Primary Care of Iron Deficiency Anemia

Authors: Taylor Ruter, PharmD Candidate 2023; and Allison Hein, PharmD, BCPS

Executive Summary:

- Iron deficiency is the most common cause of anemia worldwide.
- Identifying and addressing the underlying cause of iron deficiency is an essential aspect of treatment.
- Diagnosis of iron deficiency anemia can be challenging as patients typically present with nonspecific complaints.
- The most common cause of iron deficiency is blood loss. Other possible causes include impaired iron absorption, low dietary intake and increased demand.
- IV iron should be reserved for individuals with a lack of response to, intolerance of, or inability to adhere to oral iron.
- Oral iron supplements should be taken every other day without food and apart from antacids.
- Providers should have a low threshold for initiating IV iron in older adults due to their increased potential for intolerance and malabsorption of oral iron.
- Low molecular weight iron dextran is the preferred IV iron formulation due to its low cost and single-visit dosing.

Abbreviations	
FCM	Ferric carboxymaltose
FG	Ferric gluconate
H2	Histamine-2
Hct	Hematocrit
Hgb	Hemoglobin
IS	Iron sucrose
IV	Intravenous
MCH	Mean cell hemoglobin
MCV	Mean cell volume
MWF	Monday, Wednesday, Friday

Iron Deficiency Anemia

- Iron is a vital micronutrient required at all stages of life to promote appropriate growth and development. It is also an essential component of hemoglobin, which is responsible for delivering oxygen throughout the body.
- Iron deficiency is the most common cause of anemia worldwide, affecting individuals of all ages, genders, and backgrounds.
- Primary health care providers play a vital role in diagnosis as they are almost always the first to note the presence of iron deficiency anemia.
- Patients with iron deficiency anemia have been found to have longer hospital stays, increased mortality, more adverse events, and lower quality of life.
- Identifying and addressing the underlying cause of iron deficiency is a crucial aspect of treatment.
- Symptomatic iron deficiency without anemia **should** be treated. Furthermore, patients with symptoms of iron deficiency or restless leg syndrome without overt laboratory evidence of reduced iron **should not** be treated.

Signs and Symptoms	Cause	Evaluation

• Fatigue
• Pallor
• Exertional dyspnea
• Weakness
• Headaches
• Resting tachycardia
• Dry or rough skin
• Smooth, sore tongue
• Guaiac-positive stool
• Pica
• Restless leg syndrome
	• Blood/iron loss (most common):
	  ○ Heavy menstrual bleeding
	  ○ Gastric ulcer disease
	  ○ Colorectal cancer
	• Decreased iron absorption
	  ○ Celiac disease
	  ○ Atrophic gastritis
	  ○ Bariatric surgery
	• Low dietary intake
	• Increased demand (e.g., pregnancy)
	• Chronic inflammation (e.g., heart failure)
		• History
		• Physical examination
		• Complete blood count
		• Iron studies

Stages

Depletion of storage iron
- Normal Hgb/Hct
- Low serum ferritin

Decrease in transport iron
- Normal Hgb/Hct
- Low serum iron
- High total iron binding capacity
- Low transferrin saturation

Decreased Hgb production
- Low Hgb/Hct
- High RDW
- Low MCV and MCH
- Low reticulocyte count

Oral vs. IV Iron Therapy

	Advantages	*Disadvantages*	*When to use*
Oral Iron	• Effective for most patients • Low risk of serious adverse events • Very low initial cost	• Gastrointestinal side effects are common, which can result in low adherence • Inadequate for severe or ongoing blood loss • May have higher total costs due to longer duration of treatment	• **All uncomplicated patients who are able to tolerate oral therapy**
IV Iron	• Effective for most patients • More rapid correction and resolution of symptoms • Assured compliance • No gastrointestinal side effects • Ability to administer large doses in a single infusion	• Requires monitored infusion and ability to treat potential allergic or infusion reactions • Higher initial costs	• **Lack of response to, intolerance of, or inability to adhere to oral iron (common in older adults)** • Extensive or ongoing blood loss • Impaired iron absorption • Preference to replete stores in 1-2 visits • Coexisting inflammatory state that interferes with iron hemostasis

Principles of Oral Iron Therapy

- All oral formulations are thought to be equally effective with similar side effect profiles.
- Every other day administration appears to result in equivalent or better iron absorption than daily dosing, with the added benefit of fewer side effects.
- Oral iron should be taken without food, especially calcium-containing foods and drinks (milk), calcium supplements, cereals, dietary fiber, tea, coffee and eggs.
- Supplements should be taken either 2 hours before or 4 hours after ingestion of antacids, as low gastric pH facilitates iron absorption.
- Avoid enteric-coated and sustained-release formulations to ensure maximal iron absorption.
- Common side effects include metallic taste, flatulence, constipation, nausea, vomiting, and black/green stools.
- Strategies to improve tolerability include: MWF dosing, formulations with less elemental iron, IV therapy, administering the medication with food or milk (reduces effectiveness), or using a stool softener or bulk-forming laxative.
- Treatment duration should extend 3-6 months after hemoglobin has normalized to completely replenish iron stores.

