Anaemia in Children

Authors: Karen Edmund; Barbara Paterson; Andrew White. (First written 2001, revised by Andrew White 2002)

Topic Reviewers: Brad Palmer (RN-CDC Darwin); Monica Ostigh (RAN, Jabiru Clinic); Bernard Egan (RAN, Bulman Clinic); Helen Collinson (RAN, Adelaide River); Monica Harris (RAN, locum); Kaz Knudsen (RAN, WA); Kylie Harris (RAN, Docker River); Pam Moll (RAN, Haasts Bluff); Dyan Kelaart (RAN, Yuendumu Clinic); Vicki Gordon (RAN, Mutitjulu Clinic); Dr Ian Dumbrell (Port Keats)

Introduction

Additional evidence about screening, diagnosis and treatment for childhood anaemia has emerged since the third edition of the CARPA STM was completed.

This background paper attempts to document past and emerging evidence for screening, diagnosis and treatment of anaemia in children aged 0–14 years living in rural and remote communities of the NT, and makes recommendations for NT remote area protocol development, further investigation and research. This is not a complete literature review.

The areas covered by this discussion paper are as follows:

1. Prevalence of anaemia and iron deficiency in the NT
2. Physiology of iron deficiency and iron deficiency anaemia
3. Types of anaemia in NT remote area Aboriginal children
4. Causes of iron deficiency and iron deficiency anaemia
5. Consequences of iron deficiency and iron deficiency anaemia
6. Diagnosis of iron deficiency and iron deficiency anaemia
7. The use of the HemoCue haemoglobinometer as a screening and a diagnostic test
8. Treatment of iron deficiency anaemia .

Anaemia is a major public health problem. The high prevalence of iron deficiency anaemia (IDA) in remote area Aboriginal children mandates a population-based approach. Consideration must be given to population-based interventions for the prevention (by high dietary iron intake and minimisation of infections) and management of IDA.

Prevalence of anaemia and iron deficiency in the NT

There are a number of reports of the prevalence of anaemia in Aboriginal children in Northern Australia.[2-8] Only five NT papers describe the use of venous blood and laboratory analysis to determine anaemia (Hb<110 g/L) prevalence.[2-5] Two of these studies (in children aged six months–six years in remote area Top End communities) reported the prevalence of anaemia to be 42–52%.[2,5] The other three studies were in hospitalised Top End children aged six months to three years. These studies reported prevalence rates of 21–40%.[3,4] Other published studies of children aged 0–5 years living in remote area Aboriginal communities in the Kimberley region of Western Australia report anaemia prevalence between 20–60%.[6,7] The NT growth assessment and action nutritional survey in October 2000 (unpublished data Epidemiology Branch, THS) used the HemoCue haemoglobinometer to screen 2590 children

aged 0–4 years. The prevalence of anaemia (Hb <110 g/l) ranged from 20–65% across different communities. The prevalence in all children aged 0–4 years was 43% in the Top End and 52% in Central Australia. School-aged screening haemoglobinometer data were available for the Top End only. A total of 1802 Top End children aged 5–14 years were screened in 1999, with an estimated anaemia prevalence of 19%. Haemoglobinometer data from the Katherine district of the NT in 1993 estimated anaemia prevalence of 39%.[8]

There has been one Top End hospital-based study that determined the prevalence of IDA. This study analysed blood samples in 161 children aged five months–10 years admitted to Royal Darwin Hospital (RDH) in 1993. IDA was diagnosed on the basis of FBE, blood film and iron studies. This study described 48% (77/161) of children as anaemic (Hb <110 g/L) and 40% (64/161) had IDA. Of the anaemic children, 83% (64/77) had IDA (Ingrid Bucens, unpublished data). There are no other published studies of IDA prevalence in the Top End of the NT and no known Central Australian studies.

Physiology of iron deficiency and iron deficiency anaemia

Humans are inefficient in absorbing iron from plant sources. Much of the world's population has a diet from which sufficient iron cannot be obtained to meet physiological requirements, especially in infancy, early childhood and pregnancy when demands are the highest. Iron requirements are mean daily intakes (RDIs) of: infants (0–6 months) 0.5 mg/day if breastfed, 3 mg/day if formula fed; 7–12 month olds 9 mg/day; young children 6–8 mg/day; lactating women 12–16 mg/day.[9,10]

Iron requirements are higher for infants who were premature or growth restricted at birth, as stores are lower and growth is more rapid. Normal term infants have stores to maintain iron for about four months. Iron in non-haem form usually makes up most of the iron for infants. Absorption is variable and varies with iron stores and other components in the diet. Non-haem iron absorption is increased by ascorbic acid, meat, fish and poultry, and decreased by bran, polyphenols, oxylates, phytates, vegetable fibre, tannins and phosphates.[9–13] Ascorbic acid, such as in orange juice, more than doubles the absorption of non-haem iron.[9,11,12] Tea is reported to decrease the absorption of non-haem iron by up to 75%.[9,12] (This means that changing a child from having tea to juice with the meal could increase absorption eight times). Haem iron is much better absorbed and less influenced by other components of the diet. Haem iron itself increases non-haem iron absorption. Iron in breast milk is about 0.5–1 mg/L and absorption is high (about 50%). Iron in cow's milk is also 0.5–1 mg/L but absorption is only about 10%.[11,12]

Infection blocks iron usage, affects iron utilisation and can decrease haemoglobin levels by 5–10 g/L.[2,9] However, it usually causes a normochromic normocytic anaemia and does not cause iron deficiency as such.[2, 9] In the Kruske Top End anaemia study[2], children given intramuscular iron had a rise in haemoglobin to 110 g/L by six weeks, but many children dropped their haemoglobin levels to below 105 g/L at 12 weeks due to infection in spite of adequate iron. These infections were frequently trivial viral infections, as well as more severe bacterial or chronic infections. Of note, the mean cell volume (MCV) of a red blood cell can take up to three months (the life span of red cells) to regain a normal volume. Thus, a dual population of microcytic-hypochromic and normal red cells circulate in children treated with adequate iron who have recurrent infections.[9] This was

also described in the Kruske study.[2] (See section on diagnosis of IDA for further information about MCV and other blood film appearances).

Recommendations

- Dietary iron deficiency and recurrent viral or bacterial infections are the most significant risk factors for IDA in NT Aboriginal children.
- Key nutritional advice for families with children should be:
  - Encourage the intake of meat, fish, chicken and green leafy vegetables
  - Reduce tea intake during meals
  - Increase orange juice during meals
  - Acute, recurrent and chronic infections may be the reason for a slow Hb response to supplemental iron
  - Acute, recurrent and chronic infections must be looked for in children with anaemia
  - Acute, recurrent and chronic infections must be treated early and appropriately.

Types of anaemia in NT remote area Aboriginal children

IDA is the predominant type of anaemia in remote Aboriginal children. Recent Top End studies (one community-based, one hospital-based) report 83–88% of anaemia being due to IDA.[2] (Bucens, unpublished data.)

Children are also at risk of folate deficiency anaemia, which is usually dietary in origin. This may coexist with IDA but may also occur without iron deficiency. Recent NT studies indicate that folate deficiency is rare in remote area Aboriginal children. A recent RDH study estimated that 0.6% (1/161) of remote area Aboriginal children were folate deficient. A Top End community-based study estimated the prevalence of folate deficiency to be 9.8% (5/51).[2] In Central Australia, 5% of children admitted to hospital over a 20 month period because of gastroenteritis were folate deficient (personal communication, Jim Thurley). B_{12} deficiency also appears to be rare.[2] (Bucens, unpublished data.) Other types of anaemia are also rare in remote area Aboriginal children.[2–4] The contribution of Vitamin A and other micronutrients to anaemia in NT remote area children is currently unknown.

Causes of iron deficiency and iron deficiency anaemia

Iron deficiency can be due to: low iron stores at birth; inadequate iron in the diet; chronic infection; or losses due to diarrhoea, parasites or cow's milk feeding.[13,14] In Australian Aboriginal children iron deficiency is felt to be due to late introduction and insufficient intake of iron-rich solids in breastfed children, low birth weight and parasite and worm infestation.[2,6,15] There is no published data that examines dietary intake patterns and the relative contributions of diet to anaemia in NT remote area Aboriginal children. There is also little evidence about the role of worms and parasites in the aetiology of anaemia in Top End Aboriginal children and there are no published intervention trials. The only data known to the authors are shown in table 1. The only other available information is the clinical impression that there has been minimal change in Top End anaemia prevalence in children aged 0–4 years despite widespread community deworming programs over the last 10 years.

In Study 1 the stool specimens were analysed within two hours, thus the results are likely to be accurate.[16] However, the sample size for this study is unknown. Study 2 may have underestimated the worm load due to the stool

collection method.[17] The prevalence of helminths in Study 3 (D. Brewster unpublished data) is also likely to be an underestimate, as most NT children with diarrhoeal disease and worms are likely to have been fully dewormed prior to admission to hospital as per standard NT protocols for diarrhoeal disease and poor growth in children.

Hookworm is a well known cause of IDA worldwide.[9] Thirty years ago it was not uncommon for NT Aboriginal infants to present shocked with haemoglobin levels of 35 g/L due to acute gastrointestinal blood loss due to acute heavy hookworm infestation.[18] Fortunately, this is now extremely rare (personal communication, A. Walker). In 1995, hookworm infection was reported by Provic[19] to be 'endemic' in the Top End of the NT with Ancylostoma duodenale likely to be the sole species. There have been widespread Top End community deworming programs using Pyrantel and albendazole since that study, thus hookworm prevalence is likely to have decreased since that time. Prevalence of hookworm in the three recent local studies are shown in table 1. A recent study in an Aboriginal community in tropical Western Australia found that the highest mean number of parasite species and the highest prevalence of A. duodenale (93%) was in children aged 5–14 years.[6] Sustained control programs appear to have eradicated hookworms from Queensland.[19]

Only heavy infestations of Trichuris trichuria have been reported to cause iron deficiency.[20,21] In contrast, mild Trichuris infestations are well known to cause significant growth faltering.[22] In Jamaican children, iron deficiency anaemia was associated with heavy Trichuris infections that had over 10 000 eggs per grams of faeces, but not with less intense infections.[20] In Panama egg loads greater than 5000 eggs per grams of faeces were associated with anaemia in children, but not lower worm burdens.[21] Joint infestations with mild to moderate load of Trichuris and hookworm were also more likely to cause anaemia than hookworm alone.[21]

Strongyloidiasis causes malabsorption, diarrhoea and growth faltering.[23,24] More severe Strongyloides malabsorption can cause nutritional anaemia. However, these children should have significant diarrhoea and will not be asymptomatic.[23,24]

Giardiasis causes malabsorption, diarrhoea and growth faltering.[25,26] Malabsorption with more severe and prolonged giardiasis can cause nutritional anaemia.[25,26] There is no published data on NT Giardia prevalence or its association with IDA in the NT.

Maternal IDA has also been shown to affect newborn babies. Infants of IDA mothers have lower iron stores at birth and higher rates of anaemia in the first months of life.[27,28]

Table 1: Prevalence of helminth infestations in Top End adults and children, 1993–98

	Study 1 East Arnhem island Aboriginal community16	Study 2 Pilot screening program in a Top End Aboriginal community17	Study 3 Aboriginal children admitted to Royal Darwin Hospital
Year of study	1997	1997	1993–98
Number of stool specimens analysed	Unknown	28	5324
Age range	'Whole community, including children'	Adults, age not stated	Children aged 0–14 years
Hookworm	25%	3.6%	0.8%
Trichuris	88%	25%	3.4%
Strongyloides	15%	3.6%	3.5%

Recommendations

- Dietary iron deficiency and recurrent viral or bacterial infections are likely to be the most significant risk factors for IDA in NT Aboriginal children.
- Data is not sufficient to decide on the prevalence of hookworm or Trichuris in the NT or the contribution of hookworm or Trichuris to anaemia in the NT.
- A prevalence study which examines the relative contribution of parasites, worms and diet to IDA in remote area Aboriginal children should be conducted in the Top End and Central Australia

Consequences of iron deficiency and iron deficiency anaemia

There is a postulated link between IDA and delayed psychomotor development. Correlational studies have mostly found associations between IDA and poor cognitive and motor development, and behavioural problems. Two examples of this type of reports are: 1) mild iron deficiency has been shown to be associated with low infant developmental scores[29]; and 2) studies of iron deficient adolescents show comparably lower test scores for academic performance, (including vocabulary, reading knowledge, use of reference material, arithmetic concepts and problem solving) and students are more disruptive, irritable and restless in the classroom.[30]

Longitudinal studies show that children with anaemia in infancy continue to have poorer cognition, school achievement and more behaviour problems in later childhood.[31–33] However, these uncontrolled observational studies do not allow causal inference from being made, as there is evidence that anaemia is associated with socioeconomic disadvantages which are independent factors in poor cognitive development.

A review of therapeutic trials on the effect of iron deficiency on cognitive development of children was published in 2001.[34] In children older than two years most studies showed clear benefit from iron treatment (four studies), and benefit was highly likely in the three studies compared, with two studies where no benefit was shown. Very few RCT trials in children under two years were identified and there is no good evidence from RCT that short-term iron treatment benefits development in iron-deficient infants. In several studies identified, anaemic children failed to catch up to non-

anaemic children with iron treatment. However, longer follow-up and larger studies are required before firm conclusions can be drawn.

Iron deficiency also leads to reduced cell mediated immunity and neutrophil activity, but whether this leads to increased risk of infectious disease is not clear.[35,36]

Diagnosis of iron deficiency and iron deficiency anaemia

Iron deficiency

The best way to diagnose iron deficiency is with the full blood examination (FBE) and blood film.[13] With early iron deficiency the only feature will be increased red cell distribution width (RDW), an index of variation in red cell size (anisocytosis).[9,14] With early depletion of iron in the bone marrow the RDW increases (>14.5% is abnormal).[9,12] Increased RDW is more sensitive than serum iron, transferrin, total iron binding capacity, ferritin, haemoglobin or red cell size in the diagnosis of iron deficiency.[9,13,14] When red cells become iron deficient the mean cell volume (MCV) reduces (microcytosis).[12] Transferrin receptor levels are an accurate method of determining iron levels.[37] However, this test is not currently available in the NT. An increase in haemoglobin after a therapeutic trial of administration of iron is another indicator of iron deficiency. An increase of 10 g/L is convincing evidence.[9,14]

Iron deficiency anaemia

The World Health Organisation (WHO) states that anaemia should be diagnosed at a haemoglobin level of less than 110 g/L.[12] This is the most common convention adopted worldwide.[8,9] The third edition of the CARPA STM stated that anaemia should be diagnosed when the haemoglobin is less than 100 g/L.[1]

Clinical examination is a poor indicator of IDA. Unless the IDA is severe there will be no clinical features.[9] The best way to diagnose IDA is also with the FBE and blood film.[13] With IDA, as well as anaemia, there will be microcytosis (low MCV) and increased RDW. There are also other morphological abnormalities seen on the blood film, such as pencil cells.[9,14] With increased levels of iron deficiency there may also be reduced serum iron, reduced serum ferritin and increased iron binding capacity, and red cell protoporphyrin.[9,14] However, these iron studies are not useful in children who are subject to chronic infection. False positives and false negatives are commonly found due to the increased inflammatory load.[13] Transferrin receptor levels are likely to be more accurate,[37] but are not available in the NT.

Recommendation

- Anaemia should be defined as Hb <110 g/L
- Only the full blood examination and blood film are needed to diagnose iron deficiency and IDA
- Iron studies are misleading in the diagnosis of IDA and are best omitted.

The use of the HemoCue haemoglobinometer as a screening and a diagnostic test

The HemoCue haemoglobinometer as a screening test

A finger prick blood sample tested on various types of haemoglobinometer has been routine practice in screening for anaemia in the NT for the past 30 years. Currently the HemoCue haemoglobinometer is used. IDA, as tested

on the HemoCue hemoglobinometer, is considered against the WHO criteria for a screening test below.[38]

IDA is an important health problem for Aboriginal children in the NT due to its high prevalence and important sequelae. The natural history of IDA is also well understood.[9,10,14] Iron deficiency is the early precursor stage where there is depletion of the body's iron stores prior to the development of anaemia.[9,10,14] Ideally, iron deficiency should be identified and treated before it develops into anaemia. In reality current practice aims to treat anaemia at an early stage, i.e. mild anaemia, rather than treating later on when the anaemia is severe enough to cause symptoms.

The HemoCue haemoglobinometer, which is currently in use in NT health centres, has been demonstrated to be a reliable and valid method of screening for anaemia. The HemoCue haemoglobinometer is also simple, quick and easy and is a more acceptable test than a venous blood sample. There should be a suitable test, i.e. a test with high sensitivity, specificity and positive and negative predictive values. Mills and Meadows[39] found that the HemoCue haemoglobinometer used to detect anaemia had a sensitivity of 85% and specificity of 94% after compensation for a fixed positive bias. Calibration with a single standard specimen (as per operating manual recommendations) or with four standard specimens did not uncover this bias. To allow for operating errors of the Coulter Counter and the HemoCue haemoglobinometer they recommended using at least 30 measurements from a range of standard specimens. Their adjustment for machine bias was made by determining the mean difference between HemoCue results and Coulter Counter results in the laboratory taken from a finger prick blood sample. Other evaluations of the HemoCue haemoglobinometer found it easy to use with readings comparable to those of the laboratory Coulter Counter for venous and capillary blood specimens (correlation coefficients between 0.89 and 0.99).[40,41]

Recent local data has been obtained from an anaemia iron treatment study in children aged six to 59 months in a remote area Aboriginal community in 1999.[2] Paired (capillary and venous) (n=141) blood samples were taken from each child and analysed for anaemia (Hb<110g/L). Capillary samples were measured by the community HemoCue and venous samples were measured by a laboratory based Coulter Counter model-M. Analysis of these paired data has demonstrated that the HemoCue had a sensitivity of 91% and a specificity of 88% compared to the venous Coulter measurements when used to detect anaemia (Sue Kruske, unpublished data). Confidence intervals have not yet been constructed for these data. Of note, only 24 out of 141 children in this sample did not have anaemia, thus the confidence intervals for the specificity test are likely to be wide. Further validation of the HemoCue haemoglobinometer in remote communities in the NT is recommended with a larger non-anaemic group.

The positive and negative predictive values (PPV and NPV) of any test vary with the prevalence of the condition.[42] Using our local data, we have calculated that the positive predictive value of the HemoCue in detecting anaemia (Hb<110g/L) in NT remote Aboriginal children aged under five (with 50% anaemia prevalence) will be 88% and the negative predictive value will be 91%. These values indicate that anaemia will be over-diagnosed by 12% and under-diagnosed by 9% if the HemoCue is used in communities with anaemia prevalence of 50%. These are quite reasonable values for a screening test but are only achievable when the HemoCue is used strictly according to the manufacturer's instructions. The PPV and NPV drop quite significantly when the anaemia prevalence reaches less than 20%. Further

validation of the HemoCue is recommended with a larger non-anaemic sample size.

