Investigation and Management of Iron Deficiency
Revised 2004

Scope

This guideline provides recommendations for the investigation and management of iron deficiency in patients of all ages. Iron deficiency may be an indication of an underlying disorder, which should always be identified and managed. A summary of this document in flow chart format appears in Appendix 1.

RECOMMENDATION 1: Screening

Screening of the general population for iron deficiency is not recommended.

RECOMMENDATION 2: Primary prevention

a) Encourage all individuals to consume a diet with sufficient iron to prevent iron deficiency (see Appendix 4 and insert: Iron content of various foods).
b) Individuals who are at risk of developing iron deficiency because of physiological, nutritional or social factors should be counselled regarding their risk factors and encouraged to consume adequate dietary iron. Populations that have an increased risk include infants, toddlers, adolescents, menstruating, pregnant or lactating women, vegetarians, regular blood donors, certain post operative patients, patients with chronic renal failure, as well as certain ethnic groups like First Nations and Indo-Canadians (Appendix 2).

Note: Primary prevention strategies must not preclude appropriate investigation and treatment of known iron-deficiency or iron-deficiency anemia.

RECOMMENDATION 3: Assessment of possible iron deficiency

Clinical assessment: Identification of patients at risk of iron deficiency should be based upon a directed history (dietary, social, demographic, cultural, physiological factors as well as other conditions like neoplasms, medications, GI disease etc – see Appendix 2 for common causes), review of symptoms, and physical examination.

Diagnosis of iron deficiency: Laboratory investigation of iron deficiency should be based on clinical suspicion, not on presence of anemia. In the early stages, iron deficiency can exist without overt anemia, but with non-hematological symptoms (see Rationale).

- Serum ferritin is the best diagnostic test for iron deficiency. A ferritin concentration below 15 µg/L for adults and 12 µg/L for children indicates iron deficiency. These cutoffs include most cases of iron deficiency, however, deficiencies can occur in the low normal range.
• Ferritin measurements may be unreliable in patients with concurrent acute or chronic inflammation, malignancy, hepatic or kidney disease. Patients with persistently elevated serum ferritin levels, without chronic inflammatory disorder should be tested for iron overload (See separate guideline: Investigation and Management of Iron Overload).

• Serum iron and transferrin saturation (iron and iron binding capacity) should only be measured when the ferritin values are reported as normal or high in the face of clinically suspicious iron deficiency, or in patients with kidney failure.

• A hematology profile can suggest iron deficiency. It is not the diagnostic test of choice, but is required to assess the severity of anemia. A constellation of the following findings is highly suggestive of iron deficiency: microcytic, hypochromic anemia and mild thrombocytosis.

• Monitored trial of iron: In patients with anemia, likely resulting from iron deficiency due to an obvious cause, a monitored trial of iron therapy may be both diagnostic and therapeutic. Oral iron preparations are given at a dose of 180 mg elemental iron per day for adults and 6 mg elemental iron per kg per day for children. A rise in hemoglobin of 10-20 g/L in 2-4 weeks supports the diagnosis of iron deficiency.

**Recommendation 4:** The cause of iron deficiency must be determined

Iron deficiency is often multifactorial (Appendix 2) and even in patients with an obvious cause of iron deficiency, the possibility of another serious underlying cause like colon cancer must be considered.

**Recommendation 5:** Treatment of iron deficiency

Patients with iron deficiency should receive dietary advice, as well as iron supplementation. Although iron replacement therapy may begin as soon as iron deficiency is detected, *it is essential to determine and correct the underlying causes of iron deficiency.*

• **Iron therapy:** (Appendix 3) should be given for all patients with iron deficiency anemia. A rise in hemoglobin should be observed by two weeks. The anemia should be corrected within 2-4 months if appropriate doses of iron are administered and the underlying cause of iron deficiency is corrected. Therapy should continue for an additional 4 to 6 months to replenish iron stores.

  Response to iron replacement should be monitored initially at two to four weeks. The frequency of subsequent monitoring depends upon the severity of the anemia and the clinical impact upon the patient.

