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Iron Deficiency – Diagnosis and Management

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Scope

This guideline provides recommendations for the diagnosis, investigation and management of iron deficiency in patients of all ages.

Key Recommendations

- Use a case-finding approach to identify individuals at risk of iron deficiency and iron deficiency anemia (Table 1). There is no indication for population-based general screening.
- Determine the cause of iron deficiency. Consider age and clinical presentation when investigating for cause.
- Iron deficiency by itself causes symptoms for patients, even in the absence of anemia, and warrants investigation and treatment.
- Ferritin is the test of choice for the diagnosis of iron deficiency.
- Ferritin values occur on a continuum. The suggested cut-offs are estimated ranges that should be interpreted using clinical judgment based on the patient's age, gender, risk profile (Table 1) and symptoms.
- Serum iron, iron binding capacity, and transferrin saturation/fraction saturation are not routinely useful for investigating iron deficiency anemia.
- Take a nutrition history and provide dietary education to address dietary risk factors.
- Caregivers of infants and toddlers should receive guidance to prevent excessive cow's milk intake.
- Prescribe oral iron supplements as first line therapy for iron deficiency. One preparation is not preferred over another; patient tolerance should be the guide. Anemia should correct in 2–4 months. Continue oral iron for 4–6 months after anemia corrects to replenish iron stores.
- Consider prescribing IV iron when there is inadequate response to oral iron, intolerance to oral iron therapy, or ongoing blood loss.

Definitions

Iron deficiency: insufficient total body iron stores, caused by increased requirements, decreased intake, increased loss, and/or decreased absorption[1] (see Table 1).

Anemia: low hemoglobin level, most frequently defined as a hemoglobin value over two standard deviations below the gender- and age-adjusted mean.[1] A hemoglobin value below the local, lab-specific lower reference interval indicates anemia.

Iron deficiency anemia (IDA): anemia due to insufficient body iron stores[1]. The following laboratory findings are typical for IDA: microcytic anemia, hypochromia, and decreased ferritin. IDA may be normocytic if anemia is mild or in early iron deficiency.[2]

Identification of Patients at Risk for Iron Deficiency and Iron Deficiency Anemia

Screening of the general population for iron deficiency is not recommended.[3] Use a case-finding approach to identify patients at risk of iron deficiency and iron deficiency anemia (Table 1).

Common risk profiles, by age, include:

- Infants and toddlers (refer to page 7)
- Adolescents and adults: endurance athletes, regular blood donors, disordered eating
- Pre-menopausal women: especially those with menorrhagia, vegetarian diet
- All adults age >65
- All ages: low socioeconomic status, lack of balanced diet, inadequate nutritional intake

Table 1: Common causes of and risk factors for iron deficiency and IDA in adults

Note: Please refer to *Iron Deficiency in Children* and *Iron Deficiency in Obstetrics* on pages 7–8 for causes and risk factors in children, pregnancy and the perinatal period.

Increased Requirements	Decreased Intake
• Pregnancy (2nd/3rd trimester) • Lactation • Rapid growth spurts (infants, children, adolescents)	• Low socioeconomic status • Vegetarian or vegan diet • Lack of balanced diet or poor intake • Eating disorder • Alcohol use disorder • Age > 65[4] • Recent immigration from developing regions with lower access to iron-rich foods, higher rates of infectious disease, and higher rates of multiparity[5], especially Southeast Asia, Africa[6]
Increased Loss	**Decreased Absorption**

• Menstruating girls and women (at least 10% are estimated to have iron deficiency)[4]
• GI bleeding
  o Colon cancer
  o Gastric/small bowel cancer
  o Hemorrhoids
  o Peptic ulcer disease
  o Inflammatory bowel disease
  o Angiodysplasia
  o Esophagitis
• Regular blood donation
• Post-operative patients with significant blood loss
• Hematuria (gross or microscopic)
• Intravascular hemolysis
• Endurance athletes
	• Upper GI pathology:
	  o Chronic gastritis (incl. H pylori gastritis, atrophic gastritis/ pernicious anemia)
	  o Celiac disease
	  o Crohn's disease
	  o Gastric lymphoma
	• Medications that decrease gastric acidity or bind iron, e.g. antacids/PPIs
	• Gastrectomy or duodenal bypass
	• Bariatric surgery
	• Chronic renal failure

Signs and Symptoms in Adults

Even in the absence of anemia, isolated iron deficiency causes symptoms and warrants investigation and treatment. Early stage iron deficiency can exist without overt anemia, but with other non-hematological symptoms[7] due to deficiency of iron-containing cellular enzymes and unsaturated myoglobin. Some patients may be asymptomatic.

Signs and symptoms of iron deficiency and IDA in adults:

- Fatigue
- Cold intolerance
- Headaches
- Restless leg syndrome*
- Irritability/depression
- Nail changes, e.g. koilonychia (spoon nails)
- Angular cheilitis
- Pica/pagophagia (ice craving)
- Decreased aerobic work performance
- Hair loss
- Adverse pregnancy outcome
- Impaired immune function

Testing

Initial investigational tests

The recommended initial tests for iron deficiency and for IDA, in otherwise well patients, should usually be limited to serum ferritin and complete blood count (CBC). Refer to page 4 for guidance on additional testing in patients with comorbid conditions.

Table 2: Initial Investigational Tests

Investigation	Application	Notes
Serum Ferritin	• Diagnostic test of choice for iron deficiency • **Adults (ug/L)**[10, 11] < 15 diagnostic of iron deficiency 15-30 probable iron deficiency >30 iron deficiency unlikely >100 normal iron stores ≥600 consider test for iron overload[12] • **Children (ug/L)** < 12 diagnostic of iron deficiency 12-20 possible iron deficiency	Ferritin values occur on a continuum; cut-offs are suggested and clinical interpretation is required: • The likelihood of iron deficiency increases with lower ferritin concentrations, including those that overlap with the normal reference interval. The normal reference interval is derived from healthy outpatients without signs of iron deficiency or chronic illness. • In adults, iron deficiency is unlikely if ferritin >30 ug/L (or >70-100 in a patient with chronic inflammatory disease,[13] or >50 in the elderly[2]) • Ferritin is an acute phase reactant and may be unreliable in patients with chronic disease, active inflammation, or malignancy. Testing ferritin is not recommended during acute infection or hospitalization. • Non-hematologic symptoms can occur when the serum ferritin is in the low normal range (< 30 ug/L)
Hematology Profile (CBC)	• Hemoglobin value is required to assess severity of anemia • May suggest iron deficiency • Not diagnostic test of choice for iron deficiency	The following findings CBC and peripheral smear findings are highly suggestive of iron deficiency: • hypochromia (low mean corpuscular hemoglobin concentration (MCHC)) • microcytosis (low mean corpuscular volume (MCV)) Patients with microcytic anemia should not be given iron supplements until iron deficiency is confirmed by testing ferritin. Low MCV in the setting of normal ferritin may indicate hemoglobinopathies such as thalassemia especially in high risk ethnic groups. Long term iron therapy is harmful for these patients.

