REVIEW

Nutritional support in the premature newborn

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The theory and practice of nutritional support in the premature newborn has assumed increasing importance with survival of greater numbers of very immature infants. After birth, many do not tolerate full enteral feeding until gastrointestinal motor function has matured. During this process some will develop necrotising enterocolitis (NEC), a devastating failure of adaptation to postnatal life that may result in death, or severe complications. The feeding strategy that minimises the risk of NEC remains to be defined. In addition, promoting growth rates and nutrient accretion equivalent to those achieved during fetal development while optimising neurodevelopmental and long term health outcomes represents an important challenge for neonatologists. This review will focus on the problems associated with enteral nutrition, the requirement for parenteral nutrition, and the long term consequences of early nutritional interventions, underlining the need for prolonged follow up in assessing the potential benefits of different approaches to feeding.

Prospects for the premature infant have improved dramatically over the past 30 years, with the result that even those born as early as 24 weeks' gestation now have a 50% chance of survival. This achievement came not only through specific advances in management of respiratory failure, but by progress in many other aspects of obstetric and neonatal intensive care. During this time, nutritional support has assumed increasing importance, not least because early interventions are now known to have implications for health that extend far beyond childhood.[1] Optimum nutrition should permit adequate growth free from metabolic and other complications in the short term, with fulfilment of both genetic growth and developmental potential in the long term. It is evident that scientific evaluation of feeding interventions must now include assessment of such outcomes together with parameters of adult health.[2 3]

A postnatal growth rate equivalent to in utero fetal nutrient accretion (10–15 g/kg/day) represents a widely accepted goal for nutritional support.[4] The fact that in the most vulnerable infants this is rarely achieved reflects both the heterogeneity of clinical and nutritional status among this group, and the practical difficulties of nutrient supply both in qualitative and quantitative terms. In addition, it also points to the necessity of looking beyond simple failure to meet recommended nutrient intakes as the only cause of poor growth. Early enteral feeding is commonly limited by immaturity of gastrointestinal motor function,[5] manifested principally as delayed stomach emptying, gastro-oesophageal reflux, abdominal distension, and infrequent stooling. Failure to adapt to enteral feeding can give rise to necrotising enterocolitis (NEC), an important cause of morbidity and mortality. In the absence of clear evidence, there is little agreement on which enteral feeding regimen might minimise the risk of NEC.[6] Parenteral nutrition (PN), first introduced in the late 1960s, is widely used during the early weeks of life. Broad consensus exists with respect to intake of parenteral nutrients,[7] but there are many uncertainties concerning optimal composition of feeds.

Embleton[8] has highlighted in infants less than 30 weeks' gestation that intakes of both energy and protein consistently fall below those recommended. This is probably representative of the situation in many newborn units, and results in a cumulative nutritional deficit up to the time of discharge. Although not all variation in growth can be attributed to diet, low nutrient intake is certainly one of the most important factors. There is a need to try and reduce this deficit as it has implications for long term health outcomes, including future cognitive development.[9] It has also been argued that undernutrition is, by definition, unphysiological and undesirable, and any measure that diminishes it is inherently good provided that it is safe.[10] One of the practical expressions of this philosophy is so called ''aggressive nutrition''. This can be defined as the attempt to minimise or eliminate interruption to nutrient flow from the time of umbilical cord division until the establishment of full feeding.[10] Safety aspects of ''aggressive nutrition'' requiring further evaluation include the provision of comparatively high amino acid intakes from day one, given the large renal solute load that this represents. The recognition that very premature infants are often undernourished at the point they leave hospital has lead to the development of energy and nutrient enriched post-discharge formula feeds. More effective nutritional support in the early weeks of life may well diminish the need to use such ''catch up'' formula.

