University of Basrah
Al-Zahraa Medical College

Ministry of Higher education
and Scientific Research

Block: Child Health.

Lecture: Anaemia

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Nelson Textbook of Pediatrics, 21th edition.
Nelson Essentials of Pediatrics, 7th Edition 2015
Pediatric Decision-Making Strategies
Illustrated Textbook of Pediatrics
Short Atlas in Pediatrics

Learning objectives:

- Iron deficiency anemia.
- Hemolytic anemia:
  - Thalassemia syndrome/SCA.
  - G6PD.
  - Cong. Spherocytosis.
  - Autoimmune hemolytic anemia.
- Aplastic anemia/bone marrow failure.

Definition:

Disorders in which the red cell mass is decreased.

The principal effect is decreased oxygen-carrying capacity of the blood.

Their severity is best expressed in terms of hemoglobin concentration.

Relative or absolute ….???

It is essential that the specific cause of anemia be determined. The initial laboratory approach to the diagnosis of anemia follows:

— Hematocrit, hemoglobin, or red cell count to determine degree of anemia. In most cases, these three variables are closely correlated. Hemoglobin concentration is the most direct measure of oxygen-carrying capacity.

— Red cell indices, MCV, MCH, and MCHC to determine whether normocytic, macrocytic, or microcytic and normochromic or hypochromic red cells are present on average

— Measurement of red cell distribution width (RDW) to obtain a measure of anisocytosis

— Reticulocyte count or index to estimate whether marrow response suggests inadequacy of red cell production or an appropriate erythropoietic response to hemolysis (or acute bleeding). The latter is usually readily apparent clinically.

— Examination of the blood film to determine red cell size and shape, hemoglobin content.

Classification of anemias:

A- Decrease Red Cell production

1- Acquired

- Megaloblastic anemia
- Iron deficiency anemia

2- Hereditary

- Thalassemia

B- Increased red cell destruction

A- Acquired

- TTP, DIC
- autoimmune hemolytic anemia

B- Hereditary

- Hemoglobinopathy (Sickle cell disease)
- Membranopathy (hereditary spherocytosis)
- Enzymopathy (glucose-6-phosphate dehydrogenase deficiencies)

IRON-DEFICIENCY ANEMIA

- The most widespread and common nutritional disorder in the world.

Developmental stages of iron deficiency

- **Iron depletion**: storage iron decreased or absent
- **Iron deficiency**: storage iron absent with low serum iron concentration and transferrin saturation
- **Iron-deficiency anemia**: storage iron absent, low serum iron concentration and transferrin saturation, and low hemoglobin level

IRON-DEFICIENCY ANEMIA

Etiology

- Stores are depleted sooner in low-birth weight infants
- early clamping (<30 sec) puts the infant at risk for iron deficiency
- excessive consumption of cow's milk
- Blood loss, particularly in older children and adolescents.

Pathogenesis

Lack of iron decreases heme synthesis, which leads to reduced hemoglobin synthesis and defective erythropoiesis.

Clinical manifestations

- Most children with iron deficiency are asymptomatic
- **Pallor** is the most important clinical sign of iron deficiency but is not usually visible until the hemoglobin falls to 7-8 g/dL, when the hemoglobin level falls to <5 g/dL, **irritability, anorexia, and lethargy** develop, and systolic flow murmurs are often heard
- Impaired neurocognitive function in infancy
- **pica**, the desire to ingest nonnutritive substances, and **pagophagia**, the desire to ingest ice. The pica can result in the ingestion of lead-containing substances and result in concomitant **plumbism**

Laboratory features

1- S. Ferritin

2- S.Iron ↓, TIBC ↑, Saturation (<15%)

