East of England Neonatal ODN
(Hosted by Cambridge University Hospitals)

# East of England Neonatal Network

# Enteral Feeding of Preterm Infants on the Neonatal Unit.

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**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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**Approved by:**

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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.**

## Section 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 (38). 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 Section 6**

## Section 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 Koletzko et al 2014 & 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 | Koletzko 2014 | Preterm infant 1000g - 1800g ESPGHAN 2010 |
|---|---|---|---|
| Energy (Kcal/kg) | 95 -115 | 110-130 | 110 -135 |
| Protein (g/kg) | 2 | 3.5 – 4.5 | 4.0 – 4.5 (<1.0kg)<br>3.5 – 4.0 (1.0 – 1.8kg) |
| Sodium (mmol/kg) | 1.5 | 3.0 – 5.0 | 3.0 – 5.0 |
| Potassium (mmol/kg) | 3.4 | 1.9 – 5.0 | 2.0 – 3.5 |
| Calcium (mmol/kg) | 3.8 | 3.0 – 5.0 | 3.0 – 3.5 |
| Phosphate (mmol/kg) | 2.1 | 1.9 – 4.5 | 1.9 – 2.9 |

## Section 3: Feeding the Preterm Infant (Algorithm 1 and Appendix 2)

### 3.1 When to start feeding

Enteral feeds in preterm infants should commence as close to birth as possible, preferably within the first 24 hours of life, unless clinically contraindicated (7). There is growing evidence to support earlier enteral feeding in the high risk infant (8).

Infants considered high risk should include:

- <28 weeks gestation or <1000g birth weight
- infants re-establishing feeds after an episode of Necrotising enterocolitis (NEC) or following gastrointestinal surgery
- Perinatal hypoxia-ischaemia with significant organ dysfunction
- hypotensive/unstable ventilated neonates
- Absent or reversed end diastolic flow in infants <34 weeks

Caution should be taken when initiating feeding in the following subgroups. Treatment should be as moderate / high risk depending on individual clinical assessment.

- Preterm SGA infants (<2nd percentile and <34 weeks gestation)
- Severe term SGA infants (<0.4$^{th}$ percentile and >34 weeks gestation).
- complex congenital cardiac disease
- dexamethasone treatment
- Indomethecin or Ibuprofen treatment for PDA
- polycythaemic infants

### 3.2 Trophic feeding or Minimal Enteral Feeding (MEF)

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 should 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 (12,13,14,15,16) however available evidence and current best practice suggest the following:

In medium and standard risk infants a rate of increase of 30ml/kg/day is safe.

In a group of selected high risk infants an initial period of trophic feeds followed by a rate of increase of 20ml/kg/day might be indicated.

### 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 (GRV) and colour of aspirate may indicate level of gut maturity rather than gut dysfunction (17) and as the colour and volumes vary in the early stages of feeding, significant increases in GRV 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 (18). Use of diluted feeds is not recommended (72).
Possible signs of intolerance:
1. Vomiting
2. Gastric residuals >50% 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 <50% of previous 4 hour feed volume.
2. Residual volumes are present during low volume/trophic feeding.

### 3.5 Mode of Feed delivery – continuous or bolus feeds?

The clinical benefits and risks of continuous versus bolus tube feeding cannot be reliably discerned from the limited information available from randomised trials to date (22). Therefore there is insufficient evidence to make universal recommendations regarding the best tube feeding method for premature infants less than 1500 grams.

However data suggests that:

- Bolus feeding may be more physiologic in the preterm infant (19)
- Bolus fed infants may experience less feed intolerance especially if feeds are delivered over an extended period of time (1,74) and have a greater rate of weight gain(20)
- Higher behavioral stress responses in bolus fed infants have been reported (23)
- Growth may be compromised in continuous feeding as human milk fat adheres to the tubing (21)
- There is no difference in time to achieve full enteral feeds between the two feeding methods (22)

- There any no significant differences in somatic growth and incidence of NEC between the two feeding methods (22)

Feed frequency in trophic feeding has not been evaluated and is constricted by the small volumes involved. Debate is greater with considering feed frequencies when 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 (25)

### 3.6 Management of Gastrooesophageal reflux disease (GORD)

Given the physiological nature of GOR in preterm infants it is important to carefully consider whether this is pathological GORD which would benefit from treatment. Most preterm infants will not require anything more than simple positioning approaches. When considering when to escalate treatment beyond simple positioning or alteration of the feed regime it is important to consider carefully the risk:benefit ratio of any proposed treatment. (A more detailed guideline is in development).

### 3.6.1 GORD – Continuous or bolus feeds

There are no trial data that evaluated the effects of continuous versus bolus tube feeding on GORD in preterm and low birthweight infants (79)

Recommendations as to the best method of feed delivery in respect of GORD management therefore cannot be made.

### 3.6.2 GORD – gastric or transpyloric feeds

The delivery of milk feeds directly to the small bowel (transpyloric feeding) rather than the stomach (gastric feeding) has the theoretical advantage of decreasing the potential for GOR and GORD, however there are also potential problems (24)

Transpyloric feeding tubes are difficult to position and have to have their position confirmed with imaging. There is also a significant risk of tube migration back into the stomach.

There is a possible higher risk of necrotising enterocolitis in infants fed via the transpyloric route (80).

### 3.6.3 GORD - Use of Feed Thickeners

There is little empirical evidence to support the use of feed thickener in the management of GORD in paediatric populations (83-85).

Although no reported link between thickened feeds and undesirable gastrointestinal effects in infants have been found (84,86) there is growing clinical concern regarding the use of thickened fluids in preterm infants and the development of necrotising enterocolitis (NEC) (87,88,90).

A case series investigation is currently in development within the East of England Network to investigate the potential link between use of Carob bean thickeners and the incidence of NEC within the region.

Extreme caution should be used when considering the use of feed thickening agents within the preterm population.

Exploration of alternative methods for the management of GOR in preterm infants, for example the use of a prone, side lying left lateral feeding position is to be encouraged (91).

# Section 4: Types of milk and indications for use (Algorithm 2)

## 4.1 Breast Milk

Breast milk expressed by an infant's own mother is the standard of care for preterm infants (26, 27).
Mothers should be counseled 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 (28).
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 (29-32).
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)

Maternal colostrum produced by mothers of preterm infants in the first few days after delivery is particularly rich in immuno-protective, anti-infective agents and growth factors. When administered directly onto the buccal mucosa this colostrum may serve to protect the infant from infection, stimulate the development of the gastrointestinal tract and modulate the immune system. Studies suggest that the administration of buccal colostrum in the first few days of life is a safe practice that may act as a prophylactic measure against sepsis, NEC and ventilator associated pneumonia

Colostrum can be administered into the buccal cavity by a syringe or gloved finger where it is not swallowed by the infant but absorbed locally by the buccal mucosa. This process can be used for all sick and preterm infants including those who are fragile critically-ill and ventilated (33,34,35).

