All Wales Enteral Feeding for Preterm Infants: reference document

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CONTENTS

1.0 Introduction

As survival rates for preterm infants improve, increased emphasis is being put on improving the quality of outcomes by concentrating on optimising nutritional management. Suboptimal nutrition in the early neonatal period contributes to postnatal nutritional deficiencies and hence slower growth, especially in the smallest, most immature infants. Delayed introduction of nutrition can result in nutritional deficits and increased infection rates. Conversely over nutrition and excessive growth acceleration may lead to adverse health issues such as metabolic syndrome, diabetes, obesity and cardiovascular disease in later life (1). The Welsh Government is committed to giving every child a good start in life and a key aspect of this work is to encourage and support breastfeeding across Wales. This includes increasing the number of mothers choosing to express their milk for infants born prematurely as well as breastfeeding rates on discharge from hospital. There is a commitment for all neonatal units in Wales to achieve accreditation with the Baby Friendly Initiative, United Nations Children's Fund (2).

The goals of nutritional support in feeding the preterm infant include:

- meeting the recognised nutritional requirements of the preterm infant
- achieving an acceptable standard of short-term growth
- preventing feeding-related morbidities, especially the prevention of Necrotising Enterocolitis (NEC)
- optimising long-term outcomes.

There still remains a marked difference in nutritional management in neonatal units across the Wales Neonatal Network despite the introduction of a feeding guideline in 2015. Variation in practice is not unique to Wales; in the United States (US), differences in practice were found to be greatest between Neonatal units, although they also existed between individual Neonatologists within the same units (3).

Although there is uncertainty around the definitive practice of nutritional support in preterm infants, standardisation of practice across the Wales Neonatal 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 standardised feeding regimen (SFR) in the form of clinical practice guidelines (4)
- quality improvement literature suggests that a continuing cycle of process planning, consistent implementation, review and audit of practice is highly effective in clinical medicine (5).

A number of preterm infants are cared for in more than one neonatal unit in Wales – a standardised approach to enteral feeding will support consistency of their nutritional care.

Table 1 provides the WHO definitions of preterm and low birth weight infants:

Table 1: WHO definitions of preterm and low birthweight infants (6, 7)

Preterm infants		**Low birthweight infants**	
Description	**Gestation**	**Description**	**Birth weight**
Moderate to late preterm	32 to 37 weeks	Low birthweight (LBW)	<2.5kg
Very preterm	28 to 32 weeks	Very low birthweight (VLBW)	<1.5kg
Extremely preterm	<28 weeks	Extremely low birthweight (ELBW)	<1.0kg

This guidance document 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 Wales.

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 preterm infants.

Evidence supporting recommendations can be found in Appendix 2.

2.0 Nutritional requirements of the preterm infant.

Nutritional requirements are high in preterm infants; they are born when the in-utero growth rates are 2-3 times greater compared with an infant born at term. Despite this, the increased nutrient demands in preterm infants are variable and not evenly spread over time.

Current recommendations for the preterm infant are based on published evidence; the most recent being Koletzko et al (2014) (8) and European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (2010) (9). Table 2 summarises these recommendations for some of the main nutrients:

Table 2: Summary of Koletzko and ESPGHAN nutritional recommendations for preterm infants (8, 9)

Nutrient (per kg/day)	Term infant	Preterm infant (Koletzko, 2014)	Preterm infant 1.0-1.8kg (ESPGHAN, 2010)
Energy (kcal)	95-115	110-130	110-135
Protein (g)	2.0	3.5-4.5	4.0-4.5 (<1.0kg) 3.5-4.0 (1.0-1.8kg)
Sodium (mmol)	1.5	3.0-5.0	3.0-5.0
Potassium (mmol)	3.4	1.9-5.0	2.0-3.5
Calcium (mmol)	3.8	3.0-5.0	3.0-3.5
Phosphate (mmol)	2.1	1.9-4.5	1.9-2.9

These variable increases cannot be met simply by increasing the volume of breast milk.

Hence, the development of specialist formulas and breast milk fortifiers (BMF) for use in the preterm population has occurred. There is a move to calling these 'Human Milk Fortifiers (HMF)' but for the purposes of this document they shall be referred to as BMF.

3.0 Growth

Growth refers to increases in weight, head circumference and length.

3.1 Appropriate weight for gestational age

Term infants born with LBW have nutritional requirements that differ from those born with appropriate birth weight. These requirements also differ from those of infants who are preterm and appropriate weight for gestational age, as well as those who are preterm and small for gestational age. Actual requirements are unknown. An infant who is small at term is likely to have better stores of some nutrients compared to the infant born prematurely but of a similar weight. 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 mother's own milk (MOM) achieves the best outcome (10). Until more evidence is available it seems appropriate to recommend breast milk to all growth restricted infants, both term and preterm.

In the absence of MOM:

- a standard term formula should be used for term infants

- a preterm formula should be used for growth restricted preterm infants.

The achievement of adequate growth in preterm infants is important in relation to optimal neurodevelopmental outcomes. However, growth can be difficult to achieve in preterm infants and accurate length measurements are often difficult to obtain (11).

3.2 Growth monitoring

The weekly completion of an appropriate growth chart is the best indicator of growth for an infant. All growth parameters should be plotted on an appropriate growth chart. Within Wales the Badgernet system is used to record data for these infants and this information is transferrable between units in Wales.

A study by Fenton et al (2018) suggests the optimum time period over which to express weight gain is '5-7 or more days' (12). Therefore, calculating weight velocity for preterm infants per kg/day over the previous 7 days is practical and provides a realistic assessment of growth; when the infant reaches term corrected age weight gain should be calculated in g/day.

3.2.1 Weight

All infants should have an accurate weight measurement taken at birth; any evidence of oedema should be documented. For the purpose of growth monitoring, weight should be measured 2-3 times per week. All weights are to be recorded in nursing/medical notes and plotted weekly, as a minimum, on the growth chart. Weights recorded on Badgernet should only be entered on the date that the infant was weighed.

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.

3.2.2 Head Circumference

Head circumference should be measured on the day of birth and weekly thereafter; measurements should be plotted on the growth chart.

3.2.3 Length

Length is an additional indicator of growth although it is difficult to measure accurately. Frequency of measurement, method and equipment used is at each unit's discretion; as a minimum, length should be measured and plotted at the point of discharge. Ideally, all measurements should be performed by one identified trained individual with a helper in order to maintain standardised practice. Suitable equipment is available e.g. Leicester Incubator Measure (for infants ≤44cm) (13).

3.3 Expected growth

Growth velocity rates of approximately 15g/kg/day in weight, ~1 cm/week in length and ~0.5–1 cm/week in head circumference are commonly used as goal growth rates for preterm infants in the NICU; however, these rates may underestimate foetal growth and do not account for the changes in growth velocity as postmenstrual age at birth and postnatal age advance (13). Parents frequently ask how much weight their infant is expected to gain on a daily basis - the most frequently used range for preterm infants is 15–20g/kg/day. Once the infant reaches term, a weight gain of approximately 30g/day would be expected.

Poor growth occurs when growth continues but at a lower rate than required to follow the percentile (i.e. insufficient growth velocity). Factors that may affect the diagnosis of poor growth include:

- progressive weight loss or static weight over several days (other than the early postnatal period)
- weight velocity alone decreasing over 2 weeks (14).

3.4 Growth failure (GF)

Despite awareness of the importance of early nutrition postnatal GF remains a nearly universal complication of extreme prematurity (15). Only 17% of ELBW infants are small for gestational age (SGA) at birth but the majority experience postnatal GF (15).

Postnatal GF has been defined as:

- <10th percentile for gestational age (GA); or
- if growth trajectory falls to a lower centile than that established once the infant has regained birthweight.

Infants born preterm accumulate significant nutrient deficits by the time of discharge from hospital (16, 17) and it is difficult to correct such accumulated deficiencies. These can manifest as growth deficits that persist through infancy and early childhood (18) into adolescence (19).

Factors contributing to nutrient deficits are numerous, though fluid restriction is often the greatest contributor. Most infants will meet their nutritional requirements with feed volumes of 150-180mL/kg/day; therefore, interruption and reductions in feeds to below 150mL/kg/day should be minimised. For infants who are formula-fed and have restricted fluid intakes or poor tolerance of feed volumes, consider using a high energy term formula; examples of these include Infatrini®, Similac® High Energy and SMA High Energy®.

Conversely volume increases above 180mL/kg/day 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 breast milk fortification
- potential sodium depletion
- anaemia
- sepsis/trauma in the short term
- steroid treatment: length can be affected for up to 4 weeks after cessation of treatment
- high energy requirements secondary to cardiac/respiratory condition
- low serum urea as an indicator of protein status
- organic causes of growth failure.

Breast milk composition is variable, and all strategies should be explored to optimise the nutritional value of the EBM (see breast milk handling and storage section for more information).

For an infant exclusively fed on fortified EBM at maximum tolerated volumes, a combination of poor growth and a serum urea level of <4mmol/L and falling may be an indicator of inadequate protein intake. These infants may benefit from a short period of time on a combination of fortified EBM and preterm formula. If available, EBM with a higher protein content that has been frozen and stored earlier in the infant's neonatal course should be considered.

Refer infants who have poor growth to a paediatric dietitian for assessment and advice. Professionals often need to use clinical judgements based on short-term outcomes, such as growth, brain development, or survival. These can become more pressing than the potential long-term health risks of obesity, metabolic syndrome and cardiovascular disease.

3.5 Catch up growth

There is no universally accepted definition of this term; a review by Steward reported that definitions included (20):

- weight and length return to >10th percentile
- change in standard deviation score (SDS) of 0.67 for either weight or length i.e. moving one centile band
- return to birthweight centile.

Results for the EPICure study (18) suggest that such growth is not achieved as their results showed the following;

- at 2½ years of age: children born preterm were smaller and lighter than children born full term, although most measurements fell within the normal range
- at 6 years of age: growth was achieved at normal rate for previous the 3-4 years but did not demonstrate signs of catching up with their peers.

Poor growth has been shown to be detrimental by Vohr et al, 2007, who demonstrated that a weight of <10th percentile at 30 months corrected gestational age (CGA) was associated with lower motor and cognitive scores on Bayley's assessment (21).

Caution should be taken in relation to rapid catch-up growth in infants with growth restriction as studies have shown an increased risk of health morbidities in adulthood, including type 2 diabetes and metabolic syndrome (22).

3.6 Recommendations for growth post-discharge

As suggested by Lapillone (2014), the recommendations for infants following discharge from hospital include (22):

- to promote human milk feeding
- minimise nutrient deficits
- promptly address deficits once identified
- avoid over-nourishing or promoting postnatal growth acceleration once deficits corrected.

4.0 Feeding the preterm infant (see Algorithm 1 & Appendix 5)

4.1 When to start feeding

Start enteral feeding within the first 24 hours of life unless clinically contraindicated, e.g. surgical issues or complex ventilation (23). There is growing evidence to support early enteral feeding even in high risk infants (24, 25, 25a).

Feed infants according to Algorithm 1.

Infants can start trophic feeds when MOM is available followed by advancement at 30mL/kg as soon as possible, once tolerating trophic feeds for at least 24 hours. Some units may choose to use donor milk in the absence of MOM. Other units will wait for MOM. This feeding plan will be appropriate for most infants.

Re-establishment of feeds following NEC	Preterm infants with IUGR (<2nd centile and >34+0 weeks gestation at birth)
Perinatal hypoxic-ischaemia with significant organ dysfunction, post cooling	<28 weeks gestation at birth and <1000g at birth
Corticosteriod treatment	Absent/ reversed end-diastolic flow in infants born <34 weeks gestation
Infants with significant polycythaemia	Term infants with severe IUGR (<0.4th centile and > 34+0 weeks
Preterm SGA infants (<2nd centile and <34 weeks gestation at birth)	Complex congenital cardiac disease
Pharmacological treatment for PDA	

Infants that may **not be able to tolerate** feeding at a rate of 30mL/kg may include the following and for infants with gut malformations feeding will be managed in conjunction with surgical colleagues.