NECROTISING ENTEROCOLITIS

Feeding policies during early life on neonatal intensive care units are commonly influenced by concerns relating to minimising the risk of NEC. This condition[11] frequently presents as feed intolerance with bile stained gastric residuals,

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Abbreviations: NEC, necrotising enterocolitis; PN, parenteral nutrition

Key points 1

- In the preterm infant replication of in utero growth and nutrient accretion at the same post-conceptional age is a reasonable aim
- In practice, this is difficult to achieve and early temporary cessation of growth is common, with variable degree of later catch up
- Attention is becoming focused on early nutritional support, with a view to minimising the nutritional deficits accumulated during the initial periods of illness and gastrointestinal immaturity

abdominal distension, blood in the stools, apnoea, and acidosis. It may develop insidiously, or be a rapidly progressive illness culminating in shock followed by death. The characteristic finding on abdominal radiography is intramural gas produced by bacteria that have invaded the bowel wall. Immediate management entails withdrawal of enteral feeding, and intravenous delivery of fluids and broad spectrum antibiotics. A survey by the British Paediatric Surveillance Unit in the UK over one year recorded a total of 300 cases of NEC, 65% of whom were <1500 g birth weight.[12] Almost a third required surgical intervention and overall mortality was 22%. Nearly 90% were before term (the median gestational age being 29 weeks) with presentation most frequently in the second week of life. The estimated incidence of NEC from this survey was 0.23/1000 live births, or around 2/1000 NICU admissions. In the USA, prevalence between units varies from 4% to 20%.[13]

Recognised risk factors in addition to prematurity include early introduction and rapid incrementation of enteral feeding (>25 ml/kg/day),[14] and hyperosmolar feeds.[15] These considerations militate against attempting complete enteral feeding in the first few weeks of life in the high risk premature infant, and in favour of PN. There is some evidence that feeding with human milk is protective against NEC.[16–18] Immaturity of gastrointestinal motor function, digestion, immunity, and circulation are all implicated in the pathogenesis. Enteric bacteria may ferment malabsorbed carbohydrates creating an acidic intraluminal environment that adversely affects mucosal blood flow. Changing intestinal flora (for example, through antibiotic therapy given during episodes of suspected sepsis) subsequently reduces the risk of later developing NEC.[19]

An alternative method of manipulating gut bacterial flora and thereby influencing risk of NEC entails the use of prebiotics and probiotics in infant feeds. Prebiotics are non-digestible food components that beneficially affect the host by stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thereby improve health. A systematic review of the literature concluded that further evaluation of prebiotics is necessary before their use can be advocated in preterm infants.[20] Probiotics are live bacteria that colonise the gastrointestinal tract and promote health benefits in the host. The bacterial genera most often used are lactobacilli and bifidobacteria that form part of the normal intestinal microflora in humans. Evidence that probiotics have a beneficial effect in the premature newborn is limited[21] although a recent randomised trial points to a possible role in preventing NEC.[22] In this study, infants with birth weight <1500 g were randomised to either receive a daily feeding supplement containing *Bifidobacteria infantis, Streptococcus thermophilus*, and *Bifidobacteria bifidu,s* or no supplement. One of 73 of the study group and 10 of 73 of the control group developed clinically significant NEC; all three deaths from NEC occurred in the control group.

Delaying introduction of enteral feeding (complete enteral starvation) was seen as a possible way of reducing risk of NEC, but probably has no impact and merely delays clinical presentation.[23] Recently, Berseth and colleagues[24] compared a feeding regimen including daily incrementation of enteral feed, with one where feeds were initially maintained at 20 ml/kg for the first 10 days. The study was closed early because 7 of 70 infants in the advancing feed volumes group developed NEC compared with only 1 of 71 in the static volume group. Unlike in many neonatal units, however, enteral feeding was often not started until around 10–11 days of age, once pressor agents had been withdrawn and umbilical vascular catheters removed. In addition, small for gestational age infants at high risk of NEC were excluded from the trial, both these factors making it uncertain that the findings have general application.

