

GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Iron Deficiency - Investigation and Management

Effective Date: June 15, 2010

Scope

This guideline provides recommendations for the investigation and management of iron deficiency in patients of all ages. **An underlying disorder may be the cause of an iron deficiency. If so, this needs to be identified and managed;** the investigation for the cause of iron deficiency is beyond the scope of this guideline.

Diagnostic Codes: 280 (Iron Deficiency Anemias)

Prevention and Risk Factors

- I. Encourage all individuals to consume a diet with sufficient iron to prevent iron deficiency. Refer to Appendix A for recommended daily intake and foods high in iron.

Screening

- I. **Screening of the general population for iron deficiency is not recommended.**¹
- II. Identify patients at risk of iron deficiency based upon a directed history, symptom review, and physical examination.

Table 1: Causes of Iron Deficiency and Iron Deficiency Anaemia (IDA)

Increased Requirements	Decreased Intake
Growing infants and children Menstruating women ^{2,3} Pregnancy ^{4,5} Lactation Multiparity Parturition	Low socioeconomic status Vegetarian diet Lack of balanced diet or poor intake Alcoholism Elderly High risk ethnic groups (<i>First Nations, Indo-Canadians*</i>)
Increased Loss	Decreased Absorption
Menorrhagia GI bleeding Regular blood donors Post-operative patients with significant blood loss Hematuria Intestinal parasites (travel or immigration from an endemic area) Intravascular hemolysis: hemoglobinuria Extreme physical exercise (endurance athletes) Pathological (hemolytic anemias)	Dietary factors (<i>tannins, phytates in fibre, calcium in milk, tea, coffee, carbonated drinks</i>) Upper GI Pathology: <ul style="list-style-type: none">• Chronic gastritis• Gastric lymphoma• Celiac disease• Crohn's disease Medications that decrease gastric acidity or bind iron (refer Appendix B) Gastrectomy or intestinal bypass Duodenal pathology Chronic renal failure patients

*India has the highest prevalence of iron deficiency anemia among women in the world, including adolescents: 60-70 percent of Indian adolescent girls are anemic. Consider iron deficiency as a possibility in South Asian adolescent girls and adult women, and in those that have recently immigrated.⁶

Diagnosis/Investigation of Iron Deficiency

Iron deficiency in adult men and postmenopausal women is most likely to have a serious underlying cause of blood loss. Bleeding from the gastrointestinal tract accounts for approximately two-thirds of all causes in iron deficient patients.^{7,8} Testing for malabsorption is recommended if small bowel disease is clinically suspected, or if oral iron supplementation results in refractory response despite compliance.

Signs and Symptoms

- I. Early stage iron deficiency can exist without overt anemia, but with other non-hematological symptoms.⁹
- II. Investigate based on clinical suspicion, not only on presence of anemia. Other symptoms include:
 - a. Adults: hair loss, fatigue, cold intolerance, restless leg syndrome, irritability.
 - b. Children: tiredness, restlessness, attention-deficit/hyperactivity disorder (ADHD), irritability, growth retardation, cognitive and intellectual impairment.

Testing

Table 2: Initial Investigation Tests

Investigation	Application	Notes
Hematology Profile (CBC)	<ul style="list-style-type: none"> • can suggest iron deficiency • hemoglobin value is required to assess severity of anemia • not diagnostic test of choice for iron deficiency 	A constellation of the following findings on CBC is highly suggestive of iron deficiency: <ul style="list-style-type: none"> • anemia • microcytosis • hypochromia
Serum Ferritin	<ul style="list-style-type: none"> • diagnostic test of choice¹⁰ • serum ferritin levels and iron status: <ul style="list-style-type: none"> Adults (ug/L) <ul style="list-style-type: none"> • less than 15 → diagnostic of iron deficiency • 15 – 50 → probable iron deficiency • 50 – 100 → possible iron deficiency • more than 100 → iron deficiency unlikely • persistently more than 1000 → consider test for iron overload Children (ug/L) <ul style="list-style-type: none"> • less than 12 → diagnostic of iron deficiency 	<ul style="list-style-type: none"> • may be unreliable in patients with chronic disease or malignancy • non-hematologic symptoms can occur when the serum ferritin is in the low normal range (less than 50 ug/L) • higher levels of serum ferritin do not exclude iron deficiency • persistently elevated serum ferritin levels (greater than 1000 ug/L), but without chronic inflammatory disorder → recommend testing for iron overload (refer to Iron Overload – Investigation and Management at BCGuidelines.ca)

