IRON DEFICIENCY ANEMIA (IDA)

Clinical Practice Guideline | March 2018

OBJECTIVE

Alberta clinicians (specifically primary care and emergency department physicians) will be able to diagnose iron deficiency anemia (IDA), treat using oral and parenteral iron supplementation and provide ongoing management; will understand why red blood cell transfusion (RBC) may be harmful and is only occasionally required for the treatment of IDA.

TARGET POPULATION

Patients ≥5 years of age, hemodynamically stable, seen in emergency departments and primary care settings

EXCLUSIONS

Patients <5 years of age, all patients who are hemodynamically unstable, chronic kidney disease, rare genetic causes of and treatment of IDA, other types of iron deficiency, and the pre-latent stage of iron deficiency

RECOMMENDATIONS

ASSESSMENT

INVESTIGATION FOR IDA

- ✓ Identify patients at risk for iron deficiency anemia

Table 1: Possible Features, Signs and Symptoms of IDA

ADULTS AND ADOLESCENTS
• Anticipated ongoing bleeding (e.g., menstruation, gastrointestinal) • Head and neck manifestations including pallor (e.g., facial, conjunctival or palmar), blue sclerae, atrophic glossitis or loss of tongue papillae, angular cheilitis, alopecia • Koilonychia (spoon nails) • Restless leg syndrome • Fatigue, shortness of breath, chest pain, lightheaded, syncope weakness, headache • Irritability and/or depression • Pica (craving/consumption of non-food substances e.g., dirt, clay, chalk) and pagophagia (ice craving) • Decreased exercise tolerance • Regular blood donors, particularly females donating more than twice a year and males donating more than three or four times a year
SCHOOL-AGED CHILDREN (e.g., >5 to <18 years old)
• Tiredness, restlessness, irritability • Pica and pagophagia • Growth retardation • Cognitive and intellectual impairment • Signs of attention-deficit/hyperactivity disorder (ADHD) • Breath-holding spells

PRACTICE POINT

Investigating the underlying cause of IDA is as important as treating the IDA.

Table 2: Common and/or Possible Causes of IDA

INCREASED REQUIREMENT	DECREASED INTAKE
Rapid growth (infants and adolescents) Menstruation Pregnancy (second and third trimesters) Lactation	Low SES, malnutrition Diet (e.g., vegetarian, vegan, iron poor) Elderly Alcoholism
INCREASED LOSS	**DECREASED ABSORPTION**
Gastrointestinal • Esophagitis • Erosive gastritis • Peptic ulcer • Inflammatory bowel disease (IBD) e.g., ulcerative colitis, Crohn's disease* • Benign tumors • Intestinal/stomach cancer • Angiodysplasia • Hemorrhoids • Hookworm infestation • Occult blood loss secondary to cow's milk protein-induced colitis • Chronic or high dose use of salicylates or NSAIDs Genitourinary • Menorrhagia • Chronic hematuria Hemolysis • Intravascular hemolysis Other • Regular blood donors • Frequent epistaxis • Hemorrhagic telangiectasia (rare)	Dietary factors (carbonated drinks, coffee, etc.) Gastrointestinal • Gastrectomy • Duodenal bypass • Bariatric surgery • Helicobacter pylori • Celiac disease • Atrophic gastritis • Pediatric short bowel syndrome • Inflammatory bowel disease (IBD) e.g., ulcerative colitis, Crohn's disease* • Chronic kidney disease
**Inflammatory conditions may be associated with iron deficiency due to poor iron absorption and anemia of chronic inflammation.*	

DIAGNOSIS

PRACTICE POINT

The recommended laboratory tests and cut-off values take into account the available evidence on benefits and limitations of tests and cut-off values for detecting IDA. The aim is to provide the most effective and simplified approach to detecting IDA in the primary care setting.

- ✓ Order complete blood count (CBC) and serum ferritin when IDA is suspected.
- ✓ Add serum iron, total iron binding capacity and transferrin saturation <18 years old.
- ✓ Findings and interpretation as follows:

Table 3: Lab Tests and Respective Cut-off Values for Detection of IDA†

TEST AND CUT-OFF VALUES	
Hemoglobin (Hb) <120 g/L females (>11 years old) <135 g/L males (>14 years of age) <125 g/L females (12-14 years old) <115 g/L males (<12 years old)	
PLUS ONE OR BOTH OF:	**IMPORTANT CONSIDERATIONS/CAVEATS OF THESE ADDITIONAL TEST RESULTS**
Mean Corpuscular Volume (MCV) <75 fl	✓ A decrease reflects advanced stage of iron deficiency. ✓ Patients with iron deficiency anemia may present with a normal MCV therefore correlation with serum ferritin is required. ✓ Other common causes of low MCV include: o Thalassemia trait: Hb is typically lower limit of normal and profound anemia is not present o Anemia of inflammation: MCV is rarely <75
Ferritin <30 µg/L male <13 µg/L female <10 µg/L male and female (<12 years old)	✓ Gold standard test for diagnosing iron deficiency ✓ Provides an indication of total body iron stores, but has limitations as it is an acute phase reactant and may be unreliable in patients with chronic disease or cancer. ✓ In the setting of an inflammatory process, serum ferritin <100 suggestive of iron deficiency. However, an upper limit, beyond which patients will not respond to iron replacement therapy, has not been established.
†Lab cut-offs are specific to detecting IDA only. These values should not be used to diagnose patients with iron depletion or other conditions. These reference levels vary slightly depending on source. Use actual reference ranges, cut-off values, critical results as indicated by your local lab service provider.	