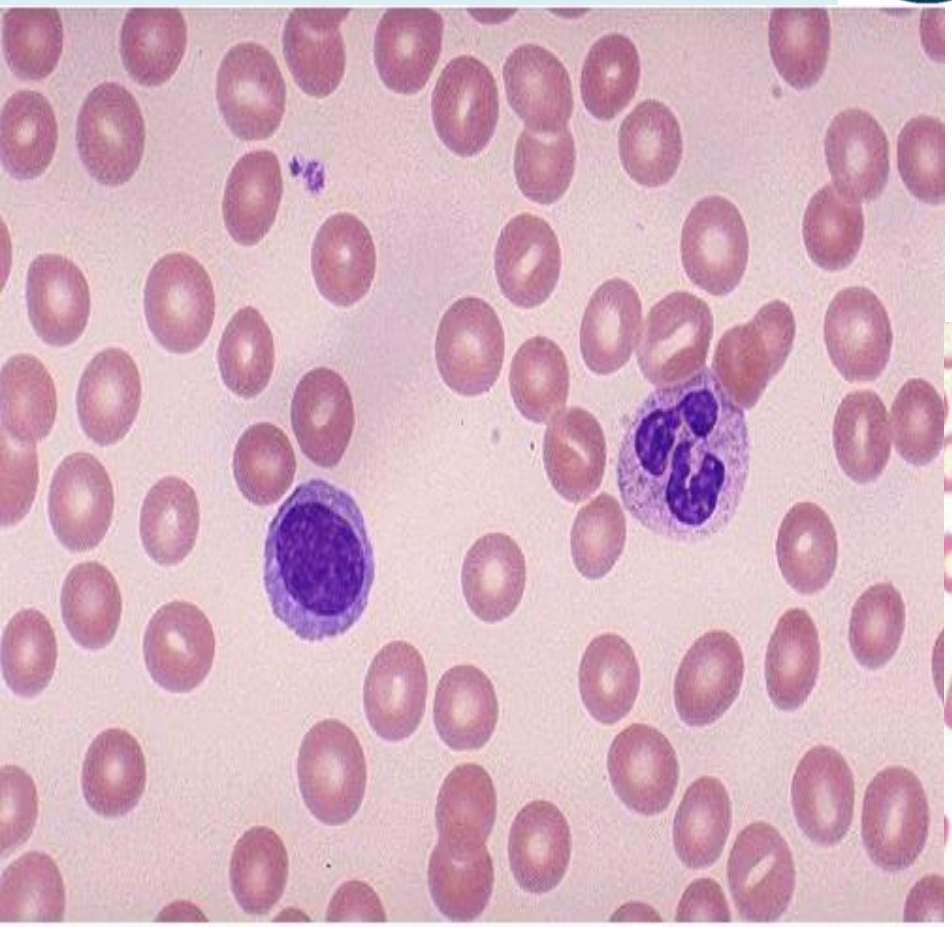
3- sTfR ↑

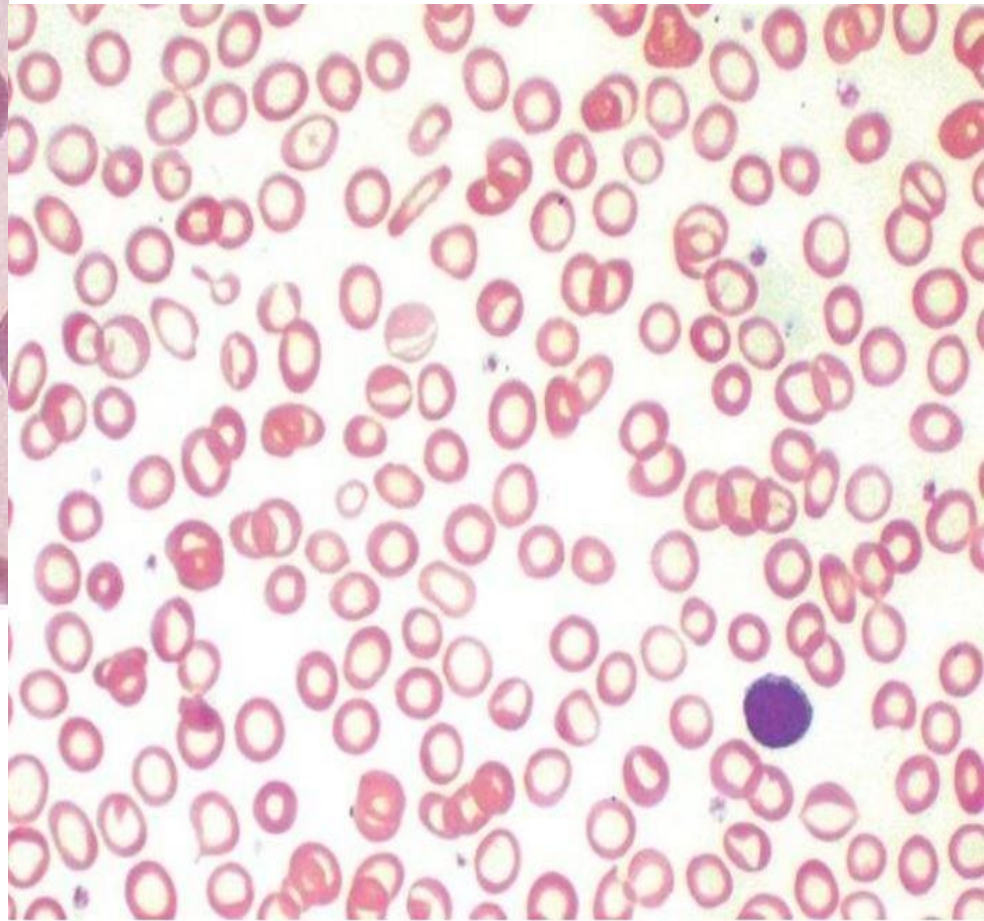
3- Reticulocyte count normal or decrease

4- Free erythrocyte protoporphyrins accumulate

5- MCV ↓, MCH ↓(MCHC ↓), Hb ↓, RDW ↑

6- Elliptocytic or cigar-shaped red cells are often seen





Differential diagnosis

α- or β-thalassemia, anemia of chronic disease, lead poisoning.

Prevention

Breastfeeding should be encouraged, with the addition of supplemental iron at 4 months of age

Treatment

Ferrous salts (A daily total dose of 3-6 mg/kg of elemental iron in 3 divided doses)

Parenteral iron preparations are only used when malabsorption is present or when compliance is poor, because oral therapy is otherwise as fast, as effective, much less expensive and less toxic

