East of England Neonatal Network

Clinical Guideline: Enteral Feeding - Iron supplementation

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

Used by: Medical Staff, Neonatal Nurse Practitioners, Dietitian, Nursery Nurses.

Key Words: iron, enteral feeding, Sytron

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Approved by:

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Audit Standards:

Audit points

- Inpatients born < 37 weeks gestation who weigh <1.5 kg are prescribed Sytron 0.5ml once daily from 4 weeks unless receiving preterm formula or EBM fortified with SMA BMF.
- Inpatients born < 37 weeks gestation who weigh >1.5 kg are prescribed Sytron 1ml once daily from 4 weeks unless receiving preterm formula or EBM fortified with SMA BMF.
- Babies born < 37 weeks on term or specialist formulas are prescribed Sytron 1ml once daily at discharge until 6 months corrected age.
- Babies born < 37 weeks on SMA Gold Prem 2 Nutrient Enriched Post Discharge Formula (NEPDF) are prescribed Sytron 1.0ml once daily on discharge until 6 months corrected age or transfer to term formula (whichever is earlier)

1.0 Introduction

Infants born during the third trimester have iron stores proportional to body weight, therefore the smaller the infant the lower the iron store. In very low birthweight infants this store generally lasts for approximately 2 months or until birthweight has doubled. In addition to low stores infants may also lose significant volumes of blood through phlebotomy; however this may be reduced in cases where delayed cord clamping has occurred. (1)

The greatest need for iron in the neonatal period is for erythropoiesis, which has 3 phases:

Phase 1: Immediately after birth haemoglobin falls, serum ferritin increases and reticulocyte activity decreases. Iron supplementation is not thought to be beneficial for this 'physiological anaemia', though there may be an element of iron deficiency (2)
Phase 2: From 6-8 weeks of age erythropoiesis increases secondary to the early anaemia. Iron stores are liberated from ferritin and there is increased duodenal absorption.
Phase 3: Ongoing dependence on dietary iron. In the preterm infant this occurs much earlier than in the term neonate as low stores are rapidly depleted by the high requirements for growth.

Long-term growth and neurodevelopmental outcomes are affected by iron deficiency in the neonatal period while both iron deficiency and iron excess will affect developing organ systems. Maternal conditions such as iron deficiency, diabetes mellitus, hypertension and smoking may further reduce iron stores in the preterm infant. However, due to the potential for oxidant-mediated tissue injury, iron overload from transfusions, formula and supplements should be avoided.

Iron supplementation is therefore necessary for many infants born prematurely but clear guidelines are needed for appropriate timing and dosage of supplementation. Historically guidance has recommended that supplementation be considered for all infants <34 weeks, however current evidence suggests the later preterm (34w-36+6) or the marginally low birth weight infant (2.0-2.5kg) would also benefit from iron supplementation with respect to iron deficiency and iron deficiency anaemia at 6 months and behaviour problems at 3.5 year follow up.

There is limited evidence available to enable development of definitive strategies for iron supplementation. The following guidelines are therefore based upon a combination of available current evidence, national and network best practice and aim to ensure optimum iron provision within a safe and practical framework.

Available evidence to support these guidelines can be found in Appendix 1.

2.0 Which infants require iron supplementation and how much should they receive?

The assessment of an infant's need for supplementary iron should be based on birth weight, gestation and feeding regimen. International guidelines (3) suggest earlier and higher levels of supplementation be given to the VLBW infant (<1500g) in order to achieve a combined supplement and enteral feed intake of:

Birth weight 1500-2000g	2mg/kg/day	from 2-6 weeks of age
Birth weight <1500g	2-3mg/kg/day	from 2 weeks of age

For practical application all infants born **<37 weeks** gestation should be considered for iron supplementation from 4 weeks of age according to the following criteria:

2.1 Breast Milk

Unfortified breast milk, both term and preterm is low in iron. Although absorption of iron from breast milk is good it would still not provide the minimum 2mg/kg/day recommended. Where infants are breastfed exclusively or tube fed with expressed breast milk (EBM) or donor breast milk (DBM)
I**ron supplementation IS recommended.**

2.2 Fortified Breast Milk

There are two breast milk fortifiers available for addition to EBM in the UK. One is fortified with iron, whereas the other is not.
Iron supplementation IS recommended where Nutriprem Human Milk Fortifier is used.
Iron supplementation IS NOT recommended where SMA Breast Milk fortifier is used.

