Drugs Used in Blood Disorders

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Pharmacology

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Reference Text Book

- Basic & Clinical Pharmacology
  Bertram G. Katzung, Todd W. Vanderah

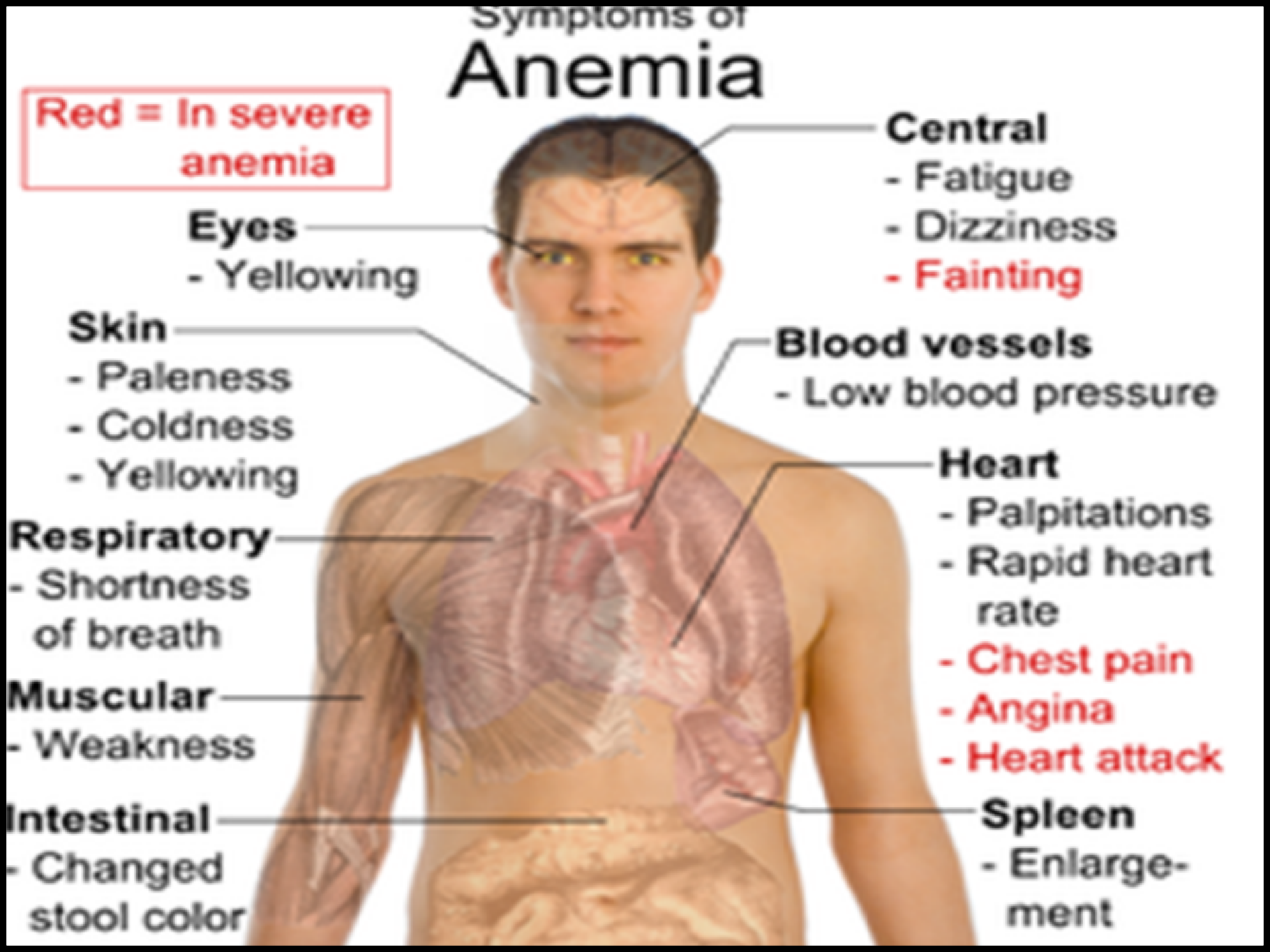
Hemato-Lymphoid System

- Agents used in Anemias and Hematopoietic growth factors: Chapter 33
- Drugs used in Thromboembolic Diseases: Chapter 34
- Drug treatment in hematopoietic malignancies: Chapter 54
- Antimalarial drugs:Chapter 52
- Antiviral drugs: Chapter 49

