Iron
Newborn use only

2020

Alert

Avoid >5 mg/kg/day as routine supplementation.
Check serum ferritin prior to the commencement of medicinal iron following any haemolysis.
Consider delaying/temporarily ceasing medicinal iron with (1) multiple transfusions, particularly >100 mL/kg (2) serum ferritin concentrations >350 microgram/L or (3) have received a transfusion in the last 7 days.

Indication

1. Prophylaxis in preterm infants <37 weeks and/or birthweight <2.5 kg
2. Supplementation during erythropoietin therapy
3. Treatment of iron deficiency anaemia

Iron content in dietary food

	Iron content		
	140 mL/kg/day	**160 mL/kg/day**	**180 mL/kg/day**
Preterm EBM	0.04 mg/kg/day	0.05 mg/kg/day	0.054 mg/kg/day
EBM+S26 HMF	0.04 mg/kg/day	0.05 mg/kg/day	0.054 mg/kg/day
EBM+FM 85	2.1 mg/kg/day	2.4 mg/kg/day	2.7 mg/kg/day
EBM+Nutricia BMF	0.04 mg/kg/day	0.05 mg/kg/day	0.054 mg/kg/day
Neocate Gold	1.4 mg/kg/day	1.6 mg/kg/day	1.8 mg/kg/day
Pre Nan Gold	2.5 mg/kg/day	2.9 mg/kg/day	3.2 mg/kg/day
Aptamil Gold + Preterm	2.2 mg/kg/day	2.6 mg/kg/day	2.9 mg/kg/day
S26LBW	2.0 mg/kg/day	2.2 mg/kg/day	2.5 mg/kg/day
Elecare/Elecare LCP	1.7 mg/kg/day	1.9 mg/kg/day	2.2 mg/kg/day
Pepti-Junior	1 mg/kg/day	1.2 mg/kg/day	1.4 mg/kg/day
Term Aptamil	0.78 mg/kg/day	0.9 mg/kg/day	1 mg/kg/day
S26 Gold Newborn	1.12 mg/kg/day	1.3 mg/kg/day	1.4 mg/kg/day
Nestle NAN Supreme 1	0.98 mg/kg/day	1.12 mg/kg/day	1.26 mg/kg/day

Action

Iron is needed to produce haemoglobin and certain iron-containing enzymes.
Ferrous sulfate corrects iron deficiency by re-saturating iron storage organs.

Drug type

Mineral

Trade name

ORAL: Ferro-Liquid Oral, Maltofer Syrup
IV – Venofer, Ferrosig iron, Ferrum H, Ferinject

Presentation

ORAL
Ferrous sulfate (Ferro-Liquid Oral) – 30 mg/mL oral liquid (= 6 mg of elemental iron/mL)
Iron polymaltose (Maltofer) – 37 mg/mL (= 10 mg of elemental iron/mL)
IV
Iron sucrose (Venofer) – 100 mg of elemental iron/5 mL infusion
Iron polymaltose (Ferrosig iron, Ferrum H) – 100 mg of elemental iron/2 mL
Ferric carboxymaltose (Ferinject) 50 mg of elemental iron/mL injection

Dose

ORAL
1. Iron prophylaxis in preterm infants <37 weeks and/or birthweight <2.5 Kg.[5-8]
   Iron can be from the diet or medicinal iron
   2 mg/kg/day – can be started from 2 weeks of age and continue up to 6–12 months of age[8-9]
   Consider delaying/temporarily ceasing iron with (1) multiple transfusions, particularly >100 mL/kg/day, (2) serum ferritin >350 microgram/L or (3) transfusion in the previous 7 days
2. Supplementation during erythropoietin therapy
   Oral: 3–6 mg/kg/day[10-11]
   IV: 1 mg/kg/day[12-13]
   IV dose of 20 mg/kg/dose can be given weekly[13]
3. Treatment of iron deficiency anaemia[8]
   3–6 mg/kg/day and to continue for 3 months after correction of anaemia[8]

IV
Supplementation on parenteral nutrition >4 weeks
   Preterm infants: 200–250 microgram/kg/day[14] or 1400 microgram/kg weekly[13]
   Term infants: 50–100 microgram/kg/day[14] or 700 microgram/kg weekly[13]
Supplementation during erythropoietin therapy
   1 mg/kg/day[12]
Treatment of iron deficiency anaemia:

	Total iron dose (mg) = (12.5 – observed Hb (g/dL) x body weight (kg) x 3.4 x 1.4[15] Oral iron must be ceased 24 hours before IV iron and should not be given until at least 7 days after last parenteral administration[16] IV iron must be prescribed as mg of elemental iron (e.g. as iron polymaltose) in mL of sodium chloride 0.9% over 4 hours (see Preparation below) A test dose of 1 mL can be given over 10 minutes prior to the infusion
Dose adjustment	Therapeutic hypothermia: No information. ECMO: No information. Renal impairment: No information. Hepatic impairment: No information.
Maximum dose	Prophylaxis: 5 mg/kg/day. Treatment: 6 mg/kg/day in iron deficiency anaemia or on erythropoietin.
Total cumulative dose	
Route	ORAL IV
Preparation	**ORAL** No preparation. **IV** Draw up required amount of elemental iron from the vial and add to a total volume of sodium chloride 0.9% to a final concentration of no more than 2 mg/mL Example dilution: Total dose of IV iron required is 60 mg. Using e.g. Ferrosig ampoules containing 100 mg elemental iron per 2 mL, draw up 1.2 mL (60 mg) of iron. Add 1.2 mL (60 mg) to 48.8 mL sodium chloride 0.9% to result in a final volume of 50 mL with a concentration of 0.024 mL (1.2 mg) per 1 mL.
Administration	**ORAL:** Administer undiluted. **IV:** Infusion over 4 hours. A test dose of 1 mL can be given over 10 minutes prior to the infusion.
Monitoring	Periodic haemoglobin and reticulocyte count. Can take 2 weeks for haemoglobin concentrations to rise. Regular serum ferritin if treating iron deficiency anaemia. If the baby has had multiple transfusions, then iron studies would be useful to check for iron overload. **IV:** Monitor infusion site and for signs of hypersensitivity during and at least for 30 minutes after administration. Continuous cardiorespiratory monitoring, oxygen saturations and temperature.
Contraindications	Anaemia not due to iron deficiency, e.g. chronic haemolytic anaemia Iron overload conditions: haemochromatosis, haemosiderosis Hypersensitivity to iron Uncontrolled hyperparathyroidism Infectious hepatitis – parenteral iron tends to accumulate in inflamed tissues Acute renal infections – parenteral iron tends to accumulate in inflamed tissues
Precautions	
Drug interactions	**<u>ORAL iron</u>** Ascorbic acid favours absorption. Absorption is better if medicinal iron is supplemented with breast milk or between meals; however, given with or soon after food may reduce gastrointestinal side effects.[17] Not suitable for jejunal administration as enteral absorption occurs in duodenum and upper jejunum. Iron absorption from fortified milk is intact despite its high calcium content. **<u>IV iron</u>** Oral iron is not to be administered concomitantly with IV iron preparations as the absorption of oral iron is reduced. Oral iron therapy should not commence until at least one week after the last iron injection. Concomitant administration of angiotensin converting enzyme (ACE) inhibitors may increase the incidence of adverse effects associated with parental iron preparations e.g. erythema, abdominal cramps, vomiting and hypotension.
Adverse reactions	**<u>ORAL iron</u>**

	GI irritation: Abdominal pain, diarrhoea, constipation, dark stools (green or black), gastric mucosal erosion **IV iron** General: Flushing, sweating, chills and fever; chest and back pain Hypersensitivity, anaphylaxis Gastrointestinal: Nausea and vomiting, abdominal pain Central nervous system: Headache; dizziness Musculoskeletal: Joint and muscle pain; arthralgia; sensation of stiffening of the arms, legs or face Cardiovascular: Tachycardia, hypotension, circulatory collapse Respiratory: Bronchospasm with dyspnoea Haematological: Generalised lymphadenopathy Dermatological: Rash, urticarial, angioneurotic oedema Adverse reactions may be delayed by 1–2 days after treatment with Ferrosig iron or Ferrum H (iron polymaltose) injection **Oral and IV** Increased RBC haemolysis and haemolytic anaemia in preterm infants with low vitamin E concentrations Rickets – with large doses of iron over a prolonged period Acute toxicity – more severe GI effects including haematemesis and melaena, lethargy, pallor, cyanosis and shock
Compatibility	Can be administered with Pentavite
Incompatibility	Do not mix IV solutions with other compounds
Stability	IV preparations: Venofer: Once diluted, use product immediately and discard unused portions Ferrosig: Once diluted, use product immediately and discard unused portions. However, if necessary, can store at 2–8°C for not more than 12 hours
Storage	Store below 25°C. Protect from light
Excipients	Ferro-Liquid Oral: Sucrose, sorbitol, sodium bisulfite; strawberry flavour Maltofer: Ethanol, methyl hydroxybenzoate, propyl hydroxybenzoate, water – purified, sodium hydroxide, sorbitol solution (70%) (non-crystallising), and sucrose Ferrosig and Ferrum H injections (iron polymaltose compound): Hydrochloric acid or sodium hydroxide (for pH adjustment) Venofer (iron sucrose): Sodium hydroxide (for pH adjustment)
Special comments	Infants on erythropoietin or infants with uncompensated blood loss may initially need higher doses and could be receiving iron supplementation in addition to preterm formula or fortified human milk.
Evidence	**Efficacy** Enteral iron prophylaxis in preterm and low birthweight infants A Cochrane 2012 review by Mills et al found (1) enteral iron supplementation of both preterm (<33 weeks GA) and low birth weight infants (<2500 g) of either term or preterm confers an improvement in haemoglobin and ferritin concentrations after eight weeks postnatal age and reduces the risk of anaemia, (2) no significant benefit in providing more than 2–3 mg/kg/day of elemental iron, (3) commencement of iron early (<28 days postnatal age) results in improved haematological parameters from as early as eight weeks of age onwards, and (4) less abnormal clinical neurological examination in early iron supplementation (commencement at <28 days of age) group (17% versus 35%; P = 0.02).[6] (LOE I GOR A) McCarthy 2019 systematic review investigated the effects of enteral iron supplementation in preterm (<37 weeks' gestation) and low-birthweight (LBW, <2500 g) infants.[5] Iron supplementation was as either medicinal iron, infant formula or human milk fortifier. Iron at 2–4 mg/kg/d was found to have no effect on ferritin, haematocrit or haemoglobin concentrations in VLBW (<1500 g) infants. Higher dose (average 7–10 mg/kg/d) had no effect on ferritin, iron, transferrin saturation, transferrin receptors or total iron-binding capacity (TIBC). In marginally LBW infants (2000–2499 g), 2 mg/kg/d increased circulating iron, ferritin, transferrin saturation, transferrin receptors, mean corpuscular volume (MCV) and haemoglobin at 6 months and increased ferritin concentrations at 12 months. Long term (≥8 weeks) supplementation was associated with a decreased prevalence of iron deficiency and anaemia in preterm and LBW infants. Neither short-term nor long-term supplementation had effect on growth parameters including weight, head circumference and length. Short-term supplementation had no effect on neurological development. There was a trend towards benefit of early initiation: 35% of the late initiation group had an abnormal neurological examination result compared to 19% of the early initiation group. Long-term supplemented