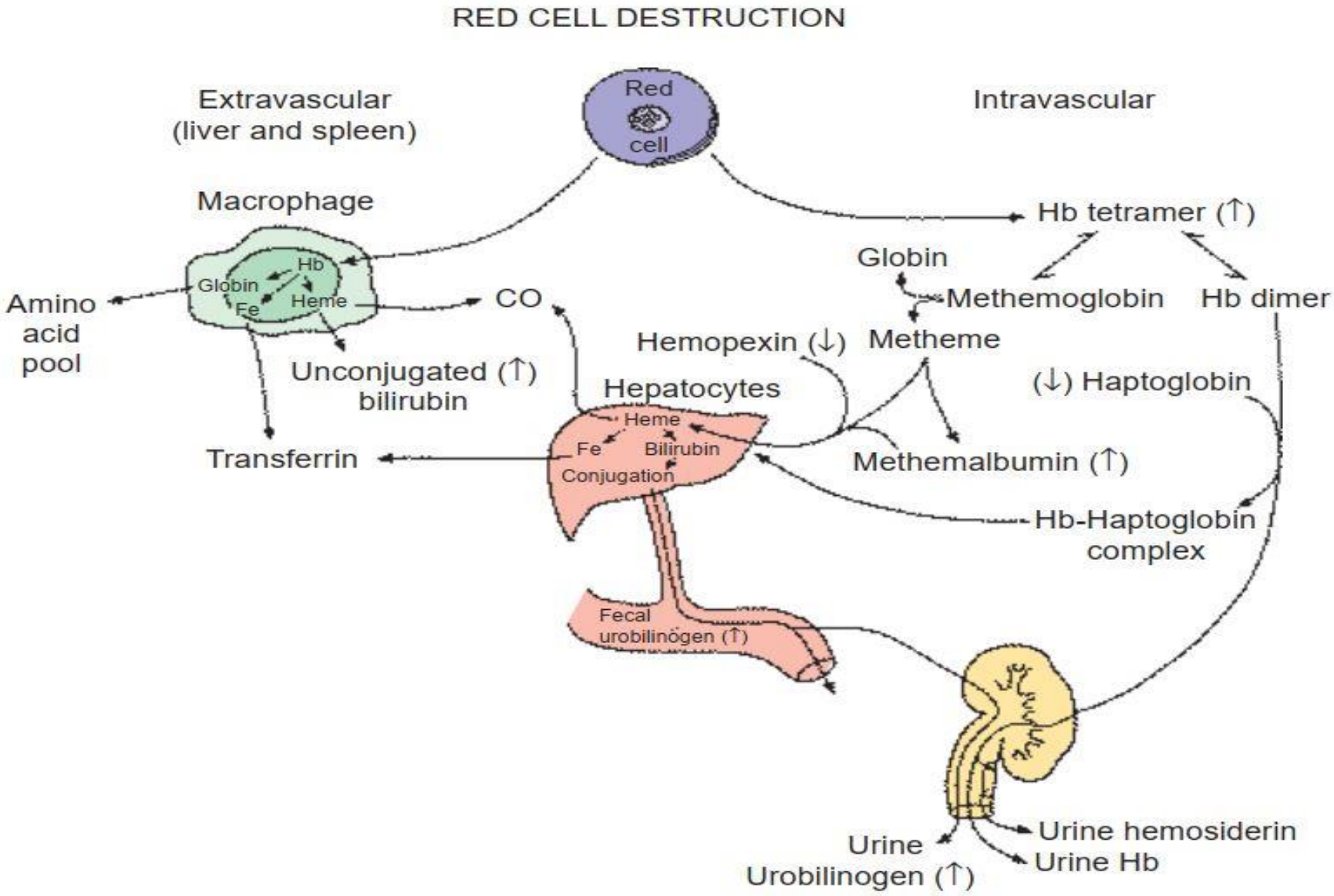
TIME AFTER IRON ADMINISTRATION	RESPONSE
12-24 hr	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite
36-48 hr	Initial bone marrow response; erythroid hyperplasia
48-72 hr	Reticulocytosis, peaking at 5-7 days
4-30 days	Increase in hemoglobin level
1-3 mo	Repletion of stores

HEMOLYTIC ANEMIAS

- Hemolysis is defined as the premature destruction of red blood cells (RBCs) (a shortened RBC life span). Anemia results when the rate of destruction exceeds the capacity of the marrow to produce RBCs.
- During hemolysis, RBC survival is shortened, the RBC count falls, erythropoietin is increased, and the stimulation of marrow activity results in heightened RBC production, reflected in an increased percentage of reticulocytes in the blood. Thus, hemolysis should be suspected as a cause of anemia if an elevated reticulocyte count is present. (acute blood loss, therapy with iron, B12, floate)

Hemolytic Anemias

- Erythroid hyperplasia.
- Increased biliary excretion of heme pigment derivatives and increased urinary and fecal urobilinogen
- Three heme-binding proteins in the plasma are altered during hemolysis (haptoglobin ↓ and hemopexin ↓, methemalbumin ↑).
- An aplastic crisis (parvovirus B19).


RED CELL DESTRUCTION
Extravascular
(liver and spleen)
Red
cell
Intravascular
Macrophage
Hb tetramer (↑)
Globin
Hb
Globin
Fe
Heme
Amino
acid
pool
CO
Methemoglobin
Hb dimer
Hemopexin (↓)
Metheme
Unconjugated (↑)
bilirubin
Hepatocytes
(↓) Haptoglobin
Heme
Fe
Bilirubin
Conjugation
Transferrin
Methemalbumin (↑)
Hb-Haptoglobin
complex
Fecal
urobilinogen (↑)
Urine hemosiderin
Urine Hb
Urine
Urobilinogen (↑)

