Anemia

Tong Chen
Department of Hematology
Huashan Hospital

Content

- General information of anemia
- Iron-Deficiency Anemia
- Aplastic Anemia
- Hemolytic Anemia

Key Points

- Definition and classification of anemia
- Pathogenesis, clinical manifestations, laboratory features and treatment of iron deficiency anemia
- Pathogenesis, clinical manifestations, laboratory features and treatment of aplastic anemia
- Pathogenesis, classification, clinical manifestations, laboratory features, diagnosis of hemolytic anemia

Anemia

- Definition
  - Reduction in blood transport of oxygen due to a deficiency in red blood cells
- Mechanisms of Anemia
  - Erythrocyte loss (bleeding)
  - Decreased Erythrocyte production
    - Low erythropoietin
    - Decreased marrow response to erythropoietin
    - Bone marrow hypoplasia
  - Increased Erythrocyte destruction (hemolysis)

Laboratory Definition of Anemia

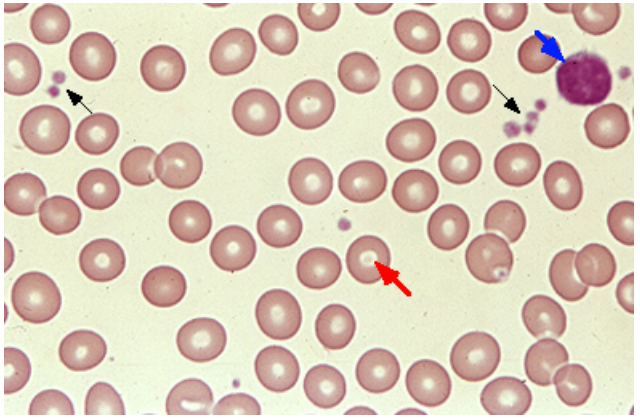
- Hgb:
  - Women: <12.0(g/dL)
  - Men: < 13.5(g/dL)
- Hct:
  - Women: < 36%
  - Men: <41%

Classification Criteria of Anemia

- MCV
  - If > 100 → Macrocytic anemia
  - If 80 – 100 → Normocytic anemia
  - If < 80 → Microcytic anemia
- Bone marrow proliferative capacity/reticulocyte index
  - If reticulocyte index>2.5 hyperproliferative anemia
  - If reticulocyte index<2.5 hypoproliferative anemia

Classification of Anemias by MCV

- Microcytic (<80 fL)
  - Iron deficiency
  - Thalassemia
  - Anemia of chronic disease
- Macrocytic (>100 fL)
  - Vitamin B12 deficiency
  - Folate deficiency
  - Myelodysplasia
  - Chemotherapy
  - Liver disease
  - Increased reticulocytosis
  - Myxedema
- Normocytic
  - Anemia of chronic disease
  - Aplasia
  - Protein-energy malnutrition
  - Chronic renal failure
  - Post-hemorrhagic



Symptoms of Anemia

- Decreased oxygenation
  - Exertional dyspnea
  - Dyspnea at rest
  - Fatigue
  - Bounding pulses
  - Lethargy, confusion
- Decreased volume
  - Fatigue
  - Muscle cramps
  - Postural dizziness
  - syncope

Initial Evaluation

- History and Physical Exam
  - Eating ice or clay
  - Dyspnea
  - Conjunctival pallor
  - Chest Pain
  - Medications
- Laboratory evaluation
  - CBC with differential
  - Peripheral Smear
  - Reticulocyte count

Causes of Anemia

- Erythrocyte Loss
  - Bleeding
    - Chronic (gastrointestinal, menstrual)
    - Acute/Hemodynamically significant:
      - Gastrointestinal
      - Retroperitoneal
- Low Erythropoietin
  - Kidney Disease
    - Normochromic, normocytic
    - Low reticulocyte count
    - Frequently, peripheral smear in uremic patients show “burr cells” or echinocytes
    - Target hemoglobin for patients on dialysis is 11 to 12 g/dL
      - Administer erythropoietin or darbopoietin weekly
      - Good Iron stores must be maintained

Causes of Anemia

- Decreased Response to Erythropoietin
  - Iron-Deficiency
  - Vitamin B12 Deficiency
  - Folate Deficiency
  - Anemia of Chronic Disease
- Destruction of Red Blood Cells
  - Hemoglobinopathies
    - Sickle Cell Anemia
  - Hemolytic Anemia

Causes of Anemia

- Decreased Erythrocyte production
  - Aplastic Anemia
    - Decrease in all lines of cells – hemoglobin, hematocrit, WBC, platelets
    - Parvovirus B19, EBV, CMV
    - Acquired aplastic anemia

! Anemia is not a disease but a sign of underlying diseases

Iron Deficiency
&
Iron Deficiency Anemia

Iron Stores

- Humans contain ~2.5 g of iron, with 2.0 - 2.5 g circulating as part of heme in hemoglobin
- Another ~0.3 g found in myoglobin, in heme in cytochromes, and in Fe-S complexes
- Iron stored in body primarily as protein complexes (ferritin and hemosiderin)

Body Iron Distribution (1)

- Metabolically Active Iron
  - Haemoglobin
  - “Serum” iron bound to a protein transferrin in blood
  - Tissue Iron: in cytochromes and enzymes
  - Myoglobin: oxygen reserve in muscles

Body Iron Distribution (2)

- Storage Iron
  - Ferritin: found in blood, tissue fluids, and cells
  - Haemosiderin: found in macrophages and assessed by staining bone marrow with Prussian Blue stain