children had a significantly lower prevalence of behavioural problems than those in the placebo group (3% vs 13%, respectively) at 3.5 years and had significantly lower scores in externalising-type behaviours (aggression/attention seeking) at 7 years. No article reported on iron overload.[5] (LOE I GOR A)

Moreno-Fernandez 2019's descriptive review of reports published between 2008 and 2018 included 16 studies enrolling 1743 neonates of 24–36 weeks gestation and drew similar conclusions as McCarthy et al.[18]

Iron prophylaxis in marginally low birthweight infants: In a trial by Berglund et al, 285 infants with marginally low birth weights 2000–2500 g were randomised to 0, 1 or 2 mg/kg/day of medicinal iron from 6 weeks to 6 months of age. A dose of 2 mg/kg/day significantly reduced the risk of IDA at 6 months relative to placebo.[7] Thirty-six percent and 10% of the infants who received the placebo developed iron deficiency and IDA, respectively, but only 4% and 0% of the infants in the group that received 2 mg/kg/day did. Iron supplements did not adversely affect infant growth, infections or other morbidity. In a follow-up study, they observed a significantly higher proportion of abnormal behavioural scores at 3.5 years of age in the placebo group.[19] (LOE II GOR B)

Iron supplementation at discharge and post-discharge in VLBW infants: Preterm infants with an average birth weight of 1.46 kg were given an iron intake of 6 versus 3 mg/kg/day at discharge and about 3 versus 2 mg/kg/day at 3 to 9 months. There was no difference between the 2 groups in anaemia prevalence or neurodevelopment at 12 months, but the high-iron group had higher glutathione peroxidase concentrations (a marker of oxidative stress), lower plasma zinc and copper concentrations, and more respiratory tract infections, suggesting possible adverse effects from the higher intake.[20] (LOE II GOR B)

Iron fortified formulas at discharge in LBW infants: Preterm infants with birth weights <1800 g do not achieve iron sufficiency on a formula containing ≤3 mg/L.[21] Formulas containing 5–9 mg/L of iron appear to meet the iron requirements of erythropoiesis in healthy preterm infants during the first 6 months of life.[22] However, 18% of the infants receiving the 9 mg/L formula and 30% of those receiving the 5 mg/L formula developed iron deficiency (serum ferritin concentration <10 microg/L) between 4 and 8 months of age in this study.[22] (LOE II GOR B). NOTE: Common commercially available formulas in Australia contain 5–8 mg/L of iron.

Early versus late iron supplementation in VLBW infants: Franz et al randomised 204 infants with an average birth weight of 0.87 kg into an early iron group receiving 2 to 4 mg/kg/day of iron supplements from about 2 weeks and a late iron group that did not receive iron supplements until 2 months of age. There were no differences in serum ferritin and haematocrit at 2 months of age but infants in the late iron group had received more blood transfusions.[23] (LOE II GOR B)

Iron supplementation as per serum ferritin: ESPGHAN 2013 cut-offs for definition of iron deficiency anaemia: 0–1 week: Hb <135 g/L and serum ferritin <40 microg/L; 1 week – 2 months: Hb <90 g/L and serum ferritin <40 microg/L. Serum ferritin <10 microg/L is considered low from 6 months of age.[24] (LOE V)

