbent length. The latter requires two measurers using appropriate equipment and techniques if reproducible measurements are to be obtained. Measurements of length must be interpreted using charts for length, and measurements of height must be interpreted using charts for height.

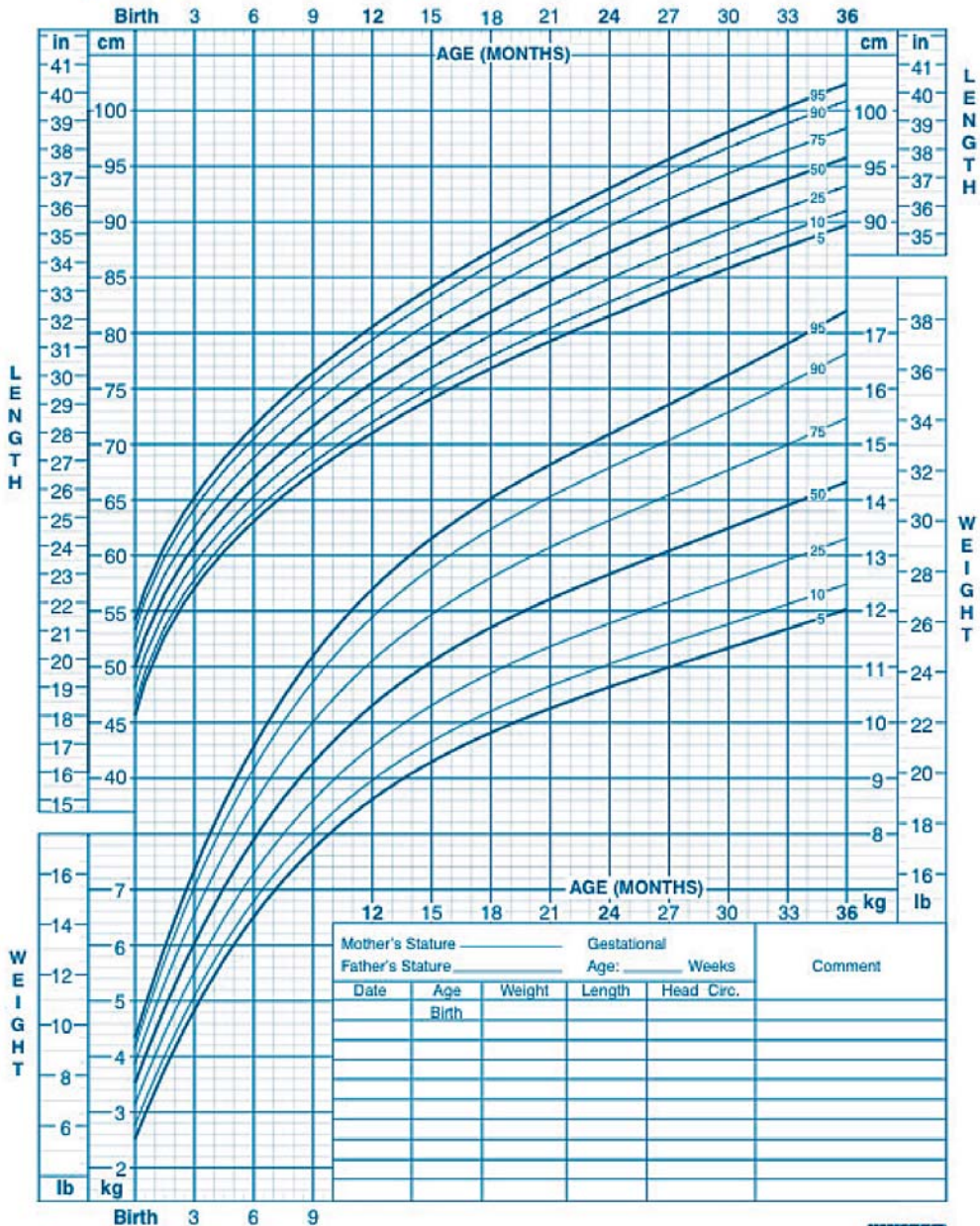
## References

- 1 Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL: 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 11 2002;246: 1–190.
- 2 Haschke F, van't Hof MA (eds): Euro-Growth. *J Ped Gastroenterol Nutr* 2000; 31:suppl 1.
- 3 WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards. Geneva, WHO, 2006. [www.who.int/childgrowth/en/](http://www.who.int/childgrowth/en/).
- 4 WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl* 2006;450: 76–85.

**Birth to 36 months: Boys**  
**Length-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_

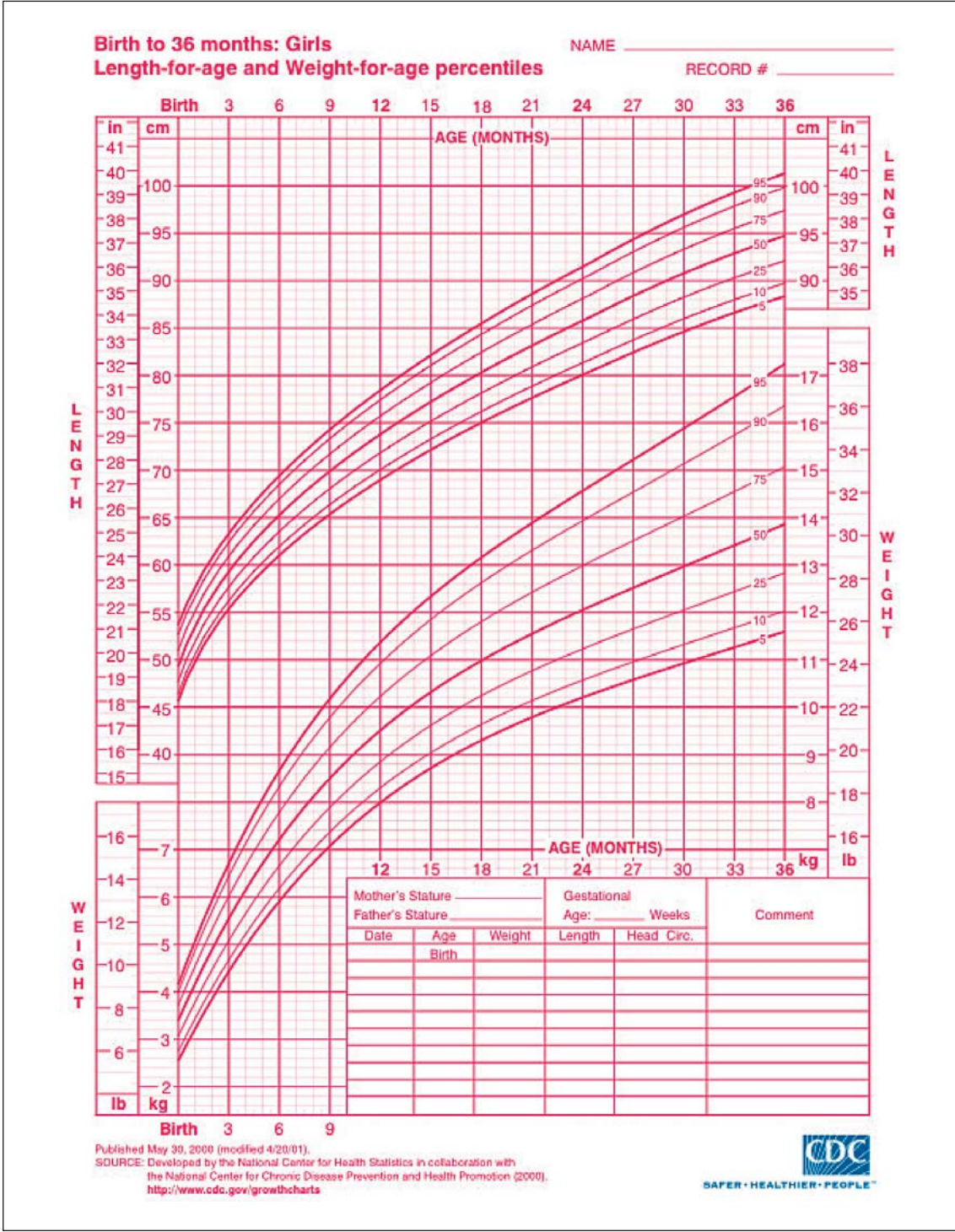


Published May 30, 2000 (modified 4/20/01).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