Infants undergoing cooling	Unstable/hypotensive ventilated infants
Infants with serious gut malformations	

4.2 Trophic feeding / Minimal Enteral Nutrition (MEN)

Trophic feeds, also known as minimal enteral nutrition, are small volumes of milk given to stimulate the bowel. These can be given for up to 7 days and are not intended to contribute to the infant's nutrition (25).

- trophic feeds should commence as soon as possible after delivery unless contraindicated e.g. gut malformation
- trophic feeds should be considered in < 28^{+0} weeks or high-risk infants in order to utilise maternal colostrum and stimulate gut trophic hormones
- the maximum volume classed as a "trophic feed" is 1mL/kg/hour or 24mL/kg/day (26)
- there is no recognised consensus on method of delivery (25)
- trophic feeds can be initiated and advanced during ibuprofen treatment (27)
- early trophic feeding of preterm infants with IUGR and abnormal antenatal Doppler results may not be detrimental in relation to incidence of NEC or feeding intolerance (28)
- infants should be assessed at least daily for tolerance of their trophic feeds and a decision made to continue trophic feeding or progress to advancement of feeds
- the decision as to whether to include these fluids within the daily fluid requirement is left to the clinician's discretion.

4.3 Rate of feed advancement

A Cochrane review (2013) comparing slow daily advancements (15-20mL/kg/day) versus fast daily advancements (30-35mL/kg/day) suggested that fast increments of enteral feed volume did not increase the risk of NEC (29). A subsequent Cochrane review (2017) also concluded that slow advancement of feeding in VLBW infants does not reduce the risk of NEC, feed intolerance and death (30) However, as there was no sub-group analysis of ELBW infants a more cautious approach to feeding this group should be considered. Dutta (2015) recommended a starting volume of 15-20mL/kg/day for infants weighing <1.0kg (31). The Cochrane review findings were reflected in a recent publication (2019) of a large multi-centred controlled trial of two incremental milk feeding rates of 18ml/kg/day versus 30ml/kg/day; this publication concluded no detrimental outcomes with feeding infants at the faster rate (25a).

4.4 Assessing feed tolerance

Intolerance to feeding, defined as the inability to digest enteral feeds associated with increased gastric residuals, abdominal distension and/or vomiting, is frequently encountered in the preterm infant and often leads to the disruption of a feeding plan (32). In most cases feeding intolerance represents a benign condition related to gut immaturity; however, its presentation may overlap with that of impending NEC. Therefore, careful clinical assessment is essential to prevent unnecessary restriction of enteral feeds which may lead to prolonged reliance on parenteral nutrition (PN), delay to full enteral feeding and poor growth (32).

Diluted feeds are not recommended (33).

4.4.1 Signs of intolerance (32)

- vomiting
- gastric residuals >50% of previous 4-hour feed volume, particularly if persistent or increasing in volume

- abdominal distension/increasing abdominal girth.

If there are concerns regarding NEC, refer to the following guideline on Welsh Neonatal Network: http://www.walesneonatalnetwork.wales.nhs.uk/sitesplus/documents/1034/NEC%20guideline%202017%20network.pdf

4.4.2 Suggested intervention if signs of intolerance present (34)

- senior medical review
- consider abdominal x-ray
- consider septic screen and IV antibiotic therapy
- consider bowel obstruction e.g. malrotation
- continue with trophic feeds rather than nil enterally, if safe to feed.

4.4.3 Management of gastric residual volume (GRV)

Gastric residuals should not be checked routinely. Small amounts of gastric aspirate are used to check the pH before giving a naso gastric (NG) feed.
If aspirates are checked, use the following as a guide to replacing partially digested gastric aspirates as this will replenish acid and enzymes that aid the digestive process (35):

- if GRV ≤5mL/kg or ≤50% of the previous feed volume (whichever is higher), replace all GRV and feed. If this recurs, subtract the residual volume from the current feed, replace the GRV and give the calculated remaining feed volume (31)
- if the gastric aspirate is >5mL/kg or >50% of the previous feed volume, replace up to 50% of the feed volume with GRV and do not give the current feed (31). If this happens again consider changing to slow bolus feeds or withholding feeds, depending on clinical condition (36)
- if gastric residuals are increasing or bile stained, seek senior medical review.

4.5 Feeding frequency and method of delivery

Due to poor coordination of sucking and swallowing, preterm infants will often require feeding via a tube (37). Delivery of feeds can be in the form of an oro-gastric (OG) or naso-gastric (NG) feeding tube and there is no benefit of one route over another (38).

Most infants on neonatal units receive feeds via the bolus rather than continuous method of feeding and there is insufficient evidence to support one method of administration over another for preterm infants less than 1.5kg (36). However, there are some circumstances where a continuous feed may be more beneficial, e.g. significant reflux and transpyloric feeding. Therefore, best practice suggests:

- bolus feeding may be more physiological in the preterm infant (39)
- higher behavioural stress levels have been reported in bolus fed infants (40). However, Bergman (41) reported that as the stomach capacity of a term infant at birth is approximately 20mL, smaller bolus feeds can improve stress levels whilst supporting the development of normal gastrointestinal physiology
- there is no evidence to suggest bolus feeds need to be pushed in, they can be gravity fed (42); gravity bolus feeds are most commonly administered
- infants receiving bolus feeds at a slower rate have less gastric aspirates than infants having bolus feeds over a much quicker time (43)
- bolus feeding every 2 hours has been associated with less prominent jaundice and less time requiring Continuous Positive Airways Pressure (CPAP) however similar incidence of NEC and feeding problems has been reported in 2 or 3 hourly bolus feeding (44)
- 2 hourly bolus feeds achieve full feeds faster than 3 hourly and is associated with a reduced amount of time on PN and less feed stoppages in VLBW infants (45)
- bolus fed infants may experience less feed intolerance and have a greater rate of weight gain (46)
- there is no difference in time to reach full enteral feeds between continuous and bolus feeding methods (36)
- there is no significant difference in somatic growth and the incidence of NEC between bolus and continuous feeding (36)

- continuous feeding in infants ≤ 0.85kg may lead to less feed intolerance (47)
- there are concerns regarding nutrient losses in infants fed breast milk via continuous pump feeding because the milk fat adheres to the enteral feeding tubing, resulting in loss of fat, calcium and phosphorous (48).
- there is no beneficial evidence for transpyloric feeding (37) or gastric feeding either as bolus or continuous feeding (49) for preterm infants with gastro-oesophageal reflux disease (GORD).

Infants <32 weeks should receive 1-2 hourly feeds moving to 2- 3 hourly feeds as they grow (44).

Gastric administration of feeds is preferred.

4.6 Cue based feeding

During the time when preterm infants are learning to feed in the neonatal unit, motor and sensory neuropathways are developing (50). Stress during feeding may promote altered sensory–motor pathways in the brain that guide the infant away from oral feeding and adversely affect the ability and desire to feed both in the neonatal unit and after discharge (51).

"Traditional" feeding regimens use criteria such as the infant's weight, gestational age and being free of illness, and even caregiver intuition to initiate or delay oral feeding. However, these criteria could compromise the infant and increase anxiety levels and frustration for parents and caregivers.

Cue-based feeding, as opposed to volume-driven feeding, leads to improved feeding success including increased weight gain, shorter hospital stays and fewer adverse events, without increasing staff workload while simultaneously improving parents' skills regarding infant feeding (52).

5.0 What to feed

5.1 Mothers own Milk

A mother's own milk (MOM) is the best feed for her preterm infant and is associated with improved short-term and long-term outcomes (53). The immune system of preterm infants is immature placing them at an increased risk for serious complications. MOM provides a variety of immuno-protective and maturation factors that are beneficial to the preterm infant (54).

5.1.1 Pre-delivery

It is recommended that the early expression of breast milk within 1-2 hours of birth (55) is discussed with mothers at the time they are showing signs of preterm delivery. Health boards should provide written information for mothers regarding early expression and feeding.

5.1.2 At delivery

Skin-to-skin is recommended following delivery for all infants to improve lactogenesis and establish breast milk production. There is some evidence and increasing practice to support this approach in moderately preterm infants following delivery (56). Precautions regarding maintenance of delivery room temperature are recommended.

Hand expression is an essential skill and should be taught as soon as possible after delivery. In a term infant initial rapid sucking to stimulate lactogenesis within the first 24 hours occurs. Hand expression used in conjunction with a rapid-phase early initiation programme on a breast milk pump has been demonstrated to improve lactogenesis and successful long-term milk production when used within the first 24-48hours (57, 58).

5.1.3 Colostrum

Colostrum is the first milk and "contains cytokines, anti-microbial peptides and proteins, hormones, cellular immune components and other biological substances that have immuno-modulatory effects on lymphoid tissue" (59). It can be used to prime the immune system and gastrointestinal tract. This can be achieved by providing buccal colostrum and trophic feeds.

The composition of colostrum changes rapidly within the first 24 hours. It is important that it is collected in specific syringes or pots to reduce the likelihood of the fat adhering to the container. The syringes or pots should be labelled sequentially, and colostrum given to the infant in the order that it is expressed.

Administration of buccal colostrum may be beneficial; common practice is to give 0.2mL every 3 hours for the first 72 hours of life. In addition to buccal colostrum, enteral feeds should be commenced as per Algorithm 1 (page 17) following this initial period, mouth care should be continued using MOM.

5.1.4 Breast milk

Once primary lactogenesis has occurred and the mother has produced 3 x 20mL of colostrum, using combined early phase pumping and hand expression, mothers can proceed to a maintenance breast feeding pump programme which mimics a mature sucking pattern seen in established breast feeding.

Frequent (at least 8-10 times in 24 hours including once at night) and effective expressing (combining hand and pump expression) is crucial to ensuring a mother is able to maximise her individual milk production so that she can maintain her supply. Double pumping is also recommended. There are many factors that may impact on the amount of milk a mother produces. The focus should primarily be on enabling the mother to achieve her potential. In general, mothers should be aiming for a minimum of 750mL/day by day 10 in order to maximise potential for sufficient milk volumes at discharge (2). Recording daily expressing volumes can give a good indication as to whether mothers require additional support.

Early regular, daily, skin-to-skin can be provided for most preterm infants and is associated with both improved milk production and long-term successful breast feeding. All units should have a skin-to-skin guideline including documentation of duration and frequency.

Milk from mothers who deliver prematurely differs from that of those who deliver at term. The nutritional content of breast milk varies with prematurity and postnatal age (60). Preterm breast milk is initially higher in protein, fat, free amino acids and sodium; these levels reduce to that of term breast milk over the first few weeks following delivery (61).

5.2 Breast Milk Fortification

In general, a multi-nutrient breast milk fortifier (BMF) does not need to be added if >50% of feed requirement is provided by a preterm formula. However, it can be considered if there is associated poor growth and/or poor tolerance of volume. In practice this would depend on having adequate volumes of milk to fortify accurately.

The average composition of breast milk does not meet ESPGHAN guidelines for the nutritional requirements of preterm infants (9).

However, a preterm infant can meet their energy requirements from breast milk alone if expressing techniques and milk handling are optimised, e.g. by using hind breast milk.

Infants born <1.0kg will require at least 200mL/kg/day of unfortified breast milk to meet requirements for energy.

Breast milk will not meet the protein requirements of preterm infants especially in infants <1.5kg birthweight (62-65). Moreover, infants born <1.0kg would require up to 240mL/kg/day to meet their protein requirements, increasing to 330mL/kg/day after two weeks. Clearly these volumes are undesirable. Fortification of breast milk with a BMF should be considered for preterm and/or low birthweight infants to optimise their nutrient intake.