Refer to *Appendix C: Algorithm for Investigation of Iron Deficiency in Non-Anemic Adults*.

* Iron therapy may improve restless legs syndrome severity and restlessness. Iron supplementation is recommended if serum ferritin is ≤ 75 ug/L.[8, 9]

Additional tests for the diagnosis of iron deficiency in patients with chronic disease, inflammation or malignancy

Anemia of chronic disease (ACD) may co-exist with an element of true iron deficiency. However, ferritin values may be falsely elevated in chronic disease as ferritin is an acute phase reactant. In this specific situation, ordering a **fasting** serum iron and transferrin saturation **may** be helpful to diagnose iron deficiency that may be missed by solely relying on ferritin. A typical iron deficiency profile for such patients (e.g. those with inflammatory bowel disease) is:

- low serum iron,
- low or normal transferrin (i.e. total iron binding capacity), **and**
- fasting transferrin saturation below 20%.

The clinical approach for such patients is the same as for iron deficiency in otherwise well patients (investigate for cause, supplement with iron and refer as appropriate). Patients with a true iron deficiency which co-exists with anemia of chronic disease will respond to a diagnostic trial of iron supplementation.

Guidance for the investigation and management of iron deficiency in the setting of specific chronic diseases is provided:

- **Chronic Kidney Disease (CKD):** Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[14] recommend including CBC, absolute reticulocyte count, serum ferritin and TSAT as well as other tests (vitamin B12) in the initial evaluation of anemia in patients with CKD and anemia. Note that ferritin levels in patients with CKD may be elevated due to inflammation, and so many not accurately reflect iron status and need for supplementation. TSAT <24% is the current recommended threshold to confirm iron deficiency. In patients with CKD, if iron deficiency and other nutritional deficiencies are rectified, and anemia persists, consider erythropoiesis stimulating agents, which would require specialist referral.
- **Heart Failure:** Canadian Cardiovascular Society guidelines[15] recommend consideration of IV iron therapy for heart failure patients with all of the following: ejection fraction ≤40%, serum ferritin < 100 mg/L or between 100–299 mg/L, and TSAT <20%.

If ferritin is unexpectedly elevated, in a patient without chronic disease, active inflammation, or malignancy, C-reactive protein (CRP) can help support the diagnosis of an inflammatory process. Refer to the BC Guideline: C-Reactive Protein and Erythrocyte Sedimentation Rate Testing for information on the use of CRP.

Investigation of the Etiology of Iron Deficiency

Once iron deficiency/IDA is diagnosed, the etiology must be identified. Clinical evaluation of the cause of iron deficiency is important. It should be based upon a directed history, symptom review and physical examination.

Directed history should include:

- nutrition and physical activity history
- pregnancy status and number of pregnancies
- history of blood loss, including GI bleeding, hematuria, menorrhagia, and blood donation
- GI symptoms including changes in bowel habits, abdominal pain, dyspepsia, and unexplained weight loss
- family history including colorectal cancer[16]

Menorrhagia is the most frequent cause of iron deficiency among pre-menopausal women. Consider referral to gynecologist for management of heavy menses and/or consider bleeding disorder, e.g. von Willebrand disease screening.

Testing for malabsorption is recommended if small bowel disease is clinically suspected, or if oral iron supplementation results in inadequate response despite compliance.

Iron deficiency/IDA in ***adult men and post-menopausal women and in pre-menopausal women without menorrhagia*** is more likely to have a serious underlying cause of blood loss including malignancy.[16] Consider upper/lower endoscopy.

Investigation of overt and occult GI and GU bleeding

Primary care providers are encouraged to consult with colleagues including local gastroenterology services or the RACE line to obtain rapid advice and avoid unnecessary travel and wait times.

FIT and FOBT Testing

FIT and FOBT testing are not indicated for investigation of overt GI bleeding and are not needed for patients being referred. Given the risk of false negatives, FIT and FOBT testing should not be used to rule out GI bleeding.

Overt GI bleeding

Overt GI bleeding that is otherwise unexplained, new, or out of pattern requires GI evaluation. Consider referral for GI evaluation.

BC colon cancer screening guidelines recommend that patients with signs or symptoms of colon cancer (e.g. unexplained GI bleeding, unexplained iron deficiency anemia) proceed directly to specialist referral for possible endoscopic investigation.[17, 18] If any doubt remains about whether to refer for GI investigations, referral is strongly encouraged due to the potentially severe consequences of delayed identification of colorectal cancer. Age-specific risk for colon and rectal cancer is elevated among those born circa 1990 compared to older cohorts.[19]

Overt GU bleeding

Consider referral to urologist for further work-up, especially for gross painless hematuria.

Unexplained iron deficiency/IDA

Adult males, post-menopausal females and pre-menopausal females with unexplained iron deficiency/IDA should receive:

- referral for GI investigations (upper/lower endoscopy)
- screening for GU bleeding with urinalysis
- screening for celiac disease

Management

The objective of treatment is to replenish iron stores: normalize hemoglobin levels and ferritin.[16] Target normal ferritin >100 µg/L.

Iron replacement therapy should begin as soon as iron deficiency is detected, whether or not anemia is also present.

The exception is: patients with microcytic anemia should not be given iron supplements until iron deficiency is confirmed by testing ferritin. Low MCV in the setting of normal ferritin may indicate hemoglobinopathies such as thalassemia. Long term iron therapy is harmful for these patients.