**Fig. 1.** CDC length-for-age and weight-for-age for boys (birth to 3 years).



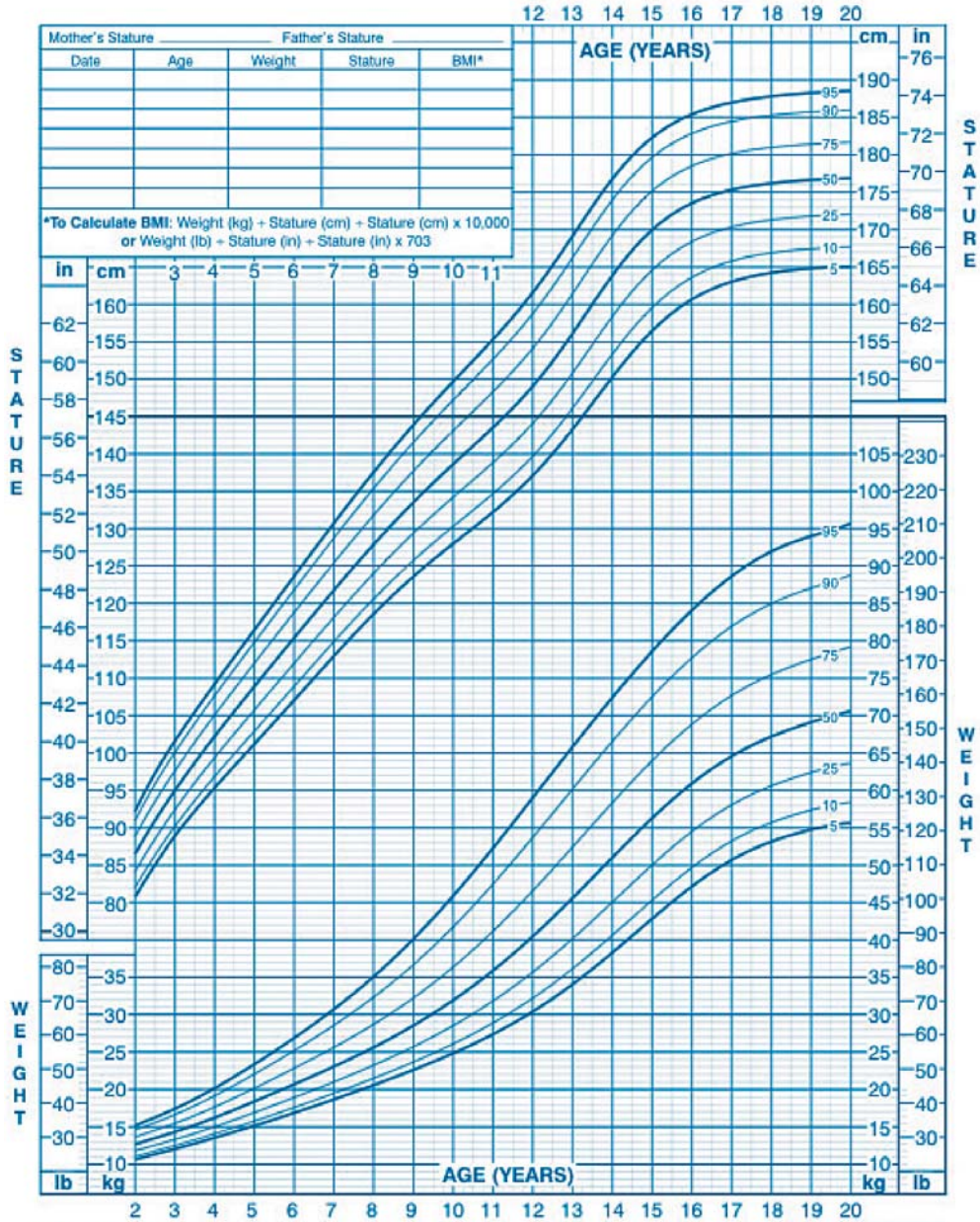


**Fig. 2.** CDC length-for-age and weight-for-age for girls (birth to 3 years).

**2 to 20 years: Boys**  
**Stature-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 11/21/00).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>

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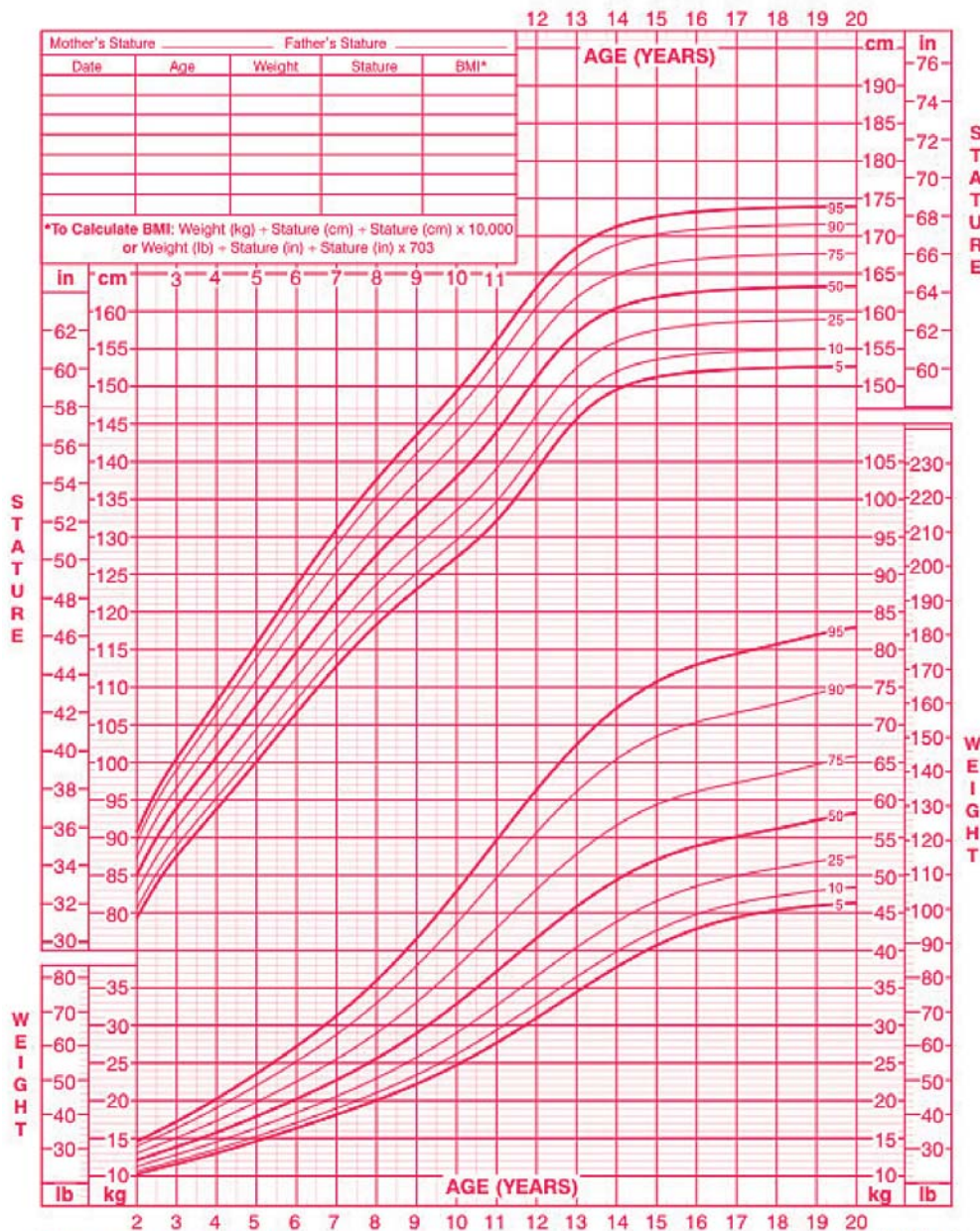


**Fig. 3.** CDC stature-for-age and weight-for-age for boys (2–20 years).

**2 to 20 years: Girls**  
**Stature-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 11/21/00).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>

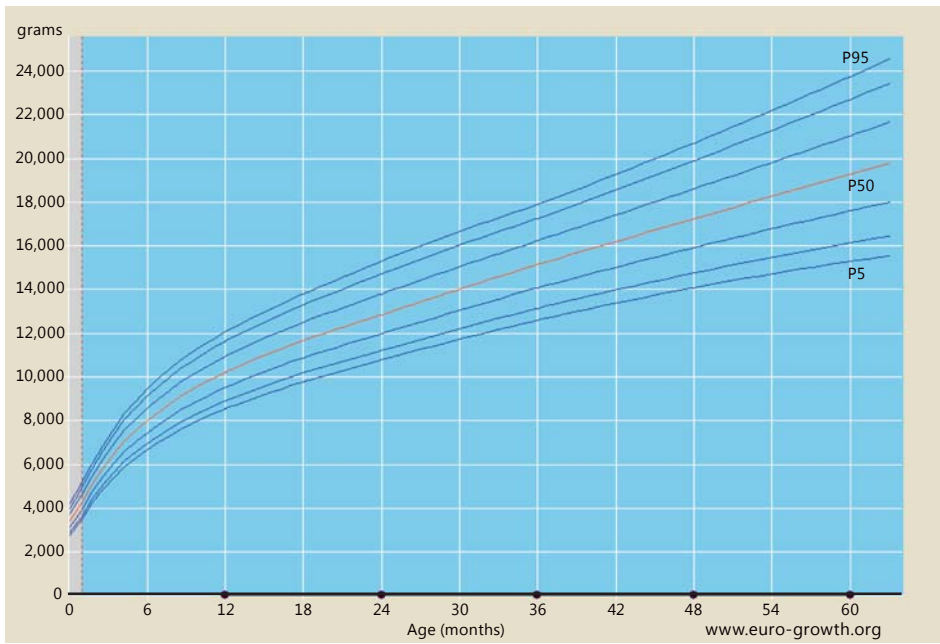


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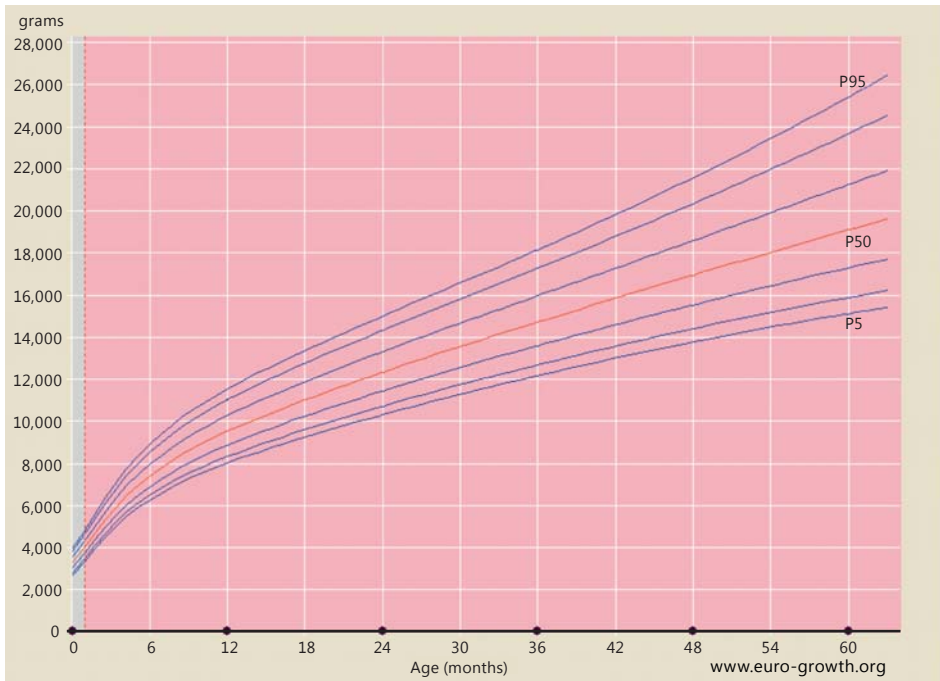
**Fig. 4.** CDC stature-for-age and weight-for-age for girls (2–20 years).