Nutritional Iron Balance

- Intake
  - Dietary iron intake
  - Medicinal iron
  - Red cell transfusions
  - Injection of iron complexes
- Excretion
  - Menses
    - Losses can be as much as 4 - 37mg/menstrual cycle
  - Gastrointestinal bleeding
  - Loss of epidermal cells from the skin and gut
  - Other forms of bleeding

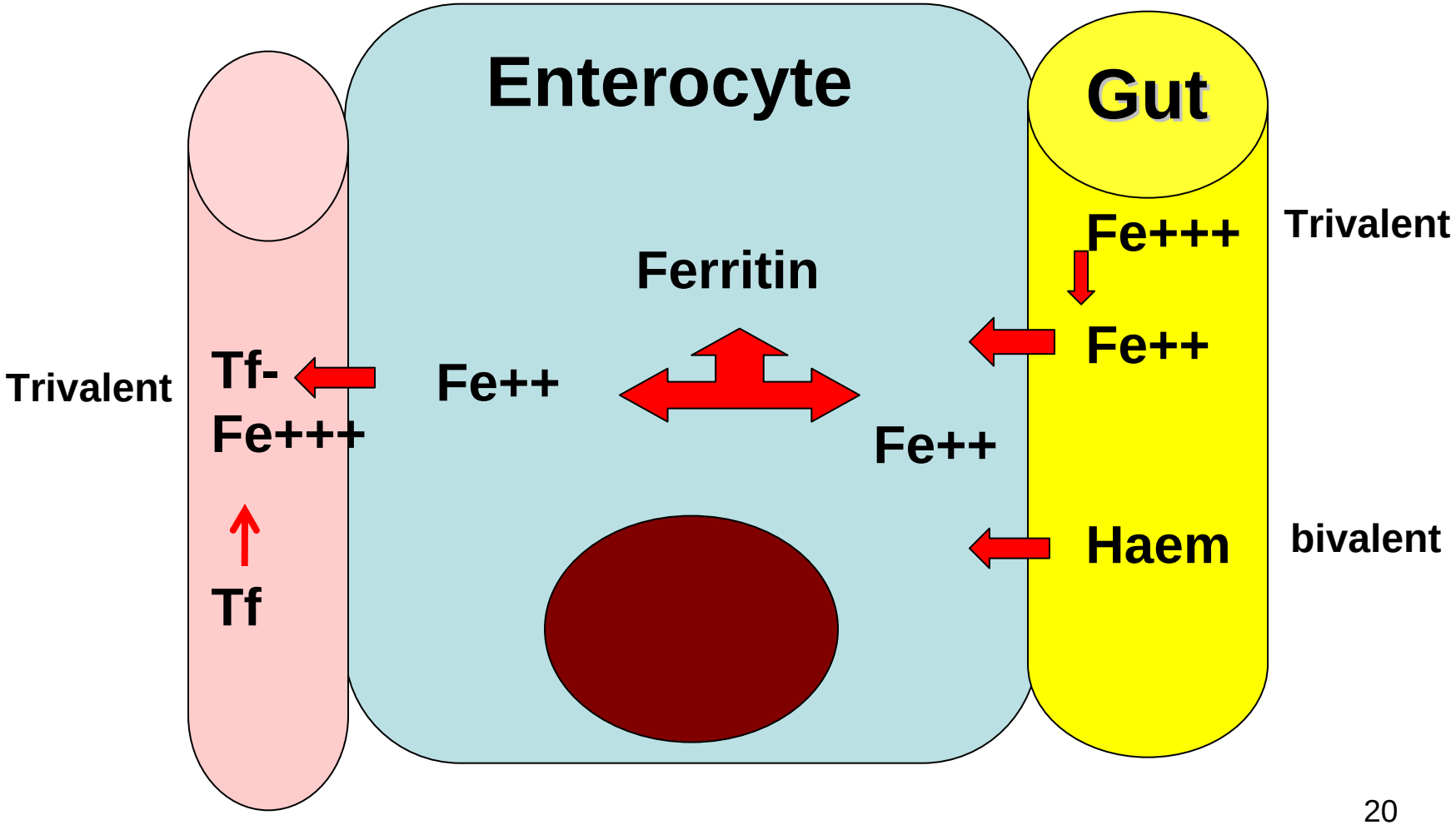
Iron Absorption (1)

- That process is facilitated by the acidic contents of the stomach, which maintains the iron in solution
- Iron bioavailability is affected by the nature of the foodstuff
  - with heme iron (e.g., red meat) being most readily absorbed
- Percentage of iron absorbed from individual food items compared with the percentage for an equivalent amount of ferrous salt
  - iron in vegetables: about one-twentieth as available
  - egg iron one-eighth
  - liver iron one-half
  - heme iron one-half to two-thirds

Iron Absorption (2)

- Absorbed mainly in duodenum
- Iron absorption is influenced by a number of physiologic states
- Quantity absorbed regulated by enterocyte
- Multiple proteins involved in control of iron transport
  - Erythroid hyperplasia
  - Patients with anemias associated with high levels of ineffective erythropoiesis
- Haem iron enters the enterocyte through different process than inorganic iron

Iron Absorption (3)



Iron Deficiency Anemia

- Facts and Figures
  - Most common cause of anemia
  - 500 million cases worldwide
  - Prevalence is higher in less developed countries
- Unique Physical Exam findings
  - Cheilosis
    - fissures at the corners of the mouth
  - Koilonychia
    - spooning of the fingernails