There are no specific guidelines with respect to iron supplementation in preterm infants with high serum ferritin concentrations. High serum ferritin has been suggested to be associated with high incidence of ROP.[30] Serum ferritin concentrations >350 microg/L are generally accepted as high level.[12,17,31] ESPGHAN 2005 recommendations suggested to limit serum ferritin concentrations to <500 micrograms/L.[14] (LOE V)

Some preterm infants with elevated serum ferritin may simultaneously have iron deficient erythropoiesis, suggesting inability to release ferritin bound hepatic iron to the bone marrow.[32] Park et al[31] compared serum ferritin in 46 very low birthweight infants with respect to (a) no transfusion, (b) transfusion volumes <100 mL/kg during the NICU stay and (c) transfusion volumes ≥100 mL/kg. When the infants reached enteral feeding of 100 mL/kg, iron supplementation (2 mg/kg) was started. No infant developed iron deficiency defined as serum ferritin <10 ng/mL. Mean serum ferritin was comparable at discharge among 3 groups. Maximum serum ferritin during the NICU stay was significantly higher in transfused ≥100 mL/kg (555.6±476.3, 352.1±276.7, 705.7±388.7 respectively). (LOE IV, GOR C)

Parenteral iron prophylaxis during Rh EPO therapy

There is a paucity of studies in relation to intravenous iron in neonates. Carnielli et al,[13] in their RCT of recombinant human erythropoietin (r-HuEPO) therapy for low birth weight infants <1750 g administered IV iron polymaltose at 20 mg/kg weekly (equivalent to 2.8 mg/kg/day) as an IV infusion over 3 hours from 2nd day of life to 8th week of life (or hospital discharge). Meyer et al 1996 compared oral and IV iron supplementation in 42 preterm infants (<33 weeks' gestation, birth weight <1500 gm) being treated with recombinant human erythropoietin. Infants were randomly assigned to receive either oral iron (12 mg/kg/day) or IV iron sucrose (6 mg/kg per week). Both groups were given rHuEpo 600 U/kg per week in 3 divided doses subcutaneously. Iron sucrose was given over an hour in 10 ml of normal saline solution. IV iron was ceased temporarily for a week when serum ferritin increased to 275 micrograms/L. Supplements were given weekly thereafter. Both iron preparations were safe and well tolerated. The IV supplemented group did not have a decline in serum ferritin during EPO therapy. There was also a significant improvement in weight gain after IV administration of iron.[36] Their study showed that IV iron sucrose of 6 mg/kg/week is enough to achieve erythropoiesis during Rh EPO therapy in stable infants. Ohls et al,[12] in their RCT of EPO in infants <750 g administered 1 mg/kg/day IV iron-dextran in the first 14 days of life through PN solutions. The combination of EPO and IV iron resulted in fewer transfusions during their first 3 weeks of life in their study. No adverse effects were reported. Pollak et al, in their RCT trial of recombinant human erythropoietin (r-HuEPO) therapy for low birth weight infants <31 weeks and birthweight <1300 g, administered 2 mg of intravenous iron sucrose/kg/day diluted in sodium chloride 0.9% to a final concentration of 2 mg/mL and infused daily over 2 hours in one of 3 arms. No side effects were reported in this arm.[37] Infants in this study were 3 weeks of age and clinically stable at the time of enrolment. A parenteral dose less than 2 mg/kg/day has been suggested by the authors to reduce the potential adverse effects of parenteral iron.
ANMF consensus: IV iron dose of 1 mg/kg/day is sufficient during Rh EPO therapy. (LOE II GOR B)

James BE et al,[34] reported no adverse effects in 5 preterm infants given iron dextran at a dose of 10–450 microg/kg per day. No complications were observed in a study of 14 very low birth weight infants receiving IV iron dextran supplementation at a dose of 200–250 microg/kg per day.[35]

Enteral iron supplementation after packed red cell transfusion
Post-mortem liver iron study by Ng et al[39] showed elevated liver iron stores with increasing volumes of transfusions. VLBW infants who received <180 mL of packed cells did not exhibit excessive hepatic iron storage, and those who received > 180 mL had hepatic iron concentrations > 40 micromol/g dry weight and/or histochemical liver iron grading ≥2. Authors concluded that routine iron supplementation in the latter group of infants would probably be unnecessary.[39] Park et al investigated the iron status (serum ferritin) of very low birth weight infants receiving multiple erythrocyte transfusions and found that total volume of erythrocyte transfusion was not correlated to maximum serum ferritin concentrations until volume of transfusion was >100 mL/kg.[31]
ANMF Consensus: Preterm infants receiving red cell transfusion volumes greater than 100 mL/kg may not need routine iron supplementation or require periodic (2-weekly) serum ferritin concentrations. (LOE IV GOR C)

Oral iron therapy during recombinant human erythropoietin therapy: The European multicentre erythropoietin group administered oral iron 2 mg/day from day 14 onwards in their trial. If serum ferritin fell below 100 microgram/L, dose of iron was increased.[40]. Emmerson et al,[41] in their RCT of RhEPO vs placebo used 6.25 mg oral iron daily from 4 weeks of age to discharge. Shannon KM et al 1995 commenced at 3 mg/kg/day of oral iron and increased to 6 mg/kg/day during their multicentre RCT of rhEPO. Messer et al started 3 mg/kg/dose of oral iron and increased to 8 mg/kg/day in their rhEPO stdy. Carnielli et al 1998 administered IV iron 20 mg/kg weekly equivalent to 3 mg/kg/day.[42]