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

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 150ml/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 micromol/l or
- weight gain is <15g/kg/day on maximum volumes tolerated or
- IUGR where birth weight for gestational age is <9$^{th}$ 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. Combination feeds, when required, can be given either:

- Mixed together
- Alternating feeds of EBM+BMF
- Preterm formula used once the daily supply of fresh MEBM has either run out or until the next expression.

There is no evidence to support one practice over the other, but the method that involves the least amount of milk handling and is easiest for each unit practice is likely to be the best for individual infants.

BMF should never be added as a supplement to preterm formula.

The use of BMF post discharge has not been shown to improve long term growth or neurodevelopmental outcome at 18 months.(36)

Due to concerns regarding precipitation, phosphorus should not be added to feeds where either breastmilk fortifier has been added or where >half of the feed volume is made up of formula milk unless advised by a Paediatric Dietitian.

Phosphate and iron (Sytron) should never be added to the same bottle.

### 4.3 Supplemental Protein Powder

Nutriprem protein supplement can be considered for extremely low birth weight infants <1000g who require up to 4.5g protein/kg/day in order to sustain growth.

It can be added alongside breastmilk fortifier and to Nutriprem preterm formula.

It should not be used with breastmilk without the prior addition of breastmilk fortifier as it does not contain complete nutrition.

Supplemental Protein Powder should only be used under the guidance of a dietitian.

### 4.4 Donor Breast Milk (DBM)

In the absence of a mother's own expressed breast milk (either fresh or frozen and thawed) DBM might be the milk of choice for an infant at high risk of NEC. Existing evidence does not raise any safety concerns with respect to the use of DBM though the feasibility of use and role of donor milk in current neonatal practice remains to be established (37,38).

There may be neurocognitive benefits from DBM (39) but there may also be an adverse impact on cognitive development as a result of inadequate nutrient provision. This is because DBM has a relatively poor nutritional profile.

Use should be limited to either the establishment of feeds in the potentially high risk infant or for the short term support of a preterm infant whose mother is seeking to establish expression.

Potential indications for use of DBM include:

- Gestational age <28 weeks
- ELBW < 1000g
- previous proven NEC
- <32 weeks and IUGR [<9$^{th}$ centile for weight and A/REDF]
- Post GI surgery and following surgical NEC procedures.
- Congenital heart disease with potential for gut hypo-perfusion.

Consideration should also be given to infrequent situations where MEBM is either not available or contraindicated, for example, HIV positive mothers, maternal chemotherapy/ other drug treatments or mothers who have undergone double mastectomies. (37)

Current evidence and practice would suggest that the introduction of DBM into neonatal practice does not have an adverse effect on maternal breast feeding rates.

The East of England is served by donor milk banks at the Rosie Hospital in Cambridge and by the Herts Milk Bank in St Albans. Both milk banks are fully compliant with the requirements of the current NICE Guidelines for the management of donor milk banks (100) and levy a charge of £150 per litre of DBM to cover processing and management costs. NICE guidance also mandates receiver unit compliance with tracking of received DBM.

The introduction of anonymised DBM has challenged the Islamic concept of milk kinship. Such concerns should not lead to DBM being with-held from vulnerable infants, as safeguards are in place through the requirements of NICE that guarantee traceability of DBM from donor to recipient.

### 4.5 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

- 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 of Nutriprem 1 or Hydrolsed Nutriprem and 135mls/kg of SMA Pro Gold Prem 1
- Infants born <1000g will have their protein requirements met by 165 - 180ml/kg Nutriprem 1 or Hydrolysed Nutriprem, or 150mls/kg SMA Pro Gold Prem 1.

Recommended maximum volumes of the preterm formulas:

| | |
|---|---|
| Nutriprem1 | 180mls/kg |
| SMA Pro Gold Prem 1 | 150mls/kg |
| Hydrolysed Nutriprem | 180mls/kg |

Volumes >180ml/kg are not usually necessary and other reasons for poor growth should be sought before further volume increases are introduced (see section 5).

### 4.6 Nutrient Enriched Post Discharge Formulas (NEPDF)

Feeding preterm infants NEPDF once home does not have any significant effect on growth and development at 18 months of age, however there is a group of infants in whom a period of feeding with a NEPDF would support adequate and appropriate weight gain in the initial period at home.

There are two NEPDFs available in the UK, Nutriprem 2 and SMA Pro Gold Prem 2.

NEPDF should be considered for the following infants once they are >1.8 – 2.0 kg and/or just before discharge.

- Preterm infants born prior to 34 weeks and <1.8 – 2.0 kg who at discharge have higher energy requirement (e.g. CLD on home oxygen)
- Infants who have had ongoing poor growth (e.g. have crossed down > 2 centiles on their growth chart during their neonatal stay)

Careful post-discharge monitoring of these patients is recommended.

Preterm Infants who are formula fed, have shown adequate growth during their NICU stay and do not have increased energy requirements should be commenced on a standard term formula and discharged home once tolerance and appropriate weight gain established.

There are European recommendations that state that a ready to feed (RTF) rather than a powdered format should be utilized for ex-preterm, under weight and immunocomproised infants for the first few weeks post discharge (40). However the very small risk associated with potentially contaminated powder formulations needs to be balanced against the cost of RTF formulas (especially to the GP if an infant is discharged on NEPDF).

There are no nutritional recommendations for infants born 34-37 weeks, though the topic is currently the subject of a BAPM working group. 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 (44).