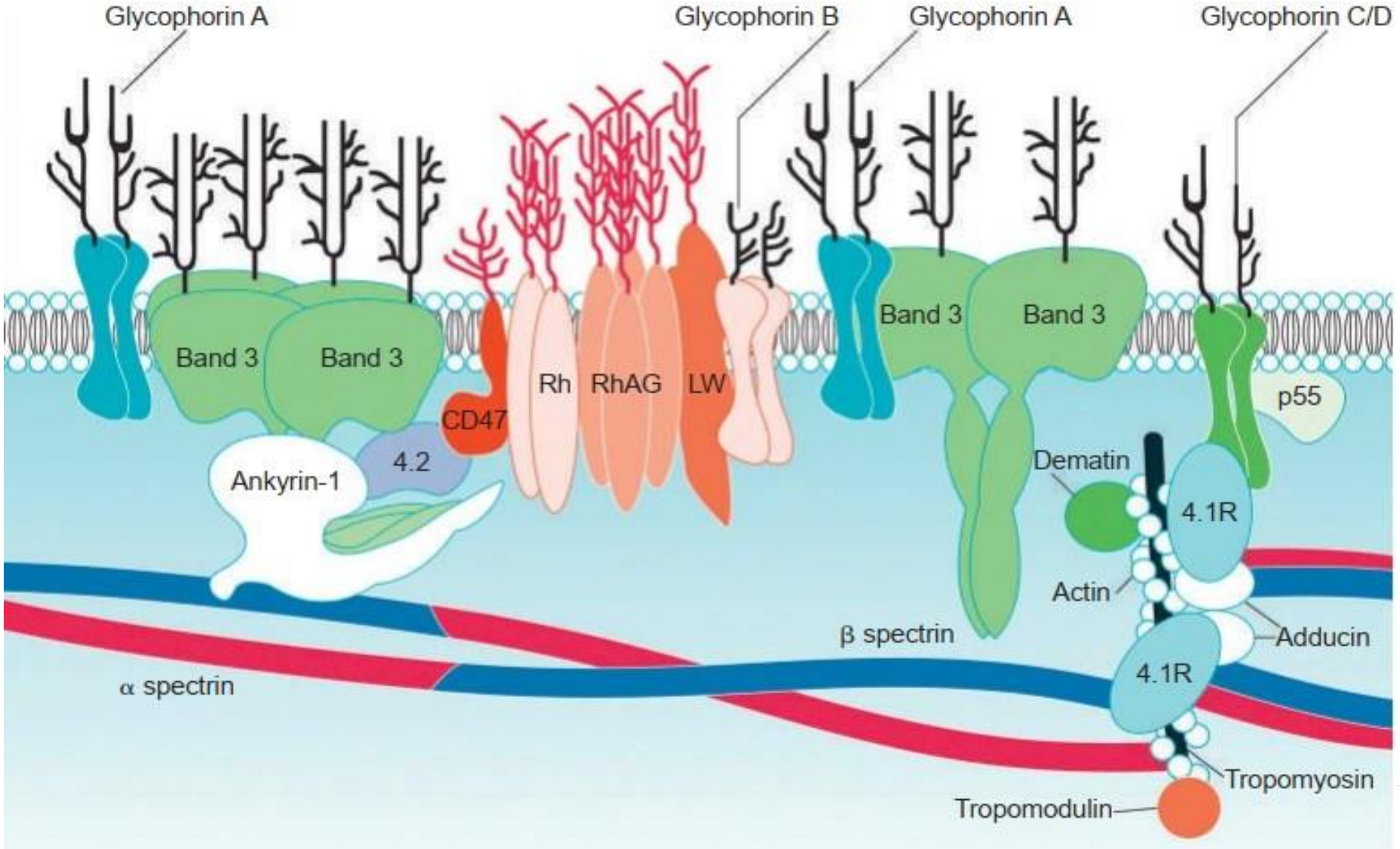
Hemolytic anemias may be classified as either **cellular**, resulting from intrinsic abnormalities of the membrane, enzymes, or hemoglobin; or **extracellular**, resulting from antibodies, mechanical factors, or plasma factors. Most cellular defects are inherited (paroxysmal nocturnal hemoglobinuria is acquired), and most extracellular defects are acquired (abetalipoproteinemia with acanthocytosis is inherited)

HEREDITARY SPHEROCYTOSIS

Prevalence of approximately 1 in 5,000 persons. It is the most common inherited abnormality of the red blood cell (RBC) membrane

Etiology

- Autosomal dominant or, less commonly, as an autosomal recessive disorder. As many as 25% of patients have no previous family history
- 5 proteins, which are key components of the cytoskeleton responsible for RBC shape (α & β spectrin, band 3, ankyrin, or protein 4.2)


Glycophorin A
Glycophorin B
Glycophorin A
Glycophorin C/D
Band 3
Band 3
Rh
RhAG
LW
CD47
Band 3
Band 3
p55
Dematin
4.1R
4.2
Ankyrin-1
Actin
β spectrin
Adducin
4.1R
α spectrin
Tropomyosin
Tropomodulin

Clinical manifestations

- In the **neonatal period**, HS is a significant cause of hemolytic disease and can be manifest as anemia and hyperbilirubinemia sufficiently severe to require phototherapy or exchange transfusions
- After **infancy**, splenomegaly is common; there is no correlation between spleen size and disease severity. Bilirubin gallstone formation
- **Children** with HS are also susceptible to aplastic crises, primarily as a result of parvovirus B19 infection, and to hypoplastic crises associated with various other infections

Diagnosis

- Reticulocytosis (6-20%, with a mean of approximately 10%) and indirect hyperbilirubinemia.
- The hemoglobin level usually is 6-10 g/dL
- Blood films shows polychromatophilic reticulocytes and spherocytes

The diagnosis of HS can be established from a positive family history and the presence of typical clinical and laboratory features of the disease: splenomegaly, spherocytes on the blood smear, reticulocytosis, and an elevated mean corpuscular hemoglobin concentration.