The following additional tests may be considered when clinical features and hematology profile is suggestive of iron deficiency, but ferritin is normal. Consider consulting with a laboratory physician before ordering these additional tests.

Table 3: Additional Tests

Investigation	Application	Notes
1. Serum Iron 2. Iron Binding Capacity 3. Transferrin Saturation/ Fraction Saturation	<ul style="list-style-type: none"> low serum iron and high iron binding capacity and transferrin saturation of < 0.15 <p>→ these tests may help in the diagnosis of iron deficiency</p>	<ul style="list-style-type: none"> these tests are recommended when serum ferritin is reported as normal or high and: <ul style="list-style-type: none"> iron deficiency is suspected clinically, or a patient with kidney failure, or chronic infection, inflammation or malignancy is present
Monitored Therapeutic Trial of Iron	<ul style="list-style-type: none"> patients with probable iron-deficiency anemia → a monitored therapeutic trial may be both diagnostic and therapeutic (refer Appendix B – usual adult/pediatric dosing) 	<ul style="list-style-type: none"> unreliable in iron malabsorption or ongoing blood loss ↑ in hemoglobin of 10-20 g/L in 2 - 4 weeks is diagnostic of iron deficiency^{3,11}

* More sophisticated tests (e.g. serum free transferrin receptor and others), that are unaffected by concurrent diseases are being investigated but not yet available in most diagnostic facilities.

** Quantitative, specific determination of **serum transferrin level is not indicated** as part of an iron deficiency testing profile.

Table 4: Laboratory Differentiation of Iron Deficiency Anemia (IDA) versus Anemia of Chronic Disease (ACD)

Investigation	Results In		
	IDA	ACD	ACD + IDA
Serum Ferritin	↓	↑	↓ or normal
Serum Iron	↓	↓	↓
Iron Binding Capacity	↑	↓	↓ or low normal
Transferrin Saturation/ Fraction Saturation	↓	↓ or normal	↓

Management:

Care Objectives

I. Determine the Cause of Iron Deficiency

- The etiology is often multifactorial; even when there is an obvious cause, investigation of serious underlying causes (e.g. colon cancer in adults) is recommended.

II. Aim of Treatment

- Normalize hemoglobin levels and red cell indices; replenish iron stores.¹²
- Individualize disease-specific management depending on underlying cause.¹³

Lifestyle Management

- It is recommended that patients with iron deficiency receive dietary advice (refer Appendix A).