PRACTICE POINT

Iron deficiency in adult men and postmenopausal women is most likely to have a serious underlying cause of blood loss and must be investigated.

If patients are experiencing ongoing blood loss (either through menstrual bleeding or non-physiological but unavoidable bleeding such as intestinal angiodysplasia) and they have a low ferritin, iron replacement should be initiated as they will eventually become anemic.

- ✓ Investigate the cause(s) of an IDA diagnosis

Table 4: Cause and Actions

CAUSE:	ACTION:
Overt blood loss gastrointestinal (GI)	✓ Refer for upper and lower GI investigations.
Confirmed IDA but no overt blood loss or history of GI	✓ Refer for upper and lower GI investigations: all premenopausal women and/or women with hysterectomy <50 years of age with GI symptoms; all postmenopausal females and all males with/without GI symptoms. ✓ Screen for celiac disease in all patients. X DO NOT use fecal blood testing (i.e., FIT) – it is of no benefit in the investigation of IDA. *NOTE: Contrast X-rays alone are not adequate investigations given many relevant GI conditions could be missed.*
Frequent blood donors	✓ Stop donation until iron stores return to normal. ✓ Encourage donation at reduced frequency. ✓ Recheck to ensure iron deficiency is corrected or if not corrected investigate further.
No overt blood loss	✓ Those with signs or symptoms specific to a system e.g., bleeding from gastroenterological, gynecological, urological source should be referred to the appropriate specialty. ✓ Consider screening for von Willebrand's in women and adolescents with menorrhagia. ✓ Investigate for hematuria. If present, consistently or intermittently, additional investigation should follow for: o RBC in the urine indicative of GU bleeding o Hemoglobinura (positive dipstick without RBC on micro) could be indicative of hemolysis

MANAGEMENT

TREATMENT

- ✓ Treat all IDA patients that are hemodynamically stable, regardless of the presence of symptoms, with oral and/or intravenous iron supplementation and provide general information regarding an iron-rich diet refer to https://myhealth.alberta.ca/health/pages/conditions.aspx?hwid=ue4500&4500-sec.
- ✓ See treatment algorithm (Appendix A).
- ✓ See Table 8 (Appendix B) for a review of considerations when selecting an oral iron product.
- ✓ See Table 9 (Appendix C) for a review of considerations when selecting an IV iron product.

MONITORING

- ✓ Order a CBC and reticulocytes at two to four weeks to see if the patient is responding to replacement regimen. See Optimizing Oral Iron Dosage (Appendix B).
- ✓ Indicators of response to (i.e., targets for) iron therapy include:
  - Reticulocytosis in four days
  - Increasing hemoglobin >10g/L in four weeks
- ✓ Correction of IDA should be observed within two to four months if appropriate iron dosages are administered and underlying cause of iron deficiency is addressed.

Table 5: Monitoring Algorithm

IF PATIENT IS RESPONDING TO THERAPY	IF PATIENT IS NOT RESPONDING TO THERAPY:
✓ Continue to monitor hemoglobin and Ferritin monthly/bimonthly to ensure levels remain within the normal range. ✓ For school-aged children, treat for 3-4 months then stop as long as all parameters have normalized (CBC, ferritin and iron studies).	✓ Reassess iron dosage, and ensure underlying cause has been addressed.
✓ Continue with iron supplementation for an additional 4-6 months (all patients) until Hgb/MCV and Ferritin normalize and to replenish iron stores.	✓ If prescribed oral iron, rule out cause of poor response. If the cause is non-adherence and hemoglobin is not lower than 90g/L, try another oral formulation that may be better tolerated (see Appendix B). *Note: Non-adherence is the most common cause of oral iron failure.*
✓ Once IDA has resolved and iron stores normalize, a low dose of oral iron may be necessary for maintenance if there is an ongoing need for additional iron (e.g., growth spurt, menstruation, dietary habits). *Note: women with menses and ongoing IDA should be evaluated for a bleeding disorder.* ✓ If iron supplementation is discontinued consider repeating CBC, iron studies and ferritin in 4-6 months.	✓ If there is not an adequate response to an appropriate oral treatment dose for a three-month period, OR ✓ If the patient has not tolerated a trial of two different oral agents, OR ✓ If hemoglobin continues to decline (e.g., <90 g/L) ✓ Adults: Initiate IV iron therapy (as per Appendix A algorithm). ✓ Pediatrics (<18 years old): refer to Pediatric Hematology
✓ Consider referral for dietary advice if IDA is primarily diet related.	✓ Refer to hematology if no response to IV iron and another cause for the anemia is suspected.