Individualize disease-specific management depending on underlying cause.[20] Even when there is an apparently obvious cause the etiology may be multifactorial.

Dietary iron intake

To help prevent iron deficiency, encourage all individuals to consume a diet with sufficient iron. This may include establishing individualized iron intake goals according to recommended daily intake based on sex, age, pregnancy status, and diet. Refer to Associated Documents for recommended daily intake values, and foods high in iron. Consider dietitian referral. Patients can also call 8-1-1 to speak to a dietitian.

Treatment with Oral Iron

Oral iron replacement is almost always preferred to intravenous (IV) therapy. Refer to *Appendix A: Oral Iron Formulations and Adult Doses* for a list of commonly used oral iron preparations, doses, and costs.

Advise patients that iron can be toxic to children and should always be safely stored.

Oral iron intolerance is very common:

- Oral iron preparations may cause nausea, vomiting, dyspepsia, constipation, diarrhea or dark stools.
- Strategies to minimize these effects include:[21]
  - o start at a lower dose and increase gradually after 4 to 5 days (to reach target dose in a few weeks)
  - o give divided doses
  - o give the lowest effective dose
  - o take supplements with meals (note: iron absorption is enhanced when supplements are taken on an empty stomach; however, tolerance and adherence may be improved when iron is taken with meals)
  - o try a different iron preparation
  - o try alternative dosing schedules such as every other day dosing[22] (resolution of symptoms and replenishment of iron stores may take longer)

Iron absorption can be decreased by various medications and supplements such as multivitamins, calcium, or antacid tablets. Space administration by at least 2 hours apart. Avoid taking iron supplements with tea, coffee or milk.

Iron absorption from iron salts can be enhanced by taking them on an empty stomach (at least 1 hour before or 2 hours after eating), or with 600–1200 mg vitamin C. This does not apply to other types of iron preparations such as polysaccharides or polypeptides whose absorption is not affected by food.

Monitoring Response to Oral Iron

1. The frequency of subsequent monitoring depends upon the severity of the anemia, the underlying cause of the iron deficiency, and the clinical impact on the patient. ***Reassess patients with moderate to severe anemia by testing CBC as early as 2–4 weeks. Hemoglobin should increase by 10-20 g/L by 4 weeks. It may take up to 6 months to replenish iron stores.***
2. Hemoglobin will correct within 2 to 4 months if appropriate iron dosages are taken as prescribed and underlying cause of iron deficiency is corrected.
3. Continue iron therapy an additional 4 to 6 months (adults) after correction of anemia to replenish the iron stores.[23] Ferritin should be re-checked 3 to 6 months after normalization of hemoglobin in anemic patients, or after initiation of iron supplementation in non-anemic patients. Target normal ferritin >100 µg/L.
4. If ferritin and hemoglobin are not responding as anticipated, consider adherence, ongoing bleeding, malabsorption, or alternate diagnosis.
5. If the patient's clinical status is compromised by moderate to severe anemia, consider blood transfusion. Once the patient is stable, iron replacement can commence.

IV Iron Therapy

IV iron should not be considered a routine treatment. Access to IV iron and the processes to order it depend on local availability and protocols. Refer to *Appendix B: Intravenous Iron Formulations and Adult Doses* for a list of commonly used parenteral iron formulations and doses.

Intravenous therapy may be initiated when there is:

- complete or partial failure of oral iron therapy trial (in compliant patients)
- intolerance to oral iron therapy
- inadequate iron absorption
- continued blood loss
- urgent surgery in an iron-deficient patient/pre-operative indication
- chronic kidney disease, including dialysis patients[24]

Maximum hemoglobin response to IV iron usually occurs within 2 to 3 weeks of the last dose.

Intramuscular (IM) Therapy

IM iron therapy is not generally recommended because risks include unpredictable absorption, anaphylaxis, and local complications (e.g., pain, permanent staining of the skin, sarcoma formation).[25] IM iron therapy may be appropriate in certain contexts and clinical judgment is required.

Iron supplementation: ongoing care

Once anemia has corrected and iron stores have normalized, a low maintenance dose may be prescribed if there is an ongoing need for additional iron (e.g., menorrhagia, rapid growth, regular blood donation, vegetarian diet). Consider similar supplementation for patients who have iron deficiency but not anemia. Ensure adequate dietary intake is established and maintained (refer to Associated Documents and consider dietitian referral; patients can also call 8-1-1 for dietitian services).

Iron Deficiency and IDA in Infants, Children and Adolescents

Iron deficiency and IDA in children are associated with motor and cognitive deficits which may be irreversible.[26]

Common causes and risk factors

- **All ages:** Increased requirements due to growth, low socioeconomic status, lack of balanced diet, (including ethnic groups with low iron high fibre/phytates diet e.g., Asians), celiac disease, bleeding from any source, e.g., frequent nosebleeds, GI diseases including short gut syndrome, cow's milk protein colitis
- **Infants < 6 months:** maternal iron deficiency, prematurity/low birth weight (low blood volume at birth, phlebotomy), feeding inappropriate milk substitutes other than breastmilk or commercial infant formula, history of fetal-maternal hemorrhage, history of twin-twin transfusion
- **Toddlers (6–36 months):** prematurity, exclusive breastfeeding beyond 6 months, cow's milk before 9 months, excessive cow's milk >750 mL/day, bottle use beyond 12–15 months, picky eating (insufficient intake or diversity of solid food), obesity[27]
- **Adolescents:** menorrhagia, disordered eating, vegetarian diet (refer to *Vegetarian and Vegan Diets* on page 9), extreme physical exercise/endurance athletes, low body weight

Signs and symptoms

- Some patients may be asymptomatic
- **All ages:** tiredness, restless legs, inattention, poor school performance, irritability/depression, growth retardation, unexplained cognitive and intellectual impairment, breath-holding spells, developmental delay, pica/pagophagia
- **Infants:** poor feeding, lethargy, failure to thrive, cardiomegaly, tachypnea
- **Adolescents:** presyncope, syncope, headache, irritability, fatigue, exercise intolerance, restless legs