Treatment and Monitoring

- I. Commonly used oral iron preparations include: ferrous gluconate, ferrous fumarate, and ferrous sulfate. One preparation is not preferred over another; patient tolerance should be the guide. (Refer Appendix B).
- II. The usual adult dose is 180 mg of elemental iron/day in divided doses.¹⁴ Therapeutic doses can range from 100 to 200 mg of elemental iron/day, depending on severity of symptoms, ferritin levels, age of the patient, and gastrointestinal side effects.
- III. Iron intolerance is very common;
 - a. Oral iron preparations may cause nausea, vomiting, dyspepsia, constipation, diarrhea or dark stools.
 - b. Strategies to minimize these effects include: start at a lower dose and increase gradually over 4 to 5 days; giving divided doses or the lowest effective dose, or taking supplements with meals (*note: iron absorption is enhanced if supplements are taken on an empty stomach; however, it may not be tolerated*).
 - c. Although sustained release iron preparations tend towards less gastrointestinal side effects, they may not be as effective as standard film coated products due to reduced/poor iron absorption.¹⁵
- IV. Iron absorption can be decreased by various medications and supplements; space administration apart by at least 2 hours. (Refer to Appendix B)
- V. Iron absorption from pharmaceutical preparations can be enhanced by taking them on an empty stomach (at least 1.5 to 2 hours after a meal), with acidic juices or vitamin C, and not with other multivitamin, calcium, or antacid tablets.
- VI. Iron replacement therapy may begin as soon as iron deficiency is detected; however, it is essential to determine and correct the underlying causes of iron deficiency (see Appendix B and Table 1).¹
- VII. Oral iron therapy in iron deficient anemia will increase hemoglobin by 10-20 g/L in 2 to 4 weeks. Order a Hematology Profile initially at 2 to 4 weeks to monitor response to replacement regime.
- VIII. Anemia will correct within 2 to 4 months if appropriate iron dosages are administered and underlying cause of iron deficiency is corrected.
- IX. **Continue iron therapy an additional 4 to 6 months (adults) after the hemoglobin normalizes to replenish the iron stores.**¹⁶ The frequency of subsequent monitoring depends upon the severity of the anemia, the underlying cause of the iron deficiency, and the clinical impact upon the patient.
- X. **If the patient's clinical status is compromised by moderate to severe anemia, consider admission to an acute care facility and blood transfusion.** Once the patient is stable, iron replacement can be commenced.
- XI. **Oral iron replacement is preferred to intravenous (IV) therapy.** It is safer, more cost-effective, and convenient when compared to IV therapy.¹⁷ However, intravenous therapy may be substituted when there is: inadequate iron absorption, continued blood loss, noncompliance or intolerance to oral iron therapy. Internal medicine/hematologist consultation is recommended.¹³ (Refer Appendix B)
- XII. **Complete or partial failure of monitored iron therapy trial (in compliant patients) may be due to insufficient absorption or ongoing loss (e.g. hemorrhage) or both. It should be investigated appropriately. Intravenous iron preparations may be considered in these patients.**
- XIII. **Intramuscular (IM) iron therapy is not recommended** except in institutions with facility for treating anaphylactic reactions.¹⁸ Additional risks of IM iron therapy include unpredictable absorption and local complications (e.g. pain, staining of the skin, sarcoma formation).¹⁹

Ongoing Care

Iron Supplementation

- I. Once anemia has corrected and iron stores have normalized; a low maintenance dose may be prescribed if an ongoing need for additional iron (e.g. menorrhagia, growth spurt). Dietary modification may also be considered (refer Appendix A). Consider similar supplementation for iron depleted but **not** anaemic patients.

Note: Exercise caution in supplementation in patients at risk for iron overload. See *Iron Overload: Investigation and Management* at www.BCGuidelines.ca

Special Circumstances

Iron Deficiency in Pediatric Populations

- I. IDA in children is associated with motor and cognitive deficits which may be irreversible.²⁰
 - a. Consider the introduction of iron rich foods/formula (refer Appendix A) or routine iron supplementation for asymptomatic children aged 6-12 months who are at increased risk (refer Table 1) for IDA.¹
 - b. Recommended dose is 1 to 2 mg/kg/day of elemental iron (max 15 mg of elemental iron/day).²¹
- II. Recommend infants and toddlers with suspected IDA begin treatment with oral ferrous sulphate.
 - a. Recommended treatment dose for infants and children is 3 to 6 mg of elemental iron/kg/day in divided doses (refer Appendix B).
- III. **Advise patients that iron can be toxic to children and should always be safely stored.**