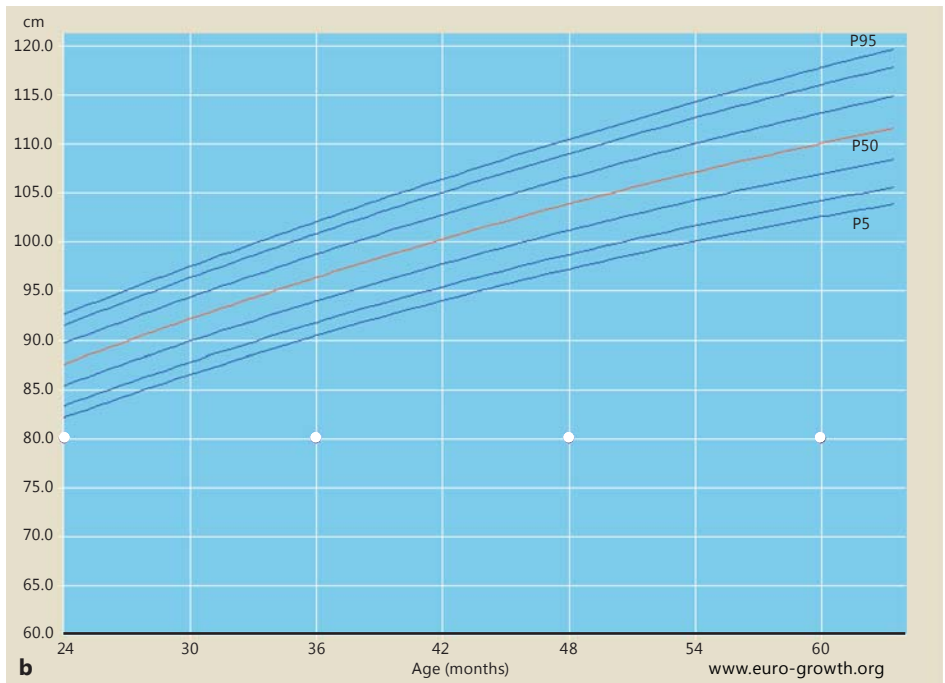
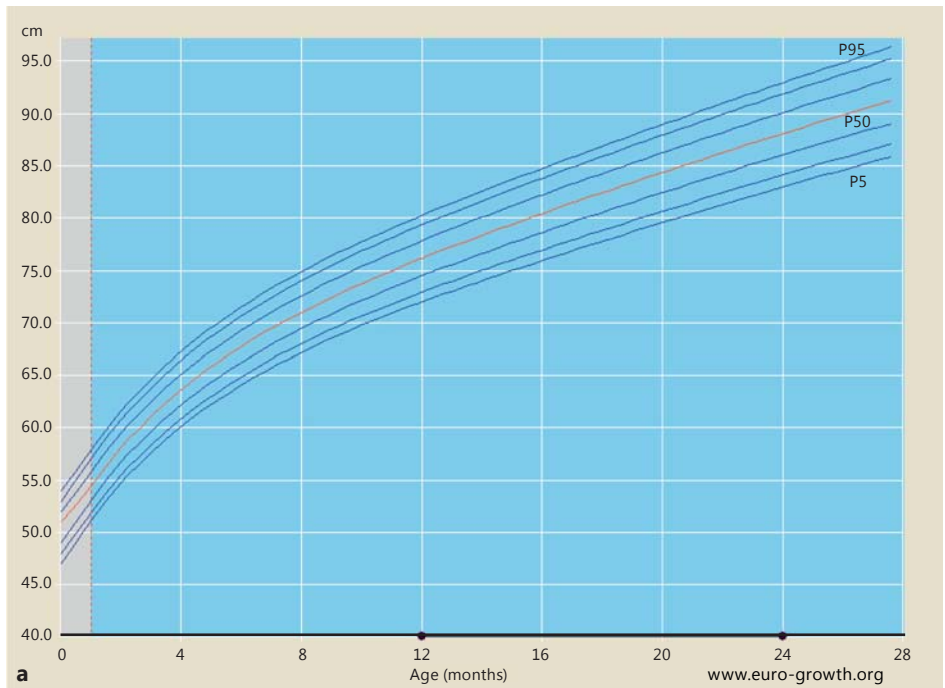


**Fig. 7.** Euro Growth weight-for-age for boys (birth to 5 years).

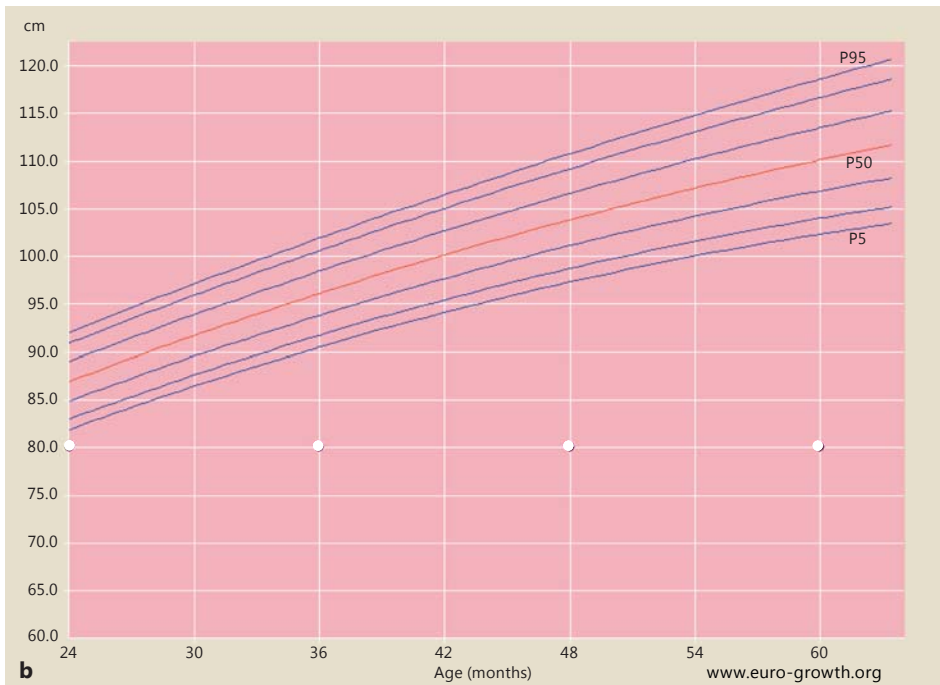
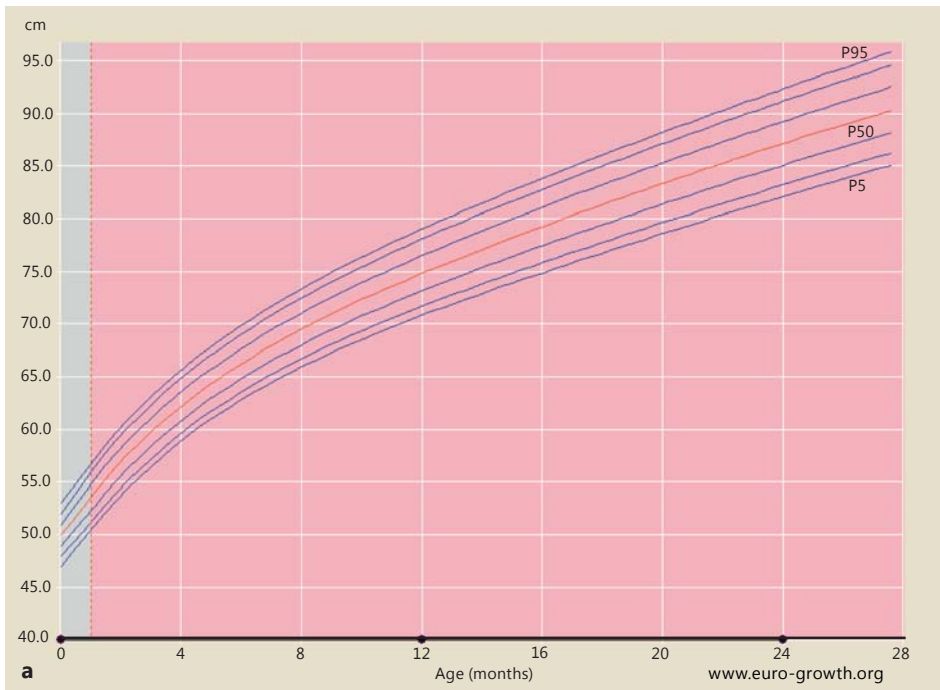


**Fig. 8.** Euro Growth weight-for-age for girls (birth to 5 years).





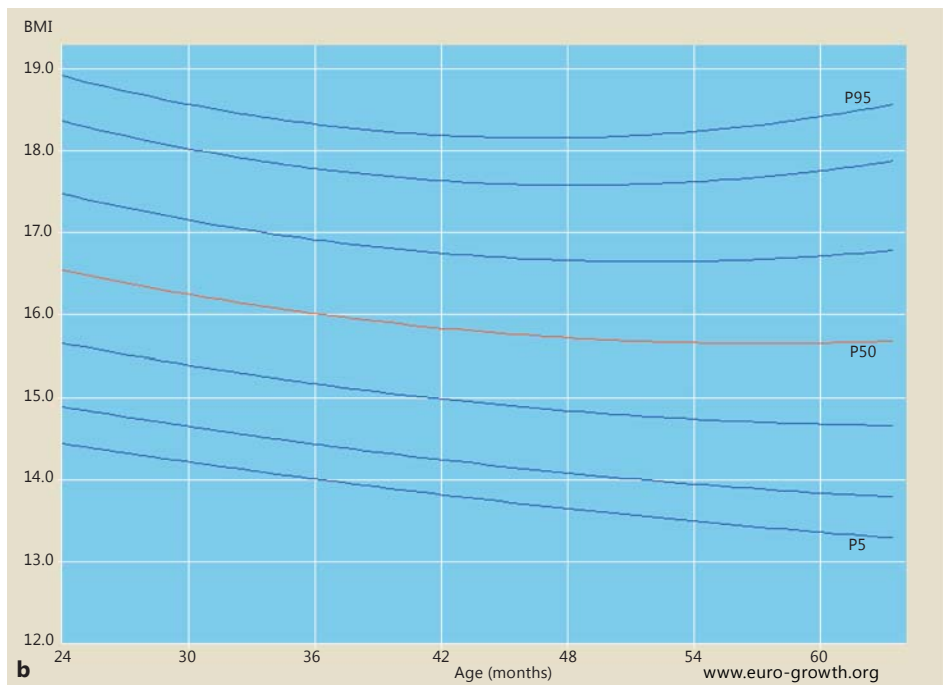
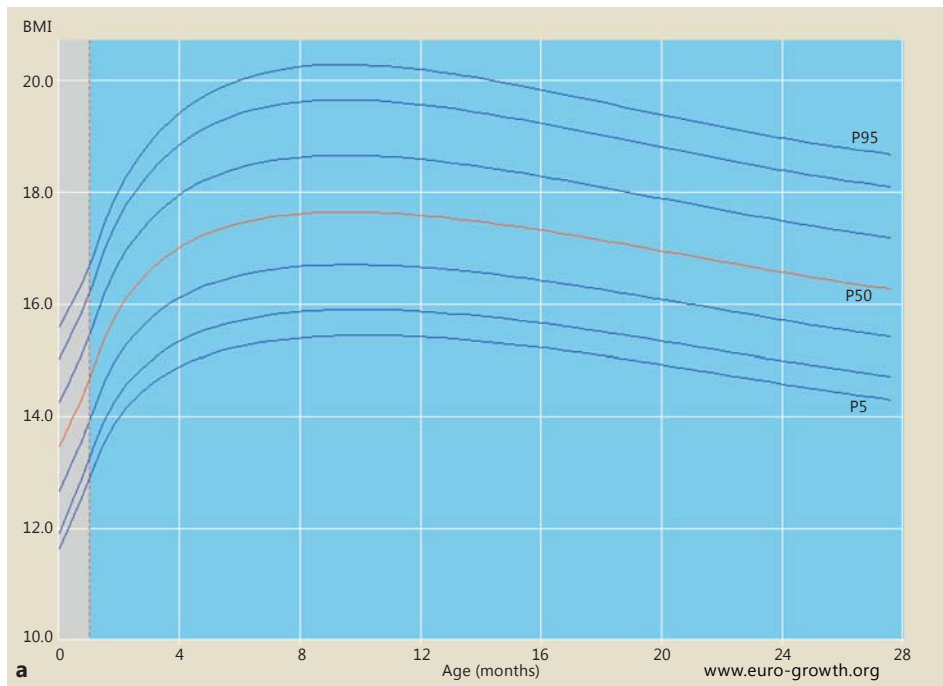
**Fig. 9. a** Euro Growth length-for-age for boys (birth to 2 years). **b** Euro Growth height-for-age for boys (2–5 years).