Causes of Iron Deficiency

- Increased demand for iron and/or hematopoiesis
  - Rapid growth in infancy or adolescence
  - Pregnancy
  - Erythropoietin therapy
- Increased iron loss
  - Chronic blood loss
  - Menses
  - Acute blood loss
  - Blood donation
  - Phlebotomy as treatment for polycythemia vera
- Decreased iron intake or absorption
  - Inadequate diet
  - Malabsorption from disease (sprue, Crohn's disease)
  - Malabsorption from surgery (post-gastrectomy)
  - Acute or chronic inflammation

Laboratory Iron Studies (1)

- Serum iron level
  - The amount of circulating iron bound to transferrin
  - Normal range for the serum iron is 50 to 150μg/dL
- TIBC: total iron-binding capacity
  - An indirect measure of the circulating transferrin
  - The normal range for TIBC is 300 to 360 μg/d
- Transferrin saturation
  - Obtained by the following formula: serum iron × 100 ÷ TIBC
  - Normally 25 to 50%

Laboratory Iron Studies (2)

- Serum Ferritin
  - Iron storage
  - The normal value for ferritin varies according to the age and gender of the individual
  - Adult males have serum ferritin values averaging about 100 μg/L, while adult females have levels averaging 30 μg/L
  - As iron stores are depleted, the serum ferritin falls to <15 μg/L
    - is virtually always diagnostic of absent body iron stores

Laboratory Iron Studies (3)

- Bone Marrow Iron Stores
  - The serum ferritin level is a better indicator of iron overload than the marrow iron stain.
  - In addition to storage iron, the marrow iron stain provides information about the effective delivery of iron to developing erythroblasts.
  - Normally, 20 to 40% of developing erythroblasts (sideroblasts) will have visible ferritin granules in their cytoplasm

Laboratory Iron Studies (4)

- Red Cell Protoporphyrin Levels
  - Under conditions in which heme synthesis is impaired, protoporphyrin accumulates within the red cell
  - Reflect an inadequate iron supply to erythroid precursors to support hemoglobin synthesis
  - Normal values are less than 30 μg/dL of red cells
- Serum Levels of Transferrin Receptor Protein (TRP)
  - Erythroid cells have the highest numbers of transferrin receptors
  - Normal values are 4 to 9 μg/L
    - Elevated serum levels of TRP reflect the increasing total erythroid marrow mass or absolute iron deficiency

Laboratory Diagnosis

- Microcytic hypochromic anemia
- Often pencil cells and target cells on blood film
- Decreased serum ferritin
- Decreased serum iron, increased TIBC, decreased % transferrin saturation
- Absent bone marrow haemosiderin: (rarely required for diagnosis)

Differentiation Diagnosis

	MCV	Serum Iron	TIBC	%Saturation	Ferritin
Iron Deficiency	Decreased	Low	High	Low	Low
Anemia of Chronic Disease	Normal to Decreased	Low	Low	Low	Normal to Increased
Thalassemia	Decreased	Normal to High	Normal	Normal to High	Normal or Increased

Treatment of Iron Deficiency

- Red Blood Cell Transfusion
  - Symptoms of anemia
  - Cardiovascular instability
  - Continued and excessive blood loss
  - Require immediate intervention
- Oral Iron Therapy
  - Ferrous sulfate
  - Ferrous fumarate
  - Ferrous gluconate
- Parenteral Iron
  - Sodium ferric gluconate (Ferrlecit)
  - Iron sucrose (Venofer)

Oral Iron Therapy

- For iron replacement therapy up to 300 mg of elemental iron per day is given
  - 100 mg, tid, po
  - Oral iron preparations could be taken on an empty stomach
  - Ascorbic acid enhance iron absorption enhance iron absorption
  - Complication
    - gastrointestinal distress is the most prominent and is seen in 15 to 20% of patients
- The goal of therapy to iron deficiency anemia
  - To repair the anemia
  - To provide stores of at least 0.5 to 1.0 g of iron
- Sustained treatment for a period of 6 to 12 months after correction of the anemia will be necessary to achieve this.

Parenteral Iron

- Intravenous iron
- Unable to tolerate oral iron
- Persistent gastrointestinal blood loss
- The amount of iron needed is calculated by the following formula:
  - Body weight (kg) × 2.3 × (15 - patient's hemoglobin, g/dL) + 500 or 1000 mg (for stores)
- The ways given:
  - Administer the total dose of iron required to correct the hemoglobin deficit and provide the patient with at least 500 mg of iron stores
  - Give repeated small doses of parenteral iron over a protracted period

Parenteral Iron

- Complication
  - Anaphylaxis
    - A history of multiple allergies or a prior allergic reaction to dextran
    - May be dose-related
    - Patients with sensitivity to iron dextran have been safely treated with iron gluconate
- A large dose (>100 mg) of iron dextran: diluted in 5% dextrose in water or 0.9% NaCl solution
  - a test dose (25 mg) of parenteral iron is recommended
  - infused over a 60- to 90-min period (for larger doses)

Iron Supplementation in special populations

- Pregnant Women
  - During the last two trimesters, daily iron requirements increase to 5 to 6 mg
- Infancy
  - Normal-term infants are born with sufficient iron stores to prevent iron deficiency for the first 4–5 months of life
  - Thereafter, enough iron needs to be absorbed to keep pace with the needs of rapid growth
  - Nutritional iron deficiency is most common between 6 and 24 months of life