Safety
Iron during NICU stay: In systematic reviews by Mills et al and McCarthy et al,[5-6] only a small number of studies reported on clinical morbidities including necrotising enterocolitis, retinopathy of prematurity, chronic lung disease, periventricular leukomalacia, oxidative stress and sepsis. Patel et al,[4] in a retrospective analysis of 598 VLBW infants ≤1500 g found that the cumulative dose of supplemental enteral iron exposure was independently associated with an increased risk of BPD (adjusted relative risk [RR] per 50 mg increase: 1.07, 95% CI 1.02–1.11; p = 0.002). Similarly, a greater total volume of RBC transfusion was independently associated with a higher risk of BPD (adjusted RR per 20 mL increase in

	RBCs transfused, 1.05; 95% CI, 1.02–1.07; p < 0.001). A prospective observational study in VLBW infants by Inder et al showed an independent significant association of retinopathy of prematurity with high serum iron concentrations at 7 days of age and may be an association with 28-day serum ferritin concentrations (OR: 1.86; 95% CI 0.99-4.83).[2] Given the iron content of blood, and previous research which has suggested that preterm infants who receive multiple transfusions are at risk of iron overload,[39] Brown et al 1996 suggests that the measurement of ferritin concentrations in preterm neonates who have received transfusions may be useful to guide the initiation of iron therapy, but again this remains untested.[43] Iron post-NICU: Excess iron has been associated with decreased growth, impaired cognitive development and an increased risk of infection, with evidence also emerging of altered gut microbiota in infants and young children.[44,45] A meta-analysis has shown that iron supplementation leads to increased risk for malaria and other infections in malaria regions.[46] **Bioavailability** The absorption of iron from human milk is >50% and from cow milk-based formulas is approximately 4–12%. Absorption is better from whey predominant formula than casein-based formula. Only 1–7% of iron in soy milk-based formula is absorbed. The absorption and retention of oral medicinal iron depends upon the postnatal age and iron status of the infant. Absorption is better if medicinal iron is supplemented with breast milk or between meals. Approximately 25–30% of the administered iron is absorbed. Approximately 10–25% of the iron supplemented between feeding is incorporated into erythrocytes within 2 weeks. Ascorbic acid favours absorption. Iron absorption from fortified breast milk appears to be intact despite the high calcium content of the fortifier.[17]
Practice points	Prior to prescription of iron, consider factors including (1) whether delayed cord clamping was performed with current haematocrit and or haemoglobin, (2) iron being received from the diet, (3) amount of blood loss through bloodletting or haemorrhage and (4) any packed red cell transfusions received . Common 0–6 month cow's milk infant formulas in Australia containing 5–8 mg/L provide an average 1 mg/kg/day of iron and therefore require supplemental iron in preterm and low birthweight infants. The current iron supplementation and blood transfusions policies in tertiary neonatal intensive care units are less likely to result in iron deficiency during their NICU stay as was evident in a study by Park SH et al 2015. However, iron deficiency is likely post-discharge in preterm infants<37 weeks or low birthweight infants <2.5 Kg if iron intakes are inadequate.[3] National blood authority defines iron deficiency anaemia in infancy as low haemoglobin for the age plus low serum ferritin (<20 microg/L or <50 microg/L in the presence of systemic infection, chronic disease, liver disease).[8] ESPGHAN 2019 recommendations in preterm infants, particularly birthweight <1800 g: (1) Iron intakes of <2 mg/kg/day are likely to result in iron deficiency in preterm infants, at least in those with birth weights <1800 g. (2) Because high enteral iron intakes have been associated with possible adverse effects, an intake of 2 to 3 mg/kg/day is recommended. (3) Prophylactic enteral iron supplementation (given as a separate iron supplement, in preterm formula or in fortified human milk) should be started at 2 to 6 weeks of age (2–4 weeks in extremely-low-birthweight infants). (4) Infants who receive erythropoietin treatment and infants who have had significant, uncompensated blood losses may initially need a higher dose, requiring a separate iron supplement in addition to preterm formula or fortified human milk. (5) Enteral iron doses >5 mg/kg/day should be avoided in preterm infants because of the possible risk of retinopathy of prematurity. (6) Iron supplementation should be delayed in infants who have received multiple blood transfusions and have high serum ferritin concentrations.[9] ESPGHAN 2014 recommendations for birthweights 2000–2500 g – 1–2 mg/kg/day for up to 6 months of age.[24] American Academy of Pediatrics (AAP) recommendations: Supplementation of preterm neonates recommended at 2 mg/kg/ day of enteral iron, either as an iron mixture, or in the form of iron-fortified formula. It is recommended that this supplementation commence within two months of birth and be continued until 12 months of age.[33]