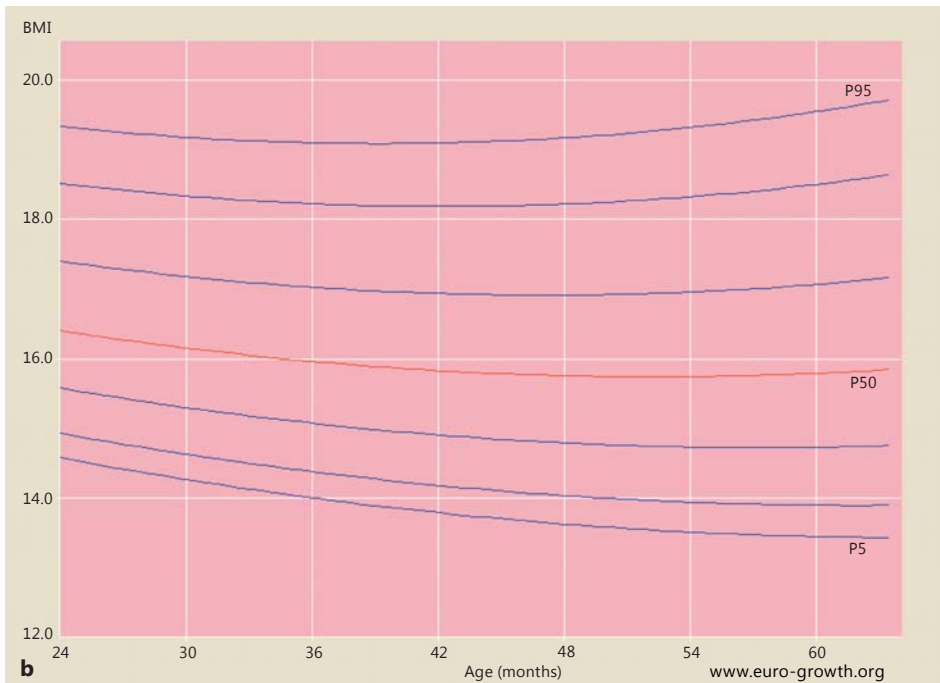
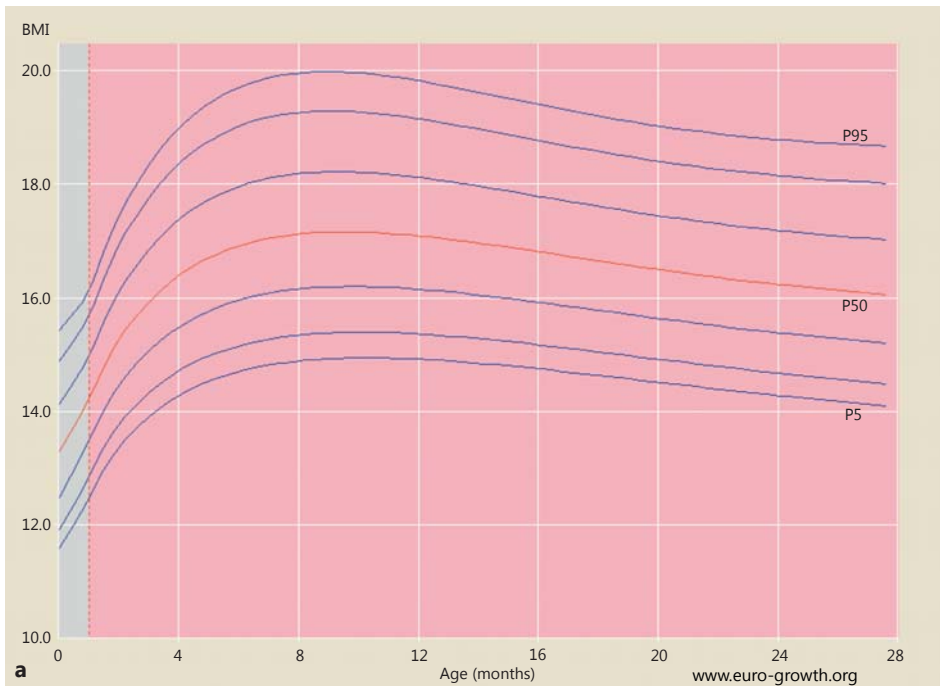
**Fig. 10. a** Euro Growth length-for-age for girls (birth to 2 years). **b** Euro Growth height-for-age for girls (2–5 years).







**Fig. 11. a** Euro Growth BMI for boys (birth to 2 years). **b** Euro Growth BMI for boys (2–5 years).



**Fig. 12. a** Euro Growth BMI for girls (birth to 2 years). **b** Euro Growth BMI for girls (2–5 years).

## 4.3 Reference Nutrient Intakes of Infants, Children and Adolescents

Berthold Koletzko • Katharina Dokoupil

Tables with reference nutrient intakes are presented as published by (in alphabetical order): Australia and New Zealand; Germany, Austria and Switzerland; the Nordic nutrition recommendations; the UK; the USA and Canada; the WHO with the Food and Agriculture Organization (FAO) and the United Nations University (UNU).

**Tables 1 and 2.** Australia and New Zealand nutrient reference values for diary food energy (table 1) and nutrients (table 2) in healthy infants, children and adolescents (modified from nutrient reference values including recommended dietary intakes from Australia and New Zealand 2005, 2006)

**Table 1.** Energy (male/female)

Age, months	Energy, kJ/day	Age, years	Energy, MJ/day
1	2,000/1,800	3	3.4/3.2
2	2,400/2,100	4	3.6/3.4
3	2,400/2,200	5	3.8/3.6
4	2,400/2,200	6	4.1/3.8
5	2,500/2,300	7	4.3/4.0
6	2,700/2,500	8	4.5/4.2
7	2,800/2,500	9	4.8/4.5
8	3,000/2,700	10	5.1/4.7
9	3,100/2,800	11	5.4/4.9
10	3,300/3,000	12	5.8/5.2
11	3,400/3,100	13	6.2/5.5
12	3,500/3,200	14	6.6/5.7
15	3,800/3,500	15	7.0/5.8
18	4,000/3,800	16	7.3/5.9
21	4,200/4,000	17	7.6/5.9
24	4,400/4,200	18	7.7/6.0

**Table 2.** Nutrient values (male/female)

Age	Total fat, g/day	n-6 poly-unsaturated fats, g/day	n-3 poly-unsaturated fats, g/day	Total LC n-3 (DHA + EPA + DPA), mg/day	Calcium, mg	Magnesium, mg
0-6 months	31	4.4	0.5		210	30
7-12 months	30	4.6	0.5		270	75
1-3 years		5	0.5	40	500	80
4-8 years		8	0.8	55	700	130
9-13 years		10/8	1.0/0.8	70	1,000 (9-11 years)	240
14-18 years		12/8	1.2/0.8	125/85	1,300 (12-13 years) 1,300	410/360

Age	Iron, mg/day	Iodine, µg/day	Zinc, mg/day	Vitamin A, mg retinol equivalent/day	Vitamin D, µg/day	Vitamin K, µg/day
0-6 months	0.2	90	2.0	250 (retinyl esters)	5.0	2.0
7-12 months	11	110	3	430	5.0	2.5
1-3 years	9	90	3	300	5.0	25
4-8 years	10	90	4	400	5.0	35
9-13 years	8	120	6	600	5.0	45
14-18 years	11/15	150	13/7	900/700	5.0	55

Age	Thiamine, mg/day	Riboflavin, mg/day	Niacin, mg niacin equivalent/day	Vitamin B <sub>6</sub> , mg/day	Folate, µg dietary folate equivalent/day	Vitamin B <sub>12</sub> , µg/day	Vitamin C, mg/day
0-6 months	0.2	0.3	2 (preformed niacin)	0.1	65 (folate)	0.4	25
7-12 months	0.3	0.4	4	0.3	80	0.5	30
1-3 years	0.5	0.5	6	0.5	150	0.9	35
4-8 years	0.6	0.6	8	0.6	200	1.2	35
9-13 years	0.9	0.9	12	1.0	300	1.8	40
14-18 years	1.2/1.1	1.3/1.1	16/14	1.3/1.2	400	2.4	40

Age	Linoleic acid, g/day	α-Linolenic acid, g/day
1-3 years	5	0.5
4-8 years	8	0.8
9-13 years	10/8	1.0/0.8
14-18 years	12/8	1.2/0.8

Age	Dietary fiber, g/day	Water, l/day
0-6 months	-	0.7
7-12 months	-	0.8
1-3 years	14	1.4
4-8 years	18	1.6
9-13 years	24/20	2.2/1.9
14-18 years	28/22	2.7/2.2

Age	Carbohydrate, g/day	Protein, g
0-6 months	60	10 (1.43 g/kg body weight)
7-12 months	95	14 (1.60 g/kg body weight)

LC = Long-chain.

