

Iron Replacement in Iron Deficiency Anemia

September 25, 2019

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WHO Definition of Anemia

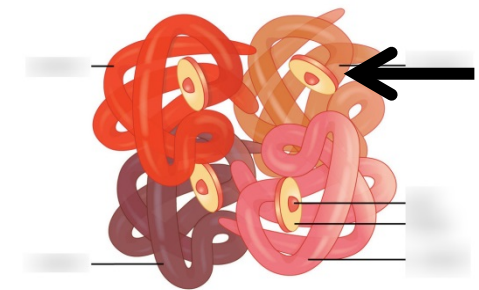
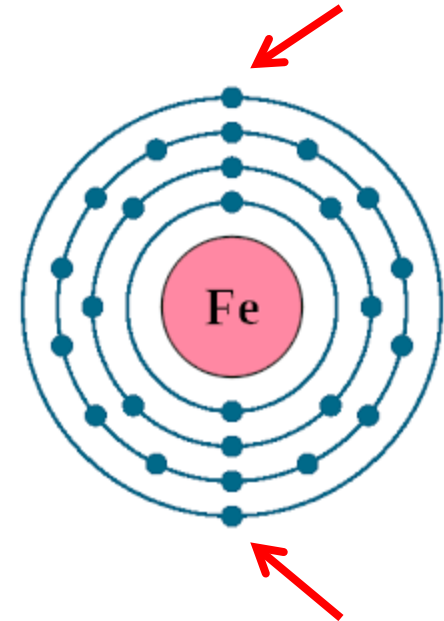
Population	Hb diagnostic of anemia (g/L)
Children 6 mo – 6 yrs	< 110
Children 6 – 14 yrs	< 120
Adult men	< 130
Adult non-pregnant women	< 120
Adult pregnant women	< 110

The two most common anemias: iron deficiency anemia, anemia of inflammation (chronic disease)