	ESPGHAN 2018 recommendations: Preterm and term infants need parenteral iron 200–250 microgram/kg/day and 50–100 microgram/kg/day respectively during long-term PN >4 weeks duration.[14] ESPGHAN 2014 summary on iron requirements in infants and toddlers:[24] 1. General prevalence of IDA (defined as serum ferritin <10–12 microgram/L) in European infants and toddlers is <2% before 6 months, 2–3% at 6–9 months and 3–9% at 1–3 years of age 2. If low before 6 months of age; 0.9–1.3 mg/kg/day at 6–12 months; 0.5–0.8 mg/kg/day at 1–3 years 3. Breastfed infants <6 months: Iron supplementation do not reduce iron deficiency anaemia in populations with already low (<5–10%) prevalence of IDA at 6 months 4. In low-birthweight infants <6 months, iron supplements (1–3 mg/kg/day depending on birthweight) prevent IDA and possibly improve neurodevelopment 5. Iron supplements at 4–12 months prevent IDA and may improve neurodevelopment but only in populations with high (>10%) prevalence of IDA at 6–12 months of age 1 g of haemoglobin contains 3.5 mg of iron. Based on these numbers, 1 mL of bloodletting with an average 150 g/L of haemoglobin results in net iron loss of 0.5 mg of iron. Packed red cells, on average, contain 180 g/L (48 g in a 260 mL adult red cell pack) of haemoglobin and haematocrit of 0.50–0.70.[1] 1 mL of packed red cells contain 0.6 mg (0.5–1 mg) of iron. The amount of iron lost through blood collection can be calculated using the following formula: Blood Iron (mg) = Hb (g/dL) x 3.5 (mg/mL) x blood loss (mL).[35] The term infant with normal iron stores at birth, who benefitted from delayed cord clamping, is breastfed, and is growing at a rate consistent with the World Health Organization standard growth curves, requires no additional iron beyond what is found in human milk until 4–6 months of age.[47] Serum ferritin concentrations: Umbilical cord serum ferritin concentrations increased with advancing gestational age, from a mean of 63 microg/L at 23 weeks to 171 microg/L at 41 weeks gestation (p <0.001).[25] Higher ferritin concentrations were reported in preterm infants who received intrauterine transfusion, recipients of twin-twin transfusions or received transfusions of more than 100 mL of packed red cells.[26-28] Lundström, et al studied ferritin concentrations in LBW infants receiving iron supplementation who did not receive transfusion. By age 2 months ferritin concentrations averaged 60–70 microg/L and remained between 20 and 40 microg/L up to 6 months of age.[29] Parenteral iron therapy for iron deficiency: Surico et al[38] compared intramuscular and intravenous administration in 33 children with severe iron deficiency who failed to respond to oral iron. Mean age was 3.1 years (range 0.7–13.5). Intravenous iron (iron saccharate) was given daily as a 2-hour infusion in a normal saline solution, at an average dose of 28 mg/kg (range 10–50) depending on haemoglobin values, administered over an average time of 6.5 days (range 3–10). The infusion was preceded by a 10-min infusion test dose. Intramuscular iron (iron polymaltose complex) was given twice per week at an average dose of 20 mg/kg (range 8.5–40), depending on haemoglobin values at diagnosis, over an average period of 26 days (range 14–56). Parenteral iron doses have been calculated taking into account haemoglobin values and weight of children at diagnosis, according to the following formula: Total iron dose (mg) = (desired Hb – observed Hb) x 80 mL x BW x 0.034[38] A non-neonatal age group study by Martini et al used IV iron saccharate to treat iron deficiency anaemia in children with juvenile chronic arthritis using the formula: Total iron dose (mg) = (12.5 – haemoglobin(g/dL) x body weight x 3.4 x 1.4 In this formula, 12.5 is the ideal haemoglobin, 3.4 is the milligrams of iron in 1 g haemoglobin and 1.4 a multiplication factor accounting for iron stores.[15]
References	1. Australian Red Cross. Red cells. https://transfusion.com.au/blood_products/components/red_cells. Accessed on 11 July 2020. 2. Inder TE, Clemett RS, Austin NC, Graham P, Darlow BA, Health P, Practice G. High iron status in very low birth weight infants is associated with an increased risk of retinopathy of prematurity. The Journal of pediatrics. 1997 Oct 1;131(4):541-4.