The BMFs available in the UK are hydrolysed and historically have been based on bovine milk protein. There is limited evidence that bovine based fortifiers place infants at higher risk of NEC (66). A BMF based on human milk protein, is being introduced to the UK market but as yet clear evidence for its benefit over bovine-based products has still to be established.

BLISS (67) recommended the following, based on evidence and practice within the UK and Ireland:

- fortify EBM in all infants with a birth weight <1.5kg and <34 weeks gestation
- consider fortification in infants with a birth weight of 1.5kg-2.0kg and <34 weeks gestation

and prior to fortification, infants should:

- receive ≥50% total feeds as breast milk
- tolerate feed volumes at a minimum of 150mL/kg/day, preferably 180mL/kg
- have a serum urea <4mmol/L and falling.

There may be some infants who require breast milk fortification at volumes <150ml/kg/day to optimise their nutrition e.g. fluid restricted infants. Consider fortification at half strength for the first 24 hours, increasing to full strength at tolerated.

Infants with a birthweight >2kg are unlikely to require BMF (67).

Serum urea levels should be checked weekly to monitor the effect of the BMF.

5.2.1 Preparation of breast milk with BMF

Current practice varies throughout the UK and Ireland. There is insufficient evidence to support one practice over another. BMF should be added to breast milk based on manufacturer's instructions but wastage of breast milk must be avoided, and hygienic protocols must be followed to reduce the risk of contamination. Each sachet of BMF needs to be added to a specific volume of breast milk, as per manufacturer's instructions. However, when a smaller volume of breast milk needs to be fortified, the BMF can be weighed to provide the correct ratio of fortifier to breast milk.

Figure 1 provides examples of how to calculate the required weight of BMF to be added to the prescribed volume of breast milk.

For example:
If using **Nutriprem**® BMF when standard addition is 1 x 2.2g sachet Nutriprem® BMF added to 50mL breast milk:

- 2.2 ÷ 50 = 0.044g Nutriprem® BMF per mL of breast milk
- Multiply 0.044g by volume of breast milk required (mL) = grams of Nutriprem® BMF to add to required volume of breast milk

If using **SMA® BMF** when standard addition is 1 x 1g sachet SMA® BMF added to 25mL breast milk:

- 1 ÷ 25 = 0.04g SMA® BMF per mL of breast milk
- Multiply 0.04g by volume of breast milk required (mL) = grams of SMA® BMF to add to required volume of breast milk

NB: Class III scales should be used within the hospital setting for weighing of the BMF

Figure 1: Example of how to calculate the required weight of BMF to be added to the prescribed volume of breast milk

Fortified breast milk is not sterile and concerns regarding its storage include the reduction of some anti-infective properties of human milk (68, 69), increased bacterial loads, contamination of breast milk (70, 71) and increasing osmolality secondary to hydrolysis of glucose polymers by human milk amylase (72, 73). Many of these effects can be reduced by adding the BMF as close to feeding as possible (74, 73).

Do not add BMF as a supplement to preterm formula.

5.2.2 Individualised fortification

Moving forward, evidence is now strongly suggesting that standardised fortification is not ideal (75, 76), however it is the current practice within the UK. Research and clinical practice are indicating that significant improvements in growth parameters can be achieved by either targeted or adjustable fortification (75, 77).

Individualised fortification would necessitate the use of a human milk analyser to identify the level of supplementation required to meet the infant's nutritional requirements. This will create variation in practice across the network due to logistical, resource and financial implications. Evidence for individualised fortification should be considered when these guidelines are reviewed in the future.

5.2.3 When to stop BMF

BMF is not available on prescription in the community and is generally discontinued at the time of discharge although many units are now providing some level of fortification following discharge if clinically indicated (78, 79).

5.2.4 Post discharge use of BMF

Practice across units varies and BLISS recommended that infants are assessed individually to determine whether fortification post-discharge would be of benefit (67); if growing appropriately they would not require post discharge fortification.

Therefore, post-discharge fortification should be considered for:

- any preterm infant who is fully breast feeding, weight is < 2nd centile and receiving BMF prior to discharge, or
- infants <34 weeks gestation and <2.0kg who are fully breast feeding and receiving BMF prior to discharge.

There is limited evidence to suggest the most appropriate duration of post-discharge fortification. The use of BMF post-discharge varies across the UK, however, some units within the UK are discharging infants with a supply of BMF to optimise nutrient intake from MOM in the form of 'BMF shots'. This will support the transition and establishment of breast feeding in the longer term. We would therefore recommend a pragmatic but individualised approach to the provision of fortification post-discharge.

Practice varies between units that provide BMF shots. A recent small review of UK units suggested the following is common practice for those providing BMF shots (see Figure 2, page 14).

Based on the information in figure 2 and depending upon the initial number of daily 'BMF shots', it would take approximately 4 weeks before the 'BMF shots' are discontinued. However, individual assessment and monitoring should be carried out weekly and consideration made to:

- continue 'BMF shots' for longer if weight gain is sub-optimal; or
- stop 'BMF shots' earlier if weight gain is >250g per week.

How to use BMF post discharge

The number of BMF shots per day is based on approximately 150mL/kg/day and 50% requirement prior to discharge from hospital. BMF shots are given before a breast feed and given throughout the day.

E.g. For Nutriprem® BMF (1 sachet is usually added to 50mL breast milk)

- 1 sachet Nutriprem® BMF mixed with 3mL breast milk provides a 4mL 'BMF Shot'

  2.1kg infant feeding 150mL/kg/day = 315mL/day
  315mL ÷ 50mL = 6.3 sachets Nutriprem® BMF /day
  50% requirement = 3.1 sachets per day = 3 Nutriprem® BMF 'shots' /day
- Continue 3 x Nutriprem® BMF 'shots' per day for 1 week
- Reduce by 1 x Nutriprem® BMF 'shot' per day per week until nil shots required

For SMA® BMF (2 sachets are usually added to 50mL breast milk)

- 2 sachets SMA® BMF mixed with 3mL breast milk provides a 4mL 'BMF Shot'

  2.1kg infant feeding 150mL/kg/day = 315mL/day
  315mL ÷ 25mL = 12.6 sachets SMA® BMF /day
  50% requirement = 6.3 sachets per day = 3 SMA® BMF 'shots' /day
- Continue 3 x SMA® BMF 'shots' per day for 1 week
- Reduce by 1 x SMA® BMF 'shots' per day per week until nil shots required

NB This is based on work developed by Queen Charlottes Neonatal Unit (London)

Figure 2: Suggestion for weaning of BMF following discharge from hospital

5.3 Supplemental Protein Powder

Cow & Gate Nutriprem® Protein Supplement (80) is a supplemental protein powder that can be added to fortified breast milk. It can also be added to Nutriprem® 1 low birthweight formula and Hydrolysed Nutriprem®. This is purely a protein supplement and does not contain any added vitamins or minerals. It should not be added to unfortified breast milk.

Nutriprem® Protein Supplement should only be used under the guidance of a dietitian.

ELBW infants require up to 4.5g protein/kg/day in order to optimise growth (8, 9). Supplemental protein powder can be considered in ELBW infants with poor growth in order to optimise their nutrition.

The protein supplement is available in 1g sachets; each sachet should be added to 100mL of a suitable milk.

Serum urea should be monitored following the commencement of the protein supplement.

Infants receiving breast milk fortified with SMA® BMF or SMA Gold Prem® 1 **do not require** the additional protein supplement. It should also not be added to Nutriprem® 2 or SMA® Gold Prem 2.

5.4 Donor breast milk (DBM)

Optimising MOM should be the gold standard. However, when there is insufficient MOM available an alternative source of enteral nutrition is required. Suitable options are DBM or formula milk. Preterm infants often tolerate human milk better than formula milk and concerns exist that formula could increase the risk of severe bowel problems including NEC (81).

DBM has a lower density of several nutrients compared to the infant's own mothers' milk or artificial formula. Therefore, the use of DBM needs to be balanced alongside the known benefits of achieving recommended nutrient intakes in preterm infants" (82).

Consider restricting DBM to:

- establishing feeds in the high-risk infant with the gradual introduction of alternative feeds once full volumes are achieved, or
- short-term support of a preterm infant whose mother is establishing milk expression.

If the decision is made to use DBM, the following criteria should be considered (82):

- gestational age <28^{+0} weeks
- birthweight <1.0kg
- <32^{+0} weeks with IUGR (weight <9^{th} percentile and abnormal antenatal Doppler's (AREDF))
- previous proven NEC +/- laparotomy
- post gastrointestinal surgery
- congenital heart disease with potential for gut hypoperfusion e.g. hypoplastic left heart syndrome.

Parental consent should be obtained prior to commencing DBM.

5.5 Preterm and Post Discharge Formulas

5.5.1 Preterm formulas

MOM is the gold standard source of nutrition for infants. However, in the absence of MOM or DBM, infants born <34^{+0} weeks gestation and/or with a birthweight <2.0kg should be fed a liquid 'ready to feed' (RTF) preterm formula. All term formulas, including hydrolysed and amino acid formulas, do not meet the nutritional requirements of a preterm infant and should not be used unless clinically indicated.

Increase feed volume up to a minimum volume of 150mL/kg/day, increasing as indicated by weight gain and volume tolerance.

Volumes >180mL/kg/day are not usually necessary and other reasons for poor growth should be investigated before increasing feed volume further (Appendix 1). Use of SMA Gold Prem® 1 in volumes >150mL/kg/day should be considered carefully by the medical team in light of its higher protein content.

If there is insufficient MOM and supplementation with preterm formula is required, it can be given in the following circumstances:

- until the next expression of breast milk is available, or
- as a mixed feed of MOM and formula; these should be mixed together immediately prior to feeding the infant, or
- alternating MOM and formula feeds.

There is no evidence to support one practice over another, but the method chosen should support maximising maternal milk production whilst ensuring practicality and involving the least amount of milk handling.

Preterm formulas, suitable for use from birth, include:

- Cow & Gate Nutriprem® 1 (whole protein formula)
- SMA Gold Prem® 1 (partially hydrolysed protein formula)
- Cow & Gate Hydrolysed Nutriprem® (extensively hydrolysed protein formula).

For infants with cholestasis a feed high in medium chain triglycerides (MCT) is recommended. SMA Gold Prem® 1 currently contains 13.6%. In the absence of MOM, use Aptamil Pepti Junior® (50% MCT) for infants with cholestasis or those requiring an MCT formula post-surgery. Aptamil Pepti

Junior® may need to be reconstituted at a concentration greater than the manufacturer's standard dilution of 12.8% to optimise energy and protein provision.

For infants who are not receiving MOM, WHO recommends pre-term formula is used until the infant reaches 2kg and suggest a standard infant whey-based formula until 12 months CGA (83).

5.5.2 Nutrient Enriched Post Discharge Formulas (NEPDF)

Preterm formula is not available in the community. Therefore, in the absence of adequate MOM, preterm infants <34^{+0} weeks gestation and/or with a birthweight <2.0kg will require a suitable NEPDF to enable adequate growth following discharge.

NEPDFs are higher in energy, protein, fat, long chain polyunsaturated fatty acids (LCPs), calcium, phosphorus, iron and vitamin A than a standard term formula.

NEPDFs may be beneficial for growth restricted infants to promote optimal growth following discharge from hospital.

The decision to use NEPDF or standard term whey-based formula at discharge will be made by the neonatal team. Growth and feeding of the infant should be kept under regular review. NEPDF can be continued until a maximum of 6 months CGA. However, if growth is appropriate these milks could be discontinued earlier. Once NEPDF is discontinued, standard term whey-based formula should be commenced and continued until 12 months CGA. Growth and feeding should be kept under regular review by health professionals.