Diagnosis

If the diagnosis is less certain, the recommended tests that have a high predictive value for HS are the flow cytometric **EMA (eosin 5 maleimide)** binding test and the **cryohemolysis test**. Although no test for HS is 100% reliable, the EMA binding test had a diagnostic sensitivity and specificity of 93% and 98%, respectively, in a recent large study. Other assays, such as the **acidified glycerol lysis test** and **osmotic gradient ektacytometry**, also have increased sensitivity for HS. The classic incubated osmotic fragility test can detect the presence of spherocytes in the blood; however, it is not specific to HS and may be abnormal in other hemolytic anemias.

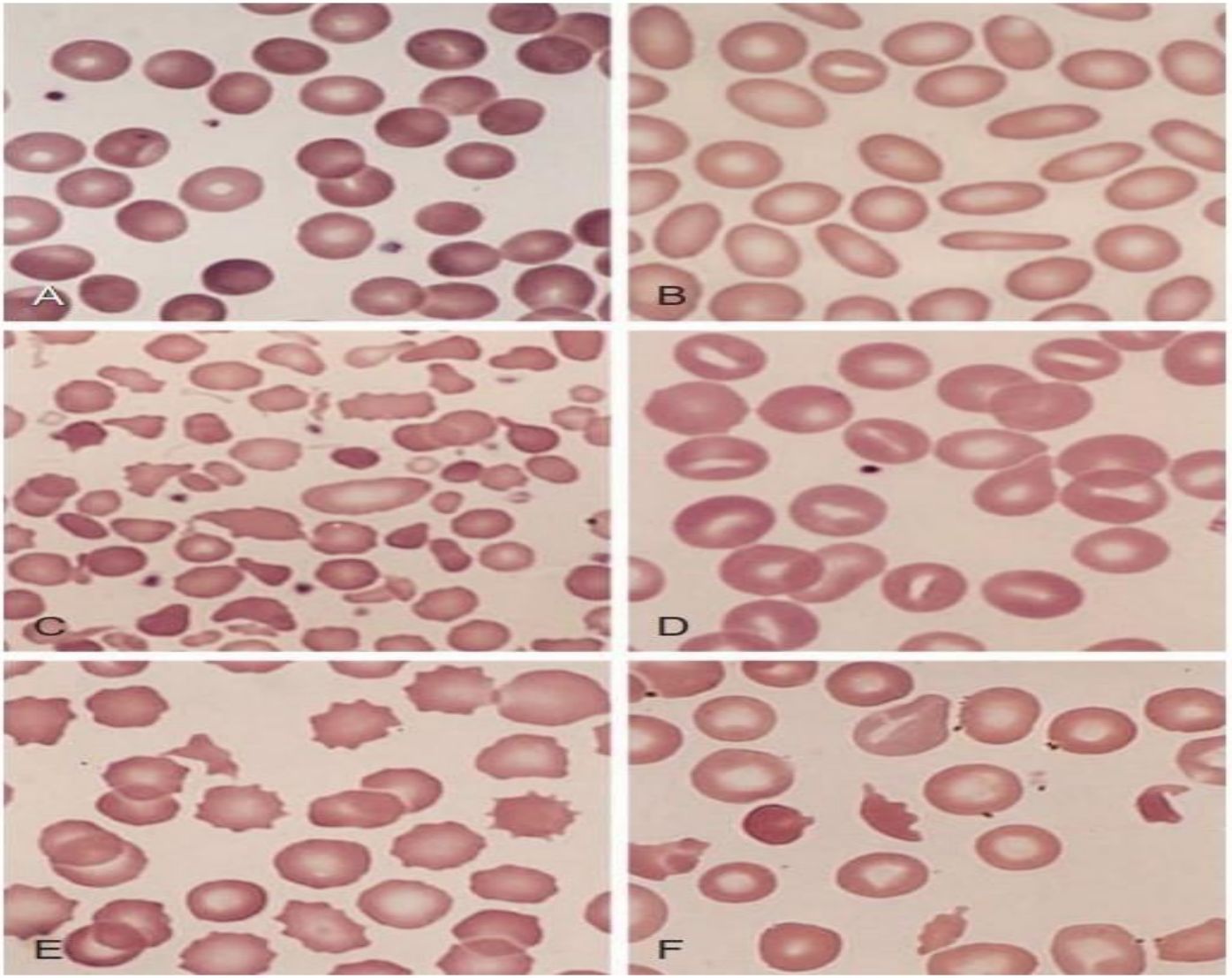


Figure 458-4 Morphology of abnormal red cells. **A,** Hereditary spherocytosis. **B,** Hereditary elliptocytosis. **C,** Hereditary pyropoikilocytosis. **D,** Hereditary stomatocytosis. **E,** Acanthocytosis. **F,** Fragmentation hemolysis.

Differential diagnosis

Isoimmune and autoimmune hemolysis.

Rare causes of spherocytosis include thermal injury, clostridial septicemia, and Wilson disease

Treatment

- General Supportive Care.
- Guidelines for Splenectomy (Splenectomy is **recommended** for patients with severe HS. It should be **considered** for patients with moderate HS and frequent hypoplastic or aplastic crises, poor growth, or cardiomegaly. It is generally **not recommended** for patients with mild HS)

SICKLE CELL DISEASE

Pathophysiology

Hemoglobin S (HbS) is the result of a single base-pair change, thymine for adenine, at the sixth codon of the β-globin gene. This change encodes valine instead of glutamine in the 6th position in the β-globin molecule

- *Sickle cell anemia* (HbSS) (homozygous HbSS)
- *Sickle cell disease* refers to not only patients with sickle cell anemia, but also to **compound heterozygotes** where one β-globin allele includes the sickle cell mutation and the second β-globin allele includes a gene mutation other than the sickle cell mutation, such as HbC, β-thalassemia, HbD, and HbOArab.

