Enteral nutrition for preterm infants:

translating ESPGHAN guidelines into practice

Survival rates of preterm infants have improved dramatically, making the nutritional management of preterm infants increasingly important to all health professionals working in neonatal care. Promoting good nutritional status is a key component of neonatal care, and it is vital that health professionals are aware of the nutrient needs of preterm infants and understand how to translate nutritional research, knowledge and recommendations into everyday practice.

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The survival of preterm infants has increased dramatically over the last two decades due to advances in obstetric and neonatal medicine, and advanced nursing care based on years of experience and a strong research base. Increasing survival, duration and complexity of intensive care means that nutritional management becomes increasingly important. It is therefore vital that all health professionals working in neonatal care understand how to translate nutritional research, knowledge and recommendations into everyday practice.

Improved obstetric management and the use of antenatal steroids mean that babies are now healthier at birth than ever before. Technological improvements in respiratory support, including better ventilators and surfactants, have had dramatic impacts on reducing early respiratory deaths. Promoting and achieving good nutritional status is the keystone upon which other systems depend. Nutritional status determines risks of necrotising enterocolitis (NEC)[1], blood stream infections, growth and cognitive outcome[2]. Recent evidence also highlights that nutrition in early life has long-term effects, and directly relates to the chances of developing later life diseases such as hypertension, heart disease and type 2 diabetes.

PRETERM INFANTS HAVE UNIQUE NEEDS

Preterm infants do not benefit from the later stages of pregnancy when optimal nutrient stores are normally established. This is true for every major nutrient, from protein and energy, to minerals and vitamins[3,4]. Adipose tissue, the major energy store in term infants, is extremely limited in preterm babies. Preterm babies do not have any significant 'energy' stores, and must rely on small amounts of fat, carbohydrate (eg glycogen) and protein. Limited fat stores mean that the largest 'energy' store is protein in muscles and other organs. Use of body protein for energy will impair function. Estimates suggest a 1000g baby only has sufficient energy for 2-3 days before death would result without exogenous dietary supply.

The preterm brain is extremely vulnerable to under-nutrition. There are few controlled trials, but those and observational studies suggest that sub-optimal macronutrient supply (protein and energy) in early life will result in ~5-10 IQ point deficit in later childhood. Breast milk is the best form of nutrition: aside from reducing the incidence of NEC and infections, it is estimated to improve cognitive outcome by the equivalent of 4-6 IQ points. There are few other interventions in neonatal practice with that magnitude of effect.

NUTRIENT INTAKES

It is not possible to determine the precise daily intake of nutrients that any individual baby needs, so recommendations are based on many different types of evidence. Expressed breast milk (EBM) is the best milk for all preterm babies, but alone will not meet the nutrient needs of most very preterm babies. Many will therefore benefit from the use of breast milk fortifiers (BMF). Despite support from nursing staff and lactation specialists, many mothers chose not to initiate expression, or find it difficult to maintain EBM supply during the many weeks of neonatal care. Specialised formulae are therefore required as the nutrient composition in

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term formula will not meet the needs of preterm infants appropriately.

The Committee of Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) established an *ad hoc* expert panel to make appropriate recommendations which were published in 2010 (*TABLE 1*). They aimed to update previous EPSGAN recommendations (1987) by reviewing new evidence. While there were similarities to other key international opinions, there were also some minor differences for certain nutrients. The focus of the 2010 ESPGHAN recommendations was enteral intakes in stable, growing preterm infants up to a weight of approximately 1800g[5]. These recommendations did not then consider other aspects of feeding (eg when to start and increase milk) or nutrition in the first few days (eg parenteral nutrient requirements). A detailed scientific workshop was subsequently organised by the charitable Child Health Foundation at which an extensive literature review and discussion was organised.

THE 2010 ESPGHAN GUIDELINES

The recommendations cover all major nutrients. The committee advocates the use of EBM for preterm infants as standard practice, providing it is fortified where necessary to meet requirements. Despite an extensive literature search it was clear that there is a lack of robust evidence-based data for several nutrients. Ranges of advisable intake are provided both per kilogram body weight per day (kg/d) and per 100 kcal. There is an increased focus on protein needs, which may not be met using current formulae or EBM with BMF for infants at highest risk. The current recommendation is for an energy intake of 110-135kcal/kg/d: while higher intakes appear generally safe in the short term, there is limited evidence of improved lean growth and some evidence of excessive fat accretion.

PROTEIN INTAKES

There are only a few trials that define optimal protein intakes despite good evidence that inadequate intakes results in worse growth, and lower cognitive attainment. Precise quantification of protein needs is difficult, because the actual biological requirement is for amino acids (the building blocks of protein) rather than for protein *per se*. This means that the source or quality of the protein is also important. Protein from breast milk may have a more appropriate combination of amino acids than other sources. There may also be functional differences between breast milk proteins and those in formula that mean a direct 'gram for gram' comparison is not appropriate. Nevertheless, there is good evidence that protein intakes are frequently sub-optimal in both breast and formula-fed infants. The current recommendation is for a protein intake of 3.5-4g/kg/d for babies 1-1.8kg in weight: higher intakes are likely to be safe and might well be needed in the smallest infants, and in those where support of 'catch-up' growth is needed. The composition of many fortifiers and formulae over the last few years may not have adequately met protein needs in all babies. Increasing the milk volume intake is often not possible (for example due to high gastric aspirates) and might be inappropriate if it also results in excess energy intake. Newer formulae and BMF compositions will help address this problem, as will innovative products such as protein supplements.