There are two NEPDFs available in the UK, Nutriprem® 2 and SMA Gold Prem® 2. Both formulas are available in RTF format for hospital use. However, RTF preparations are expensive in primary care; justification for their use in the community should be considered.

RTF preparations for use following discharge can be purchased from a community pharmacy if families wish.

Powdered infant formulas (PIF) are not sterile and are at risk of contamination with Salmonella and Enterobacter sakazakii (84). To support the safe preparation of powdered NEPDF post discharge, parents/carers should be provided with advice on safely making up infant formula. Instructions for making up feeds from PIF can be found at: https://www.unicef.org.uk/babyfriendly/wp-content/uploads/sites/2/2008/02/start4life_guide_to_bottle_-feeding.pdf (85).

However, there may be circumstances where RTF will be required (i.e. immunocompromised infants, infants from immunocompromised mothers, or underweight infants) (84) or when RTF may be requested for multiple births. If RTF preparation is required following discharge from the neonatal unit, it may be advisable to request this specifically with the infant's GP. The monthly requirement should be specified on the prescription letter or discharge summary.

Weight, length and head circumference should be monitored closely and interpreted together using an appropriate growth chart. If there is inadequate growth following discharge from hospital, review potential causes and/or refer to a paediatric dietitian.

5.6 Late preterm Infants

Currently there are no recommendations regarding nutritional requirements for infants born between 34^{+0} and 37^{+0} weeks gestation. Their nutrient stores are likely to be better and they are more likely to establish feeding quicker than those born <34 weeks gestation. Currently a BAPM working group is reviewing the evidence in relation to late preterm infants and their requirements. However, in the interim period the following considerations have been made.

MOM is the feed of choice. However, in the absence of MOM, a standard term formula should be used. Some late preterm infants may require additional nutrients to promote growth, BMF or a formula with a higher energy content than standard term formula may be considered.

Growth restricted term infants >37 weeks should also be offered term infant formula in the absence of MOM or donor milk (10).

5.7 Specialist term formulas (Appendices 3 and 4)

Specialist term formulas are not designed for use in the preterm population so will not fully meet their nutritional requirements. Energy needs might be met by increased volumes but are often poorly tolerated.

Many of the specialist term formulas need to be reconstituted from powder. Powdered infant formulas are non-sterile and have potentially inconsistent composition when reconstituted; they should be made in a milk kitchen or special feeds unit and prepared in line with FSA/WHO guidelines (86). Powdered formulas can be made at an increased concentration. However, clinicians should be aware that this will not address the nutrient imbalance and will increase the osmolality of the feed.

High energy liquid formulas are available but the protein: energy ratio is not optimal for preterm infants.

Specialist term formulas may be required for post-surgical infants, fluid restricted infants and those requiring disease-specific formulas (see Appendix 3).

Some units choose to use hydrolysed formulas when breast milk is not available. However, there is little evidence to suggest that feeding protein hydrolysate formulas during the initial admission affects the risk of feed intolerance or NEC (87).

There are some specialist term formulas which contain probiotics, but these milks should be made with water at a temperature <70^{o}C to provide the probiotic benefit. This does not meet the recommendations for the preparation of feeds in a hospital setting; they should not be prepared in line with the manufacturers' guidelines and therefore the probiotic benefit is likely to be reduced.

Soya formula is not usually recommended for infants; however, they may be required for management of certain medical conditions such as galactosaemia or galactokinase deficiency (88). There is no longer a soya formula that is suitable for those following a vegan diet (88).

For infants with cholestasis and/or post-surgery who require an MCT-based feed, use SMA Gold Prem® 1 (13.6% MCT) or Aptamil Pepti Junior® (50% MCT). An increased concentration of Aptamil Pepti Junior® may be required to optimise energy and protein provision.

All infants born <35 weeks gestation will need vitamin and iron supplementation according to local health board policy.

Specialist term formulas should only be used when absolutely necessary and always under the direction of a paediatric or neonatal dietitian.

5.8 Probiotics

Some units choose to use probiotics routinely. However, there is insufficient clinical evidence to suggest that probiotics will protect infants from NEC, sepsis or death (89).

6.0 Feeding and gastro-oesophageal reflux disease (GORD)

6.1 GORD – Continuous or bolus feeding

GORD is common in preterm infants; promoting conservative strategies such as positioning and side lying before commencing treatment is advisable (90).

A Cochrane review in 2014 did not identify any research that evaluated the effects of continuous feeding versus bolus feeding on GORD in preterm and LBW infants and recommended that further research is needed (49).

6.2 Gastric or transpyloric feeding

In an attempt to improve feed tolerance in infants with GORD transpyloric feeding has been explored. Gastric feeding stimulates digestive processes whereas transpyloric feeding has the potential benefits of delivering nutrients past the gastroesophageal and pyloric junctions.

Feeds are given continuously via transpyloric route and therefore may improve symptoms in an infant with GORD. A Cochrane review in 2013 (37) compared gastric and transpyloric tube feeding in preterm and LBW infants; the data did not provide any beneficial effect of transpyloric feeding for preterm infants.

Transpyloric feeding is not routinely recommended and has been associated with a greater incidence of gastrointestinal disturbances and mortality; these findings need to be interpreted and applied cautiously because of the methodological weakness in the included trials.

Practically it is easier to pass and check the position of gastric feeding tubes. Transpyloric tubes are difficult to position correctly and will require radiological confirmation of correct position. Often transpyloric tubes migrate back into the stomach.

6.3 Use of feed thickeners

There is little evidence to support the use of feed thickener in the management of GORD (91-93). A study found that thickening mothers expressed breast milk (MEBM) was not effective (94).

There is concern that thickening feeds for preterm infants increases the risk of NEC (95-96).

Algorithm 1: Initiating and advancing enteral feeds

Advancing feeding on NICU

Infants can start feeding at 30mL/kg as soon as possible when mother's own milk (MOM) is available. Some units may choose to use donor milk in the absence of MOM. Other units will wait for MOM. This feeding plan will be appropriate for most infants including;

Re-establishment of feeds following NEC
Perinatal hypoxic-ischaemia with significant organ dysfunction, post cooling
Corticosteroid treatment
Infants with significant polycythaemia
Preterm SGA infant (<2nd centile and <34weeks gestation at birth)
Pharmacological treatment for PDA

Preterm infants with IUGR (<2nd centile and >34+0 weeks gestation at birth)
<28 weeks gestation at birth or <1000g at birth
Absent/reversed end-diastolic flow in infants born <34 weeks gestation
Term infants with severe IUGR (<0.4th centile and >34+0 weeks gestation at birth)
Complex congenital cardiac disease

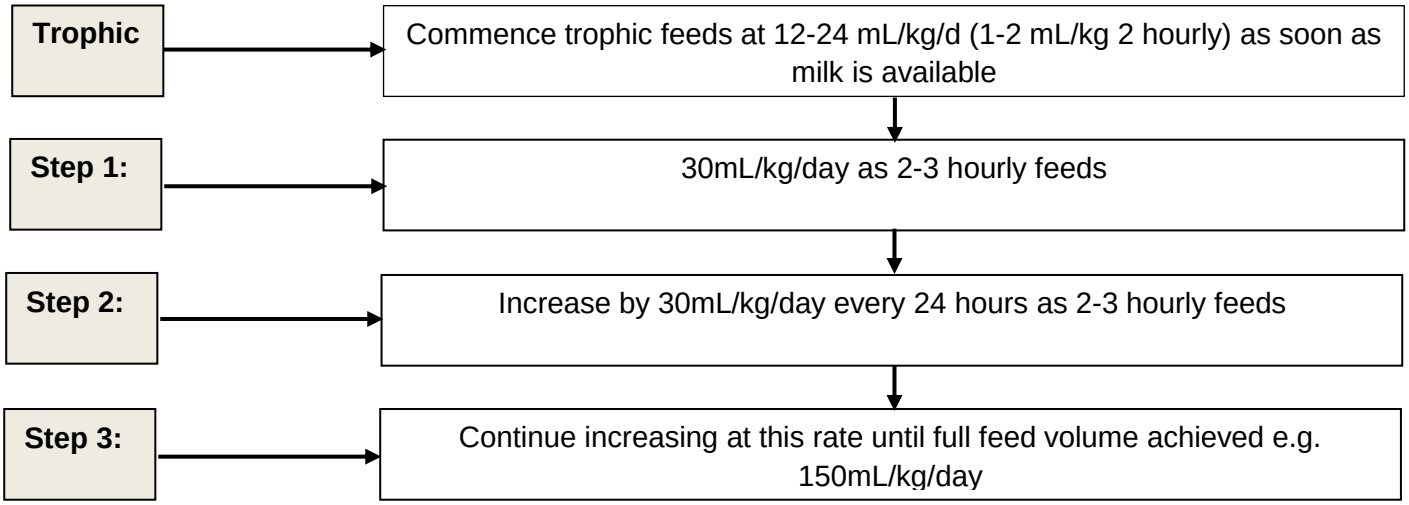
There are some infants that may **not be able to tolerate** feeding at a rate of 30mL/kg e.g.

Infants undergoing cooling
Unstable/hypotensive ventilated infants
Infants with serious gut malformations

For infants with gut malformations, feeding will be managed in conjunction with surgical colleagues.

Rate of Feeding

- Commence buccal colostrum as soon as possible after birth, e.g. give 0.2mL every 3 hours, this can be given in addition to trophic feeds or when not feeding yet started
- Give trophic feeds, 2-3 hourly at rate of 12-24mL/kg/day as tolerated as soon as possible following birth
- Once infants are tolerating trophic feeds, commence Step 1of feeding pathway and proceed through the steps as tolerated
- For infants with poor tolerance, trophic feeds may be continued longer, then proceed to Step 1 of feeding pathway.