Diagnosis

- Serum ferritin is the diagnostic test of choice for iron deficiency. The ferritin cut-offs for children are different from the ferritin cut-offs for adults. Refer to Table 2 for guidance on interpreting ferritin levels.
    - o Ferritin <12 ug/L is diagnostic of iron deficiency.
    - o Ferritin 12-20 ug/L indicates possible iron deficiency. Consider iron supplementation.
    - o Toddlers frequently have intercurrent viral infections that can falsely elevate ferritin.
    - o Ferritin >20 ug/L indicates normal iron stores in pre-pubertal children. The recommended ferritin cut-offs are lower for children compared to adults because children have not yet had sufficient time to build iron stores, and due to the iron demands of growing tissues.[28]

- Take a thorough dietary history:
  - **Infants < 6 months:** should consume breastmilk or formula. Animal milk (cow, goat, etc.) should not be consumed before 9–12 months.[29]
  - **Infants 6–9 months:** first foods should be iron-rich foods, offered at least twice a day.[29]
  - **Infants 0–12 months** who are not exclusively receiving breastmilk and are at risk of iron deficiency may benefit from formula with higher iron levels.
  - **Toddlers 12–24 months** should not consume more than 750 mL per day of cow's milk[30] because its volume can displace other iron rich foods.
  - Refer to BC Pediatric Nutrition Guidelines for more information on children age six months to six years.[29]
  - Refer to Associated Documents for age and sex-specific recommended daily iron intake and a list of iron-rich foods.

Treatment

- **Advise patients that iron can be toxic to children and should always be safely stored.**
- Provide dietary counselling. Dietitian referral is recommended. Patients and caregivers can also call a dietitian at 8-1-1. Refer to Associated Documents on page 11 for recommended dietary intake and a list of foods high in heme and non-heme iron.
- Recommend infants and toddlers with iron deficiency begin treatment with liquid oral iron salts. Refer to *Appendix B: Liquid Iron Formulations and Pediatric Doses* for recommended treatment doses, strengths and bottle sizes of liquid iron products for use in children, and guidance on tolerability.
- Blood transfusion is very rarely required for iron deficiency anemia in children because onset of anemia is gradual allowing for physiologic compensation and the response to iron supplementation is prompt. Judicious transfusion is indicated for very severe anemia in the setting of hemodynamic compromise/severe signs of anemia requiring emergent correction. In this case, transfused blood should be administered in small aliquots of 5 mL/kg over 4 hours with close monitoring, for prevention of fluid overload/cardiac failure.

Monitoring response

- Refer to adult Monitoring Response section for guidance.
- If hemoglobin is correcting by 4 weeks, continue oral iron and check CBC and ferritin at three months.

Iron Deficiency and Obstetrics

There is an increase in iron requirement (about 1000 mg total) during pregnancy, parturition and lactation.[31, 32]

Iron is essential for normal fetal development. It is important to prevent iron deficiency in the fetus by preventing iron deficiency in pregnant women.[33] Assess risk of iron deficiency among women planning pregnancy, especially women in high-risk groups (Table 1).

Iron supplementation for non-anemic pregnant women

Most pregnant women need to take a supplement to get enough iron.[34] An increase in iron consumption by about 15–30 mg elemental iron/day is recommended for non-anemic women, an amount readily met by most prenatal vitamin formulations. Health Canada recommends that pregnant women take a daily multivitamin that includes B12, 0.4mg of folic acid, and 16–20 mg of iron.[34]

IDA in pregnant women

IDA is the most frequent form of anemia in pregnant women. Refer to *Appendix A: Oral Iron Formulations and Adult Doses*. Anemia in pregnancy is defined as:[35–37]

- 1st trimester: hemoglobin < 110 g/L
- 2nd and 3rd trimester: hemoglobin < 105 g/L

Treatment with oral iron has been recommended when ferritin is less than 30 ug/L. Refer to Treatment with Oral Iron on page 6 for strategies to improve tolerance and compliance. Hemoglobin increase after two weeks indicates empirical confirmation of the diagnosis and response to treatment.[38] Ferritin decreases by approximately 50% in all pregnant women by the second trimester. This is a functional decrease that does not indicate iron deficiency.

If necessary, intravenous iron is considered to be safe for the second and third trimester (refer to *Appendix B: Intravenous Iron Formulations and Adult Doses*).[33]

Iron Deficiency in the Elderly

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. Iron deficiency is the second most common cause of anemia after anemia of chronic disease (the reverse is true for younger patients).

The diagnosis of absolute iron deficiency is challenging in the elderly.[39] Serum ferritin below 50 ug/L should be investigated for iron deficiency in the elderly[2] though cut-offs between 30 and 100 mg/L have been proposed.[39] Serum ferritin levels may also be increased by comorbidity.

Investigation of anemia in the elderly is recommended if the life expectancy is more than a year.[40] An individualised approach is recommended, recognizing the risks of invasive investigations and surgeries to elderly patients with increasing frailty and multimorbidity.[41]

Replacement options for elderly patients are similar to the options for younger patients. If standard dosing is not tolerated, low dose iron therapy (15 mg elemental iron per day, or 30 mg every other day) is an effective treatment in octogenarians, with significantly reduced adverse effects (refer to *Appendix A: Oral Iron Formulations and Adult Doses*).[42–44] Note: iron stores take longer to replete with lower iron doses. Refer to Treatment with Oral Iron on page 6 for strategies to improve tolerance and compliance. IV iron may also be considered in appropriate clinical situations as reviewed above (refer to *Appendix B: Intravenous Iron Formulations and Adult Doses*).

Vegetarian and Vegan Diets

Well-balanced vegetarian and vegan diets can provide sufficient iron intake for children, adolescents[45] and adults. Vegetarians require 1.8 times higher iron intake than non-vegetarians because non-heme iron is not absorbed as well as heme iron.[46] If uncertain, consider referral to a registered dietitian.

Refer to Resources section for information on getting enough dietary iron and choosing iron-rich foods, including patient handouts. Patients in BC can also phone a dietitian at 8-1-1.