**Table 3.** German, Austrian and Swiss reference values (male/female) for the average daily energy and nutrient intakes in populations of healthy children and adolescents (modified from reference intakes for Germany, Austria and Switzerland 2002)

Age	Energy, kcal/kg/day	Protein, g/kg/day	Fat, % of energy	Essential fatty acids, % of energy	Calcium, mg/day	Magnesium, mg/day
0–<4 months	110	2.0–2.2	45–50	4.5	500	40
4–<12 months	95	1.2–1.6	35–40	3.8	500	60
1–<4 years	100	1.2	30–35	3.5	600	80
4–<7 years	90	1.1	30–35	3.5	700	120
7–<10 years	75	1.0	30–35	3.5	800	170
10–<13 years	60/55	1.0	30–35	3.5	900	230/250
13–<15 years	55/45	1.0	30–35	3.5	1,000	310
15–<19 years	45/40	0.9/0.8	30–35	3.5	1,200	400/350

Age	Iron, mg/day	Iodine, µg/day	Zinc, mg/day	Vitamin A, mg retinol equivalent/day	Vitamin D, µg/day	Vitamin K, µg/day
0–<4 months	6	50	5	0.5	10	5
4–<12 months	8	80	5	0.6	10	10
1–<4 years	8	100	7	0.6	5	15
4–<7 years	8	120	10	0.7	5	20
7–<10 years	10	140	11	0.8	5	30
10–<13 years	12/15	180	12	0.9	5	40
13–<15 years	12/15	200	15/12	1.1/1.0	5	50
15–<19 years	12/15	200	15/12	1.1/0.9	5	70/60

Age	Thiamine, mg/day	Riboflavin, mg/day	Niacin, mg niacin equivalent/day	Vitamin B <sub>6</sub> , mg/day	Folate, µg total folate/day	Vitamin B <sub>12</sub> , µg/day	Vitamin C, mg/day
0–<4 months	0.3	0.3	5	0.3	80	0.5	40
4–<12 months	0.4	0.5	6	0.6	80	0.8	50
1–<4 years	0.7	0.8	9	0.9	120	1.0	55
4–<7 years	1.0	1.1	12	1.2	160	1.5	60
7–<10 years	1.1	1.2	13	1.4	200	1.8	65
10–<13 years	1.2	1.4/1.3	15/14	1.6/1.5	240	2.0	70
13–<15 years	1.4/1.2	1.5/1.4	17/15	1.8/1.6	300	3.0	75
15–<19 years	1.6/1.3	1.8/1.7	20/16	2.1/1.8	300–400	3.0	75

**Table 4.** Nordic nutrition recommendation values (male/female) for dietary energy and nutrient intakes for healthy infants, children and adolescents (adapted from the Nordic nutrition recommendations 2012: Norway, Sweden, Finland, Denmark and Iceland)

Age	Energy, MJ/day	Protein, % of energy	Fat, % of energy	Essential fatty acids, % of energy		Calcium, mg/day	Magnesium, mg/day
				n-6	n-3		
<6 months	–					–	–
6–11 months	3.2	7–15	30–45	4	1	540	80
12–23 months	4.1	10–15	30–40	3	0.5	600	85
2–5 years	5.3	10–20				600	120
6–9 years	7.7	10–20				700	200
10–13 years	9.8/8.6	10–20				900	280
14–17 years	12.3/9.6	10–20				900	350/280

Age	Iron, mg/day	Iodine, µg/day	Zinc, mg/day	Vitamin A, mg retinol equivalent/day	Vitamin D, µg/day	Vitamin E, α-TE
<6 months	–	–	–	–	–	–
6–11 months	8	50	5	300	10	3
12–23 months	8	70	5	300	10	4
2–5 years	8	90	6	350	10	5
6–9 years	9	120	7	400	10	6
10–13 years	11	150	11/8	600	10	8/7
14–17 years	11/15	150	11/9	900/700	10	8

Age	Thiamine, mg/day	Riboflavin, mg/day	Niacin, mg niacin equivalent/day	Vitamin B <sub>6</sub> , mg/day	Folate, µg total folate/day	Vitamin B <sub>12</sub> , µg/day	Vitamin C, mg/day
<6 months	–	–	–	–	–	–	–
6–11 months	0.4	0.5	5	0.4	50	0.5	20
12–23 months	0.5	0.6	7	0.5	60	0.6	25
2–5 years	0.6	0.7	9	0.7	80	0.8	30
6–9 years	0.9	1.1	12	1.0	130	1.3	40
10–13 years	1.2/1.0	1.3/1.2	15/14	1.2/1.1	200	2.0	50
14–17 years	1.4/1.2	1.7/1.4	19/16	1.6/1.3	300	2.0	75

**Table 5.** UK dietary reference values for food energy and nutrients for healthy infants, children and adolescents in the UK (modified from reference intakes in the UK 2006)

Age	Energy, kcal/day	Protein, g/day	Fat, % of energy	Essential fatty acids, % of energy	Calcium, mg/day	Magnesium, mg/day
0–<3 months	545/515	12.5	–	–	525	55
4–<6 months	690/645	12.7	–	–	525	60
7–<9 months	825/765	13.7	–	–	525	75
10–<12 months	920/865	14.9	–	–	525	80
1–<3 years	1,230/1,165	15	–	–	350	85
4–<6 years	1,715/1,545	20	–	–	450	120
7–<10 years	1,970/1,740	28	–	–	550	200
11–<14 years	2,220/1,845	42	–	–	1,000/800	280
15–<18 years	2,755/2,110	55	–	–	1,000/800	300

Age	Iron, mg/day	Iodine, µg/day	Zinc, mg/day	Vitamin A, µg retinol equivalent/day	Vitamin D, µg/day	Vitamin K, µg/day
0–<3 months	1.7	50	4.0	350	8.5	–
4–<6 months	4.3	60	4.0	350	8.5	–
7–<9 months	7.8	60	5.0	350	7	–
10–<12 months	7.8	60	5.0	350	7	–
1–<3 years	7	70	5.0	400	7	–
4–<6 years	6	100	6.5	400	–	–
7–<10 years	9	110	7.0	500	–	–
11–<14 years	15	130	9.0	600	–	–
15–<18 years	15	140	9.5/7.0	700	–	–

Age	Thiamine, mg/day	Riboflavin, mg/day	Niacin, mg niacin equivalent/day	Vitamin B <sub>6</sub> , mg/day	Folate, µg total folate/day	Vitamin B <sub>12</sub> , µg/day	Vitamin C, mg/day
0–<3 months	0.2	0.4	3	0.2	50	0.3	25
4–<6 months	0.2	0.4	3	0.2	50	0.3	25
7–<9 months	0.2	0.4	4	0.3	50	0.4	25
10–<12 months	0.3	0.4	5	0.4	50	0.4	25
1–<3 years	0.5	0.6	8	0.7	70	0.5	30
4–<6 years	0.7	0.8	11	0.9	100	0.8	30
7–<10 years	0.7	1.0	12	1.0	150	1.0	30
11–<14 years	0.9/0.7	1.2/1.1	15/12	1.2/1.0	200	1.2	35
15–<18 years	1.1/0.8	1.3/1.1	18/14	1.5/1.2	200	1.5	40

**Tables 6 and 7.** USA and Canada dietary reference intakes (male/female) for infants, children and adolescents (modified from dietary reference intakes from the USA 1997/2000/2005/2010)

**Table 6.** Energy

Age, months	Energy, kcal/day	Age, months	Energy, kcal/day
1	472/438	12	844/768
2	567/500	15	908/837
3	572/521	18	961/899
4	548/508	21	1,006/952
5	596/553	24	1,050/997
6	645/593	27	1,086/1,033
7	668/608	30	1,121/1,077
8	710/643	33	1,157/1,113
9	746/678	35	1,184/1,139
10	793/717	3 – 18 years	Depends on physical activity level
11	817/742		

**Table 7.** Nutrient values (male/female)

Age	Protein, g/day	Fat, g/day	n-6 polyunsaturated fatty acids, g/day	n-3 polyunsaturated fatty acids, g/day	Calcium, mg/day	Magnesium, mg/day
0-<6 months	9.1	31	4.4	0.5	200	30
7-<12 months	11.0	30	4.6	0.5	260	75
1-<3 years	13	30-40	7	0.7	700	80
4-<8 years	19	25-35	10	0.9	1,000	130
9-<13 years	34	25-35	12/10	1.2/1.0	1,300	240
14-<18 years	52/46	25-35	16/11	1.6/1.1	1,300	410/360

Age	Iron, mg/day	Iodine, µg/day	Zinc, mg/day	Vitamin A, mg retinol equivalent/day	Vitamin D, µg/day	Vitamin K, µg/day
0-<6 months	0.27	110	2	400	10	2
7-<12 months	11	130	3	500	10	2.5
1-<3 years	7	90	3	300	15	30
4-<8 years	10	90	5	400	15	55
9-<13 years	8	120	8	600	15	60
14-<18 years	11/15	150	11/9	900/700	15	75

Age	Thiamine, mg/day	Riboflavin, mg/day	Niacin, mg niacin equivalent/day	Vitamin B <sub>6</sub> , mg/day	Folate, µg total folate/day	Vitamin B <sub>12</sub> , µg/day	Vitamin C, mg/day
0-<6 months	0.2	0.3	2	0.1	65	0.4	40
7-<12 months	0.3	0.4	4	0.3	80	0.5	50
1-<3 years	0.5	0.5	6	0.5	150	0.9	15
4-<8 years	0.6	0.6	8	0.6	200	1.2	25
9-<13 years	0.9	0.9	12	1.0	300	1.8	45
14-<18 years	1.2/1.0	1.3/1.0	16/14	1.3	400	2.4	75/65



**Tables 8–10.** WHO/FAO/UNU recommended dietary nutrient intake values for infants, children and adolescents (modified from the WHO/FAO/UNU expert groups 2004, 1994, 1985, 2007)

**Table 8.** Energy, protein and fat (male/female)

Age	Energy <sup>a</sup> , kcal/day	Protein, g/day	Fat, % of energy
3–6 months	700	13	
6–9 months	810	14	30–40
9–12 months	950	14	30–40
1–2 years	1,150	13.5	30–40
2–3 years	1,350	15.5	
3–5 years	1,550	17.5	
5–7 years	1,850/1,750	21	
7–10 years	2,100/1,800	27	
10–12 years	2,200/1,950	34/36	
12–14 years	2,400/2,650	43/44	
14–16 years	2,650/2,150	52/46	
16–18 years	2,850/2,150	56/42	

The WHO/FAO/UNU (2007) calculated a maintenance value of 0.66 g protein/kg body weight/day for children and infants from 6 months to 18 years.