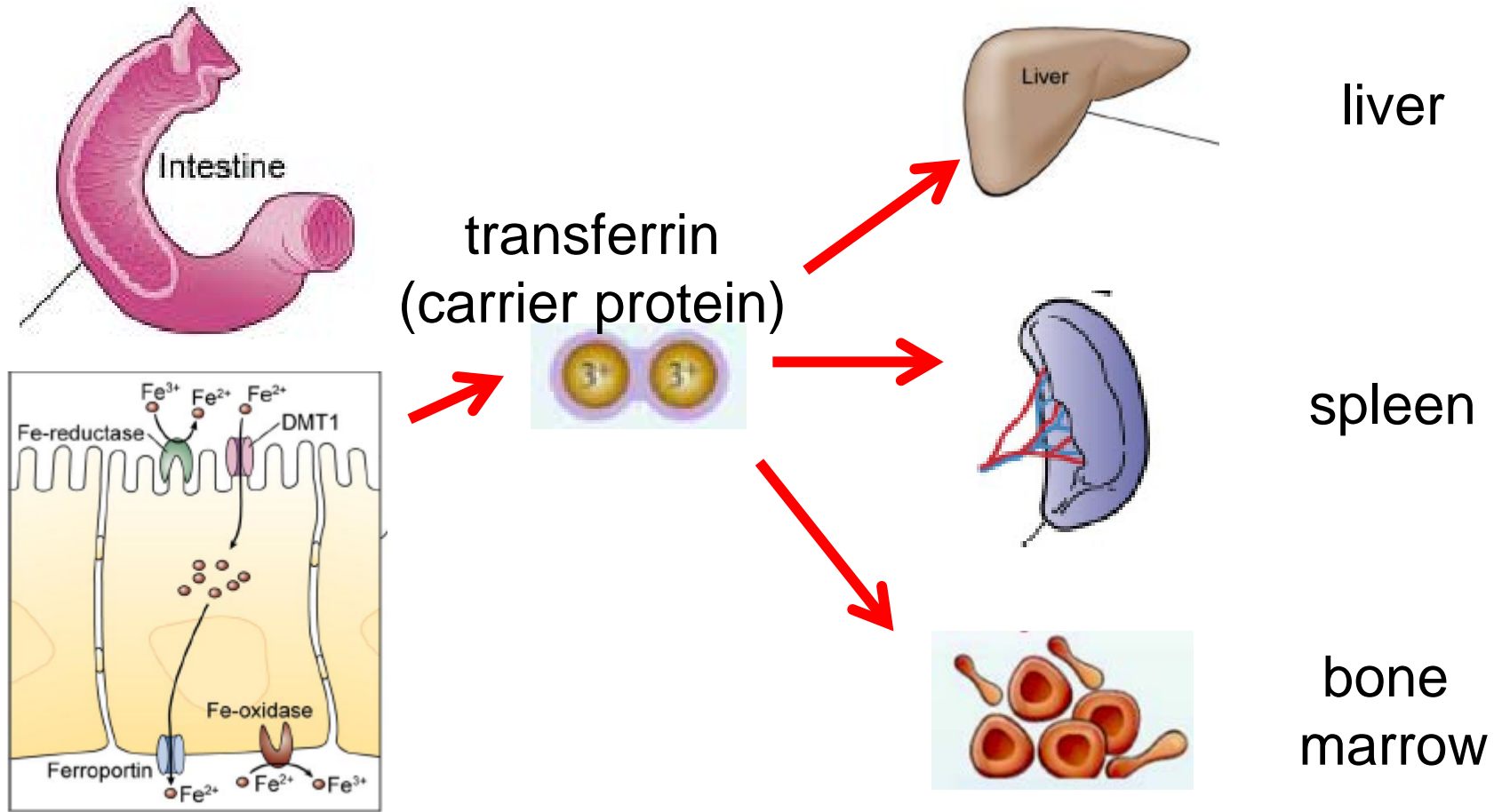


Functions of Iron

- vitally important biological element
- a transitional metal able to accept and donate electrons, functions as an oxidant or reductant in many biochemical reactions
- in mammals, main functions are:
 - oxygen transport as part of hemoglobin and myoglobin
 - part of an enzyme required for DNA synthesis (ribonucleoside reductase)
 - energy production in cytochromes in the mitochondria of cells



Iron Absorption, Transport and Storage



oxidized ferric iron Fe^{3+} is reduced to ferrous iron Fe^{2+} in the gut

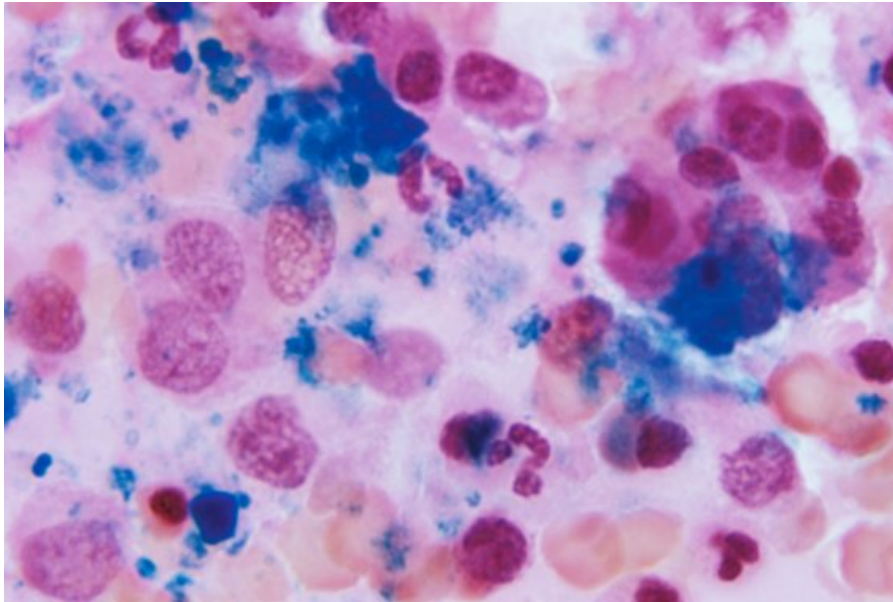


Iron Absorption, Transport and Storage

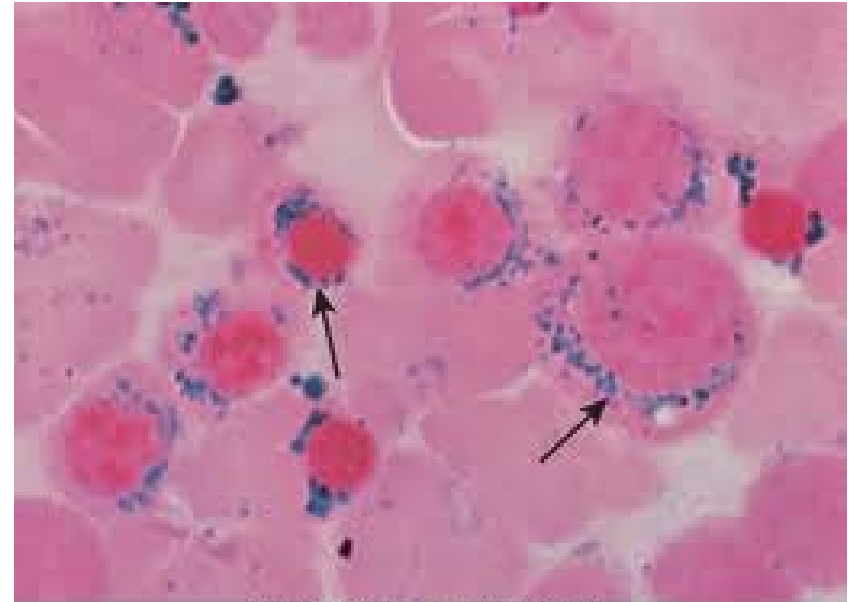
- total body iron 3500mg (M), 2500mg (F), use 25 mg/day
- location of iron:
 - hemoglobin 2000 mg (M), 1500 mg (F)
 - storage 600-1000 mg (M), 200-300 mg (F)
 - tissue iron (enzymes) plus other: 200 mg
- iron absorption from gut 1-2 mg/day, tightly controlled
- about 25% of heme iron (from hemoglobin and myoglobin) is absorbed vs. 5% of non-heme iron
- iron loss is not controlled
 - 1-2 mg/day: shedding of enterocytes, skin cells
 - plus 1-2 mg/day in pre-menopausal women
 - menstruation 20-50 mg per month



Iron in Bone Marrow



In macrophages
(storage iron)



In erythroid
precursors



Iron deficiency Anemia

- The most common nutritional deficiency
 - 5% of women
 - 5-30% of pregnant women
 - 26% of major orthopedic surgery patients
 - 50% of cardiac surgery patients



Causes of Iron Deficiency

- Increased demand: infancy, adolescence, menstrual blood loss, pregnancy, erythropoietin therapy
- **blood donation:** 2 donations (F) or 3-4 (M) will deplete iron stores. About 200 mg iron per blood donation.
- Insufficient intake: iron-poor diet, including vegetarian, vegan
- Decreased absorption: GI surgery or disease
- Chronic blood loss: bleeding from GI or GU tract
- Drug-related: glucocorticoids, salicylates, NSAIDs, PPIs,
- Genetic iron-refractory iron deficiency anemia (rare)

Camaschella. NEJM 2015;372:1832

Shuchman. CMAJ 2014;186(11):817



Effects of Iron Deficiency Anemia

- weakness, fatigue
- difficulty concentrating, poor work productivity
- decreased cognitive performance
- delayed mental and motor development in children
- pica (consumption of dirt, clay)



Tests for Iron Deficiency



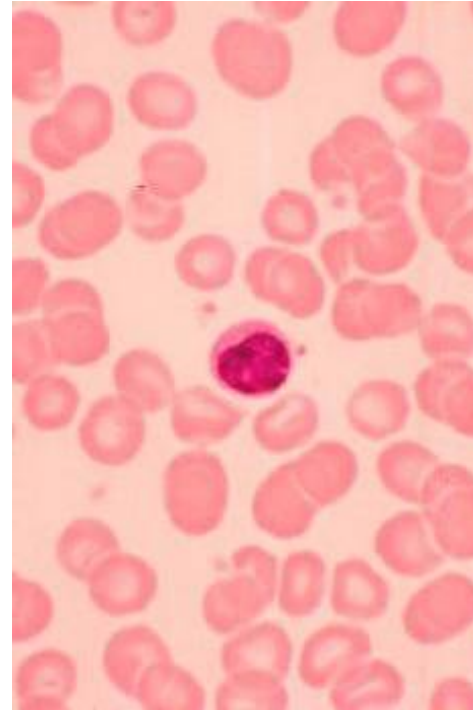
- Hemoglobin (iron in red cells)
 - normal 140-175 g/L (male), 120-153 g/L (female)
- Ferritin (storage iron)
 - normal 12-300 ng/mL (male), 12-150 ng/mL (female)
 - rises with acute inflammation, so may be normal in iron deficiency, measure TSAT too
- Others
 - MCV (mean red cell volume), serum iron, iron binding capacity (transferrin), transferrin saturation (TSAT)
 - may be needed to differentiate IDA from other types of anemia



Peripheral Blood Film



**Microcytic
(and hypochromic)**



**Normocytic
(and normochromic)**



Diagnosis of Iron Deficiency Anemia

- Hb less than 130 g/L (male) or less than 120 g/L (female)

AND one of:

- Ferritin \leq 30 $\mu\text{g/L}$ within past 6 months
 - or ferritin less than 100 $\mu\text{g/L}$ and transferrin saturation less than 20%
- MCV \leq 75 fL , previously normal



Sources of Iron

- Dietary
- Oral iron preparations
- Intravenous iron preparations
- Red blood cells (transfusion)



Dietary Iron

- Non-heme iron (inorganic iron)
 - eggs, fortified grain products e.g. cereal, pasta
 - vegetables, dried fruits
 - legumes e.g. beans, lentils, peas, soybeans
- Heme iron (from breakdown of hemoglobin or myoglobin in animals)
 - fish, meat, poultry
 - better absorbed than non-heme iron

<https://www.canada.ca/en/health-canada/services/nutrients/iron.html>



Oral Iron Preparations

	Iron per tab/cap	Elemental iron per tab/cap	Approximate cost per month \$
Ferrous fumarate	300 mg	100 mg	5-10
Ferrous gluconate	300 mg	35 mg	5-10
Ferrous sulphate	300 mg	60 mg	5-10
Heme iron polypeptide (Proferrin, Optifer)	11 mg	11 mg	24-50
Polysaccharide-iron complex (FeraMAX)	150 mg	150 mg	35



Oral Iron Administration

- e.g. ferrous sulfate 300 mg tab
 - take at bedtime
 - empty stomach, at least 2 hours after meals
 - take with 500 mg Vitamin C (not needed with heme iron products)
 - avoid taking with calcium or magnesium supplements, these decrease iron absorption (take them in the morning).
 - calcium also inhibits heme iron absorption.
 - avoid taking with milk or caffeinated beverages



Oral Iron Side Effects

- constipation
- nausea, vomiting, diarrhea
- abdominal pain
- metallic taste
- dark stools



Indications for IV Iron

- Failure of trial of oral iron
- Oral iron cannot be tolerated
- Poor absorption of oral iron e.g. gastric bypass, celiac disease, gastritis
- Severe anemia (Hb<90), especially if ongoing bleeding
- Need rapid iron replenishment e.g. urgent surgery for cancer



Intravenous Iron Preparations

- Iron sucrose (Venofer®)
 - use in IDA other than CKD is off-label
- Iron isomaltoside (Monoferric®)
 - indicated for IDA intolerant to or unresponsive to oral iron, CKD
- Sodium ferric gluconate (Ferrlecit)
 - Use in IDA other than CKD is off-label
- Ferumoxytol (Feraheme) – unavailable in Canada since 2016, adverse effects
- Iron dextran – has been phased out due to adverse effects

IDA iron deficient anemia, CKD chronic kidney disease



IV Iron - Costs

- Venofer: approximately \$150 for 300 mg dose, will need 1 to 3 doses
- Monoferric: approximately \$275 for 500 mg dose, will need 1 to 3 doses
- Private insurance may cover the cost
- Ontario Drug Benefit plan may cover some of the cost if there has been a failed trial of oral iron (August 2015)



Side effects of IV iron

- Common (about 5%)
 - muscle cramps, joint pain, headache, injection site swelling, chest discomfort, nausea, vomiting, diarrhea
- Uncommon (1-2%)
 - hypotension
- Rare (less than 1 in a million)
 - severe allergic reaction or anaphylaxis
- All patients should be observed for 30 minutes after infusion for allergic or hypotensive reaction
- Epinephrine must be available



Infusion of IV Iron

- Iron sucrose (Venofer)
 - supplied in 5 mL vials, 20 mg elemental iron per mL
 - 300 mg in 100 mL NS over 2 hours, or
 - 200 mg in 250 mL NS over 2 hours (patients less than 50 kg)
- Iron isomaltoside (Monoferric)
 - supplied in 1, 5, 10 mL vials, 100 mg elemental iron per mL
 - 500 mg in 50 mL NS over 30 min, or
 - 1000 mg in 100 mL NS over 1 hour

Examples from SHSC



Slower infusion if...