Aplastic Anemia

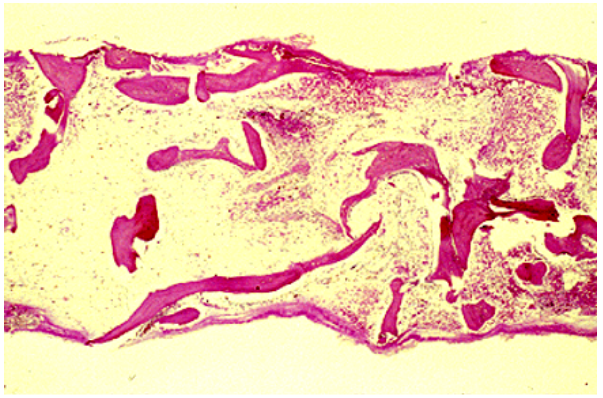
Tong Chen
Department of Hematology
Huashan Hospital

General Information

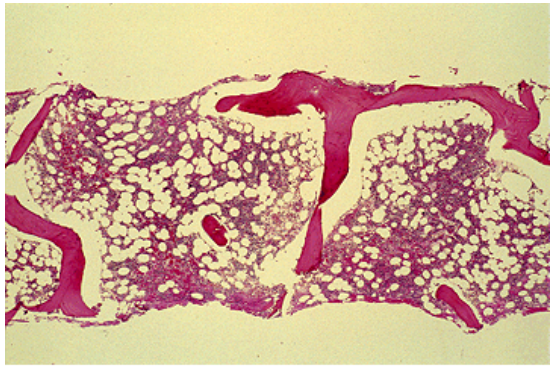
- a syndrome of bone-marrow failure characterized by
  - peripheral pancytopenia
    - low WBC, low RBC, low PLT
  - marrow hypoplasia.
- distinguished from iatrogenic (therapeutic-related) marrow aplasia

Definition

- Pancytopenia
  - Anemia
  - Neutropenia
  - Thrombocytopenia
- Reticulocyto-penia
- Aplastic bone marrow
  - Hypocellular with all elements down; mostly fat and stroma
  - Residual hematopoietic cells are normal
  - No malignancy or fibrosis
  - No megaloblastic hematopoiesis



Bone marrow in aplastic anemia Bone marrow biopsy in aplastic anemia. There are virtually no hematopoietic cells, and the marrow space consists of fat and stroma. Courtesy of Stanley L Schrier, MD.



Normal bone marrow Low power view of a normal bone marrow biopsy. The overall cellularity is between 30 and 70 percent, with the remainder of the space being occupied by fat and stroma. Courtesy of Stanley L Schrier, MD.

Classification

- Acquired
  - stereotypical in its manifestations
  - with the abrupt onset of low blood counts in a previously well young adult
- Constitutional: the genetic diseases
  - Fanconi's anemia (genetic defect in a cluster of proteins responsible for DNA repair)
  - dyskeratosis congenita

Epidemiology

- Europe and Israel
  - 2 cases per million persons annually
- Thailand and China
  - 5 to 7 cases per million annually
- Age distribution
  - biphasic age distribution
  - the major peak in the teens and twenties and a second rise in the elderly

Etiology of Aplastic Anemia

- **IRRADIATION**
- **DRUGS**
  - Anticipated myelosuppression
    - Alkylating agents: cyclophosphomide, melphalan, chlorambucil, busulfan
    - Antimetabolites: azathioprine, 6mp, hydroxyurea, MTX
    - Others: daunorubicin, doxorubicine, carmustine, lomustin,amsacrine
  - Occasionally myelosuppressive
    - Chloramphenicol, gold, arsenic, sulfonamides, mephenytoin, trimethadione, pheylbutazone, quinacrine, indomethacin, diclofenac, felbamate
- **TOXINS**:
  - benzene, glue vapors
- **MALIGNANCY**
  - Hairy-cell; ALL, AML (rarely); myelodysplastic syndromes
- **CLONAL DISORDERS**:
  - paroxysmal nocturnal hemoglobinuria
- **IMMUNE MEDIATED APLASIA**:
  - eosinophilic fasciitis, SLE, GVHD
- **INHERITED DISORDERS**:
  - Fanconi's anemia
- **PREGNANCY**
- **INFECTIONS**
  - Non-A, non-B, non-C hepatitis, EBV, parvovirus infection, HIV

Pathophysiology

- Autoimmunity
  - In the late 1960s, it was the first time to postulate an autoimmune basis for aplastic anemia
  - Cytotoxic T lymphocytes were found to mediate the destruction of hematopoietic stem cells in aplastic anemia
    - overproduce interferon-γ and tumor necrosis factor (TNF)
    - T-cell diversity implicate an autoimmune pathophysiology in aplastic anemia
  - Relevance of autoantibodies to the pathophysiology of aplastic anemia is unclear

Pathophysiology

- Stem cells
  - universal laboratory finding: reduction in the number of hematopoietic stem/progenitor cells
    - CD34+ cells, long-term culture-initiating cells (LTC-ICs)
  - the principal targets of the immune attack : the more mature hematopoietic stem cells
  - T cells kill hematopoietic stem cells: in an HLA-DR–restricted manner via Fas ligand
    - The most primitive hematopoietic stem cells express little or no HLA-DR or Fas
    - responsible for the slow hematopoietic recovery that occurs in aplastic anemia patients following immunosuppressive therapy