	Daily intake kg/day	Per 100kcal
Energy	110-135kcal	
Protein <1kg bodyweight	4-4.5g	3.6-4.1g
1-1.8kg bodyweight	3.5-4g	3.2-3.6g
Lipids	4.8-6.6g	4.4-6.0g
Carbohydrate	11.6-13.2g	10.5-12g
Iron	2-3mg	1.8-2.7mg
Vitamin D	800-1000IU/day	

TABLE 1 Key ESPGHAN recommendations.

ENERGY AND FAT INTAKES

Although the proportion of energy intake provided by carbohydrates (eg glucose and polysaccharides etc) is quite tightly defined (10.5-12g/100kcal), there are no studies that allow precise determination of the optimal carbohydrate intake.

Dietary lipids provide the remainder of energy intakes, but also provide essential fatty acids and fat soluble vitamins. Lipids are essential for all cell membranes. There are very high levels of long-chain polyunsaturated fatty acids in the brain and retina. The essential fatty acids alpha-linolenic and linoleic acids, must be provided in the diet, and are needed for the production of docosahexaenoic acid (DHA) and arachidonic acid (AA). Clinical trials examining the effects of additional DHA and AA in formula suggest benefits on early visual and brain development, and possibly immune effects, but there are few data showing unequivocal long-term benefit. Breast milk is an excellent source of essential dietary lipids.

CALCIUM, PHOSPHORUS AND VITAMIN D

It is difficult to match the *in-utero* accretion of minerals in preterm infants. ESPGHAN provide recommendations for formula composition, and recommendations on the calcium to phosphorus ratio. In clinical practice very few babies need additional calcium if they receive a modern preterm formula or breast milk with added BMF. Phosphorus depletion is much more common, particularly in babies on unfortified breast milk.

Unlike macronutrients (protein, fat, carbohydrate) the plasma phosphate level is a simple way of assessing dietary phosphate adequacy.

Vitamin D is involved in a bewildering array of physiological processes including neurological function and bone mineralisation. While skin synthesis of vitamin D is of major importance in children and adults, preterm infants are solely dependent on dietary sources and recommendations assume no contribution from skin synthesis. Vitamin D undergoes hepatic and renal conversion into the active form, which in turn promotes mineral absorption from the gut, and facilitates adequate bone formation. Although there are many different forms (vitamin D_2 and vitamin D_3 are the major forms) recommendations are only for vitamin D and are provided in international units (IU). The ESPGHAN recommendation of 800-1000 IU per day is the only nutrient for which a daily intake as opposed to a per kg per day intake is made. In order to meet this at low intake volumes without providing excessive intakes when volume consumption is high, it is necessary to use a vitamin supplement in the first few months. Additionally, an increased recognition of the high prevalence of vitamin D inadequacy in the general population has led to recommendations that supplemental vitamin D continues to be provided during infancy.

IRON

Iron deficiency results not only in anaemia, but also in worse cognitive outcome. However, iron is toxic, and while intestinal uptake can be down-regulated, humans possess no mechanism for excretion of excess iron. Free iron increases oxidant damage, may increase the risk of retinopathy of prematurity (ROP) and increases the risk of bacterial proliferation. A careful balance is therefore required. Although iron is essential from birth, gut re-absorption and blood transfusions in the most preterm infants mean that supplemental iron is rarely required in the first 2-4 weeks unless blood loss (including that from frequent blood tests) is excessive. Preterm formula will meet iron requirements, but additional iron will be needed for infants who have not been recently transfused and where their sole dietary intake is from EBM. It is important to note that BMFs available in the UK do not contain additional iron – this is the only major nutrient where intakes in BMF-supplemented infants do not match those fed on preterm formula. Although ESPGHAN recommendations are for supplemental iron from 2-4 weeks of age, in practice few infants need additional iron before 4-6 weeks of age. Given that most infants <28 weeks' gestation receive at least one blood transfusion, many practitioners find that extra iron need only be started in the weeks just prior to hospital discharge.

PRE- AND PROBIOTICS

Human breast milk contains high levels of oligosaccharides, especially in colostrum and early milk. Most of these resist digestion in the small bowel, and reach the large bowel where they are fermented. Here they promote the growth of certain 'healthy' bacteria (probiotic bacteria) such as bifido-bacteria or lactobacillus. While it is not possible for milk formulae to match the oligosaccharide composition of breast milk, the addition of prebiotics such as galacto-oligosaccharide and fructo-oligosaccharide increases faecal bifido-bacteria counts, reduces stool hardness, and may also affect feed tolerance[6]. There are also preliminary data suggesting effects on immune function, but there are no controlled trials showing reduction in rates of sepsis or NEC. Although the literature surrounding the use of probiotics in preterm infants as prophylaxis against NEC is encouraging, routine use is highly contentious[7]. ESPGHAN stated further data were required before probiotics could be considered essential dietary components.

CHALLENGES AND INNOVATIONS

Promoting good nutritional status is a key component of neonatal care. Use of breast milk must be encouraged, macronutrient intakes need optimising and micronutrient intakes need careful consideration. Modern milk formulae and BMF are being adapted to meet the changing needs of preterm babies and help overcome some of the difficulties faced in the past. The updated ESPGHAN guidelines are just the start. It is important that all those working in neonatal care are aware of the nutrient needs of preterm infants, and how these can be met using EBM and innovative products. An increased focus on the role of inadequate protein intakes has encouraged a re-formulation of some existing products and highlighted the need for new products such as protein supplements.

Conflict of interest statement

Dr Embleton supports the use of breast milk and does not endorse any specific company or product. His research studies have received support from infant formula manufacturers but he has no personal or financial relationship with any commercial organisation. *Infant* has donated an honoraria for the writing of this article to charity.

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