### 4.7 Specialised Term Formulas (Appendix 1)

Specialised term formulas are used when an infant requires either an extensively

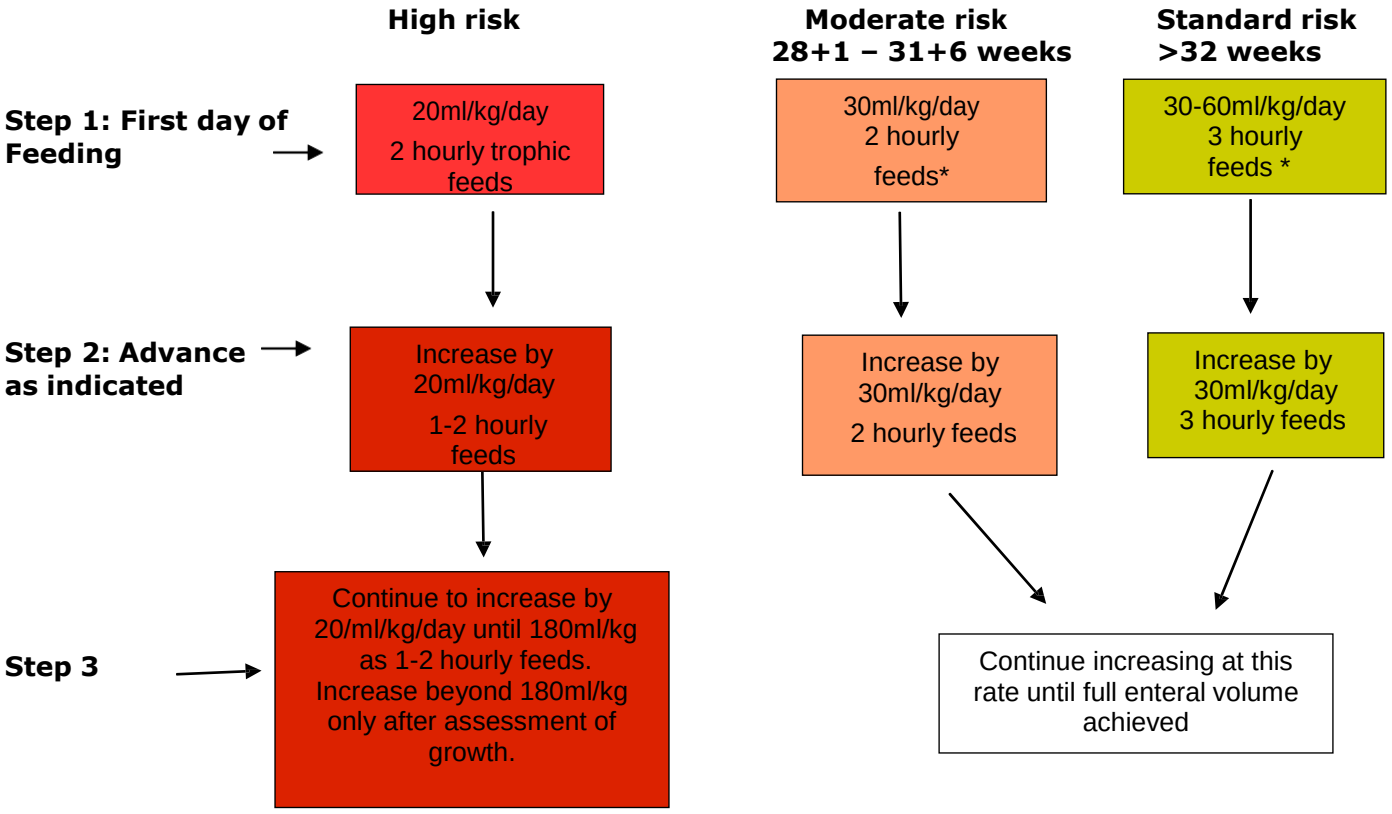
hydrolysed formula (EHF) or an amino acid formula (AAF).

None of the specialised term formulas are designed for use in the preterm population so will not meet nutritional requirements, even at volumes of 180mls/kg. Concentration of formulas may be tolerated but will not address the nutrient imbalance. Clinicians should be aware of the resulting increase in osmolarity when concentrating these formulas.
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 national guidelines for the Use of Powdered feeds in a Hospital Environment (41,42). 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 (43).

## Algorithm 1 Initiating and advancing enteral feeds.

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




**Commence feeding as close to birth as possible.**

**Initiate trophic feeds as soon as possible and maintain only as long as clinically indicated.**

**Infants can move between risk categories following individual clinical assessment.**

**High risk** defined as:

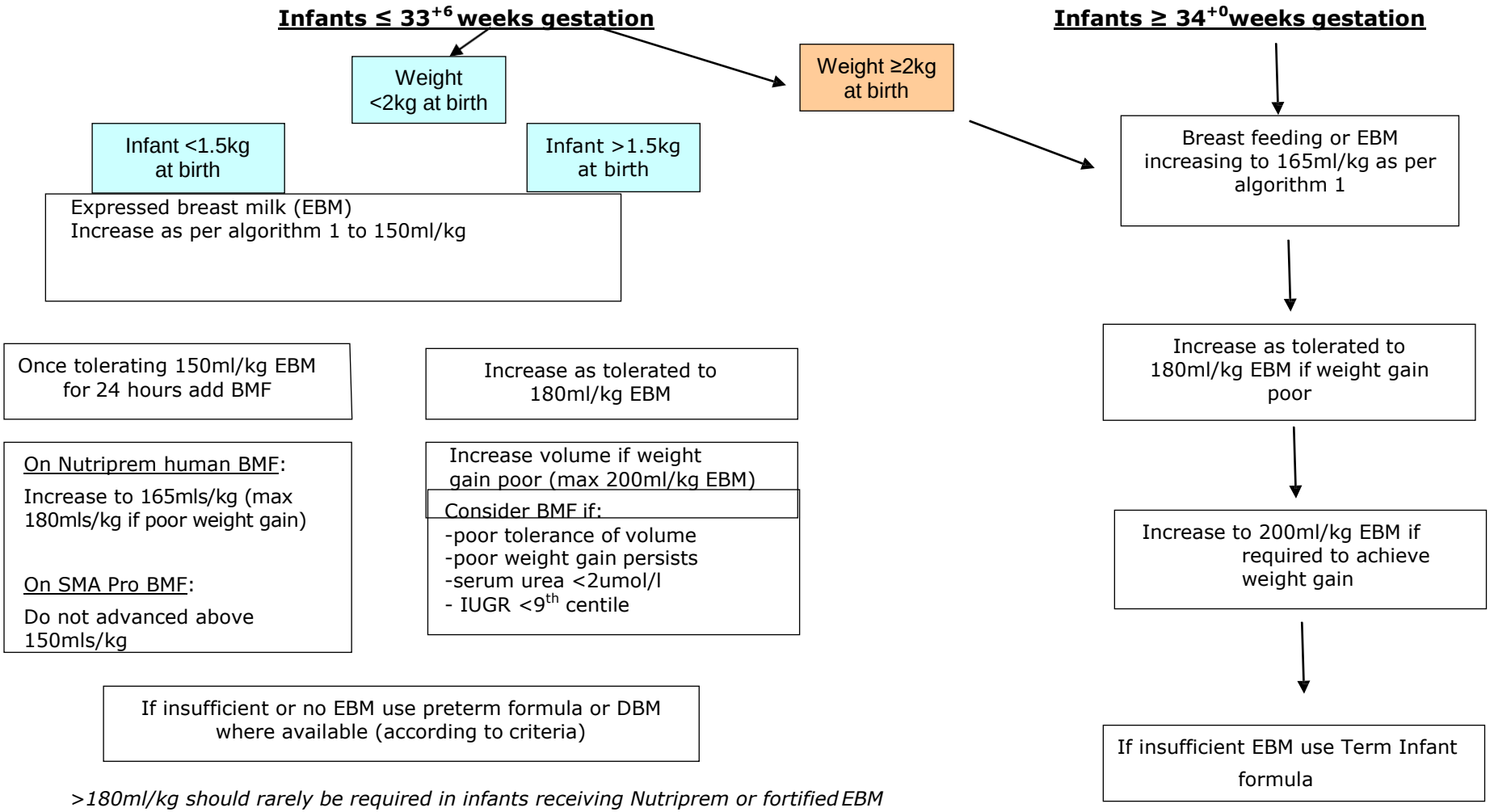
<28 weeks gestation
< 1000g birth weight
Unstable /hypotensive ventilated neonates
Re-establishment of feeds following NEC or gastrointestinal surgery
Perinatal hypoxia-ischaemia with significant organ dysfunction
Absent or reversed end diastolic flow in infants <34 weeks