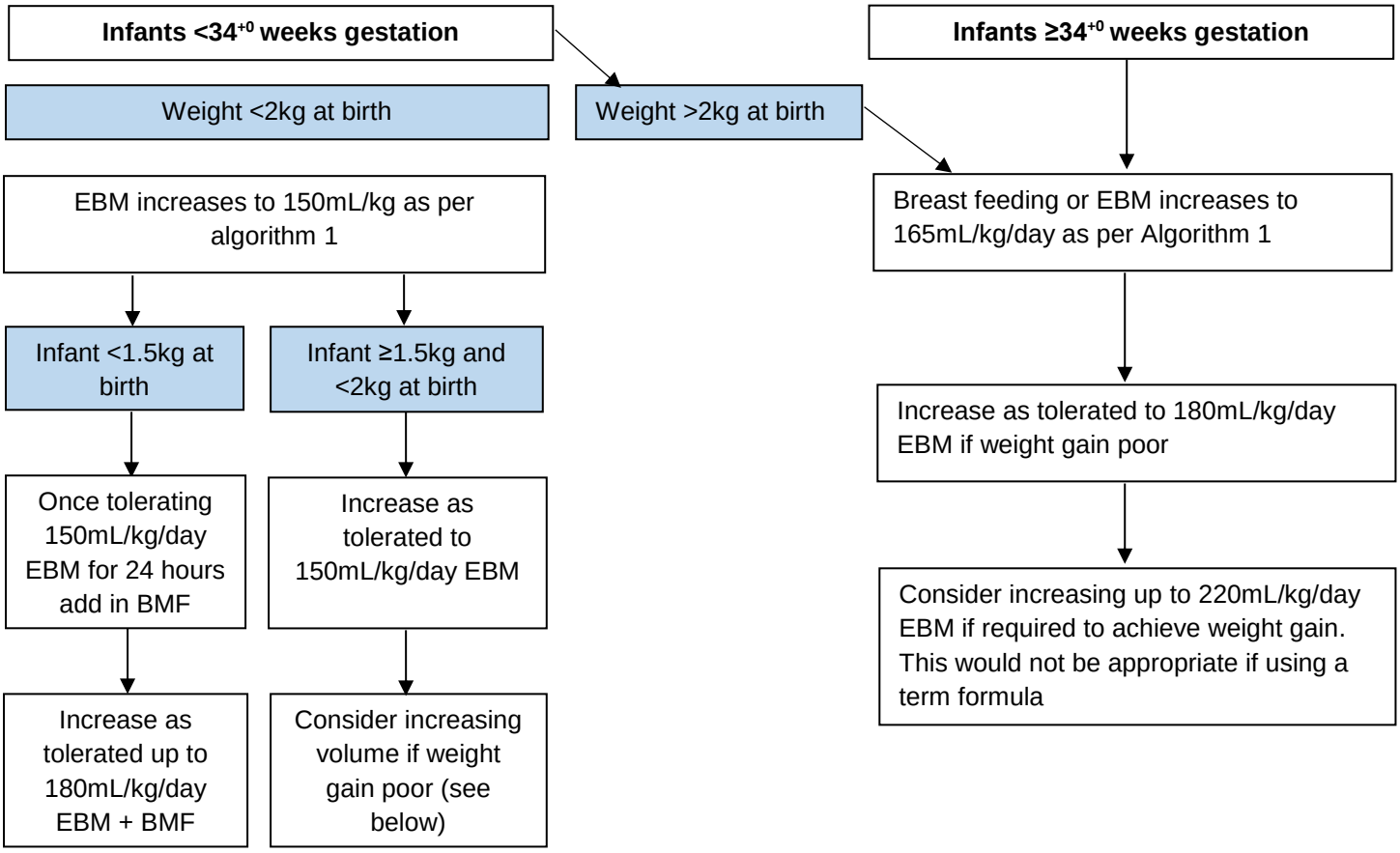
This algorithm is to be used in conjunction with Algorithm 2

For infants with feed intolerance: delay increasing feed volume or consider reducing volume but continue to feed unless signs and symptoms of NEC or obstruction are present.

>180mL/kg/day should rarely be required in infants receiving preterm formula or fortified EBM. Alternative reasons for poor growth should be examined before volumes >180mL/kg/day are implemented (Refer to All Wales Enteral Feeding for Preterm Infants: guidance document Appendix 1).

Algorithm 2: Choice of Milk

Fresh maternal breast milk is the first milk of choice for all infants unless clearly contraindicated. If insufficient or no MOM available, consider DBM or preterm formula



For fluid restricted infants <1.5kg BW, consider BMF at ½ strength with feeds at 120mL/kg for 24 hours then increase to full strength BMF.

For infants >1.5kg but <2kg BW consider BMF if there is:

- Poor tolerance of volume
- Poor weight gain persists
- Serum urea <4mmol/l and falling
- IUGR < 9th centile

If growth remains poor, consider:

- adding BMF
- changing some of the milk to a term high energy milk.

In the absence of MOM use a term formula for infants born ≥ 34 weeks gestation

To improve breast milk production, ensure skin to skin contact is undertaken daily and breast milk expressing techniques are optimised. In the absence of any maternal breast milk use DBM where available, or preterm formula

>180mL/kg/day should rarely be required in infants receiving preterm formula or fortified EBM. Alternative reasons for poor growth should be examined before volumes >180mL/kg/day are implemented (Refer to All Wales Enteral Feeding for Preterm Infants: reference document Appendix 1).

APPENDIX 1: The evidence

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 lengthen the time to reach full enteral feeding (3). One study suggested that trophic feeding had several benefits including greater energy intake, improved growth, improved milk tolerance, reduced PN, less sepsis, fewer days of oxygen and were discharged from hospital earlier (97). A Cochrane review concluded that early introduction of feeding did not increase the incidence of NEC (26). A later Cochrane review that assessed the effect of delayed rather than early introduction of progressive milk feeds for the very preterm or VLBW infant concluded that there was no evidence that delaying enteral feeding beyond 4 days after birth reduces the risk of NEC in this group, including those with growth restriction; delaying the time before progressing feeds resulted in delayed time to reach full feeds; however, there was only limited data for the extremely preterm or ELBW infants (98).

The ADEPT trial (Abnormal Doppler Enteral Prescription Trial) concluded that growth restricted preterm infants born after AREDF 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 (24).

Perinatal hypoxia is thought to cause diversion of blood flow to the brain and heart in preference to other organs, leading to hypoxic ischaemia of the intestines. It has also been suggested that dysregulation of the premature intestinal circulation in response to feeding or bacteria has caused intestinal hypoxic ischaemia (99).

Indomethacin has been used for closure of PDA but is associated with reduced blood flow to other organs. A Cochrane review found that ibuprofen was as effective as indomethacin in closing PDA but reduced the risk of NEC; oral ibuprofen seemed to be most beneficial compared to intravenous preparations or either preparation of indomethacin (100). Various suggestions have been made regarding development of NEC in congenital heart disease (CHD) including circulatory changes and inflammatory processes; further research in this area is required. A randomised study of 177 infants comparing indomethacin with ibuprofen for the treatment of PDA and comparing fasting with enteral feeding suggested that continuing trophic feeds of 15mL/kg/day during treatment with ibuprofen did not affect NEC; moreover infants achieved enteral feeds of 120mL/kg/day earlier and at a lower postnatal age in the enterally fed group (27). However, only 40 infants received ibuprofen due to drug shortages compared to 137 infants who received indomethacin. A cautious approach to feeding neonates with known cardiac morbidities or prescribed medications for these conditions would therefore seem sensible.

No work has yet addressed whether initial feeds should be exclusively breast milk (MOM or DBM) or whether initial feeds should be delayed if only formula is available. Most evidence suggests that any enteral feed given early is better than gut starvation (25).

Trophic Feeding/Minimal enteral nutrition

Trophic feeds are small volumes of milk given to stimulate gastrointestinal physiological, endocrine and metabolic maturity which are maintained for up to 7 days, are not intended to contribute to nutrition but enable the infant to transition to full enteral feeds more quickly. Trophic feed volumes vary in practice from 0.5-1mL/kg given intermittently (101) to 5-25mL/kg/day (102). Trophic feeds are typically a maximum of 24mL/kg/day (26). There is no recognised consensus on duration or method of delivery (25). One paper suggested starting trophic feeds early and keeping volumes at trophic levels for some days, before advancing feed volumes relatively rapidly, however, the authors recommend that further research is needed (103). Another study showed no advantage for trophic feeding in an ELBW population in a randomised control trial (104). A Cochrane review of 9 trials (754 infants) concluded that there were no beneficial or harmful effects of early trophic feeding over enteral starvation for very preterm and VLBW infants; due to the lack of extremely preterm, ELBW or growth restricted infants in included studies the authors suggested the review findings had limited applicability to these infants (26), Another paper concluded that the duration of trophic feeds and the rate of advancement of feed volumes may be modifiable risk factors for NEC in preterm infants (105). Karagianni et al. found no significant difference on the incidence of NEC and feeding intolerance between early and later trophic feeding and suggested that early trophic feeding of preterm infants with IUGR and abnormal antenatal Doppler may not have a significant impact on incidence of NEC or feed intolerance (106). However, the standard of evidence presented in this paper leaves its conclusions open to criticism. None of the papers make recommendations for optimal duration of trophic feeds and all call for further research. However, absence of trophic feeding has been known for some time to increase bacterial translocation and gut atrophy (107).

The benefit of colostrum for infants of all gestations, including immunological and trophic gut priming benefits, is well known and accepted practice. However, one Cochrane review of 6 studies (335 subjects) suggests that

further trials are required to more precisely and reliably evaluate the effects of oropharyngeal colostrum on outcomes such as NEC, late-onset invasive infection, and/or mortality in preterm infants (107).

Rate of feed advancement

Early studies suggested that trophic feeds accelerate maturation of gastrointestinal function, with slow advancement providing protection against NEC (108). However later evidence suggested that there was little benefit in the slow advancement of feeds in preterm infants (30). The results of ADEPT suggest that starting enteral feeds early in growth restricted preterm infants with abnormal antenatal Doppler is beneficial but analysis of the sub-group of growth restricted infants, <29 weeks gestation, revealed that this cohort tolerated little milk in the first 10 days and achieved full feeds 9 days later than expected from the trial regimen. A longer duration of minimal enteral feeds and a slower rate of advancement to facilitate gut adaptation, especially in the first few days of life, may be required (109). This sub-group are at a very high risk of NEC (39% subjects in the ADEPT trial developed NEC) but exclusive use of breast milk reduces the risk.

A later Cochrane systematic review conducted in 2017 (including preliminary data from the Speed of increasing Feed Trial (SIFT) (110), presented at a neonatal conference, found that advancing enteral feed volumes at slower rates (<24mL/kg/day) does not reduce the risk of feed intolerance, NEC or death in very preterm or VLBW infants, including extremely preterm or ELBW infants, or infants who experience in utero growth restriction/compromise (30). Moreover, advancing the volume of enteral feeds at faster rates (30-40mL/kg/day) shortens the time taken to regain birthweight and establish full enteral feeds; this practice may also reduce the risk of late onset invasive infection. Furthermore, the meta-analysis of data showed borderline higher risk of incidence of invasive infection among infants who received slow advancement of enteral feed volumes (30).

However, only 20% of the infants included in this latter Cochrane review were growth restricted at birth. When considered with the results of the Kempley et al study (109) it would seem sensible to take a more cautious approach with extremely preterm infants and those with growth restriction at birth.

The recently published controlled trial of two incremental milk feeding rates in preterm infants (SIFT) concluded there was no significant difference, when very preterm or very low birth weight infants, were feed an increasing rate of 30mL/kg, compared to a lower rate of 18mL/kg; this was the case for development of NEC, late onset sepsis and survival without moderate or severe neurodevelopmental disability at 24 months (25a).In this trial the faster rate of feeding (30mL/kg) reached full feed volumes at a median of 7 days compared to 10 days for the slower fed group(18mL/kg), this resulted in less time on PN.

Assessing feed tolerance

Feed intolerance is frequently associated with preterm infants and is the inability to digest enteral feeds presenting as increased GRV, abdominal distention and/or emesis leading to the disruption of the patient's enteral feeding plan (111). The main objective when feeding VLBW infants is to achieve full enteral feeds in the shortest time, whilst maintaining optimal growth and nutrition and avoiding the adverse effects of rapid feed advancement (31).

Enteral feeding in the VLBW infant is frequently stopped, or feeding advances withheld based on 'feeding intolerance' (1). However, postnatal growth restriction and failure to thrive have been identified as a major issue in preterm and ELBW infants (34). Nevertheless, enteral nutrition is favoured to total parenteral nutrition (TPN) because it avoids the problems associated with intra-vascular catheterisation, infection, adverse effects of TPN, and fasting. Despite that, TPN in these infants remains vital and should be used as an adjunct to enteral feeding (31).

Traditionally, it has been routine practice in most neonatal units to measure the volume and colour of gastric residuals prior to enteral bolus feeding in preterm infants, especially in the first few days of life. When establishing enteral feeding it is extremely common to experience an increased volume of gastric residuals but in the absence of other clinical signs Mihatsch et al (2002) found no correlation between light green gastric residuals and either NEC or feeding intolerance in preterm infants and suggested that light green gastric residuals should not delay advancement of enteral feeds (112). Li et al (2014) suggest performing gastric residual aspiration and evaluation only in the presence of other signs of feeding intolerance or NEC as there is little evidence to support routine aspiration to measure GRV (35). Moreover, there is a lack of standardised practice between neonatal units regarding gastric residuals and wide variations exist as to what constitutes significant volumes, importance of colour and frequency of evaluation.