3. Domellof M. Iron requirements, absorption and metabolism in infancy and childhood. Curr Opin Clin Nutr Metab Care 2007;10:329–35.
4. Patel RM, Knezevic A, Yang J, Shenvi N, Hinkes M, Roback JD, Easley KA, Josephson CD. Enteral iron supplementation, red blood cell transfusion, and risk of bronchopulmonary dysplasia in very-low-birth-weight infants. Transfusion. 2019 May;59(5):1675-82.
5. McCarthy EK, Dempsey EM, Kiely ME. Iron supplementation in preterm and low-birth-weight infants: a systematic review of intervention studies. Nutrition Reviews. 2019 Dec 1;77(12):865-77.
6. Mills RJ, Davies MW. Enteral iron supplementation in preterm and low birth weight infants. Cochrane Database of Systematic Reviews. 2012(3).
7. Berglund S, Westrup B, Domellöf M. Iron supplements reduce the risk of iron deficiency anemia in marginally low birth weight infants. Pediatrics 2010;126:e874-83.
8. National blood authority, Australia. Paediatric and neonatal iron deficiency anaemia guide. December 2017. https://www.blood.gov.au/system/files/Paediatric-and-Neonatal-Iron-Deficiency-Anaemia-Guide-Final-Dec17.pdf
9. Agostoni C, Buonocore G, Carnielli VP et al for the ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: Commentary from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. Journal of Pediatric Gastroenterology and Nutrition 2010;50:1-9
10. Messer J, Haddad J, Donato L, Astruc D, Matis J. Early treatment of premature infants with recombinant human erythropoietin. Pediatrics. 1993 Oct 1;92(4):519-23.
11. Shannon KM, Keith JF, Mentzer WC, Ehrenkranz RA, Brown MS, Widness JA, Gleason CA, Bifano EM, Millard DD, Davis CB, Stevenson DK. Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants. Pediatrics. 1995 Jan 1;95(1):1-8.
12. Ohls RK, Harcum J, Schibler KR, Christensen RD. The effect of erythropoietin on the transfusion requirements of preterm infants weighing 750 grams or less: a randomized, double-blind, placebo-controlled study. J ped. 1997 Nov 1;131(5):661-5.
13. Carnielli VP, Da Riol R, Montini G. Iron supplementation enhances response to high doses of recombinant human erythropoietin in preterm infants. Arch Dis Child Fetal Neonatal Ed 1998;79:F44-8.
14. Domellöf M, Szitanyi P, Simchowitz V, Franz A, Mimouni F, Braegger C, Bronsky J, Cai W, Campoy C, Carnielli V, Darmaun D. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. Clinical Nutrition. 2018 Dec 1;37(6):2354-9..
15. Martini A, Ravelli A, Di Fuccia G, Rosti V, Cazzola M, Barosi G. Intravenous iron therapy for severe anaemia in systemic-onset juvenile chronic arthritis. The Lancet. 1994 Oct 15;344(8929):1052-4.
16. Ferrosig injection. Iron polymaltose complex. Product info. Accessed on 20 July 2020.
17. Rao R, Georgieff MK. Iron therapy for preterm infants. Clinics in perinatology. 2009 Mar 1;36(1):27-42.
18. Moreno-Fernandez J, Ochoa JJ, Latunde-Dada GO, Diaz-Castro J. Iron deficiency and iron homeostasis in low birth weight preterm infants: A systematic review. Nutrients. 2019 May;11(5):1090.
19. Berglund SK, Westrup B, Hagglof B, Hernell O, Domellöf M. Effects of iron supplementation of LBW infants on cognition and behavior at 3 years. Pediatrics 2013;131:47-55.
20. Friel JK, et al. A randomised trial of two levels of iron supplementation and developmental outcome in low birth weight infants. J Pediatr 2001;139:254–60.
21. Hall RT, Wheeler RE, Benson J, Harris G, Rippetoe L. Feeding iron-fortified premature formula during initial hospitalization to infants less than 1800 grams birth weight. Pediatrics 1993;92(3):409–414.
22. Griffin IJ, Cooke RJ, Reid MM, McCormick KP, Smith JS. Iron nutritional status in preterm infants fed formulas fortified with iron. Arch Dis Child Fetal Neonatal Ed 1999;81(1):F45–49.
23. Franz AR, MihatschWA, Sander S, et al. Prospective randomised trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams. Pediatrics 2000;106:700–6.
24. Domellöf M, Braegger C, Campoy C, Colomb V, Decsi T, Fewtrell M, Hojsak I, Mihatsch W, Molgaard C, Shamir R, Turck D. Iron requirements of infants and toddlers. Journal of pediatric gastroenterology and nutrition. 2014 Jan 1;58(1):119-29.
25. Siddappa AM, Rao R, Long JD, Widness JA, Georgieff MK. The assessment of newborn iron stores at birth: a review of the literature and standards for ferritin concentrations. Neonatology. 2007;92(2):73-82.
26. Berger HM, Lindeman JH, van Zoeren-Grobben D, Hudkamp E, Kanhai HH, Schrijver J. Iron overload, free radical damage, and rhesus haemolytic disease. The Lancet. 1990 Apr 21;335(8695):933-6.

