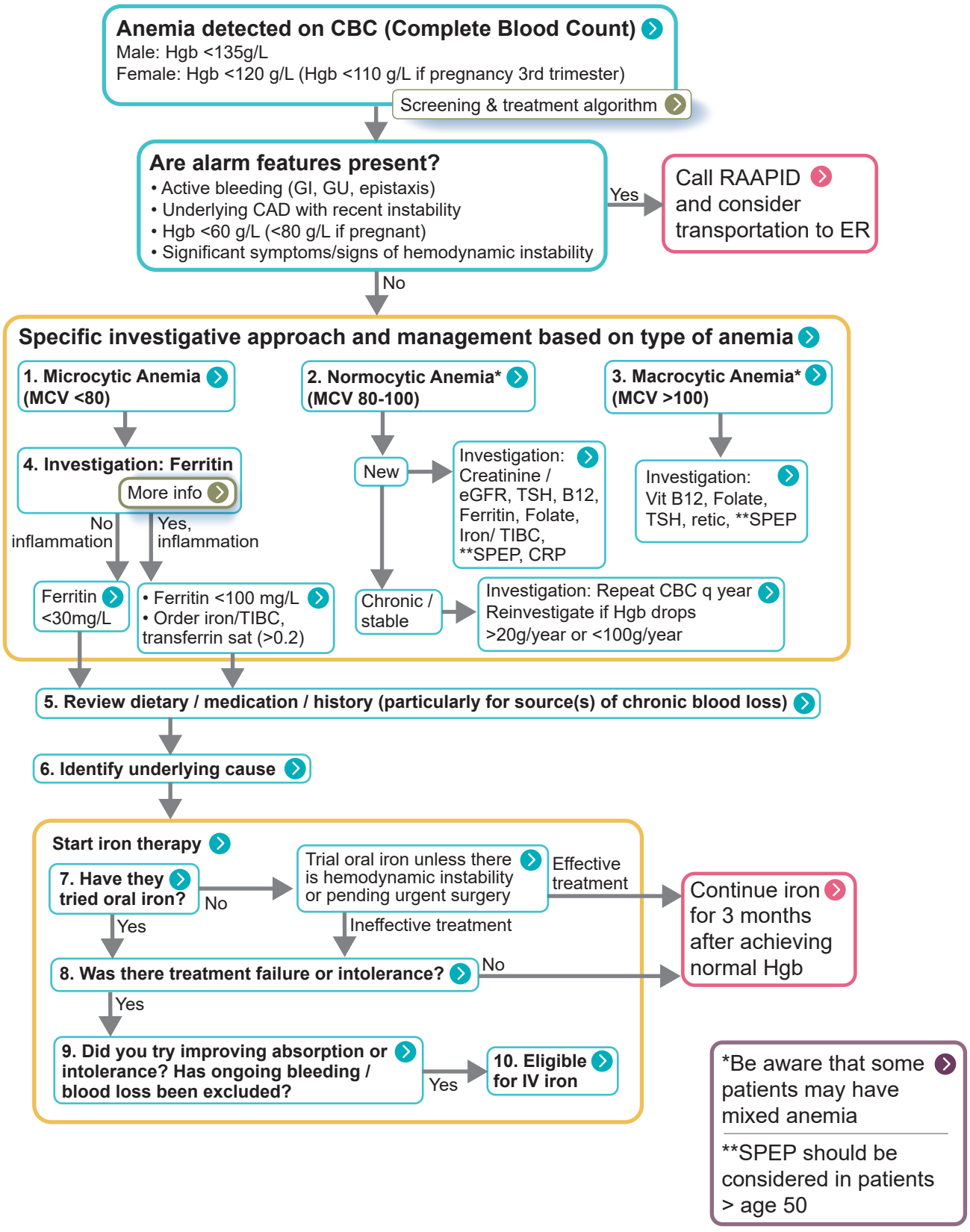
Iron Deficiency Anemia (IDA) Primary Care Pathway



PATHWAY PRIMER: IRON DEFICIENCY ANEMIA (IDA)

Anemia is a common finding in primary care. Iron deficiency anemia (IDA) is the most common cause of anemia – some studies indicating the prevalence as high as one in five menstruating women could suffer from iron deficiency anemia.[i]

The accurate diagnosis of IDA is contingent on ordering and interpreting the appropriate blood indices: hemoglobin, ferritin and/or iron binding as defined as transferrin saturation. It is important to consider that anemia may be mixed - with concomitant B12 and iron deficiency resulting in an automated picture of 'normocytic anemia'.

