# 2AGENTS USED IN ANEMIAS

## A. Iron

### 1. Basic pharmacology

**a) Approximate distribution**

(1) 70% in hemoglobin
(2) 10% in myoglobin
(3) 10-20% stored as ferritin and hemosiderin
(4) <1% in enzymes (e.g. cytochromes), and transferrin

**b) Intake** -Average US diet contains 10-15 mg of which 0.5-1 mg is absorbed.

**c) Absorption**

(1) Heme iron is absorbed intact from duodenum and jejunum
(2) Non-heme iron must be converted to ferrous iron (Fe2+)
(3) Absorption is by active transport
(4) Within mucosal cell, ferrous iron is converted to ferric (Fe3+)
(5) Ferric iron is split from heme

**d) Fate**

(1) In case of demand, ferric iron is bound to transferrin for immediate transport via the blood to bone marrow
(2) Stored as ferritin or hemosiderin in liver and spleen
(3) Ferritin in plasma is in equilibrium with body storage and can be used to estimate total body stores

**e) Iron balance**

(1) Maintained by changes in absorption regulated by the concentrations of transferrin and ferritin in mucosal cells
(2) In iron deficiency transferrin goes up, ferritin goes down
(3) In iron overload transferrin goes down, ferritin goes up

### 2. Indications for iron therapy-

Prevention or treatment of iron deficiency anemia (microcytic hypochromic anemia)

**a) Increased requirements**

(1) Frequently present in premature infants
(2) Children during rapid growth period

(3) Pregnant and lactating women

**b) Inadequate absorption:**
Postgastrectomy or severe small bowel disease

**c) Blood loss**
(1) Menstruation
(2) Occult gastrointestinal bleeding

**3. Iron therapy**
**a) Oral preparations**
(1) Only ferrous salts (sulfate, gluconate, fumarate)
(2) Response within a week, normal in 1-3 months
(3) **Adverse effects**: GI distress (take with or after meals); black stool may obscure recognition of GI bleeding

**b) Parenteral iron therapy**
(1) Usually iron dextran, deep i.m. or i.v. infusion (also iron-sucrose and iron sodium gluconate)
(2) Indicated post-gastrectomy/small bowel resection, malabsorption syndromes, intolerance of oral preps
(3) **Adverse effects**: local pain and tissue staining with i.m., headache, fever, nausea, vomiting, back pain, arthralgias, urticaria, bronchospasm, anaphylaxis/death (rare)

**4. Clinical toxicity**
**a) Acute:** accidental ingestion of iron tablets
(1) May be fatal in small children
(2) Necrotizing gastroenteritis
(3) After short improvement, metabolic acidosis, coma and death
(4) **Treatment:**
    (a) Gastric aspiration, lavage with phosphate or carbonate solution
    (b) Activated charcoal is ineffective
    (c) Deferoxamine, a potent iron chelating substance i.m. or i.v.

**b) Chronic (iron overload)**
(1) Seen in an inherited disorder, hemochromatosis
(2) Patients receiving repeated red cell transfusions
(3) Excess iron deposited in heart, liver pancreas leading to organ failure
**(4) Treatment:**
    (a) Intermittent phlebotomy
    (b) Iron chelation

## B. Vitamin B12 and folic acid

**1. Basic pharmacology**

**a) Chemistry and pharmacokinetics of vitamin B12**

(1) Deoxyadenosylcobalamin and methylcobalamin are the active forms

(2) Cyanocobalamin and hydroxycobalamin (therapeutic drugs) are converted to the active forms

**(3) Absorption**

(a) Vitamin B12 is absorbed only after complexing with "intrinsic factor"

(b) Absorption (1-5 µg/day) occurs in the distal ileum by a specific transport system

(c) Deficiency often caused by lack of intrinsic factor or bowl disease (transport)

(d) Absorbed vitamin B12 is bound to plasma transcobalamin II for distribution

**(4) Storage:** liver is major storage site containing 3-5 mg of vitamin B12

**b) Chemistry and pharmacokinetics of folic acid**

(1) Richest sources are yeast, liver, kidney, and green vegetables

(2) Absorption

(a) Average diet contains 500-700 µg

(b) Polyglutamate forms must be hydrolyzed to monoglutamate

(c) Monoglutamate form inters bloodstream by active and passive transport

**(3) Storage**

(a) 5-20 mg of folates are stored in liver and other tissues

(b) Folates are excreted and destroyed by catabolism

(c) Since normal daily requirements are ~ 50 µg, diminished intake will result in deficiency and anemia within 1-6 months