**Caution should be taken initiating feeds in the following subgroups. The decision to manage as either "high risk" or "moderate risk" is at clinician's discretion.**

Severe SGA infants (<0.4$^{th}$ percentile **and** >34 weeks gestation)
Preterm SGA infant (<2nd percentile **and** <34 weeks gestation)
Indomethecin or Ibuprofen for PDA
Complex congenital cardiac disease
Dexamethasone treatment
Polycythaemic infants

**Algorithm 2 – choice of milk**

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




*>180ml/kg should rarely be required in infants receiving Nutriprem or fortified EBM (150ml/kg SMA Pro Gold Prem 1).*
*Alternative reasons for poor growth should be examined before volumes >180ml/kg are implemented.(section 5)*

# Section 5: Growth

## 5.1 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 (44). 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.

## 5.2 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 (45).

## 5.3 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, and preferably weekly in the smallest, most preterm infants once off ventilator support. 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.

### 5.4 Growth failure

Infants born preterm accumulate significant nutrient deficits by the time of discharge from hospital (46,47). These can manifest as growth deficits that persist through infancy and early childhood (48) into adolescence (49).
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, SMA Pro High Energy, Similac 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 the addition of a protein powder supplement to fortified EBM or a short period of time on a proportion of feed as preterm formula. Alternatively the use of higher protein containing EBM that has been frozen and stored earlier in the infant's neonatal course might be considered.

## Section 6: Evidence supporting Enteral Feeding Guidelines

### 6.1 When to start feeding – the evidence

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 (50). A 2014 Cochrane review concluded that delaying the introduction of progressive enteral feeds beyond 4 days of life did not reduce the risk of NEC in very preterm or very low birthweight preterm infants, included growth restricted infants. The application of these findings to extremely low birth weight infants was less clear (51). 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).

### 6.2 Trophic feeding – the evidence

Trophic feeding or Minimal Enteral Feeding (MEF) refers to introducing small amounts of enteral feeds (preferably breast milk) at intakes of 5 – 25 ml/kg/day (52). The rationale behind this feeding strategy is to prime the gastrointestinal mucosa to promote growth and stimulate secretion of several enteral hormones that support gut function (53,54). There is no recognised consensus on duration or method of delivery(10).

Evidence from 2005 suggests that trophic feeding is beneficial for reducing length of stay and infection rates without increasing the risk of NEC (9). A 2007 study suggests starting trophic feeds early, not advancing initially, then advancing relatively rapidly(56) whereas no advantage was found for trophic feeding an extremely low birth weight population in a randomised control trial published in 2008 (57). In 2010 a further study suggested 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).

The most recent evidence comes from a 2013 Cochrane review (55).This review looked at data from 9 trials including predominantly very preterm (<32 weeks) or very low birth weight (< 1500 grams) infants (there were few extremely preterm/ extremely low birth weight infants included in the studies). Early trophic feeding was defined as feeding starting within the first 3 days but continued for varying durations. Volume ranged from 12 – 24 ml/kg. Control groups did not receive any enteral nutrition for 7 days.

Primary outcomes that were assessed include; feed intolerance, days to establish full enteral feeding and Necrotising Enterocolitis – clinical, radiological or histo-pathological. It is important to note that heterogeneity assessments were made and sub-group analyses were conducted to adjust for differences in study design, participants, feed type and completeness of outcome assessments.

The authors concluded that available data from RCTs do not provide strong evidence that early trophic feeding compared to enteral fasting confers any substantial benefits for very preterm or very low birth weight infants. However at the same time, it is important to note that early trophic feeding did not increase the incidence of any adverse effects i.e. Necrotising Enterocolitis.

A balanced view should be taken between the evidence linking a lack of luminal nutrients to gut atrophy, and the paucity of evidence associating early feeds with adverse effects in preterm, low birth weight infants. This view would support introduction of early feeding in extreme, very preterm and low birth weight infants to support their gut development.

## 6.3 Rate of increase of feeds – the evidence

Retrospective analysis of NEC cases undertaken in the early 90s led to the recommendation of limiting feed advancement to 20ml/kg/day(58), 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 (59).

A more recent Cochrane review undertaken in 2017 (13) identified 10 randomised controlled trials in which a total of 3753 infants participated (2804 infants were participants in the SIFT trail for which secondary outcome data had just been published) (14). Although most participants were stable very preterm infants of birth weight appropriate for gestation, about one-third were extremely preterm or extremely low birth weight (ELBW), and about one-fifth were small for gestational age (SGA), growth-restricted, or had demonstrated absent or reversed end-diastolic flow velocity (AREDFV) on antenatal Doppler. The included trials typically defined slow advancement of feed as daily increments of 15 to 20 mL/kg, and faster advancement as daily increments of 30 to 40 mL/kg.

The authors of the Cochrane review concluded that available trial data do not provide evidence that advancing enteral feed volumes at daily increments of 15 to 20 mL/kg (compared with 30 to 40 mL/kg) reduces the risk of NEC or death in very preterm / VLBW infants, extremely preterm / ELBW infants, SGA /growth-restricted infants, or infants with antenatal AREDFV.
They also concluded that infants who had slow advancement of feed volumes established full enteral feeding and regained birth weight several days later than infants who had faster rates of advancement of feed volumes They consequently spent longer on parenteral nutrition which may increase the risk of invasive infection (mean difference of 3 days longer to establish enteral feeds over 8 trails. Two of the trials that reported on cohorts <1001g did not report on this outcome). The clinical importance of these effects however is unclear, as longer-term growth or developmental outcomes were either not assessed as part of the study or as yet unavailable at the time of the review (SIFT). Neither did the included trials show consistent evidence of any effect on duration of hospital admission.

Evidence to this point suggests that there is little benefit in advancing feeds in increments less than 30ml/kg/day in all preterm infants, however in none of the studies is the practical aspect of tolerance of such volumes in extremely preterm/ extremely low birthweight infants clearly defined. A meta-analysis was carried out within the Cochrane review (13), demonstrating no difference in feed tolerance across six of the included trials (659/3753 infants), however only a small number of the reviewed studies included infants <1000g, and the SIFT trail, that accounted for the vast majority of infants in the review did not report on either feed tolerance and associated feed interruption.