When iron deficiency anemia is identified – a rigorous evaluation of etiology should be undertaken. While etiology may be evident on history (example – heavy menstrual blood loss or a history of frequent blood donation), consideration should be given to all conditions which could cause blood loss or reduced iron absorption. Red cell distribution width (RDW) is a measure of variation in red blood cell size. A high RDW is consistent with IDA.

While investigating IDA and managing the antecedent cause, consideration should be given to iron supplementation. Generally, this is best accomplished through oral iron supplementation. This guide will provide practical guidance for oral iron replacement – which can be limited by GI tolerability or urgency of iron replacement.

Intravenous iron is particularly helpful in select situations – although limited by access to administration. This document will address indications for IV iron and pathways to help you facilitate getting this therapy for appropriate patients.

EXPANDED DETAILS

1. **Microcytic anemia**

   A microcytic anemia is defined as anemia associated with MCV <80. It is commonly caused by iron deficiency, and can also be caused by thalassemia, anemia of chronic disease, and rarely, sideroblastic anemia or lead poisoning. A ferritin, iron, transferrin saturation and TIBC should be ordered for microcytic anemias to assess for iron deficiency. There are numerous references with variable cut offs for determining iron deficiency. Most commonly, ferritin <30 is reflective of iron deficiency, and in those with inflammation, a ferritin of <100 associated with a transferrin saturation <0.20 may reflect iron deficiency. Ferritin is an acute phase reactant, therefore in patients with inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease and other chronic disease, a ferritin <100 may be consistent with iron deficiency. Thalassemias are the next most common cause of low MCV, and a characteristic pattern is an MCV that is persistently low with little variation in the size of the cells, meaning a normal RDW. In the event of a persistently low MCV with a ferritin >100, a screen for thalassemia can be sent.

2. **Normocytic anemia**

   A normocytic anemia is defined as anemia associated with MCV 80-100. This is a common condition and not necessarily reflective of sinister pathology.

   - **Causes of normochromic normocytic anemia:**
     - Age associated reduced bone marrow activity

- Medication related bone marrow activity
- Infection
- Malignancy
- Chronic kidney disease (CKD)
- Heart failure
- Obesity
- Chronic inflammatory conditions (rheumatoid arthritis, systemic lupus erythematosus, vasculitis etc.)

- **Mixed anemias which may *appear* as normocytic**
  - When evaluating the onset of 'new' normochromic, normocytic anemia, consider that the laboratory picture could be reflective of 'mixed' anemia's (example: very recent blood loss, mixed iron/B12 deficiency)
  - New onset normochromic normocytic anemia should be fully investigated.
  - Negative investigations should reassure that CBC can be followed on a yearly basis.

3. Macrocytic anemia

A macrocytic anemia is defined as an anemia associated with an MCV >100. Common causes include liver disease, alcohol consumption, B12 deficiency, folate deficiency, reticulocytosis, thyroid disease, bone marrow disorders (example: myelodysplasia in older adults) and medications, such as methotrexate, hydroxyurea, valproate, phenytoin, azathioprine and antiretroviral therapy.

4. Investigation: Ferritin

- **Iron deficiency**

  Iron deficiency can be present with or without anemia. There are many definitions of iron deficiency, although typically ferritin <30, and certainly <20 reflect iron deficiency.

5. Review dietary/medication/history

- **Common causes of iron deficiency**
  - Blood Loss → menorrhagia, GI losses, severe epistaxis, frequent blood donation
  - Poor intake → malnourished, strict vegan/vegetarian, eating disorder
  - Poor absorption → celiac, inflammatory bowel disease, post GI surgery, pernicious anemia
- **History**
  - Bleeding
    - Menstruation
    - How often do you menstruate and how many days does it last?
    - How often are you changing a pad or tampon?
    - Do you have menstrual clots and what is the size?
    - Do you experience overflow while using a tampon or pad?
    - Do you miss school/work or other obligations due to heavy periods?
    - Other bleeding sources
    - Do you experience chronic bright red blood per rectum?
    - Do you have black tarry stools?

- Do you have frequent epistaxis?
- Do you have easy bruising or bleeding?