2.3 Preterm Formulas

Nutriprem 1/ Nutriprem Hydrolysed / SMA Gold Prem 1 are the formulas in use within the Network. Volumes of 150 - 180ml/kg meets the 2-3mg/kg/day recommended for VLBW infants
Iron supplementation is NOT recommended.

2.4 Nutrient Enriched Post Discharge Formulas (NEPDF)

Formula fed infants born prior to 34 weeks and weighing <2000g who at discharge have raised requirements for energy (eg CLD on home oxygen) or infants who have had poor growth (eg crossed down >2 centiles during their neonatal stay) should be discharged on either Nutriprem 2 or SMA Gold Prem 2. Nutriprem 2 will provide 2mg/kg/day if a volume over 165ml/kg is taken. SMA Gold Prem 2 does not meet this minimum requirement within achievable feed volumes. As weaning progresses volume of formula consumed will decrease with the expectation that solid food will then contribute to iron intake.
Iron supplementation IS recommended where SMA Gold Prem 2 is used.
Iron supplementation IS NOT recommended where Nutriprem 2 is used.

2.5 Infants on NEPDF who change to term formula before 6 months

NEPDFs are most important in the first few weeks after discharge, and some infants will gain excess weight if NEPDF is continued for as long as 6 months.
Any infant changing to term formula before 6 months should receive iron supplementation until 6 months corrected age or established on a good weaning diet, whichever is the earlier.

2.6 Standard Term Infant Formulas

Term formulas contain sufficient iron to meet the requirements of the term infant. They are not routinely recommended for infants born <2kg but when used may not provide 2-3 mg/kg/day unless very high volumes are consumed. For any infant born <37 weeks discharged on one of these formulas
Iron supplementation IS recommended.

2.7 Nutrient Enriched Term Formulas – Infatrini, SMA High Energy, Similac HE, Infatrini Peptisorb.

These are concentrated nutrient dense formulas designed to meet the requirements of term infants within a reduced volume They may be useful in the Neonatal unit where a long term fluid restriction is required in an older preterm.
Iron supplementation IS recommended.

2.8 Specialised Formulas – Pepti Junior, Pregestimil, Neocate, Puramino, Monogen, etc

These formulas have certain nutrients modified to make them suitable for a variety of dietary treatments in the term infant. They are used in preterm infants when no equivalent preterm formula is available.
Iron supplementation IS recommended.

2.9 **Infants ≥37 weeks who are born weighing less than 2.5kg should also be considered for iron supplements especially if exclusively breastfed.**
As many will have been discharged prior to 4 weeks of age the GP should be asked to prescribe until 6 months of age.

3.0 Practical Management of iron supplementation

The recommended supplement is Sytron (sodium feredetate, 1ml Sytron = 5.5mg elemental iron).

3.1 Inpatient provision: (see 4.0 algorithm)

Iron supplementation is recommended from **4** weeks of age for all preterm infants <37 weeks gestation who meet the feeding criteria below. In addition, consideration should be given to supplementing infants born ≥37 and <2.5kg who also meet the feeding criteria, especially those who are exclusively breastfed:

Milk choice	**Supplement dose**
Breast feeding / EBM /DBM	0.5ml/day for infants <1500g bodyweight Then progressing to 1ml/day for infants >1500g bodyweight
EBM + SMA Breast Milk Fortifier EBM + Nutriprem Human Milk Fortifier	No supplementation required 0.5ml/day for infants <1500g bodyweight Then progressing to 1ml/day for infants >1500g bodyweight
Preterm formula – SMA Gold Prem 1, Nutriprem 1, Hydrolysed Nutriprem	No supplementation required
Term formulas Specialist term formulas Nutrient Enriched Term Formulas	0.5ml/day for infants <1500g bodyweight Then progressing to 1ml/day for infants >1500g bodyweight
NEPDF – Nutriprem 2	No supplementation required
NEPDF – SMA Gold Prem 2	1ml/day on commencement of formula

Where infants are on a combination of milks – EBM+BMF and Preterm formula or breast feeding and NEPDF a pragmatic decision based on proportion of each should be made. If the infant is regularly having more than 100ml/kg of the formula, no iron supplement is required. If the contribution of formula is less than this, prescribe iron as above. If uncertain seek dietetic advice or err on the side of caution and prescribe.