In the Northern Territory there are adequate facilities to diagnose and treat anaemia. All rural and remote health centres have a HemoCue haemoglobinometer and each test costs approximately $1 for the use of the cuvette (personal communication, DHCS). The haemoglobinometer, HemoCue cuvettes, iron and albendazole are part of the normal NT health centre imprest system and budget. Medicare currently funds formal FBE testing (Medicare rebate for an FBE as of 3/97 is $14.65). Public and private laboratory services are available to investigate anaemia if considered necessary. If all Aboriginal children of school age were to have annual screening for anaemia then approximately 12 000 children would be screened every year.[43] The cost of false positive screening tests for 10%, 20%, 30% and 40% prevalence of anaemia would be $28,700, $12,892, $8,790, and $5,625 respectively.

The HemoCue haemoglobinometer as a diagnostic test

The CARPA STM third edition recommended that venous blood be taken for FBE if the Hb is below 80g/L and treatment depends on the FBE result.[1] The alternative would be to use the HemoCue as a diagnostic test, treat on the HemoCue result and not perform an FBE. There is evidence to support using the HemoCue for diagnosis of IDA. If we use the local data as described above, the haemoglobinometer has a very high predictive value where the prevalence of anaemia is high (as in remote area Aboriginal children in the NT). Approximately 80–90% of the children with true anaemia will have IDA[2] (Ingrid Bucens, unpublished data) thus making the PPV and NPV for IDA high also. Near-patient testing and diagnosis also has the advantage of allowing immediate results and explanations to be given to the patient, and treatment can be started without having to wait for laboratories to confirm the diagnosis. In rural and remote health centres the time from taking the blood specimen to the result reaching the health centre can be 2–3 days. Loss to follow-up is also common.

The haemoglobinometer should not be used to diagnose anaemia in children at risk of ‘complicated anaemia’ (i.e. children aged under six months, children with a Hb<90g/dl, children with cardiac failure, tachycardia or tachypnoea, children with signs or symptoms that indicate non dietary anaemia e.g. hepatosplemomegaly, and children who have IDA that does not resolve with treatment). These children should always have an FBE and film to diagnose anaemia. Iron therapy should always be started immediately and medical review should also be arranged.

Recommendations

- The HemoCue haemoglobinometer is an acceptable screening tool for detection of anaemia in remote area Aboriginal children living in populations where the anaemia prevalence is >20%.
- Further validation of the HemoCue is recommended with a larger non-anaemic sample size
- The HemoCue haemoglobinometer is an acceptable diagnostic tool for anaemia in remote area Aboriginal children living in populations where the anaemia prevalence is >20% who are aged >6 months
- Iron treatment can be instituted on the basis of the result of the HemoCue haemoglobinometer in children aged >6 months
- A laboratory venous FBE and film should be performed:

- If the Hb on the HemoCue haemoglobinometer is <90 g/l in children aged >6 months
- If the Hb on the HemoCue haemoglobinometer is <110 g/L in children aged under six months
- The Hb appears to be refractory to iron therapy and not increasing when rechecked in one month
- In children who have any other abnormal features
- In children living in populations where the anaemia prevalence is <20%.

    - The manufacture's instructions for the HemoCue haemoglobinmeter should be followed carefully
    - A follow-up Hb measurement should be performed one month after treatment is commenced
    - If the Hb has not increased in one month a formal FBE and film should be performed
    - Any questions or concerns about the diagnosis or treatment for anaemia should be directed to the responsible medical officer

Treatment of iron deficiency anaemia

Principles of managing the individual child with IDA include: treatment of disease contributing to the iron deficiency; administration of supplemental iron; replenishment of stores; and provision of maintenance amounts of iron. There is no place for dietary therapy alone in the treatment of iron deficiency. Dietary intake is important in the prevention of IDA and to maintain haemoglobin levels after treatment.

Given the high prevalence of IDA in NT remote area children consideration must be given to community wide interventions for the prevention and management of IDA.

Hookworm and Trichuris treatment to treat anaemia in NT remote area children

Current practice in the Top End of the NT is to treat anaemia with three days of albendazole. This guideline was developed assuming that the major helminths implicated in anaemia in the NT were hookworm and Trichuris. However, this evidence is in doubt (see above). Single dose albendazole is effective in treating hookworm and reducing anaemia.[44–46] Trichuris treatment requires three days of albendazole for significant reduction in worm load.[47–50]

Current practice in the Top End of the NT is to treat growth faltering with three days of albendazole. This guideline was developed assuming that the major helminths and parasites that caused growth faltering are Strongyloides, Giardia, hookworm and Trichuris. This evidence is much more robust.[22–24,26,51]

Many remote area NT children have both growth faltering and anaemia. Management of these children becomes complicated if there is one antihelminth regimen for growth faltering and a different antihelminth regimen for anaemia. We consider that there is not adequate evidence to change current practice and further investigation is needed.