○ Poor intake
- Are you vegan or vegetarian?
- Are you calorie restricting?
- Do you have frequent vomiting?

○ Poor absorption
- Do you have known GI conditions like celiac, pernicious anemia, inflammatory dowel disease (IBD), etc.
- Have you had part of your gastrointestinal tract removed, such as bariatric surgery, or ileostomy?
- Do you experience frequent bloating, nausea, diarrhea or constipation?

6. Identify underlying cause

Table 1: Causes of iron deficiency

Decreased Iron Availability		Increased Iron Need	
Intake/Absorption	**Sequestration**	**Physiologic State**	**Blood Loss**
- Dietary restriction (e.g. vegan) - Antacid/Proton pump inhibitors (PPI) meds - Malabsorption/celiac - Gut resection - Gastroesophageal reflux disease/Gastritis (including Atrophic gastritis, particularly in the elderly)	- Inflammatory diseases - Congestive heart failure - CKD - Obesity - Iron refractory IDA (congenital, rare)	- Pregnancy - Childhood - Extreme exercise - Eating disorder	- Gastrointestinal IDA Pathway for CRC Diagnosis - Algorithm (specialistlink.ca) Note: If the above link is broken: Clinical Pathways & specialty access (specialistlink.ca) - Genitourinary - Vaginal AbnormalUterineBleeding_Pathway_Sept2020 (specialistlink.ca) Note: If the above link is broken: Clinical Pathways & specialty access (specialistlink.ca) - Epistaxis - Iatrogenic - Blood donation

Table 2: Work up for iron deficiency – referral checklist

Problem of ID, IDA	Considerations
1. Ensure common causes are identified on history and managed before referral	a. Is there adequate oral intake of heme iron sources (is the patient vegetarian)? b. Is there a history of blood donation? c. Have there been previous/recent surgeries?
2. Other GI causes to be excluded‡	a. Celiac disease b. Inflammatory bowel disease (IBD) c. Helicobacter pylori (H. pylori) infection d. Previous bowel surgery
3. Unexplained	GI for endoscopy†*
4. Overt GI blood loss†	GI for endoscopy*
5. Gynecological bleeding#	Gynecologist to exclude uterine pathology*
6. Urinary bleeding	Urologist to exclude kidney, ureter, and bladder pathology including stones*
7. Bleeding in other organ system	Appropriate specialty as appropriate*