<sup>a</sup>These energy intake recommendations are based on the need to match energy expenditure; thus, the recommendations listed in the table are for energy expenditure which includes basal energy plus the need for physical activity to sustain healthy growth and prevent obesity.

**Table 9.** Calcium, vitamin D and magnesium (WHO 2007; male/female)

Age	Calcium, mg/day	Vitamin D, IU/day	Magnesium, mg/day
0–6 months	300 (human milk) 400 (cow's milk)	–	26 (human milk-fed) 36 (formula-fed)
7–12 months	400	–	54
1–3 years	700	600	65
4–8 years	1,000	600	110
9–13 years	1,300	600	200/200
14–18 years	1,300	600	340/300

**Table 10.** Trace elements and vitamins (male/female)

Age	Iron, mg/day				Iodine, µg/day	Zinc, mg/day, depends on:			Vitamin A, µg retinol equivalent/day	Vitamin D, µg/day	Vitamin K, µg/day
	15% bioavail-ability	12% bioavail-ability	10% bioavail-ability	5% bioavail-ability		high avail-ability	moderate avail-ability	low avail-ability			
0–6 months	–	–	–	–	90	1.1	2.8	6.6	375	5	5
7–12 months	6.2	7.7	9.3	18.6	90	0.8 <sup>a</sup>	4.1	8.4	400	5	10
1–3 years	3.9	4.8	5.8	11.6	90	2.4	4.1	8.3	400	5	15
4–6 years	4.2	5.3	6.3	12.6	90	2.9	4.8	9.6	450	5	20
7–9 years	5.9	7.4	8.9	17.8	120 <sup>c</sup>	3.3	5.6	11.2	500	5	25
10–18 years	9.7/9.3 <sup>d</sup> 21.8 <sup>f</sup> 12.5/20.7 <sup>g</sup>	12.2/11.7 <sup>d</sup> 27.7 <sup>f</sup> 15.7/25.8 <sup>g</sup>	14.6/14.0 <sup>d</sup> 32.7 <sup>f</sup> 18.8/31.0 <sup>g</sup>	29.2/28.0 <sup>d</sup> 65.4 <sup>f</sup> 37.6/62.0 <sup>g</sup>	150 <sup>e</sup>	5.1/4.3	8.6/7.2	17.1/14.4	600	5	35–55

Age	Thiamine, mg/day	Riboflavin, mg/day	Niacin, mg niacin equivalent/day	Vitamin B <sub>6</sub> , mg/day	Folate, µg folate equivalent/day	Vitamin B <sub>12</sub> , µg/day	Vitamin C, mg/day
0–6 months	0.2	0.3	2	0.1	80	0.4	25
7–12 months	0.3	0.4	4	0.3	80	0.7	30
1–3 years	0.5	0.5	6	0.5	150	0.9	30
4–6 years	0.6	0.6	8	0.6	200	1.2	30
7–9 years	0.9	0.9	12	1.0	300	1.8	35
10–18 years	1.1	1.3/1.0	16	1.3/1.2	330	2.4	40

<sup>a</sup> Human milk-fed. <sup>b</sup> Formula-fed. <sup>c</sup> 6–12 years. <sup>d</sup> 11–14 years. <sup>e</sup> 13–18 years. <sup>f</sup> Premenarche. <sup>g</sup> 15–17 years.

## References

- Australian Government, Department of Health and Ageing, National Health and Medical Research Council: Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes. Sydney, Australian Government, Department of Health and Ageing, National Health and Medical Research Council, 2006.
- Department of Health: Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (Report on Health and Social Subjects). London, HMSO, 1991.
- Food and Nutrition Board, Institute of Medicine: Dietary Reference Intakes (DRIs). Washington, National Academies, 1997, 1998, 2000, 2005. www.nap.edu.
- Food and Nutrition Board, Institute of Medicine: Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, National Academies, 1997.
- Food and Nutrition Board, Institute of Medicine: Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B<sub>6</sub>, Folate, Vitamin B<sub>12</sub>, Pantothenic Acid, Biotin, and Choline. Washington, National Academies, 1998.
- Food and Nutrition Board, Institute of Medicine: Dietary Reference Intakes (DRIs) for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, National Academies, 2000.
- Food and Nutrition Board, Institute of Medicine: Dietary Reference Intakes (DRIs) for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Washington, National Academies, 2005.
- German Nutrition Society (DGE), Austrian Nutrition Society (OGE), Swiss Society for Nutrition Research (SGE), Swiss Nutrition Association (SVE): Referenzwerte für die Nährstoffzufuhr (Reference Values for Nutrient Intake), ed 1. Frankfurt/Main, 2000.
- Nordic Council of Ministers: Nordic Nutrition Recommendations 2012: Integrating Nutrition and Physical Activity, ed 5. Nordic Council of Ministers, 2012.
- WHO: Energy and Protein Requirements. Geneva, WHO, 1985.
- WHO: Fat and Oils in Human Nutrition. Geneva, WHO, 1994.
- WHO: Report on Diet, Nutrition, and the Prevention of Chronic Diseases. Geneva, WHO, 2003.
- WHO: Vitamin and Mineral Requirements in Human Nutrition, ed 2. Geneva, WHO, 2004.

## 4.4 Feeding My Baby – Advice for Families

Berthold Koletzko • Katharina Dokoupil

This text has been written as a quick guide for families in an affluent country setting in Europe and is based on information provided to families compiled by the Committee on Nutrition of the German Society of Pediatrics and Adolescent Medicine [1] and the German National Consensus Recommendations by the German Young Families Network [2]. Modifications may be necessary for other settings.

Whether breastfeeding or infant formula is applied, feeding your baby not only provides nutrition but also comprises tender loving care, attention and closeness.

### Breastfeeding

- Breastfeeding is the natural way of feeding for healthy infants
- Breast milk is easy to digest, always available, comes at the right feeding temperature, and carries little infectious risk
- The protective components of breast milk help to reduce the infant's risk of infectious diseases, particularly with respect to diarrhea
- Breastfeeding supports close skin-to-skin contact between mother and infant

- For most babies, full or exclusive breastfeeding offers adequate nutrition during the first 4–6 months of life. However, even a shorter period of full or exclusive breastfeeding with additional supplemental feeding is worthwhile – any breastfeeding is strongly encouraged
- The introduction of complementary solid foods should not discourage continued breastfeeding. Rather, breastfeeding should continue after the introduction of complementary feeds. Mother and child decide how long to continue breastfeeding

### Practical Recommendations for Breastfeeding

Aim at attaching the baby to your breast within the first hour after birth. Particularly during the first days after birth, you should ask for help, support, and practical advice on how to position your baby. Your child should turn towards you with its whole body and take not only the nipple but a larger portion of the breast into its mouth. You can breastfeed also after a caesarean section – do not hesitate to ask for support and help.

To promote the normal maturation process of breast milk, let your baby suckle consecutively on

both breasts during the first days. Initially, the breast produces colostrum, which is rich in antibodies that will contribute to protecting your child from infections; a larger amount of milk, with increasing protein and fat content, will be produced a few days after birth. Temporary supplementary feeding with water or other liquids should only be offered if it is deemed necessary by the pediatrician or other health care professionals.

Breastfeed your baby whenever it wishes to suckle, also at night. In the first weeks, most infants take 8–12 meals within 24 h. Breastfeeding promotes a gradual loss of the mother's body weight and the extra body fat stores that were deposited during pregnancy. The amount of fat loss increases with the duration of full breastfeeding. Additional active weight reduction during breastfeeding with the use of restrictive diets is not recommended because it may have undesirable effects on milk composition.

Breastfeeding women should consume a varied diet and plenty of liquids. A good supply of iodine (iodized salt, supplements with 100–150 µg/day) and long-chain n-3 fatty acids (200 mg docosahexaenoic acid/day, provided by 1–2 weekly meals of sea fish including fatty fish) is recommended. Breastfeeding women should refrain from smoking and the consumption of significant amounts of alcoholic drinks. Only very few mothers of babies with proven food intolerances are advised to exclude allergenic foods from their own diets upon individual advice from their pediatrician or dietitian. However, the preventive exclusion of certain foods from the maternal diet to reduce the risk of allergies in infants is not justified and not recommended.

### **Infant Formula**

If breastfeeding is discontinued before 1 year of age, a commercial infant formula should be used. In the first months of life, only infant formula should be used, which can be continued through-

out the first year of life. Follow-up formulas are only appropriate after the timely introduction of complementary feeds into the infant's diet.

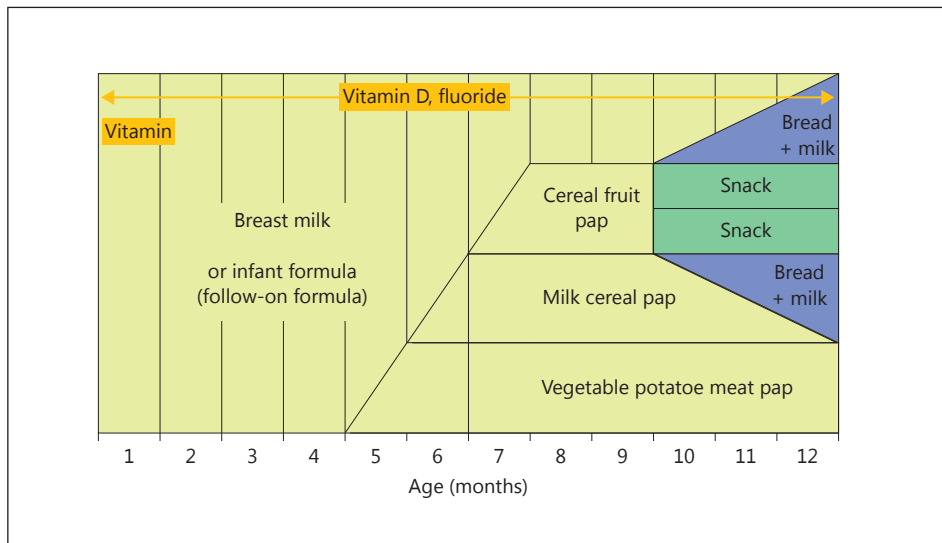
In infants who are not fully breastfed and who have a parent or sibling suffering from allergic diseases, the pediatrician should be consulted regarding the preventive use of infant formula based on hydrolyzed protein during the first 4–6 months of life.