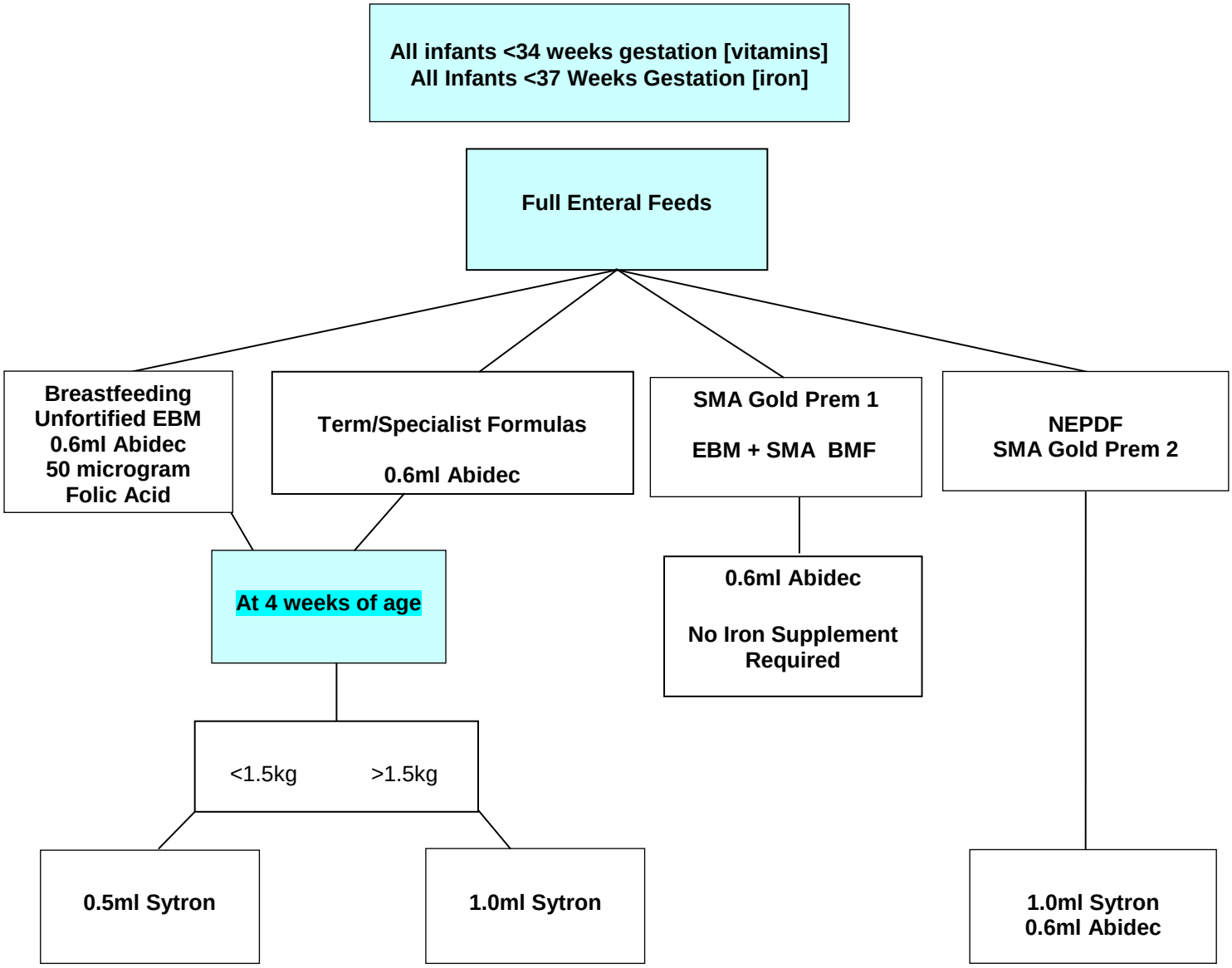
3.2 At Discharge: (see 4.0 algorithm)