27. Caglar MK, Kollee LA. Determination of serum ferritin in the evaluation of iron depletion and iron over load in chronic twin-to-twin transfusion syndrome. Journal of perinatal medicine. 1989;17(5):357.
28. Arad I, Konijn AM, Linder N, Goldstein M, Kaufmann NA. Serum ferritin levels in preterm infants after multiple blood transfusions. American journal of perinatology. 1988 Jan;5(01):40-3.
29. Lundström U, Siimes MA, Dallman PR. At what age does iron supplementation become necessary in low-birth-weight infants? The Journal of pediatrics. 1977 Dec 1;91(6):878-83.
30. Romagnoli C, Zecca E, Gallini F, Girlando P, Zuppa AA. Do recombinant human erythropoietin and iron supplementation increase the risk of retinopathy of prematurity? European journal of pediatrics. 2000 Jul 1;159(8):627.
31. Park SH, Kim HM. The iron status of very low birth weight infants receiving multiple erythrocyte transfusions during hospitalization in the neonatal intensive care unit. Pediatric gastroenterology, hepatology & nutrition. 2015 Jun 1;18(2):100-7.
32. Winzerling JJ, Kling PJ. Iron-deficient erythropoiesis in premature infants measured by blood zinc protoporphyrin/heme. The Journal of pediatrics. 2001 Jul 1;139(1):134-6.
33. Baker RD, Greer FR. Clinical Report—Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). Pediatrics. 2010 Sep 29:peds-2010.
34. James BE, Hendry PG, MacMahon RA. Total parenteral nutrition of premature infants. 2. Requirement for micronutrient elements. Aust Paediatr J 1979;15:67–71.
35. Friel JK, Andrews WL, Hall MS, et al. Intravenous iron administration to very-low-birth-weight newborns receiving total and partial parenteral nutrition. JPEN J Parenter Enteral Nutr 1995;19:114–8.
36. Meyer MP, Haworth C, Meyer JH, Commerford A. A comparison of oral and intravenous iron supplementation in preterm infants receiving recombinant erythropoietin. The Journal of pediatrics. 1996 Aug 1;129(2):258-63.
37. Pollak A, Hayde M, Hayn M, et al. Effect of intravenous iron supplementation on erythropoiesis in erythropoietin-treated premature infants. Pediatrics 2001;107:78–85.
38. Surico G, Muggeo P, Muggeo V, Lucarelli A, Martucci T, Daniele R, Rigillo N. Parenteral iron supplementation for the treatment of iron deficiency anemia in children. Annals of hematology. 2002 Mar 1;81(3):154-7.
39. Ng PC, Lam CW, Lee CH, To KF, Fok TF, Chan IH, Wong E. Hepatic iron storage in very low birthweight infants after multiple blood transfusions. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2001 Mar 1;84(2):F101-5.
40. Maier RF, Obladen M, Scigalla P, Linderkamp O, Duc G, Hieronimi G, Halliday HL, Versmold HT, Moriette G, Jorch G, Verellen G. The effect of epoetin beta (recombinant human erythropoietin) on the need for transfusion in very-low-birth-weight infants. New England Journal of Medicine. 1994 Apr 28;330(17):1173-8.
41. Emmerson AJ, Coles HJ, Stern CM, Pearson TC. Double blind trial of recombinant human erythropoietin in preterm infants. Archives of disease in childhood. 1993 Mar 1;68(3 Spec No):291-6.
42. Shannon KM, Keith JF, Mentzer WC, Ehrenkranz RA, Brown MS, Widness JA, Gleason CA, Bifano EM, Millard DD, Davis CB, Stevenson DK. Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants. Pediatrics. 1995 Jan 1;95(1):1-8.
43. Brown MS. Effect of transfusion and phlebotomy on serum ferritin levels in low birth weight infants. Journal of Perinatology 1996;16:39-42.
44. Lonnerdal B. Excess iron intake as a factor in growth, infections, and development of infants and young children. Am J Clin Nutr. 2017;106(suppl 6): 1681s–1687s.
45. Paganini D, Zimmermann MB. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review. Am J Clin Nutr. 2017;106(suppl 6): 1688s–1693s.
46. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. J Nutr 2001; 131:616S–633S.
47. Yang Z, Lönnerdal BO, Adu-Afarwuah S, Brown KH, Chaparro CM, Cohen RJ, Domellöf M, Hernell O, Lartey A, Dewey KG. Prevalence and predictors of iron deficiency in fully breastfed infants at 6 mo of age: comparison of data from 6 studies. The American journal of clinical nutrition. 2009 May 1;89(5):1433-40.

VERSION/NUMBER	DATE

Original	22/10/2015
Revised version 2.0	10/08/2017
Version 3.0	17/09/2020
Current version 3.1	12/10/2020
REVIEW (5 years)	12/10/2025

Authors Contribution

Original author/s	John Sinn
Current version author/s	Srinivas Bolisetty, John Sinn
Evidence Review	Timothy Schindler
Expert review	Thomas Young, Karel Allegaert
Nursing Review	Eszter Jozsa, Samantha Hassall, Kirsty Minter
Pharmacy Review	Carmen Burman
ANMF Group contributors	David Osborn, Nilkant Phad, Bhavesh Mehta, Wendy Huynh, Michelle Jenkins, Thao Tran, Cindy Chen
Final editing and review of the original	Tim Schindler, Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty