HEME ABNORMALITIES: ALL THINGS IRON (DEFICIENCY)

Kate MacInnes, MD, FRCPC

January 20, 2024

Presenter Disclosure

- Presenter: Kate MacInnes, MD, FRCPC

- I have had relationships with commercial interests:
  - *Participated on Advisory Board for Janssen and Gilead*
  - *Received honoraria as a speaker from Pfizer, Astrazeneca, BeiGene*

Objectives

Review Mechanisms and pathophysiology of iron deficiency anemia (IDA)

Work-up of IDA

Treatment approach

Case

- 65F with fatigue, SOBOE, progressive microcytic anemia
- PMH: RA, DM2, COPD, HTN
- Occasional heartburn, no bleeding history, no melena
- Hb 100, MCV 75, ferritin 50, % sat 14, TIBC

Background

- Iron deficiency is common
- Frequently affected = toddlers, adolescent girls, and women of childbearing age
- Impacts cognition, emotion, pain and education status

Looker, AC et al. Prevalence of iron deficiency in the United States. *JAMA*. 1997;277(12):973.

Who is most at risk?

- Infants and children <5yo
- Menstruating women
- Second/third trimester of pregnancy
- Post-partum
- Adolescents (rapid growth)
- Vegetarians/vegans
- Blood donors
- Elite endurance athletes
- IRIDA

Camaschella C. Blood 2019:133;30-40

Type of cause	Condition	Pathophysiologic mechanism
Increased iron requirements	Infants, preschool children, adolescents	Rapid growth
	Pregnant women: second and third trimesters	Expansion of maternal and fetal erythroid mass
	ESA treatment	Acute expansion of erythroid mass
Low iron intake	Malnutrition*	Insufficient dietary iron: low heme iron or scarcely bioavailable iron (eg, chelated by phytates)
	Vegetarians, vegans	
Decreased intestinal iron absorption	Gastrectomy, duodenal bypass, bariatric surgery	Decreased absorptive surface
	Gluten-induced enteropathy	
	Autoimmune atrophic gastritis	Increased pH
	Helicobacter pylori infection	Increased pH and blood loss
	Drugs: proton pump inhibitors, H_2 blockers	Blocking of gastric acid secretion
	Genetic IRIDA†	High serum hepcidin levels
Chronic blood loss	Hookworm infestation*	Bleeding from gastrointestinal tract
	Gastrointestinal benign and malignant lesions	
	Salicylates, corticosteroids, nonsteroidal anti-inflammatory drugs	
	Heavy menses, hematuria	Bleeding from genitourinary system
	Intravascular hemolysis (PNH, march hemoglobinuria)	Urinary loss of hemoglobin (iron)
	Drugs: anticoagulants, antiplatelet compounds	Systemic bleeding
	Defects of hemostasis (hereditary hemorrhagic telangectasia, von Willebrand disease)	
	Frequent blood donors	Repeated blood letting

Camaschella C. Blood 2019:133;30-40

When it's multifactorial

Multiple causes (absolute iron deficiency associated with inflammation)	Chronic infections in malnutrition*	Reduced intake, increased proinflammatory cytokines
	Chronic kidney disease	Decreased iron absorption, increased blood loss, reduced hepcidin excretion and increased production, drugs, ESAs
	Chronic systolic heart failure	Decreased iron absorption, increased inflammation, blood loss
	Inflammatory bowel diseases	Decreased iron absorption, increased blood loss, high hepcidin
	Postoperative anemia of major surgery	Blood loss, increased proinflammatory cytokines

Camaschella C. Blood 2019:133;30-40

Absolute vs. Functional

- Absolute
  - *Low total body stores and thus absent bone marrow iron stores*
  - *Low serum ferritin levels*
  - *Decreased iron intake, absorption, or increased blood loss*

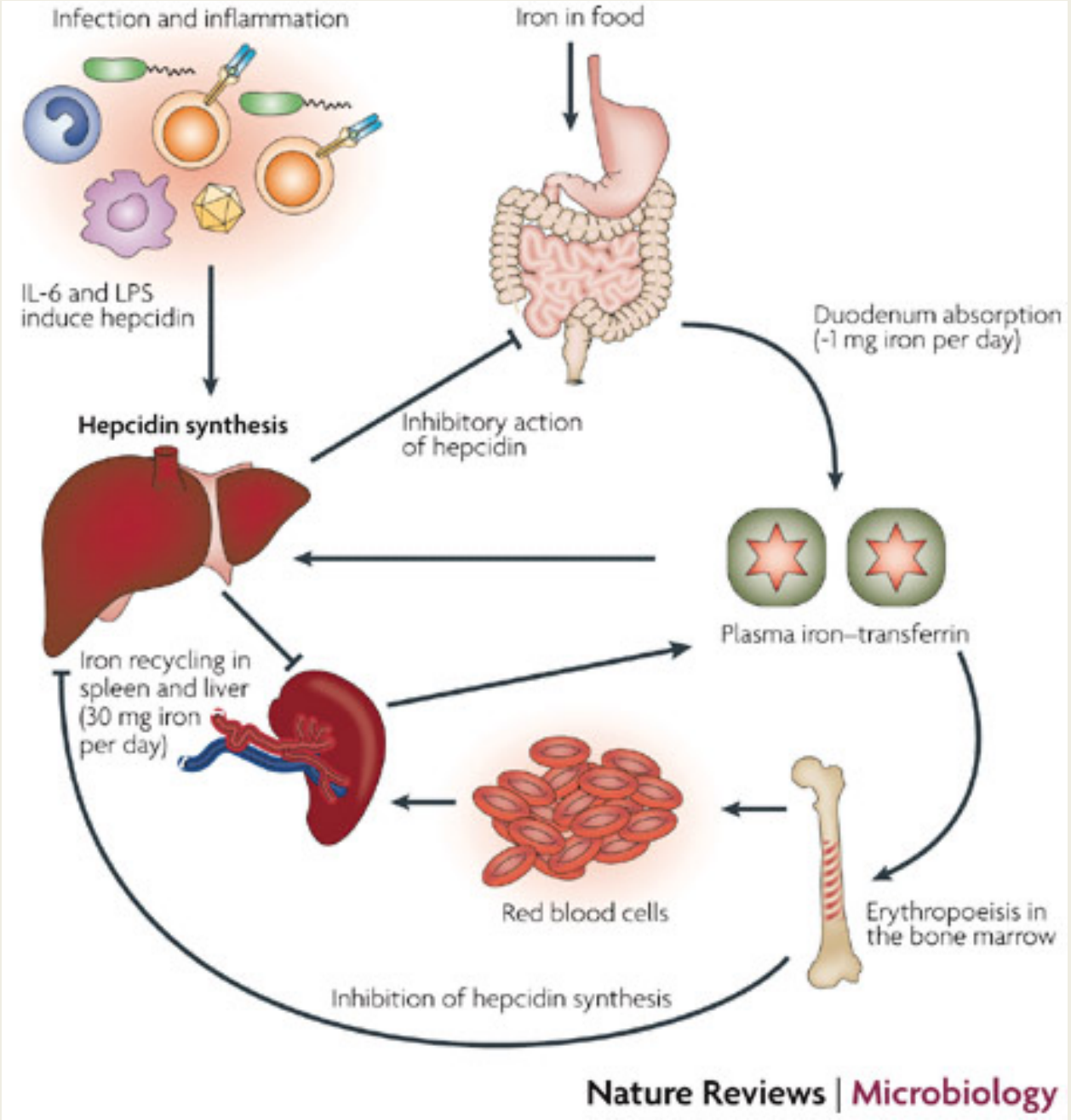
- Functional
  - *Normal or increased body iron stores*
  - *Iron is not available to erythroid precursors*
  - *Settings of inflammation and chronic disease*

- Not mutually exclusive

Iron Metabolism: The Players

- Ferritin – linked to iron status
- Transferrin receptor 1 (TfR1) – upregulated in iron deficient state
- Transferrin
- Hepcidin

Iron Metabolism



Drakesmith, H & Prentice, A. Viral Infection and Iron Metabolism. *Nature Reviews Microbiology* 6, 541-552 (July 2008).

Dietary Iron

- Ferric hydroxides, ferric-protein and Heme-protein complexes
- Meat > vegetables
- Average Western diet = 10-15mg iron daily
- Only 1-2mg/day is absorbed

Daily Iron Requirements

	Urine, sweat, feces (mg)	Menses (mg)	Pregnancy (mg)	Growth (mg)	Total (mg)
Adult male	0.5-1				0.5-1
Postmeno-pausal female	0.5-1				0.5-1
Menstruating female	0.5-1	0.5-1			1-2
Pregnant female	0.5-1		1-2		1.5-3
Children	0.5			0.6	1.1
Female (age 12-15)	0.5-1	0.5-1		0.6	1.6-2.6

Hoffbrand, Moss, Pettit. "Hypochromic Anemias." Essential Haematology, 5th edition. 2006.

