What's new in enterally feeding the preterm infant?

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INTRODUCTION

Over the last two decades many aspects of neonatal care have undergone extensive changes, management of enteral feeding included.

In this article current evidence around feed initiation and progression will be reviewed. The feed options available will also be discussed as will management of feed intolerance.

WHEN TO START

In stable low-risk preterm infants it is increasingly accepted that enteral feeds should be started on day 1.[1]

In high-risk infants, there is also a move to earlier enteral feeding for many of the same reasons as in lower risk infants; however, audit of practice shows that there remains a more cautious approach.[2] Infants at highest risk of developing necrotising enterocolitis (NEC) are those born extremely preterm, those with growth retardation, those with poor blood flow in utero and unstable infants on ionotropes.

There is a Cochrane review suggesting that there is insufficient data to prove safety of early enteral feeding[3]; however, it included only 2 trials with a total of 74 participants, very few of which were high risk. In another review authors concluded that the data available could not exclude an increased risk of NEC in the group given early feeds whether trophic or advancing.[4] These reviews are based on randomised controlled trial data, which unfortunately is limited, where as there is a substantial amount of evidence from other types of trials suggesting benefit.[1] An issue not resolved by the work carried out so far is the question of whether to initiate feeds with formula or human milk, those units with access to donor milk are spared the decision of whether to delay feeds in high-risk infants if human milk is not (yet) available. However evidence suggests any enteral feed early on may be better than gut starvation.

A large multicentred trial is currently being carried out in the UK which will help shed some light on issues around whether early or delayed feeds are beneficial for high-risk neonates.[5]

HOW TO PROGRESS

Once a decision has been made to begin enteral feeds there is a choice of progressively increasing volumes on a daily basis or keeping at subnutritional levels for up to around 7 days; this is known as minimal enteral, or trophic, feeding.[6] This is usually defined as around 1 ml/kg/h; with no consensus on method of delivery.

A review of trophic feeds versus advancing feeds for high-risk infants has recently been published.[7] In summary, the authors suggest starting trophic feeds early, not advancing at first, then advancing reasonably rapidly. Interestingly no advantage was found for trophic feeding in a randomised controlled trial of extremely low birthweight infants.[8] This latter trial is useful as it was carried out with babies entering the era of antenatal steroids and postnatal surfactant and therefore reflects a more contemporary population; compared to older studies carried out in the 1980s and early 1990s.[7] A paper published in 2003 remains one of the largest randomised controlled trials of trophic versus advancing feeds;[9] it generated much discussion as it was stopped early due to an excess of NEC in the group assigned to advancing feeds. However on examining this paper it is interesting to note that death rate did not differ between the groups and those on the trophic feeds had significantly more central lines and parenteral nutrition which in itself could increase risk of infection. Enteral feeds were not started until around day 9 in either group, and only 51% of advancing compared to 63% of trophic infants received antenatal steroids. There is further evidence that caution still needs to be exercised with feed advancing protocols following a recent multicentred case controlled study.[10] It found that NEC cases received trophic feeds for a shorter time than controls and reached full enteral feeds more rapidly. There are limitations due to the study design, a randomised trial to replicate the work of Berseth and her group in today's population of preterm infants is needed. However this paper does suggest that enteral feeding is a modifiable factor in the aetiology of NEC; the challenge remains to identify those few infants at most risk while avoiding overcautious feeding of the majority.

With respect to feed advancement, the recommendation for advancement after a period of trophic feeds is echoed in recent Cochrane review.[11] There was found to be no advantage when increasing at 15–20 ml/kg/day compared to 30–35 ml/kg/day; however, this review did not include many high-risk infants and the majority were formula fed. Interestingly, despite a faster achievement of full enteral feeds and regaining of birth weight in the group with the rapid increase in feeds, length of stay did not differ between the groups.

Nutrition practices on neonatal units in the USA were reviewed in 2006 and published in 2009.[2] It was found that there was earlier initiation of enteral feeds and larger volume increases that a similar survey in 2001.[12] In the most recent study non-ventilated infants were started on enteral feeds by day 2 compared to day 3 in those

who were ventilated; however there was no difference in feed advancement, which was between 5 and 30 ml/kg/day with most infants advanced at 10–20 ml/kg/day, a level which the authors commented is probably too cautious. A total of 88% had breast milk as their first enteral feed in this study compared with 80% having sterile water or glucose solution in a previous study.[13]

It would be useful to have more evaluation of type of milk used as numerous studies have found better tolerance and lower risk of NEC when the feed is human milk.[14–16] Unfortunately, studies using mothers own milk versus formula exclusively can never be randomised controlled trials, and for many it would be considered unethical to randomise to formula milk for the most at risk infants if donor milk was available. Further studies evaluating donor milk versus formula for early enteral feeding would be a useful addition to the knowledge base. However one group using an exclusively human milk fed cohort observed a reduced risk of sepsis in infants achieving full enteral feeds before 14 days.[17] This allowed a better evaluation of benefits of feed advancement with out confounding by feed type, showing that even with all human milk feeding, early feeding is a separate strategy associated with benefits.