Pathophysiology

- Bone marrow microenvironment
  - The most compelling argument is that most patients transplanted for aplastic anemia are cured with allogeneic donor stem cells and autologous stroma
  - Bone marrow stroma cells in AA
    - Subnormal cytokine production of fibroblast
    - Over-adipogenetic differentiation
    - Aplastic anemia does not appear to result from defective stroma or growth factor production

Clinical Features

- Onset of symptoms
  - Gradual: resulting from anemia and thrombocytopenia
    - pallor, weakness, dyspnea, shortness of breath, fatigue, bruising, epistaxis, vaginal bleeding, and unexpected bleeding
  - Dramatic: resulting from neutropenia, monocytopenia, and thrombocytopenia
    - fever, chills, and pharyngitis or other sites of infection
    - bleeding

Laboratory Studies

- Blood: pancytopenia
  - varying degrees of pancytopenia
  - low reticulocyte index
    - relative reticulocyte count is usually less than 1 percent
    - Absolute reticulocyte counts are usually fewer
  - macrocytes may be present
    - Mean corpuscular volume (MCV) is commonly increased
  - the absolute neutrophil and monocyte count are low with mild lymphopenia

Laboratory Studies

- Bone marrow
  - aspiration
    - usually appears diluted on smear
    - the fatty biopsy specimen may be grossly pale on withdrawal
    - aspirated specimen shows only red cells, residual lymphocytes, and stromal cells
    - hematopoietic cells occupying <25% of the marrow space
  - Biopsy
    - virtually 100% fat
    - Residual hematopoietic cells should have normal morphology, except for mildly megaloblastic erythropoiesis
    - megakaryocytes are invariably greatly reduced and usually absent

Laboratory Studies

- Ancillary Studies
  - Chromosome studies
    - to exclude Fanconi's anemia in children or young adults
    - to exclude MDS in older patients
  - FACs analysis
    - CD3, CD4, CD8
      - to prove immunologic abnormality
    - CD55, CD59
      - to exclude PNH
  - Serologic studies
    - Provide evidence of viral infection (EBV, hepatitis, HIV, etc.)

Diagnosis

- combination of pancytopenia with a fatty, empty bone marrow
  - history of exposures
  - serological testing: HIV, hepatitis; EBV, parvovirus
  - red cell CD59 for PNH if history suggestive
  - determine severity of aplastic anemia
    - Severe cases:
      - very low rate of spontaneous remission
      - Mortality of 70%

Severity of Disease

- Severe Aplastic Anemia (SAA)
  - Marrow of less than 25% normal cellularity OR marrow <50% normal cellularity with fewer than 30% of the cells being hematopoietic
  - 2 of 3 abnormal peripheral blood values
    - corrected reticulocyte count $<1\%$ or absolute reticulocyte count < 60,000 /μL
    - ANC<500/μL(0.5×10^9/L)
    - Platelets <20,000/ μL(20×10^9/L)
- Very Severe Aplastic Anemia (VSAA)
  - ANC <200/μL(0.5×10^9/L)

Differential Diagnosis

- Pancytopenia with splenomegaly: hypersplenism
- Pancytopenia without splenomegaly
  - Aplastic Anemia
    - Congenital: Fanconi's; Dyskeratosis congenita; Shwachman-Diamond syndrome; Amegakaryocytic thrombocytopenia
    - Acquired
  - Acute leukemia
  - Large granular lymphocyte leukemia
  - MDS
  - Marrow replacement with tumor or fibrosis
  - Severe megaloblastic anemia (folate or B12 deficiency)
  - PNH
  - Overwhelming infection HIV or viral hemophagocytic syndrome of EBV

Treatment : Mild Aplastic Anemia

- Remove Offending Agents
- Supportive care
  - Selective transfusion therapy to avoid sensitization
- Consider Definitive therapy
  - Immunosuppressive therapy
  - Allogeneic bone marrow transplantation

BMT: the best therapy for the young patient with a fully histocompatible sibling donor

- Therapy choice influenced by age and disease severity
  - <20 years old
    - Allogeneic BMT if matched sib available
      - 50-80% cure rate, with low incidence clonal disorders
      - Condition pre-transplant with ATG/cyclophosphomide
      - Consider unrelated donor, but survival only half matched sib
  - 20-45 years old
    - Allogeneic BMT if in excellent health w/fully matched sib
  - >45 years old
    - Immunosuppression only
    - BMT with conditioning before BMT showing increased survival

Immunosuppression

- Immunosuppression is NOT curative
- is the treatment of choice to the patients lack a suitable marrow donor
- Goal is sustained remission
  - independence from transfusion and a leukocyte count adequate to prevent infection
  - 20-36% have recurrent aplastic anemia
  - 15% cases develop clonal disorder, PNH, MDS or acute leukemia
- Combination therapy is best
  - Antithymocyte globulin (ATG)
    - Toxic side effect is serum sickness, tx with steroid
    - Can lower platelet counts
  - Cyclosporine
  - High dose corticosteroids

BMT vs. immunosuppression

- Long-term survival is equivalent with transplantation and immunosuppression
- successful transplant cures marrow failure
- adults who have a matched family donor
  - Increasing age and the severity of neutropenia are the most important factors weighing in the decision
    - older patients do better with ATG and cyclosporine
    - transplant is preferred if granulocytopenia is profound

Other Therapies

- Androgens
  - occasional patients will respond or even demonstrate blood count dependence
- Hematopoietic growth factors
  - Some patients may respond to combinations of growth factors after immunosuppression has failed
- Splenectomy
  - occasionally increase blood counts in relapsed or refractory cases