A follow up analysis from the ADEPT trail in 2013 sought to describe the feeding and gastrointestinal outcomes in growth restricted < 29 weeks gestation infants and to define the rate of feed advancement best tolerated by the group (60). Analysis demonstrated that 90% of babies <29 weeks had feed intolerance and 39% developed NEC. (This latter risk was reduced by the use of MEBM as the majority feed during advancement). This high risk group were very slow to tolerate enteral feeds. The median volume of feed tolerated was much lower in the first 10 days of life than the target trial regimen, and the subsequent rates of advancement remained lower that targeted throughout, with a median age of 28 days to reach full feeds. The group

concluded that although the benefits of starting feeds early in growth restricted preterm infants are well established, they may require an increased period of trophic feeding and a slower rate of feed advancement in order to facilitate gut adaptation.

Subsequent publication of the full SIFT trail (15) demonstrated that advancing milk feeds at a faster 30ml/kg/day rate compared to a slower 18ml/kg/day does not affect survival without moderate or severe neurodevelopmental disability at 24 months corrected for gestational age. Nor did it affect risk of late onset sepsis, necrotising enterocolitis or death in VLBW infants. However there was an unexpected, unexplained increase in the risk of moderate to severe motor impairment in the faster increment group that needs to be considered. (15).

In addition a further economic evaluation that ran alongside the SIFT trail suggested that a faster rate of increase in feed volume for VLBW infants was more costly overall and less effective in achieving the primary outcome of survival without moderate or severe neurodevelopmental disability when compared to a slower rate of advance. The study concluded that based on the results of the economic evaluation carried out, increasing milk feed volumes at a faster rate in VLBW infants is not a cost effective strategy and cannot therefore be recommended. (16).

In light of the considered evidence relating to cost effectiveness and clinical outcomes associated with rapid advancement of feeds, plus the fact SIFT did not report on feed intolerance and feed interruption, a pragmatic approach to rate of feed advancement in the most at risk group of infants ought to be considered and built into the steps recommended in the Standardised Enteral Feeding Regimen.

### 6.4 Assessing feed tolerance – the evidence

Feeding tolerance is the ability of the newborn to ingest and digest milk without complications; feeding intolerance is a common issue in preterm infants.
Clinical signs of intolerance may include vomiting, increased abdominal girth, abdominal tenderness, the presence, absence or quality of bowel sounds, and/or the presence of abnormal stools. However, all of these signs can occur in a healthy premature infant tolerating feedings (61). It is therefore extremely important to put these findings into a clinical context.
Traditionally gastric residuals (GR) have been used as part of assessment of feed tolerance. There has been an emphasis on both quality and volume of gastric residuals, with an implicit assumption that a low volume of milky aspirates should be used as confirmation that feeds can be advanced. However, there is paucity of evidence supporting the routine use of this technique, particularly in the early stages of introducing feeds. Wide variations exist as to what constitutes significant GR volume, the importance of GR colour and frequency of GR evaluation, and the colour or volume standards that dictate discarding or returning GRs.
Physiologically, gastric residuals are likely a benign consequence of delayed gut maturation and motility in VLBW infants. GR are dependent on a number of factors, making them an unreliable marker of feed tolerance. Factors influencing GR include size and position of NGT, position of the holes within the NGT in relation to the gastric mucosa, aspiration technique, infant position between feeds (residuals are increased with supine and left lateral positioning), feed viscosity/thickness. Gastric motility changes more rapidly to a normal pattern if feeds are started early and offered frequently rather than being withheld. Studies have shown that clearly defining feeding intolerance can lead to dramatic improvements in nutritional outcomes.(73) Although

there is general agreement on the clinical signs that would indicate feed intolerance, there is inconsistency in the interpretation of these signs and in particular the value of gastric residual volumes.
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 (63,16). The majority of the researchers, however, consider the presence of GRV more than 50% of previous feeding as being a possible indicator of feed intolerance (62 -71). Kairamkonda et al required the GRV more than 50% to occur during 2 consecutive feedings, while Khashu et al required the GRV more than 50% to occur during 2 of the 3 previous feedings to be classified as FI. Other studies defined feed intolerance after 1 episode of a GRV more than 50% of the previous feeding volume.
The presence of large GR volumes or green-coloured residuals prior to feeding often prompts subsequent feedings to be withheld or reduced because of possible Necrotising Enterocolitis resulting in delays in enteral feeding. However when aspirates occur in isolation, whatever their colour, they should not immediately induce the neonatologist to withhold feeds. Cessation or delays in enteral feeding may result in prolongation of PN exposure with its associated risks, and extrauterine growth restriction, a known risk factor for poor neurodevelopmental and growth outcomes in preterm very low birth weight infants.

### 6.5 Mode of Feed Delivery, Continuous or bolus feeds? The evidence

Preterm babies are generally unable to suck oral feeds and so require feeding through a tube. These feeds can be either as a continuous infusion or by the provision of intermittent boluses. Continuous feeds are given by an enteral feeding infusion pump, usually over a 24-hour period, whereas bolus feeds are given over a short time, usually over a 15- to 30-minute period at an agreed number of times per day. There is no accepted definition for bolus feeding though one hourly, two-hourly or three hourly are the most commonly practiced intervals. Bolus feeds can be delivered via a syringe, slowly by gravity, or by compressing the syringe while using pressure until the feed is delivered (75).

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 (19). They also experience less feed intolerance and have a greater rate of weight gain when fed a bolus technique compared to continuous infusion (20).
In an attempt to ascertain the preferred method of feed delivery in preterm infants a Cochrane review conducted in 2011 compared the clinical benefits and risks of continuous versus bolus nasogastric tube feeding for infants < 1500 grams (22). Although this review revealed that it took infants longer to reach full enteral feeds when fed by the continuous tube feeding method, the most recent study presented (76) reported that continuously fed infants weighing < 1299 grams reached full enteral feeds faster than those fed intermittently.
Overall, the seven included trials found no differences in time to achieve full enteral feeds between the two feeding methods, neither were there any significant difference in somatic growth and incidence of NEC.
One study noted a trend toward more apnoeas during the study period in infants fed continuously compared to those fed intermittently, whereas others suggested that infants < 1000 to 1250 grams birth weight gained weight faster and that there was a trend toward earlier discharge for infants less than 1000 grams birth weight fed continuously compared to bolus tube feeds.