Iron Deficiency in Pregnancy

- I. There is an increase in iron requirement during pregnancy, parturition and lactation. Total iron loss associated with pregnancy and lactation is about 1000 mg.
 - a. An increase in iron consumption by about 15-30 mg of elemental iron/day is recommended for non-anemic women, an amount readily met by most prenatal vitamin formulations (refer Appendix A).²²
 - b. Women with iron deficiency anemia should receive an additional iron supplement as per treatment guidelines above.²³
- II. **Iron is mandatory for normal fetal development.** It is important to prevent iron deficiency in the fetus by preventing iron deficiency in pregnant women.²⁴
- III. Iron deficiency anemia is the most frequent form of anemia in pregnant women. Anemia in pregnancy is defined as:
 - 1st trimester - hemoglobin of less than 110 g/L
 - 2nd trimester - hemoglobin of less than 104 g/L
 - 3rd trimester - hemoglobin of less than 110 g/L
- IV. If necessary IV iron is considered to be safe for the second and third trimester (refer Appendix B).¹¹

Iron Deficiency in the Elderly

- I. Anemia in the elderly is a common clinical finding, often multifactorial, and has significant impact on quality of life, functional decline, and mortality. Treatment of iron deficiency and its underlying cause(s) may improve outcomes.
 - a. Investigation of anemia in the elderly is recommended if the life expectancy is more than a year.²⁵
 - b. Replacement options are similar to younger patients. Low dose iron therapy (15 mg elemental iron per day) is an effective treatment in octogenarians if standard dosing is not tolerated, with significantly reduced adverse effects (refer Appendix B).^{14,17,21,26} Iron stores take longer to replete with lower iron doses.

Rationale

Iron deficiency is the most common single nutritional deficiency,²⁷ affecting many older infants, young children, adolescents, and pre-menopausal women. Iron deficiency may develop from decreased dietary intake, increased requirements for iron, decreased iron absorption, or increased iron loss (refer Table 1).

The clinical consequences of iron deficiency are both hematologic (due to anemia) as well as non-hematologic (deficiency of iron containing cellular enzymes). The latter include decreased aerobic work performance, hair loss, developmental delay, cognitive and intellectual impairment, adverse pregnancy outcome, and impaired immune function.

The laboratory features of iron deficiency include a constellation of findings in the hematology profile, and reduced iron measurements (ferritin, iron and transferrin saturation) (refer Tables 2 and 3). An overall sharp growth rate has been observed in overall iron testing in the province, with transferrin testing in particular, growing at a much more rapid rate than would be anticipated. This guideline has been developed to provide guidance to physicians on standard testing for iron deficiency.

Oral iron therapy is preferred to intravenous therapy (IV). There is a lack of evidence from good quality randomized controlled trials or systematic reviews that clinical outcomes are improved with IV versus oral iron

administration.^{28,29,30} There is evidence, however, to support the use of IV iron in patients with chronic kidney disease, including dialysis patients.³¹ Use of IV iron in other situations, e.g. in those who failed oral iron therapy, is being investigated.

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Resources

HealthLink BC: www.HealthLinkBC.ca

In B.C. dial 8-1-1 for easy access to non-emergency health information and services.

TTY (deaf and hearing-impaired) call 7-1-1.

Translation services are available in over 130 languages on request.

HealthLink BC Dietician Services: www.HealthLinkBC.ca

Dial 8-1-1 for free nutrition information and resources for B.C. residents.

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List of Abbreviations

ACD – anemia of chronic disease

ADHD – attention-deficit/hyperactivity disorder

ASA – acetylsalicylic acid

CBC – complete blood count

IDA – iron deficiency anemia

IM – intramuscular

IV – intravenous

Appendices

Appendix A - Daily Reference Intake and Foods High in Iron

Appendix B - Iron Replacement Regimes

Associated Documents

The following documents accompany this guideline:

- Summary

This guideline is based on scientific evidence current as of the Effective Date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

A **PDA** version of this guideline is also available at www.Clinipearls.ca/BCGuidelines

The principles of the Guidelines and Protocols Advisory Committee are to:

- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

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DISCLAIMER

The Clinical Practice Guidelines (the "Guidelines") have been developed by the Guidelines and Protocols Advisory Committee on behalf of the Medical Services Commission. The Guidelines are intended to give an understanding of a clinical problem, and outline one or more preferred approaches to the investigation and management of the problem. The Guidelines are not intended as a substitute for the advice or professional judgment of a health care professional, nor are they intended to be the only approach to the management of clinical problems.