Diagnosis

- The most commonly used procedures for newborn diagnosis include **thin layer/isoelectric focusing** and **high-performance liquid chromatography (HPLC)**.
- A confirmatory step is recommended, with all patients who have initial abnormal screens being retested during the first clinical visit and after 6 months of age to determine the final hemoglobin phenotype
- In newborn screening programs, the hemoglobin with the greatest quantity is reported first, followed by other hemoglobin in order of decreasing quantity.

Clinical manifestations and treatment of sickle cell anemia

- Fever and Bacteremia: Fever in a child with sickle cell anemia is a medical emergency
- Aplastic Crisis (Human parvovirus B19)
- Splenic Sequestration is a life-threatening complication occurring primarily in infants and young children with sickle cell anemia

Sickle Cell Pain

- Dactylitis, referred to as hand-foot syndrome, is often the first manifestation of pain in infants and young children with sickle cell anemia.

Clinical manifestations and treatment of sickle cell anemia

- Acute vasoocclusive pain
- Avascular necrosis (femoral head)
- Priapism is defined as an unwanted painful erection of the penis

- Neurologic complications associated with sickle cell anemia are varied and complex, ranging from acute ischemic stroke with focal neurologic deficit to clinically silent abnormalities found on radiologic imaging.

- Primary prevention of overt stroke can be accomplished using **transcranial Doppler ultrasonography (TCD)** assessment of the blood velocity in the terminal portion of the internal carotid and the proximal portion of the middle cerebral artery.
- Children with sickle cell anemia with an elevated time-averaged mean maximum (TAMM) blood-flow velocity >200 cm/sec are at increased risk for a cerebrovascular event. A TAMM measurement of <200 cm/sec but ≥180 cm/sec represents a conditional threshold. A repeat measurement is suggested within a few months because of the high rate of conversion to a TCD velocity >200 cm/sec in this group of patients.

Pulmonary Complications

- Lung disease in children with sickle cell anemia is the second most common reason for hospital admission and is associated with significant mortality.

- ACS refers to a life-threatening pulmonary complication of sickle cell disease defined as a new radiodensity on chest radiography plus any 2 of the following: fever, respiratory distress, hypoxia, cough, or chest pain

Therapeutic considerations

Hydroxyurea

myelosuppressive agent, is the only drug proven effective in reducing the frequency of painful episodes. The typical starting dose of hydroxyurea is 15-20 mg/ kg given once daily, with an incremental dosage increase every 8 wk of 5 mg/kg, and if no toxicities occur, up to a maximum of 35 mg/kg per dose.

Hematopoietic Stem Cell Transplantation

The only cure for sickle cell anemia is transplantation with human leukocyte antigen (HLA)–matched hematopoietic stem cells from a sibling or unrelated donor.

The most common indications for transplant are recurrent ACS, stroke and abnormal TCD

Red blood cell transfusions are frequently used in the management of children with sickle cell anemia

THALASSEMIA SYNDROME.

Thalassemia refers to a group of genetic disorders of globin chain production in which there is an imbalance between the α-globin and β-globin chain production

β0-Thalassemia refers to the absence of production of the β-globin.

β+-Thalassemia indicates a mutation that makes decreased amounts of normal β-globin

α0-mutation indicates no α-chains produced from that gene

α+ mutation produces a decreased amount of α-globin chain.

Pathophysiology

- Two related features contribute to the sequelae of β-thalassemia major:

inadequate β-globin gene production leading to decreased levels of normal hemoglobin (HbA) and unbalanced α- and β-globin chain production (α-globin tetramers (α4))

This ineffective erythropoiesis and the compensatory massive marrow expansion with erythroid hyperactivity characterize β-thalassemia.

- In the α-thalassemia syndromes, 2 genes with 2 maternal and 2 paternal alleles control α-globin production, which varies from complete absence (hydrops fetalis) to only slightly reduced (α-thalassemia silent carrier). In the α-thalassemia syndromes, an excess of β- and γ-globin chains are produced. These excess chains form Bart hemoglobin (γ4) in fetal life and HbH (β4) after birth

Clinical Manifestations

- Depending on the mutation and degree of fetal hemoglobin production, transfusions in β-thalassemia major are necessary beginning in the 2nd months to 2nd year of life, but rarely later
- The classic presentation of children with severe disease includes thalassemic facies (maxilla hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fractures, marked hepatosplenomegaly, and cachexia and is now primarily seen in countries without access to chronic transfusion therapy.

Chronic transfusion therapy dramatically improves the quality of life and reduces the complications of severe thalassemia

- Newborn screening..??
- Infants
  - Microcytosis, hypochromia and targeting characterize the red cells.
  - Nucleated red cells, marked anisopoikilocytosis, and a relative reticulocytopenia are typically seen.
  - The hemoglobin level falls progressively to <6 g/dL unless transfusions are given.
  - The unconjugated serum bilirubin level is usually elevated.
  - Elevated serum ferritin and transferrin saturation.
  - Bone marrow hyperplasia

- DNA diagnosis of the β-thalassemia mutation, along with testing for common genetic modifiers of the clinical phenotype, is recommended.