ONGOING MANAGEMENT

✓ Once the cause of IDA has been identified, ongoing need for iron supplementation and/or management of the condition will be determined accordingly and is beyond the scope of this clinical practice guideline.

Higher Risk

- ✓ In addition to specific conditions, patient populations that may/will require ongoing monitoring for IDA, and possibly further iron supplementation include but are not limited to:
  - Pregnancy
  - Elderly
  - Patients with underlying conditions predisposing to IDA, e.g., GI malabsorption, celiac disease, hereditary hemorrhagic telangiectasia, hemolysis and dysfunctional uterine bleeding

Background

Iron is crucial to biologic functions, including respiration, energy production, DNA synthesis, and cell proliferation.[1] Iron is biologically conserved in several ways including recycling after the degradation of red cells and iron retention in the absence of an excretion mechanism. Because excess iron levels can be toxic, absorption is limited to one to two mg daily, and most of the iron required daily (approximately 25 mg per day) is provided through recycling by macrophages that phagocytose senescent erythrocytes.[2] The latter two mechanisms are controlled by hepcidin, a hormone that maintains total-body iron within normal ranges, avoiding both iron deficiency and excess.[2] The degree of iron store repletion is determined by the rapidity with which iron deficiency develops in the context of blood loss or a substantial reduction in iron absorption. Hepatocytes are thought to be a long-term reservoir for iron and release it more slowly than macrophages.

Iron deficiency is defined as the reduction of iron stores that precedes overt iron-deficiency anemia (IDA) or may persist but not progress to IDA. IDA is a serious condition whereby low levels of iron are associated with anemia and the presence of microcytic hypochromic red cells. [2]

A recent systematic review of 29 guidelines was published in 2015.[3] These guidelines were developed by professional associations throughout the world including the United States (n = 8), Europe (n = 6), Britain (n = 4), Canada (n = 3), other international organizations (n = 2), France (n = 2), Poland (n = 1), Australia (n = 1), Mexico (n = 1), and Japan (n = 1). Findings from this guideline summary reveal that, for the most part, Iron Deficiency (ID) guideline recommendations are somewhat heterogenous largely because different patient populations were addressed.

Recommendations in this guideline were informed by available evidence located as well as the guideline development committees' expertise, experience and consensus.

Screening

To our knowledge, there is no evidence to routinely screen for (i.e., order iron studies) for iron deficiency anemia (IDA) in patients >5 years of age in the absence of signs, symptoms or risk factors for IDA.

CAUSES OF IDA

Most of the common causes of IDA identified in Table 2 and in most cases, iron resistance is due to disorders of the gastrointestinal tract.

DIETARY DEFICIENCY

Dietary iron deficiency should be rare in first world countries because of iron availability in many foods, i.e., heme-iron in meats and non-heme iron in some vegetables as well as iron-fortified bread, cereals and other grain products. Typically, dietary iron deficiency can be observed in adults restricting dietary sources of iron and not appropriately supplementing their restricted diets, e.g., strict vegans.[2]

BLEEDING

Overt bleeding is the most common cause of iron deficiency in adults. Adults without an obvious source of blood loss and a new diagnosis of IDA must be evaluated for an occult gastrointestinal malignancy. This is especially true and important for individuals >50 years of age, non-menstruating women, and those at increased risk of colorectal cancer based on family history or other risk factors.[4]

IMPAIRED ABSORPTION

Certain gastrointestinal conditions may lead to iron deficiency due to impaired absorption such as in gastrectomy and gastric bypass surgery. IDA is very common in patients with partial or total gastrectomy.[5] This is likely due to poor iron absorption and chelation from lack of gastric hydrochloric acid and ascorbic acid as well as loss of free iron in exfoliated cells.[4] Regardless, these patients typically will have an increased risk of gastric cancer (two to three-fold risk) after 20 years, as well as an increased risk of colorectal cancer.[4] Bariatric surgery can lead to iron deficiency, but iron supplementation is usually recommended after surgery to prevent the problem.