Other Therapies

- Supportive Care
  - broad-spectrum, empirical antibiotics treatment
    - pneumonia, sinusitis, typhlitis, indwelling plastic catheters contamination, fungal infection
  - Transfusion
    - Both platelet and erythrocyte numbers can be maintained by transfusion
      - to maintain the platelet count >10,000/μL (10×10^9/L)
      - to maintain a hemoglobin value of 70 g/L
        - » the iron chelator deferoxamine should be added at around the fiftieth transfusion in order to avoid secondary hemochromatosis

Hemolytic Anemia

Tong Chen
Department of Hematology
Huashan Hospital

Anemia

- Definition
  - Reduction in blood transport of oxygen due to a deficiency in red blood cells
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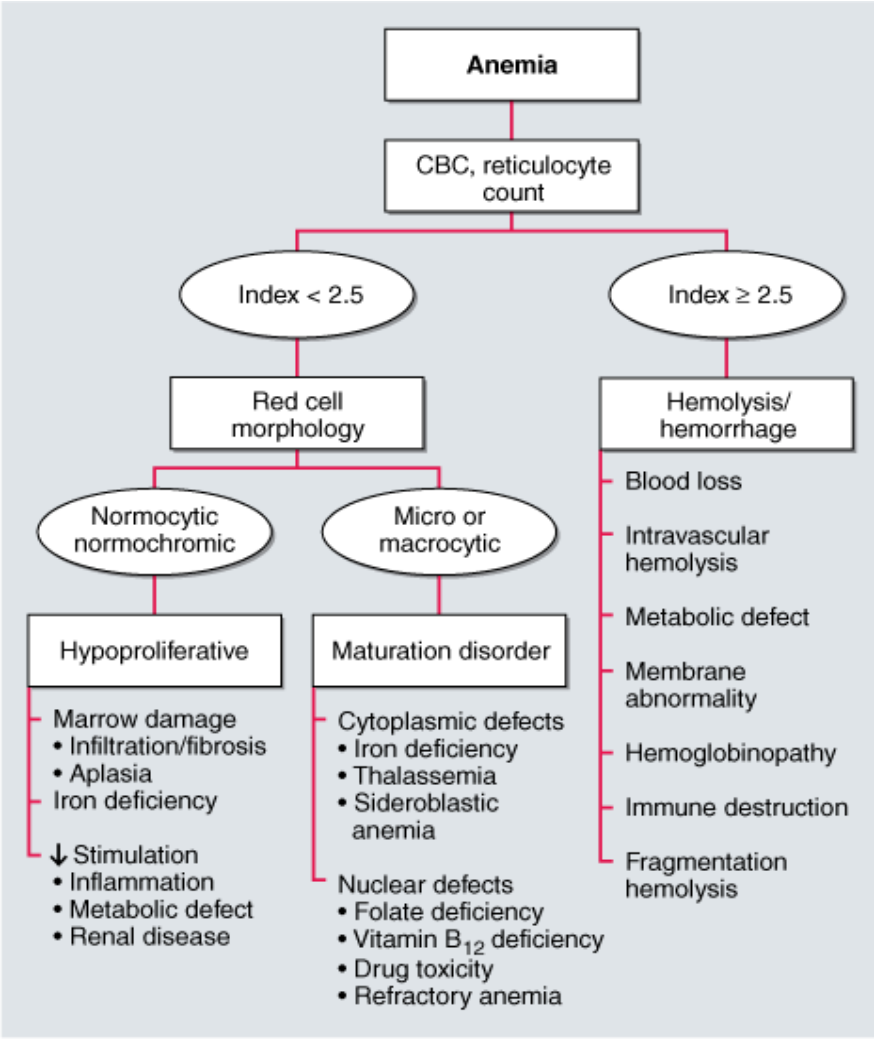


Mechanism

- The life span of RBC may be shortened in a number of disorders, often resulting in anemia if the bone marrow is not able to replenish adequately the prematurely destroyed RBC
  - a molecular defect (hemoglobinopathy or enzymopathy) inside the red cell
  - an abnormality in membrane structure and function
  - an environmental factor such as mechanical trauma or an autoantibody

Clinical Features

- Complaint
  - fatigue and other symptoms of anemia
  - jaundice and even red-brown urine
- Physical examination
  - jaundice of skin and mucosae
  - Splenomegaly

Laboratory Tests

- the presence of hemolysis
  - Anemia
  - The plasma level of unconjugated bilirubin may be high enough to produce readily apparent jaundice (detectable usually when serum bilirubin is >34 μmol/L or 2 mg/dL)
  - Lactate dehydrogenase (LDH), particularly LDH-2, is elevated by accelerated RBC destruction.
- erythroid hyperplasia
  - elevated reticulocyte count
  - erythroid hyperplasia of the bone marrow

Classification of Hemolytic Anemia

- Intravascular hemolysis
- Extravascular hemolysis

- Inhereted hemolytic anemia
- Acquired hemolytic anemia

Intra/extra Vascular Hemolysis

	Intravascular	Extravascular
Cause	RBC lysed in the vasculature	RBC engulfed by spleen and liver macrophages
Examples	Heart valves, PNH	Autoimmune, spherotysis, sickle cells
Blood film	Shcitiocytes(Fragmented RBCs)	Spherocytes
Methemoglonin	Yes	No
Haptoglobin	Decreased or absent	Slightly decreased or normal
Hemglobinuria	Yes	No
Hemosiderinuria	Yes	No
LDH	Increased	Increased or normal
Direct Coombs'	Negative	May be positive
Jaundice	Yes	Yes
Blood Transfusion	Useful	Not useful in autoimmune