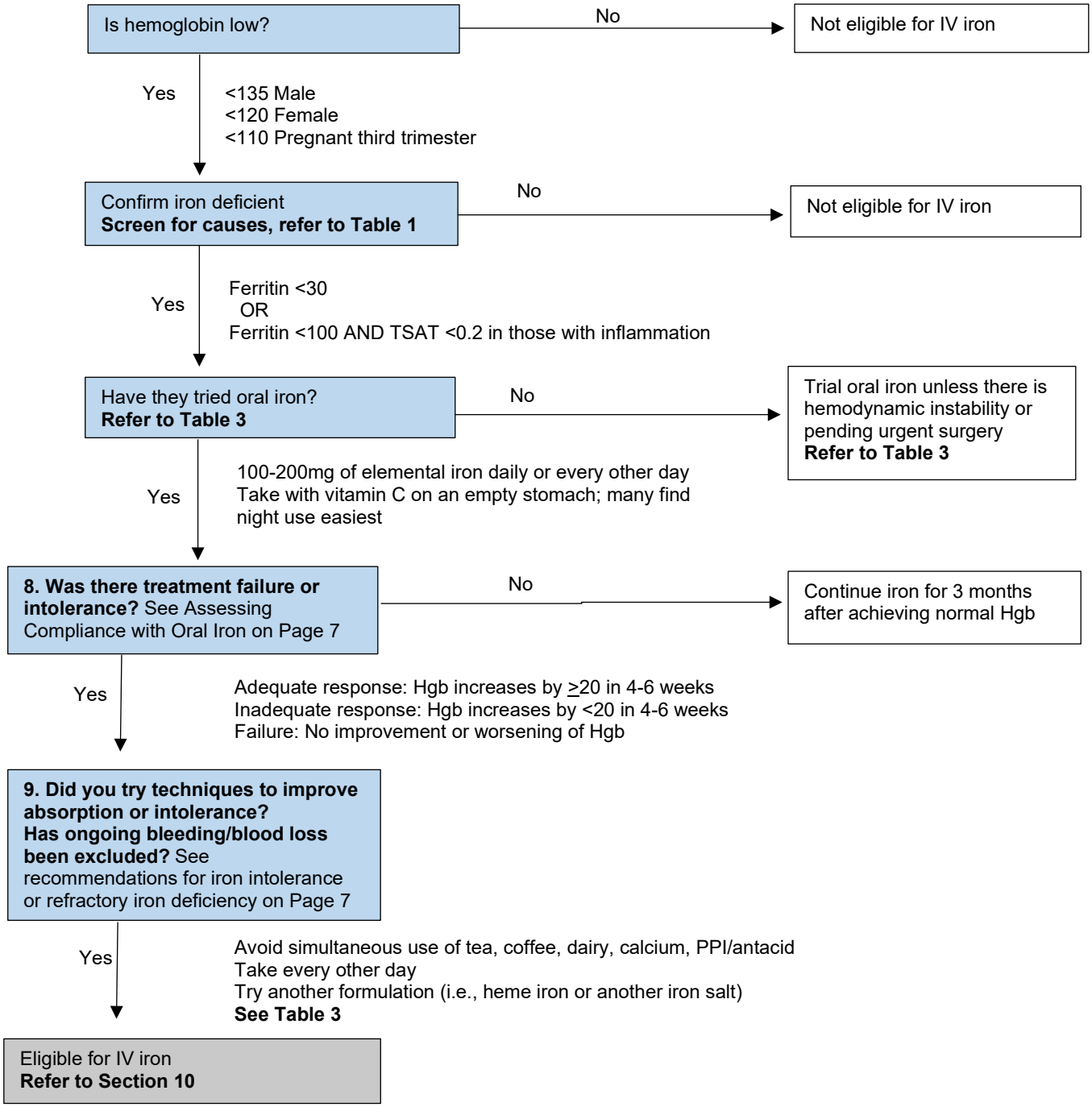
†**Gastrointestinal blood loss** is common and can be either overt (visible) or hidden. Iron deficiency can be the first presentation of an asymptomatic malignancy; therefore, timely investigation of this, after screening for other common causes is important, particularly in patients over age 50 years. A family history of malignancy is important to obtain.

‡ **Investigations to exclude the GI tract as the underlying cause of ID and IDA** include: (a) celiac screen (e.g., lgA transglutaminase antibodies for celiac disease); (b) IBD screen [e.g. C-reactive protein and fecal calprotectin (stool)], if associated symptoms present and; (c) stool antigen for Helicobacter pylori.
A family history of celiac disease and IBD is important to obtain.

#Uterine blood loss is common in females of reproductive age. History should include specific questions to assess for menorrhagia. Refer to gynecologist for management input and to exclude uterine pathology, as appropriate. In patients with menorrhagia without uterine pathology, and with other bleeding symptoms, screening for underlying bleeding disorders (e.g., von Willebrand disease, etc.), is required.
***NOTE:**
a. **Patients already followed by other specialty for ID and IDA** need not be assessed by a hematologist
b. Patients already responding to oral iron therapy need not be assessed by a hematologist

7. Start iron therapy

Figure 1: Iron supplementation pathway



Oral iron therapy

- If oral iron therapy has not been trialed, trial oral iron unless there is hemodynamic instability or pending urgent surgery
- Begin with 100-200mg of elemental iron daily or every other day. Recommend taking with vitamin C on an empty stomach; many find night use easiest

Table 3: Oral iron preparation available in Alberta for patients (≥5 years age)

Iron type	Formulation (elemental iron)	Comments
Ferrous gluconate	a. Tablet 300 mg (35 mg)	• Ferrous salt tablets 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 • Randomized control trial (RCT) suggested that ferrous sulfate may be slightly more effective than polysaccharide iron complex (PIC) in young children o RCT in healthy young women: ferrous sulfate tablet, taken every second day increases iron absorption
Ferrous fumarate	a. Tablet 300 mg (100 mg) b. Suspension 300 gm/5mL (20 mg/mL)	
Ferrous sulfate	a. Tablet 300 mg (60 mg) b. Suspension 30 mg/mL (6 mg/mL) c. Drops 75 mg/mL (15 mg/mL)	
Heme iron polypeptide (e.g. Proferrin®)	a. Tablet 11 mg (11 mg as heme iron)	• Not suitable for vegetarians as made from animal products o Not dosed as elemental iron
Polysaccharide iron complex (PIC) (e.g. Feramax®)	a. Capsule 150 mg (150 mg) b. Powder (15 mg per ¼ teaspoon)	• Powder may be more palatable for pediatric patients o Little to no evidence that PIC is more effective than other iron salts, but may be better tolerated resulting in better compliance, although usually more expensive