Currently, management of enteral feeding varies considerably and standardisation of approach alone may have benefits. Patole and de Klerk[25] have undertaken a systematic review and meta-analysis of observational studies reporting the incidence of NEC before and after implementation of standardised feeding regimens. They found a pooled risk ratio of 0.13 (confidence interval 0.03 to 0.50) and attributed the reduced risk of NEC to minimisation of variation in enteral feeding practices. Unfortunately, it is difficult to determine which elements within nutritional support are the key factors, and nurse management of tube feeding in individual patients is likely to be just as important as the feeding policies elaborated by neonatologists.[26] Large, multicentre randomised controlled trials comparing different rates of enteral feed advancement are required to define feeding strategies that will minimise the risk of NEC. PN coupled with minimal enteral feeding (preferably with breast milk) is the approach commonly advocated for the initial nutritional management of high risk infants.

PARENTERAL NUTRITION

In the most vulnerable preterm infants immaturity of gastrointestinal function initially precludes meeting nutritional requirements using the enteral route alone. PN—used

Key points 2

- NEC affects around 2%–5% of infants with birth weight <1500 g, almost a third need surgical intervention and overall mortality rate is around 22%
- The aetiology of NEC is multifactorial, but rapid increments in enteral feeding is one of the recognised risk factors in preterm infants who account for 90% of cases
- Human milk seems to confer some protection
- Following a standardised feeding protocol and thereby reducing variation in feed management may also be beneficial
- Early introduction of small volume enteral feed and cautious increase in volume, coupled with PN to meet nutritional demands is a widely favoured approach to prevention of NEC in the preterm, if of unproved benefit
- Probiotics look promising with respect to reducing risk of NEC but evidence of efficacy is limited and further studies are needed

widely since the early 1970s—has almost certainly contributed to improved clinical outcomes. Enthusiasm for enteral feeding may have increased over the past two decades together with decreased reliance on PN to the detriment of growth in some patients. In particular, limitation of protein intake seems to be an important factor in restricting weight gain.[27] While provision of PN was once concomitant with enteral starvation, this should no longer be the case as risk of cholestasis is increased and time to full enteral feeding delayed. Complete enteral starvation is now commonly avoided by giving small volumes of milk during PN—so called trophic, minimal enteral, or hypocaloric feeding. In one randomised controlled trial, benefits included a reduction in sepsis rate and oxygen dependency, improved growth, and earlier discharge from hospital.[28]

Whereas immaturity of gastrointestinal function in the preterm infant is the most common indication for PN, it is also used in infants with acquired gastrointestinal disease such as NEC, or with congenital anomalies including ileal atresia and gastroschisis that initially preclude enteral feeding. Broad agreement exists over PN regimens,[29] although many questions remain unanswered. These include when to introduce PN, how quickly to build up nutrient intake, the ideal composition of amino acid solutions and fat emulsions, and precise micronutrient requirements. The relative advantages of standard feed mixes compared with individualised prescriptions are also debated,[30 31] while perennial problems of complications, including central venous catheter related sepsis, remain an argument in favour of avoiding PN when at all possible. Perhaps the biggest questions are at what point, and in which patients, are the risks associated with PN outweighed by its potential advantages. Although there can be no doubt that PN has been a life sustaining intervention in the surgical infant with congenital or acquired disease causing gastrointestinal failure, its role in the premature newborn with an intact but immature gut remains unclear. Nevertheless, it seems extremely likely that PN has contributed to improved survival and outcome, particularly in the most premature and sick infants in whom enteral feeding cannot be relied upon to sustain growth in the early weeks of life. An important consideration in relation to starting PN must be the fact that the premature newborn has very limited nutritional reserve[32] and rapidly becomes catabolic.

