East of England Perinatal Networks

NHS

Clinical Guideline: Enteral Feeding of Preterm Infants on the Neonatal Unit.

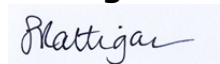**Author:**   Lynne Radbone, Principal Paediatric Dietitian

Developed in conjunction with the East of England Perinatal Network Neonatal Nutrition Working Group.

For use in: EoE Neonatal Units
Guidance specific to the care of neonatal patients

Used by: Medical Staff, Neonatal Nurse Practitioners, Dietitians

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Audit Standards:
- **100% of babies on the neonatal unit have feeds initiated and advanced in line with algorithm 1 and where deviation exists a documented explanation is provided.**
- **100% of babies on the neonatal unit receive feeds in accordance with algorithm 2.**
- **100% of babies on the neonatal units have their weight recorded daily on the NICU and at least 2 times per week in SCBU.**

1. Introduction

As survival rates for preterm infants improve more emphasis is being put on improving the quality of outcome by concentrating on optimising nutritional management. Suboptimal nutrition commencing in the early neonatal period contributes to postnatal malnutrition and accumulation of growth deficits, especially in the smallest most immature infants. Delaying the introduction of luminal nutrition can result in nutritional deficits and reduced resistance to infection. Conversely over nutrition and excessive growth acceleration may lead to adverse health issues such as diabetes, obesity and cardiovascular disease in later life.(1)

The goals of nutritional support in the preterm include:
- Achieving an acceptable standard of short term growth.
- Meeting the recognised nutritional requirements of the preterm infant.
- Preventing feeding-related morbidities, especially the prevention of Necrotising Enterocolitis (NEC).
- Optimising longterm outcomes.

Nutritional management in Neonatal Units across the Network is marked by a lack of uniformity(36). In the US, differences in practice were found to be greatest between Neonatal units, though they also existed between individual Neonatologists within the same institutions.(2)

Although there is uncertainty around the definitive practice of nutritional support in preterm infants standardisation of practice across the Network is recommended for two reasons:

- A significant and prolonged decline in the incidence of NEC, nearing virtual elimination in some centres, has been reported consistently since the implementation of a standardized feeding regimen (SFR) in the form of clinical practice guidelines.(3)

- Quality improvement literature suggests that a continuing cycle of process planning, consistent implementation, review and audit of practice is highly effective in clinical medicine.(4)

This guideline aims to use available evidence alongside national and network best practice to provide, within a practical reproducible framework, both optimal nutritional care and the individual nutritional needs of infants born prematurely in the East of England.
It is designed to be used in conjunction with individual clinical assessment processes where decisions are made regarding the initiation and advancement of feeds in premature infants.

Evidence supporting recommendations can be found in Appendix 2

2.0 Nutritional requirements of the preterm infant.

Evidence based estimations form the basis of published nutritional requirements for preterm infants, the most recent being Tsang 2005 & ESPGHAN 2010 (5,6)
These calculated requirements are high as preterm infants are born at a time when in utero growth rates would have been 2-3 times greater than a baby born at term, however, the increased nutrient demands are not evenly spread. These variable increases are not met by a straight increase in volume of breast milk provision and have led to the development of specialist formulas and breast milk fortifiers for use in the preterm population.

Nutrient	Term infant	Preterm infant Tsang 2005		Preterm infant 1000g -1800g ESPGHAN 2010
		ELBW	VLBW	
Energy (Kcal/kg)	95 -115	130-150	110-130	110 -135
Protein (g/kg)	2	3.8-4.4	3.4-4.2	4.0 – 4.5 (<1.0kg) 3.5 – 4.0 (1.0 - 1.8kg)
Sodium (mmol/kg)	1.5	3.0-5.0	3.0-5.0	3.0 – 5.0
Potassium (mmol/kg)	3.4	2.0-3.0	2.0-3.0	2.0 – 3.5
Calcium	3.8mmol/kg	2.5-5.5 mmol/kg	2.5-5.5 mmol/kg	3.0 – 3.5 mmol/kg
Phosphate (mmol/kg)	2.1	2.0-4.5	2.0-4.5	1.9 – 2.9

3.0 Feeding the preterm infant.
(See Algorithm 1 & Appendix 5)

3.1 When to start feeding

Stable non high risk preterm infants should commence feeding as close to birth as possible.(7) There is growing evidence to support a move to earlier enteral feeding in the high risk infant(8).
Infants considered high risk should include:

- <28 weeks gestation or <1000g birth weight
- Preterm SGA infants (<2nd percentile and <34 weeks gestation)
- Absent or reversed end diastolic flow in infants <34 weeks
- infants re-establishing feeds after an episode of Necrotising enterocolitis (NEC)
- Perinatal hypoxia-ischaemia with significant organ dysfunction.
- infant with congenital gut malformations (eg gastroschisis)
- hypotensive/unstable ventilated neonates

Caution should be taken when initiating feeding in the following subgroups. Treatment as high risk should be at individual clinical assessment.

- Severe SGA infants (<0.4th percentile and >34 weeks gestation).
- complex congenital cardiac disease
- dexamethasone treatment
- Indomethecin or Ibuprofen treatment for PDA
- polycythaemic infants

3.2 Trophic feeding

Trophic feeds are small volumes of milk given to stimulate the bowel which are maintained for up to 7 days and not intended to contribute to nutrition.

- The maximum volume classed as a "trophic feed" is 1ml/kg/hour or 24ml/kg/day.(9)
- Trophic feeds should be considered in very premature or very high risk infants in order to utilize maternal colostrum and stimulate gut trophic hormones.
- There is no recognised consensus on duration or method of delivery.(10)
- Trophic feeds should commence as soon after delivery as possible where clinically indicated.
- Trophic feeds can be initiated and advanced during Indomethicin/Ibuprofen treatment.(11)
- Trophic feeding of preterm infants with IUGR and abnormal antenatal Doppler results may not have a significant impact on incidence of NEC or feed intolerance.(12)
- Individual infants should be assessed daily for tolerance and decisions made with regard to continuation of trophic feeding or standard advancement of feeds.

3.3 Rate of advance of feeding

Current data do not provide evidence that slow advancement of feeding in very low birth weight infants reduces the risk of NEC (12,13) however available evidence and current best practice suggest the following:

- In standard risk infants a rate of increase of 30ml/kg/day is reported safe.
- In high risk infant evidence points towards a period of trophic feeds followed by a rate of increase of 10-20ml/kg/day.
- There should be a low threshold for withholding stepped increases secondary to intolerance in the high risk infant.(14)

3.4 Assessing feed tolerance

Careful clinical assessment is essential to prevent unnecessary limitations of enteral feeds, reliance on parenteral nutrition, delay to full feeding and poor growth. Gastric residual volume and colour of aspirate may indicate level of gut maturity rather than gut dysfunction(15) and as volumes vary in the early stages of feeding significant increases should not be used in isolation when deciding to limit advancement of feeds(1). For the early detection of VLBW infants at risk for NEC, gastric residual volumes and bloody residuals in combination represent an early relevant marker.(16) Use of diluted feeds is not recommended.