- Age greater than 65 years
- Baseline systolic BP less than 100 mmHg
- Severe asthma or eczema
- Severe respiratory or cardiac disease
- Treatment with beta blockers, ACE inhibitors or ≥ 3 anti-hypertensive meds
- Nephrology patients



Contraindications to IV Iron

- Active systemic infection e.g. sepsis
 - because iron is a nutrient for bacteria
- History of allergic or hypotensive reaction
 - need facilities for resuscitation available
- Known iron overload

A recent trial in patients with chronic kidney disease revealed more infections and cardiovascular complications with IV iron than with oral iron



Dose of Iron Replacement

- There are formulas e.g. Ganzoni formula:
weight (kg) x ([target – actual Hb in g/dL] x 2.4) +
iron stores (mg)

$$\text{Example: } 70 \times (12-9) \times 2.4^* + 500$$

$$= 70 \times 3 \times 2.4 + 500 = 1004 \text{ mg}$$

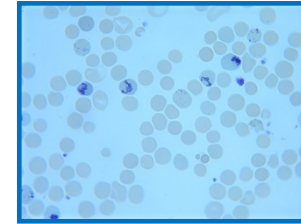
- One review revealed average iron deficit was 1400-1500 mg in 7 studies
- Or estimate 200 mg iron per 10 g/L desired Hb rise and add 500 mg for stores

* accounts for blood volume and amount of iron in Hb



Response to IV Iron Therapy

- Reticulocytosis in 5-10 days
- Increase in Hb in 3-7 days
- Hb rises 1-2 g/L per day, so by 2-4 weeks will have a rise in Hb of 20-30 g/L if no ongoing bleeding
- Continue oral iron for 3-6 months if tolerated and to replenish stores
- Low dose maintenance may be necessary in some patients (growth spurt, menstruation, diet)



Transfusion for Iron Replacement

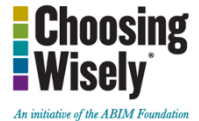


Risks of Transfusion

RISK OF EVENT	EVENT
1 in 13	RBC sensitization (↑ risk hemolytic reaction, HDFN)
1 in 100	Transfusion-associated circulatory overload (TACO)
1 in 7,000	Delayed hemolytic transfusion reaction
1 in 10,000	Transfusion related acute lung injury (TRALI)
1 in 40,000	ABO-incompatible transfusion per RBC transfusion
1 in 40,000	Serious allergic reaction per unit of component



Choosing Wisely



2

Don't transfuse red blood cells for iron deficiency without hemodynamic instability.

Blood transfusion has become a routine medical response despite cheaper and safer alternatives in some settings. Pre-operative patients with iron deficiency and patients with chronic iron deficiency without hemodynamic instability (even with low hemoglobin levels) should be given oral and/or intravenous iron.

Patients with chronic iron deficiency without hemodynamic instability (even with low Hb levels) should be given oral and/or IV iron



1

Don't transfuse blood if other non-transfusion therapies or observation would be just as effective.

Blood transfusion should not be given if other safer non-transfusion alternatives are available. For example, patients with iron deficiency without hemodynamic instability should be given iron therapy.

Patients with iron deficiency without hemodynamic instability should be given iron therapy



Transfusion for Iron Replacement

- “Blood transfusion is not an appropriate treatment for iron deficiency and puts patients, particularly the elderly, at risk of TACO. Iron deficiency should be diagnosed and appropriately corrected with iron supplements”.
- Obtain valid consent before recommending this