  *If the patient’s clinical status is compromised, admission to an acute care facility and blood transfusion must be considered.* Once the patient is stable, iron replacement can be commenced.

• **Iron supplementation:** Once the anemia has been corrected and iron stores have normalized, a low maintenance dose may be prescribed if there is an ongoing need for additional iron e.g. heavy periods or growth spurt. Dietary modification may also be considered. Similar supplementation may be considered for iron deficient but not anemic patients.

  Note: Caution should be exercised in recommending long-term iron supplements for patients at risk of iron overload. (Refer to guideline on Investigation and Management of Iron Overload)

A schematic diagram of evaluation and management of iron deficiency is provided in Appendix 1.
Rationale:

Iron is an important constituent of hemoglobin, myoglobin, and many iron-containing enzymes critical to cellular metabolism.\(^1\) Iron intake and its absorption vary markedly, depending on dietary and environmental factors. Dietary aspects of iron are described in Appendix 4.

Iron deficiency is the most common single nutritional deficiency,\(^2\) affecting mainly older infants, young children,\(^3\) adolescents\(^4\) and pre-menopausal women. Iron deficiency may develop from inadequate dietary intake, increased demand for iron, impaired iron absorption, or iron loss (Appendix 2). Breastfed infants receive enough iron from breast milk for the first four to six months after birth. Thereafter, infants become increasingly vulnerable to iron deficiency. In one study, seven per cent of otherwise healthy nine month old infants in Vancouver were iron deficient.\(^5\) Breast milk, cow's milk and low-iron formula are poor sources of iron and contribute to anemia in this population.\(^6\) Certain ethnic groups e.g. First Nations and Indo-Canadians have much higher incidence of iron deficiency, primarily due to dietary deficiency. In adolescents, rapid growth and menarche impose additional strain on iron stores. The situation is worse in vegetarian adolescent girls.\(^7,8\)

Premenopausal women are in the demographic group that is most vulnerable to iron deficiency. Iron deficiency occurs in about 25% of pre-menopausal women due to the increased iron loss from menstruation.\(^9\) The increased requirements for iron during pregnancy and lactation\(^10\) also increase the risk of iron deficiency in this group. 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 2/3 of the iron deficient patients.\(^11,12\) An upper GI source (peptic ulcer, use of aspirin and NSAIDs,\(^13\) gastritis or esophagitis) is found in 21-41%, a colonic source is found in 13-34% and the remainder will not have an identifiable source of bleeding.\(^14\) Iron deficiency anemia is more prevalent in isolated First Nations communities. Intervention by means of supplementation and education can be effective.\(^15\) Recent studies have shown that the incidence of anemia in two-year old children\(^3\) and teenage girls\(^7\) of South Asian origin is more than double that of the white population.

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,\(^6\) developmental delay, cognitive and intellectual impairment,\(^4,6\) adverse pregnancy outcome, and impaired immune function.\(^1\)

The laboratory features of iron deficiency\(^16\) include a constellation of findings in the hematology profile (microcytic, hypochromic anemia with anisocytosis, poikilocytosis, and mild thrombocytosis), and reduced iron measurements (ferritin, iron and transferrin saturation). Similar findings except for low iron may be present in patients with hemoglobinopathies e.g. thalassemia, and should be excluded as clinically appropriate.

Reduced ferritin is the most useful indicator of iron deficiency. Serum ferritin is an acute phase reactant, and its concentration is increased in the presence of infections, systemic inflammations, malignancies, hepatopathies, and chronic renal failure.\(^17\) Thus, while a low serum ferritin is diagnostic of iron deficiency, normal serum ferritin values do not exclude a deficiency state, and other tests like serum iron and transferrin saturation may be indicated. In some cases, a monitored trial of iron therapy may be given. An increase in hemoglobin of 10-20 g/L in 2-4 weeks \(^2,16\) is diagnostic of iron deficiency. Newer tests (free erythrocyte protoporphyrin, serum free transferrin receptor and others), that are unaffected by concurrent diseases are being investigated. They are not yet available in most diagnostic facilities.