Indications for specialist referral

- Failure of oral supplementation trial
- Suspected or overt GI/GU bleeding
- Moderate to severe anemia with unknown cause

Resources

References

1. Anemia Review Panel. Anemia Guidelines for Family Practice. 3rd ed. Toronto: MUMS Guideline Clearinghouse; 2014.
2. Kaushansky K, editor. Williams hematology. Ninth edition. New York: McGraw-Hill; 2016. 2 p.
3. US Preventive Services Task Force. Screening for iron deficiency anemia, including iron supplementations for children and pregnant women: recommendation statment. Am Fam Physician. 2006 Aug 1;74(3):461.
4. Cooper M, Greene-Finestone L, Lowell H, Levesque J, Robinson S. Iron sufficiency of Canadians. Health Rep. 2012 Dec;23(4):41–8.
5. Pottie K, Greenaway C, Feightner J, Welch V, Swinkels H, Rashid M, et al. Evidence-based clinical guidelines for immigrants and refugees. CMAJ. 2011 Sep 6;183(12):E824–925.
6. World Health Organization. The global prevalence of anaemia in 2011 [Internet]. WHO. 2015 [cited 2019 May 19]. Available from: http://www.who.int/entity/nutrition/publications/micronutrients/global_prevalence_anaemia_2011/en/index.html
7. Cook JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol. 2005 Jun;18(2):319–32.
8. Trotti LM, Becker LA. Iron for the treatment of restless legs syndrome. Cochrane Database Syst Rev. 2019 04;1:CD007834.
9. Winkelman JW, Armstrong MJ, Allen RP, Chaudhuri KR, Ondo W, Trenkwalder C, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2016 Dec 13;87(24):2585–93.
10. Ioannou GN, Spector J, Scott K, Rockey DC. Prospective evaluation of a clinical guideline for the diagnosis and management of iron deficiency anemia. Am J Med. 2002 Sep;113(4):281–7.
11. Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. Clin Chem. 1998 Jan;44(1):45–51.
12. Guidelines and Protocols Advisory Committee. HFE-Associated Hereditary Hemochromatosis Investigations and Management - Province of British Columbia [Internet]. 2013 [cited 2019 May 19]. Available from: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/iron-overload
13. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. Am J Hematol. 2017 Oct;92(10):1068–78.
14. KDIGO. Anemia in CKD [Internet]. Kidney Disease Improving Global Outcomes (KDIGO); 2012 [cited 2019 May 20]. Available from: https://kdigo.org/guidelines/anemia-in-ckd/
15. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol. 2017 Nov 1;33(11):1342–433.
16. Goddard AF, James MW, McIntyre AS, Scott BB, British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. Gut. 2011 Oct;60(10):1309–16.
17. BC Cancer Agency. Colon screening program fact sheet for health care providers [Internet]. BC Cancer; 2013 [cited 2019 May 19]. Available from: http://www.bccancer.bc.ca/screening/Documents/COLON_GuidelinesManual-HealthcareProvidersFactSheet.pdf
18. Guidelines and Protocols Advisory Committee. Colorectal Screening for Cancer Prevention in Asymptomatic Patients [Internet]. 2013 [cited 2019 May 19]. Available from: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/colorectal-cancer-screening
19. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974–2013. JNCI J Natl Cancer Inst [Internet]. 2017 Aug 1 [cited 2019 May 20];109(8). Available from: https://academic.oup.com/jnci/article/109/8/djw322/3053481
20. Clark SF. Iron deficiency anemia. Nutr Clin Pract Off Publ Am Soc Parenter Enter Nutr. 2008 May;23(2):128–41.
21. Canadian Pharmacists Association. Compendium of products for minor ailments [Internet]. c2016 [cited 2019 Feb 20]. Available from: http://www.myrxtx.ca
22. Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol. 2017 Nov;4(11):e524–33.
23. Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc [Internet]. Washington (DC): National Academies Press (US); 2001 [cited 2019 May 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK222310/
24. Rozen-Zvi B, Gafter-Gvili A, Paul M, Leibovici L, Shpilberg O, Gafter U. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis. Am J Kidney Dis Off J Natl Kidney Found. 2008 Nov;52(5):897–906.
25. Silverstein SB, Gilreath JA, Rodgers GM. Intravenous Iron Therapy: A Summary of Treatment Options and Review of Guidelines. J Pharm Pract. 2008 Dec 1;21(6):431–43.
26. Bhargava S, Meurer LN, Jamieson B, Hunter-Smith D. Clinical inquiries. What is appropriate management of iron deficiency for young children? J Fam Pract. 2006 Jul;55(7):629–30.
27. Hartfield D. Iron deficiency is a public health problem in Canadian infants and children. Paediatr Child Health. 2010 Jul;15(6):347–50.
28. Abdullah, Kawsari, Zlotkin, Stanley, Parkin, Patricia, Grenier, Danielle. Iron-deficiency anemia in children [Internet]. Canadian Pediatric Surveillance Program; 2011 [cited 2019 May 19]. Available from: https://www.cpsp.cps.ca/uploads/publications/RA-iron-deficiency-anemia.pdf
29. Provincial Health Services Authority, Province of British Columbia. Pediatric Nutrition Guidelines (Six Months to Six Years) for Health Professionals [Internet]. 2016 [cited 2019 Jan 7]. Available from: http://www.health.gov.bc.ca/library/publications/year/2017/pediatric-nutrition-guidelines.pdf
30. Canadian Pediatric Society. Nutrition for healthy term infants, six to 24 months: an overview [Internet]. [cited 2018 Oct 5]. Available from: https://www.cps.ca/en/documents/position/nutrition-healthy-term-infants-6-to-24-months
31. Bothwell TH. Iron requirements in pregnancy and strategies to meet them. Am J Clin Nutr. 2000;72(1 Suppl):257S-264S.
32. Reveiz L, Gyte GML, Cuervo LG. Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD003094.
33. Milman N. Prepartum anaemia: prevention and treatment. Ann Hematol. 2008 Dec;87(12):949–59.
34. Health Canada. Prenatal nutrition guidelines for health professionals: iron [Internet]. 2009 [cited 2018 Jul 9]. Available from: https://central.bac-lac.gc.ca/.item?id=H164-109-4-2009E&op=pdf&app=Library
35. Milman N, Bergholt T, Byg K-E, Eriksen L, Hvas A-M. Reference intervals for haematological variables during normal pregnancy and postpartum in 434 healthy Danish women. Eur J Haematol. 2007 Jul;79(1):39–46.
36. Chiossi G, Palomba S, Costantine MM, Falbo AI, Harirah HM, Saade GR, et al. Reference intervals for hemoglobin and hematocrit in a low-risk pregnancy cohort: implications of racial differences. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2018 Mar 23;1–8.
37. Lockitch, G. Handbook of diagnostic biochemistry and hematology in normal pregnancy. Boca Raton, Florida: CRC Press; 1993. 235 p.
38. Pavord S, Myers B, Robinson S, Allard S, Strong J, Oppenheimer C, et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol. 2012 Mar;156(5):588–600.
39. Camaschella C. Iron deficiency. Blood. 2019 Jan 3;133(1):30–9.
40. Balducci L. Epidemiology of anemia in the elderly: information on diagnostic evaluation. J Am Geriatr Soc. 2003 Mar;51(3 Suppl):S2-9.
41. Girelli, Domenico, Marchi, Giacomo, Camaschella, Clara. Anemia in the Elderly. HemaSphere. 2018 Jun;2(3):e40.