In summary starting enteral feeds early in the majority of infants is beneficial. Whether and how long to keep at trophic feeds cannot be confidently stated, however for low-risk infants an increase of around 30 ml/kg/24 h has been reported as being safe. In high-risk infants there is less data, with more evidence for trophic feeds over several days followed by an increase of around 10–20 ml/kg/24 h with a low threshold for delaying feed increases with signs of feed intolerance or other clinical signs which concern the team. Evidence suggests more caution with formula fed infants, as discussed later in this article.

FEED TOLERANCE

There are many factors that aid decisions as to the progression of feeds. One is tolerance as judged by the volume aspirated from the stomach prior to a feed. Unfortunately many studies that report on feed tolerance are not powered to detect differences in NEC and report it only as a secondary outcome. Volume and colour of aspirate may be more an indicator of gut immaturity rather than gut dysfunction;[18 19] however these are important signs used in the decision about increasing feeds, particularly in high-risk infants and when taken into consideration with other signs. When aspirates occur in isolation, whatever their colour, they should not immediately lead to withholding of feeds. Evidence from formal trials cannot be exclusively used to inform the progression of feeds, the overall impression nursing staff and parents build up when looking after an infant over a period of time is vital to take into account. With increasing rates of skin to skin holding of babies by parents, the parents may be able to contribute more to the assessment of a baby's condition as they become aware of their own babies' pattern of behaviour.

Passage of meconium is delayed in preterm compared with term infants and takes longer the more premature the infant.[20] Feeds appear to be better tolerated and increased more rapidly in infants who pass meconium most rapidly.[21] Thus methods to speed up meconium passage have been evaluated. Routine glycerine enemas have been associated with less time to full enteral feeds and less sepsis,[22] however this was a retrospective observational study. In a randomised controlled trail no benefit was seen.[23]

When feed intolerance does occur there is evidence that carrying on with minimal enteral feeding (MEF)/trophic feeding rather than going nil enterally is associated with less sepsis and shorter time to full enteral feeds with out any increase in NEC, however it is important to note that this was not a randomised controlled trial.[24]

There have been investigations into other mechanisms to aid feed tolerance including the use of erythromycin,[25] there was no overall recommendation in this paper but some indication that this treatment may be of use at higher doses in infants >32 weeks who are more likely to have developed the appropriate receptors. The use of an antimicrobial in this context remains contentious.

There is some evidence that probiotics may have a positive effect on upper gut function,[26] but further evidence is needed to establish whether this is a clinically useful effect. The type of milk used will also have an effect on feed tolerance as discussed later.

TYPES OF FEED

Breast milk expressed by the infants own mother is the first choice of feed. Numerous benefits have been shown in the short and long term.[14–17 27 28]

If a mother's own milk is unavailable and the baby is in a high-risk category donor milk from a milk bank is the next choice. Although not formally evaluated, anecdotally donor milk is similar to mother's own milk with respect to markedly improved feed tolerance. It also retains anti-infective properties and reduces the risk of NEC.[29]

The most recent paper reviewed by Quigley *et al* was that of Schanler *et al*, the study being carried out in 2000.[29] No advantage of donor milk over formula was found when used to supplement mothers own milk, however the overall incidence of NEC was less than expected giving the study less power than hoped to detect a difference between groups.[30] The analysis was carried out as intention to treat, this resulted in 21% of the donor milk allocated group receiving formula instead of donor milk but remaining in the donor milk group for analysis.

Another point to consider is the feeding protocol in this study; babies were not randomised until day 5 postnatally and they were not given any enteral nutrition until that time (Richard Schanler, Department of Paediatrics, Schneider Children's Hospital, North Shore, Manhassett, NY, USA, personal communication). It would be useful to know if giving donor milk during these early days would have made a difference to the outcome. In the UK in many neonatal units these early days are when donor milk is most frequently used. Figure 1 shows that 49% of babies received donor milk only up to day 5 during 2008 at Queen Charlottes and Chelsea Neonatal Unit, London. This reflects the early days when many mothers may be struggling to initiate their lactation, particularly if they are unwell themselves.