Manufacturers' recommendations on the preparation of bottles should be carefully followed. Both too low and too high concentrations of formula are detrimental. Milk bottles must always be freshly prepared and fed within approximately 2 h. Leftovers should be discarded to prevent an increased risk of bacterial infections. Frozen and then defrosted breast milk must be handled similarly. It is important to keep bottles and nipples clean and dry. Powdered formulas must be prepared with fresh and clean drinking water. The use of water filters is not recommended. If the water contains high levels of nitrate (>50 mg/l; found particularly in domestic wells) or water pipes made of lead are used (found in some old buildings), bottled water suitable for preparing infant formula should be used. The suitability of water from domestic wells should be assessed in each case.

Infant formulas based on soy protein as well as so-called special formulas are only indicated under limited special conditions and should only be used upon the recommendation of a pediatrician or other qualified health care professional. Self-prepared bottle feeds from cow's milk, the milk of other animals (goat's, mare's, and sheep's milk) and other sources (such as almond milk) pose serious risks and should not be used.

### **Feeding Solid Foods (Complementary Foods or 'Beikost')**

After 6 months, breast milk alone does not adequately meet the nutrient requirement of a healthy baby. For their optimal development, all infants



**Fig. 1.** Recommended feeding concept in the first year of life. Modified from Ernährungskommission der Deutschen Gesellschaft für Kinder und Jugendmedizin (DGKJ) [1].

require additional nutrients, such as the trace elements iron and zinc, after the age of 6 months. The introduction of solid foods over time should gradually get the child used to an increasing variety of foods and, around the age of about 1 year, to regular family foods. The first complementary foods should be given no later than at 6 months of life but not before the age of 4 months. As the first solid food, a mixture of pulpy vegetables, potatoes and meat can be recommended, which provides iron and zinc with high bioavailability (fig. 1). In about monthly intervals, additional meals consisting of cereals with milk and a fruit-grain pap may be introduced. From the age of about 10 months, (initially soft) bread may be offered. Gluten-containing cereals (wheat, rye, and barley e.g. in porridge, bread, biscuits, and rusks) should initially be given only in small quantities to reduce the risk of developing intolerances (celiac disease). No benefits of a generally low-allergen diet in infancy have been shown. Therefore, the exclusion or delayed introduction of complementary food products considered allergenic is not recommended.

## Beverages

When 3 meals per day of complementary feeding are given, children should be offered water; avoid providing sugary drinks or adding sugar to the water. Prior to reaching 3 solid food meals per day, no liquid in addition to breast milk or infant formula is needed, except in cases of fever, vomiting, or diarrhea. Cow's milk should regularly be offered as a drink only after the first year of life to avoid potential adverse effects, for example on iron absorption.

## Further Advice and Information

Do not hesitate to ask your pediatrician if you have any further questions on the feeding of your infant.

## References

- 1 Ernährungscommission der Deutschen Gesellschaft für Kinder und Jugendmedizin (DGKJ); Bühler C, Genzel-Boroviczeny O, Jochum F, Kauth T, Kersting M, Koletzko B, Mihatsch W, Przyrembel H, Reinehr T, Zimmer P: Ernährung gesunder Säuglinge. Empfehlungen der Ernährungscommission der Deutschen Gesellschaft für Kinder- und Jugendmedizin. *Monatsschr Kinderheilkd* 2014;162:527–538.
- 2 Koletzko B, Bauer CP, Brönstrup A, Cremer M, Flothkötter M, Hellmers C, Kersting M, Krawinkel M, Przyrembel H, Schäfer T, Vetter K, Wahn U, Weissenborn A: Säuglingsernährung und Ernährung der stillenden Mutter. Aktualisierte Handlungsempfehlungen des Netzwerks Gesund ins Leben – Netzwerk Junge Familie, ein Projekt von IN FORM. *Monatsschr Kinderheilkd* 2013; 161:237–246.

## 4.5 Increasing Dietary Energy and Nutrient Supply

Katharina Dokoupil · Berthold Koletzko

Infants and children with growth faltering often need an enhanced intake of energy and nutrients. Increasing the energy density, i.e. the amount of energy per food portion or per millilitre of a liquid food, can increase the total energy intake even when the total amount of food taken remains limited. Such an increase in energy density can be achieved by using one or several elements of a stepwise approach.

### Elements of a Stepwise Approach to Increase Energy and Nutrient Supply

- (1) Analysis of needs, diet and feeding situation
- (2) Individual, professional counselling on dietary choices and on feeding practice
- (3) Offer meals and snacks more frequently, including a small late meal before going to bed
- (4) Preferential choice of energy-dense foods, drinks and snacks
- (5) Enrichment of formula and home foods with glucose polymers and/or oils
- (6) Use of drinkable supplements (sip feeds)
- (7) Tube feeding (nocturnal/continuous)
- (8) Parenteral nutrition

### Infants: Options for Increasing Energy Density of Expressed Human Milk or Infant Formula

#### *Increased Concentration of Infant Formula*

The use of 15% powder instead of 13% increases the energy density by 15%. The concentration should be increased stepwise according to individual tolerance. Concentrations >17% (+30% energy density) should usually be avoided.

*Disadvantage:* The increased formula density increases renal solute load and may reduce tolerance.

#### *Addition of Glucose Polymers*

Glucose polymers (dextrin maltose or glucose polymer mixtures) can be added with stepwise increasing concentrations from 1 up to 4 g/100 ml, which adds ~3.9–15.6 kcal/100 ml milk/formula. The concentration should be increased stepwise according to individual tolerance.

*Disadvantage:* The supply of essential nutrients per kilocalorie is reduced and may not always be sufficient, particularly for catch-up growth.

#### *Addition of Glucose Polymer-Fat Mixtures to Infant Formula*

Preparations of glucose polymers with either vegetable oil (e.g. soybean oil) or medium chain tri-

glycerides (MCT) from coconut oil can be added in stepwise increasing concentrations from 1 to 4 g/100 ml, which adds ~5.1–10.5 kcal/100 ml milk/formula. The concentration should be increased stepwise according to individual tolerance. Usually, mixtures with vegetable oils providing long-chain fats should be used. Mixtures with MCT are only indicated in cases of severe fat malabsorption (e.g. marked cholestasis). MCT may be quickly hydrolysed when added to human milk, which can limit tolerance.

*Disadvantage:* The supply of essential nutrients per kilocalorie is reduced.

#### *Addition of Oils or Fat Emulsions*

Vegetable oils can be mixed with milk/formula and provided at ~1 g/kg body weight per day (9 kcal/g). Added oils tend to separate (oil droplets on the surface) and, depending on the mode of feed delivery, may only be delivered in part to the recipient infant. An enteral vegetable oil (long-chain triglyceride) in water emulsion providing 4.5 kcal/ml is available which can be mixed with milk/formula.

*Disadvantage:* The supply of essential nutrients per kilocalorie is reduced.

#### *Use of Enteral Infant Feed*

High-energy infant feeds (~1 kcal/ml) with a balanced nutrient composition are a preferable alternative to adding energy in the form of carbohydrates or fat, which dilute the nutrient density (content of essential nutrients per 200 kcal), particularly for infants who need a high energy and nutrient density over prolonged time periods.

### **Children: Preferential Choice of Energy-Dense Foods, Drinks and Snacks**

- Energy-dense foods, e.g. deep-fried foods (French fries), fatty foods
- Energy-dense drinks, e.g. milk shakes, high-fat milk/chocolate drinks. For many children it is

easier to drink extra calories than to take them with more solid foods

- Energy-dense snacks, e.g. ice cream without or with extra whipped cream, chocolate, chocolate mousse or energy-dense puddings (with cream), potato chips (fried in oil), nuts, nuts with raisins

### **Children: Options for Increasing the Energy Density of Foods**

#### *Addition of Fats and Oils to Foods*

Use of extra butter/margarine/vegetable oils/cream/fatty cheese, e.g. extra fat, cream and cheese with vegetables, starchy foods, milk products. Increase the concentration stepwise according to individual tolerance.

*Disadvantage:* The supply of essential nutrients per kilocalorie is reduced and may not always be sufficient, particularly for catch-up growth.

#### *Addition of Glucose Polymers to Drinks and Semisolid Foods*

Glucose polymers can be added in stepwise increasing concentrations up to 5–10 g/100 g (19.5–38 kcal/100 g) for preschool children and up to 10–15 g/100 g (38–58.5 kcal/100 g) for school-age children to drinks (e.g. milk, tea, juice) and semi-solid foods (e.g. soups, pureed vegetables). Increase the concentration stepwise according to individual tolerance.

*Disadvantage:* The supply of essential nutrients per kilocalorie is reduced and may not always be sufficient, particularly for catch-up growth.

#### *Use of Liquid Feeds with High Energy and Nutrient Density*

High-energy liquid feeds (sip feeds, ~1–1.5 kcal/ml) with a balanced nutrient composition are a good alternative, particularly for children who need a high energy and nutrient density over prolonged time periods.



## 4.6 Dietary Assessment in Children

Pauline Emmett

### Key Words

Assessment of groups of children · Diet records · 24-hour recall · Food frequency questionnaire · Misreporting of intake · Nutrient analysis · Interpretation

### Key Messages

- Assessment of nutrient intake is only valid at a group level and is suitable for research projects
  - The choice of assessment methods depends on the question to be addressed, the age of the subjects and the resources available
  - It is essential to plan the work carefully in advance and obtain expert advice if meaningful results are to be achieved
  - Methods for analysis of nutrients and the assessment of misreporting of intake should be determined in advance
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### Introduction

This Annexe will deal with methods to use for the dietary assessment of groups of children usually as part of a research project [1]. It is important from the outset to understand the aim of the research as this will have a bearing on the method to use for the assessment. There will also be a need to consider the amount of time available in face-

to-face or other contact with the subject, the type and number of staff required for the dietary assessment, as well as the type and number of staff needed to handle the data and interpret it. A calculation to decide how many subjects need to be studied to adequately answer the research question is also necessary. All these considerations should be built into any plan for the research and particularly included in the plans to raise funds, which need to be adequate to achieve the research goals.