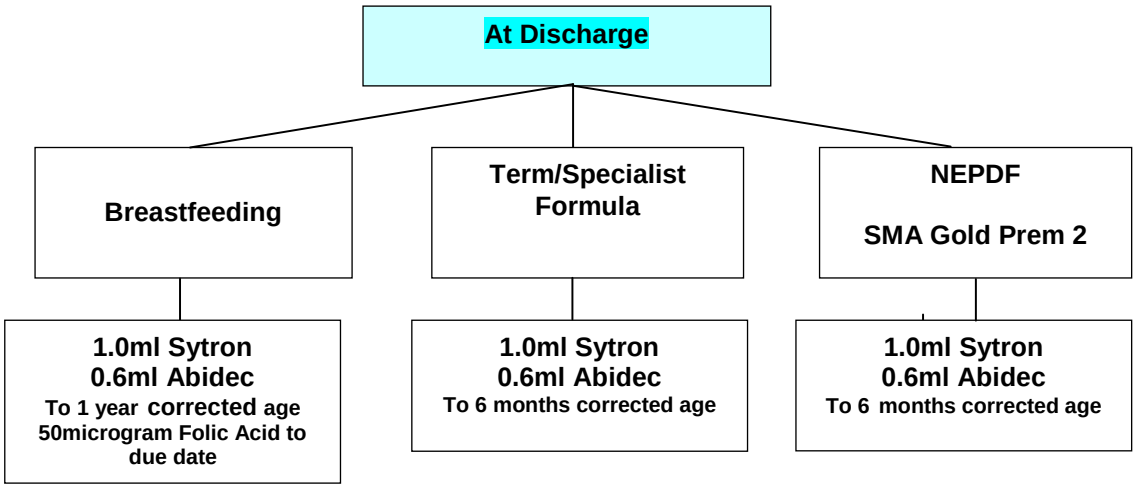
Milk choice	Supplement dose
Breast feeding	1ml Sytron once daily until 1 year corrected age.
NEPDF- Nutriprem 2	No supplementation required.
NEPDF- SMA Gold Prem 2	1ml Sytron once daily until 6 months corrected age or on a mixed weaning diet: whichever is earlier.
Normal infant formula Specialist term formula Nutrient Enriched Term Formulas	1ml Sytron once daily until 6 months corrected age.

3.3 Dispensing Sytron to infants

Sytron is a sugar free pink elixir usually given as a once daily dose.
It should not be given at the same time as calcium or phosphate preparations as insoluble compounds may be formed which will reduce the availability of each mineral.
Iron supplements are thought to be better absorbed if given before or between feeds rather than after feeds, but from a practical point of view can be mixed with feeds to reduce osmolality and prevent blocking tubes when tube feeding. Sytron can be given orally or via gastric or jejunal tube (4).

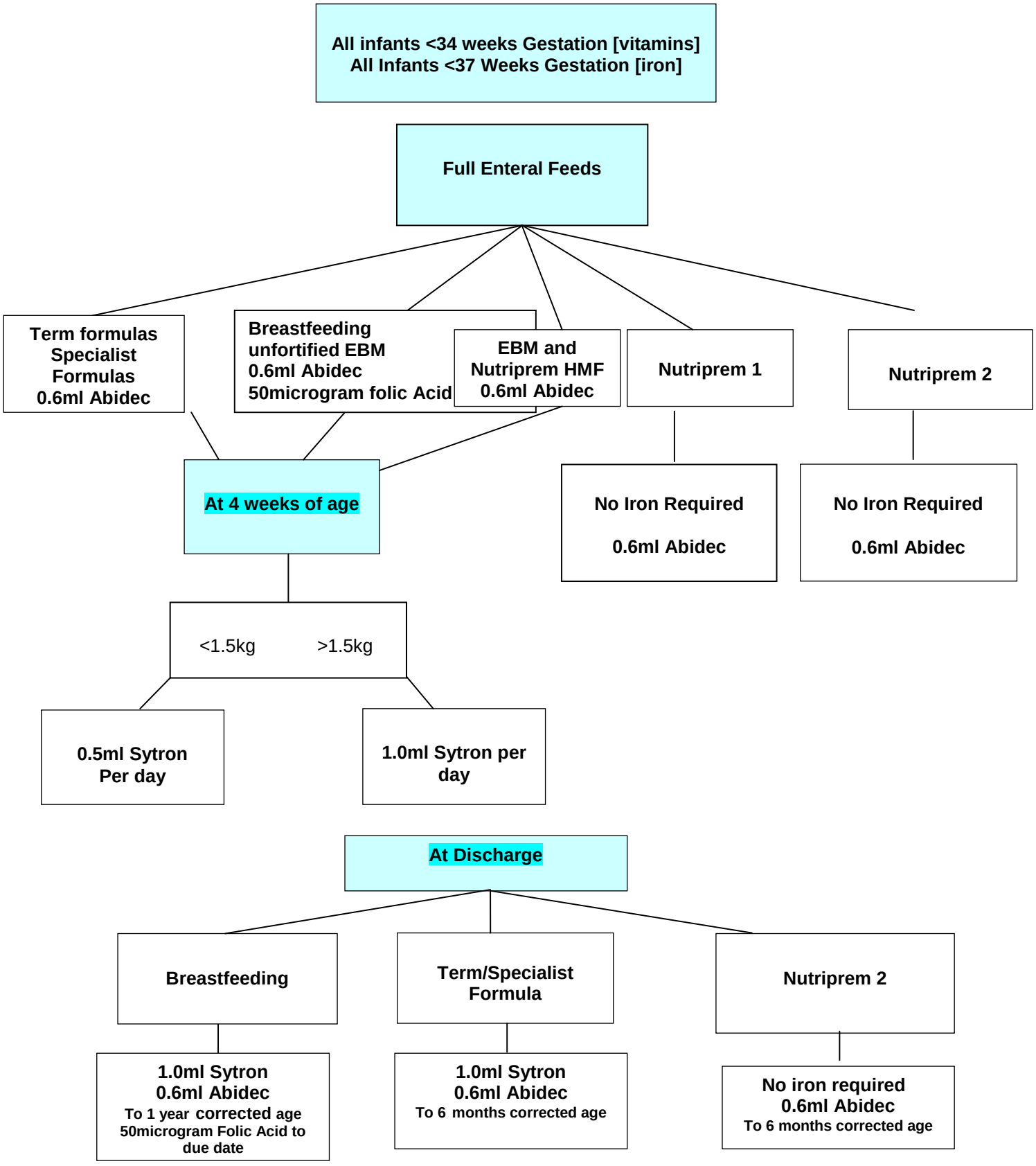
4.0 Algorithm for Iron & Vitamin supplementation – SMA range of feeds





Infants born ≥37 weeks and <2.5kg should be considered for iron supplementation from 4 weeks of age, especially if exclusively breastfeeding.

Algorithm for Iron and vitamin supplementation –Nutriprem range of feeds



Infants born ≥37 weeks and <2.5kg should be considered for iron supplementation from 4 weeks of age, especially if exclusively breastfeeding.

Appendix 1 – Evidence in support of guidelines.

When should iron supplementation be started?

Premature infants are theoretically at risk of iron induced oxidant injury due to lower iron binding capacity and less mature antioxidant systems than term infants. Excess iron may be a risk factor in the development of conditions such as bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) and blood transfusions have been linked to development of ROP though this is not thought to be due to iron overload (5). In contract available data suggest that infants who receive iron supplementation have a slightly higher haemoglobin level, improved iron stores and a lower risk of developing iron deficiency anaemia when compared with those who are un-supplemented. However, it is unclear whether iron supplementation in preterm and low birth weight infants has long term benefits in terms of neurodevelopmental outcome and growth.(6)

How much iron do premature infants need?

Estimated iron accretion during the third trimester is 1-2mg/kg/day. Early recommendations have been to provide 2mg/kg/day iron starting by 2 months from either supplemented milk and/or iron supplements up to a maximum of 15mg/day in total (7-9).

In 2005 guidelines from ESPGHAN confirmed that iron intakes <2mg/kg/day are likely to result in iron deficiency, especially in those born weighing <1800g. Guidance suggested between 2-3mg/kg/day from 2-6 weeks of actual age (2-4 in ELBW infants) but delayed in infants who have had multiple blood transfusions. As there is likely to be an intake above which the oxidative properties of iron may be harmful (particularly as there is no mechanism for regulated iron excretion in the preterm infant) ESPGHAN expressed caution with enteral iron doses >5mg/kg/day (10).

International guidelines published in 2014 (3) differentiate iron requirements according to birth weight, with the recommendation that earlier and higher levels of supplementation be given to the VLBW infant (<1500g) in order to achieve a combined supplement and formula intake of:

Birth weight 1500-2000g	2mg/kg/day	from 2-6 weeks of age
Birth weight <1500g	2-3mg/kg/day	from 2 weeks of age

The guidelines also consider the impact of transfusions and phlebotomy losses on iron requirements (3) recommending the measurement of weekly ferritin levels in order to individually determine iron supplement requirements. Although not currently common practice within the UK, measuring ferritin levels in infants who have received multiple transfusions or significant uncompensated phlebotomy losses may be a useful method of safely identifying iron needs in this population.
Where such a strategy is adopted recommendations for the management of infants outside of the reference range of 35 – 350microg/l are as follows:
<35microg/l - increase total iron provision to 3-6mg/kg/day for a limited period.
>350microg/l - stop iron supplementation.

Where the above strategy is not adopted considerations should be given to delaying the introduction of iron supplementation for 1-2 weeks from that recommended in the infant who has received multiple blood transfusions.

The levels of iron in milks fed to preterm infants vary from 0.05mg/100ml in human milk to 1.4mg/100ml in some preterm formulas, absorption being greatest from breast milk. To achieve a set amount per kg/day would therefore require a variable dose of supplement. As this is difficult to manage in practice iron supplementation is usually prescribed as a daily dose, accepting that the smaller infants will get more and larger infants less, but within a safe range.

Iron and the >34 week infant

Historically recommendations have focused on the needs of the <34 week infant. However, more recent publications and anecdotal case reports have drawn attention to the iron status of late preterm (34w-36^{+6}) or marginally low birth weight (2-2.5kg) infants, a group still at risk of iron deficiency secondary to reduced gestation and low birth weight, but often exempt from neonatal unit guidelines. A group in Sweden studied 285 infants who received either no supplementation, 1mg/kg/day or 2mg/kg/day. At 6 months of age iron deficiency was identified in 36% of those who received no supplements compared to 3.8% in those who received 2mg/kg/day and iron deficiency anaemia in 10% and 0% in the same groups. Iron deficiency anaemia was present in 18% of infants within the non-supplemented group who had been exclusively breastfed at 6 weeks of age**.** (11) Later developmental follow up of these infants aged 3.5 years showed a significant increase in behavioural problems in the group who received no supplementation, but no differences in cognitive outcomes.(12)

How long should supplementation continue for?

The provision of fortified formulas and prescribed iron during the hospital stay and the use of selected post discharge formulas (NEPDF) mean that iron supplementation above that provided by the post discharge formula (if using Nutriprem 2) is no longer required. Although the long term benefits of iron supplementation in the preterm and lowbirth weight baby remains uncertain (6), their iron requirements probably remain high for the first year of life (secondary to blood volume expansion and rapid growth) therefore infants being breastfed, those discharged on term formulas, and those using either of the post discharge formulas as a complement to breast feeding should continue iron supplementation. Those infants from cultural backgrounds where late weaning practices delay the provision of adequate iron from dietary sources may also benefit from a continuation of supplementation. Both ESPGHAN and the new 2014 published guidelines recommend iron supplementation continues after discharge until 6-12 months of age depending on diet (10, 3)

Iron supplementation and parenteral nutrition (PN)

Iron supplementation is not thought to be required whilst on PN unless it is the sole source of nutrition for more than two months or if iron deficiency develops. The optimal form for parenteral iron has not been determined but 100-200micrograms/kg is recommended when used (13-14).

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