With respect to other enteral feeds there has been some evidence that hydrolysed protein based formula aids gastrointestinal transit[31] and accelerates enteral feed advancement.[32] However a recent study did not find any advantage of hydrolysed over whole-protein formula[33] or breast milk[34] and a review of the literature up to august 2006 concluded that there was insufficient evidence to warrant routine use of these feeds for preterm infants.[35]

FEED ADMINISTRATION

There continues to be debate around bolus versus continuous tube feeding with a Cochrane review unable to recommend one method over the other due to lack of sufficient evidence.[36] Infants randomised to continuous feeding appeared to have a short-term advantage in achieving full enteral feeds in one study; however, no assessment was made of growth and tolerance in the longer term. There is a risk that this may have been compromised as human milk fat is lost in the tubing with continuous feeding.[37] The same group have recently reported higher behavioural stress responses in bolus versus continuous fed infants,[38] the implications of this need further considerations and balancing with the advantages of bolus feeding reported in other studies.

Feed frequency with MEF has not been evaluated and is variable, somewhat constricted by the very small volumes administered. Once higher volumes are given and feeds are advanced there is more choice and debate overfeed frequency. In general smaller infants are given 1 or 2 hourly feeds moving to 3 and sometimes 4 hourly as they grow and are judged able to tolerate larger bolus volumes (although 4 hourly is probably not physiological in babies on human milk and is certainly a much longer interval than normal in breastfed babies). A recent retrospective evaluation of two time periods on a unit where 2 hourly feeds were employed followed by 3 hourly found that the more recent years when 3 hourly feeds were instituted was associated with a longer time on continuous positive airway pressure (CPAP) and phototherapy.[39] Although there are problems with comparisons of two different time periods, as 3 hourly was used in the most recent time period one would have expected if anything decreasing time on CPAP, suggesting that 2 hourly has true advantages over 3 hourly.

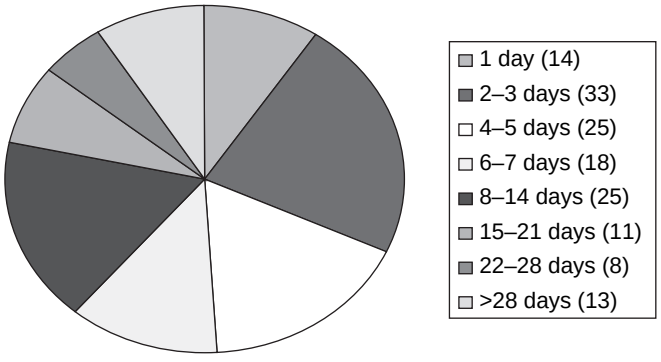

Figure 1 Number of infants per days on donor breast milk during 2008 at Queen Charlottes Neonatal Unit, London, UK. Data reproduced with permission of Gillian Weaver, Milk Bank Manager, Queen Charlottes Neonatal Unit, London, UK.

HUMAN MILK: NUTRITIONAL ASPECTS

With the increasing use of human milk for preterm infants there is a need for guidance on assessment as to whether all nutritional requirements are being met. Whereas formula milk comes with information on levels of its constituent nutrients, human milk does not and due to the large variability in composition of some components of human milk extra care is needed to tailor the feed to the baby. Due to high mineral needs the preterm infant fed exclusively human milk usually needs a phosphorus supplement initially; this should be titrated to keep serum levels with in normal. Calcium will be needed but can be given with a multinutrient fortifier. With higher requirements of many vitamins a multivitamin containing vitamin A and D is advisable once parenteral vitamins have been stopped. Protein and energy are more variable in expressed human milk so do not lend themselves so easily to routine supplementation.

During the first few weeks of lactation human milk protein levels drop, reaching mature milk levels after 2–3 weeks (see figure 2). If fed at sufficient volume this early milk will supply protein needs for most infants for the first weeks, but eventually additional protein will be needed, particularly for less mature babies (<1500 g birth weight). Protein supplementation is usually achieved with the addition of a multi nutrient fortifier, which is discussed later.

Human milk fed preterm infants can receive sufficient energy but this depends on expressing technique and how the milk is subsequently handled. The fat and therefore energy content can be optimised by instructing mothers to completely empty the breast at each expression to ensure collection of all the fat rich hind milk.[40] In such circumstances milk energy has been found to be a mean of 87 kcal/100 ml with a SD of 18 kcal.[41] Figure 3 shows the increasing levels of fat present in milk

