Clinical Guidance: Best Practices in the Management of Iron Deficiency and Iron Deficiency Anemia

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Do	• Do **screen for iron deficiency** and iron deficiency anemia in patients at risk, especially in people who menstruate, are pregnant, or lactating.[1-4] • Do **diagnose** patients with ferritin <30 mcg/L (adults) or <20 mcg/L (pediatric) with iron deficiency and offer iron repletion.[4-6] • Do **find the cause of iron deficiency** so that iron does not continue to be lost and any serious condition (e.g., colon cancer) is treated as early as possible.[7] • Do **use intravenous (IV) iron** when oral iron is not tolerated or ineffective.[1-4] • Do **refer to your practice setting clinical decision support** tools/protocols/guidelines specific to iron deficiency.
Stop	• Stop an IV iron infusion if a patient has **symptoms of an infusion reaction**.[1-4]
Consider	• Consider that most people with iron deficiency anemia have **normal red blood cell mean corpuscular volume.**[1-4] • Consider that **iron deficiency without anemia may require treatment**.[1-4] • Consider **investigating for underlying reasons** (e.g., ongoing blood loss, large iron demands, malabsorption) if oral supplementation is ineffective.[8] • Consider that **increasing dietary iron alone** is not sufficient as a treatment for iron deficiency anemia.[7] • Consider that the likelihood of anaphylaxis (1:200,000) or minor infusion reactions (1:100–250) with IV iron **are low** but should be weighed against benefits.[9]

Background

Globally, iron deficiency is the most prevalent micronutrient insufficiency that negatively impacts health, quality of life, and functioning.[10] Iron deficiency is characterized by inadequate iron stores or availability, leading to compromised red blood cell production and decreased hemoglobin concentration.

Iron deficiency can occur without anemia (non-anemic iron deficiency, or NAID), but prolonged, untreated deficiency may progress to iron deficiency anemia (IDA). IDA is the most common cause of anemia, affecting more than 1.2 billion individuals, including 7% of Canadians, although many are unaware.[1,2]

Iron Deficiency Definitions[10]

- **Iron deficiency** is a decrease in the total content of iron in the body.
- **Iron deficiency anemia** occurs when iron deficiency is sufficiently severe to reduce erythropoiesis. Iron deficiency anemia is a late manifestation of iron deficiency, but iron deficiency may be severe despite normal hemoglobin.
- **Absolute iron deficiency** is caused by reduced iron intake, defective absorption, chronic blood loss, or physiologically increased requirements.
- **Functional iron deficiency** occurs when iron stores are adequate but utilization is inadequate. It can develop in the context of inflammatory states (e.g., chronic kidney disease, malignancy).

Impacts of Iron Deficiency

Iron deficiency is associated with:[2,10]

- Decreased health-related quality of life
- Impairment in cognitive performance in young children
- Adverse outcomes in pregnancy for both mothers and newborns
- Decreased physical capacity in adults
- Cognitive decline in the elderly

Symptoms of NAID/IDA are related to decreased oxygen delivery to the entire body and can seriously impact quality of life, although many patients have no symptoms.[1]

Causes of NAID/IDA[2,4,5,11]

Increased demand:

- Physiological state (growth, pregnancy)
- Blood loss (heavy menstrual bleeding, gastrointestinal bleeding)

Decreased availability:

- Decreased intake (vegan diet, increased consumption of cow's milk in children)
- Decreased absorption (active celiac disease, H. pylori, post-bariatric surgery)
- Multiple causes (absolute iron deficiency associated with inflammation)

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Screening

Screening should occur in patient populations with risk factors for NAID/IDA, including those with: [4,13-15]

- **Higher iron demands:** menstruating, pregnant, lactating people; children/adolescents undergoing rapid growth
- **Comorbid conditions:** gastrointestinal disorders, post-bariatric surgery, chronic kidney disease, chronic intravascular hemolysis
- **Increased loss:** heavy menstrual periods, chronic gastrointestinal blood loss
- **Decreased availability:** particularly conditions that cause chronic inflammation or affect nutrient absorption, active celiac disease, dietary restrictions, large consumption of cow's milk
- **Social determinants of health:** lower socioeconomic status, minority race or ethnicity

Patient Discussion

Menstruation

- How often do you menstruate and how many days does it last?
- How often are you changing a pad or tampon? What level of absorbency of pads or tampons are you using? Do you experience overflow?
- Do you have menstrual clots and what is the size?
- Do you miss school/work or other obligations due to heavy periods?