Hematopoiesis:

Requires a constant supply of:

- Essential elements:
  - Iron
  - vitamin B12
  - folic acid
- Hematopoietic Growth Factors
  - Erythropoietin
  - Myeloid Growth Factors
  - Megakaryocyte Growth Factors


Symptoms of
Anemia
Red = In severe anemia
Central
- Fatigue
- Dizziness
- Fainting
Eyes
- Yellowing
Skin
- Paleness
- Coldness
- Yellowing
Blood vessels
- Low blood pressure
Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack
Respiratory
- Shortness of breath
Muscular
- Weakness
Intestinal
- Changed stool color
Spleen
- Enlarge-ment

Iron deficiency anemia (**microcytic hypochromic anemia**)

- Pallor
- fatigue, dizziness
- exertional dyspnea
- Generalized symptoms of tissue hypoxia

The cardiovascular adaptations to chronic anemia

- Tachycardia
- Increased cardiac output
- Vasodilation.

Iron

- Iron deficiency is the most common cause of chronic anemia – microcytic hypochromic anemia
- Most of the iron used to support hematopoiesis is derived from damaged RBCs.
- Normally small amounts are lost each day and thus, daily requirements are small.


Iron Rich Foods
Fruits
Dark Chocolate
Broccoli
Red Meat
Legumes
Leafy Greens
Whole Grains
Tofu
Pumpkin Seeds

Iron

- Daily requirements may increase and iron deficiency may develop in certain circumstances;
  - growing children
  - pregnancy
  - menstruation

Iron

- Iron content in the body in normal adults:

	Iron content (mg)	
	Men	Women
Hemoglobin	3050	1700
Myoglobin	430	300
Enzymes	10	8
Transport (transferrin)	8	6
Storage (ferritin)	750	300
Total	4248	2314

Iron

Pharmacokinetics:

1. Absorption:

- The average diet contains 10-15 mg of elemental iron daily.
- Normally, 5-10% of which (0.5-1 mg) is absorbed, in the duodenum and proximal jejunum.
- Iron absorption increases in response to low iron stores or increased iron requirements:

Iron

A. 1-2 mg/day are absorbed in menstruating women.
B. 3-4 mg/day are absorbed in pregnant women.

- Iron in vegetables and grains, is often tightly bound to organic compounds and is much less available for absorption.
- Iron in meat protein is efficiently absorbed, because heme iron can be absorbed intact.

Iron

- Nonheme iron in food and iron in inorganic iron salts must be reduced to ferrous iron (Fe^{2+}) to be absorbed from intestinal mucosal cells.
- Ferrous iron is transported efficiently across the luminal membrane of intestinal enterocytes by the divalent metal transporter (DMT1).
- Regulated by mucosal cell iron stores.

Iron

- **Iron is actively transported into the blood by ferroportin (FP) or complexed with apoferritin (AF) and stored as ferritin.**

- **Excess iron is stored in the mucosa as ferritin, (a water-soluble complex consisting of a core of ferric hydroxide covered by a shell of specialized protein called apoferritin).**