Nutrients are needed to support growth, and requirements for water, electrolytes, nitrogen, fat, and carbohydrate vary with age as well as with illness. Greater use of insulin infusions has been advocated to sustain an adequate energy intake in the face of hyperglycaemia, rather than restricting carbohydrate supply.[33] The requirement for amino acids is both quantitatively and qualitatively different in early infancy than later life, with histidine, tyrosine, taurine, cysteine, proline, and alanine being semi-essential. Recent innovations in PN include the development of lipid emulsions combining soy and olive oils, which have a lipid profile more similar to breast milk and contain a lower proportion of polyunsaturated and higher content of monounsaturated fatty acids compared with long used soybean oil based emulsion.[34] Soy emulsions contain only small amounts of arachidonic and docosahexaenoic acid, important for early visual and neural development. They supply large amounts of linoleic acid and α-linolenic acid that may impair long chain polyunsaturated fatty acid synthesis through substrate inhibition. A recent clinical trial evaluated an emulsion with olive oil and soy oil in a ratio of 4:1, containing less polyunsaturated fatty acid content and more α-tocopherol relative to a standard soy oil emulsion.[35] Findings showed improved vitamin E status but also suggested increased metabolism of linoleic acid. Such emulsions certainly seem more physiological than standard soy oil preparations, but further evaluation is needed before routine use can be recommended.

Nitrogen is supplied as synthetic L-crystalline amino acid solutions with some variation in design of different solutions. Optimal amino acid composition remains undefined, but efforts to develop products that more closely represent human milk protein continue.[36] While one of the most abundant amino acids in both plasma and breast milk, glutamine is not included in amino acid preparations for PN. Glutamine is unstable in solution, and has usually been regarded as a non-essential amino acid. However, glutamine provides an important metabolic fuel for rapidly dividing cells of the gastrointestinal tract and the immune system. It is an intermediate in a large number of metabolic pathways and a precursor that donates nitrogen for the synthesis of purines, pyramidines, nucleotides, and amino sugars. In addition, glutamine plays a key part in acid base balance by acting as the most important substrate for renal ammonia production. Some studies in adult patients have suggested that glutamine supplementation may decrease sepsis and mortality in the critically ill.[37] In a recent large study of 1433 infants, the safety and efficacy of parenteral glutamine was assessed in a double blind trial.[38] Infants between 401 g and 1000 g were randomised either to receive a conventional amino acid solution, or a study amino acid solution with 20% glutamine. No effects were found on mortality, late onset sepsis, tolerance of enteral feeding, NEC, or growth among the 721 infants in the glutamine group. Although this study showed no benefit from glutamine, most infants did not reach a full nitrogen intake until 10 days of age, and to keep the solutions isonitrogenous intake of other amino acids was reduced in the glutamine group (for example, infants in this arm had a significantly greater fall in plasma tyrosine). In view of the important metabolic roles of glutamine, further clinical evaluation is required.

ROLE OF BREAST MILK IN THE NEONATAL UNIT

The superiority of human milk for preterm infants was long taken for granted and led to the setting up of milk banks for the collection and processing of milk, donated by breast feeding mothers in the community. In the 1970s the nutritional heterogeneity of donor milk was acknowledged together with its frequently poor quality (particularly its low energy and mineral content). In addition, the potential immunological benefits of breast milk were thought to be negated by pasteurisation. Heat treatment also adversely affected protein utilisation and fat absorption, and weight gain was inferior to that with formula feeds. In the following decade, concern regarding the risk of viral transmission (particularly HIV and hepatitis B) complicated the logistics of

Key points 3

- It is self evident that PN is a lifesaving intervention for infants with severe congenital or acquired gastrointestinal disease when nutritional requirements cannot be met using the enteral route
- The role of PN in the premature infant with an intact but immature bowel is less well defined than in infants with other causes of intestinal failure, but widespread use has almost certainly contributed to improved outcomes
- Many technical problems relating to PN have been resolved since its introduction almost 40 years ago, but questions regarding optimal intake of nutrients remain important areas for research