42. Gray, J., Canadian Pharmacists Association. Therapeutic choices. 5th ed. Ottawa, Ontario: Canadian Pharmacists Association; 2007.
43. Anemia Review Panel. Anemia Guidelines for Family Medicine. 2nd ed. Toronto: MUMS Guideline Clearinghouse; 2008.
44. Rimon E, Kagansky N, Kagansky M, Mechnick L, Mashiah T, Namir M, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med. 2005 Oct;118(10):1142–7.
45. Amit M. Vegetarian diets in children and adolescents. Paediatr Child Health. 2010;15(5):303–8.
46. Health Canada. Dietary Reference Intakes [Internet]. Government of Canada; 2005 [cited 2018 Aug 13]. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables/reference-values-elements-dietary-reference-intakes-tables-2005.html
47. Dipchand, A., Friedman, J., Bismilla, Z., Gupta, S., Lam, C. The Hospital for Sick Children - Handbook of Pediatrics. 11th ed. Toronto: Elsevier Canada; 2009.

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Appendices

- Appendix A: Oral Iron Formulations and Adult Doses
- Appendix B: Intravenous Iron Formulations and Adult Doses
- Appendix C: Algorithm for Investigation of Iron Deficiency in Non-Anemic Adults
- Appendix D: Liquid Iron Formulations and Pediatric Doses

Associated Documents

The following printable patient handouts are available in **eight languages**:

- HealthLink BC File 68c: Iron and Your Health (recommended daily dietary allowance by age, sex, pregnancy and breastfeeding status; vegetarian diets; advice on how to get the most iron from foods)
- HealthLinkBC File 68d: Iron in Foods (list of foods high in heme and non-heme iron)

Practitioner Resources

- Pathways – PathwaysBC.ca

  An online resource that allows authorized practitioners and their office staff to quickly access current and accurate referral information, including specialist wait times. Pathways also makes available hundreds of patient and physician resources that are categorized and searchable.

Patient and Caregiver Resources

- HealthLink BC
  - Patients and caregivers can call 8-1-1 to speak to a registered dietitian
  - Online resources on dietary iron for all ages are available at healthlinkbc.ca
- First Nations Health Authority
  - Guide to Your Baby's First Solid Foods: fnha.ca
  - Traditional Foods Fact Sheets: fnha.ca

List of Abbreviations

ACD	anemia of chronic disease
CBC	complete blood count
Fe	iron
GI	gastrointestinal
GU	genitourinary
ID	iron deficiency
IDA	iron deficiency anemia
IM	intramuscular
IV	intravenous
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
TSAT	transferrin saturation

This guideline is based on scientific evidence current as of January 2019.

The guideline was developed by the Guidelines and Protocols Advisory Committee in collaboration with BC's Agency for Pathology and Laboratory Medicine, and adopted by the Medical Services Commission.

THE GUIDELINES AND PROTOCOLS ADVISORY COMMITTEE

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

Appendix A: Oral Iron Formulations and Adult Doses

This Appendix is a supplement to the *BC Guideline Iron Deficiency – Investigation and Management*.

One iron preparation is not preferred over another; patient tolerance should be the guide. While polysaccharide and polypeptide formulations can be taken with food to reduce GI side effects, they are more expensive than the iron salt formulations and are not a PharmaCare benefit. Remind patients that products are kept behind the counter in the pharmacy and to see a pharmacist to confirm the product.

Adverse GI reactions (nausea, vomiting, dyspepsia, constipation, diarrhea, and dark stools) are dependent on the dose of elemental iron. These adverse reactions are temporary and will likely disappear with continued treatment, with the exception of dark stools which can remain for the duration of therapy.

Therapeutic doses can range from 100 to 200 mg of elemental iron/day,[21, 47] depending on severity of symptoms, ferritin levels, age of the patient, and GI side effects. If poor tolerability with oral iron, consider a lower dose, a different formulation or alternative dosing schedules (such as every other day dosing).[24] Resolution of symptoms and replenishment of iron stores may take longer.

Iron Product	Formulation (elemental iron)	Usual Adult Daily Dose	Therapeutic Considerations[42, 21 †]	Cost per 30 Days[‡] and Pharmacare Coverage
ferrous sulfate	Tablets 300 mg (60 mg Fe)	1 tablet BID-TID	• Needs acid in the stomach to get absorbed. • To increase absorption, take on an empty stomach — at least 1 hour before or 2 hours after eating, with 600–1200 mg vitamin C[51]. • Absorption may be decreased if taking antacids or medications that reduce stomach acid. § • To reduce adverse GI reactions with iron salts, start with a low dose and increase gradually after 4 to 5 days. If bothersome, take initially with food and gradually shift the timing away from meals to improve absorption. • Iron suspension formulations may stain teeth. This can be prevented by drinking through a straw or mixing with water or fruit juice.	$4–8 (Regular benefit)
	Suspension 30mg/mL (6 mg Fe/mL)	10 mL BID-TID		$ 20–35 (Regular benefit)
ferrous gluconate	Tablet 300 mg (35 mg Fe)	1–2 tablet BID-TID (Max 5 tablets/day)		$5–10 (Regular benefit)
ferrous fumarate	Capsule/Tablet 300 mg (100 mg Fe)	1 capsule OD-BID		$6–12 (Regular benefit)
	Suspension 60 mg/mL (20 mg Fe/mL)	5 mL OD-BID		$ 20–35 (Regular benefit)
	Tablet 200 mg (65.7 mg Fe)	1 tablet BID-TID		$6–10 (Non-benefit)
polysaccharide iron	Capsules 150mg (150 mg Fe)	1 capsule OD	• Taken with or without food. • Does not need acid in the stomach to get absorbed. Good choice if taking medications that reduce stomach acid. • Capsule can be opened and contents mixed into water or sprinkled over soft food. • Virtually tasteless.	$20-25 (Non-benefit)
	Powder 60 mg/teaspoon (60 mg Fe)	1 tsp BID-TID		$35–100 (Non-benefit)
heme iron polypeptide	11 mg heme Fe	1 tablet OD-TID	• More bioavailable than nonheme iron. • Taken with or without food. • Does not need acid in the stomach to get absorbed. Good choice if taking medicines that reduce stomach acid. • Contains animal (cow) products.	$20–80 (Non-benefit)