The authors concluded that the small sample sizes, methodologic limitations, and conflicting results of the studies make it difficult to make universal recommendations regarding the best tube feeding method for premature infants less than 1500 grams and that the clinical benefits and risks of continuous versus intermittent nasogastric tube milk feeding cannot be reliably discerned from the limited information available from randomised trials to date (22).
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 (1,74). Occasionally intolerance is seen in a bolus fed preterm infant as duodenal motility decreases following a feed (72), however a bolus feed administered over a longer period of time results in a return of motility and improved tolerance (73). Higher behavioural stress responses have also been identified in bolus fed infants (23)

There are reported risks that growth could be compromised as human milk fat adheres to the tubing during continuous feeding (21).

### 6.6 The management of gastro oesophageal reflux disease (GORD) – the evidence

#### 6.6.1 GORD - Continuous and bolus feeds

GORD is particularly common among the preterm and low birthweight population. These babies are prone to frequent bouts of reflux and regurgitation, often up to 5 times per hour (77) which in turn can lead to obstructive or central apnoea. Infants who develop Chronic Lung Disease are prone to GORD, which may in turn complicate enteral feeding and worsen an already compromised respiratory system by causing asymptomatic aspiration or by triggering bronchospasm.

Delayed gastric emptying and transient lower oesophageal sphincter relaxation have both been found to be key factors in GORD (78).
Continuous feeding is generally thought to cause less gastric distension and offer less pressure to the lower oesophageal sphincter whilst permitting significantly faster gastric emptying when compared to bolus feeding. Whereas bolus feeding is purported to affect greater gastric distension as a result of the quick delivery of a larger feed volume, that subsequently weakens the lower oesophageal sphincter, resulting in GORD.
A Cochrane review undertaken in 2014 did not find any randomised trails that evaluated the effects of continuous versus bolus tube feeding on GORD in preterm and low birthweight infants (79), therefore recommendations as to the best method of feed delivery in respect of GORD management cannot be made.

#### 6.6.2 GORD - Gastric and transpyloric feeding

The delivery of milk feeds directly to the small bowel (transpyloric feeding) rather than the stomach (gastric feeding) has the theoretical advantage of decreasing the potential for GOR and GORD, however there are also potential problems (24).

On a practical level transpyloric feeding tubes are difficult to position and, unlike gastric tubes, have to have their position confirmed with imaging. There is also a significant risk of tube migration back into the stomach.

Clinically, digestion in the stomach is by-passed and potentially pathogenic organisms (which would have been neutralised by stomach acid) may be delivered directly into the upper small bowel thereby contributing to a possible higher risk of necrotising enterocolitis in infants fed via the transpyloric route (80).

Although two observational studies have suggested that transpyloric feeding may reduce the frequency or degree of GOR and GOR-related apnoea (81,82) the 2013 Cochrane review (24) did not find any evidence to support this view. (However it is important to be aware that none of the included studies set out to assess the effect of transpyloric versus gastric tube feeding on the incidence of GOR related apnoea). Uncertainty therefore still exists as to whether GOR is an important cause of apnoea in preterm infants and as such further clinical trials are warranted to evaluate whether transpyloric feeding is an effective prevention or treatment option in preterm infants with clinical GORD.

### 6.6.3 GORD - Thickened feeds

Thickened feeds are a popular intervention for the management of GORD in infants however despite its frequent recommendation, there is little evidence to support the use of feed thickener in the management of GORD in paediatric populations (83-85).

Although studies have found no reported link between thickened feeds and undesirable gastrointestinal effects in infants (84,86) there is a growing clinical concern regarding the use of thickened fluids in populations with still developing GI systems (ie preterm infants) and the incidence of necrotising enterocolitis (NEC).

In 2004 a link was proposed between the use of Carob bean thickener and the development of NEC in two extremely low birthweight infants in the UK (87) and in the USA in 2011/2012 concerns were raised over the use of Xanthan gum and the incidence of late onset colonic NEC (88) in preterm infants. These reports led to a US Food and Drug Administration consumer advisory warning (89) and a case series investigation that concluded that there was sufficient evidence to propose that the use of Xantham gum thickeners in preterm infants can significantly increase their risk of developing NEC. (90).
Recent concerns have been raised by the surgical and neonatal transfer teams serving the East of England network as to the growing number of infants being repatriated from around the region with NEC who have received thickened feeds as part of their neonatal treatment. The level of concern is such that a case series investigation is in development to explore a possible link between use of Carob bean feed thickeners and the development of NEC in possible sub sections of the preterm population.

Despite the lack of evidence to support a causative link between feed thickeners and NEC there is sufficient clinical concern, both locally, national and internationally to recommend extreme caution in the use of feed thickening agents within the preterm population and to recommend the exploration of other alternative methods for the management of GOR in preterm infants, for example the use of a side lying feeding position (91).

### 6.7 Maternal breast milk – the evidence

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. Evidence suggests the reduction in NEC and late onset sepsis risk associated with the use of human milk (thought to be related to a combination of immune modulation and gut priming with beneficial bacteria) appears to be dose dependent (92).

### 6.8 Maternal breast milk (handling and storage) – the evidence

The breast should be completely emptied at each expression to ensure the collection of all the fat rich hind milk (93). 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 (94).

For further information about lactation management in the preterm population see local policy and the UNICEF Baby Friendly Initiative documentation (95).

Freshly expressed breast milk should be stored in designated fridges at a temperature of 2-4°C for upto 48 hours or kept frozen at -20°C for upto 3 months in the hospital environment.

For further information refer to "Guidelines for the Preparation and Handling of Expressed and Donor Breast Milk and Special Feeds for Infants and Children in Neonatal and Paediatric Health Care Settings" (41).

### 6.8 Donor breast milk (DBM) – the evidence

In the absence of a mother's own expressed breast milk (MEBM) donor milk might be the next milk of choice for a high risk category infant, however, 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 (37,38).

One observational study has suggested that DBM offers similar feed tolerance to MEBM (96), whilst the most recent Cochrane review concluded that the use of DBM, compared to preterm formula, in preterm and low birth weight infants reduced the risk of NEC, whilst having a negative effect on short term growth, The review highlighted the limitations of the included studies, in that the majority were conducted many years ago when neonatal practices were very different than they are now and that few of the studies included the current established practice of use of fortified MEBM (97). Future publication of the outcomes from the DoMINO study (Donor milk for improved neurodevelopmental outcomes) will hopefully provide valuable information as to whether DBM confers the same neurodevelopmental advantage seen when preterm infants are fed with MEBM rather than formula (39).

DBM is very different from maternal expressed breast milk (MEBM), particularly in regard to processing and composition. Although increasing numbers of mothers of preterm infants are donating their surplus milk whilst their baby is receiving neonatal care, the majority of DBM is received from mothers of term infants who are a number of weeks old, and which is consequently of a very different nutritional profile to that of preterm breastmilk. It has a lower density of a number of key nutrients than MEBM, including energy and protein, and although recent studies have suggested that DBM is more nutrient rich than previously thought (98) use has to be balanced against the established benefits of providing adequate nutrition early in the neonatal

period.

All milk is also heat treated and frozen before use which further changes its composition.

In light of these observations it can probably be assumed that any benefits conferred by the use of DBM will be different from those offered by MEBM (99) and will need to be considered when constructing guidance for use. Despite the lack of high quality data to support the use of DBM, use is widespread, and indications for use inconsistent across the country. In contrast a survey undertaken within the East of England (EOE) in 2015 showed fairly consistent application of current EOE criteria across the 17 units within the network, whilst demonstrating a need for more equitable access to DBM across the region.

Nationally, an increasingly raised concern is whether the introduction of DBM to a neonatal unit has a negative impact on the use of MEBM within the unit, and whether there is a longer term impact on breast feeding rates, both in the unit and on discharge. A systematic review carried out by members of the BAPM Framework on DBM working group concluded that current evidence and practice would suggest that the introduction of DBM into neonatal practice does not have an adverse effect on maternal breast feeding rates (37).

The East of England is served by two donor milk banks, one at the Rosie Hospital in Cambridge and the other at the Herts Milk Bank in St Albans. Both milk banks are supported by SERV (Service by Emergency Rider Volunteers) who help to transport DBM around the region. Both milk banks are fully compliant with the requirements of the current NICE Guidelines on the management of donor milk banks (100) and are regularly audited against these guidelines. In order to meet the recommendations mandated for the screening of donors, microbiological testing of donations, pasteurizing, tracking and managing of DBM, each unit as to levy a charge of £150 per litre of DBM to cover costs. The NICE guidance also stipulates requirements that have to be fulfilled by receiver units in respect of tracking of DBM. New documentation was introduced by the Rosie milk bank in 2016 in order to support this element of the guidance.

As part of the BAPM Framework the use of DBM for Muslim infants was considered as the introduction of anonymised DBM has challenged the Islamic concept of milk kinship. This is where the sharing of milk (historically via a wet nurse) creates ties of kinship and thus the potential for marriage prohibition within families.

Current guidance from NICE requires every sample of DBM to be traceable from donor to recipient, and that such records are retained for 30 years, therefore reassurance can be given that any such concerns could be addressed. In order to strengthen the process further a recommendation has been made that future revision of the NICE guidance should extend the timeframe for retention of records beyond 30 years, and recommend the use of bar code checking of DBM to enhance the robustness of the tracking process.

## 6.9 Breast Milk Fortification – the evidence

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 (101).

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 human BMF (Cow & Gate) and SMA Pro BMF (Nestle). Both are bovine based products. Neither formulation have clear indications for introduction or guidance for infant suitability, so historically practice has varied considerably across the Network (42).

Fortification of EBM using dried human milk fortifiers has been studied (102,103) and showed improved growth but low serum phosphate levels due to inadequate bone mineral concentrations. These formulations are not available in the UK.

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 (104,105) whilst those investigating gastric emptying have been contradictory (106,107). Storage concerns include the reduction of anti-infective components (108), increased bacterial loads (109) and increasing osmolality over time secondary to hydrolysis of glucose polymers by human milk amylase (110). 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(111). 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 (112).

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 (101,111). 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 (112).

There is no evidence to support the use of multinutrient breast milk fortifiers after hospital discharge. A Cochrane review undertaken in 2013 found no benefit to growth parameter in infancy or any statistically significant effects on neurodevelopmental outcomes at 18 months of age (113).

## 6.10 Breastmilk Protein Supplement – the evidence

Nutriprem breastmilk supplement is indicated for use in extremely low birth weight infants <1000g, to support meeting their higher protein requirements of 3.6–4.1g/100kcal (4.0–4.5g/kg/d) as recommended by ESPGHAN (6).

It is intended for use with Nutriprem breastmilk fortifier, Nutriprem 1 and hydrolysed Nutriprem only. These have lower amounts of protein per 100mls compared to SMA Pro breastmilk fortifier and SMA Pro Gold Prem 1.

The product is available in 1g sachets and provides an additional 0.82g protein per 100mls of milk.
The amount of powder needed to meet the required amount of protein per 100mls of milk should be weighed out and added to breastmilk after breastmilk fortifier or to Nutriprem 1 or Hydrolysed Nutriprem. Once added the milk should be used immediately. A pragmatic approach should be taken though in that once added the milk should be used within a 4 hour period in line with milk preparation guidelines.

It should be acknowledged that the osmolitity is 40 mOsmol/kg H20 per 1g of protein, which will contribute to the overall osmolitity of the total feed.
Serun Urea should be monitored when Nutriprem protein supplement has been commenced.

## 6.11 Preterm Formulas – the evidence

All the Preterm formulas are designed to meet the basic nutritional requirements of most preterm infants weighing 1 – 1.8kg when fed between 150 and 165ml/kg

There are currently three formulas available in the UK. Nutriprem 1, SMA Pro Gold Prem 1 and Hydrolysed Nutriprem. All are presented in 70ml ready to feed plastic bottles and are for hospital use only. They are unavailable in the community setting.

Preterm formulas can be used as soon as enteral feeding is indicated. Term formulas should not be used in preterm infants 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 (114).

<u>Nutriprem 1</u>
Whole protein formula designed to meet the ESPGHAN requirements for preterm infants weighing 1 – 1.8kg. It can be given at volumes up to 165mls/kg and even 180mls/kg in preterm infants with poor growth.

<u>SMA Pro Gold Prem 1</u>
SMA Pro Gold Prem 1 has recently been reformulated to contain higher amounts of

protein (2.9g per 100mls) and thus meet the higher protein requirements of extremely low birth weight infants <1000g, however caution should be taken when feeding infants born >1000g as their protein requirements can easily be exceeded using this formulation.
Due to its higher protein content SMA Pro Gold Prem 1 should not be delivered in volumes >150mls/kg/day, particularly in infants born >1000g.
SMA Pro Gold Prem 1 is based on partially hydrolysed protein and contains 40% of its fat as medium chain triglycerides (MCT). It can be a useful formula to use in the preterm surgical infant where either MEDM is not available or where feed tolerance is an issue.

Nutriprem Hydrolysed
Suitable for infants with a surgical diagnosis due to its hydrolysed protein content. However it contains lactose which sometimes is not tolerated infants post GI surgery especially if they have had a significant resection.
The nutritional composition is comparable to Nutriprem 1.

## 6.12 Nutrient Enriched Post Discharge Formulas (NEPDF) – the evidence

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. A recent Cochrane report (115) has stated that feeding preterm infants NEPDF once home does not have any significant effect on growth and development at 18 months of age, and therefore the use of NEPDF at home is not supported by the available evidence. It light of this some CCGs are no longer supporting the prescription of NEPDF in the community.

There will however be a group of preterm infants who would benefit from a period of feeding with a NEPDF in order to support adequate and appropriate weight gain in the initial period at home.

Preterm infants born prior to 34 weeks and <1.8 – 2.0kg who at discharge have higher energy requirement (e.g. CLD on home oxygen) or who have had ongoing poor growth (e.g. have crossed down > 2 centiles on their growth chart during their neonatal stay) should be considered for NEPDF at home once they are >1.8- 2.0kg and/or just before discharge.

Preterm Infants who have had adequate growth during their NICU stay and do not have increased energy requirements can be discharged home on standard term formula.
There are two NEPDFs available in the UK, Nutriprem 2 and SMA Pro Gold Prem 2. Both are available in a ready to feed (RTF) format, as are all term first stage formulas, which are preferable for hospital use.
European guidance recommends a RTF rather than a powdered format for ex-preterm, underweight and immune-compromised infants for the first few weeks post discharge (38) due to the potential risk of contamination of powder with Enterobacter Sakazakii and Salmonella. However this format is considerably more expensive than the powdered NEPDF and subsequently prescription by GPs is frequently challenged and often refused.
Nutriprem 2 and SMA Gold Prem 2 are available on prescription for preterm infants

from 35 weeks until 6 months corrected age, but in practice are only likely to be required until the infant is 3 months corrected or is demonstrating good catch-up growth. Therefore careful post-discharge monitoring of these patients is recommended.

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## Appendix 1

## Specialist Term Formulas used in the Neonatal Unit

| Formula | Indications | Nutrient modification |
|---|---|---|
| Pepti Junior (Cow & Gate)<br>Pregestimil (Mead Johnson) | Malabsorption / post NEC / post GI surgery | Hydrolysed protein / low lactose / MCT fat<br>Needs concentrating to meet preterm requirements |
| Infatrini Peptisorb | High energy/ Malabsorption / post NEC / post GI surgery in infants >37 weeks | Hydrolysed protein / low lactose / MCT fat |
| Nutramigen (Mead Johnson) Similac Alimentum (Abbot) Althera (Nestle) | Cow's milk protein intolerance | Hydrolysed protein / low lactose |
| Neocate (SHS)<br>Nutramigen Puramino (Mead Johnson) Alfamino (Nestle) | Severe malabsorption | Amino acid<br>Puramino and Alfamino contain MCT<br>Needs concentrating to meet preterm requirements |
| Monogen (SHS) | Chylothorax | 80% MCT fat |
| Renastart (Vitaflo)<br>Kindergen (SHS) | Renal insufficiency | Low protein, potassium and phosphate |
| Energivit (SHS) | Protein free formula for use in metabolic regimens | Protein free |
| SMA Pro 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 1

## 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 HBMF | 82 | 2.7 | 3.5 | 10 | 2.7 | 1.8 | ns | 2.3 | 1.7 | 247 | 5 | 450 |
| EBM + SMA Pro BMF | 85.2 | 3.06 | 4.2 | 8.58 | 2.8 | 2.5 | 2.1 | 2.5 | 1.9 | 470 | 4.2 | 390 |
| Nutriprem 1 | 80 | 2.6 | 3.9 | 8.4 | 3.0 | 2.0 | 1.6 | 2.4 | 2.0 | 361 | 3 | 375 |
| SMA Pro Gold Prem 1 | 80 | 2.9 | 4.0 | 8.1 | 2.2 | 3.0 | 1.8 | 2.9 | 2.5 | 370 | 3.7 | 308 |
| Nutriprem 2 | 75 | 2.0 | 4.0 | 7.5 | 1.2 | 2.0 | 1.2 | 2.2 | 1.5 | 100 | 1.7 | 340 |
| SMA Pro Gold Prem 2 | 73 | 2.0 | 3.8 | 7.7 | 1.6 | 1.9 | 0.8 | 2.0 | 1.5 | 125 | 1.2 | 290 |
| SMA Pro First | 67 | 1.25 | 3.6 | 7.1 | 1.0 | 1.6 | 0.7 | 1.1 | 0.8 | 75 | 0.9 | 295.5 |
| Cow & Gate First | 66 | 1.3 | 3.4 | 7.3 | 0.8 | 1.7 | 0.55 | 1.25 | 0.9 | 55 | 1.2 | 335 |
| Infatrini | 101 | 2.6 | 5.4 | 10.3 | 1.6 | 2.4 | 0.8 | 2.5 | 1.6 | 81 | 1.9 | 360 |
| Infatrini Peptisorb | 100 | 2.6 | 5.4 | 10.3 | 1.4 | 2.8 | 1.0 | 2.0 | 1.3 | 81 | 1.7 | 350 |
| SMA Pro High Energy | 99 | 2.6 | 5.4 | 10 | 1.1 | 2.5 | 1.0 | 2.0 | 1.4 | 120 | 1.7 | 377 |
| Similac High Energy | 100 | 2.6 | 5.4 | 10.1 | 1.09 | 2.3 | 1.1 | 2 | 1.36 | 100 | 1.7 | 333 |
| Pepti Junior | 66 | 1.8 | 3.5 | 6.8 | 0.8 | 1.7 | 0.8 | 1.3 | 0.9 | 52 | 1.3 | 210 |
| Pregestimil | 68 | 1.89 | 3.8 | 6.9 | 1.3 | 1.9 | 1.2 | 2.0 | 1.64 | 77 | 1.25 | 280 |
| Neocate LCP | 67 | 1.8 | 3.4 | 7.2 | 1.1 | 1.8 | 1.0 | 1.6 | 1.5 | 56 | 1.2 | 340 |
| Nutramigen Puramino | 68 | 1.89 | 3.6 | 7.2 | 1.4 | 1.89 | 1.2 | 1.6 | 1.13 | 61 | 0.85 | 350 |
| Monogen | 74 | 2.2 | 1.9 | 12 | 1.5 | 1.6 | 0.74 | 1.1 | 1.1 | 57 | 1.2 | 280 |
| Kindergen | 101 | 1.5 | 5.3 | 11.8 | 2.0 | 0.6 | 1.0 | 0.56 | 0.6 | 26 | 5.4 | 215 |
| Renastart | 99 | 1.5 | 4.8 | 12.5 | 2.1 | 0.6 | 1.0 | 0.6 | 0.6 | 25.6 | 1.1 | 225 |
| Energyvit | 74 | ns | 3.8 | 10 | 1.2 | 1.9 | 1.2 | 1.5 | 1.5 | 58.8 | 1.3 | 190 |
| Duocal /100g | 492 | ns | 22.3 | 72.7 | <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 | 0.4 | ns | ns | ns | ns | ns | ns | nr |

Data correct as of January 2018

## Appendix 2 Feed volumes by weight

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

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

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