OTHER

One exception to note is iron-refractory iron-deficiency anemia (IRIDA). This disorder is very rare but clinicians should be aware of it to emphasize how essential the suppression of hepcidin is to the body's response to pharmacologic iron. Iron-deficiency anemia is defined as "refractory" when there is an absence of hematologic response (an increase of <1 g of hemoglobin) after four to six weeks of treatment with oral iron.[6] IRIDA is caused by a genetic mutation that essentially disrupts iron equilibrium-specifically control by hepcidin. This type of anemia is variable, more severe in children, and unresponsive to treatment with oral iron. Typical findings include significant microcytosis and exceptionally low transferrin saturation in the presence of normal or borderline-low ferritin levels as well as high hepcidin levels.[7] The diagnosis ultimately requires sequencing of genetic mutation. IRIDA represents less than 1% of the cases of iron-deficiency anemia observed in clinical practice.[2]

ASSESSMENT

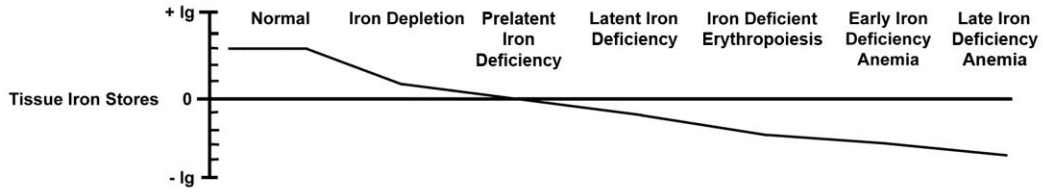
Patients who have iron-deficiency anemia often have vague signs and symptoms and are commonly asymptomatic therefore they often go undiagnosed.[2] Non-specific but common symptoms of iron deficiency include fatigue, weakness, difficulty concentrating and low work productivity resulting from

low delivery of oxygen to body tissues and decreased activity of iron-containing enzymes.[2] It is unknown how long the non-hematologic effects manifest themselves before anemia develops. Signs of iron deficiency in tissue are subtle and may not respond to iron therapy.[2]

DIAGNOSIS [3,8]

Because a definitive diagnosis of IDA cannot be made on signs and symptoms alone, traditional laboratory measures and results will determine iron status, iron deficiency and related conditions (e.g., functional iron deficiency, iron-deficiency anemia, IRIDA, and anemia of chronic diseases) and these are well established.[3] Table 6 depicts the sequence of events (left to right) that occur with gradual depletion of body stores of iron. Serum ferritin and stainable iron in tissue stores are the most sensitive laboratory indicators of mild iron deficiency and are particularly useful in differentiating iron deficiency from the anemia of chronic disorders. The percentage saturation of transferrin with iron and free erythrocyte protoporphyrin values do not become abnormal until tissue stores are depleted of iron. Subsequently, a decrease in the hemoglobin concentration occurs because iron is unavailable for heme synthesis. Red blood cell indices do not become abnormal for several months after tissue stores are depleted of iron.[3]

Table 6: Sequence of events that occur with gradual depletion of iron stores in the body (in the absence of chronic inflammatory disease).[9]



Serum Ferritin (µg/1)	60	20	<12	<12	<12	<12	<12
Stainable Tissue Iron (0-4+)	2+	1+	0	0	0	0	0
Transferrin Saturation (%)	35	35	35	20	<16	<16	<16
Free Erythrocyte Protoporphyrin (µg/dl)	30	30	30	75	>100	>100	>100
Hemoglobin (g/dl)	14	14	14	14	13	<12	<12
Mean Corpuscular Volume (μ^3)	90	90	90	90	88	86	<82
Mean Corpuscular Hemoglobin Concentration (0/0)	33	33	33	33	33	31	<28

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Laboratory Measures and Results

A complete blood count (CBC) demonstrates a microcytic, hypochromic anemia with a normal or reduced red blood cell (RBC) count.[10] These laboratory findings may be present before the onset of clinical symptoms of anemia thus iron deficiency should be suspected. It should be noted that early stage iron deficiency can exist before any hematological changes occur with the exception of a low serum ferritin result which would indicate iron deficiency.[10]

Serum ferritin concentration is the most commonly recommended indicator for determining iron deficiency and IDA and considered a gold standard.[3] A low serum ferritin concentration does indeed reflect a state of iron depletion however, there is considerable variation in serum ferritin cut-offs recommended by different expert groups to diagnose iron deficiency and IDA. The diagnosis of iron-deficiency anemia in the context of inflammation requires significantly higher threshold levels for ferritin to define iron-deficiency anemia. Table 7 shows the variation in ferritin cut-off values among different guidelines addressing different patient populations.

There are very few studies that demonstrate appropriate serum ferritin concentrations to detect iron deficiency in otherwise healthy individuals or populations. The commonly reported threshold of 15 µg/L is likely specific but can be expected to miss as many as half the cases of iron deficiency.[10] While a serum ferritin concentration cut-off of 30 µg /L is more sensitive, it will generate many false-positive diagnoses. Therefore, the evidence available to support any recommended serum ferritin cut-off for diagnosis of iron deficiency is at best-limited and is one of several tests that can be used to detect iron deficiency.[11]

Table 7: Varying ferritin threshold values for IDA reported for various patient populations from various guidelines throughout the world.[3]