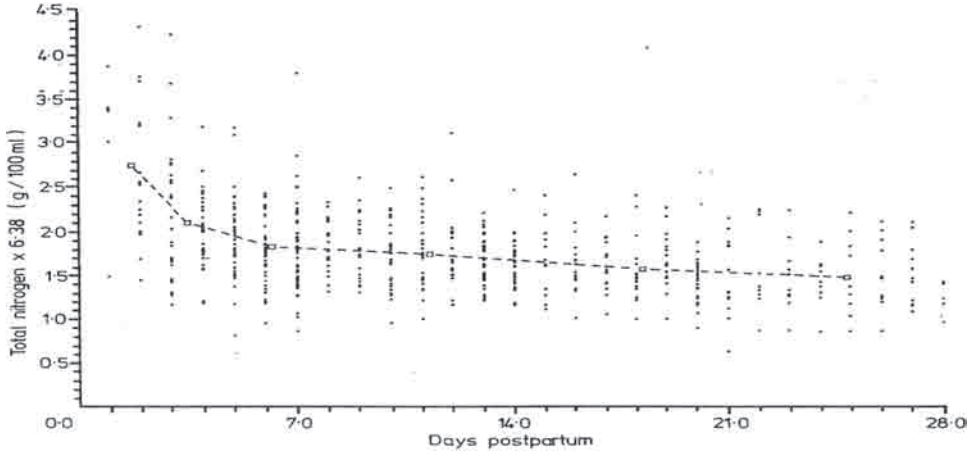

Figure 2 Reduction in protein levels of preterm human milk during the first 28 days. The protein content (determined as total nitrogen×6.38) of all 588 samples analysed are plotted against time (days) postpartum. The mean protein content is shown (squares) for days 1 and 2, days 3 and 4, days 5 and 7, and for weeks 2, 3 and 4, and these values are joined by a dashed line. From Lucas and Hudson.[52]

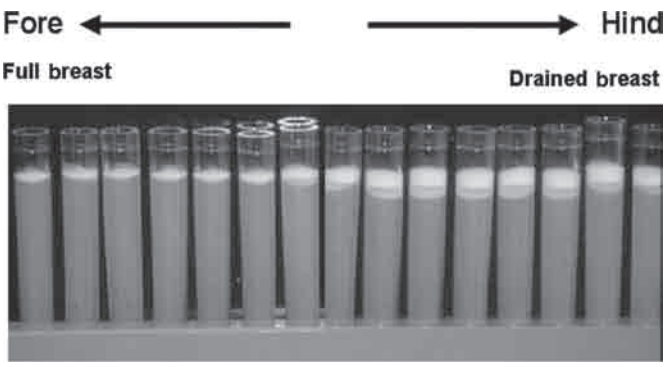

Figure 3 Increase in fat in milk samples collected every 60 s during a 15 min breast expressing using an electric pump. Copyright Peter Hartmann/Donna Geddes, Perth, Western Australia, Australia.

expressed over 15 min from a full breast, it clearly illustrates the effect on total milk fat content should the expression be finished at 5 or 10 min leaving the highest calorie milk in the breast.

Once expressed, the fat portion of the milk is prone to separation and adhesion to container sides and tubing.[42] In addition handling the milk when it is cold is likely to increase fat loss as the fat solidifies, however warming must be performed carefully and according to guidelines to avoid risk of overheating. Continuous tube feeding can lead to very large losses of fat, which can be partly rectified when the syringe nozzle is positioned facing upwards.[43]

Once milk protein levels have reduced so that an infant receives less than 3 g protein per kg, serum urea tends to be <1.6 mmol/litre.[44] Although accuracy of serum urea in identifying protein intake has been questioned in the past, the balance of current evidence suggests that it is useful.[45 46] Before adding protein as a supplement it is useful to check that the infant is receiving the maximum volume he or she can tolerate. If despite this serum urea remains low additional protein should be given. This is most easily given as a multi nutrient fortifier rather than single nutrients for practical reasons, that is, the current products do not increase osmolarity of the milk to the same degree as some of the individual supplements, it avoids the risk of error inherent in the measuring out of several supplements rather than just one and those in sachets are usually sterile.

There are different approaches towards the use of fortifiers. One is to fortify once there are biochemical signs of inadequate protein intake as suggested above, another is to do so once a certain volume of feed has been reached, often 100 or 150 ml/kg. The latter approach will entail some infants being given more than 4 g protein/kg. At intakes beyond this level weight gain appears to plateau (see Tsang *et al*).[47 48] In addition once fortification has been started it can be given at a fixed or variable rate depending again on milk analysis.[49] The varying of fortification depending on milk protein content is only really feasible if a rapid accurate method of breast milk analysis is available in which the diurnal variation in milk protein content is factored into the assessment.

With respect to updated assessment of nutritional requirements for all preterm infants whether human milk or formula fed new European guidelines are soon due to be published by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

SUMMARY

The advances in enteral feeding of preterm infants have to some degree mirrored the improvements in medical care allowing earlier and faster rates of feeding. Despite some increase in knowledge around NEC it remains a condition which is still a real threat on neonatal units.[50] Among other factors it is linked to enteral feeding practices however there remains a lack of guidance on how to identify which baby is most at risk. One thing that does seem to make a difference is implementation of standardised feeding guidelines,[51] and the use of human milk.

Competing interests None.

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