**2. Clinical pharmacology:** treatment of macrocytic or megaloblastic anemias

a) Vitamin B12 and folic acid used only for prevention or treatment of deficiencies

b) Important to determine whether vitamin B12 or folic acid deficiency is the cause since folic acid will not prevent the irreversible neurological damage

c) Vitamin B12 deficiency caused by malabsorption usually requires lifelong parenteral injection of cyanocobalamin or hydroxocobalamin

d) Response is rapid and return to normal in 1-2 months

e) Folic acid deficiency due to inadequate intake or diminished storage is treated with oral doses of folic acid

# II. HEMATOPOIETIC GROWTH FACTORS

## A. Erythropoietin

**1. Basic pharmacology**

a) 34-39 kDa glycoprotein

**b) Functions:**

(1) Stimulates proliferation and differentiation of erythroid cells

(2) Promotes release of reticulocytes from bone marrow

c) Produced by the kidney

d) Usually inverse relationship between hemoglobin level and serum erythropoietin level, but not in chronic renal failure

e) Recombinant human erythropoietin (Epoetin alfa, Epogen) is produced in a mammalian cell expression system

**2. Indication for erythropoietin therapy**

a) Chronic renal failure

b) Some patients with aplastic anemia, hematologic malignancies, anemias associated with AIDS, cancer

(1) In these patients, erythropoietin is most effective if endogenous erythropoietin levels are disproportionately low

(2) Higher does required than in chronic renal failure, but responses are still incomplete

c) Treatment of anemia of prematurity

d) Post phlebotomy

**3. Erythropoietin therapy**

a) Given IV or subcutaneously

b) Increase in reticulocyte count seen in about 10 days

c) Increase in hemoglobin seen in 2-6 weeks

**4. Clinical toxicity**

a) Hypertension

b) Thrombotic complications

c) Allergic reactions

d) Increased risk of tumor progression in cancer patients

## B. G-CSF and GM-CSF

**1. Basic pharmacology**

a) G-CSF (granulocyte colony stimulating factor) and GM-CSF (granulocyte-macrophage colony stimulating factor) are myeloid growth factors

b) Recombinant human G-CSF (filgrastim, Neupogen) is produced in a bacterial expression system
c) Recombinant human GM-CSF (sargramostim, Leukine) is produced in a yeast expression system
d) Pegfilgrastim (Neulasta): Filgrastim conjugated to polyethylene glycol-longer half-life
e) **Functions:**
(1) Both G-CSF and GM-CSF stimulate proliferation and differentiation of myeloid cells
(2) G-CSF promotes release of hematopoietic stem cells from bone marrow (GM-CSF is less efficient)
(3) GM-CSF also stimulates proliferation and differentiation of erythroid and megakaryocytic precursors

**2. Indications for G-CSF/GM-CSF therapy**

a) After intensive myelosuppressive chemotherapy
(1) Accelerates rate of neutrophil recovery
(2) Reduces duration of neutropenia
(3) Reduces febrile neutropenia, antibiotic use, days of hospitalization

b) Can also be used after chemotherapy for acute myeloid leukemia (AML)
(1) Accelerates neutrophil recovery, reduce infection
(2) No evidence for increased relapse rate

c) Treatment of congenital neutropenia, cyclic neutropenia, neutropenia associated with myelodysplasia and aplastic anemia

d) High dose chemotherapy with autologous stem cell transplant

e) Mobilization of peripheral blood stem cells for autologous transplant

**3. Clinical toxicity**
a) G-CSF preferred since it is better tolerated in general
b) G-CSF can cause bone pain, splenic rupture (very rare)
c) GM-CSF can cause fever, arthralgia, myalgia, peripheral edema, pleural/pericardial effusion
d) Allergic reactions

## C. Interleukin-11

**1. Basic pharmacology**
a) IL-11 is produced by stromal cells in the bone marrow

b) Recombinant human IL-11 (Oprelvekin, Neumega) is produced in a bacterial expression system
c) Stimulates growth of megakaryocytic progenitors
d) Increases peripheral platelets

**2. Indication for IL-11 therapy**
a) Patients with thrombocytopenia after cytotoxic chemotherapy
(1) Can be used if platelet transfusions are refractory, or to prevent adverse reactions of transfusions
(2) Usually given for 14-21 days after chemotherapy, or until the platelet count rises above 50,000/uL

**3. Clinical toxicity**
a) Fatigue
b) Headache
c) Dizziness
d) Cardiovascular effects (dyspnea, atrial arrhythmia)
e) Hypokalemia

**D. New agents for thrombocytopenia**

**a) Romiplostim (AMG 531)**- A novel protein known as a "peptibody" with two domains; a peptide domain that binds the thrombopoietin receptor (Mpl), and an antibody Fc domain that increases half-life a

**b) Eltrombopag**-A small molecule thrombopoietin receptor agonist