NUMBER OF GUIDELINES	FERRITIN	PATIENT POPULATION ADDRESSED
10	*12-15 µg/L*	*General (men, women children, CKD, digestive diseases*
9	25-30 µg/L	General (with chronic disease or peri-op bleed), inactive IBD, CKD, on chemotherapy, peri-gestational
3	45-50 µg/L	General- "iron deficiency probable", digestive disease
12	100 µg /L	Mainly CKD, general- "iron deficiency possible", heart disease, active IBD, for anesthesia
2	200 µg/L	CKD hemodialysis and receiving hemodialysis

According to Thomas et al 2013, moderate quality evidence suggests that mean cell volume (MCV) and mean cell haemoglobin (MCH) values are useful at diagnosis and trends from ongoing assessment over weeks or months but they have no utility for assessing acute changes in iron availability secondary to therapy with erythropoiesis-stimulating agents (ESAs).[8]

The percentage of hypochromic red cells (%HRC) is the best-established variable for the identification of functional iron deficiency and thus has the greatest level of evidence. Reticulocyte haemoglobin content (CHr) is the next most established option. But both tests have limitations e.g., sample stability or equipment availability. Other parameters may be as good but there is no evidence that they are any better, and generally there is less evidence for newer red cell and reticulocyte parameters.[8]

Red cell indices can provide a sensitive indication of iron deficiency in the absence of chronic disease or haemoglobinopathy.[4]

One-half of guidelines reviewed by Peyrin-Biroulet et al. proposed transferrin saturation (TSAT) be considered as an alternative or complementary diagnostic test to serum ferritin.[3]

Other biochemical assessment tests (transferrin saturation, and soluble transferrin receptor [sTfR], as well as erythrocyte protoporphyrin) can be used to determine iron status but also present challenges in interpretation. While sTfR concentration is an indicator of functional iron deficiency and is not an acute-phase reactant, it lacks assay standardization, common reference ranges, and common cut-offs.[12]

This clinical practice guideline has purposefully recommended a more simplified approach to lab testing for IDA based on review and evaluation of current evidence and the committee's expertise and opinion regarding detection of IDA in the general patient population i.e., those without inflammatory conditions.

TREATMENT

To treat iron deficiency, the guidelines reviewed by Peyrin-Biroulet et al.2015, varied in their recommendations as to treatment approach primarily because of the heterogenous patient populations addressed among the guidelines reviewed. For this guideline, the management of iron

deficiency includes two concurrent components: 1. correcting the iron deficiency diagnosis and 2. treating the underlying disorder leading to the iron deficiency.

The treatment of iron deficiency may involve some or all of the following: dietary advice; oral iron supplements; intravenous iron infusion; and less commonly, blood transfusion. Once replacement has been achieved, many patients require dietary advice to ensure deficiency does not recur. The goal of treatment should be to restore haemoglobin levels and red cell indices to normal levels and to replenish body stores with iron supplementation.[13] Some guidelines do recommend specific treatment targets for Hb and/or Serum ferritin and/or TSAT % at specific intervals of time but these targets vary and are typically condition-specific guidelines e.g., CKD.[3]

Oral Iron Intake

Diet and Oral Iron supplements

Regardless of the source, all patients should receive iron supplementation both to correct anemia and replenish body stores.[14] Guidelines differ in their recommendations for daily dosage and the type of iron salt supplement recommended. This guideline suggests the type and dosages that have been best tolerated based on patient experience, but tolerance will be patient specific and may require trial of different iron salt formulations and/or dosages. Once oral iron corrects the IDA, it should be continued for at least three months to replenish iron stores.[4]

Limited information on efficacy when comparing one to another, so most decisions are based on tolerability, adherence and cost. Typical adult treatment dose is 100 to 200 mg elemental iron per day. The Nutrition and Gastroenterology Committee of the Canadian Paediatric Society recommends that assuming 10% of the iron in a mixed diet is absorbed, the required elemental iron intake is approximately 8 mg/day for children aged four to 12 years. Children with IDA should also receive iron supplementation. The recommended therapeutic dose of oral iron is 3 to 6 mg/kg/day of elemental iron, for three to four months with adequate follow-up.[15]

Starting doses vary depending on patient tolerance and potential benefit of starting low and increasing slowly in less acute situations. Oral iron at treatment doses should be tried for three months before considering other routes of iron supplementation. Three to six months of treatment are required for repletion of iron stores.[2]

Adding a source of vitamin C (e.g., 125ml orange juice or if not tolerated, a 250-500mg ascorbic acid supplement) may enhance the absorption of dietary or oral iron.[16,17] A 250-500 mg ascorbic acid supplement can be taken up to twice daily with an iron supplement to enhance absorption, but there is no evidence for its effectiveness in treating IDA.[4]

Oral iron should be avoided after bariatric surgery and in inflammatory bowel disease and when blood loss exceeds absorption (e.g. heavy uterine bleeding and hereditary hemorrhagic telangiesctasia).[18]