Formulations	*Elemental iron content*	*Cost*	*Example products (Elemental iron content per unit)*
Ferrous sulfate	20%	$	325 mg tablet (65 mg)
Ferrous gluconate	12%	$	324 mg tablet (37.5 mg)
Ferrous fumarate	33%	$$	324 mg tablet (106 mg)
Polysaccharide-iron complex		$$	Ferrex 150 capsule (150 mg)
Ferric maltol		$$$	30 mg capsule (30 mg)
Ferric citrate		$$$	1 g tablet (210 mg)

Principles of IV Iron Therapy

- All IV formulations are thought to be equally effective with similar side effect profiles. Formulations vary by cost, institutional availability, and the number of visits required to administer a full dose (~1000 mg).
- Low molecular weight iron dextran is the preferred agent due to its low cost and single visit dosing regimen.
- Providers should have a low threshold for initiating IV iron in older adults due to the increased prevalence of constipation and achlorhydria in the elderly population.
- IV iron should be avoided in active infection, as many infectious organisms utilize iron for growth.
- Possible side effects include nausea, extravasation, anaphylaxis and infusion reactions. If a patient has a reaction to IV iron, it is reasonable to try an alternative IV formulation.
- Premedication should be reserved for patients with a history of asthma, chronic inflammatory conditions or those with fewer than one drug allergy. Individuals with asthma or multiple drug allergies should receive methylprednisolone 125mg IV and famotidine 20mg IV prior to any IV iron administration. Those with inflammatory conditions should receive an additional four-day course of oral prednisone 1mg/kg daily after the infusion.
- IV therapy is more reliable and distributes to the reticuloendothelial system more quickly than oral iron; however, it does not provide a more rapid increase in hemoglobin levels.

Formulations *(From most to least commonly used)*	*Brand name*	*Elemental iron concentration*	*Cost*	*Test dose required*	*Dosing* *(Full treatment course dose ~1000mg)*
Iron sucrose (IS)	Venofer**	20mg/mL	$	No*	Multiple doses of 100 to 300mg
Ferric carboxymaltose (FCM)	Injectafer**	50mg/mL	$$	No	**Weight ≥50kg:** 1 or 2 doses of 750mg, given 7 or more days apart **Weight <50kg:** 1 or 2 doses of 15mg/kg, given 7 or more days apart
Iron dextran, low molecular weight (LMW ID)	INFeD	50mg/mL	$	Yes, 25mg prior to 1st dose	Single dose of 1000mg (diluted in 250mL normal saline) given over 1 hour **OR** Multiple doses of 100mg
Ferric gluconate (FG)	Ferrlecit	12.5mg/mL	$	No*	Multiple doses of 125 to 250mg
Ferumoxytol	Feraheme	30mg/mL	$$	No	Single dose of 1020mg **OR** 2 doses of 510mg, given 3 to 8 days apart
Ferric derisomaltose	Monoferric	100mg/mL	$$$	No	**Weight ≥50kg:** Single dose of 1000mg **OR** up to 3 doses of 500mg, given over 7 days **Weight <50kg:** Single dose of 20mg/kg

** Test dose not required, but recommended in individuals with a history of multiple drug allergies*
*** Typically included on formulary*

Monitoring Response to Therapy

- Follow up on hemoglobin, reticulocyte count, and tolerability of oral iron therapy 2 weeks after initiation.
- For patients on IV iron, follow up 4 to 8 weeks after initiation. No iron parameters should be monitored for at least 4 weeks after initiating IV iron, as it interferes with iron assays.
- Patients should note an improved feeling of well-being within the first few days of treatment.
- The hemoglobin concentration will rise slowly, usually starting after one to two weeks of treatment, and should normalize by 6 to 8 weeks.

- Some medications can impair iron absorption. Common drug interactions include proton pump inhibitors, H2 receptor antagonists, antacids, cholestyramine, and tetracyclines.
- Possible explanations for a lack of response to therapy include nonadherence, impaired absorption, ongoing or current blood loss, or an incorrect initial diagnosis.
- Differential diagnoses to consider upon treatment failure include anemia of chronic disease, nutrient deficiencies, lead poisoning, inherited anemias and bone marrow abnormalities.