Other bleeding sources

- Do you donate blood?
- Do you experience chronic bright-red blood per rectum or have tarry black stools?
- Do you have frequent nosebleeds?
- Do you notice blood in your urine?
- Do you have easy bruising or bleeding?

Intake

- Do you follow a vegan or vegetarian diet?
- Are you restricting calories?
- Do you have frequent vomiting?

Poor absorption

- Do you have known gastrointestinal conditions (e.g., celiac disease, pernicious anemia, inflammatory bowel disease)?
- Have you had part of your gastrointestinal tract removed, such as bariatric surgery, or ileostomy?
- Do you experience frequent bloating, nausea, diarrhea, or constipation?

Diagnosis

A diagnosis may be missed because the common symptoms of NAID/IDA (i.e., fatigue, poor exercise tolerance, and symptoms of depression) can often be overlooked as pressures of daily life. The diagnosis of iron deficiency involves careful history taking and physical examination, which are essential in identifying risk factors and possible etiology, guiding laboratory testing, and identifying the underlying cause of the iron deficiency.[4]

Investigations

To further investigate NAID/IDA, clinicians should order a complete blood count (CBC) and ferritin in all patients. "Iron studies" (serum iron, total iron binding capacity [TIBC or transferrin], and transferrin saturation) should be ordered in patients with concomitant inflammation AND ferritin ⩾30 mcg/L (adults) or ⩾20 mcg/L (pediatric).[5,6] CBC alone is an inadequate screen for iron deficiency, as low hemoglobin and microcytosis (low mean corpuscular volume) are neither sensitive nor specific for iron deficiency.[4]

Adult (⩾18)	Pediatric (<18)	Interpretation of Ferritin Results [5,6]
<30 mcg/L	<20 mcg/L	Result consistent with iron deficiency
30–50 mcg/L	20–50 mcg/L	In the absence of concomitant inflammation, probable iron deficiency
51–100 mcg/L		Possible iron deficiency, if risk factors are present
101–300 mcg/L		Iron deficiency unlikely
⩾600 mcg/L		Consider test for iron overload

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Management of NAID/IDA [8,16-20]

Studies show improvement in energy levels, cardiovascular health, cognition, energy, and health-related quality of life with iron therapy. Blood transfusions for severe IDA should be restricted for cardiovascular compromise (hypotension, chest pain, syncope, tachycardia) or debilitating symptoms. Often, there is time to address the cause of IDA and fuel self-driven erythropoiesis with iron supplementation (oral/IV). Reassess CBC, ferritin, or iron studies 1–3 months following initiation of therapy, which should demonstrate notable improvement in the absence of ongoing losses or high demands (e.g., pregnancy). [20]

Management	Oral Iron	IV Iron
Indication	• Minimum three-month trial to correct hemoglobin level and treat symptoms of iron deficiency • More time may be required, depending on the severity of IDA and ongoing losses	• Severe anemia (hemoglobin concentration of less than 90 g/L) • Patients unresponsive or intolerant to oral iron • Patients in need of rapid correction before an operative procedure • Second or third trimester of pregnancy; see the Toronto Policy on IV Iron in Pregnancy • See the Management of IV Iron in the Treatment of IDA

Formulations and common doses/ administration times	• Available as tablet, suspension, liquid
	• Ferrous fumarate (Palafer®) 300 mg daily [21]
	• Ferrous sulfate (Fer-In-Sol®, Feosol®) 300 mg daily
	• Ferrous gluconate (Fergon®) 300 mg daily
	• Polysaccharide iron complex (FeraMAX®, Triferexx®, Polyride Fe®) 150 mg daily
	• Liposomal iron (Ferosom®) 30 mg daily
	• Heme iron polypeptide (Proferrin® ES, OptiFer® Alpha) 11 mg 1–3 times a day, or (Hemaforte® heme iron) 35 mg daily [22]
	• Ferric maltol (ACCRUFeR®) 30 mg twice a day [23]
		• Ferrous gluconate (Ferrlecit®) 125 mg (60 min.) [24]
		• Iron sucrose (Venofer®) 100 mg (2–180 min.) [25]
		• Ferric derisomaltose (Monoferric®) 20 mg/kg (20–30 min.) [26]
		• Ferric carboxymaltose (Ferinject®) 15 mg/kg (3–15 min.) [27]
		• Dosing depends on the iron deficit:
		  ◦ Calculate “iron deficit” (total dose needed) using hemoglobin deficit equation
		  ◦ Divide iron deficit into appropriate individual doses
		  ◦ Administer doses 1–2 times weekly, until total dose complete (interval varies by product; check product monograph)
		  ◦ Should be avoided in patients with risk factors for hypophosphatemia