- Coinheritance of an α-thalassemia mutation is common, and it decreases the severity of the β-thalassemia disease

Management and Treatment of Thalassemia

Transfusion Therapy

- β-Thalassemia major is a clinical diagnosis that requires the integration of laboratory findings and the clinical course.
- Of patients with homozygous β0-thalassemia (the most severe mutations), 15-20% may have a clinical course that is phenotypically consistent with thalassemia intermedia.
- In contrast, 25% of patients with homozygous β+-thalassemia, typically a more benign genotype, may become transfusion-dependent thalassemia major.

Management and Treatment of Thalassemia

Transfusion Therapy

- Transient clinical events, such as a sudden fall in hemoglobin secondary to an episode of parvovirus requiring transfusion, do not necessarily indicate the patient is a transfusion-dependent patient.

- The long-term observation of the clinical characteristics, such as growth, bony changes, and hemoglobin, are necessary to determine chronic transfusion therapy.

Guidelines for Transfusion Therapy.

Patients at risk for transfusion therapy should have an extended red cell phenotype and/ or genotype. Patients should receive red cells depleted of leukocytes and matched for, at least, D, C, c, E, e, and Kell antigens. Cytomegalovirus-negative units are indicated in stem cell transplantation candidates. Transfusions should generally be given at intervals of 3-4 wk, with the goal being to maintain a pretransfusion hemoglobin level of 9.5-10.5 g/dL. Ongoing monitoring for transfusion-associated transmitted infections (hepatitis A, hepatitis B, hepatitis C, HIV).

Chelation Therapy (after 1 yr of transfusion therapy and correlates with the serum ferritin >1,000 ng/mL and/or a liver iron concentration of >2,500 µg/g dry weight) (deferoxamine, deferasirox, and deferiprone)

Nontransfusion-Dependent Thalassemia: β-Thalassemia Intermedia

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most frequent disease involving enzymes of the hexose monophosphate pathway, is responsible for 2 clinical syndromes, episodic hemolytic anemia and chronic nonspherocytic hemolytic anemia.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

The most frequent disease involving enzymes of the hexose monophosphate pathway, is responsible for 2 clinical syndromes, episodic hemolytic anemia and chronic nonspherocytic hemolytic anemia.

This is X-linked deficiency.

Clinical Manifestations

Most individuals with G6PD deficiency are asymptomatic, unless triggered by infection, drugs, or ingestion of fava beans.

Typically, hemolysis ensues in about 24-48 hr after a patient has ingested a substance with oxidant properties. In severe cases, hemoglobinuria and jaundice result, and the hemoglobin concentration may fall precipitously. Drugs that elicit hemolysis in these individuals include aspirin, sulfonamides, rasburicase, and antimalarials, such as primaquine