References:

1. Causes and diagnosis of iron deficiency and iron deficiency anemia in adults - UpToDate. Accessed November 8, 2022. https://www.uptodate.com/contents/causes-and-diagnosis-of-iron-deficiency-and-iron-deficiency-anemia-in adults?search=iron%20deficiency%20anemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
2. Treatment of iron deficiency anemia in adults - UpToDate. Accessed November 8, 2022. https://www.uptodate.com/contents/treatment-of-iron-deficiency-anemia-in-adults?search=iron%20deficiency%20anemia&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2
3. Warner MJ, Kamran MT. Iron Deficiency Anemia. [Updated 2022 Aug 8]. In: StatPearls [Internet].Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
   Available from: https://www.ncbi.nlm.nih.gov/books/NBK448065/

Provoked Deep Vein Thrombosis

Authors: Ashley Green, PharmD Candidate 2023, and Rachelle Davis, PharmD, BCACP

Executive Summary

A provoked DVT is usually caused by a known event, which can be a transient or persistent risk factor. A majority of provoked DVTs can be treated within primary care. Typical treatment duration is three months.

- Distal DVT may not need to be treated with anticoagulation. A small population of patients may favor observation through serial ultrasound if criteria is met.
- Patients do not require more than 3 months of anticoagulation for their first DVT occurring in the setting of a major transient risk factor
- Extended anticoagulation past 3 months is recommended for patients with persistent risk factors
- Preferred anticoagulation for both treatment and extended phase is apixaban, dabigatran, edoxaban, or rivaroxaban
    - Apixaban and rivaroxaban doses should be reduced when used during extended phase anticoagulation

Abbreviations	
CHEST	American College of Chest Physicians
CrCl	Creatinine clearance
DVT	Deep vein thrombosis
DOAC	Direct oral anticoagulant (includes apixaban, dabigatran, edoxaban, and rivaroxaban)
LMWH	Low molecular weight heparin
PE	Pulmonary embolism
SUBQ	Subcutaneous
CHEST	American College of Chest Physicians
CrCl	Creatinine clearance

Treatment Decision

Management of DVT depends on the location, proximal vs distal. The management of proximal DVT is straightforward, while the treatment of distal DVT is controversial. Acute PE is the most significant complication of DVT; however studies have shown very low risk of developing PE in patients with a distal DVT. There may be a small population of patients that can avoid anticoagulation as many episodes resolve without anticoagulant treatment and there is a very low risk of developing PE.[1]

Table 1: Proximal vs. Distal DVT

Location	Definition	Management
Proximal	DVT in the lower extremity located in the popliteal, femoral or iliac veins	Treat with anticoagulation
Distal	DVT located below the knee in the calf veins; most are in the posterior tibial and peroneal veins	Assess and treat as outlined below

Patients (with distal DVT) <u>with</u> any of the following may favor choosing anticoagulation[2]:

- Symptoms
- Positive D-dimer
- Extensive thrombosis (e.g., >5 cm in length, multiple veins, >7 mm maximum diameter)
- Thrombosis close to the proximal veins
- Active cancer
- Prior DVT or PE
- Inpatient status
- Current COVID-19 infection

Patients with distal DVT that is confined to the muscular veins of the calf may favor observation for DVT extension with proximal vein compressive ultrasound every 2-4 weeks (if extension does not occur with two weeks, it is unlikely to occur). Patients who have a high or moderate risk for bleeding may also observation[2].

Treatment

There are three phases of DVT management, initiation, treatment, and extended phase (see **Table 2**). Continuation of anticoagulation following the treatment phase varies based on whether the DVT was provoked by a transient or persistent factor (see **Table 3**).[2]

Table 2: Phases of DVT Management[2]

Phase	Duration	Comments
Initiation phase	~5-21 days	• Initial provision of anticoagulant following diagnosis • Duration is dependent on anticoagulant regimen
Treatment phase	3 months	• Period after initiation that completes treatment for the acute DVT • All patients should be assessed for extended therapy after completion of the treatment phase
Extended phase	No planned stop date	• Period of anticoagulant use at full or reduced dose for the goal of secondary prevention • Reevaluate extended phase anticoagulation at least annually

Table 3: Examples of Transient and Persistent Risk Factors (Not All Inclusive)[3,4]

Major Transient Factors (occur within 3 months of DVT diagnosis)	Minor Transient Factors (occur within 2 months of DVT diagnosis)	Persistent Factors
• Surgery with general anesthesia for ≥ 30 minutes • Confined to bed in the hospital for ≥3 days with an acute illness • Cesarean section	• Surgery with general anesthesia for < 30 minutes • Admission to hospital for <3 days with an acute illness • Estrogen therapy • Pregnancy and puerperium • Confined to bed out of the hospital for ≥3 days with acute illness • Leg injury associated with decreased mobility for ≥3 days	• Active cancer (e.g., ongoing chemotherapy, recurrent or progressive disease) • Inflammatory bowel disease • Autoimmune disorders (e.g., antiphospholipid syndrome, rheumatoid arthritis) • Chronic infections • Chronic immobility (e.g., spinal cord injury)

All patients should be assessed for extended therapy after the 3-month treatment phase. Continued anticoagulation after the treatment phase may be influenced by the patient's risk of bleeding (see **Table 4**) in addition to the precipitating factor.