milk banking. With the development of formula milk specifically aimed at meeting the requirements of the premature infant, the use of breast milk on the neonatal unit inevitably declined. However, the possibility that human milk feeding conferred important clinical advantage was supported by a study comparing different formula feeds and banked breast milk with respect to growth and development. Data collected during this large trial suggested that NEC was 6–10 times higher in preterm infants fed formula than those fed breast milk, with even pasteurised donor milk having a protective effect.[16] A recent systematic review by McGuire and Anthony[7] found only four small trials suitable for inclusion in a meta-analysis comparing human milk and formula feeds in relation to the risk of NEC. The evidence, however, again pointed to a lowered risk (albeit of borderline statistical significance) in babies receiving donor human milk. Breast milk is also associated with neurodevelopmental advantage[39] possibly because of its long chain n-3 fatty acid content, or through the action of its various biologically active peptides.[40]

Perhaps against the odds, some milk banks continued to function,[41] and a limited resurgence has followed.[42] The problem of nutritional inadequacy has to some extent been resolved by widespread use of milk fortifiers providing additional protein, carbohydrate, and minerals. Numerous studies have shown that breast milk fortification with human milk or bovine protein, minerals, and vitamins can influence short term outcomes including growth, nutrient retention, and bone mineralisation. Fortified human milk may not produce as much weight gain as preterm formula milk feeds, but is associated with a reduction in late onset sepsis and NEC, and earlier discharge from hospital.[43] One large study examining the effect of human milk fortification on subsequent developmental outcome was unable to show an advantage at 18 months of age.[44]

FEEDING PREMATURE INFANTS AFTER DISCHARGE FROM HOSPITAL

During hospital stay, the feeding of both human milk with an added human milk fortifier and of preterm formula often generates a slower growth rate and different body composition than that achieved by the fetus in utero, with a relative low lean body mass and a lower bone mineral content associated with osteopenia and a risk of fractures in early life.[45–49] Ongoing growth monitoring must be regarded as an important component of clinical follow up. At discharge, infants can be divided into four different groups based on simple anthropometry:

(1) infants with a birth weight, and a body weight at discharge, appropriate for post-conceptional age (appropriately grown)
(2) infants born at an appropriate weight for gestational age but with a discharge weight below the reference growth chart (postnatal growth restriction)
(3) infants born small for gestational age (<10th centile for birth weight) with a discharge weight still below the reference growth chart (intrauterine growth retardation)
(4) infants born small for gestational age, but now with a discharge weight appropriate for post-conceptional age, having shown early postnatal catch up growth

The relative proportions of these groups will reflect population characteristics in any one neonatal unit, as well as the feeding policies followed. Early postnatal catch up is unusual, although it has been reported that about 80% of very low birthweight infants with postnatal growth retardation (pattern 2) and small for gestational age infants (patterns 3 and 4) show catch up growth by 2–3 years of age.[50] Catch up growth seems to be faster and more complete in girls than in boys, and in growth restricted appropriate for gestational age infants. Bone mineralisation shows catch up within 6–12 months and becomes appropriate for skeletal and body size achieved.[51]

Increasing evidence suggests that either low birth weight or rapid early weight gain or the combination of both may predispose to adverse long term effects, such as increased risk for hypertension, cardiovascular disease, type 2 diabetes, and osteoporosis in adulthood.[52–54] Poor growth rate in the early weeks of life is associated with reduced head growth and impaired neurodevelopment at 1 year corrected age.[55] In a recent study of 219 infants with birth weight <1250 g, postnatal growth pattern and developmental status at 2 years of age were assessed.[56] Poorer neurodevelopmental scores were found in small for gestational age infants who remained small at 9 months of age, and those appropriately grown infants who at 9 months had crossed down the weight centiles. Thus the course of postnatal growth is an important independent factor in terms of developmental outcome. The potential benefits of diets providing a higher concentration of