Abbreviations: BID twice daily; **Fe** elemental iron; **GI** gastrointestinal; **IV** intravenous; **IM** intramuscular; **mg** milligrams; **mL** milliliters; **PO** orally; **TID** three times daily.

† Treatment with oral iron may take as long as six to eight weeks in order to fully ameliorate the anemia, and as long as six months to replenish iron stores.

‡ Estimated retail prices as of January 2019 based on the adult dose range. All prices are subject to change. In most situations, oral iron products are least expensive when purchased over the counter. However, PharmaCare benefits may reduce the cost to the patient when a prescription is provided. PharmaCare coverage is subject to the patient's plan rules, including any deductible requirement. Patients can discuss with their pharmacist for more information.

§ Iron absorption may be decreased by antacids or supplements containing aluminum, magnesium, calcium, zinc, proton pump inhibitors, and histamine2 receptor antagonists.

Appendix B: Parenteral Iron Formulations and Adult Doses

This Appendix is a supplement to the *BC Guideline Iron Deficiency – Investigation and Management*.

Iron Product	Formulation (elemental iron)	Usual Adult Daily Dose	Adverse Reactions	Therapeutic Considerations**	Cost per 30 Days and PharmaCare Coverage††
iron sucrose	Injection (IV): 20 mg Fe/mL	100 to 300 mg IV intermittent per session, given as a total cumulative dose of 1000 mg over 14 days	CNS: headache, fever CVS: hypotension GI: metallic taste, nausea, vomiting MSK: muscular pain, cramps	• Hypotension may occur from rapid IV administration; doses greater than 300 mg associated with significant hypotension.	$405/1000mg (Non-benefit)
iron dextran complex	Injection (IV or IM): 50 mg Fe/mL	Based on body weight and hemoglobin; IV intermittent (maximum 1000 mg/day); or IM up to 100 mg Fe per site (maximum 250 mg/day)	CNS: fever MSK: arthralgia, myalgia	• A test dose of 25mg elemental iron (0.5 mL) must be given before administering the first therapeutic dose.[2] • Total dose depends on patient's weight and hemoglobin level.[2] • IM iron therapy is not recommended because risks include unpredictable absorption and local complications (e.g. pain, permanent staining of the skin).	$297/1000 mg (Regular benefit)
ferric gluconate complex	Injection (IV): 12.5 mg Fe/mL	125 mg (10 mL) IV per dose; up to 1000 mg over 8 sessions	CNS: generalized seizures CVS: hypotension, hypertension, vasodilation GI: diarrhea, nausea	• Indicated for treatment of iron-deficiency anemia in patients 6 years and older with chronic kidney disease undergoing hemodialysis in conjunction with supplemental erythropoietin therapy.	$460/1000 mg (Non-benefit)

Maximum hemoglobin response to IV iron usually occurs within 2 to 3 weeks of the last dose.

Abbreviations: BID twice daily; **CNS** central nervous system; **CVS** cardiovascular system; **Fe** elemental iron; **GI** gastrointestinal; **IV** intravenous; **IM** intramuscular; **max** maximum; **mg** milligrams; **mL** milliliters; **MSK** muscular skeletal.

Reference: Vancouver Coastal Health Pharmaceutical Sciences Clinical Services Unit. Iron Dextran and Iron Sucrose. Vancouver Coastal Health Parenteral Drug Manual. Vancouver British Columbia. Vancouver Coastal Health – 2008.

Iron Dextran dose: total dose (mg) required to restore hemoglobin (Hgb in g/L) to normal: 50 x (0.00442 [desired Hgb – observed Hgb] x LBW + [0.26 x LBW])
LBW in kg (male) = 50 kg + (2.3 x inches over 5 feet)
LBW in kg (female) = 45.5 kg + (2.3 x inches over 5 feet)