A further consideration when dealing with children is their ability to supply reliable dietary data themselves. Children below the age of 8–10 years do not usually have the cognitive skills necessary to recall or record foods eaten accurately enough for assessment [2]. Therefore, it will be necessary to involve parents or caregivers in supplying this information; however, they may not be totally reliable as well, since they are not necessarily with the child on all eating occasions, they may not be fully motivated to cooperate with a research project, they may have difficulty finding time to cooperate, and so on [2]. Older children may be a good source of information but do not necessarily understand the full details of the foods they eat; thus, it is usually necessary to obtain an expansion of child-supplied information from parents/caregivers.

**Table 1.** Main methods for the assessment of diet in groups of children [1], listing the requirements, efficacy, and approximate time needed for each method

	Diet record	24-hour recall	FFQ
<i>Requirements for data collection</i>			
Literacy	Essential	Not essential	Not essential
Memory	Recorded at time	Essential	Essential
Estimation of frequency	No	No	Yes
Estimation of portion size	Recorded at time	Recalled	Standard portion or minimal description
Photo of meal	Possible	No	No
Time for child/parent	20 min × 3 days minimum	45 min × 3 days minimum	10–20 min total
Time for staff	5–10 min to explain method; 10 min per day to check foods	45 min × 3 days minimum; checks during interview	Missing answers could be checked; 10 min with occasional subjects
Scannable data	No	No	Yes
<i>Obtaining nutrient data</i>			
Time for staff	30 min × 3 days minimum per subject; all nutrients included	30 min × 3 days minimum per subject; all nutrients included	45 min per nutrient; covers all subjects
Comprehensive nutrient database	Yes	Yes	Only nutrients in representative foods needed
Individual foods	Yes	Yes	No
Foods eaten daily	Very good	Very good	Not very good
Foods eaten 1–2 times/week	Not very good	Not very good	Fairly good
Energy estimation	Very good	Very good	Reasonable
Nutrient estimations	Very good	Very good	Reasonable

A great deal of careful planning needs to take place before embarking on this type of research project, and it makes sense to obtain expert advice at this critical stage. Poor decisions made during planning can easily lead to research being undertaken that can never achieve the intended goals because of an inadequate design.

## Dietary Methods

Some suitable dietary methods [3] are explained below, and their requirements and efficacy are listed in table 1.

### Diet Records/Diaries

The child/parent is asked to keep a record of all the foods and drinks consumed by the child over a period of time [3], typically between 3 and 7

days. Recordings tend to become less accurate if too many consecutive days are requested as fatigue tends to set in. Food can be weighed if suitable scales are provided or recorded in household measures. Some instruction from staff regarding the best way to achieve the recording is desirable but not always possible, in which case written instructions are important. Now that digital photography is accessible to most people via mobile telephones, a helpful adjunct to recording foods is to photograph them at the mealtime. The written description is still important, as foods are not always completely recognisable in photographs, but this will certainly help the subject to record exactly what was eaten. It is also important to record any food left on the plate uneaten.

When the diet records (and photographs) are received, they should be assessed by staff and the subject contacted to talk through the record and to clarify any parts that are not explicit. This can be done face to face or by telephone [4].



## 24-hour Recall

The child/parent is asked to recall everything consumed by the child over the previous day (24 h) [5]. This can be done either face-to-face or by telephone, but if the child and parent are to be interviewed together, a face-to-face session might be more effective. The method relies on memory and knowledge. The child may not accurately remember the foods eaten. It has been found that children can only recall foods eaten up to a few hours previously; they sometimes recall phantom foods which were not eaten, and the more complex the meal, the more likely they are to be inaccurate in their recall [2]. On the other hand, parents can only aid their child to recall meals at which they were present, and this is unlikely to be the case with all meals eaten by the child.

In order to characterise a diet, more than one recall for each child is necessary. Therefore, the child and parent need to go through this procedure several times (3 times is probably the minimum), each a few days apart; this is time-consuming for both the subjects and the staff.

## Food Frequency Questionnaires

The child /parent is presented with a list of foods and drinks and asked to indicate the frequency with which they are usually consumed by the child from a predetermined list of frequencies [6]. Sometimes the list includes an indication of the usual portion size consumed. Such a list can be administered as a self-completion questionnaire or in an interview by trained staff (particularly if literacy is a problem).

It is imperative that the food frequency questionnaire (FFQ) is designed for the particular population under study; otherwise, it will be ineffective and could be misleading [6]. The food/drinks listed must be the ones that this population are likely to consume; this is specific to the age, country, ethnicity and background of the

subjects. For example, when studying infants, formula milk, breast milk and infant food must be covered, and when studying children living in different countries, foods specific to each country must be covered.

The concept of the frequency of eating different foods is cognitively quite difficult, and it is unlikely that a child below the age of 12 years would be able to cope with it; therefore, parents will usually need to complete the FFQ on behalf of the child [2]. If they are doing this at home, then it would be best done in consultation with the child (and others with knowledge) about meals eaten away from the parent. Portion sizes are also a difficult concept to communicate and interpret. The simplest answer is to allocate standard portion sizes, but these must be adjusted to the age of the child.

Although an FFQ is relatively cheap and quick to use, the interpretation of the answers given to produce calculated nutrient intakes is not simple and requires expert input. It is important to plan for this stage in advance.

## Nutrient Analysis

Nutrient analysis of the food records and 24-hour recalls collected requires trained staff and a suitable dietary analysis programme which can accommodate all the foods eaten and provide up-to-date nutrient contents for all the nutrients of interest [7]. Obtaining this type of analysis package needs careful thought, since foods change over time and off-the-shelf versions of these packages do not always cover culturally specific foods, new foods on the market or some specific nutrients. It is best to involve an expert dietician/nutritionist in this process as the interpretation of the records requires an intimate knowledge of foods. For an FFQ, nutrient analysis is only required for a list of representative foods; thus, this stage is much quicker to deal with, but it does not provide individual details of foods consumed.

## Misreporting of Intake

All dietary methods are subject to misreporting [2, 8]. This can be due to misunderstanding, memory lapse, deliberate changes to the diet to make recording easier, deliberate misreporting and so on. It has been shown that the level of misreporting can be related to the characteristics of the method (FFQ often overestimate) or subject (obese people and adolescents are more likely to under-report) or the type of food (snacks are more likely to be missed than meals). Therefore, it is important to take this into consideration during analysis. There are several methods available to assess the level of misreporting of energy intake which can be tailored to the age, sex and size of the individual and take their usual physical activity level into account [9, 10].

## Interpretation

The average nutrient content of the diet can be used in group analysis but is not accurate at the individual level [2]. Thus, differences in energy and nutrient intake between groups of children can be compared using normal statistical meth-

ods. Often the analysis is performed with and without the energy reporting status considered, sometimes with different results obtained. To interpret dietary data, it is also helpful to compare food group intakes, bearing in mind that the statistical methods used need to be able to cope with the fact that some food groups are not eaten at all by some children. An understanding of differences in foods eaten can help in the communication of results to the general public.

## Conclusion

- The diet is a very important part of environmental exposure and integral to the growth and development of children; therefore, it is important to study it
- The diet is complex and difficult to characterise by simple methods; therefore, when starting a project to assess the diet, advanced planning is the key to success
- The chance of obtaining useful dietary data will be greatly enhanced by obtaining expert advice at the beginning and building ongoing nutritional expertise into the project

## References

- 1 Emmett PM: Assessing diet in birth cohort studies. *Paediatr Perinat Epidemiol* 2009;23(suppl 1):154–173.
- 2 Livingstone MBE, Robson PJ, Wallace JMW: Issues in dietary intake assessment of children and adolescents. *Br J Nutr* 2004;92(suppl 2):S213–S222.
- 3 Bingham SA, Cassidy A, Cole TJ, Welch A, Runswick SA, Black AE, et al: Validation of weighed records and other methods of dietary assessment using the 24 h urine nitrogen technique and other biological markers. *Br J Nutr* 1995;73:531–550.
- 4 Candilo KDI, Oddy W, Miller M, Sloan N, Kendall G, Klerk NDE: Follow-up phone calls increase nutrient intake estimated by three-day food diaries in 13-year-old participants of the Raine Study. *Nutr Diet* 2007;64:165–171.
- 5 Reilly JJ, Montgomery C, Jackson D, MacRitchie J, Armstrong J: Energy intake by multiple pass 24 h recall and total energy expenditure: a comparison in a representative sample of 3–4-year-olds. *Br J Nutr* 2001;86:601–605.
- 6 Cade J, Thompson R, Burley V, Warm D: Development, validation and utilisation of food-frequency questionnaires – a review. *Public Health Nutr* 2002;5:567–587.
- 7 Price GM, Paul AA, Key FB, Harter AC, Cole TJ, Day KC, et al: Measurement of diet in a large national survey: comparison of computerized and manual coding of records in household measures. *J Hum Nutr Diet* 1995;8:417–428.
- 8 Livingstone MBE, Black AE: Markers of the validity of reported energy intake. *J Nutr* 2003;133:895S–920S.
- 9 Black AE: The sensitivity and specificity of the Goldberg cut-off for EI:BMR for identifying diet reports of poor validity. *Eur J Clin Nutr* 2000;54:395–404.
- 10 Rennie K, Coward WA, Jebb SA: Estimating under-reporting of energy intake in dietary surveys using an individualised method. *Br J Nutr* 2007;97:1169–1176.



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**110 Nutritional Care of Preterm Infants**  
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There is no other time in life when the provision of adequate and balanced nutrition is of greater importance than during infancy and childhood. During this dynamic phase characterized by rapid growth, development and developmental plasticity, a sufficient amount and appropriate composition of nutrients both in health and disease are of key importance for growth, functional outcomes such as cognition and immune response, and the metabolic programming of long-term health and well-being.

This compact reference text provides concise information to readers who seek quick guidance on practical issues in the nutrition of infants, children and adolescents. After the success of the first edition, which sold more than 50,000 copies in several languages, the editors prepared this thoroughly revised and updated second edition which focuses again on nutritional challenges in both affluent and poor populations around the world. Serving as a practical reference guide, this book will contribute to further improving the quality of feeding of healthy infants and children, as well as enhancing the standards of nutritional care in sick children.