Note: Adverse effects – GI side effects, common, and dose dependent

- Nausea, constipation, diarrhea, vomiting, bloating, dark stool, metallic taste
- If intolerant to one preparation, consider switching to another. Using lower dose every other day also helps

Treatment outcomes

- Adequate response: considered if Hgb increases by ≥20 in 4-6 weeks
  - Ongoing management: Continue iron for 3 months after achieving normal Hgb
- Inadequate response: considered if Hgb increases by <20 in 4-6 weeks
- Failure: considered if no improvement or worsening of Hgb

Assessing compliance with oral iron

- There are many formulations of oral iron with various side effects, tolerability and frequency of dosing.
- Common side effects include bloating, constipation, nausea and darkening of the stools.
- Oral iron is best absorbed on an empty stomach, and non-heme irons can be taken alongside vitamin C for increased absorption.

- Patients should be counseled to avoid concurrent use (within 1-2 hours) of proton pump inhibitors, calcium, dairy, tea or coffee, as these are known to reduce absorption of iron.
- Paradoxically, some irons have improved absorption when taken less frequently, such as one pill every 2 days rather than one pill daily.
- Concurrent consumption of foods with high iron content is also encouraged.

Recommendations for iron intolerance or refractory iron deficiency

- Although taking iron on an empty stomach is ideal, taking with food can reduce GI side effects.
- Irons such as feramax can be taken every two days rather than once daily.
- Ask whether there is concurrent use of medications/foods known to block iron absorption.
  - Avoid simultaneous use of tea, coffee, dairy, calcium, PPI/antacid
- Try another formulation (i.e., heme iron or another iron salt)

10. IV Iron therapy

IV iron therapy should be considered if:

Problem of ID, IDA	Considerations
(i) Unresponsive or intolerant to oral iron despite dosage optimization and change of preparation*	a. Primary care physicians who have hospital privilege (**to obtain hospital privilege for IV iron infusion, please contact cal.medicalstaffoffice@ahs.ca**) b. Refer to one of many private infusion clinics listed below. The links to their request forms are also included. There is a cost associated with using a private clinic that varies from $100-$200 to use the facility per visit, and additional cost of the IV iron prescription, depending on drug coverage. **North Alberta - Alternate (Private) Infusion Options** https://webfiles.pfizer.com/file/cebbaad1-a291-40c6-9042-0ecec33bbf59?referrer=3d560995-33e1-433f-85cf-a1638b95c2e7 **South Alberta – Alternate (Private) Infusion Options** https://webfiles.pfizer.com/file/862062fe-9c86-40d7-9d4b-7f8bcb2d3912?referrer=3d560995-33e1-433f-85cf-a1638b95c2e7 c. Specialists (e.g., Gynecology, GI, internists, etc.) who are already following the patient [see above]. d. Internists, hematologists, only if not already followed by other specialists
(ii) Pregnant patients requiring urgent correction of IDA or if Hb <80 g/L	Refer to patients' maternity provider (obstetrician or family physician) NOTE: IV iron should NOT be given to pregnant women during the first trimester.
(iii) Preoperative patients requiring urgent correction of IDA	Refer to AHS Patient Blood Management Program (F: 403-944-4571, P: 403-944-4710, E: CZ.PBM@ahs.ca)

Table 4: IV iron preparations (for adults >18 years) 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 including administration cost)	Comments
Iron Sucrose (Venofer®)	E.g. Total iron deficit 1000 mg, (consider: 200 mg IV x 5 doses)	$393.80	• **CAUTION:** dosages >300 mg are associated with increased risk adverse reaction due to iron overload
Erric Gluonate Complex (Ferrlecit®)	E.g., total iron deficit 1000 mg, (consider 125 mg IV x 8 doses)	$453.60	
Iron isomaltoside (Monoferric®)	E.g., total iron deficit 1000 mg, (consider given as a single dose, max per dose: 20 mg/kg)	$530.00	• Covered in selected insurance • Private infusion sites • Can take prescription to Alberta Health Services facility

Note. From: Toward Optimized Practice Iron Deficiency Anemia Committee. 2018 March. Iron deficiency anemia clinical practice guideline. Edmonton, AB: Toward Optimized Practice (http://www.topalbertadoctors.org)

11. Ongoing monitoring

- Recheck CBC monthly
- Continue therapy until Hgb and iron indices normal, then for 3 more months

BACKGROUND

About this pathway

- This pathway is intended to provide evidence-based guidance to support primary care and specialty care providers in caring for Iron Deficiency Anemia.