Giardia and Strongyloides treatment to treat anaemia in NT remote area children

Strongyloides may cause anaemia, but these children will also have significant diarrhoea.[23,24] Empirical treatment for unproven Strongyloides without diarrhoea or growth faltering is thus not recommended. If Strongyloides is isolated from faeces then albendazole is recommended daily for three days.[52]

[Editor: Ivermectin is the preferred treatment for proven strongyloides (for people over five years old) in the fourth edition of the CARPA STM. There is an approximately 20–40% higher cure rate with ivermectin than albendazole. However, ivermectin is mainly recommended for proven cases of strongyloides, which is a different clinical situation to presumptive treatment on the basis of anaemia. Ivermectin is not a good treatment for the other important helminth infections that are more likely to be the cause of anaemia. This is discussed in detail in the Worms-Strongyloides chapter of the Reference Book.]

Giardia can be isolated from asymptomatic persons, thus the detection of Giardia lamblia in stools is not necessarily pathogenic.[27]. We do not recommend its empirical therapy for anaemia.

Iron treatment for anaemia

Effective treatment is available in the NT as oral (Fergon) or intramuscular iron (Ferrum H).

Oral iron

Formulation. Fergon is made up of ferrous gluconate 60 mg/ml. Nine milligrams ferrous gluconate is equivalent to 1 mg elemental iron thus Fergon = 6.6 mg elemental iron per ml.[52]

Dose. The dose for treatment of iron deficiency is 1 ml/kg/day or 1 ml/kg twice per week.[2,10,52,53] Twice weekly-supervised regimens have been used successfully in the NT[2] and elsewhere.[53,54] All regimens require that treatment should continue for three months to enable stores to be replenished. [2,10,52-54] During and after treatment adequate iron must be received in the diet to maintain stores.[10] Doses have been calculated for remote area use based on 1 ml/kg of Fergon which contains 60 mg ferrous gluconate per ml. These doses are shown in table 2.

Side effects and problems. Problems with oral iron treatment may include: mild gastrointestinal symptoms; toxicity in overdose; treatment duration of three months; poor palatability; and frequent vomiting.[2,10,14] In practice few side effects have been reported. Oral iron should be dispensed in small amounts in child-proof containers to prevent accidental ingestion.

Table 2: Oral iron (Fergon) doses

Weight kg	Dose
5–9	5 ml
10–14	10 ml
15–20	15 ml

*Iron tablets (FGF 1 tablet daily) may be easier in older children.

Intramuscular iron

Formulation. Ferrum H is an iron polymaltose complex with 100 mg iron/2 ml. Imferon is an iron dextran with 100 mg elemental iron/2 ml.[52] Only Ferrum H is used in the NT.
Dose. Several different dosage calculations are quoted.

1. CARPA STM third edition doses are calculated using the formula:
   Iron dose (mg) = weight in kg x desired rise in Hb (g/dl) x 3.
   The source of this formula is unknown.
2. 'Standard paediatric dosing' in many children's hospital handbooks (including at RDH) is based on the following formula:
   Iron dose (mg) = weight in kg x (15 – existing Hb g/dl) x 3.
   The source of this formula is the paediatric haematology textbook edited by Wintrobe.[14] However, when we tried to find the primary source for the formula from Wintrobe the reference given was wrong. We have contacted the editors and are awaiting further information. The rationale Wintrobe provides for the formula is that the total dose is calculated from the amount of iron needed to restore the haemoglobin deficit plus an additional amount to replenish the stores.
3. The manufacturer of Ferrum H (Vifor International) states the formula used for calculation of the iron doses displayed in their product information is the following:
   Iron dose (mg) = weight in kg x (target Hb–current Hb g/l) x 0.24 + (15 x weight).
   The source of this is MIMS[52] and a German paper.[55] The rationale behind the formula is that the iron dose = iron deficit = haem iron deficit + iron reserve deficit. 0.24 is derived from: iron component of haemoglobin = 0.34%, blood volume = 7% body weight and 1000 is conversion factor from g to mg (i.e. 0.0034 x 0.07 x 1000 = 0.24). Iron reserve deficit is calculated using the formula 15 mg/kg if weight is up to 34 kg. This is a conservative estimate derived from the calculation of adult stores of iron being approximately 1200 mg for men and 800 mg for women.[56] The doses quoted in MIMS are obtained from Formula 3 using 130 g/L as the target Hb.

Formula 3 appears to have the clearest rationale and evidence base. However, calculated doses are higher than those obtained from using formulas 1 and 2. We have recommended doses that are a simplification of the manufacturer's recommendations. (We have given conservative doses from the dosing chart in MIMS for each weight and haemoglobin range, and made recommendations that Hb is checked in four weeks and further iron given if necessary.) These doses are displayed them in table 3.