ANNUAL
SHOT
REPORT
2011

SHOT: Serious Hazards of
Transfusion

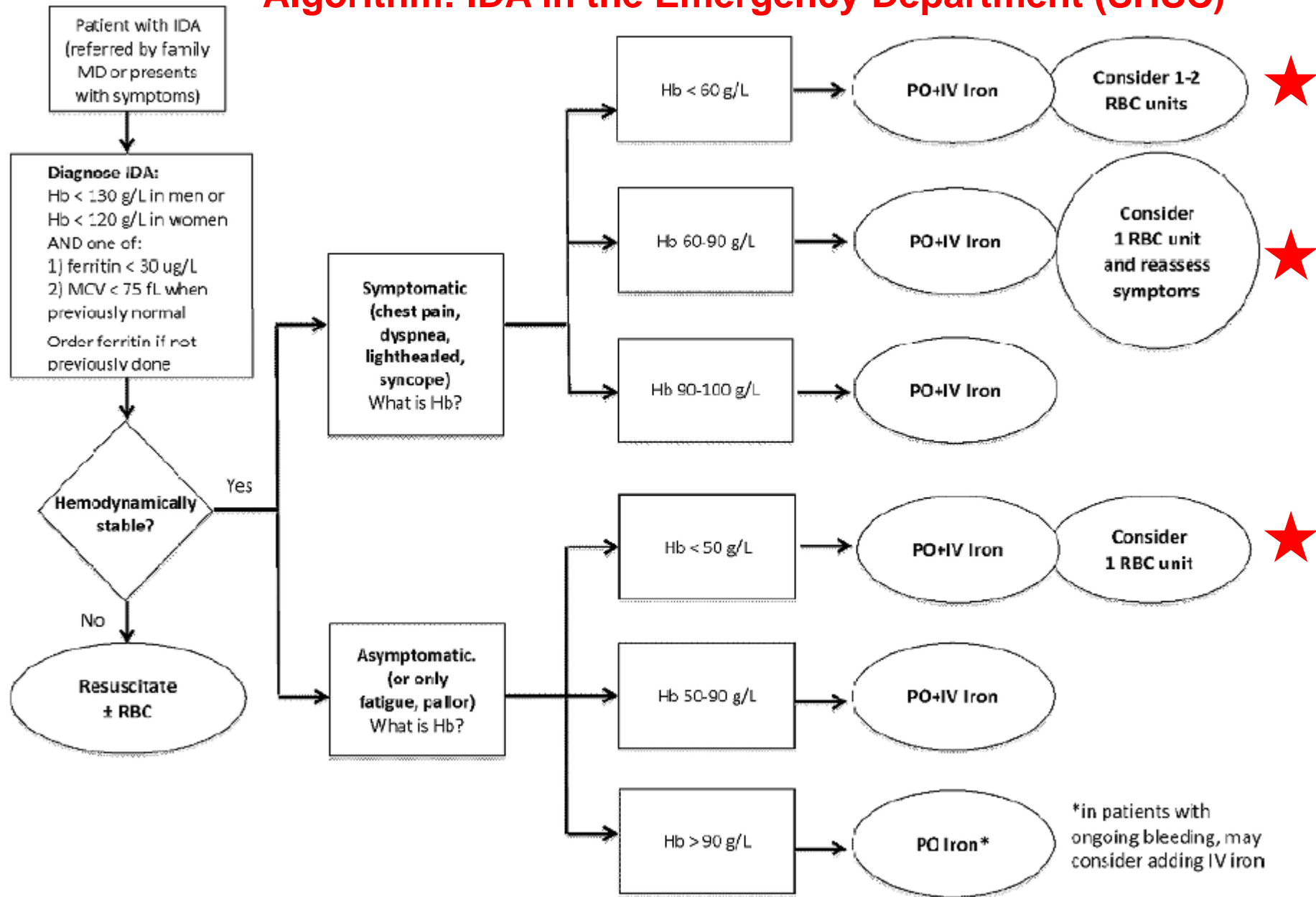


When to Choose RBC Transfusion

- Major hemorrhage e.g. trauma, variceal bleed
- Moderately severe GI bleed, Hb threshold 70 - 80 g/L
- Chronic IDA, hemodynamically stable but Hb \leq 50 g/L
- Severe IDA causing with cardiovascular effects such as angina, heart failure
- Chronic anemia other than IDA or B12 deficiency, Hb threshold 70, 80 or 90 g/L depending on patient e.g. nursing home patients



Algorithm: IDA in the Emergency Department (SHSC)



Summary

- Iron deficiency is common, has significant detrimental effects, and must be corrected
- Sources of iron include diet, oral iron, IV iron, and red blood cells
- The choice of replacement product depends on severity of anemia, urgency of correction, risks, costs, and patient preferences



Thanks to..

- Drs. Yulia Lin and Jeannie Callum
- Slide content, material from SHSC and Emergency Medicine Cases, Episode 65

<https://emergencymedicinecases.com/iv-iron-for-anemia-in-emergency-medicine/>



Questions?

ELEMENTS

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt									

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

Iron