Cost	• $3–$80 for one-month supply	• $390–$530 for 1,000 mg (drug cost only; does not include administration costs)
Duration	• 3–6 months, potentially longer • Continue iron for three months after achieving normal hemoglobin	• Ferrous gluconate/iron sucrose requires repeated dosing • If the underlying cause of iron deficiency can be addressed, additional treatments may or may not be required • Continue therapy until hemoglobin and iron indices are normal • Continue iron for three months after achieving normal hemoglobin
Benefits	• Inexpensive • Available over the counter • Effective in stable outpatients • Different formulations available	• Optimizes hemoglobin levels quickly in stable outpatients • Benefits those intolerant or not responding to oral iron • Increased efficacy, improved adherence, decreased discontinuation rate, and acceptable safety profile compared to oral iron • Different formulations available

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Management	Oral Iron	IV Iron
Drawbacks	• Adherence can be poor, in part due to high rates of adverse effects	• Requires visit to infusion centre or hospital for administration
Contraindications	• Patients with iron-overloaded states such as hereditary hemochromatosis, hemosiderosis, or have a history of hemolytic anemia	• Evidence of iron overload, known hypersensitivity, anemia not caused by iron deficiency, severe inflammatory diseases of the liver/kidneys • Do not use ferric carboxymaltose in patients at risk for hypophosphatemia
Potential adverse events	• Side effects are common and dose dependent, including nausea, constipation, bloating, diarrhea, vomiting, metallic taste, and dark stool	• Infusion reactions (isolated skin, respiratory, or gastrointestinal symptoms), Fishbane reaction, or rarely, anaphylaxis
Repeat blood work	After 1-3 months.[8,28] • Adequate response: Hemoglobin increases by >20 g/L • Inadequate response: Hemoglobin increases by <20 g/L • Failure: No improvement or worsening of hemoglobin	

Dietary Considerations [7,31]

While consuming enough iron through food is an important part of preventing iron deficit, people with IDA need more iron than can be consumed through diet alone.

A 2,000-calorie diet contains approximately 10 mg of elemental iron (compared with 65 mg in one 325 mg ferrous sulfate tablet). Therefore, increasing dietary iron alone is not sufficient as a treatment for IDA.

Dietary sources of iron include meat, especially organ meats; grains; fruits; and vegetables. For people who do not eat meat, plant sources of iron include whole or enriched breads or grains, iron-fortified cereals, legumes (beans, chickpeas, peanuts), green leafy vegetables, dried fruits, soy products, blackstrap molasses, bulgur, and wheat germ. Further, vitamin C can be added to enhance iron absorption. Maintaining a healthy, balanced diet is important for overall health.

Optimizing Oral Iron Therapy [8,29-31]

- Take one pill once a day or every other day
- Take on an empty stomach or with an acidic drink
- Within two hours of taking oral iron, avoid milk, tea, coffee, calcium pills, antacids, proton pump inhibitors, H2-receptor blockers, thyroid medications, and some antibiotics
- Dark stool is normal and expected
- Manage potential adverse effects, including upset stomach, bloating, and constipation, by adding fibre, fluids, and daily polyethylene glycol, or changing formulation
- Concurrent consumption of foods with high iron and vitamin C content is encouraged

For Additional Resources on NAID/IDA, Please Visit:

https://www.canadiankt.org/nurse-training-iv-iron
https:/www.hemequity.com/our-resources-for-healthcare-providers
https:/www.hemequity.com/our-resources-for-patients
https:/gynqi.com/intravenous-iron-infusions/

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