***Current Practice***

# Management of iron deficiency anaemia in children

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## Introduction

Iron is an essential cofactor of haemoglobin. Human adult haemoglobin is composed of two α and two β globin protein subunits, each of which is tightly associated with a non-protein haem group[1]. Haem group consists of an iron ion held in a porphyrin ring[2]. This iron ion, primarily found in its ferrous ($Fe^{2+}$) state, is the site for oxygen binding, and therefore, is essential for oxygen delivery to tissues. Iron deficiency impairs the synthesis of haemoglobin and erythropoiesis in the bone marrow and leads to iron deficiency anaemia (IDA).

## Epidemiology

Iron deficiency is the commonest form of anaemia in children throughout the world. The higher prevalence is reported in South Asia and Central, Western, Eastern, and sub-Saharan Africa[3]. It is particularly common among toddlers and preschool children aged between one to five years. The prevalence of IDA among Sri Lankan preschool children is estimated at 7.3%[4].

## Risk factors and aetiology

Nutritional deficiency is the most common cause of iron deficiency in children[5]. Lack of availability and inadequate intake of iron-rich food, poor weaning practices, excessive milk consumption, and consumption of iron absorption inhibitors along with meals (e.g., phytates, tannates, calcium), are common risk factors for nutritional iron deficiency. Malabsorption and chronic blood loss due to hookworm infections and gastrointestinal bleeding are other causes of IDA in children[6].

Due to the maternal transfer of adequate quantities of iron *in utero*, iron deficiency is rare before six months in term infants[7]. However, prematurity, placental abruption, fetal-maternal haemorrhage and twin-twin transfusions cause IDA in infants below six months.

## Clinical features

IDA is clinically asymptomatic and detected incidentally in most[8]. Clinical features depend on the severity of the iron deficiency and anaemia[9]. Some of the features are due to the deficiency of iron, while others are caused by associated anaemia (Table 1)[6].

**Table 1:** ***Clinical features of iron deficiency anaemia***

| *Symptoms of iron deficiency* | *Physical signs of iron deficiency* | *Symptoms of anaemia* | *Physical signs of anaemia* |
|---|---|---|---|
| Pica | Angular stomatitis | Anorexia | Pallor |
| Pagophagia | Glossitis | Fatigue | Tachycardia |
| Behavioural changes | Damaged hair | Irritability | Flow murmurs |
| Cognitive defects | Koilonychia | Dyspnoea | Cardiac failure |
| | | Palpitations | |
| | | Headache | |

Conjunctival and skin pallor are evident when the haemoglobin is below 8-9g/dL. When the haemoglobin is very low, children with IDA could develop features of heart failure like tachycardia, cardiomegaly, gallop rhythm, tender hepatomegaly and fine basal crepitations. Some studies also report that children with iron deficiency develop cognitive impairment and motor development delay even without anaemia. However, the causal relationships between these neuro-cognitive symptoms and non-anaemic iron deficiency are not conclusive.

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**Laboratory findings**

Full blood count in IDA shows low haemoglobin and microcytosis [low mean corpuscular volume (MCV)]. The mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) are low, too[10]. The red blood cell (RBC) distribution width is elevated. Reactive thrombocytosis is another haematological feature of IDA.

The blood picture in IDA shows hypochromic microcytic red blood cells, anisopoikilocytosis and pencil and teardrop cells. However, blood picture does not help to differentiate IDA from other causes of microcytic anaemia; therefore, it should not be routinely performed.

**Diagnosis**

The diagnosis of iron deficiency is confirmed by serum ferritin or serum iron studies. Serum ferritin is the most commonly performed test due to its low cost and wider availability. However, as serum ferritin is an acute phase reactant, it is elevated in many infective and inflammatory conditions. Therefore, it should be done when the child is free from acute inflammation. Serum ferritin <15µg/L is widely accepted as the cut-off to diagnose IDA[11]. However, some studies suggest that ferritin <30µg/L should be considered as iron deficiency[12]. Therefore, in routine clinical practice, it is reasonable to commence a therapeutic trial of iron in those with serum ferritin between 15-29µg/L.

Transferrin saturation is another helpful investigation to confirm iron deficiency in children[12]. Although it is customary to order a full iron profile (serum iron, total iron binding capacity and transferrin saturation), the same information on iron deficiency can be gathered from the transferrin saturation alone. Therefore, it is recommended to perform only that. In IDA, transferrin saturation is <16% (normal >30%). Serum iron is low, and the iron binding capacity is high in IDA.

If the facilities for serum ferritin and iron studies are unavailable, giving a therapeutic trial of iron as a diagnostic tool of IDA is recommended. This is especially appropriate for children aged between six months to two years. During a therapeutic trial, children are given the treatment dose of iron for one month and evaluated for the response by demonstrating a rise in haemoglobin by at least 1g/dL.

Other investigations like soluble transferrin receptor levels (high in IDA), zinc protoporphyrin (high in IDA) and serum hepcidin (low in IDA) are used only in research settings. They are not widely available or optimised for clinical use.

**Differential diagnosis**

The differential diagnoses of microcytic anaemia include thalassaemia trait, sideroblastic anaemia, lead poisoning and copper deficiency, of which the thalassaemia trait is the most important health problem in Sri Lanka[13,14]. The prevalence of β-thalassaemia trait and α-thalassaemia trait in Sri Lanka is reported as 2-3% and 8%, respectively[15,16]. Therefore, many children with asymptomatic microcytic anaemia could have thalassaemia traits. Similarly, IDA is known to co-exist with the thalassaemia trait[17]. Also, the National Thalassaemia Prevention Programme recommends screening for β-thalassaemia trait in all individuals with low MCV to avoid births of children with thalassaemia[18,19]. Therefore, screening for β-thalassaemia by performing haemoglobin high-performance liquid chromatography (HPLC) or capillary electrophoresis (CE) is recommended for all children with microcytic anaemia with or without iron deficiency. The diagnosis of β-thalassaemia trait is confirmed if the patient has haemoglobin $A_2$ >3.4%[20].

α-thalassaemia trait, conversely, cannot be diagnosed by haemoglobin HPLC or CE. It can only be diagnosed by genetic testing done in specialised laboratories[21]. If facilities are available, screening for common α-thalassaemia mutations ($\alpha^{-3.7}$, $\alpha^{-4.2}$, $--^{MED}$, $--^{SEA}$, $--^{THAI}$, $--^{FIL}$ and $--^{20.5}$) should be performed in children with persistent microcytic anaemia in whom the IDA and β-thalassaemia trait have been excluded.

**Treatment**

Oral iron is the mainstay in the treatment of IDA. Children should be prescribed 6mg/kg of elemental iron daily as a single daily dose or two divided doses, preferably before meals. The commercially available iron preparations include ferrous sulfate, ferrous gluconate, ferrous fumarate, ferric citrate, ferric maltol and sucrosomial® iron[22]. The amount of elemental iron available in each preparation differs according to the manufacturer. Therefore, the prescriber should be aware of the amount of elemental iron in each iron preparation. The response to oral iron is very rapid, and therefore it can be used effectively even in children with severe IDA and very low haemoglobin levels. Routine prescription of folic acid, vitamin C and anti-helminthic medication has not been shown to provide an added advantage in IDA; therefore, they should not be practised[23]. Oral iron's frequently reported side effects are constipation, nausea, dyspepsia, and vomiting[24].

Parenteral iron is indicated in children with IDA with intolerable side effects to oral iron and

gastrointestinal pathologies that reduce oral iron absorption. Parenteral iron formulations available for clinical use include iron sucrose, ferric gluconate, low molecular weight iron dextran, ferric carboxymaltose, and iron isomaltoside[25]. Parenteral iron is associated with serious adverse effects like hypersensitive reactions and anaphylaxis[26].

Blood transfusions are very rarely used in IDA in children. It is indicated in patients with haemodynamic instability due to anaemia and ongoing active infection. Iron therapy should be started subsequently.

Dietary iron supplementation is an essential component in IDA management. Children with IDA should be encouraged to consume food rich in haem iron with higher bioavailability, such as meat, fish and egg yolk. The absorption of non-haem iron in green leaves and pulses is increased by consuming food rich in vitamin C along with meals. Children with IDA should not consume phytates (grains and seeds) and tannates (tea and coffee) that decrease iron absorption along with meals.

**Follow up**

Response to treatment of IDA is usually assessed by repeating the haemoglobin after one month. A rise in the haemoglobin of 1-2g/dl indicates an adequate response to iron[27]. Iron treatment should be continued for three months after haemoglobin and RBC indices have normalised in patients with good responses. This is to ensure the replenishment of iron stores.

If the response to iron treatment is poor, several possibilities should be explored. After confirming that the dose and compliance are adequate, patients should be re-evaluated for non-dietary causes of iron deficiency; for example, malabsorption and chronic blood loss. Genetic diseases causing iron refractory IDA should also be considered[28].

**Prevention**

Prevention of IDA is a significant public health issue. Maternal iron supplementation during pregnancy and delayed cord clamping at delivery are proven interventions to prevent IDA during infancy. In older children, consuming iron-rich food to fulfil the recommended dietary allowance (1mg/kg/day in infancy and 7-10mg/day during childhood) is universally accepted to prevent iron deficiency. Continuous or intermittent iron supplementation is another method advocated. The WHO recommends iron supplementation only in countries where the prevalence of anaemia is >40%[29].

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