The prescribed dose per injection stated in the CARPA STM is 1.5ml given on alternate days.[1]

The manufacturer (Vifor International) recommends 0.5 ml for children weighing 0–5 kg, 1.0 ml for children weighing 5–10 kg and 2.0 ml for children weighing greater than 10 kg. The manufacturer states that these are the maximum doses that should be given per injection and per day. We are currently contacting the manufacturers to ascertain the reasons for this decision. Limiting the volume per injection is likely to reduce the incidence of abscess formation and skin staining. However, limiting the volume administered per day (and not allowing multiple sites for injection on one day) does not make sense given that doses of 5–10 mls are administered over a number of hours via the intravenous route in hospital for children who have severe IDA. Health centre reviews would be reduced if a larger volume of IM Ferrum H was authorised for administration at each

visit. We have, however, recommended following the manufacturers guidelines.

Site. Buttock injections are not recommended in children.[57–60] This is because of the concern about the lack of muscle mass, sciatic nerve damage, neurovascular bundle damage and the high incidence of local reactions. Deltoid injections are also not recommended in children aged less than 12 months. This is again because of the concern about lack of muscle mass, neurovascular bundle damage and the high incidence of local reactions. The anterolateral thigh is the only endorsed site for vaccination in infants under 12 months. Either the anterolateral thigh or the deltoid region is acceptable for children aged 13 months and over, although the anterolateral thigh remains the recommended site.[57–60]

Side effects. Problems with intramuscular iron therapy include anaphylaxis and staining of the skin.[10,14] Iron dextran (Imferon) has been estimated to cause acute hypersensitivity reactions in 0.2–3% of patients.[10,14,61,62] Iron polymaltose (Ferrum H) is reported to have lower side effects.[10,14] Vifor International (the manufacturers of Ferrum H) keep an international safety database. They have had only six cases of anaphylaxis reported in the past 10 years after both intravenous and intramuscular administration. Using sales of the product they estimate an incidence of anaphylaxis of <0.00000015% (personal communication, Maxine Orr, Sigma Pharmaceuticals Pty Ltd). There are numerous recent reports in the literature about the safe and effective use of parenteral iron.[63–65] Wintrobe states quite clearly (1999 edition, p 1001)[14] ‘indications for parenteral iron therapy include (a) unable to tolerate iron compounds when given orally, (b) repeatedly fails to heed instructions or is incapable of accepting or following them.’ A recent American paper states similar indications.[66]

Intramuscular iron therapy has been associated with increased risk of septicemia[67], thus current recommendations are to avoid the use of oral or intramuscular iron to children with a fever >38°C or signs of any systemic infection.

Table 3: Intramuscular (ferrum H) iron doses

Weight (kg)	Haemoglobin level in g/dL	
	7–9	9–11
5–7	3 mL	2 mL
8–10	4 mL	3 mL
11–13	6 mL	4 mL
14–16	7 mL	6 mL
17–19	9 mL	7 mL

Recommendations

- The high prevalence of IDA in remote area Aboriginal children mandates a population-based approach. Consideration should be given to community wide interventions for the prevention and management of IDA
- If a child in the Top End is found to be anaemic they should continue to be given three days of daily albendazole. There is insufficient evidence to change the current practice of deworming for both hookworm and Trichuris as treatment for anaemia
- A community-based study, which examines the prevalence and load of Trichuris and hookworm in NT Aboriginal remote area children should be

performed in Central Australia and the Top End of the NT. If Trichuris egg loads are found to be >5000 eggs/ml then the rationale for treating anaemia with three days of albendazole will be established
- Empirical therapy for Strongyloides or Giardia in a child with anaemia is not recommended
- If a child has growth faltering or significant diarrhoea then empirical treatment for Strongyloides is recommended (albendazole daily for three days [Editor: or ivermectin if more than five years old])
- If Strongyloides is isolated with or without anaemia or growth faltering then albendazole is recommended daily for three days.
- If Giardia is isolated in a child with growth faltering or anaemia then metronidazole TDS for seven days is recommended
- The following oral or intramuscular iron regimens are safe and effective, provided compliance is ensured.
  Oral: twice weekly supervised oral iron for three months, daily unsupervised oral iron for three months. Doses as per table 2.
  Intramuscular Ferrum H into anterolateral thigh. Total dose as per table 3. Given daily with maximum daily doses 0.5 ml (0–5 kg), 1.0 ml (5–10 kg) and 2.0 ml (>10 kg) per injection and per day.
- The decision about which iron regimen to choose should be made in conjunction with the child's family and after consideration of health centre resources.
- Oral or intramuscular iron should not be given to children with fever >38?C or signs of any systemic infection

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[Editor: There is limited evidence of folate deficiency, and it is thought to be uncommon. However, the editorial committee thought that it was reasonable to give folate to those children with more severe anaemia (Hb<9 g/dL) who are the most likely to be malnourished in a more general sense. We did not believe it was worth extra visits to the clinic so it should be combined with the visits programmed for the iron treatment. It is probably far more important to ensure that the child has an ongoing good diet in general.