Signs of intolerance:
1. Vomiting
2. Gastric residuals >25% of previous 4 hours feed volume, persistent or increasing.
3. Abdominal distension/increasing abdominal girth

Signs of Necrotising Enterocolitis (NEC):
1. Bilious/ bloody aspirates
2. Visual bowel loops/abdominal discolouration.
3. Grossly bloody/watery or abnormal stools
4. Clinically unstable or acute deterioration.

Suggested interventions if signs of intolerance present:
1. Medical review.
2. Consider septic screen and/or abdominal x-ray.
3. Consider continuing with trophic feeds rather than nil enterally (not if signs of NEC).

Available recommendations suggest undigested milk residuals should be refed and feeding continued if:
1. Residual volumes <25% of previous 4 hour feed volume.
2. Residual volumes are present during low volume/trophic feeding.

3.5 Method and frequency of feeding

Bolus V Continuous feeding
There is insufficient evidence to support one method of administration over the other, however data suggests that: (1)

- Bolus feeding may be more physiologic in the preterm infant.(17)
- Bolus fed infants may experience less feed intolerance and have a greater rate of weight gain.(18)
- Growth may be compromised in continuous feeding as human milk fat adheres to the tubing.(19)
- Infants fed continuously take the same length of time to achieve full feeds as those fed bolus feeds.(20)
- Higher behavioural stress responses in bolus fed infants have recently been reported.(21)

Gastric administration of feeds is recommended. Transpyloric feeding is not routinely recommended in preterm infants as no benefits have been found and they have been associated with a greater incidence of gastrointestinal disturbance.(22)
Feed frequency in trophic feeding has not been evaluated and is constricted by the small volumes involved. Debate is greater with advancing feeds.
Infants <32 weeks should receive 1-2 hourly feeds moving to 3 hourly as they grow. 4 hourly feeds is probably not physiologic in babies receiving human milk.(23)

4.0 Milks and Indications for use. (see Algorithm 2)

4.1 Breast Milk

Breast milk expressed by an infant's own mother is the standard of care for preterm infants.(24,25)
Mothers should be counselled and encouraged to breastfeed or express milk as soon after birth as possible, even if their long term intention is not to breastfeed. They should express as frequently as possible as a minimum daily volume of 750 – 900ml by day 10-14 after birth is required in order to sustain exclusive breastfeeding.(26)
Preterm breastmilk contains higher concentrations of protein, fat, energy and sodium in the first few weeks of lactation, but these drop to the same levels as mature term milk within 2-3 weeks of birth. Eventually more protein will be required in the form of multi nutrient fortifiers, especially in those infants <1500g birth weight.(27-30)
The energy (but not protein) needs of a preterm infant can be met by breast milk alone if expressing techniques and milk handling are optimised.

- Feed to initial volume of 150ml/kg increasing to 180-200ml/kg as indicated by weight gain and volume tolerance.
- Infants born <1000g will require 200ml/kg to meet requirements for energy.
- Infants born <1000g will require 240ml/kg to meet the higher requirements for protein, increasing to 330ml/kg after two weeks, fortification is therefore indicated in this group in order to maintain lower feed volumes. (Appendix 1)

Preterm infants fed exclusively on breast milk should receive supplementary phosphorus which should be titrated against normal serum phosphate and ALT levels.

4.2 Breast Milk Fortification (31a, 31c)

The addition of Breast Milk Fortifiers (BMF) to maternal expressed breast milk (EBM) expressed 2 weeks post delivery should be considered for the following infants born <34 weeks once they are established on 165ml/kg of enteral feeds for at least 24 hours:
1. Infants with a birth weight <1500g

2. Infants with a birth weight >1500g but <2000g where-
- volumes of 180-200ml/kg EBM are not likely to be tolerated or
- Serum urea falls <2 umol/l or
- weight gain is <15g/kg/day on maximum volumes tolerated or
- IUGR where birth weight for gestational age is <9th centile

BMF need not be added if more than half of the feed requirement is provided by preterm formula, though it should be considered if there is associated poor growth and tolerance of volume. In practice this would depend on having adequate volumes of milk to fortify accurately. Where a combination feed is required it can be given either mixed or alternating with feeds of EBM+BMF or used once supplies have run out or until the next expression. There is no evidence to support one practice over the other, but the method that is easiest in practice and that involves the least amount of

milk handling is likely to be the best for individual infants. BMF should never be added as a supplement to preterm formula.

4.3 Donor breast milk(DBM)

In the absence of a mother's own expressed breast milk, donor milk, where available, might be the milk of choice for a high risk category infant, however the feasibility of use and role of donor milk in current neonatal practice remains to be established whilst availability across the network is inconsistent. (32,33)
Potential indications for use of DBM include:
- Gestational age <28 weeks
- ELBW < 1000g
- previous proven NEC
- <32 weeks and IUGR
- <34 weeks and with absent/reversed end diastolic flow

DBM has a poor nutritional profile compared to maternal EBM, use should therefore be restricted to either establishing feeds in the at risk infant with the gradual introduction of alternative feeds once full volumes are achieved, or for the short term support of a preterm infant who's mother is establishing milk expression.

4.4 Preterm formulas

Where maternal EBM is not available preterm formulas are to be used. There is no evidence to support the routine use of term or semi elemental/elemental formulas.
Indications for use of preterm formulas (31)
- infants born <34 weeks with a birth weight <2000g where EBM/DBM unavailable.
- Feed to initial volume of 150ml/kg increasing as indicated by weight gain and volume tolerance.
- Infants born >1000g will have their protein requirements met by 165ml/kg
- Infants born <1000g will have their protein requirements met by 180ml/kg
- Volumes >180ml/kg are not usually necessary and other reasons for poor growth should be sought before further volume increases are introduced.(Appendix 1)

4.5 Nutrient Enriched Post Discharge Formulas (NEPDF)

Maternal choice and the difficulties some mothers face trying to maintain breastfeeding will result in some infants requiring some or all formula milk at the time of discharge.
Infants born prior to 34 weeks and <2kg at birth who are not breastfed or who will require supplementary feeding at discharge can be transferred to NEPDF a few days before discharge, or when they have reached 2.0kg depending on rate of weight gain.

There are two NEPDFs available in the UK, Nutriprem 2 and SMA Gold Prem 2. Only Nutriprem 2 is available in a ready to feed (RTF) format which is preferable for hospital use. European guidance recommends a RTF format for ex-preterm infants for the first few weeks post discharge (34).
Nutriprem 2 and SMA Gold Prem 2 are available on prescription for preterm infants from 35 weeks until 6 months corrected age.

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There are no recommendations for infants born 34-37 weeks. As nutrient stores are better and infants are likely to establish feeding more quickly than those born more preterm a pragmatic view needs to be taken with regard to feeding. Maternal breast milk is the feed of choice.

Growth restricted term infants >37 weeks, should be offered ordinary term formula in the absence of maternal milk.(38)

4.6 Specialised term formulas (Appendix 4)

None of the specialised term formulas are designed for use in the preterm population so will not meet nutritional requirements. Energy needs might be met by increased volumes (but are often poorly tolerated). Concentration of formulas may be tolerated but will not address the nutrient imbalance.

Specialised formulas require making up from powder within a Feed Unit/Milk Kitchen environment. They will be non sterile and have potentially inconsistent composition. All powdered feeds should be made up in accordance with the Department of Health guidelines for the Use of Powdered feeds in a Hospital Environment.(35,36)
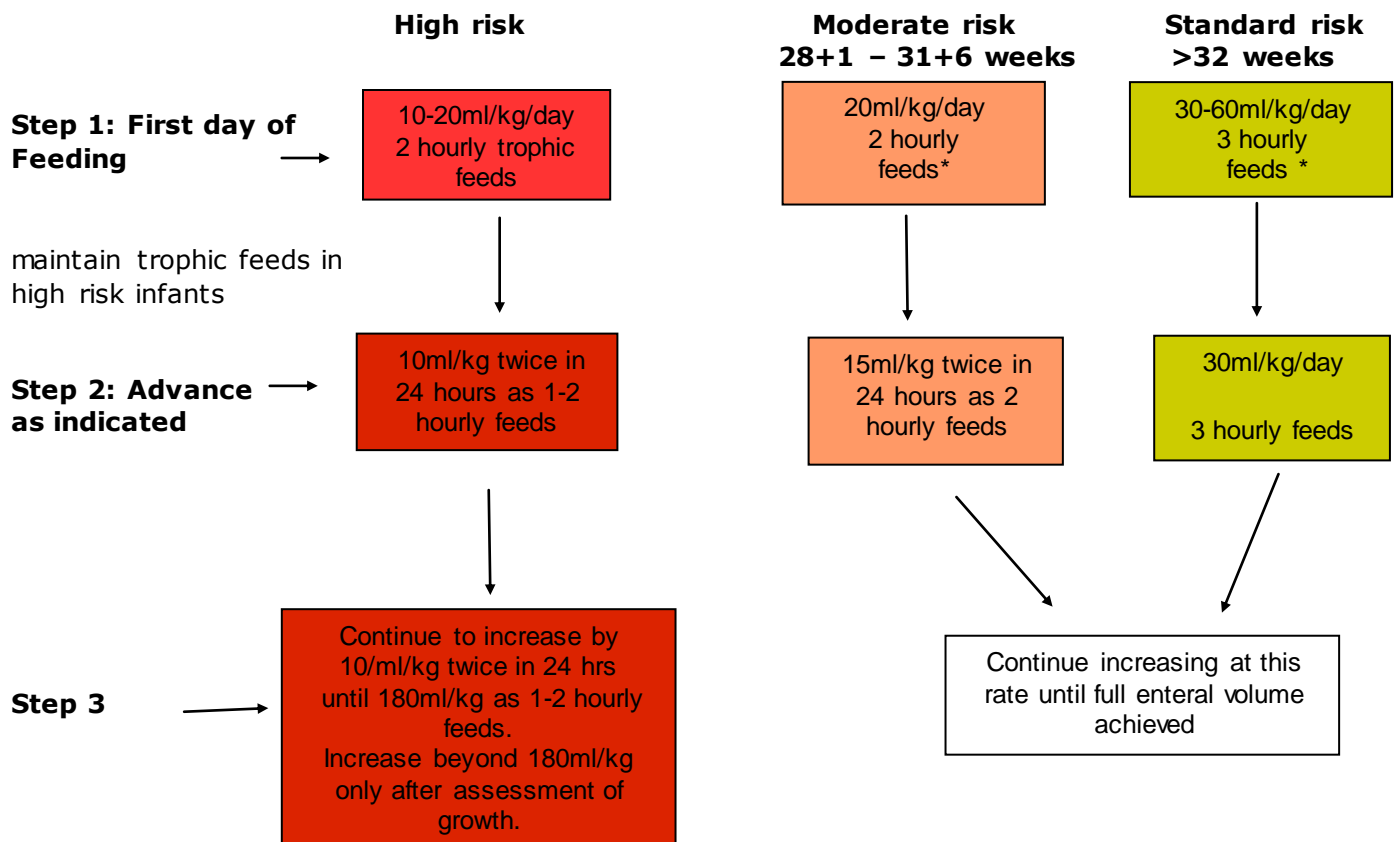
Specialsed formulas should only be used where absolutely necessary and always under the direction of a Paediatric or Neonatal Dietitian.

Soya formulas are not recommended for infants unless specifically required for treatment of galactosaemia or as part of a vegan diet.(37)

Algorithm 1 Initiating and advancing enteral feeds.

This algorithm is to be used in conjunction with Algorithm 2 – choice of milk

	High risk	**Moderate risk 28+1 – 31+6 weeks**	**Standard risk >32 weeks**
Step 1: First day of Feeding →	10-20ml/kg/day 2 hourly trophic feeds	20ml/kg/day 2 hourly feeds*	30-60ml/kg/day 3 hourly feeds *
Step 2: Advance as indicated →	10ml/kg twice in 24 hours as 1-2 hourly feeds	15ml/kg twice in 24 hours as 2 hourly feeds	30ml/kg/day 3 hourly feeds
Step 3 →	Continue to increase by 10/ml/kg twice in 24 hrs until 180ml/kg as 1-2 hourly feeds. Increase beyond 180ml/kg only after assessment of growth.	Continue increasing at this rate until full enteral volume achieved	

maintain trophic feeds in high risk infants

Commence feeding as close to birth as possible following individual clinical assessment.

Maintain trophic feeds in high risk infants as long as clinically indicated.

Infants can move between risk categories following individual clinical assessment.
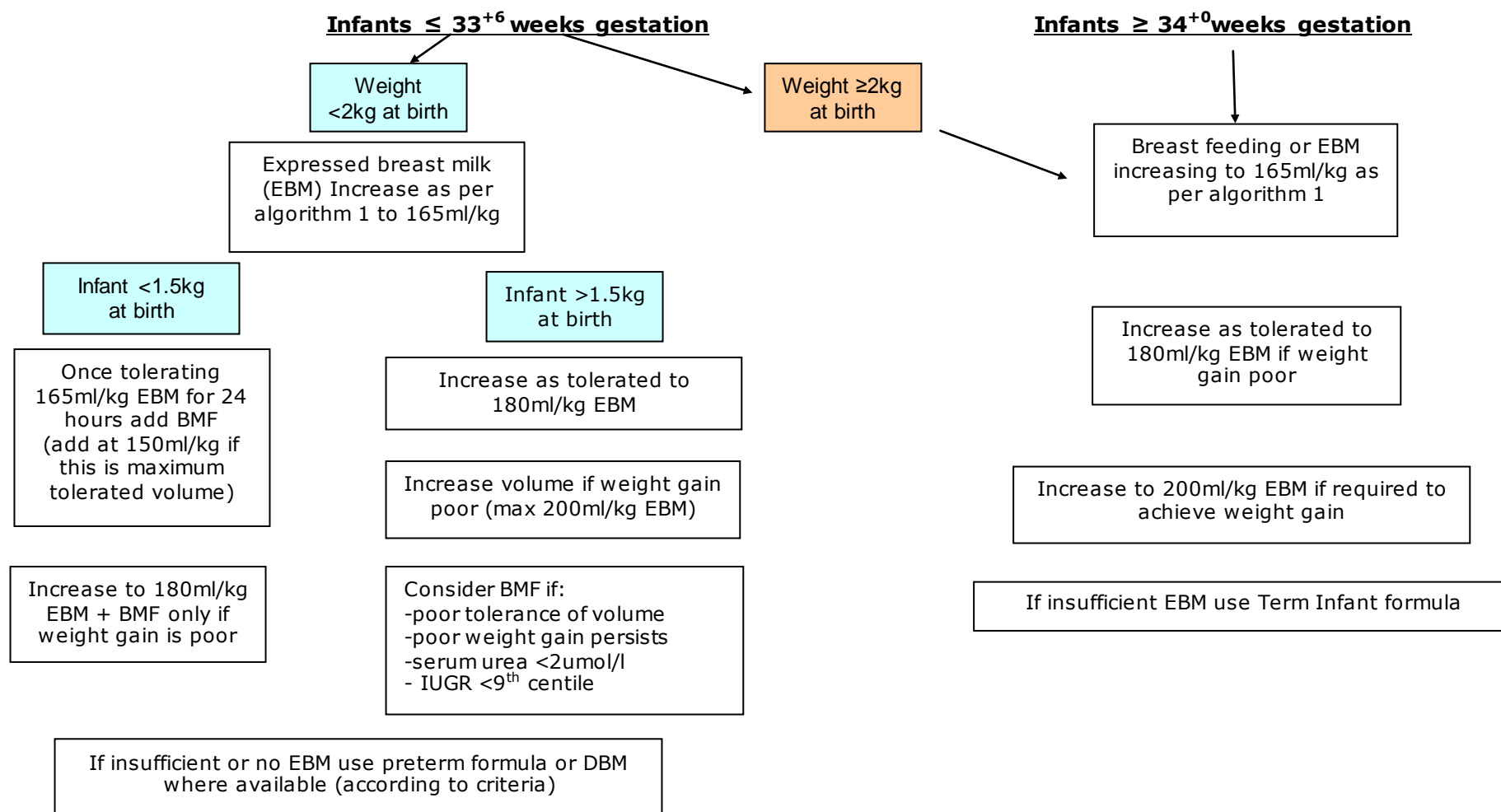
High risk defined as:
    <28 weeks gestation
    < 1000g birth weight
    Preterm SGA infant (<2nd percentile **and** <34 weeks gestation)
    Absent or reversed end diastolic flow in infants <34 weeks
    Unstable /hypotensive ventilated neonates
    Re-establishment of feeds following NEC
    Perinatal hypoxia-ischaemia with significant organ dysfunction.
    Congenital gut malformations (eg gastroschisis)

Caution should be taken initiating feeds in the following subgroups. The decision to manage as "high risk" is at clinician's discretion.
    Severe SGA infants (<0.4[th] percentile **and** >34 weeks gestation)
    Indomethecin or Ibuprofen for PDA
    Complex congenital cardiac disease
    Dexamethasone treatment
    Polycythaemic infants

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Algorithm 2 – choice of milk

Fresh maternal breast milk is the first milk of choice for all infants unless clearly contraindicated

Infants ≤ 33^{+6} weeks gestation

Infants ≥ 34^{+0} weeks gestation

Weight <2kg at birth

Weight ≥2kg at birth

Expressed breast milk (EBM) Increase as per algorithm 1 to 165ml/kg

Breast feeding or EBM increasing to 165ml/kg as per algorithm 1

Infant <1.5kg at birth

Infant >1.5kg at birth

Increase as tolerated to 180ml/kg EBM if weight gain poor

Once tolerating 165ml/kg EBM for 24 hours add BMF (add at 150ml/kg if this is maximum tolerated volume)

Increase as tolerated to 180ml/kg EBM

Increase volume if weight gain poor (max 200ml/kg EBM)

Increase to 200ml/kg EBM if required to achieve weight gain

Increase to 180ml/kg EBM + BMF only if weight gain is poor

Consider BMF if:
-poor tolerance of volume
-poor weight gain persists
-serum urea <2umol/l
- IUGR <9th centile

If insufficient EBM use Term Infant formula

If insufficient or no EBM use preterm formula or DBM where available (according to criteria)

>180ml/kg should rarely be required in infants receiving preterm formula or fortified EBM. Alternative reasons for poor growth should be examined before volumes >180ml/kg are implemented.(appendix 1)

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Appendix 1 - Growth
Appropriate weight for gestational age

Low birth weight infants (<2.5kg) born at term have nutritional requirements that differ from those of appropriate weight infants born at term. These requirements are different again to those of infants who are preterm and appropriate for gestational age as well as those who are preterm and small for gestational age.

Actual requirements are unknown. A baby who is small at term is likely to have better stores of some nutrients than the infant born prematurely. Comparatively the infant who is both preterm and small for gestation is likely to have the poorest stores of all nutrients.

Some infants born small for gestation appear to catch up in weight; others do not. Whether improving their nutritional intake is of benefit or harm is unclear, but evidence suggests the best outcome is with maternal breast milk.(38) Until more evidence is available it seems appropriate to recommend breast milk to all growth restricted term infants, with a normal term formula as first option if breast milk is not available. Infants who are preterm and growth restricted should follow advice for preterm infants.

Expected weight gain

The weekly completion of an appropriate growth chart is the best indicator of growth for an infant, however parents frequently ask how much weight their infant is expected to make on a daily basis. The most frequently used range is 15 – 20g/kg/day, but a good guide for an infant born during what would have been their third trimester would be **18g/kg/day up to 2kg then 30g/day thereafter (31b)**.

Growth monitoring

All infants should be accurately weighed at birth with note taken of any oedema present. Head circumference should be measured on the day of birth and both parameters plotted on a 2009 UK-WHO Close Monitoring Charts.

Weight should be measured two to three times per week in SCBU for the purpose of growth monitoring but daily in the NICU where the management of fluid balance is critical. All weights are to be recorded on end of bed charts and plotted weekly on the growth chart.

Length measurement is an additional growth monitoring tool, though a difficult measurement to obtain accurately. Frequency of measurement, method and equipment used is at unit discretion, though at a minimum, length should be measured and recorded at point of discharge. All measurements should be performed by one identified trained individual with a helper in order to maintain standardised practice. Lengths are to be plotted on the growth chart alongside regular weight and head circumference measurements.

Although weight is a poor measure of growth by itself, it is the only practical day to day measure that can be employed. It is needed for calculation of feeds and medications and is seen as an important indicator of progress by an infant's parents. As such measurements should be taken and plotted as accurately as possible and entered on the baby's daily data on SEND.

Growth failure

Infants born preterm accumulate significant nutrient deficits by the time of discharge from hospital (39,40). These can manifest as growth deficits that persist through infancy and early childhood (41) into adolescence.(42)

Factors contributing to nutrient deficits are numerous, though fluid restriction is often the greatest contributor. The majority of infants will meet their nutritional requirements with between 150 and 180ml/kg of an appropriate feed, therefore interruption and reductions in feeds to below 150ml/kg should be minimised. Where prolonged fluid restrictions are unavoidable in the older formula fed infant eg cardiac disease, consideration should be given to the use of nutrient dense term formulas such as Infatrini of SMA High Energy.

Conversely volume increases above 180ml/kg should only be implemented once consideration has been given to the range of other factors known to impact on growth:

- Use of the most appropriate feed for the infant.
- Adequacy of human milk fortification.
- Potential sodium depletion.
- Anaemia.
- Sepsis/trauma in the short term.
- Steroid treatment, which can delay length growth for 3-4 weeks after stopping.
- High energy requirements secondary to cardiac/respiratory condition.
- Low serum urea as an indicator of protein status.
- Organic causes of growth failure.

Due to the variable composition of breast milk a combination of poor growth and a serum urea level of <2umol/l in an infant exclusively fed maximum tolerated volumes of EBM + BMF may be an indicator of inadequate protein intake secondary to low protein levels in the EBM. These infants may benefit from a short period of time on a proportion of feed as preterm formula or the use of higher protein containing EBM that has been frozen and stored earlier in the infants neonatal course might be considered.

Appendix 2

Evidence supporting Enteral Feeding Guidelines

When to start feeding.

The objective of early feeding is to stimulate gut maturation, motility and hormone release. As starvation leads to atrophy of the gut, withholding feeds may render subsequent feeding less safe and protract the time to reach full enteral feeding.(2) A systematic review of 10 trials of early introduction of feeding conducted in 2005 (9) concluded that early introduction of feeding did not increase the incidence of NEC and shortened the time to both full feeds and discharge. These findings were confirmed by a further controlled trial along with a significant reduction in serious infections with "early" enteral feeding.(43) A more recent Cochrane review suggested there was insufficient data to prove safety of early enteral feeding(44), whilst preliminary reports from the ADEPT trial indicate that growth restricted preterm infants born after absent or reversed end-diastolic flow in the umbilical artery who are fed from the second day after birth achieve full feeds earlier than those commencing feeds on day 6 with no increase in the incidence of sepsis or NEC(8). No work has yet addressed

whether initial feeds should be exclusively breast milk (mother's own or donor) or whether initial feeds should be delayed if only formula is available. However most evidence suggests that any enteral feed given early may be better than gut starvation.(10)

Trophic feeding

Trophic feeds are small volumes of milk given to stimulate the bowel that are maintained for up to 7 days and not intended to contribute to nutrition. The maximum volume is 1ml/kg/hour or 24ml/kg/day.(9) There is no recognised consensus on duration or method of delivery.(10)

Evidence suggests that trophic feeding is beneficial for reducing length of stay and infection rates without increasing the risk of NEC (9). A more recent study suggests starting trophic feeds early, not advancing initially, then advancing relatively rapidly(45) whereas no advantage was found for trophic feeding an extremely low birth weight population in a randomised control trial published in 2008.(46) Recent studies found that available data cannot exclude important beneficial or harmful effects of trophic feeding and are insufficient to inform clinical practice(44) and that NEC cases reached full enteral feeds more rapidly and received shorter periods of trophic feeds that controls. This paper concludes that the duration of trophic feeds and the rate of advancement of feed volumes may be modifiable risk factors for NEC in preterm infants.(47) The most recent study suggests that early trophic feeding of preterm infants with IUGR and abnormal antenatal Doppler results may not have a significant impact on incidence of NEC or feed intolerance, though this study is not strong.(12) None of the papers makes recommendations for optimal duration of trophic feeds and all call for further research.

Rate of increase of feeds

Retrospective analysis of NEC cases undertaken in the early 90s led to the recommendation of limiting feed advancement to 20ml/kg/day.(48), whereas a later study comparing 15ml/kg/day with 35ml/kg/day found that infants in the faster group achieved full feeds and weight gain quicker with no increase in the incidence of NEC (49). However a study of prolonged trophic feeding before advancement was closed early because of significantly increased NEC in the non trophic feed group.(50)

Current data do not provide evidence that slow advancement of feeding in very low birth weight infants reduces the risk of NEC, showing no advantage in increasing at 15-20ml/kg/day compared to 30-35ml/kg/day.(13,14) Although time to full feeds was longer in the slowly advanced group there was no statistical differences in length of stay between the two groups.

A review of nutritional practices in the US in 2006 showed earlier initiation of feeds and higher volume increases than a similar review undertaken in 2001.(10) The range of feed increase was between 5-30ml/kg/day with the majority advancing at 10-20ml/kg/day. The authors commented that this is likely to be too cautious a figure for the majority of infants.

In standard risk infants a rate of increase of 30ml/kg/day is reported safe, whereas data is more limited in the high risk infant. Evidence points towards several days of trophic feeds followed by a rate of increase of 10-20ml/kg/day. There should be a low threshold for withholding stepped increases secondary to tolerance concerns in the high risk infant.

Assessing feed tolerance

The volume of feed aspirated from the stomach prior to a feed is one of the factors used to judge progression of feeding. Where volume and colour of aspirate may indicate level of gut maturity rather than gut dysfunction (17) they are still important signs for feed advancement when used in conjunction with other parameters. Gastric motility changes more rapidly to a normal pattern if feeds are started early and offered frequently rather than being withheld.(50) Despite this feeds are frequently stopped, or advances held on the basis of "feed intolerance". The definition of intolerance includes not only the presence and colour of gastric residuals, but also vomiting, increases in abdominal girth or abdominal tenderness, presence of abnormal or blood stained stool, presence of bowel sounds, abdominal wall discolouration, or a combination of any.(1) As all of these can occur in the healthy premature infant who is tolerating feeds(55) careful clinical assessment is essential to prevent unnecessary limitations of enteral feeds, reliance on parenteral nutrition, delay to full feeding and poor growth. Use of diluted feeds has been suggested for premature infants, however intestinal motility responses have been shown to occur earlier and to persist longer following use of full strength formula in comparison to one and two third dilutions.(56) Clearly defining feeding intolerance can lead to dramatic improvements in nutritional outcomes.(57)
Gastric residuals up to 2ml in infants <750g and up to 3ml in infants 750g – 1500g were treated as normal in the studies by Mihatsch and Bertino(54,16).
Maximum gastric residuals in premature infants who develop NEC have been shown to be 40% of feed volume compared to 14% in those who did not develop NEC, with residuals increasing dramatically over the three days before the onset of NEC.(17) For the early detection of VLBW infants at risk for NEC, both gastric residual volumes and bloody residuals represent an early relevant marker.(16) Where feed intolerance does occur possibly continuing with trophic feeds rather than stopping feeds is associated with less sepsis and shorter time to full enteral feeds with no increase in NEC, it is important to be aware that this was not a randomised control trial.(55)
 As residuals vary so much in the early stages of feeding significant increases should not be used in isolation when deciding to limit advancement of feeds(1).
Guidelines are based on the California Perinatal Quality Care Collaborative Toolkit 2008.

Frequency and method of delivery

Feeds given by intermittent bolus method promote a cyclical surge of gut hormones similar to that in adults and term infants so are considered more physiologic in the preterm infant (17). They also experience less feed intolerance and have a greater rate of weight gain when fed a bolus technique compared to continuous infusion (18). A recent Cochrane review showed no differences in time to achieve full enteral feeds and no significant difference in growth, days to discharge or the incidence of NEC and concluded that there was insufficient evidence to support one method over the other. (20). Other authors however do recommend bolus or modified bolus feeding, given over an extended period of time, for the majority of very low birthweight infants.(1,58) One study demonstrated that continuously fed infants achieved full feeds more quickly than those receiving bolus feeds, however no assessment was made of growth and feed tolerance in the longer term – there are risks that growth

could be compromised as human milk fat adheres to the tubing during continuous feeding (19). Higher behavioural stress responses in bolus fed infants have recently been reported by the same group (21), these findings need balancing against the advantages reported for bolus feeding.

Occasionally intolerance is seen in a bolus fed preterm infant with duodenal motility decreasing following a feed (56), however a bolus feed administered over a longer period of time results in a return of motility and improved tolerance.(57)

Gastric feeding stimulates digestive processes whereas transpyloric feeding has the potential benefits of delivering nutrients past the pylorus and gastro oesophageal junction for the management of gastro oesophageal reflux (GOR) disease. These feeds have to be continuous, which may account for the reduction in symptoms of GOR. Transpyloric feeding is not routinely recommended in preterm infants as no benefits have been found and they have been associated with a greater incidence of gastrointestinal disturbance.(22)

Maternal breast milk

Human milk is the preferred feed for premature infants as it offers in the short term, strong protection against infection and necrotising enterocolitis, and in the long term improved neurocognitive development. Recent evidence shows the reduction in NEC risk using human milk to be dose dependent.(59)

Maternal breast milk (handling)

The breast should be completely emptied at each expression to ensure the collection of all the fat rich hind milk(60). Handling cold milk can increase fat losses as the fat solidifies, whilst freezing with subsequent thawing can cause fat loss through the rupture of fat globules during the freezing process. The fat component in expressed milk is also prone to separation and adhesion to bottles and tubing thereby reducing the energy content of the feed.(61)

Donor breast milk

In the absence of a mother's own expressed breast milk donor milk might be the next milk of choice for a high risk category infant, however access to DBM is variable across the Network with only one Donor Milk Bank functioning within the East of England. Additionally both the role of donor milk in current neonatal practice and the feasibility, cost and impact of its use on nutrient intake, growth and development remains to be established (32,33). Observational studies suggests that donor milk is similar to mothers own milk with regard to improved feed tolerance (62) anti infective properties and reduced Necrotising enterocolitis risk(63,55). However in these studies infant growth was slower and benefits only seen when breast milk or formula was the sole source of nutrition, whereas current UK practice uses donor milk as a supplement to mother's milk. For indications other than NEC, and for long term outcomes, justification for the use of donor milk remains anecdotal.

Donor milk has an average energy content of 46Kcal/100ml (compared to 70Kcal for preterm breast milk) as the majority of donated milk tends to come from lactating mothers of older term infants. The use of donor milk should therefore normally be restricted to establishing feeds in the at risk infant with the gradual introduction of

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alternative feeds once full volumes are achieved or for the short term support of a preterm infant who's mother is establishing milk expression.

It is important to bear in mind that DBM is a human body fluid and as such carries risks of transmission of infective agents. All donor screening, handling, testing and processing of DBM in the Milk Bank is carried out according to NICE Guidelines(64). Documentation and traceability of DBM is essential. The recent NICE Guidelines contain specific recommendations for practice within hospitals receiving DBM from a central Milk Bank in addition to recommendations for central processing units.

Breast milk Fortification

Increased preterm nutritional requirements persist beyond the time when early milk composition changes to that of mature milk. This often coincides with a slowing of weight gain and a sequential reduction in serum urea, where a level <1.6mmol/l is indicative of a protein intake of <3g/kg (65).

In order to maintain the benefits of breast milk whilst optimising the nutritional status and growth of preterm infants single multi nutrient fortifiers (BMF) have been developed. The two available in the UK are Nutriprem BMF (Cow & Gate) and SMA BMF (Wyeth). Both are bovine based products. Neither formulation have clear indications for introduction or guidance for infant suitability, so practice varies considerably across the Network.(36)

Fortification of EBM using dried human milk fortifiers has been studied (66,67) and showed improved growth but low serum phosphate levels due to inadequate bone mineral concentrations.

Concerns with the use of BMFs include tolerance and effects of storage. Most studies have found no significant problems with the tolerance of fortified EBM(68.69) whilst those investigating gastric emptying have been contradictory (70,71). Storage concerns include the reduction of anti infective components (72), increased bacterial loads (73) and increasing osmolality over time secondary to hydrolysis of glucose polymers by human milk amylase (74). The majority of these effects can be reduced by adding the BMF as close to feeding as possible, though recent work shows osmolality of fortified EBM reaches a peak within 10 minutes of addition and remains consistent to 24 hours of storage(75). A Cochrane review concludes that the use of BMFs can lead to short term improvements in weight, length and head circumference and that while it is unlikely that further comparative studies with breast milk alone are to take place it recommends further research seeks to evaluate long term outcomes of BMF therapy and identify the optimum composition of BMF products.(76)

Breast milk is fortified without knowing the nutritional composition of an individual mother's EBM. As the composition of breast milk, particularly protein concentration, varies from one mother to the next and from expression to expression in the same mother, individual analysis prior to fortification would appear to be of value. Such analysis is at present impractical in day to day practice.

Serum urea has been validated as an indicator of protein adequacy after the first two weeks of life in preterm infants (65,75). Studies looking at fixed supplementation against urea determined supplementation have been inconclusive but a recent study demonstrated improvement in body weight and head circumference where protein fortification was adjusted according to serum urea levels (76).

Preterm Formulas

Preterm formulas are designed to meet the basic nutritional requirements of most preterm infants when fed between 150 and 180ml/kg.

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There are currently three formulas available in the UK. Nutriprem 1, Aptamil Preterm and SMA Gold Prem 1. The first two have a higher protein: energy ratio than the latter. All are presented in 60ml ready to feed glass bottles and are for hospital use only. They are unavailable in the community setting.

Preterm formulas can be used as soon as commencement of enteral feeding is recommended. Term formulas should not be used as they fail to meet the nutritional needs of premature infants.

There is no evidence to support the use of term elemental/semi elemental formulas in the early stages of feeding unless there is a compelling clinical reason to do so. There is no appropriate preterm formulation available in the UK, though discussions are taking place to define a suitable product profile. A partially hydrolysed premature formula has recently been introduced to the US market, but there is currently no published information as to its safety or efficacy.(1)

Appendix 3

Specialist Term Formulas used in the Neonatal Unit

Formula	Indications	Nutrient modification
Pepti Junior (Cow & Gate) Pregestimil (Mead Johnson)	Malabsorption / post NEC / post GI surgery	Hydrolysed protein / low lactose / MCT fat
Nutramigen (Mead Johnson)	Cow's milk protein intolerance	Hydrolysed protein / low lactose
Neocate (SHS)	Severe malabsorption	Amino acid
Caprilon (SHS)	Liver disease and fat malabsorption	75% MCT fat
Monogen (SHS)	Chylothorax	90% MCT fat
Kindergen (SHS)	Renal insufficiency	Low protein, potassium and phosphate
Energivit (SHS)	Protein free formula for use in metabolic regimens	Protein free
SMA High Energy (SMA) Similac HE (Abbot) Infatrini (Nutricia)	Infants>37 weeks with increased requirements or on fluid restrictions.	Nutrient enriched.
Duocal	Poor weight gain where protein intake is adequate	Fat and glucose polymer
Polycal/Maxijul	Low blood sugars	Glucose polymer
Calogen	Poor weight gain with high blood sugars	Long chain fat emulsion

Appendix 4

Nutritional Composition of Milks and Supplements

(per 100ml unless otherwise stated)

Milk/Supplement	Energy	Protein	Fat	CHO	Na	K	Fe	Ca	P	Vit A	Vit D	Osm
	kcal	g	g	g	mmol	mmol	mg	mmol	mmol	ug	ug	mosm/kg
EBM preterm	70	1.8	4	7	1.3	1.5	ns	0.6	0.5	ns	ns	~276
EBM preterm>2wks	70	1.3	4.2	7.4	0.7	1.5	ns	0.9	0.5	ns	ns	~270
EBM + Nprem BMF	86	2.1	4.2	10.4	0.9	1.7	ns	2.5	1.9	130	5	~340
EBM + SMA BMF	84.6	2.8	4.16	9.4	2	2.3	ns	2.8	2	>270	>7.6	360
Aptamil Preterm	80	2.5	4.4	7.6	2.2	2.1	1.4	3.0	2.1	180	3	370
Nutriprem 1	80	2.5	4.4	7.6	2.2	2.1	1.4	3.0	2.1	180	3	370
SMA Gold Prem 1	82	2.2	4.4	8.4	1.9	1.9	1.4	2.5	2	185	3.4	272
Nutriprem 2	75	2.0	4.1	7.4	1.3	2.0	1.2	2.4	1.6	100	1.7	315
SMA Gold Prem 2	73	1.9	3.9	7.5	1.2	1.8	1.2	1.8	1.35	100	1.5	250
SMA First	67	1.5	3.6	7.2	0.7	1.8	0.8	1.2	1.1	78	1.1	294
Cow & Gate First	67	1.4	3.5	7.5	0.9	1.6	0.5	1.30	0.8	63	1.4	350
Infatrini	100	2.6	5.4	10.3	1.1	2.4	1.0	2.0	1.3	81	1.7	325
SMA High Energy	91	2.0	4.9	9.8	1.0	2.3	1.1	1.4	1.4	100	1.4	415
Similac High Energy	101	2.6	5.4	10.3	1.09	2.31	1.1	2	1.34	100	1.7	ns
Pepti Junior	66	1.8	3.5	6.8	0.9	1.7	0.8	1.3	0.9	52	1.3	210
Pregestimil	68	1.9	3.8	6.9	1.3	1.9	1.2	2.0	1.7	77	1.3	330
Neocate	71	2.0	3.5	8.1	0.8	1.6	1.1	1.2	1.1	79	1.3	360
Caprilon	66	1.5	3.6	7.0	0.9	1.7	0.5	1.3	0.9	76	1.9	233
Monogen	74	2	2.1	12	1.5	1.6	0.7	1.1	1.1	57	1.2	280
Kindergen	101	1.5	5.3	11.8	2.0	0.6	1.0	0.6	0.6	130	5.4	215
Energyvit	74	ns	3.8	10	0.8	1.6	1.1	1.2	1.1	79	1.3	190
Duocal /100g	492	ns	72.7	22.3	<0.9	<0.1	ns	ns	ns	ns	ns	nr
Polycal/Maxijul100g	384	ns	ns	96	ns	ns	ns	ns	ns	ns	ns	nr
Calogen	450	ns	50	ns	0.3	ns	ns	ns	ns	ns	ns	nr

Data correct as of July 2010

Appendix 5 Feed volumes by weight

weigh	10ml/kg	20ml/kg	30ml/kg	40ml/kg	50ml/kg	60ml/kg	70ml/kg	80ml/kg	90ml/kg	100ml/kg	110ml/kg	120ml/kg
	1 ° feeds	1° feeds	1°feeds	1° feeds	1 ° feeds	1° feeds	1°feeds	1° feeds	1° feeds	1° feeds	1° feeds	1° feeds
500g	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.9	2	2.3	2.4
550g	0.2	0.4	0.7	0.9	1.1	1.4	1.6	1.8	2	2.2	2.5	2.8
600g	0.2	0.5	0.7	1	1.2	1.4	1.7	2	2.2	2.4	2.7	2.8
650g	0.3	0.5	0.8	1.1	1.3	1.6	1.9	2.2	2.4	2.6	3	3.2
700g	0.3	0.6	0.8	1.2	1.5	1.6	2	2.4	2.6	2.8	3.2	3.2
750g	0.3	0.6	0.9	1.2	1.6	1.8	2.2	2.4	2.8	3	3.4	3.6
800g	0.3	0.6	1	1.3	1.7	2	2.3	2.6	3	3.2	3.7	4
850g	0.3	0.7	1.1	1.4	1.8	2.2	2.5	2.8	3.2	3.4	3.9	4.4
900g	0.4	0.7	1.1	1.5	1.9	2.2	2.6	3	3.4	3.6	4.1	4.4
950g	0.4	0.8	1.2	1.6	2	2.4	2.8	3.2	3.5	3.8	4.3	4.8
1000g	0.4	0.8	1.2	1.7	2.1	2.4	2.9	3.4	3.7	4	4.6	4.8
1050g	0.4	0.8	1.3	1.7	2.2	2.6	3	3.4	3.9	4.2	4.8	5.2
1100g	0.4	0.9	1.3	1.8	2.3	2.6	3.2	3.6	4.1	4.4	5	5.2
1150g	0.5	0.9	1.4	1.9	2.4	2.8	3.3	3.8	4.3	4.6	5.3	5.6
1200g	0.5	1	1.5	2	2.5	3	3.5	4	4.5	4.8	5.5	6
1250g	0.5	1	1.5	2.1	2.6	3	3.6	4.2	4.7	5	5.7	6
1300g	0.5	1.1	1.6	2.2	2.7	3.2	3.8	4.4	4.9	5.2	6	6.4
1350g	0.5	1.1	1.7	2.3	2.8	3.4	3.9	4.6	5.1	5.4	6.2	6.8
1400g	0.6	1.1	1.7	2.3	2.9	3.4	4.1	4.6	5.2	5.6	6.4	6.8
1450g	0.6	1.2	1.8	2.4	3	3.6	4.2	4.8	5.4	6	6.6	7.2
1500g	0.6	1.2	1.9	2.5	3.1	3.8	4.4	5	5.6	6.2	6.9	7.6

weigh	10ml/kg	20ml/kg	30ml/kg	40ml/kg	50ml/kg	60ml/kg	70ml/kg	80ml/kg	90ml/kg	100ml/kg	110ml/kg	120ml/kg
	2° feeds	2° feeds	2° feeds	2° feeds	2° feeds	2° feeds	2° feeds	2° feeds	2° feeds	2° feeds	2° feeds	2° feeds
500g	0.4	0.8	1.2	1.6	2.1	2.4	2.9	3.2	3.7	4.2	4.6	4.8
550g	0.4	0	1.3	1.8	2.3	2.6	3.2	3.6	4.1	4.6	5	5.2
600g	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6
650g	0.5	1	1.6	2.1	2.7	3.2	3.8	4.2	4.9	5.4	5.9	6.4
700g	0.6	1.1	1.7	1.3	2.9	3.4	4.1	4.6	5.2	5.8	6.4	6.8
750g	0.6	1.2	1.8	2.5	3.1	3.6	4.4	5	5.6	6.2	6.9	7.2
800g	0.6	1.3	2	2.6	3.3	4	4.6	5.2	6	6.6	7.3	8
850g	0.7	1.4	2.1	2.8	3.5	4.2	4.9	5.6	6.5	7	7.8	8.4
900g	0.7	1.5	2.2	3	3.7	4.4	5.2	6	6.7	7.4	8.2	8.8
950g	0.8	1.6	2.4	3.1	3.9	4.8	5.5	6.2	7.1	7.8	8.7	9.6
1000g	0.8	1.6	2.5	3.3	4.1	5	5.8	6.6	7.5	8.2	9.1	10
1050g	0.9	1.7	2.6	3.5	4.4	5.2	6.1	7	7.9	8.8	9.6	10.4
1100g	0.9	1.8	2.7	3.7	4.6	5.2	6.4	7.4	8.2	9.2	10.1	10.4
1150g	0.9	1.9	2.8	3.8	4.8	5.6	6.7	7.6	8.6	9.6	10.5	11.2
1200g	1	2	3	4	5	6	7	8	9	10	11	12
1250g	1	2.1	3.1	4.2	5.2	6.2	7.3	8.4	9.4	10.4	11.4	12.4
1300g	1.1	2.2	3.2	4.3	5.4	6.4	7.6	8.6	9.7	10.8	12	12.8
1350g	1.1	2.2	3.4	4.5	5.6	6.8	7.8	9	10.1	11.2	12.4	13.6
1400g	1.2	2.3	3.5	4.7	5.8	7	8.1	9.4	10.5	11.6	12.8	14
1450g	1.2	2.4	3.6	4.8	6	7.2	8.4	9.6	10.9	12	13.3	14.4
1500g	1.3	2.5	3.7	5.0	6.2	7.4	8.7	10	11.2	12.4	13.7	14.8

weigh	10ml/kg	20ml/kg	30ml/kg	40ml/kg	50ml/kg	60ml/kg	70ml/kg	80ml/kg	90ml/kg	100ml/kg	110ml/kg	120ml/kg
	3 °feeds	3° feeds	3 °feeds	3 ° feeds	3 °feeds	3° feeds	3 °feeds	3 ° feeds	3° feeds	3° feeds	3° feeds	3 ° feeds
500g	0.6	1.2	1.8	2.5	3.1	3.6	4.4	5	5.6	6.2	6.9	7.2
550g	0.7	1.3	2	2.7	3.4	4	4.8	5.4	6.2	6.8	7.5	8
600g	0.7	1.5	2.2	3	3.7	4.4	5.2	6	6.7	7.4	8.2	8.8
650g	0.8	1.6	2.4	3.2	4	4.8	5.7	6.4	7.3	8	8.9	9.6
700g	0.9	1.7	2.6	3.5	4.3	5.2	6.1	7	7.8	8.6	9.6	10.4
750g	0.9	1.8	2.8	3.7	4.7	5.6	6.5	7.4	8.4	9.4	10.3	11.2
800g	1	2	3	4	5	6	7	8	9	10	11	12
850g	1	2.1	3.2	4.2	5.3	6.4	7.4	8.4	9.8	10.6	11.7	12.8
900g	1.1	2.2	3.4	4.5	5.6	6.8	7.8	9	10.1	11.2	12.3	13.6
950g	1.2	2.3	3.5	4.7	5.9	7	8.3	9.4	10.7	11.8	13	14
1000g	1.2	2.5	3.7	5	6.2	7.4	8.7	10	11	12.4	13.7	14.8
1050g	1.3	2.6	3.9	5.2	6.5	7.8	9.2	10.4	11.8	13	14.4	15.6
1100g	1.4	2.7	4.1	5.5	6.9	8.2	9.6	11	12.4	13.8	15.1	16.4
1150g	1.4	2.8	4.3	5.7	7.2	8.6	10	11.4	12.9	14.4	15.8	17.2
1200g	1.5	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18
1250g	1.5	3.1	4.7	6.2	7.8	9.4	10.9	12.4	14.1	15.6	17.1	18.8
1300g	1.6	3.2	4.9	6.5	8.1	9.8	11.3	13	15.2	16.2	18	19.6
1350g	1.7	3.3	5.1	6.7	8.4	10.2	11.8	13.4	15.2	16.8	18.6	20.4
1400g	1.7	3.5	5.3	7	8.7	10.6	12.2	14	15.7	17.4	19.2	21.2
1450g	1.8	3.6	5.4	7.2	9	10.8	12.7	14.4	16.3	18	19.9	21.6
1500g	1.9	3.7	5.6	7.5	9.4	11.2	13.1	15	16.9	18.8	20.6	22.4

weigh	20ml/kg 2° feeds	35ml/kg 2° feeds	50ml/kg 2° feeds	65ml/kg 2° feeds	80ml/kg 2° feeds	95ml/kg 2° feeds	110ml/kg 2° feeds	125ml/kg 2° feeds	140ml/kg 2° feeds	155ml/kg 2° feeds	170ml/kg 2° feeds	185ml/kg 2° feeds
1050g	1.7	3.0	4.4	5.7	7	8.3	9.6	11.0	12.2	13.5	14.9	16.0
1100g	1.8	3.2	4.6	6.0	7.4	8.7	10.1	11.4	12.8	14.2	15.5	17.0
1150g	1.9	3.3	4.8	6.2	7.6	9.1	10.5	12.0	13.4	14.8	16.3	17.7
1200g	2	3.5	5	6.5	8	9.5	11	12.5	14.0	15.5	17.0	18.5
1250g	2.1	3.6	5.2	6.8	8.4	9.9	11.4	13.0	14.5	16.1	17.7	19.2
1300g	2.2	3.8	5.4	7.0	8.6	10.3	12	13.5	15.0	16.8	18.4	20.0
1350g	2.2	3.9	5.6	7.3	9	10.6	12.4	14.0	15.7	17.4	19.0	20.8
1400g	2.3	4.1	5.8	7.6	9.4	11.0	12.8	14.5	16.3	18.0	19.8	21.5
1450g	2.4	4.2	6	7.8	9.6	11.5	13.3	15.0	16.9	18.7	20.5	22.3
1500g	2.5	4.3	6.2	8.1	10	11.9	13.7	15.5	17.5	19.3	21.2	23.0
1550g	1.6	4.5	4.1	8.4	6.6	12.3	9.1	16.0	18.0	20.0	22.0	23.9

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