A recent Canadian multi-disciplinary working group conducted a critical appraisal of the evidence; where there was little or limited evidence, they used expert consensus to provide reasonable approaches and practical suggestions to consider when feeding preterm infants (31). In relation to feed tolerance the recommendations are to only routinely aspirate small volumes from NG tubes for assessment of correct tube position prior to

feeding. The gold standard to confirm NG tube placement is X-ray but gentle aspiration of 0.25-0.5mL of gastric aspirates for testing with pH test indicator strips is acceptable practice and reduces exposure to radiation. GRVs can be influenced by body position during feeds. A number of studies found that GRVs were less if infants were positioned prone or in right lateral position compared to supine or on the left (113). The size of the feeding tube can also influence GRV with larger bore tubes aspirating up to 2-3 times the volume of smaller bore tubes (114). The position of the feeding tube within the stomach and pool of gastric fluid, aspiration technique, feed temperature and viscosity, can influence the volume of gastric residuals aspirated (114-116).

A Cochrane systematic review is currently being undertaken aiming to assess the efficacy and safety of refeeding compared to discarding gastric residuals to improve growth in preterm infants (117).

Feeding Frequency and Method of Delivery
Preterm infants will often require feeding via an enteral tube due to their poor co-ordination of sucking and swallowing *(*37*).*

Methods of feeding used include continuous feeding or intermittent bolus feeding:

- Continuous feeding uses an enteral feeding pump to deliver specific volumes of milk over a given period of time
- Intermittent bolus feeding gives a set amount of feed over a short period of time, a set number of times per day. This can be up to 4 hourly but more commonly 1-3 hourly. Bolus feeding, in most units, is done via gravity rather than pushing the milk into the infant's stomach using a syringe. A Cochrane review in 2012 reported there was insufficient evidence to suggest any benefits of pushing versus gravity tube feeding in premature or LBW infants *(42).*

A stomach capacity of 20mL at birth has been reported in 6 articles and correlates to a feeding interval of approximately 1 hour for a term infant (41*).* The author described how hourly feeding could improve stress levels as the infant is not overfed large volumes of milk, whilst supporting the development of normal gastrointestinal physiology. However, feeding all infants this frequently would be very labour intensive for staff on the units.

Another study comparing 2 or 3 hourly feeding in ELBW infants concluded that 2 hourly feeding in this group of infants was associated with less prominent jaundice and a shorter time requiring CPAP support *(44).* However, the authors reported similar incidence of NEC and feeding problems in both 2 and 3 hourly feeding groups. In this same study it was reported that there was no statistical difference in the time to reach full enteral feeds.

A retrospective review compared the feeding interval and feeding outcomes in VLBW infants; after adjustments for confounders, the authors concluded that infants fed 2 hourly reached full enteral feeds 3.7 days faster than infants fed 3 hourly, were less likely to receive PN for >28 days, and have their feeds withheld for ≥ 7 days (45).

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 physiological in the preterm infant (39*).* It has also been reported that bolus fed infants experience less feed intolerance and have a greater rate of weight gain compared to continuous feeding (46*).* Another study demonstrated that continuously fed VLBW infants, <.2kg and 24-29 weeks gestation, achieved full feeds more quickly than those receiving bolus feeds (47); however, no assessment was made of growth and feed tolerance in the longer term.

Higher behavioural stress responses have been noted in VLBW infants at 15 days postnatal age and 32 weeks post menstrual age receiving bolus feeds compared to continuously fed infants during two time periods (40*).* In the same group the bolus fed infants had a greater need of behavioural and physiologic stabilisation during feeding. This trial concluded that continuous feeding was associated with lower behavioural stress responses compared to bolus fed infants during the early postnatal life.

A study reported that infants born 24-29 weeks gestation and birthweight <1.2kg when fed continuously achieved full enteral feeds quicker than bolus fed infants and had improved gastrointestinal tolerance. The study also states that continuous feeding may be more physiologically better in relation to enteral tolerance in infants born with ELBW, ≤ 850g (47). However, concern regarding the loss of nutrients in the breast milk when an infant is fed continuously is a worry.

A study in 2010 looking at nutrient losses in continuous feeding of fortified breast milk concluded there were increased losses of fat and calcium when infants were fed continuously. As little as 6% loss of fat occurred in

bolus fed infants compared to up to 50% when infants received continuous feeding, depending on the type of feeding pump used; calcium losses were also significantly lower when the infant was bolus fed compared to continuous feeding (48*).*

To determine the best method of feeding these infants a Cochrane review was undertaken in 2011 and reported that each feeding method had beneficial and harmful effects; it so concluded that there is insufficient evidence from the seven included trials to determine the best feeding method for infants <1.5kg, also recommending further research is needed in this area, *(*36*).* Overall this review, which included seven papers, found no differences in the time to achieve full enteral feeds in either intermittent bolus feeding or continuous feeding and noted there were no significant differences in growth and incidence of NEC.

A Cochrane review in 2013 looked at 3 studies to determine whether the route of tube influenced feeding. The review stated that NG feeding tubes were more stable but may have an effect on respiratory function as the tube will obstruct the nasal passage, while the OG tubes were far more likely to become displaced. The review concluded that there was no convincing evidence to support either route *(*38*)*.

Feed intolerance is common in preterm infants and this is characterised by the volume of gastric aspirates 2-3 hour postprandially. A study looking into duodenal motor responses and gastric emptying concluded that infants fed by slow infusion over 2 hours mimicked the antral and duodenal responses to those seen in adults when milk is ingested but this was not the case when the infants were fed the same volume over a much quicker time (43*)*. The difference in the feeding rates had a significant effect on the volume of milk remaining in the stomach 2 hours after the feed had been given. This study reported that infants receiving feeds with a slower infusion rate had stomach volumes remaining one ninth of those infants who received faster bolus feeding. However, the study also reported that gastric emptying was less during the slower infusion feeding compared to the infants receiving feeds at a faster rate and concluded that intermittent feeds over 2 hours may not only provide adequate hormonal stimulus but also contribute to better gastric emptying

In an attempt to improve feed tolerance discussion around transpyloric feeding has been explored. Gastric feeding stimulates digestive processes whereas transpyloric feeding has the potential benefits of delivering nutrients past the pylorus and gastroesophageal junction for the management of GORD. These enteral feeds must be given continuously, which may account for the reduction in symptoms of gastro-oesophageal reflux (GOR). A recent Cochrane review in 2013 looked at transpyloric feeding compared to gastric tube feeding and found that the data did not provide evidence of any beneficial effect of transpyloric feeding for preterm infants. Transpyloric feeding is not routinely recommended and has been associated with a greater incidence of gastrointestinal disturbances and mortality, but these findings should be interpreted and applied cautiously because of methodological weaknesses in included trials (37*).*

Therefore, it is unclear which method of feeding helps with GORD as both have been documented to have positive and negative effects on the incidence and severity. A Cochrane review in 2014 did not identify any research that evaluated the effects of continuous feeding versus intermittent bolus feeding on GORD in preterm and LBW infants and concluded that further trials are needed (49*).*

Breast milk

MOM is overall the best milk for her preterm infant during the neonatal period and is associated with improved short-term and long-term outcomes (53). The immune system of preterm infants is immature, placing them at increased risk for serious immune-related complications. Human milk provides a variety of immune protective and immune maturation factors that are beneficial to the preterm infant's poorly developed immune system (54). NEC is a devastating disease of premature infants and is associated with significant morbidity and mortality. While the pathogenesis of NEC remains incompletely understood, it is well established that the risk of disease is increased by the administration of infant formula and decreased by the administration of breast milk. Breast milk has a well-established role in the prevention of NEC and clinically represents one of the most effective strategies in decreasing the incidence and progression of NEC (118).

The achievement of adequate growth in preterm infants is difficult, but extremely relevant in terms of long-term development. Growth is not only weight gain. It includes also head circumference and length gains, although accurate length measurements are difficult to obtain (11). A preterm infant can meet its energy requirements from breast milk alone if expressing techniques and milk handling are optimised (e.g. use of hind breast milk), but not the protein requirements. Infants born <1.0kg will require 200mL/kg/day to meet requirements for energy. Eventually more protein will be required in the form of multi nutrient BMF, especially in infants <1.5kg birthweight (62-65). Moreover, infants born <1.0kg would require up to 240mL/kg/day to meet the higher requirements for protein, increasing to 330mL/kg/day after two weeks. Clearly these volumes are undesirable and hence fortification is indicated in order to maintain realistic lower feed volumes.

Maternal breast milk handling and storage

If it is not possible for an infant to breastfeed in hospital due to prematurity the mother should be supported to express her breast milk. Hand expressing is a valuable skill and should be taught as soon as possible following delivery so that new mothers who are separated from their infant can start to express. Early (within the first hour), frequent (at least 8 to 10 times in 24 hours including once at night) and effective expressing (combining hand and pump expression) is crucial to ensuring a mother is able to maximise her individual milk production so that she can maintain her supply for as long as she wishes. There are many factors, however, that may impact on the amount of milk an individual woman may produce, so the focus should primarily be on enabling the woman to achieve her potential rather than on specific amounts (119).

The breast should be completely emptied at each expression to ensure the collection of all the fat rich hind milk (120). Optimal expressing technique (e.g. 'hands on' expression) will help to ensure this is achieved. 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 breast milk is also prone to separation and adhesion to bottles and tubing thereby reducing the energy content of the milk (121).

Freshly expressed breast milk may be kept at room temperature (up to 26^{o}C) for up to 4 hours (83). However, if it will not be used within this time for a feed, it should be refrigerated immediately following expression. Fresh breast milk can be stored in a refrigerator for up to 48 hours at 2-4^{o}C (86).

Any breast milk that will not be required for a feed within the 48 hours recommended storage time should be frozen as soon as possible, preferably within 24 hours. Breast milk may be stored frozen at -20^{o}C for up to 3 months (86).

Appropriately stored refrigerated MOM leads to minimal changes in immune components such as secretory IgA, lactoferrin and white blood cells (86).

Breast Milk Fortification

Increased preterm nutritional requirements persist beyond the time when early milk composition changes to that of mature breast 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 (122).

In order to maintain the benefits of breast milk whilst optimising the nutritional status and growth of preterm infants, multi nutrient BMF have been developed. The two available in the UK are C&G Nutriprem® BMF and SMA® BMF; both are based on cow's milk protein. Neither product has clear indications for introduction or guidance for infant suitability. Therefore, practice varies considerably across Wales and the UK. There continues to be no consistent evidence for any harm of fortification and lack of any data to suggest that fortification increases the risk of feed intolerance or NEC (123).

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 (124, 125) whilst those investigating gastric emptying have been contradictory (126, 127). Concerns regarding bowel obstructions associated with BMF were addressed by Stanger 2014 (128). In 7 premature babies 25-27 weeks, all < 1.0kg who presented with bowel obstructions secondary to intestinal concretions of BMF, Stanger concluded that BMF is an important source of nutritional support and felt to be safe. It should, however, be used with caution, especially in those with a history of NEC (128).

Storage concerns include the reduction of anti-infective components (68), increased bacterial loads (70) 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 (73).

A Cochrane review of multi-nutrient fortification of human milk for preterm infants showed small but significant increases in weight, length and head circumference measurements in the short term, but no statistical significance in growth at 12-18 months (123). The authors concluded that there continues to be no consistent evidence for any harm of fortification and a lack of any data to suggest that fortification increases the risk of feed intolerance or NEC although the evidence was of low quality.

BLISS, WHO and UNICEF/BFI all recognise the benefits of fortification of breast milk and have position statements or guidance regarding fortification (67, 83, 2) (see Appendix 2).