Appendix A – Dietary Aspects of Iron

Foods contain iron in two forms: “Heme” iron is present in red meat, fish and poultry, while the non-heme iron is present in fruits, vegetables, cereals and dairy products etc. “Heme” iron is absorbed very well (15-35% vs. 2-5% non-heme iron), and its absorption is independent of other factors present in food, while absorption of non-heme iron is markedly affected by other factors: Factors that inhibit iron absorption include decreased gastric acidity, *Helicobacter pylori* infection, tannins (tea), polyphenols (coffee, herbal teas and cocoa containing beverages – taken within one hour of the meal), phytates (legumes, grains, rice) and calcium and phosphate (antacids and calcium tablets). Factors that enhance absorption of non-heme iron are: meat, citrus juices, vitamin C (e.g. from broccoli, strawberries, tomato, spinach, citrus fruit), and EDTA fortification of foods.

Recommended Daily Dietary Allowance for Iron		
Men	Adult	8 mg
Women	Adult (age 50 on)	8 mg
	Adult (ages 19 to 50)	18 mg
	Pregnant	27 mg
	Lactating	9 mg to 10 mg
Adolescents (ages 9 to 18)	Girls	8 mg to 15 mg
	Boys	8 mg to 11 mg
Children (birth to age 8)	Ages 4 to 8	10 mg
	Ages 1 to 3	7 mg
	Infants (7 months to 1 year)	11 mg
	Infants (birth to 6 months)	0.27 mg

Table cited from: Panel on Micronutrients, Food and Nutrition Board, Institute of Medicine–National Academy of Sciences (2001). Dietary reference intakes: Recommended intakes for individuals, vitamins. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, pp. 772–773. Washington, DC: National Academy Press.

Foods with Heme Iron[‡]

Food, 75g, 2½ oz (iron values or amounts are for cooked meat, fish, shellfish and poultry)	Iron (mg)
Clams	21.0
*Liver, pork	13.4
*Liver, Chicken	8.7
Oysters	6.4
Mussels	5.0
*Liver, beef	4.9
Beef	2.4
Shrimp	2.3
Sardines	2.0
Turkey/Lamb	1.5

*Pregnant women should not eat liver. It has a very large amount of vitamin A, which can be harmful to the fetus. Liver is high in cholesterol, so people with high blood cholesterol levels should not eat it often.

[‡]Tables adapted from HealthLink BC. *Iron Content in Foods. Nutrition Series HealthLink BC File #68d, September 2007*; [5 screens]. Accessed October 15th, 2009.

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Foods with Non-Heme Iron[†]

Food	Serving	Iron (mg)
Pumpkin seeds, kernels, roasted	60 mL (1/4 cup)	8.6
Tofu, medium firm or firm	150g (3/4 cup)	2.4 - 8.0 [†]
Infant cereal, dry	28g (10 Tbsp)	6 - 7 [†]
Soybeans, dried, boiled	175 mL (3/4 cup)	6.5
Instant enriched oatmeal	1 package	4.2 - 6.0 [†]
Lentils, cooked	175 mL (3/4 cup)	4.9
Enriched cold cereal	30g	4.0 [†]
Dark red kidney beans, boiled	175 mL (3/4 cup)	3.9
Blackstrap molasses	15 mL (1 Tbsp)	3.6
Refried beans	175 mL (3/4 cup)	3.1

[†]Note: Iron amounts in enriched foods vary; check the label for accurate information. If the iron amount is given as a percentage of the daily value (DV), the standard used is 14 mg (or 7 mg for infant cereals). For example, if a serving of cereal has 25% of the daily value, it has 3.5 mg of iron (0.25 x 14 mg).