Inhereted Hemolytic Anemia

- Membrane defect
  - Hereditary spherocytoses
  - Hereditary elliptocytoses
- Hemoglobin abnormalities
  - Thalassaemia
  - Sickle cell anemia
- Metabolic (enzyme) abnormalities
  - G6PD deficiency
  - Pyruvate deficiency

Acquired Hemolytic Anemia

- Autoimmune hemolytic anemia (AHA)
  - Warm AIHA
  - Cold AIHA
- Alloimmune hemolytic anemia
  - Hereditary disease of newborn
- Drug induced hemolytic anemia
- Non-immune hemolytic anemia
  - Paroxysmal nocturnal hemoglobinuria
  - Hypersplenism

Inhereted Hemolytic Anemia

Membrane Defect

Clinical Manifestations

- Clinical features
  - Anemia
    - mild or moderate and may even be absent in an otherwise healthy individual
    - compensatory erythroid hyperplasia of the bone marrow
    - compensation may be temporarily interrupted by episodes of relative erythroid hypoplasia precipitated by infections
  - Splenomegaly
    - very common
    - systemic infections could induce further splenic enlargement
  - Jaundice
    - intermittent and tends to be less pronounced in early childhood
    - pigmented gallstones are common

Differentiation Diagnosis

- must be distinguished primarily from the spherocytic hemolytic anemias associated with RBC antibodies
  - Coombs test: positive
- in patients with cirrhosis, in clostridial infections, and in certain snake envenomations
- glucose-6-phosphate dehydrogenase (G6PD) deficiency

Treatment

- Splenectomy
  - moderate or severe hemolysis
  - RBC survival after splenectomy is normal or nearly so
  - cholecystectomy should not be performed without splenectomy
  - Splenectomy in children should be postponed until age 4

Inhereted Hemolytic Anemia

Metabolic (enzyme) abnormalities

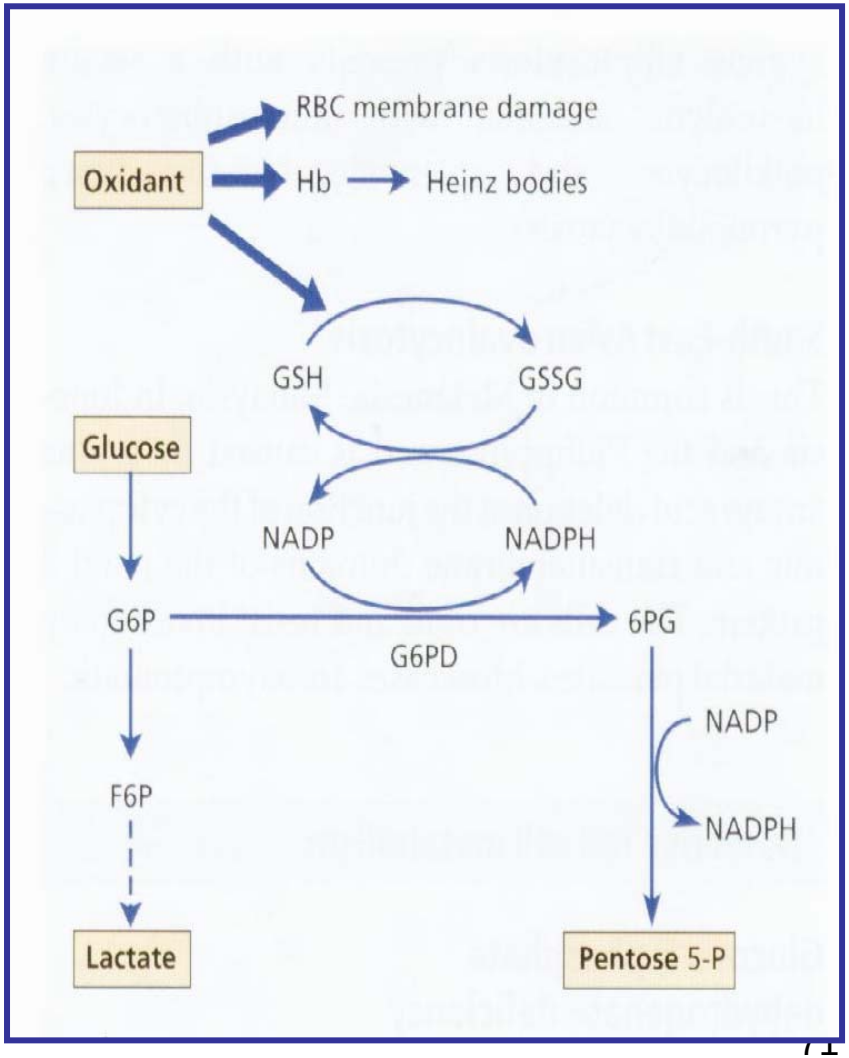
Classification of Enzyme Abnormalities

- Defects in The Embden-Meyerhof Pathway
  - pyruvate kinase (PK) deficiency
  - hexokinase deficiency
- Defects in The Hexose-Monophosphate Shunt
  - G6PD Deficiency

G6PD Deficiency

- **G6PD functions to reduce nicotinamide adenine dinucleotide phosphate (NADPH) while oxidizing glucose-6-phosphate**

- **NADPH is needed for the production of reduced glutathione (GSH) which is important to defend the red cells against oxidant stress**