Intravenous Iron Therapy

In the past, hypersensitive reactions to high-molecular-weight iron dextran resulted in limited administration of IV iron. However, with the availability of safer iron formulations such as iron sucrose and ferric gluconate, use of I.V iron is common and generally well tolerated by most patients. Mild side effects can be observed in about 35% of patients with symptoms such as abdominal pain,

nausea, headache and diarrhea. Serious adverse reactions are less common (0.03-0.04% of patients).[19,20]

Intravenous iron is the preferred option to transfusion when oral iron is not appropriate or a reasonable length trial at a treatment dose (e.g., 100 to 200 mg elemental iron per day) has failed.[21] Because the use of intravenous iron circumvents the problem of iron absorption, it is more effective and increases hemoglobin levels more quickly than oral iron.[22,23,24] Although the cost of intravenous iron therapy is considerable, it is the preferred approach in hemodynamically stable patients when compared to blood transfusion.[25,26]

Patients with malabsorption and genetic IRIDA may require intravenous iron on an ongoing basis. Intravenous administration is also preferred when a rapid increase in hemoglobin level is required or when iron-deficiency anemia caused by chronic blood loss cannot be controlled with the use of oral iron, as is the case in patients with hereditary hemorrhagic telangiectasia or active inflammatory bowel disease.[27]

Intramuscular (IM) Iron Therapy

The literature reviewed suggest that the use of intramuscular (IM) iron should be avoided, as it is painful, stains the buttocks, and has variable absorption.[18,28] In addition, there are case reports that described sarcoma development after administering IM iron.[29,30]

Transfusion

Increasingly guidelines are recommending blood transfusion should only be used in patients with risk of cardiovascular instability and/or symptomatic anemia because of the degree of anemia despite iron therapy provision in these patients.[31] This could include patients about to have endoscopic investigations before they've responded to iron treatment.[31]

When transfusions must be used, the goal should be to restore Hb to a safe level, but not necessarily achieve normal Hb levels. Other means of iron treatment should be initiated to replenish iron stores following the transfusion.

The American Association of Blood Banks (AABB) released guidelines in 2016 highlighting the fact that greater than 100 million units of blood are collected worldwide each year, yet the indication for red blood cell (RBC) transfusion is uncertain.[32] The aim of the guideline was to provide recommendations for the target hemoglobin level for RBC transfusion among hospitalized adult patients who are hemodynamically stable.

An evidence review was conducted and findings from the review suggest that when deciding on whether or not to transfuse a patient it is important to consider all of the following: the hemoglobin level, overall clinical context, patient preferences, and most appropriate and safe approach by considering alternative therapies.[32] The AABB guidelines therefore have developed specific recommendations with respect to restricting RBC transfusions. In addition, research in RBC transfusion medicine has significantly advanced in recent years and high-quality evidence is available to inform guidelines. Further concluding that a restrictive transfusion threshold is safe in most clinical settings and the current blood banking practices of using standard-issue blood should be discontinued.[32]

SPECIAL SITUATIONS

PREGNANCY

There is a normal increased iron requirement to increase maternal red blood cell mass and for fetal/placental development. Approximately 1 gram of total iron loss is associated with pregnancy and lactation.[33] Iron deficiency is typically observed in patients with borderline/low iron status prior to pregnancy or in multiple pregnancies. There is some evidence that maternal iron deficiency anemia increases the risk of preterm delivery and subsequent low birth weight as well as some evidence that there is an association between maternal iron status in pregnancy and the iron status of infants postpartum.[34,35] However, the evidence of maternal mortality, morbidity, and well-being, and on infant health and development is less clear.[34,35]

ELDERLY

IDA is commonly found in elderly patients.[36] At age 65 and older one report suggests that 10% will have IDA and at age 85 and older; 20%.[36] For patients aged 85 and older, IDA carries an increased risk of mortality (hazard ratio 1.41 [95% CI 1.13 to 1.76]) in addition to the condition causing anemia.[37] IDA requires workup for potential causes, including gastrointestinal malignancy.[38]

In general, for elderly individuals with IDA, a lower dose of iron can lead to similar increases in hemoglobin as with higher doses, but without the adverse effects. Dosing options include one half of a 300 mg ferrous gluconate tablet (i.e., 17.5 mg elemental iron) per day or the equivalent elemental iron from a liquid formulation.[39]