Laboratory Findings

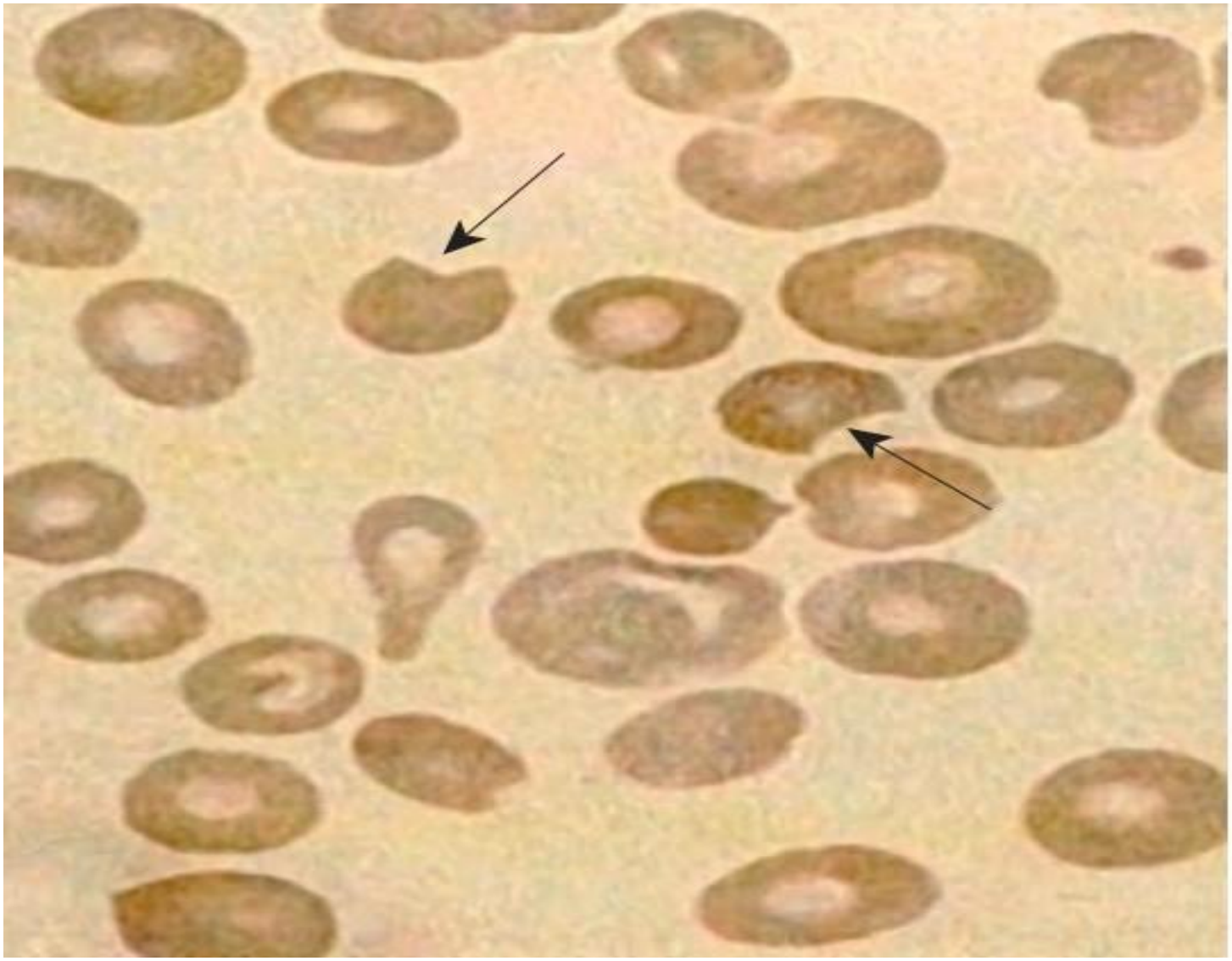
Hemoglobin ↓,

The hemoglobin binding proteins, such as haptoglobin, are saturated, and free hemoglobin may appear in the plasma and subsequently in the urine.

Heinz bodies.

Bite cells

Polychromasia



Diagnosis

The diagnosis depends on direct or indirect demonstration of reduced G6PD activity in RBCs. By direct measurement, enzyme activity in affected persons is ≤10% of normal.

Satisfactory screening tests are based on decoloration of methylene blue, reduction of methemoglobin, or fluorescence of NADPH.

- The diagnosis can be suspected when G6PD activity is within the low normal range in the presence of a high reticulocyte count.
- G6PD deficiency should be considered in any neonatal patients with hyperbilirubinemia and borderline low G6PD activity.

Autoimmune hemolytic anemias

A number of extrinsic agents and disorders may lead to premature destruction of red blood cells (RBCs). Among the most clearly defined are antibodies associated with immune hemolytic anemias. The hallmark of this group of diseases is the positive result of the **direct antiglobulin (Coombs) test**, which detects a coating of immunoglobulin or components of complement on the RBC surface. The most important immune hemolytic disorder in pediatric practice is **hemolytic disease of the newborn** (erythroblastosis fetalis), caused by transplacental transfer of maternal antibody active against the RBCs of the fetus, that is, isoimmune hemolytic anemia

Autoimmune hemolytic anemias

Autoimmune hemolytic anemias associated with “warm” antibodies

Autoimmune hemolytic anemias associated with “cold” antibodies

- Cold agglutinin disease (I/i system, mycoplasma pneumoniae and epstein-barr virus, patients with infectious mononucleosis occasionally have cold agglutinin disease, and the antibodies in these patients often have anti-i specificity)
- Paroxysmal cold hemoglobinuria (donath landsteiner (D-L) hemolysin, which is an IgG cold-reactive autoantibody with anti-p specificity)

THE INHERITED PANCYTOPENIAS

Pancytopenia refers to a reduction below normal values of all 3 peripheral blood lineages: leukocytes, platelets, and erythrocytes.

- Hypocellular marrow on biopsy is seen with inherited ("constitutional") marrow failure syndromes, acquired aplastic anemia of varied etiologies, the hypoplastic variant of myelodysplastic syndrome (MDS), and some cases of paroxysmal nocturnal hemoglobinuria with pancytopenia.

- Cellular marrow is seen (a) with primary bone marrow disease, such as acute leukemia, and MDS, and (b) secondary to systemic disease, such as autoimmune disorders, vitamin B12 or folate deficiency, storage disease (Gaucher and Niemann-Pick diseases), overwhelming infection, sarcoidosis, and hypersplenism.

- Bone marrow infiltration can cause pancytopenia in metastatic solid tumors, myelofibrosis, hemophagocytic lymphohistiocytosis and osteopetrosis.

Inherited pancytopenias account for approximately 30% of cases of pediatric marrow failure.

Fanconi anemia is the most common of these disorders.

autosomal recessive manner (one uncommon form is X-linked recessive)

Patients have abnormal chromosome fragility

At presentation, patients with FA may have:

typical physical anomalies and abnormal hematologic findings (majority of the patients); (2) normal physical features but abnormal hematologic findings (about one-third of patients); or (3) physical anomalies and normal hematologic findings (unknown percentage).

Clinical Manifestations

The most common anomaly in FA is:

- hyperpigmentation of the trunk and neck, as well as café-au-lait spots and vitiligo, alone or in combination.
- Half the patients have short stature. In some patients, growth failure is aggravated by abnormal growth hormone secretion or with hypothyroidism.
- Absence of radii and thumbs that are hypoplastic, supernumerary, bifid, or absent are common.
- The radial pulse may be weak or absent. Anomalies of the feet, congenital hip dislocation, and leg abnormalities are seen.

Laboratory Findings

Marrow failure usually ensues in the 1st decade of life. Thrombocytopenia and red blood cell macrocytosis often appears initially, with subsequent onset of granulocytopenia and then anemia. Severe aplasia develops in most cases, but its full expression is variable and evolves over a period of months to years.

Diagnosis

FA should be considered in all children and young adults with unexplained cytopenias. Abnormal hematologic findings and characteristic physical anomalies suggest the diagnosis, which is confirmed with a lymphocyte chromosomal breakage study using DEB

Treatment

If the hematologic findings are stable and there are no transfusion requirements, observation is indicated Hematopoietic stem cell transplantation is the only curative therapy for the hematologic abnormalities.

THANK YOU