UNICEF recommend that infants be tolerating full enteral feeds before BMF is added and not to consider fortification until an infant has received at least 2 weeks of exclusive mother's milk (2).

BLISS (67) recommended the following, based on evidence and practice within the UK and Ireland:

- fortify EBM in all infants with a birth weight <1.5kg and <34 weeks gestation
- consider fortification in infants with a birth weight of 1.5k-2.0kg and <34 weeks gestation

and, prior to fortification infants should:

- receive ≥50% total feeds as breast milk
- tolerate feed volumes at a minimum of 150mL/kg/day, preferably 180mL/kg
- have a serum urea <4mmol/l and falling

Despite this guidance from the above organisations, clinical practice has evolved, and fortification is commencing earlier across the world, from as little as 100mL/kg. Early versus late introduction of fortifier was not addressed by the recent Cochrane review (123) so Mimouni (2017) undertook a systematic review to address this specific issue and concluded that there is little evidence that the early introduction of human milk fortification improves long-term growth and neurodevelopmental outcome (66).

However, there may be some infants who require breast milk fortification <150mL/kg/day to optimise their nutrition e.g. fluid restricted infants. For these infants, fortification should commence at half strength for the first 24 hours, increasing to full strength at tolerated.

Early versus later introduction of BMF (first feed vs. 50-80mL/kg/day (129) and 20mL/kg/d vs. 100mL/kg/d (130) showed no strong evidence that important positive or adverse outcomes were affected, e.g. anthropometry, NEC, bronchopulmonary dysplasia (BPD), PDA, sepsis and feed intolerance. Infants received significantly more protein and some studies showed lower levels of alkaline phosphatase (ALP) in the early introduction groups. Infants included had birth weights as low as 500g. To concur with the above findings Dutta, 2015 critiqued available research and produced Canadian feeding guidelines for VLBW infants that start fortification at 100mL/kg/d at half strength for 48 hours before progressing to full strength feeds (31).

The aforementioned studies have shown no detrimental effect for preterm infants and practice within the UK is moving towards earlier introduction of BMF which would provide levels of protein closer to ESPGHAN recommendations (9) at an earlier stage.

Infants with birthweight over 2kg are unlikely to need BMF.

Individualised fortification

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 (131). 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 (67) but should be carefully interpreted in infants with severe IUGR due to lower intestinal absorption (132). Studies looking at fixed supplementation against urea determined supplementation have been inconclusive, but a study demonstrated improvement in body weight and head circumference where protein fortification was adjusted according to serum urea levels (133).

Moving forward, evidence is now strongly suggesting that standardised fortification is not ideal (75, 76), however it is the usual practice within the UK. Research and clinical practice are indicating that significant improvements in growth parameters can be achieved by either targeted or adjustable fortification (75, 77).

Targeted fortification is complex; it involves breast milk analysis and specific fortification of each expression based on the analysed composition. The use of a human milk analyser is required to identify the level of supplementation needed to meet the infant's nutritional requirements.

Adjustable fortification is more easily achieved and is based on levels of urea (77). Either method would require different procedures within each unit and would incur logistical, resource and financial implications. Evidence for individualised fortification should be considered when these guidelines are reviewed in the future.

Post discharge use of BMF
A Cochrane review included two studies, one of which fortified preterm infants of <33 weeks gestation at birth for 12 weeks post discharge and the other for 4 months post-term (134). The review found no evidence that fortification post discharge affected growth parameters through infancy; it did, however, find a significantly higher level of bone mineral content in the intervention group at 4 months and 12 months CGA. However, Teller (2016) showed that higher protein to energy ratios post discharge led to increased lean mass accretion and increased head circumference at 1 year (135).

Supplemental Protein powder
Nutriprem® protein supplement is indicated for use in ELBW infants who have higher protein requirements of 4.0–4.5g/kg/d as recommended by Koletzko and ESPGHAN (8, 9).

It is intended for use with Nutriprem® BMF, Nutriprem® 1 and Hydrolysed Nutriprem® only. These milks have lower amounts of protein per 100mL compared to SMA Gold Prem® 1 or breast milk fortified with SMA® BMF.

The product is available in 1g sachets and provides an additional 0.82g protein per 100mL of fortified breast milk.

It should be acknowledged that the osmolality of the protein supplement is 40mOsmol/kg H_20 per 1g of protein (80) and will increase the osmolality of the feed to which it is added.

Monitoring of serum urea should continue when Nutriprem® Protein Supplement has been commenced.

Donor breast milk (DBM)
When sufficient maternal breast milk is not available, alternative forms of enteral nutrition for preterm or LBW infants are DBM or artificial formula. DBM may retain some of the non-nutritive benefits of maternal breast milk for preterm or LBW infants but donor human milk has a lower density of several nutrients compared to maternal breast milk or artificial formula (82).

Preterm infants often find artificial formula more difficult to digest than human milk, and concerns exist that formula could increase the risk of severe bowel problems. If preterm infants are fed with DBM, rather than an artificial formula, this might reduce the risk of these problems. A recent Cochrane review found that preterm and LBW infants feeding with formula compared with DBM, either as a supplement to maternal expressed breast milk or as a sole diet, results in higher rates of weight gain, linear growth, and head growth. Formula fed infants were also at a higher risk of developing NEC (81).

DBM is more expensive than many formulas and may not contain sufficient amounts of key nutrients to ensure optimal growth for preterm or LBW infants (81). DBM has an average energy content of 46kcal/100mL (compared to 70kcal/100mL for preterm breast milk) as the majority of donated milk tends to come from lactating mothers of older term infants. Analyses of DBM report that donated breast milk contains on average 0.9g of protein per 100mL. One of these studies of donated milk assessed the milk protein content at 8 months of postnatal age and found the protein was 0.7 g/dL (60).

However, preterm DBM is becoming available and should be used whenever possible. The use of DBM should normally be restricted to establishing feeds in the at-risk infant with the gradual introduction of alternative feeds once full volumes are achieved. Some units may use DBM for the short-term support of a preterm infant whose mother is establishing milk expression (82).

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 (136). Documentation and traceability of DBM is essential. NICE Guidelines contain specific recommendations for practice within hospitals receiving DBM from a Milk Bank in addition to recommendations for central processing units.

BAPM (2016) suggests that current usage of pasteurised donor human milk (DHM) varies across the UK (82). One study suggests that the most commonly reported limiting factors for those not using donor-expressed breast milk (DEBM) were cost (64.6%) and access to DEBM (49.3%). This latter reason and the clustering of units initiating DEBM around Milk Banks might suggest that having more Milk Banks could further increase use of DEBM (137). This reflects local availability as well as differing opinions amongst health professionals of its benefits. Access to DBM is variable due to the geography of Wales. The location of the unit will determine which milk bank will be used.

"DHM is considered by some, but not all practitioners, as being integral to the promotion of breast feeding. The availability of DHM may have wider impacts, for example, on maternal breast-feeding rates and both positive and negative impacts have been reported; a recent meta-analysis concluded that the overall impact is positive" (BAPM) (82).

Preterm formulas

Preterm formulas have been designed to meet the ESPGHAN nutritional requirements for infants weighing 1.0-1.8kg. These are food for special medical purposes for the dietary management of preterm and low birthweight infants. The formulas are for hospital use only and available in a sterile RTF format.

Cow & Gate Hydrolysed Nutriprem® is an extensively hydrolysed formula with 60:40 whey:casein ratio "for use in infants who have a compromised ability to breakdown or absorb whole proteins or who are not tolerating standard preterm formula" (138). It may be considered for use in surgical cases however the lactose content may result in poor tolerance post GI surgery. Hydrolysed Nutriprem® is not suitable for the management of cow's milk protein allergy.

SMA® Gold Prem 1 contains 2.9g of protein per 100mL and supports the higher protein requirements of ELBW infants. Infants receiving >155mL/kg/day to optimise growth would exceed a protein intake of 4.5g/kg/day and will require closer monitoring.

All standard term formulas do not meet the nutritional requirements of preterm infants. This includes hydrolysed and amino acid formulas. A Cochrane review suggested that the use of protein hydrolysate formulas during the initial admission for preterm infants does not affect the risk of feed intolerance or NEC but recommended larger pragmatic trials are required (87)

"Safe feeding of hospitalised infants and children is paramount in enhancing their clinical outcomes" (Royle et al, 2016) (86). In the absence of any breast milk, nutritionally appropriate RTF formula should be used in health care settings (86).

Nutrient enriched post discharge formulas

In 2006 ESPGHAN recommended that formula fed preterm infants should receive NEPDF with high protein, minerals, trace elements and long-chain polyunsaturated fatty acids (LCPUFAs) until at least 40 weeks post-conceptual age (PCA), possibly until 52 weeks PCA (139).

However, a Cochrane review in 2012 found no evidence of beneficial growth outcomes at 12-18 months of age and did not support the use of NEPDF following discharge from hospital. This review was updated in 2016 with the same conclusions but only three studies in this later review included infants who were growth restricted at birth (140). There was a statistically significant effect on length at 6 months CGA which may suggest that this cohort may benefit from NEPDF following hospital discharge. There is currently a lack of long-term data assessing the impact of NEPDF on growth or long-term cardio-metabolic outcomes.

On discharge from hospital, units provide infants who require NEPDF with a prescription of powdered milk. PIFs are not sterile and are at risk of contamination with Salmonella and Enterobacter sakazakii (E. sakazakii can survive for at least 1 year in dry PIF) (84). E. sakazakii has caused diseases in all age groups but by far the majority of cases are seen in infants less than 4-6 weeks of age, especially preterm infants, underweight, immunocompromised or from immunocompromised mothers. European guidance recommends that the most effective control measure to minimise risks of Salmonella and E. sakazakii in high risk infants (preterm, underweight, immunocompromised) would be to use commercial sterile liquid formula (141). This is not currently common practice in units across Wales. Some units provide a small supply of RTF NEPDF for use initially post-discharge to enable transition to powdered formulation; this has enabled both the improved tolerance of the change to powdered formula but also standardisation of practice to reduce unnecessary spend on RTF in primary care.

Late preterm infants

The majority of research for preterm infants has been based around those of VLBW and ELBW. Late preterm infants (34 - <37 weeks gestation) account for 9-10% of all births (142), have less mature brains than the term infant, are at risk of adverse developmental outcomes (143, 144) and are also at higher risk of mortality and morbidity in comparison to term infants (145).

The advantages of breastfeeding in this group appear to be even greater than for term infants but establishment of breast feeding is frequently more problematic, and less support appears to be offered in comparison to infants born at earlier gestations (146-148).

Faster growth during the early critical period after late preterm birth is associated with better adult neurocognitive functioning (149). This catch up growth in the late preterm infants has been shown to be predominantly fat mass accretion rather than fat free mass (150-152) and this may have potential long-term health implications.

Early discharge nutrient deficits and poor growth could be prevented/addressed by utilising BMF or enriched formulas but should be limited to the period of poor feeding or poor growth and should be discontinued as soon as possible after expected term to avoid overfeeding (22).

There is no universal consensus about the most beneficial and appropriate nutritional treatment for late preterm infants. Based on the brain growth still required and the evidence showing higher accretion of fatty tissue we should consider whether BMF in breast milk or a specialist enriched formula should be considered for this group on an individual basis.

Feeding and Gastro-oesophageal reflux disease

GORD – Continuous or bolus feeding
GOR is common in infants and this may be related to the high fluid intakes and a supine body position when feeding (153). This article described a critical review of evidence and suggested that:

1. Apnoea is unrelated to GORD in the majority of infants
2. Faltering growth rarely occurs in an infant with GORD
3. A relationship with GORD and chronic airway problems has yet to be established in preterm infants.

In essence they suggest there is insufficient evidence that infants with GORD and the above issues should be treated but when there is evidence of complications, such as recurrent aspiration or cyanosis during vomiting, GORD should be treated.