Key points 4

- Infants fed donor human milk have been shown to have a developmental advantage over those fed a nutritionally more dense term formula milk
- Human milk may decrease the risk of necrotising enterocolitis
- Many neonatal units are focusing on supporting mothers in expressing adequate milk for their own infant as an alternative to milk banking
- When weight gain on mother's milk is inadequate a milk fortifier may be used
- For obvious reasons, it is unethical to perform randomised trials of mother's own breast milk compared with formula milk
- Studies on neurodevelopmental benefit of feeding mother's milk may be confounded by sociobiological factors

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energy, protein and of specific nutrients, such as long chain polyunsaturated fatty acids (LCPUFA), minerals, electrolytes and trace elements, on growth, bone mineralisation, and developmental outcomes have been investigated.[57] Although growth parameters may be improved,[58] neurodevelopment benefit has not been found.[58] A recent Cochrane review has concluded that the limited available data do not provide strong evidence that feeding preterm or low birthweight infants after hospital discharge, with calorie and protein enriched formula compared with standard term formula, affects growth rates and development up to 18 months after term.[59]

CONCLUSIONS

Early nutritional support in the preterm infant is an important intervention and requires careful study as it is likely to influence both short and long term health outcomes. Minimising relative starvation from the time of birth (''aggressive nutrition'') may reduce the need for promoting catch up growth after discharge from hospital. PN is often required in the first few weeks of life for infants with birth weight <1500 g, usually in conjunction with minimal enteral feeding. Preterm newborns should be fed human milk when possible, supplemented with fortifier if growth is suboptimal. Infants sent home below expected weight for post-conceptional age, are at increased risk of long term growth failure, and if fed on human milk, this should be supplemented with a fortifier to provide an adequate nutrient supply. If formula fed, such infants should receive special post-discharge formula with high contents of protein, minerals, and trace elements as well as LCPUFA. Post-discharge formula should be given until a post-conceptional age of 40 weeks, and possibly until about 12 weeks post-term. Careful growth monitoring must be part of routine follow up of all premature infants, and over-feeding and under-feeding avoided. Well designed trials of nutritional interventions including long term follow up are essential if optimum feeding regimens are to be clearly defined. Further research is required to determine the specific nutritional needs of infants born before term with prenatal and postnatal growth restriction, both during and particularly after hospital stay, and to evaluate the effects of nutritional interventions on long term growth, neurodevelopment, and other health outcomes. Although long term clinical follow up of infants progressing through neonatal intensive care units may help clarify the relation between early growth patterns and adult illness, such data are not routinely collected. It is more likely that long term follow up studies of the type pioneered by Lucas and colleagues[60] will give meaningful insight into this complex area. The origins of health and disease have now become an important research challenge, bringing nutritional interventions in the newborn to centre stage.[61]

Key points 5

- Poor weight gain or too rapid early growth may predispose to adult disease including hypertension, cardiovascular disease, type 2 diabetes, and osteoporosis
- Early energy deprivation is related to reduced head growth and poorer developmental outcome
- Nutrient enriched post-discharge formula can improve growth but have not been shown to have an effect on neurodevelopment

MULTIPLE CHOICE QUESTIONS (ANSWERS AFTER THE REFERENCES)

1. Parenteral nutrition in the premature newborn:

(A) has been shown in randomised trials to improve outcome
(B) must contain cysteine
(C) replicates breast milk amino acid content
(D) does not contain glutamine principally because it is a non-essential amino acid
(E) has been widely used since the 1950s

2. Preterm infants fed breast milk rather than standardised term formula are:

(A) at lower risk of NEC
(B) receive a lower energy and mineral intake
(C) have permanently undermineralised bones
(D) most commonly receive their milk from a milk bank
(E) have improved neurodevelopmental outcome

3. Necrotising enterocolitis:

(A) is rarely seen in babies with birth weight >1500 g
(B) causes death in around one in four cases
(C) occasionally requires surgical intervention
(D) is usually caused by bacterial infection
(E) is not seen in infants given total parenteral nutrition