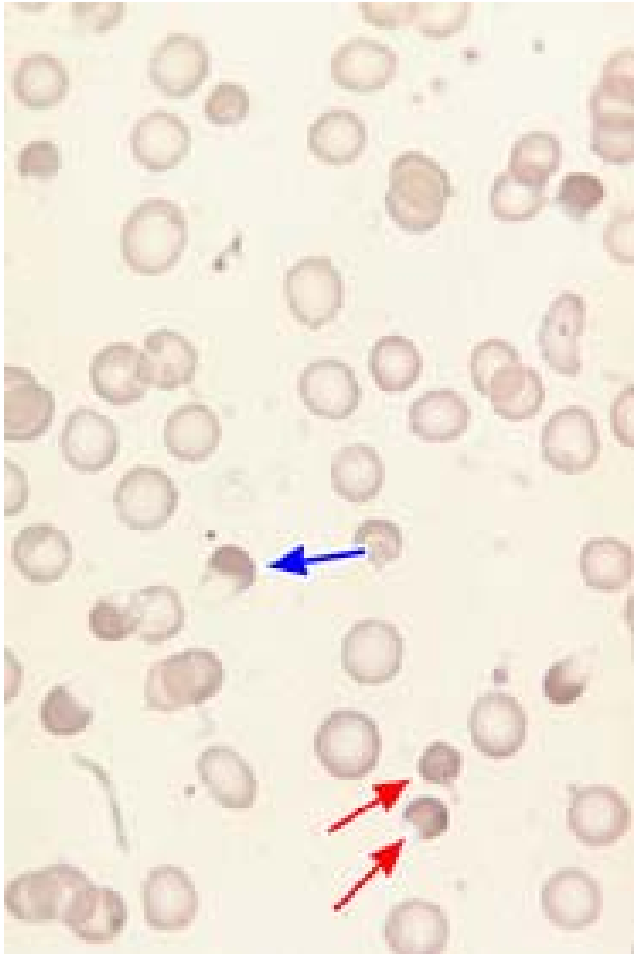


G6PD Deficiency

- More than 400 variants due to point mutations or deletions of the enzyme G6PD have been characterized which show less activity than normal.
- Worldwide over 400 million people are G6PD deficient in enzyme activity
- The G6PD gene is located on the X chromosome
  - The inheritance is sex-linked, affecting males, and carried by females
- The main races affected are in West Africa, the Mediteranean, the Middle East, and South East Asia
- Clinical problems arise when the affected individual is subjected to some type of environmental stress
  - viral and bacterial infections
  - sulfa drugs, antimalarials, and nitrofurantoin
  - naphthalene balls
  - Fava bean

G6PD Deficiency

- Between crises blood count is normal.
- The enzyme deficiency is detected by
  - One of a number of screening tests
  - direct enzyme assay on red cells
- During the crisis, the blood film may show contracted and fragmented cells, bite and blister cells.
- Enzyme assay may give a false normal level in the phase of acute haemolysis.



G6PD Deficiency

- Diagnosis
  - features of intravascular haemolysis
  - possible exposure to oxidant agents
  - tests assessing either the enzyme activity or the effects of its deficiency
  - particularly a male of African or Mediterranean descent
- Treatment
  - usually selflimited, no specific treatment is necessary
  - Adequate urine flow should be maintained if hemoglobinuria develops
  - Splenectomy does not benefit patients with chronic hemolysis
  - Prevent the patients from exposure to oxidant drugs and fava beans

Acquired Hemolytic Anemia

Autoimmune Hemolytic Anemia (AHA)

Autoimmune Hemolytic Anemia

- Immunologic destruction of RBCs mediated by autoantibodies against antigens on the RBC surface
- Classified by isotype (IgG, IgM, IgA) and the temperature at which they maximally react
- In general, cold-reacting antibodies are IgM and warm-reacting antibodies are IgG causing extravascular hemolysis

Clinical Features of “Warm” Antibodies

- occurs at all ages, but it is more common in adults, particularly women
- one-fourth of patients this disorder occurs as a complication of an underlying disease affecting the immune system
  - lymphoid neoplasms; collagen vascular diseases; congenital immunodeficiency diseases
- Pathogenesis
  - immune adherence of RBC to phagocytes mediated by the antibody and by complement components (the more important mechanism of destruction)
  - complement activation
  - IgG antibodies bind to Fc receptors on macrophages
  - activating those cells to engulf the coated RBC
  - resulting in the formation of spherocytes destroyed in the spleen

Presentation and Course

- Mildest form
  - a positive direct Coombs test
  - moderate to severe anemia
  - spherocytosis and splenomegaly
- Severe immunohemolytic anemia
  - fulminant hemolysis with hemoglobinemia, hemoglobinuria, and shock
  - be rapidly fatal unless aggressively treated
  - The direct Coombs test is positive in 98% of patients
  - usually IgG is detected with or without C3

Treatment

- mild degree of hemolysis
  - usually do not require therapy
  - glucocorticoids: prednisone
    - initial therapy consists of 1.0 mg/kg per day
    - Prednisone is continued until the hemoglobin level has risen to normal value, and then slowly over the course of several months
    - an immediate effect due to inhibiting clearance of IgG-coated RBC, and later to inhibiting antibody synthesis
  - Splenectomy
    - for patients who cannot tolerate or fail to respond to glucocorticoid therapy

Treatment

- Severe immunohemolytic anemia
  - blood transfusions
    - compatible cross-matching is impossible
    - to avoid administering RBC with antigens to which the patient may have alloantibodies
  - Glucocorticoids: high dose
  - Plasma apheresis