Management of iron deficiency includes two concurrent components: the correction of iron deficiency and the determination and treatment of the underlying disorder that exhausted the iron stores.
The correction of iron deficiency involves an appropriate diet and iron supplementation. Several iron preparations are available (Appendix 3), which vary in their degree of absorption, side effects and cost. Dietary management plays a crucial role, both in prevention of iron deficiency, and in the management of early iron deficiency. Diet modifications include: more iron-rich foods and positive modification of the factors influencing iron absorption (Appendix 4 and insert). More information can be obtained by calling the Dial-a-Dietitian in British Columbia, at 604 732-9191. 

Web site: http://www.dialadietitian.org/nutrition/VitaminsMinerals38.html

APPENDIX 1: Evaluation and Management of Suspected Iron Deficiency

**Recommendation 1:**
Screening of general population is not recommended
- Ascertain the Risk Factors
- Review of Systems
- Physical Exam

**Recommendation 2:**
Primary Prevention
Encourage a diet rich in iron
Iron supplements, if necessary

**Recommendation 3:**
Diagnosis of Iron Deficiency
- **Serum Ferritin**
  - Hematology profile (if needed)
  - Iron and transferrin saturation, monitored trial of iron therapy (certain cases only)

**Recommendation 4:**
Determine etiology
Appropriate investigation to determine the etiology of iron deficiency/anemia

**Recommendation 5:**
Dietary advice and iron supplementation
If the patient’s clinical status is compromised due to anemia, admission to an acute care facility and blood transfusion must be considered. Once the patient is stable, iron replacement can be commenced.
APPENDIX 2: Common causes of iron deficiency

Physiologic/Demographic factors predisposing to iron deficiency (Recommendation  2)

1. Infants / toddlers – prematurity, low birth weight, exclusive breast feeding without iron supplementation for > 6 months, delayed introduction of solids, excessive cow’s milk intake (> 750 mL/d), low socio-economic status
2. Adolescents - poor dietary habits/inadequate diet, under-weight, menstruation, rapid growth
3. Menstruating women (especially menorrhagia)
4. Pregnant or lactating women
5. Vegetarians (especially vegans)
6. Endurance runners
7. Regular blood donors (especially women in their reproductive years)
8. Post-operative patients with significant blood loss
9. Chronic renal failure patients
10. High risk ethnic groups – First Nations, Indo-Canadians

Pathologic causes of iron deficiency (Recommendations  3 and 4)

1. Low intake or absorption – achlorhydria, gastric surgery, celiac disease, Crohn’s disease
2. Blood loss – excessive menstrual flow, GI neoplasms, other neoplasms (genitourinary, pulmonary), ulcerative colitis/IBD, peptic ulcer, hemorrhoids, salicylate/NSAID use, hiatal hernia, diverticulosis, other neoplasms

APPENDIX 3: Iron replacement regimes

Oral is preferred to parenteral therapy. Parenteral therapy may be used if oral therapy has failed or oral therapy is not tolerated. Absorption of oral iron is better on an empty stomach and with acid drinks (juice). Ascorbic acid, either from foods, or taken as tablets, enhances absorption of iron supplements. Iron therapy should continue for 4 to 6 months or until the serum ferritin reaches 50 µg/L.

Iron preparations: Ferrous salts, sulphate, gluconate and fumarate are commonly used. The sulphate and fumarate forms are absorbed at the same rate; however, sulfate forms have a higher incidence of side effects. Ferrous sulphate is least expensive, and is recommended in the first instance.