Causes of Iron Deficiency

- Bleeding
- Malabsorption
  - *Foods*
  - *Medications*
  - *H. Pylori*
  - *Celiac Disease*
  - *Gastric bypass*
- CKD/Inflammatory disorders/CHF
- PNH
- Congenital iron deficiency
- Pulmonary hemosiderosis
- Erythropoietin

Stages

- Iron stores (mg) ≈ (8 or 10) x ferritin (ng/mL)

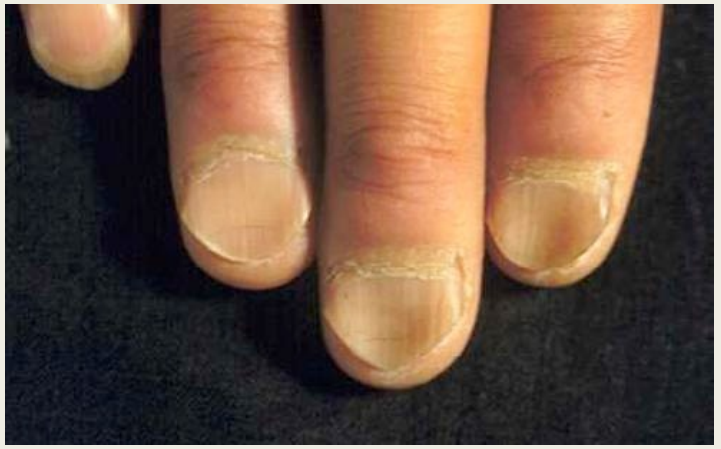
- 1. Low iron stores without anemia
- 2. Iron deficient, normocytic anemia
- 3. Iron deficient, microcytic anemia.

Symptoms

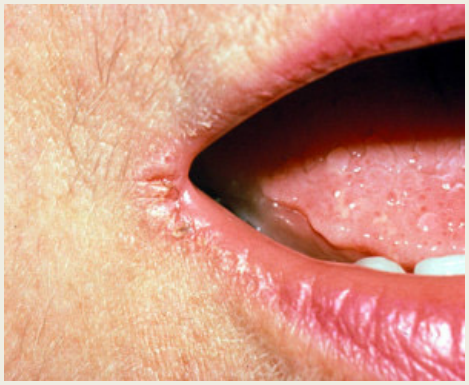
- Fatigue, decreased exercise tolerance
- Pica/Pagophagia
- Restless legs syndrome
- Beeturia
- SOB
- Angina

Clinical Signs

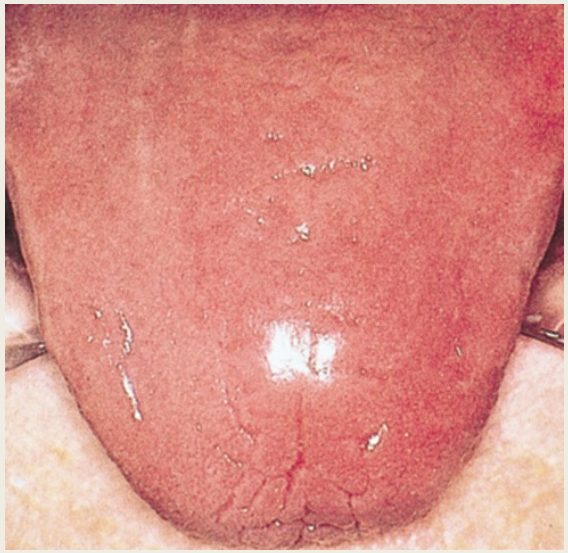
- Koilonychia
- Angular cheilosis
- Atrophic glossitis
- Plummer-Vinson



Medicalinfopictures.com



Angularcheilitis.net



Fpnotebook.com

Diagnosis - Definitive

Definitive Tests	Advantages	Limitations
Serum ferritin	Quantitative (iron stores) Well standardized	Affected by inflammation Affected by liver disease
Serum transferrin receptor	Quantitative (tissue deficiency) Unaffected by inflammation	Lacks standardization Affected by rHuEPO treatment
Bone-marrow iron	Well established High specificity	Invasive, expensive Prone to error

Cook, JD. Diagnosis and management of iron deficiency anemia.*Best Practice & Research Clinical Haematology*. 2004;18(2):319-332.

Diagnosis

- LOW ferritin (<40-100 depending on scenario)
- LOW serum iron
- HIGH (or normal) TIBC
- LOW % saturation (i.e. <20%)

Ferritin

- Landmark study:
  - *259 anemic patients >65yo*
  - *Objective: determine ferritin cut-off values to distinguish **iron deficiency anemia** from **anemia of chronic disease***
  - *Findings:*
    - Ferritin <40µg/L = iron def. anemia w/o inflammation
    - Ferritin <70µg/L = iron def. anemia with inflammation

Guyatt GH, Patterson C, Ali M et al. Diagnosis of iron-deficiency anemia in the elderly. *Am J Med* 1990;88:205-209

More recently

- In absence of inflammation:
  - *Ferritin <30 mg/L = iron deficiency*
- In presence of inflammation
  - *Ferritin <100 mg/L with <20% transferrin saturation*
  - *= iron deficiency*

Treatment

- First – what is the cause?
  - *Ideally, find and eliminate the cause*
- Second – replace iron stores
  - *Oral vs. IV iron*

Work-up

- A good history
  - *Elicit any bleeding history*
    - Menstrual
    - GI
    - Epistaxis
    - Hematuria
  - *Reasons for malabsorption*
    - Heartburn
    - Diarrhea/gluten sensitivity
    - History of bariatric surgery
    - History of blood donation
    - PPI or other antacids