Authors and conflict of interest declaration

- This pathway was developed by a multistakeholder working group comprised of primary care and specialty providers. Names of participating reviewers and their conflict-of-interest declarations are available upon request.

Pathway review process, timelines

- Primary care pathways undergo scheduled review every three years, or earlier if there is a clinically significant change in knowledge or practice. The next scheduled review is November 2025. However, we welcome feedback at any time. Please email comments to info@calgaryareapcns.ca with “Iron Deficiency Anemia” in the subject line.

Copyright information

DISCLAIMER

This pathway represents evidence-based best practice but does not override the individual responsibility of health care professionals to make decisions appropriate to their patients using their own clinical judgment given their patients’ specific clinical conditions, in consultation with patients/alternate decision makers. The pathway is not a substitute for clinical judgment or advice of a qualified health care professional. It is expected that all users will seek advice of other appropriately qualified and regulated health care providers with any issues transcending their specific knowledge, scope of regulated practice or professional competence.

PROVIDER RESOURCES

Advice options

Non-urgent advice is available to support family physicians.

- In the Calgary Zone, specialistlink.ca connects family physicians and specialists in real time via a tele-advice line. Family physicians can request non-urgent advice from a hematologist online at specialistlink.ca or by calling **403-910-2551**. The service is available from 8 a.m. to 5 p.m. (excluding statutory holidays), Monday to Friday. Calls are returned within one hour.

Resources	
IRON DEFICIENCY ANEMIA (IDA) Clinical Practice Guideline (Mar 2018, MyHealth.Alberta.ca Network)	https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/IDA-CPG.pdf ID/IDA **Diagnosis and Treatment Algorithm** (from the above CPG): https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/IDA-Summary.pdf
Iron Dosing Frequency	https://www.cfp.ca/content/67/6/436
Preoperative Anemia Management and Hemoglobin (Hgb) Optimization (Alberta Health Services Patient Blood Management Program)	Patient Blood Management Program | Alberta Health Services
Iron Deficiency Anemia (IDA) Pathway for Colorectal Cancer Diagnosis	IDA Pathway for CRC Diagnosis - Algorithm (specialistlink.ca) Note: Pathway URLs may change when pathways are updated. Please go to the pathways home page at Specialist Link if the above link is broken: Clinical Pathways & specialty access (specialistlink.ca)
Abnormal Uterine Bleeding Primary Care Pathway	AbnormalUterineBleeding_Pathway_Sept2020 (specialistlink.ca) Note: Pathway URLs may change when pathways are updated. Please go to the pathways home page at Specialist Link if the above link is broken: Clinical Pathways & specialty access (specialistlink.ca)
Alberta Obsteric Anemia and Iron Deficiency Screen and Treatment Algorithm	Alberta Obstetric Anemia and Iron Deficiency Screening and Treatment Algorithm (albertahealthservices.ca)

References

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2. Short MW, Domagalsk JE. Iron deficiency anemia: evaluation and management. Am Fam Physician. 2013;87(2):98-104
3. Stoffel NU, Zeder C, Brittenham GM, Moretti D, Zimmermann MB. Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. *Haematologica.* 2020;105(5):1232-1239.
4. Toward Optimized Practice Iron Deficiency Anemia Committee. Iron deficiency anemia clinical practice guideline. Edmonton, AB: Toward Optimized Practice 2018 (available from: http://www.topalbertadoctors.org)

PATIENT RESOURCES

Information

Getting Enough Iron	https://myhealth.alberta.ca/health/pages/conditions.aspx?hwid=ue4500&4500-sec
UpToDate: Patient education iron deficiency anemia	https://www.uptodate.com/contents/anemia-caused-by-low-iron-in-adults-beyond-the-basics

[i] *Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood 2014; 123:615*