Appendix B: Iron Preparations

Route	Iron salt	Formulation* (elemental iron)	Adult dose†	Incidence of side effects‡	Approximate medication cost for adults / month**
Oral	Ferrous sulfate	Tablets 300 mg (60 mg)	1 tablet 3-times a day	+++	\$2-3
		Sustained release tablets 160 mg (50 mg)	1-4 tablets once a day	+	\$25 (at max dose)
		Suspension 75 mg/mL (15 mg/mL)#	4 mL 3-times daily	++	\$100
		Syrup 30 mg/mL (6 mg/mL)#	10 mL 3-times daily	++	\$50
	Ferrous gluconate	Tablet 300 mg (35 mg)	1-3 tablets 2-3 times a day	++	\$3-5
	Ferrous fumarate	Tablet 300 mg (90mg)	1 tablet 2-times a day	++	\$2-20
		Suspension 300 mg/5mL (20 mg/mL)#	3 mL 3-times daily	++	\$35
Polysaccharide Iron	Polysaccharide iron capsules 150 mg (150 mg)	1 capsule once a day	+	\$24	
Intravenous	Iron sucrose	Suspension (20 mg elemental iron/mL)	Multi-dose infusions to a total 1000 mg elemental iron##	+	\$375 / 1000 mg (full course) ^Δ + facility cost
	Iron dextran complex ^Ω	Suspension (50 mg elemental iron /mL)	Usually 1000 mg elemental iron as a single infusion; depends on body wt and Hb; test dose required	+++	\$290/ 1000 mg (full course) ^α + facility cost

* **Iron absorption may be decreased** by antacids or supplements containing aluminum, manganese, calcium, zinc, proton pump inhibitors, and histamine₂ receptor antagonists. **Iron may decrease the absorption** of bisphosphonates, tetracycline antibiotics, quinolone antibiotics, levodopa, methyldopa, levothyroxine and penicillamine. **(Space administration apart by at least 2 hours).**

† Pediatric dose 3-6 mg/kg **elemental iron** per day.

‡ **Oral preparations:** Nausea, vomiting, dyspepsia, constipation, diarrhea, dark stools, bloating. **IV preparations:** Side effects of intravenous iron preparations are less common with iron sucrose than iron dextran. These include arthralgia, myalgia, pyrexia, flushing, and hypotension. Serious hypersensitivity is observed in approximately 1 in 200 with iron dextran (low molecular weight dextran) and 1 in 50,000 with iron sucrose.¹

** Pediatric cost depends on the dosage. Pricing based on PharmaCare database September 2009. PharmaCare Coverage:

^Δ= No coverage, ^α = Regular Coverage.

Liquid iron preparations could stain teeth; prevent by mixing the dose with water or fruit juice, or drinking through a straw or using a dropper to the back of the mouth and then rinsing the mouth thoroughly with juice or water.

Iron sucrose: 100-300 mg (elemental iron) IV infusion (maximum rate of 100 mg/hr, 300 mg maximum single dose) every week for a cumulative dose of 1000 mg. No test dose is required for iron sucrose. Iron sucrose may be used in patients sensitive to iron dextran.ⁱ

^Ω **Iron dextran complex** - A test dose of 25 mg elemental iron (0.5 mL) is required before administering the first therapeutic dose. If no reaction after 1 hour, the remainder of the dose may then be given over 4 to 6 hours, **OR** the rate of the infusion may be increased progressively to 3-4 mL/min.

Please review product monographs and regularly review current listings of Health Canada advisories, warnings and recalls at: <http://www.hc-sc.gc.ca/index-eng.php>

References:

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