Underlying etiologies of ID

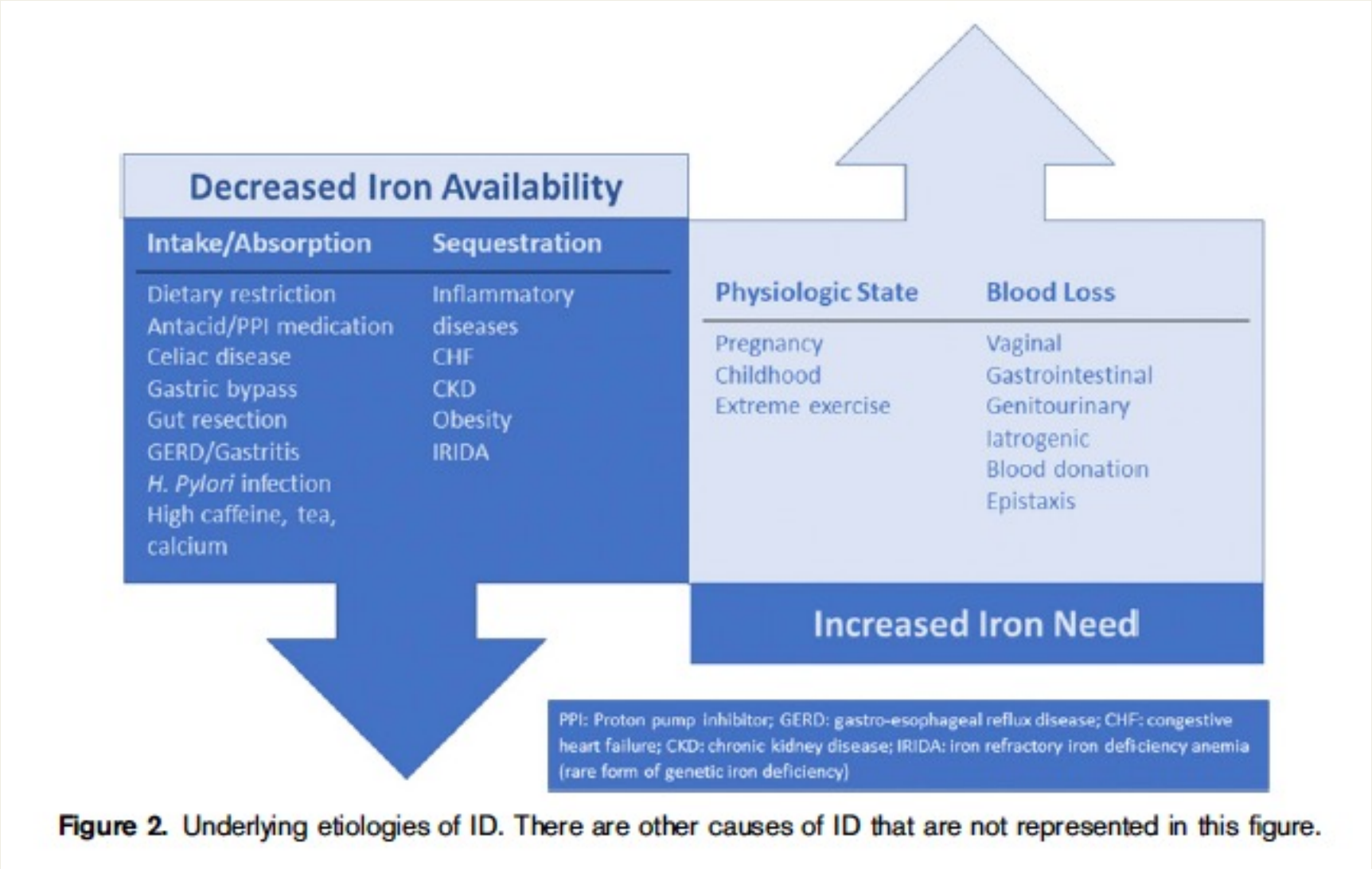


Figure 2. Underlying etiologies of ID. There are other causes of ID that are not represented in this figure.

Ning et al. Hematology ASH ed program 2019.

What tests to order?

- Diagnosis of iron deficiency?
  - *CBC, retic, peripheral smear, TIBC, %sat, ferritin*
  - *Rule out vit B12 and/or folate deficiency, TSH*

- H. pylori stool Ag
- Anti-TTG
- FOBT

- If no clear other source of blood loss, or any hint of GI bleeding, upper and lower endoscopy
  - *+/- CT enterography*
  - *Capsule endoscopy in rare cases*

- Should not need a BMBx to diagnose

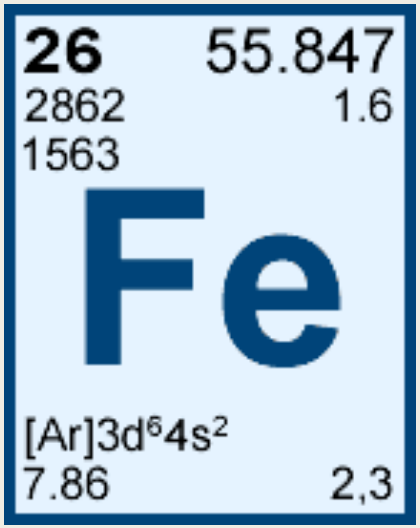
Treatment – role for pRBC transfusion

- Avoid blood transfusions unless hemodynamically unstable
  - *Cardiovascular compromise*
  - *Debilitating symptoms*

- For majority of patients there is time to implement iron supplementation

Treatment

- Oral iron supplementation
  - *First line*
  - *Inexpensive*
  - *Often poorly tolerated*
  - *When tolerated, effective*



- Limitations
  - *Side effects = poor adherence*
  - *Malabsorptive conditions*
  - *Unable to keep up with heavy blood loss*
  - *Slow to replete body's iron stores*

Oral iron formulations

Table 2. Common doses and elemental iron content of select available iron formulations in the United States and Canada

Drug class	Example	Dose per tablet (mg)	Elemental iron content per tablet (mg)	Dose	Special instructions
Iron salts	Ferrous gluconate	240	27	1-3 tablets, once per day or once every other day	Take on empty stomach; consider vitamin C; take at a different time of day than antacid or proton pump inhibitor. Acidic environment required.
		325	38		
	Ferrous sulfate	325	65	1-2 tablets, once per day or once every other day	
	Ferrous fumarate	325	106	1 tablet, once per day or once every other day	
Heme iron polypeptide	Proferrin	398	11	1-3 tablets per day	Can be taken with a meal. Acidic environment not required for absorption.
Polysaccharide iron complex	Feramax	150	150	1 tablet once per day	Can be taken with a meal. Acidic environment not required for absorption.
Ferric citrate	Auryxia	210	210	3-5 tablets once per day	Can be taken with a meal. Acidic environment not required for absorption.

The list of examples and doses in this table is not exhaustive. Liquid formulations are also available.[71] Approximately 10% of elemental iron ingested is absorbed.

Ning et al. Hematology ASH ed program 2019.

How to optimize oral iron

- Take between meals
- Avoid taking with dairy, tea, or coffee
- Avoid antacids
- (Take with vit C) – called into question now
- Once daily dosing or q2days

How long will it take?

- Reticulocytosis starts in 4-5 days
- Hb may improve by week 2
- Restoration of iron stores and ferritin = 3-6 months
- Perhaps longer depending upon the severity and ongoing losses

IV iron indications

Table 2. Indication for IV iron therapy

Condition	Reason
Oral iron intolerance	Persistent gastrointestinal adverse effects
Oral iron refractoriness	Defective absorption: gastrectomy, duodenal bypass, bariatric surgery
	Intestinal disorders (selected cases): IBD, atrophic gastritis, *Helicobacter pylori* infection, gluten enteropathy
	Genetic forms (IRIDA)
	No Hb improvement after 4 wk of oral therapy
Severe anemia (Hb <7-8 g/dL)	Need for rapid Hb improvement
Second and third trimesters of pregnancy	Need for rapid Hb increase; often intolerance to oral preparations
ESA treatment	More effective than oral iron in CKD
Chronic blood loss difficult to manage with oral iron	Heavy uterine bleeding
	Hereditary disorders of hemostasis
Other	Postoperative anemia of major surgery
	Chronic systolic heart failure

Camaschella C. Blood 2019:133;30-40

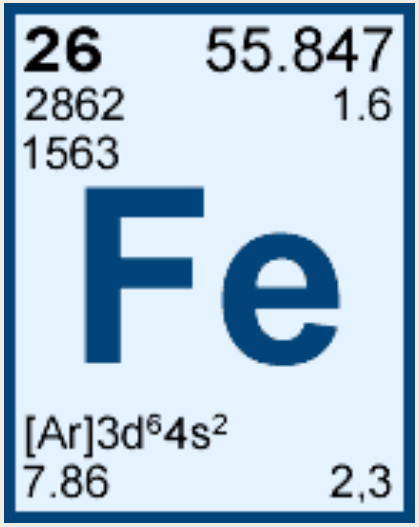
IV iron

- Parenteral Iron
  - *Greater absorption*
  - *Safe in IBD patients*
  - *Heavy blood loss*

- Limitations
  - *Infusional Time*
  - *Adverse reactions*
  - *Cost*

- Hemoglobin iron deficit (mg) =

weight (kg) x [target Hb –Pt's Hb(g/dL)] x 2.145



IV iron formulations

Table 3. Intravenous iron formulations

Compound	Brand name	Recommended amount per dose	Infusion time	Availability	Reference
Low-molecular-weight iron dextran	INFeD	100 mg after uneventful 25-mg test dose	2-6 h (+ test dose)	United States, Europe	https://www.pdr.net/drug-summary/INFeD-iron-dextran-2087; https://www.allergan.com/assets/pdf/infed_pi
Ferrous gluconate	Ferrlecit	125 mg	12.5 mg/min	United States, Europe, Canada	http://products.sanofi.us/ferrlecit/ferrlecit.html
Iron sucrose	Venofer	200-300 mg	100 mg/30 min	United States, Europe, Canada	http://www.venofer.com/Indications_Dosage
Ferumoxytol	Feraheme	510 mg	15 min	United States, Europe	https://www.feraheme.com/dosing-and-administration/
Ferric carboxymaltose	Injectafer	750 mg	15 min	United States, Europe	https://injectaferhcp.com/iron-deficiency-anemia-dosing
	Ferinject	1000 mg	15 min	United States, Europe	https://www.ferinject.co.uk/simplified-dosing-for-all-patients/
Iron isomaltoside	Monofer	≤1000 mg	>15 min	United States, Europe	https://www.medicines.org.uk/emc/files/pil.5676.pdfinu
	Monoferric	>1000 mg (maximum 20 mg/kg)	≥30 min	Canada	

Ning et al. Hematology ASH ed program 2019.

“Standard” vs. High dose IV iron

- Examined the benefits, efficacy, and retreatment rates of a higher dose of IV iron (1500 mg ferric carboxymaltose) vs. standard cumulative (1000 mg) iron sucrose
- Average iron deficit calculated to be ~1500 mg for patients.
- Significantly lower rate of re-treatment in 1500mg(5.6%) group, compared to 1000 mg group (11.1%)
- Conclusion: Total cumulative dose of 1000 mg IV iron insufficient, and 1500 mg is closer to actual deficit, requiring fewer repeat infusions

Koch et al. Anemia. 2015.

2018 Adkinson et al.

- Phase 3 Randomized controlled double blind

- Compared 2 doses of each in pts with IDA on days 1 and 8 or 9:
  - *Ferumoxytol 510 mg*
  - *Ferric carboxymaltose 750 mg*

- No anaphylaxis either group
  - *Rates of mod-severe hypersensitivity reactions similar*

- Ferumoxytol noninferior to FCM, and higher Hb rise over 4 weeks with higher dosed ferric carboxymaltose.

- Supports approach of treating with 1000 mg up front and R/A at 4 weeks

Adkinson et al. Am J Hematol. 2018 May;93(5):683-690.

RESEARCH ARTICLE

WILEY AJH

A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia

Richard Derman[1] | Eloy Roman[2] | Manuel R. Modiano[3] | Maureen M. Achebe[4] | Lars L. Thomsen[5] | Michael Auerbach[6]

Purpose: Compared safety and efficacy of iron isomaltoside and iron sucrose

Methods: Administered iron isomaltoside 1000mg infusion or 500 mg injection over 2 min vs. iron sucrose 200 mg over 30 min.

- Mean cumulative dose iron isomaltoside 1640 mg
- Mean cumulative dose iron sucrose 1128 mg

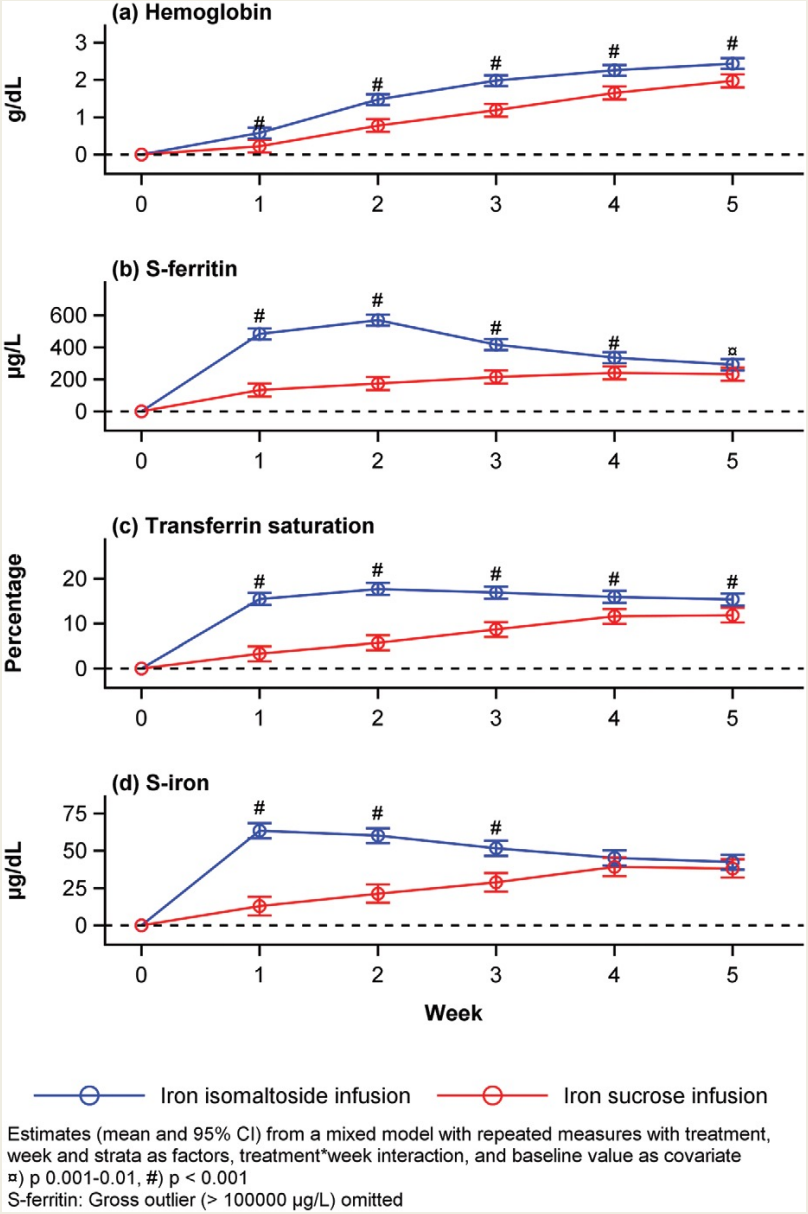
Primary endpoint: Hb increase ≥20 g/L from baseline at any point between weeks 1-5

Findings:

- Shorter time to Hb increase ≥20 g/L in isomaltoside group
- Similar tolerability
- 0.6% experienced a serious adverse drug reaction in both groups
- iron isomaltoside allowed higher cumulative iron dose in fewer administrations

Derman et al. *Am J Hematol.* 2017;92-286-291

Iron sucrose vs iron isomaltoside



Derman et al. *Am J Hematol.* 2017;92-286-291

Cost of IV iron

- In CB, IV iron is on hospital formulary, so no cost to patient

- Gluconate: 100 mg = $27.42
  - *Typical dose = 125 mg = $34.27*
  - ***Usual # doses = 4-8 ($137-$274)***

- Sucrose: 100 mg = $37.50
  - *Typical dose = 300 mg = $112.50*
  - ***Usual # doses 4-8 ($450-900)***

- Isomaltoside 100mg = $45
  - *Typical dose 1000 mg = $450*
  - ***Usual #doses 1-2 ($450-900)***

My IV iron approach

- Give 1 dose of weight-based isomaltoside (20mg/kg)
  - *Unless 2-3rd trimester pregnancy, still use sucrose*
- 4 weeks after dose, repeat CBC, ferritin, % sat
  - *Repeat monthly ongoing*
- If ferritin ≤200 or % sat ≤20, repeat IV dose q4 weeks until target achieved
- Reassess in 3-4 months ongoing IV iron needs
  - *Reduce frequency of BW if possible*

Case

- Anti-TTG negative
- H. pylori stool Ag positive
- FOBT neg

- Still awaiting endoscopy

- Oral iron therapy started. Intolerant after 2-3 weeks with +++constipation

- Gave one dose isomaltoside IV 20mg/kg
  - *Rechecked 4 weeks later, Hb 110, MCV 80, ferritin 105, % sat 18*
  - *Ordered one more dose isomaltoside*
  - *Symptoms of fatigue and SOBOE much improved*

Conclusion

- Iron deficiency is common, and should be treated (with or without anemia)
- Low serum ferritin diagnostic
  - *< 40mg/L, <50 mg/L in pregnancy*
- Difficult to assess patients with comorbidities using ferritin alone
  - *% sat <20 diagnostic*
- Oral iron dosed daily or q2d most effective
- Switch to IV iron if ++side effects or ineffective after 1 month
- Treat underlying cause

References

- Looker, AC et al. Prevalence of iron deficiency in the United States. *JAMA*. 1997;277(12):973.
- Zariwala, MG et al. Comarison Study of Oral Iron Preparation Using a Human Intestinal Model. *Scientia Pharmaceutica* 2013; 81:1123-1139.
- Patterson AJ et al. Dietary and supplement treatment of iron deficiency results in improvements in general health and fatigue in Australian women of childbearing age. *J Am Coll Nutr*. 2001;20(4):337-42.
- Bruner AB et al. Randomized study of cognitive effects of iron supplementation in non-anemic iron-deficiency adolescent girls. *Lancet* 1996;348:992-996
- Hoffbrand, Moss, Pettit. "Hypochromic Anemias." Essential Haematology, 5th edition. 2006.
- Schrier, Stanley. Causes and diagnosis of iron deficiency anemia in the adult. UpToDate.com. Last updated Aug. 20, 2014. Accessed www.uptodate.com Oct. 22, 2014.
- Schrier, Stanley, Auerbach, Michael. Treatment of the Adult with iron deficiency anemia. UpToDate.com. Last updated Oct. 9, 2014. Accessed www.uptodate.com Oct. 22, 2014.
- Jolobe, OMP. Does this elderly patient have iron deficiency anaemia, and what is the underlying cause? *Postgrad Med J*. 2000;76:195-198.
- Casper, CK et al. Clinical Aspects of Iron Deficiency. *JAMA.* 1965;191(5):359-364
- Cook JD, Skikne BS. Iron deficiency: definition and diagnosis. *J Intern Med*. 1989 Nov;226(5):349-55
- Drakesmith, H & Prentice, A. Viral Infection and Iron Metabolism. *Nature Reviews Microbiology* 6, 541-552 (July 2008).
- Sotos JG. Beeturia and iron absorption. *The Lancet.* 1999;354:1032.
- Guyatt GH, Patterson C, Ali M et al. Diagnosis of iron-deficiency anemia in the elderly. *Am J Med* 1990;88:205-209.
- Cook, JD. Diagnosis and management of iron deficiency anemia.*Best Practice & Research Clinical Haematology*. 2004;18(2):319-332.

QUESTIONS?

Regulation

- Levels of ferritin and TfR1 are linked to iron status
- Dependent on iron regulatory protein (IRP)
- Iron deficiency increases the ability of iron regulatory protein to bind to mRNA

Iron Absorption

Factors favouring absorption	Factors reducing absorption
Heme iron	Inorganic iron
Ferrous form (2+)	Ferric form (Fe3+)
Acids (HCl, vit C)	Alkalis – antacids, pancreatic secretions
Solubilizing agents (sugars, amino acids)	Precipitating agents – phytates, phosphates
Iron deficiency	Iron Excess
Ineffective erythropoiesis	Decreased erythropoiesis
Pregnancy	Infection
Hereditary hemochromatosis	Tea
Increased expression of DMT-1 and ferroportin in duodenal enterocytes	Decreased expression of DMT-1 and ferroportin, increased hepcidin

Hoffbrand, Moss, Pettit. “Hypochromic Anemias.” Essential Haematology, 5th edition. 2006.

Risks of IV iron

- Hypophosphatemia

- Most common:
  - *1.5%: Itching, dyspnea, wheezing*
  - *0.5-1%: Chest pain, nausea, hypotension, swelling, dyspepsia*
  - *0.2-0.5%: Diarrhea, flushing, headache, cardiac arrest, myalgias*
  - *Anaphylaxis <1% (1.7% with iron dextran formulations)*

- Risk highest with IV dextran formulations
  - *Dextran > gluconate > sucrose = isomaltoside*
  - *Isomaltoside: More skin reactions than sucrose*
    - Sucrose : more fatigue, GI, and nervous system complaints than isomaltoside
    - **Serious adverse reactions 0.6% in both sucrose and isomaltoside groups

Fishbane et al. *Am J Kid Dis*. 1996;28(4):529-34
Derman et al. *Am J Hematol.* 2017;92-286-291

Hypersensitivity reactions

- Complement activation-related pseudo-allergy
- Complement pathway activates mast cells and basophils
- Leads to secretion of histamine, thromboxanes, leukotrienes, and platelet-activating factor
  - *Trigger smooth muscle contraction, increased capillary permeability and loss of fluid from the intravascular space*

Fishbane reaction

- Most common reaction (1%)
- Hypotension, dizziness, flushing, myalgias, back or chest pain
- Self limited
- Usually abate within a few minutes
- Usually do not recur on re-challenge

- Do not need specific treatment

- Metallic taste and mild headache are normal physiologic response

Rampton et al. *Haematoligca. 2014;99(11):1671-76*

Predictors of Reaction

- History of drug allergy (OR 2.4)
- History of multiple drug allergy (OR 5.5)
- Fast infusion rate (rapid increase in labile free iron)
- Severe asthma or eczema
- Mastocytosis
- Severe respiratory or cardiac disease*
- Old age*
- Treatment with beta-blockers, ACEi*
- First trimester pregnancy (no evidence in first trimester)
- Anxiety (patient or staff)

*May worsen outcome of HSR, if occurs

Fishbane et al. *Am J Kid Dis*. 1996;28(4):529-34
Rampton et al. *Haematoligica. 2014;99(11):1671-76*

Prevention of HSR

- Location: give infusions in appropriately staffed sites equipped with resuscitation facilities
- Personnel: Staff should have regularly updated training in IV iron and adverse reactions
- Patient: Provide information to the patient about the risk of a HSR before the infusion, and indicate its rarity
- Administration: Check for risk factors for a HSR, document baseline VS, prepare infusion as per manufacturer's instructions
- Risk minimization: Weigh risks vs benefits for each individual patient.
  - *Monitor for HSR for ≥30 min post-infusion*

Rampton et al. *Haematoligica. 2014;99(11):1671-76*