- Ferrous sulphate – tablet 300 mg (60 mg elemental Fe)
  - Suspension 30 mg (6 mg elemental Fe) per ml
  - Dropper suspension 75 mg (15 mg elemental Fe) per ml
- Ferrous gluconate – tablet 300 mg (35 mg elemental Fe)
  - Suspension 60 mg (7 mg elemental Fe) per ml
- Ferrous fumarate – tablet 300 mg (90 mg elemental Fe)
  - Suspension 20 mg elemental Fe per ml

Some preparations are made more palatable (concentrations as above):

- Palafer (fumarate) – cherry flavor
- Ferodan (sulphate) – aromatic fruity flavor
- PMS ferrous sulphate drops – peppermint flavor
- PMS ferrous sulphate suspension – lime flavor
**Dosage: Pediatric**

1. Supplemental iron for premature babies fed on mother’s milk: 3 mg elemental iron/kg/day up to a maximum of 6 mg/kg/day (up to 15 mg/kg/day if anemic) (Children’s & Women’s Health Centre of B.C.).
2. Supplemental iron for children older than 6 months: 1-2 mg elemental iron/kg /day
3. Therapeutic doses for children are 3-6 mg elemental iron/kg/day.

Note: 1. Liquid iron preparations could stain a child’s teeth. Therefore, it is recommended that liquid iron preparations be administered by a dropper to the back of the mouth, and that the mouth is rinsed thoroughly with juice or water after the dose is given.
   2. All iron preparations should be stored in childproof containers, and kept out of reach of children to avoid iron poisoning.

**Dosage: Adult** Doses equivalent to 180 mg elemental iron/day:
- Ferrous sulphate 300 mg- 3 tablets/day
- Ferrous gluconate 300 mg- 5 tablets/day
- Ferrous fumarate 300 mg – 2 tablets/day

**Side effects:** Iron ‘allergy’ is extremely rare. However, iron intolerance is common. Common side effects include GI upset, constipation and occasionally diarrhea. Side effects may be minimized by several strategies:
- Start at a low dose and increase gradually
- Give in divided doses 2-3 times/day
- Give the lowest effective daily dose
- Give iron with meals
- Give organic iron salts e.g. fumarate
- Give iron at night
- Use alternate route e.g. parenteral

**APPENDIX 4: Dietary Aspects of Iron** (see insert: Iron content of various foods)

Foods contain iron in two forms: “Heme” iron is present in red meat, fish and poultry. “Heme” iron is highly bioavailable (15-35% absorption), and its absorption is independent of other factors present in food. Non-heme iron is present in fruits, vegetables, cereals and dairy products etc. It is absorbed to a lesser extent (2-4%) than the heme form and its absorption is markedly affected by other factors. Factors that inhibit iron absorption include decreased gastric acidity, H. 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 iron absorption are: presence of meat, citrus juices, vitamin C (e.g. from broccoli, strawberries, tomato, spinach, citrus fruit), and EDTA fortification of foods.

**Daily Reference Intake (DRI) for Iron (mg)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>6-12 months</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>1-3 years</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>4-8 years</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>9-13 years</td>
<td>8</td>
<td>8</td>
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<tr>
<td>14-18 years</td>
<td>11</td>
<td>15</td>
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<tr>
<td>19-49 years</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Over 50 years</td>
<td>8</td>
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</tr>
</tbody>
</table>

Pregnancy: 27 mg/day.
Breastfeeding mothers: 10 mg/day (19-50y) or 9 mg/day if under 19 years.
References

Sponsors

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.

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Effective Date: October 1, 2004

This guideline is based on scientific evidence current as of the effective date.

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The principles of the Guidelines and Protocols Advisory Committee are:
• to encourage appropriate responses to common medical situations
• to recommend actions that are sufficient and efficient, neither excessive nor deficient
• to permit exceptions when justified by clinical circumstances.
### Iron content of various foods*