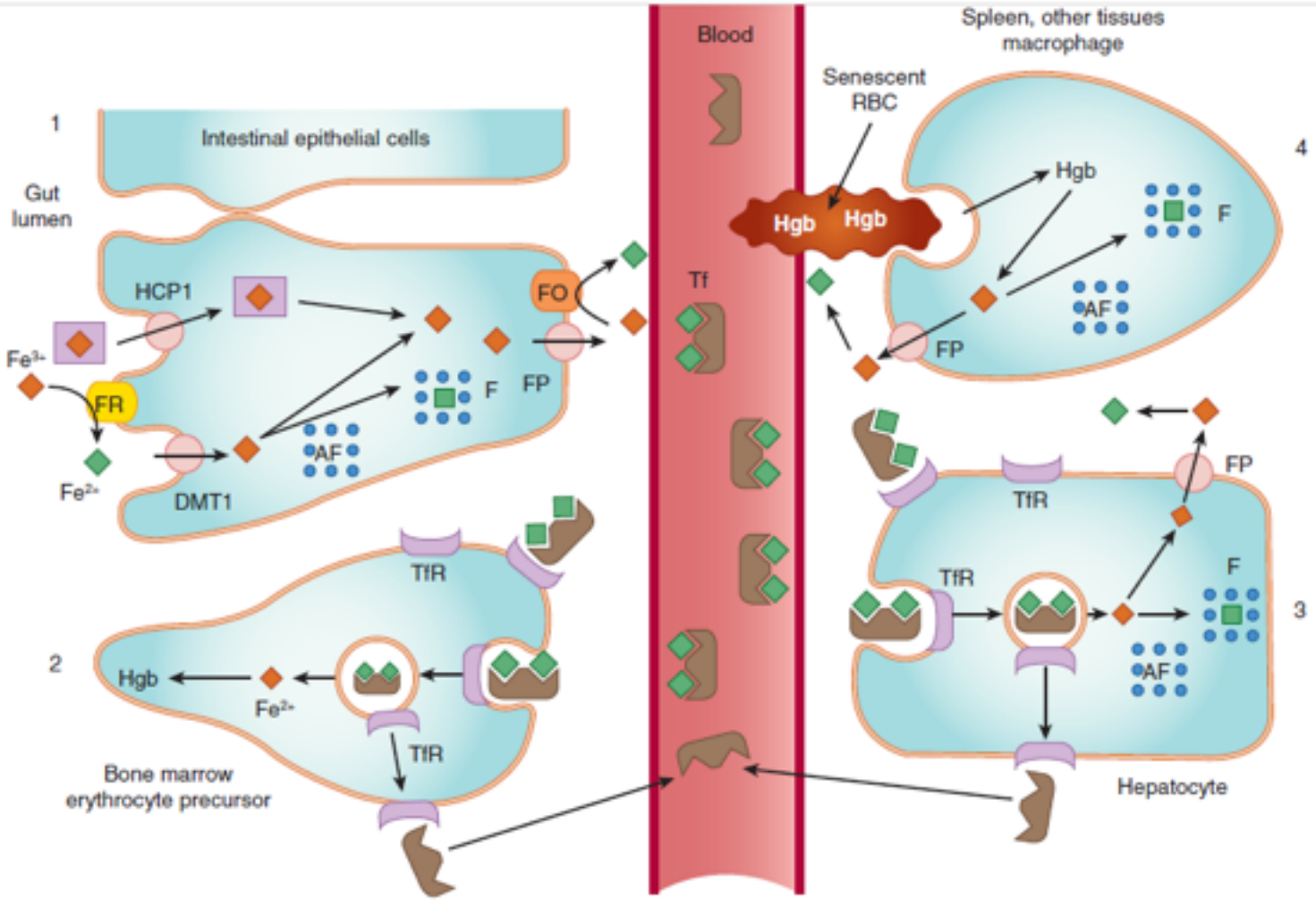


FIGURE 33–1 Absorption, transport, and storage of iron. Intestinal epithelial cells actively absorb inorganic iron via the divalent metal transporter 1 (DMT1) and heme iron via the heme carrier protein 1 (HCP1). Iron that is absorbed or released from absorbed heme iron in the intestine (**1**) is actively transported into the blood by ferroportin (FP) or complexed with apoferritin (AF) and stored as ferritin (F). In the blood, iron is transported by transferrin (Tf) to erythroid precursors in the bone marrow for synthesis of hemoglobin (Hgb) (**2**) or to hepatocytes for storage as ferritin (**3**). The transferrin-iron complex binds to transferrin receptors (TfR) in erythroid precursors and hepatocytes and is internalized. After release of iron, the TfR-Tf complex is recycled to the plasma membrane and Tf is released. Macrophages that phagocytize senescent erythrocytes (RBC) reclaim the iron from the RBC hemoglobin and either export it or store it as ferritin (**4**). Hepatocytes use several mechanisms to take up iron and store the iron as ferritin. FO, ferroxidase. (Modified and reproduced, with permission, from Trevor A et al: *Pharmacology Examination & Board Review*, 9th ed. McGraw-Hill, 2010.)

Iron

2. Transport:

- Iron is transported in the plasma bound to transferrin.
- The transferrin-iron complex enters maturing erythroid cells by transferrin receptor-mediated endocytosis.

Iron

- The iron released in endosomes is used for hemoglobin synthesis, whereas the transferrin-transferrin receptor complex is recycled to the plasma membrane, where the transferrin dissociates and returns to plasma.
- Increased erythropoiesis is associated with increased number of transferrin receptors.
- Iron store depletion and iron deficiency are associated with increased serum transferrin.

Iron

3. Storage:

- Iron is stored as ferritin in macrophages in the liver, spleen, bone, and in parenchymal liver cells.
- Ferritin is proportionately detected in serum.

Iron

4. **Elimination:**

- No mechanism for iron excretion.
- Small amounts are lost by exfoliation of intestinal mucosal cells.
- Thus, regulation of iron balance is achieved by changing absorption and storage.

Iron

Clinical Pharmacology:

A. Indications:

- The only indication is treatment or prevention of iron deficiency anemia.
- It is seen in populations with:

1. Increased iron requirements:
   a. Infants, especially premature.
   b. Children during rapid growth episodes.
   c. Pregnant and lactating women.

Iron

2. **Increased iron loss:**

   a. Chronic kidney disease – loss of RBCs during hemodialysis

   b. Blood loss – most common in adults

   - Menstruation (~ 30mg/cycle)

   - Upper gastrointestinal bleeding

Iron

3. **Inadequate iron absorption:**
   a. **Gastrectomy (?)**
   b. **Severe small bowel disease – generalized malabsorption.**

Iron

B. Treatment:

1. Oral Ferrous Iron Salts:

Elemental iron per tablet	Tablet size (mg)	Prepararion
65	325	Ferrous sulfate hydrated
36	325	Ferrous
106	325	Ferrous

Iron

- In an iron-deficient individual, ~ 50-100 mg of iron can be incorporated into hemoglobin daily, and about 25% of iron given as ferrous sulfate can be absorbed.

- Therefore, 200- 400 mg of elemental iron should be given daily for 3-6 months after correction of the cause of the iron deficiency anemia, to correct the anemia and replenish iron stores.

Iron

Oral Iron Preparations:

- **Ferrous sulfate.**
- **Ferrous gluconate.**
- **Ferrous fumarate.**
  - **All are effective and inexpensive.**

Iron

Adverse effects:

1. **Nausea, epigastric discomfort, abdominal pain, constipation and diarrhea.**

- **These effects are dose-related and can be reduced by lowering the dose or giving it with meals or immediately after meals.**

2. **Black stools are common and may obscure the diagnosis of continued gastrointestinal blood loss.**

Iron

2. **Parenteral iron therapy:**

- **Should be reserved for patients:**

1) **Unable to tolerate oral iron.**
2) **Unable to absorb oral iron. Malabsorption syndromes, small bowel resection.**
3) **With extensive chronic blood loss.**

Iron

- **Iron dextran:**
  - t is a stable complex of ferric hydroxide and low-molecular-weight dextran containing 50 mg elemental iron/mL of solution.Given by deep IM injection or IV infusion.
  - IM injection causes local pain and tissue staining.
  - IV infusion causes hypersensitivity reactions: headache, fever, arthralgia, N, V, back pain, flushing, bronchospasmand rarely anaphylaxis and death.
- **Iron-sucrose complex.**
- **Iron sodium gluconate.**
  - Given only IV , less likely to cause hypersensitivity.

Iron

Acute Iron Toxicity:

- Usually results from accidental ingestion by children as well as parenteral iron.
- 10 tablets can be lethal in children.
- Causes necrotizing gastroenteritis: vomiting, pain, bloody diarrhea, shock, lethargy and dyspnea.
- Patients may improve but may proceed to metabolic acidosis, coma and death.

Iron

Treatment of Acute Iron Toxicity:

- **Deferoxamine" Desferal":** is a potent iron-chelating compound which binds already absorbed iron and promotes its excretion in urine and feces.
- Whole Bowel Irrigation; to flush out unabsorbed pills.
- Activated charcoal is ineffective.
- Supportive therapy is also necessary.

Iron

Chronic Iron Toxicity= Hemochromatosis:

Excess iron can deposit in the heart, liver, pancreas, and other organs leading to organ failure.

- **Usually occurs in:**

1. Inherited Hemochromatosis: excessive iron absorption.

2. Patients with frequent transfusions e.g. in patients with hemolytic anemias.

Iron

Treatment of Chronic Iron Toxicity:

Intermittent phlebotomy.

Deferoxamine: is much less efficient than phlebotomy.

Deferasirox” Exjade”: oral, more convenient than deferoxamine.