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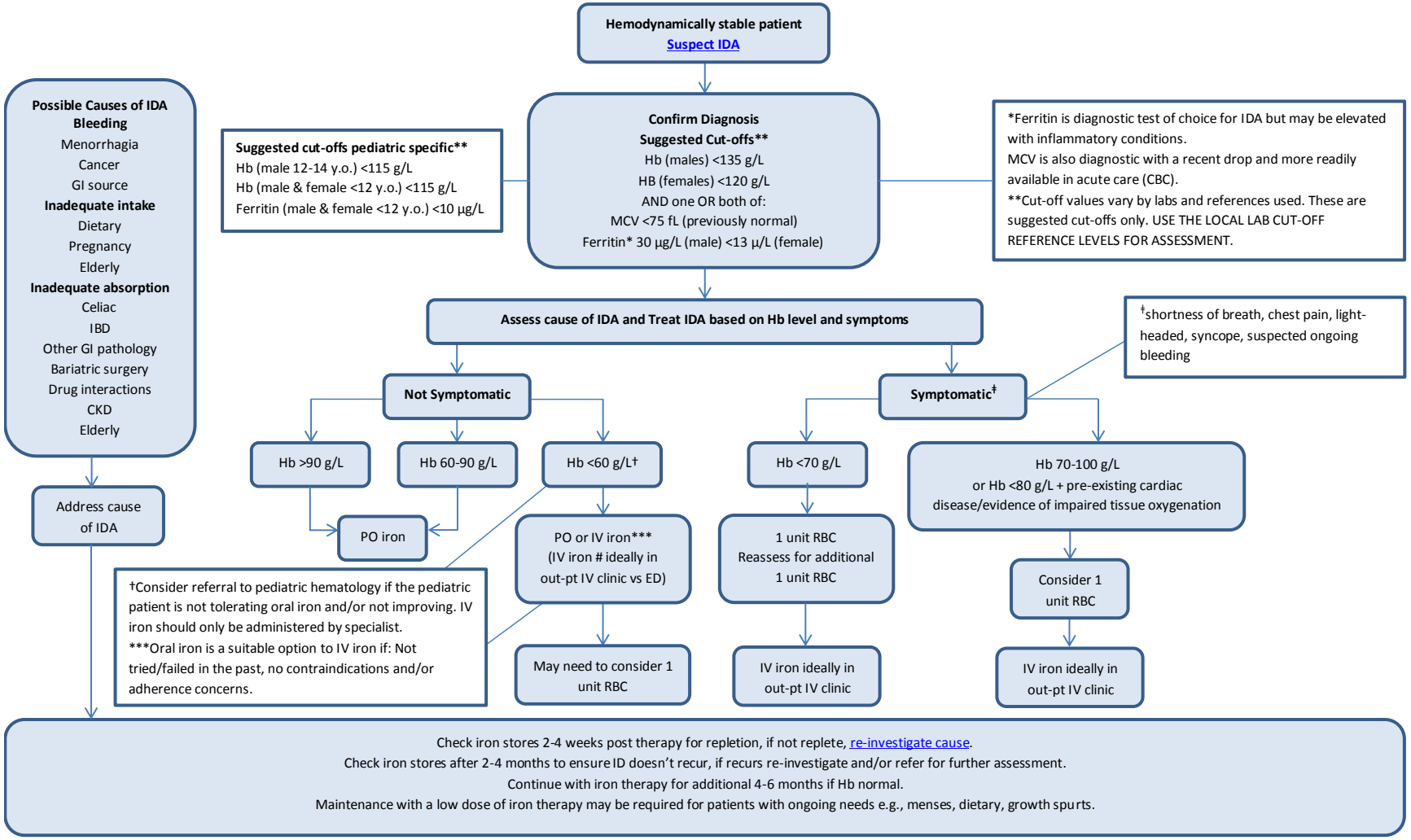
GUIDELINE COMMITTEE

The committee consisted of representatives of anatomical pathology, emergency medicine, hematological pathology, internal medicine and primary care.

March 2018

APPENDIX A – TREATMENT ALGORITHM

IDA Diagnosis and Treatment Algorithm



APPENDIX B

Table 8: Oral Iron Preparations Available in Alberta for Patients (≥5 years of age) [40,41,42,43,44]

PEDIATRIC Target dose 3-6 mg/kg/day elemental

ADULT Target dose 100-200mg elemental per day

IRON TYPE	FORMULATION (elemental iron)	USUAL MAXIMUM ADULT DOSE	COST ESTIMATE PER MONTH OF MAX DOSE (* indicates generic)		CONSIDERATIONS
Ferrous gluconate	*Tablet 300 mg (35 mg)*	*2 tablets 3-times daily*	*$ 11.70*	*	• *Least expensive* • *Similar rates of adverse effects between ferrous salts when equivalent doses of elemental iron provided* • *Avoid enteric coated or sustained-release products; tablet bypasses area of absorption, results in reduced iron intake.* • *Liquids stain teeth* • *RCT suggested that ferrous sulfate may be slightly more effective than PIC in young children.*[45] • *RCT in healthy young women: suggests dosing of one ferrous sulfate tablet, taken every second day in morning, may increase iron absorption* [46]
Ferrous fumarate	*Tablet 300 mg (100 mg)*	*1 tablet 2-times daily*	*$ 5.80*	*	
	Suspension 300 mg/5mL (20 mg/mL)	*100 mg elemental (5 mL) 2-times daily*	*$ 51.00*		
Ferrous sulfate	*Tablet 300 mg (60 mg)*	*1 tablet 3-times daily*	*$ 6.30*	*	
	Suspension 30 mg/mL (6 mg/mL)	*60 mg elemental (10 mL) 3-times daily*	*$ 34.20*	*	
	Drops 75 mg/mL (15 mg/mL)	*60 mg elemental (4 mL) 3-times daily*	*$104.33*	*	
Heme iron polypeptide (e.g., Proferrin®)	*Tablet 11 mg (11 mg as heme iron)*	*1 tablet 3-times daily*	*$104.97*		• *Not suitable for vegetarians as made from animal products.* • *Not dosed as elemental therefore cannot use dosing range above.*
Polysaccharide iron complex (PIC) (e.g., Feramax®)	*Capsule 150 mg (150 mg)*	*1 capsule once daily*	*$ 33.60*	*	• *Powder may be more palatable for pediatric patients.* • *Once daily dosing may improve adherence.* • *Little to no evidence that PIC is more effective than other iron salts but substantially more expensive.*
	Powder (15 mg per ¼ teaspoon)	*60 mg elemental (1 teaspoon) 3-times daily*	*$116.97*		