<table>
<thead>
<tr>
<th>Fruits</th>
<th>One Serving</th>
<th>Amount of iron (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currants, dried</td>
<td>½ cup</td>
<td>0.86</td>
</tr>
<tr>
<td>Raisins, dried</td>
<td>½ cup</td>
<td>0.89</td>
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<table>
<thead>
<tr>
<th>Nuts</th>
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</thead>
<tbody>
<tr>
<td>Almonds</td>
<td>1 oz</td>
<td>1.08</td>
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<tr>
<td>Peanuts</td>
<td>1 oz</td>
<td>0.63</td>
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<table>
<thead>
<tr>
<th>Vegetables</th>
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</thead>
<tbody>
<tr>
<td>Beans, green snap, cooked</td>
<td>1 cup</td>
<td>1.60</td>
</tr>
<tr>
<td>Broccoli, cooked</td>
<td>½ cup</td>
<td>0.65</td>
</tr>
<tr>
<td>Chickpeas, cooked</td>
<td>1 cup</td>
<td>4.74</td>
</tr>
<tr>
<td>Corn, cooked</td>
<td>1 cup</td>
<td>0.50</td>
</tr>
<tr>
<td>Lentils, cooked</td>
<td>1 cup</td>
<td>3.59</td>
</tr>
<tr>
<td>Soybeans, cooked</td>
<td>1 cup</td>
<td>8.84</td>
</tr>
<tr>
<td>Peas, cooked</td>
<td>1 cup</td>
<td>2.48</td>
</tr>
<tr>
<td>Potato, average sized, baked with skin</td>
<td>1</td>
<td>2.75</td>
</tr>
<tr>
<td>Potato, average sized, baked without skin</td>
<td>1</td>
<td>0.55</td>
</tr>
<tr>
<td>Spinach, raw</td>
<td>1 cup</td>
<td>1.52</td>
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<table>
<thead>
<tr>
<th>Grains and Cereals</th>
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</thead>
<tbody>
<tr>
<td>Bran muffin</td>
<td>1.5 oz</td>
<td>1.26</td>
</tr>
<tr>
<td>Blueberry muffin</td>
<td>1.5 oz</td>
<td>0.60</td>
</tr>
<tr>
<td>English muffin</td>
<td>2 oz</td>
<td>1.61</td>
</tr>
<tr>
<td>Macaroni, enriched, cooked</td>
<td>1 cup</td>
<td>1.96</td>
</tr>
<tr>
<td>Spaghetti, enriched, cooked</td>
<td>1 cup</td>
<td>1.96</td>
</tr>
<tr>
<td>White rice, enriched</td>
<td>1 cup</td>
<td>1.97</td>
</tr>
<tr>
<td>Brown rice</td>
<td>1 cup</td>
<td>0.86</td>
</tr>
<tr>
<td>White bread, enriched flour</td>
<td>1 slice</td>
<td>0.68</td>
</tr>
<tr>
<td>Whole-wheat bread</td>
<td>1 slice</td>
<td>0.86</td>
</tr>
<tr>
<td>Breakfast cereals, e.g. cornflakes</td>
<td>1 cup</td>
<td>1.80</td>
</tr>
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<table>
<thead>
<tr>
<th>Meats, Poultry, Fish, Eggs, Dairy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef, ground, cooked</td>
<td>3.5 oz</td>
<td>2.66</td>
</tr>
<tr>
<td>Lamb, roast</td>
<td>3.5 oz</td>
<td>2.12</td>
</tr>
<tr>
<td>Ham, roast</td>
<td>3.5 oz</td>
<td>1.48</td>
</tr>
<tr>
<td>Hot dog, beef</td>
<td>1</td>
<td>0.81</td>
</tr>
<tr>
<td>Chicken, roast</td>
<td>3.5 oz</td>
<td>0.67</td>
</tr>
<tr>
<td>Turkey, roast</td>
<td>3.5 oz</td>
<td>1.10</td>
</tr>
<tr>
<td>Mussels</td>
<td>3 oz</td>
<td>5.71</td>
</tr>
<tr>
<td>Salmon</td>
<td>3.5 oz</td>
<td>0.84</td>
</tr>
<tr>
<td>Shrimp</td>
<td>3 oz</td>
<td>2.62</td>
</tr>
<tr>
<td>Tuna, canned, drained</td>
<td>3 oz</td>
<td>0.51</td>
</tr>
<tr>
<td>Egg</td>
<td>1 large</td>
<td>0.60</td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>1 cup</td>
<td>0.10</td>
</tr>
<tr>
<td>Infant formula-iron fortified</td>
<td>1 cup</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*Iron from meat, poultry and fish has higher bioavailability than iron from vegetable, cereals, fruits, dairy products.

Note: For conversion to metric units 1 oz=30 g and 1 cup=250 mL