Table 4: Risk of Bleeding[5]

Risk Factors (1 point per risk factor)					
Age >65 years	Age >75 years	Previous bleeding	Cancer	Metastatic cancer	Renal failure
Liver failure	Thrombocytopenia	Previous stroke	Diabetes	Anemia	Antiplatelet therapy
Poor anticoagulant control	Comorbidity and reduced functional capacity	Recent surgery	Frequent falls	Alcohol abuse	
Low risk = 0 risk factors		**Moderate risk = 1 risk factor**			**High risk = 2 or more risk factors**

CHEST guidelines for Extended Phase therapy[2]

- Major transient risk factor
  - Recommend against extended phase anticoagulation
- Minor transient risk factor
  - Suggest against extended phase anticoagulation
- Persistent risk factor
  - Recommend extended phase anticoagulation with a DOAC
  - Suggest extended phase anticoagulation with warfarin for those who cannot receive a DOAC

Anticoagulation Selection for Treatment Phase

CHEST and American Society of Hematology guidelines recommend DOACs as the preferred treatment phase anticoagulant, with no preference given for a specific DOAC[2,4]. However, selection of specific anticoagulant may be influenced by patient co-morbidities.[5]

- Active cancer → Factor Xa Inhibitors or LMWH are preferred
- Liver disease → LMWH is preferred, DOACs contraindicated, warfarin may be difficult to control
- Renal disease → LMWH and DOACs require dose adjustments, warfarin may be more preferred with severe renal impairment
- Pregnancy → LMWH is preferred
- Cost may be a barrier to anticoagulation. Generic options include warfarin, enoxaparin, dabigatran, and fondaparinux.
- Warfarin, dabigatran and edoxaban all require initial parenteral therapy for the initiation phase of anticoagulation. If there is a desire to avoid parenteral therapy, choose apixaban or rivaroxaban.

Table 5: Anticoagulation Dosing

Class	Drug	Dosing
LMWH	Enoxaparin (parenteral)	• 1 mg/kg SUBQ Q12H or 1.5 mg/kg SUBQ Q24H • Renal (CrCl <30 mL/min): 1 mg/kg SUBQ daily
Factor Xa Inhibitor*	Apixaban	• Initiation phase: 10 mg PO BID for 7 days • Treatment phase: 5 mg PO BID • Extended phase: 2.5 mg PO BID
	Rivaroxaban	• Initiation phase: 15 mg PO BID for 21 days • Treatment phase: 20 mg PO daily with food • Extended phase: 10 mg PO daily • Renal (CrCl <30 mL/min): avoid use

	Edoxaban	• Initiation phase: 5-10 days of parenteral anticoagulation • Treatment phase: 60 mg PO daily (after parenteral agent) • Weight ≤60 kg: 30 mg PO daily • Renal (CrCl 15-50 mL/min): 30 mg PO daily • Renal (CrCl <15 mL/min): avoid use
	Fondaparinux (parenteral)	• <50 kg: 5 mg SUBQ daily • 50-100 kg: 7.5 mg SUBQ daily • >100 kg: 10mg SUBQ daily • Renal (CrCl <30 mL/min): contraindicated
Direct Thrombin Inhibitor*	Dabigatran	• Initiation phase: 5-10 days of parenteral anticoagulation • Treatment phase: 150mg PO BID (after parenteral agent) • Renal (CrCl ≤30 mL/min): avoid use
Vitamin K Antagonist	Warfarin	• Initiation phase: at least 5 days of parenteral anticoagulation • Treatment phase, initial dose: 5 mg PO daily x 3 days (reduce dose for patients expected to be more sensitive), start same day as parenteral agent, continue both for at least 5 days and until INR is ≥2 for at least 24 hours • INR goal 2-3 • Monitor and adjust dose every 2-3 days until INR is stable • See Warfarin Dose Adjustment Guidelines for modification of warfarin once INR is stable

*Renal dosing information provided in this table is specific for the DVT indication for these medications. Refer to package labeling for renal dose adjustments for other indications.

References

1. Kabashneh S, Muacevic A, Adler JR. A comprehensive literature review on the management of distal deep vein thrombosis. Cureus. 2020;12(5):e8048.
2. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. CHEST. 2021;160(6):e545-e608.
3. Kearon C, Ageno W, Cannegieter SC, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost. 2016;14(7):1480-1483.
4. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-738.