4. Infants discharged from neonatal units

(A) are frequently undernourished at discharge
(B) can be expected to show full catch up growth in almost every case
(C) should receive a nutrient enriched post-discharge formula to optimise neurodevelopment
(D) when fed breast milk, will grow better with a fortifier added
(E) sometimes show later weight faltering

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ANSWERS

1. (A) False; parenteral nutrition transformed the prognosis of infants with congenital anomalies of the bowel but was not subjected to critical evaluation in the preterm infant in the form of large scale randomised trials comparing with enteral feeding. (B) True; amino acid requirements in the preterm newborn are quantitatively and qualitatively different from requirements in adults. Cysteine, histidine, tyrosine, taurine, proline, and alanine are regarded as semi-essential because of immaturity of metabolic pathways. (C) False; the optimum composition of amino acid solutions for the premature newborn is not fully defined and composition is strongly influenced by physicochemical considerations as well as cost. Egg protein based mixtures have been modified to make them rather more like breast milk, for example reduced intake of phenylalanine and inclusion of taurine. (D) False; glutamine is abundant in plasma and breast milk and possibly conditionally essential in the sick newborn. Instability and costs are the two main reasons why it has not been incorporated routinely into PN, together with a lack of evidence for clinical benefit. (E) False; the first case of long term PN maintaining growth and positive nitrogen balance in a child with ileal atresia was published in 1968. PN became widely used in neonatal unit in the second half of the 1970s and so is a comparatively recent intervention. 2. (A) True; a number of studies have suggested that NEC is less common in infants who receive human milk, which is known to have many anti-infective and anti-inflammatory properties. Very few studies have randomly compared human milk against formula milk with NEC as a primary end point. (B) True; compared with formula milk, human milk generally contains less protein, fat and mineral. This was particularly evident with ''drip'' milk collected for milk banks. (C) False; despite the low mineral content of human milk, bone mineralisation seems to improve rapidly through early life, such that by 8–12 years of age there is no apparent effect of early diet. (D)

False; whereas most large neonatal units had access to milk banking, this is no longer the case and the emphasis is more likely to be on supporting mothers in expressing their own milk. This milk is likely to be of better nutritional quality (higher fat and protein) than banked drip milk. (E) True; despite nutritional deficiencies, human milk is associated with a better developmental outcome (in boys) than more nutrient dense term formula milk. Many factors may be implicated, including its n-3 fatty acid content and biologically active peptides. 3. (A) False; although extreme prematuriy is an important risk factor for NEC, almost a third of cases reported in the UK involved infants above this birth weight. (B) True; in the UK survey by the British Paediatric Surveillance Unit, overall mortality was 22%. (C) False; around one third of infants with definite NEC require surgical intervention, usually to remove affected bowel in the face of perforation or deteriorating clinical status despite medical management. (D) False; the aetiology of NEC is unknown and is probably multifactorial. Enteric flora play a part and occasionally specific organisms (for example, found contaminating milk feeds) have been implicated. (E) False; although the vast majority of infants who develop NEC have been enterally fed, gut starvation during PN has not been shown to reduce risk. In fact some studies suggest that this increases the risk of developing the condition. Generally trophic feeding should be given with PN, and the term TPN as short hand for PN be avoided. 4. (A) True; particularly for very low birthweight infants (<1500 g), achieving growth rates comparable to a fetus of the same postconceptional age is an elusive if desirable goal. Many of these infants are discharged home weighing much less than a term infant. (B) False; about 80% of infants may show good catch up, but this is less likely in those children who were small for gestational age at birth. (C) False; nutrient enriched post-discharge formula have certainly been shown to promote catch up growth, but there is no conclusive evidence of neurodevelopmental advantage. (D) True; breast milk fortifiers are widely used and are associated with improved growth. They seem safe, although there have been concerns that they may counteract the immunoprotective properties of breast milk. (E) True; infants who grow well and have achieved catch up by the time of discharge may show later growth faltering, and require careful monitoring as this pattern may be associated with poor developmental outcome.