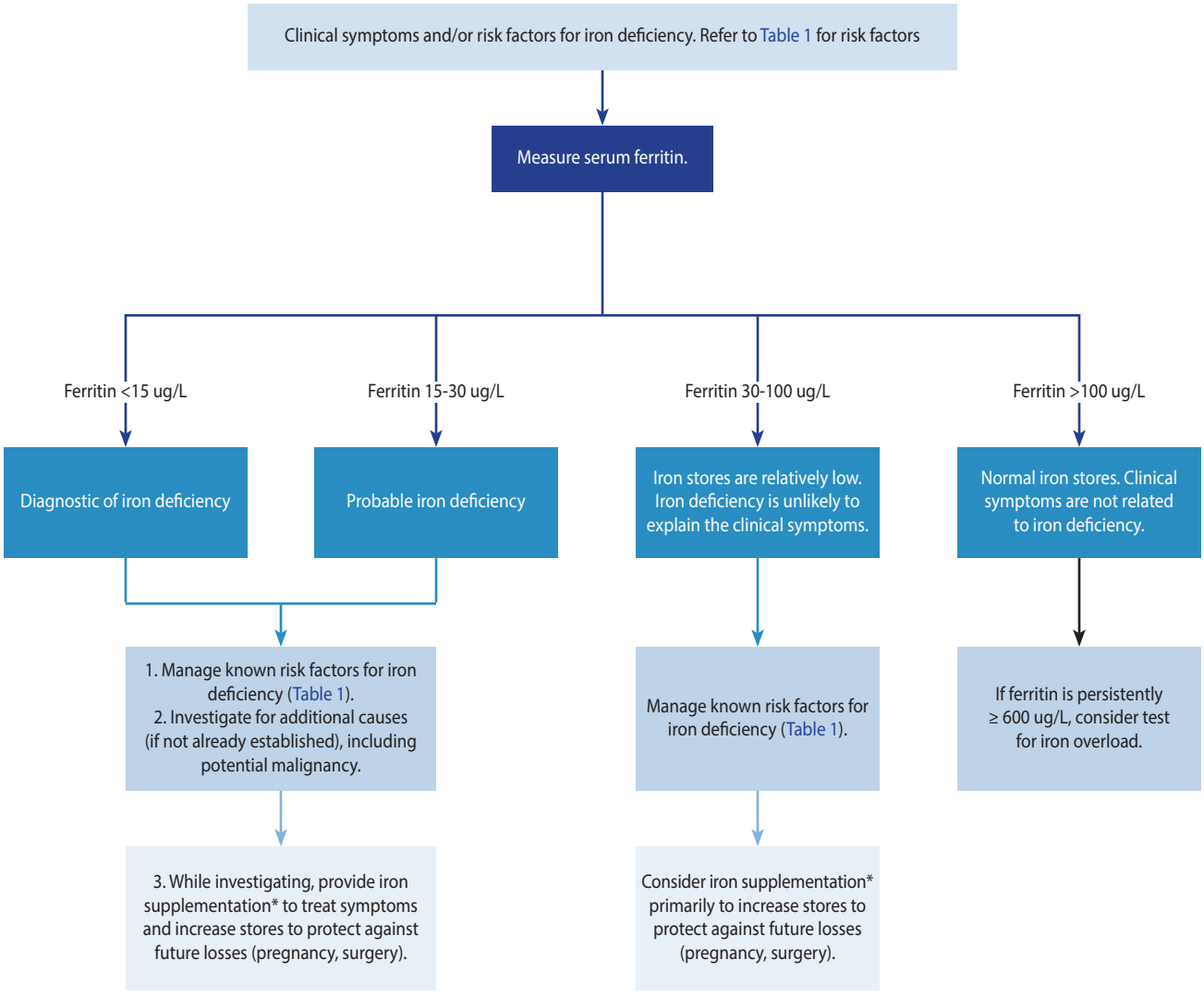
†† Prices are estimates as of January 2019 based on the maximum adult dose. All prices are subject to change.

Appendix C: Algorithm for investigation of iron deficiency in non-anemic adults

This Appendix is a supplement to the *BC Guideline Iron Deficiency – Investigation and Management*.

This algorithm does not address patients with active inflammation, infection or chronic conditions. Refer to page 4.

Ferritin values occur on a continuum. Cut-offs are suggested and clinical interpretation is required. The likelihood of iron deficiency increases with lower ferritin concentrations, including those that overlap with the normal reference interval. The normal reference interval is derived from healthy outpatients without signs of iron deficiency or chronic illness.



*Iron replacement therapy should begin as soon as iron deficiency is detected, whether or not anemia is also present. The exception is: patients with microcytic anemia should not be given iron supplements until iron deficiency is confirmed by testing ferritin. Low MCV in the setting of normal ferritin may indicate hemoglobinopathies such as thalassemia. Long term iron therapy is harmful for these patients.

Appendix D: Pediatric iron doses and liquid formulations

This Appendix is a supplement to the *BC Guideline Iron Deficiency – Investigation and Management*. Refer to page 7 for guidance on diagnosis, monitoring and treatment of iron deficiency and iron deficiency anemia in children.

- **Advise patients that iron can be toxic to children and should always be safely stored.**
- Provide dietary counselling. Dietitian referral is recommended. Patients and caregivers can call a dietitian at 8-1-1. Refer to Associated Documents for recommended dietary intake and a list of iron-rich foods.
- Recommend infants and toddlers with iron deficiency begin treatment with liquid oral iron.
- It is important to specify the strength (in mg elemental Fe/mL) in addition to dosing instructions (often in mL) to aid in selection of the intended product and prevent dosing errors. Remind patients that products are kept behind the counter in the pharmacy and to see a pharmacist to confirm the product.

Recommended treatment doses of elemental iron for infants and toddlers[32]

Age group	Dose	Daily maximum
Infants up to 12 months	Up to 3 mg of elemental Fe/kg/day (including iron from formula and other sources)	15 mg/day
Toddlers 12 months and over	3–6 mg elemental Fe/kg/day in either once a day or divided doses	60 mg/day

Pediatric liquid iron products

Iron Product	Formulation (elemental iron)	Available Package Sizes	Therapeutic Considerations[21, 42]	Cost per 30 Days and Pharmacare Coverage‡‡
ferrous sulfate	Suspension 30mg/mL (6 mg Fe/mL)	250, 500 mL bottles	• Liquid iron formulations may stain teeth. This can be prevented by drinking through a straw or mixing with water or fruit juice. • For optimal absorption, iron salts (ferrous sulfate or fumarate) should be taken on an empty stomach with water or juice, and not with dairy. • To reduce adverse GI reactions with iron salts, start with a low dose and increase gradually after 4 to 5 days. If bothersome, take initially with food and gradually shift the timing away from meals to improve absorption.	$4/500 mg Fe (Regular benefit)
	Drops 75mg/mL (15 mg Fe/mL)	50 mL bottles		$7/500 mg Fe (Regular benefit)
ferrous fumarate	Suspension 60 mg/mL (20 mg Fe/mL)	100 mL bottles		$3/500 mg Fe (Regular benefit)

- Adverse GI reactions (nausea, vomiting, dyspepsia, constipation, diarrhea, and dark stools) are dependent on the dose of elemental iron. These adverse reactions are temporary and will likely disappear with continued treatment, with the exception of dark stools which can remain for the duration of therapy. If poor tolerability with oral iron, consider a lower dose, a different formulation or alternative dosing schedules (such as every other day dosing).[22] Resolution of symptoms and replenishment of iron stores may take longer.

‡‡ Prices are estimates as of January 2019. All prices are subject to change.