Timing of follow-up and length of treatment with oral iron: usually three months of oral iron will be needed to restore significant iron deficiency — this is of course dependent on the severity, how much iron is provided in the child's usual diet and how many of the prescribed doses are missed. There is also some uncertainty in the haemocue result — so some kids may be less deficient than initially assessed. We considered saying check after two or three months of oral treatment — but went for one month so that compliance etc. could be checked at that time. If the result after one month is over the cut off level, although the child may be still iron deficient, we suggest ceasing the iron and checking at the usual six month intervals (and encouraging diet containing iron in all).]

Summary of recommendations

Policy and protocol development

- Anaemia is a major public health problem. The high prevalence of iron deficiency anaemia (IDA) in remote area Aboriginal children mandates a

population-based approach. Consideration must be given to population-based interventions for the prevention (by high dietary iron intake and minimisation of infections) and management of IDA

- Dietary iron deficiency and recurrent viral or bacterial infections are the most significant risk factors for IDA in NT Aboriginal children
- Key nutritional advice for families with children should be:
  - Encourage the intake of meat, fish, chicken and green leafy vegetables
  - Reduce tea intake during meals
  - Increase orange juice during meals

- Acute, recurrent and chronic infections may be the reason for a slow Hb response to supplemental iron
- Acute, recurrent and chronic infections must be looked for in children with anaemia
- Acute, recurrent and chronic infections must be treated early and appropriately
- Only the full blood examination and blood film are needed to diagnose iron deficiency and IDA
- Iron studies are misleading in the diagnosis of IDA in remote area Aboriginal children and are best omitted
- The HemoCue haemoglobinometer is an acceptable screening tool for detection of anaemia in remote area Aboriginal children living in populations where the anaemia prevalence is >20%
- The HemoCue haemoglobinometer is an acceptable diagnostic tool for anaemia in remote area Aboriginal children living in populations where the anaemia prevalence is >20% who are aged over six months
- Iron treatment can be instituted on the basis of the result of the HemoCue haemoglobinometer in children aged over six months
- A laboratory venous FBE and film must be performed:
  - If the Hb on the HemoCue haemoglobinometer is <90 g/L in children aged over six months
  - If the Hb on the HemoCue haemoglobinometer is <110 g/L in children aged under six months
  - The Hb appears to be refractory to iron therapy and not increasing when rechecked in one month
  - In children who have any other abnormal features
  - In children living in populations where the anaemia prevalence is <20%.

- The manufacturer’s instructions for the HemoCue haemoglobinometer should be followed carefully
- A follow-up Hb measurement should be performed one month after treatment for IDA commences
- If the Hb has not increased in one month a formal FBE and film should be performed
- Any questions or concerns about diagnosis or treatment for anaemia should be directed to the responsible medical officer
- Data is not sufficient to decide on the prevalence of hookworm or Trichuris in the NT or the contribution of hookworm or Trichuris to anaemia in the NT.
- In the Top End: If a child is found to be anaemic they should continue to be given three days of daily albendazole.
- Empirical therapy for Strongyloides or Giardia in a child with anaemia is not recommended

- If a child has growth faltering or significant diarrhoea then empirical treatment for Strongyloides is recommended (albendazole daily for three days)
- If Strongyloides is isolated with or without anaemia or growth faltering then albendazole is recommended daily for three days.
- If Giardia is isolated in a child with growth faltering or anaemia then metronidazole TDS for seven days is recommended
- The following oral or intramuscular iron regimens are safe and effective provided compliance is ensured:
  - Supervised oral: twice weekly oral iron for three months, daily unsupervised oral iron for three months. Doses as per table 2.
  - Intramuscular Ferrum H into anterolateral thigh. Total dose as per table 3. Given daily with maximum daily doses 0.5 ml (0–5 kg), 1.0 ml (5–10 kg) and 2.0 ml (>10 kg) per injection and per day.
- The decision about which iron regimen to choose should be made in conjunction with the child's family and after consideration of health centre resources
- Oral or intramuscular iron should not be given to children with fever >38°C or signs of any systemic infection.

Research

- Data is not sufficient to decide on the prevalence of hookworm or Trichuris in the NT or the contribution of hookworm or Trichuris to anaemia in the NT.
- A prevalence study which examines the relative contribution of parasites, worms and diet to IDA in remote area Aboriginal children should be conducted in the Top End and Central Australia
- Further validation of the HemoCue is recommended with a larger non-anaemic sample size
- A community-based study, which examines the prevalence and load of Trichuris and hookworm in NT Aboriginal remote area children should be performed in Central Australia and the Top End of the NT. If Trichuris egg loads are found to be >5000 eggs/ml then the rationale for treating anaemia with three days of albendazole will be established.

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