Delayed gastric emptying is reported to be a factor in GOR in infants and children (154).

Omari, 2002 reported a positive correlation between feed frequency and symptoms of GORD (155).

Clinical practice suggests that feeding infants continuously rather than bolus feeding might be effective in managing GORD (156). Continuous feeding results in a reduction in gastric distension as feeds are delivered slower than with bolus feeds. In turn there is less pressure on the lower oesophageal sphincter whilst allowing faster gastric emptying when compared to an infant who is bolus fed. Continuous nutrition could be a preferred method of feeding in smaller infants with a BW <1.25kg or hemodynamically impaired infants (157). However, both methods of feeding have clinical benefits as well as disadvantages. Conflicting results of studies comparing these methods of feeding make it difficult to formulate recommendations. A Cochrane review in 2014 found no randomized controlled trials that evaluated the effects of continuous versus bolus tube feeding on GORD in preterm and LBW infants and so recommendations on the best way to feed an infant with GORD cannot be made (49).

GORD - Gastric or transpyloric feeding
Feed tolerance in infants with GORD can be difficult to manage and the evidence suggests benefits and potential problems with either route of feeding.

A retrospective single centre study of 72 infants reported reduced episodes of apnoea and bradycardia in preterm infants with suspected GORD when fed human milk via transpyloric route; however concluded that further trials are needed to determine the impact of bypassing the stomach, in addition to the safety and efficacy of this feeding method (158).

A small retrospective chart review concluded that transpyloric feeding may be useful for diagnosis and management of suspected GOR associated apnoea in a selected group of infants (159).

Both these studies showed that transpyloric feeding may reduce GOR and GOR associated apnoea, but these findings were not reported in a Cochrane review in 2013 (37); however, the review did not aim to review GOR related apnoea.

To conclude, further trials, as suggested by Malcolm 2009, are needed to evaluate if transpyloric feeding can be used as an effective treatment in preterm infants with GORD (158).

A stepwise approach, using non-pharmalogical intentions is considered the most advisable approach to management (160).

Appendix 2: Specialist infant formulas used in the neonatal unit

(**NB:** Products are listed in alphabetical order of the manufacturer)

Formula	Manufacturer	Indications	Nutrient Modification
Hydrolysed Preterm Formula			
Hydrolysed Nutriprem®	Cow & Gate	For preterm and LBW infants who require a hydrolysed protein feed.	60% whey; 40% casein (approximately); osmolality = 395mOsm/kg water
Extensively Hydrolysed Protein Formula (EHF)			
Similac® Alimentum®	Abbott	Cow's milk protein allergy	hydrolysed casein; low lactose; 30% MCT; osmolality = 274mOsm/kg water
Aptamil Pepti® 1	Danone		hydrolysed whey; contains lactose; osmolality = 280mOsm/kg water
Nutramigen® LGG 1	Mead Johnson		hydrolysed casein; low lactose; osmolality = 290mOsm/kg water
Althera®	Nestle		hydrolysed whey; contains lactose; osmolality = 281mOsm/kg water
Extensively Hydrolysed Protein Formula (EHF) with approximately 50% MCT fat			
Aptamil Pepti Junior®	Cow & Gate	Malabsorption; post NEC; post GI surgery; conjugated hyperbilirubinaemia	whey based; minimal lactose; osmolality = 210mOsm/kg water
Pregestimil Lipil®	Mead Johnson		casein based; minimal lactose; osmolality = 280mOsm/kg water
Infatrini Peptisorb®	Nutricia		whey based; lactose free; Energy dense (1kcal/mL); osmolality = 350mOsm/kg
Amino Acid Formula			
Nutramigen Puramino®	Mead Johnson	Severe malabsorption; allergy	osmolality = 350mOsm/kg water
SMA® Alfamino®	Nestle		osmolality = 332.5mOsm/kg water
Neocate LCP®	Nutricia		osmolality = 340mOsm/kg water
High Energy Formula			
Similac® High Energy	Abbott	Increased requirements or fluid restricted infants	1kcal/mL; osmolality = 333mOsm/kg
Infatrini®	Nutricia		1kcal/mL; osmolality = 360mOsm/kg water
SMA® High Energy	SMA		0.9kcal/mL; osmolality = 387mOsm/kg
MCT Formula			
Monogen®	Nutricia	Use when a diet low in long chain fats is indicated	84% MCT; 16% LCT osmolality = 235mOsm/kg water
Renal Formula			
Renastart®	Vitaflo	Renal insufficiency	low in protein, calcium, chloride, potassium, phosphorus and vitamin A; 1kcal/mL at standard 20% solution osmolality = 225mOsm/kg water
Kindergen®	Nutricia	Renal insufficiency	low in potassium, chloride, calcium, phosphorus and vitamin A. 1kcal/mL at standard 20% solution osmolality = 215mOsm/kg water
Low Calcium Formula			
Locasol®	Nutricia	Disorders causing high blood calcium levels e.g. Williams Syndrome; hypophosphatasia	very low in calcium and vitamin D osmolality = 310mOsm/kg water
Formulas used in Inherited Metabolic Disorders (IMD)			
There are a variety of specialist infant formulas used in IMD dependent upon the specific condition. These should be used following discussion with your metabolic, neonatal or paediatric dietitian.			

Appendix 3: Nutritional composition of milks, formulas and supplements

Values are given per 100ml 'ready to feed' formula (where products are available in this format). All other feeds are per 100ml of reconstituted formula at **standard** concentration

Milk	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Na (mmol)	K (mmol)	Fe (mg)	Ca (mmol)	P (mmol)	Vit A (µg)	Vit D (µg)	Osmolality (mOsm/kg H_2O)	Date of analysis
Preterm EBM	68	1.62	3.5	7.3	1.21	1.28	0.09	0.62	0.47	90	0.2	280-310	SMA 03/17
Preterm EBM + SMA BMF (4g)	85.2	3.06	4.22	8.58	2.82	251	1.89	2.52	1.89	470	4.2	390	SMA 03/17
Preterm EBM + Nutriprem BMF (4.4g)	82	2.7	3.5	10.0	2.74	1.87	0.09	2.27	1.7	247	5.2	450	C&G 11/16 & 01/19
Preterm EBM + Nutriprem BMF (4.4g) + Nutriprem Protein Supplement (1g)	85.4	3.5	3.5	10.0	3.07	2.19	0.09	2.4	1.87	247	5.2	490	C&G 11/16 & 01/19
Mature EBM	69	1.3	4.1	7.2	0.65	1.49	0.07	0.85	0.48	58	Trace	280-310	SMA 03/17
Mature EBM + Nutriprem BMF (4.4g)	84	2.4	4.1	9.9	2.17	2.08	0.07	2.5	1.71	290	5	450	C&G 11/16 & 01/19
Mature EBM + Nutriprem BMF (4.4g) + Nutriprem Protein Supplement (1g)	87.4	3.2	4.1	9.9	2.51	2.39	0.07	2.63	1.88	294	5	490	C&G 11/16 & 01/19
Mature EBM + SMA BMF (4g)	86.2	2.74	4.82	8.48	1.5	2.2	ns	3.2	1.9	438	≥4	390	SMA 03/17
Nutriprem 1	80	2.6	3.9	8.4	3.04	2.1	1.6	2.35	2.0	361	3.0	375	C&G 04/17
Nutriprem 1 + Nutriprem protein Supplement (1g)	83.4	3.4	3.9	8.4	3.38	2.42	1.6	2.48	2.17	361	3	~415	C&G 11/16
SMA Gold Prem 1	80	2..9	4.0	8.11	2.2	3.07	1.8	2.9	2.49	370	3.47	308	SMA 08/16
Hydrolysed Nutriprem	80	2.6	4.0	8.4	3.3	2.23	1.1	2.42	1.78	396	3.1	395	C&G 11/17
Hydrolysed Nutriprem 1 + Nutriprem protein Supplement (1g)	83.38	3.42	4.0	8.42	3.64	2.54	1.1	2.55	1.95	396	3.1	~435	C&G 11/17
Nutriprem 2	75	2.0	4.0	7.4	1.2	2.0	1.2	2.2	1.5	100	1.7	310	C&G 04/17
SMA Gold Prem 2	73	1.9	3.9	7.5	1.17	1.82	1.2	1.82	1.36	100	1.5	311	SMA 01/15

Milk	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Na (mmol)	K (mmol)	Fe (mg)	Ca (mmol)	P (mmol)	Vit A (µg)	Vit D (µg)	Osmolality (mOsm/kg H_2O)	Date of analysis
Cow & Gate First Infant Milk	66	1.3	3.4	7.3	0.78	1.74	0.55	1.25	0.9	55	1.2	315	C&G 11/16
SMA PRO First Infant Milk	67	1.25	3.6	7.1	1.04	1.59	0.7	1.07	0.77	75	0.9	295	SMA 07/18
Aptamil First Infant Milk (powder info)	66	1.3	3.4	7.3	0.91	2.13	0.53	1.3	1.07	50	1.2	350	C&G 09/18
Aptamil Profutura First Infant Milk	66	1.3	3.4	7.3	0.69	1.66	0.5	1.22	0.94	65	1.3	330	C&G 11/16
Similac Alimentum	67.6	1.86	3.75	6.62	1.3	1.82	1.22	1.78	1.41	61	1.01	274	Abbott 03/18
Nutramigen LGG	68	1.91	3.4	7.5	1.38	2.1	1.23	1.91	1.7	61	1.03	290	Mead Johnson 07/16
Aptamil Pepti 1	67	1.6	3.5	7.0	0.9	2.1	0.53	1.2	0.84	53	1.3	280	C&G 01/17
Althera	67	1.7	3.4	7.3	0.86	1.8	0.73	1.7	1.4	79	1.2	281	Nestle 08/15
Aptamil Pepti Junior	66	1.8	3.5	6.8	0.8	1.7	0.77	1.3	0.9	52	1.3	210	C&G 11/17
Pregestimil Lipil	68	1.89	3.8	6.9	1.26	1.9	1.22	1.94	1.64	77	1.25	280	Mead Johnson 02/16
Infatrini Peptisorb	100	2.6	5.4	10.3	1.4	2.8	1.0	2.0	1.3	81	1.7	350	Nutricia App 01/19
Nutramigen Puramino	68	1.89	3.6	7.2	1.39	1.89	1.22	1.6	1.13	61	0.85	350	Mead Johnson 02/15
SMA Alfamino	70	1.9	3.4	7.9	1.1	2.0	0.7	1.4	1.3	72	1.0	332.5	SMA 08/15
Neocate LCP	67	1.8	3.4	7.2	1.1	1.8	1.0	1.6	1.5	56	1.2	340	Nutricia App 01/19
Similac High Energy	100	2.6	5.4	10.1	1.1	2.3	1.09	2.0	1.36	100	1.7	333	Abbott 03/18
Infatrini	101	2.6	5.4	10.3	1.6	2.4	1.2	2.5	1.6	81	1.9	360	Nutricia App 01/19
SMA High Energy	99	2.6	5.4	10	1.13	2.51	1.0	1.97	1.45	120	1.7	377	SMA 02/17
Monogen	74.6	2.2	2.2	11.6	1.55	1.78	1.1	1.5	1.16	54.6	2.0	235	Nutricia 09/16
Renastart	99	1.5	4.8	12.5	2.1	0.6	1.0	0.6	0.6	25.6	1.1	225	Vitaflo 09/15
Kindergen	101	1.5	5.3	11.8	2.0	0.6	1.0	0.6	0.6	26	1.1	215	Nutricia App 01/19
Locasol	66	1.9	3.4	7	1.2	2.1	0.52	<0.5	1.5	79	0	310	Nutricia App 01/19

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