IRON TYPE	FORMULATION (elemental iron)	USUAL MAXIMUM ADULT DOSE	COST ESTIMATE PER MONTH OF MAX DOSE (* indicates generic)	CONSIDERATIONS
Note: Retail pricing is accurate as of the date this guideline was written (2017). Pricing is provided based on a quote from an Alberta retail pharmacy and reflects one example of monthly costs. Pricing for oral supplements will vary depending on the amount prescribed and the specific pharmacy where the product is purchased.				

TIPS FOR OPTIMIZING ORAL IRON THERAPY

- Calculation of dosage should always consider *elemental iron* content of product.
- To maximize absorption, iron supplements should:
    - Be taken on an empty stomach with full glass of water or fruit juice, if appropriate (e.g., one hour before or two hours after meals).
    - Be taken in the morning or earlier in the day. (Iron absorption is decreased when Hepcidin levels are highest. Hepcidin peaks in the evening hours.)[47]
    - Be taken with a supplement or dietary source of Vitamin C (e.g., fruit juice, oranges, tomatoes).
    - NOT be taken with Calcium products (e.g.: supplements, certain antacids) or foods (e.g., dairy products such as milk, cheese, yogurt).
    - NOT be taken with high-oxalate foods (e.g., coffee, tea, spinach, kale, broccoli).
- Oral iron can cause nausea, vomiting, dyspepsia, constipation, diarrhea, metallic taste or dark stools. If your patient is experiencing GI based adverse effects, consider the following:
    - Start at a lower dose (e.g., one tablet once daily) and titrate up slowly (i.e., every four to five days).
    - Switch to liquid form for smaller dose titrations.
    - Switch to another preparation with less elemental iron.
    - Recommend taking iron with small snack or with meals (however food will decrease iron absorption by 40%).
    - Take at bedtime (however, iron absorption is lowest in evening when Hepcidin hormone levels are highest).
    - Could consider polysaccharide iron complex as an option however, it is more expensive and its effectiveness is no better than other iron salts.
- For patient information on dietary sources of iron see: https://myhealth.alberta.ca/health/pages/condtions.aspx?hwid=ue4500&#ue4500-sec

APPENDIX C

IV IRON PREPARATIONS FOR ADULTS >18 YEARS (NOTE: CHILDREN <18 YEARS REFER TO PEDIATRIC HEMATOLOGY FOR IV IRON ASSESSMENT AND TREATMENT)

Table 9: IV Iron Preparations Available in Alberta

IRON TYPE	USUAL DOSE • **Calculate** 'Iron Deficit' (total dose needed) using hemoglobin deficit equation. • **Divide** 'Iron Deficit' into appropriate individual doses. • **Administer** doses 1-2 times weekly until total dose complete (interval varies by product, check product monograph).	COST ESTIMATE for 1000 mg *(Note: drug cost only – not administration cost)*	CONSIDERATIONS
Iron Sucrose (Venofer®)	Ex: Total Iron Deficit 1000mg, consider: 200 mg IV x 5 doses[48]	$393.80	• CAUTION: Dosages >300 mg are associated with increased risk adverse reaction due to iron overload.
Ferric Gluconate Complex (Ferrlecit®)	Ex: Total Iron Deficit 1000 mg, consider: 125 mg IV x 8 doses[49]	$453.60	
Iron Dextran (Dexiron®)	Ex: Total Iron Deficit 1000 mg, consider: 100 mg IV x 10 doses[50]	$297.69	• REQUIRED: TEST DOSE (25 mg) and one hour observation before proceeding with first dose. • Only IV iron covered Alberta Health Drug Benefit List (AHDBL).
Disclaimer: *Above are general dosing examples. Consult product monograph for specific indicators, dosing and administration or when used in Alberta Health Services (AHS), refer to local protocols and parenteral monograph for more information. Parenteral iron should only be used by professionals familiar with dosing, administration and appropriate monitoring.*			