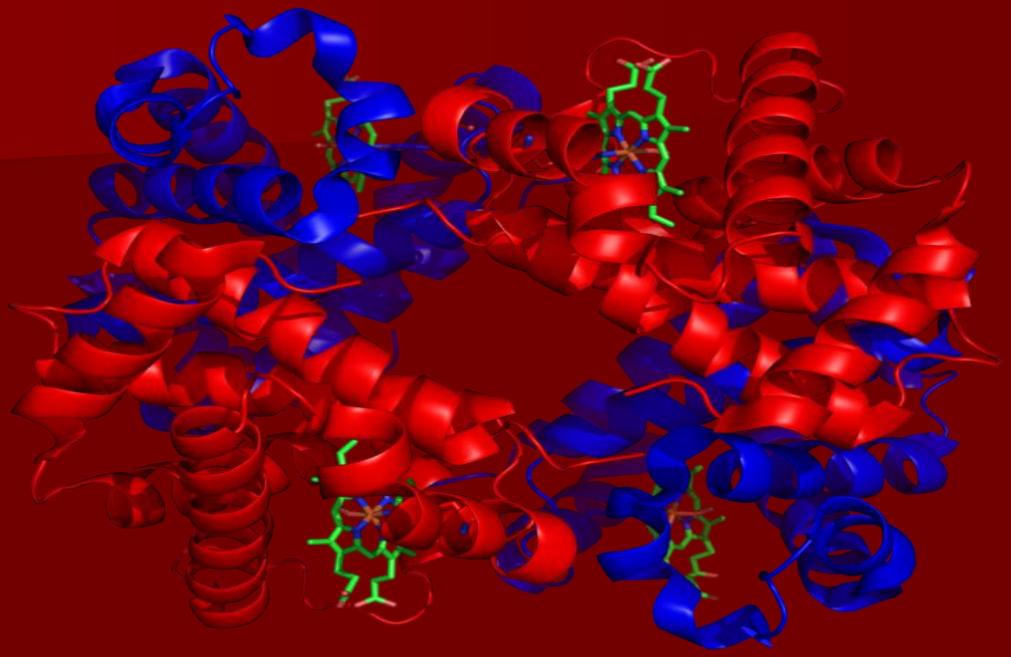
به نام خدا

Anemia in Newborns

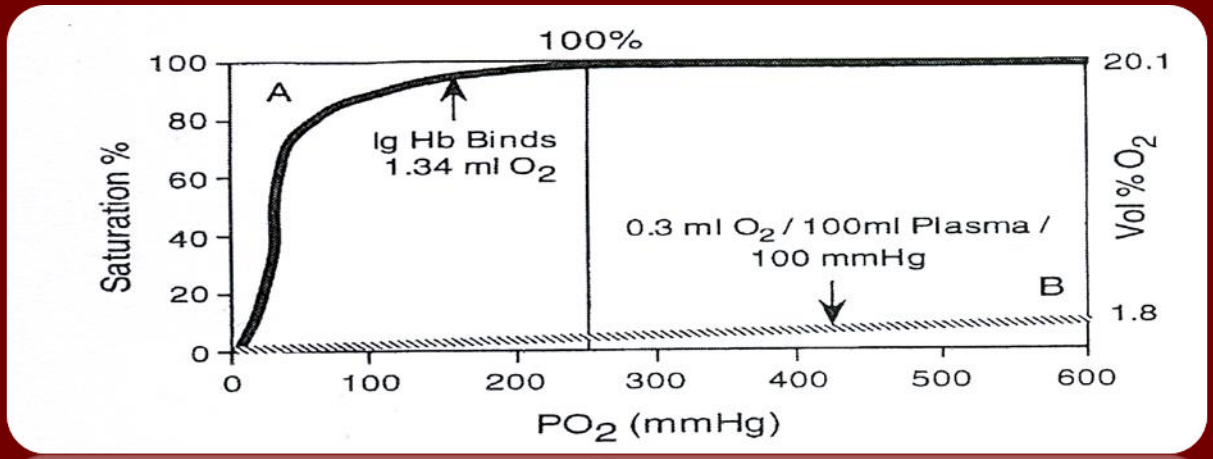
Dr. Sadeghnia



Anemia in Newborns

Oxygen Transport

- DO (mL/min)=CO dL/(min) × CaO2 (mL/dL)
- CaO2 = (SaO2 ×1.34 ×[Hgb]) + (0.0031 × PaO2)
- O2 delivered = (CO) x (CaO2) = (120 mL blood/kg/min) x (0.2 mL O2 /mL blood) = 24 mL/kg/min
- Under normal circumstances, oxygen consumption for a neonate is approximately 6 mL/kg/min



Oxygen Transport

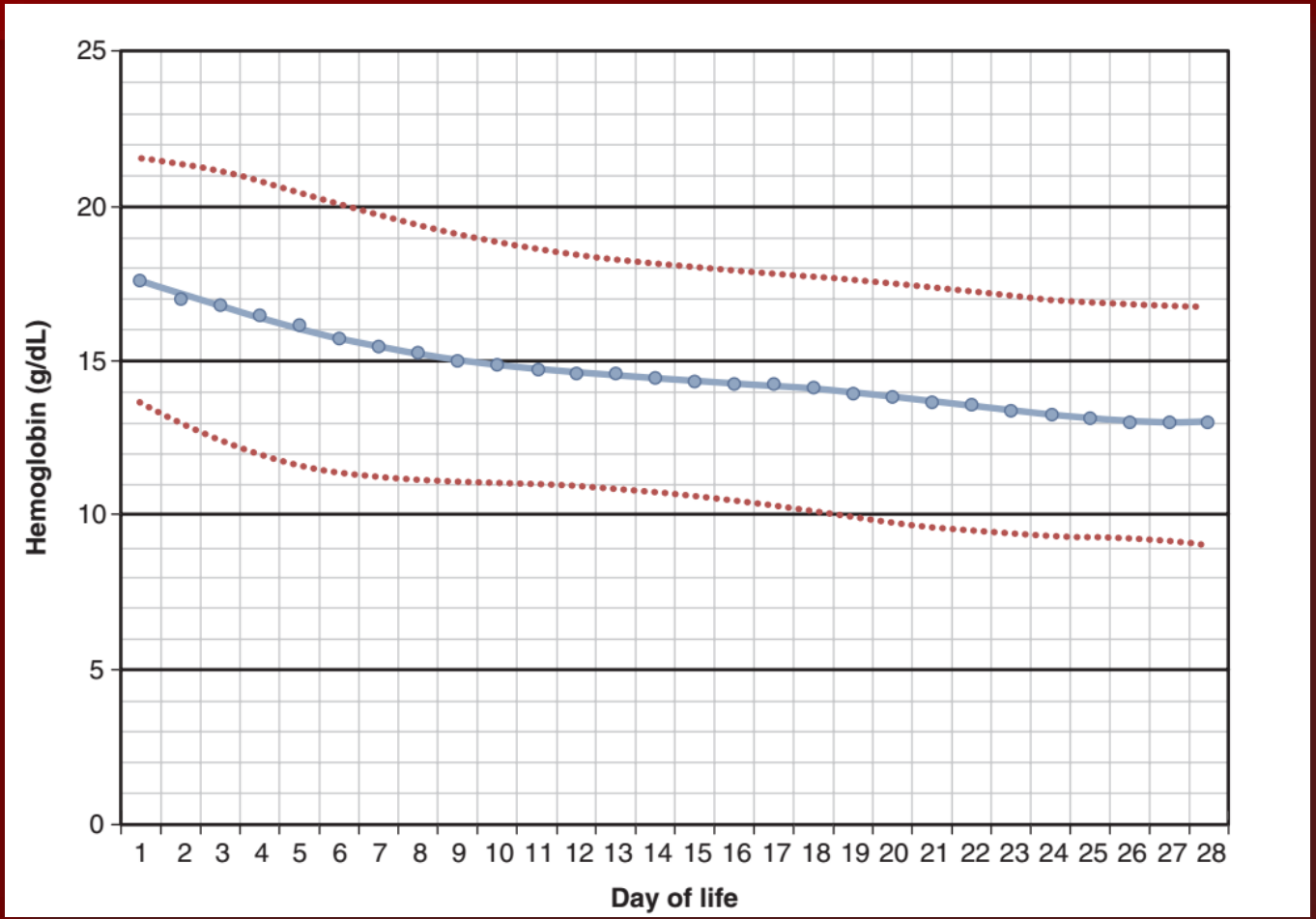
- Oxygen extraction ratio=oxygen consumption/oxygen delivery=0.15 to 0.33
- As the oxygen extraction ratio reaches or exceeds 0.4, organ and cellular function can begin to deteriorate
- Any further decrease in oxygen delivery than 7.3 mL/kg/minute of O2 results tissue hypoxia
- Therefore, approximately 25% of the oxygen has been removed from the blood by the time it returns to the heart. The mixed venous blood will therefore be approximately 75% saturated.
  - In general, a measured mixed venous saturation of 70% to 75% represents adequate tissue oxygen delivery

Defining Anemia

- Anemia is quantified by a reduction in the hemoglobin concentration or RBC mass with the threshold for defining anemia when values decrease to less than the 2.5th percentile of normal.
- Importantly, in newborns and infants, anemia must be interpreted based on the gestational age, chronologic age, weight, sex, and race.

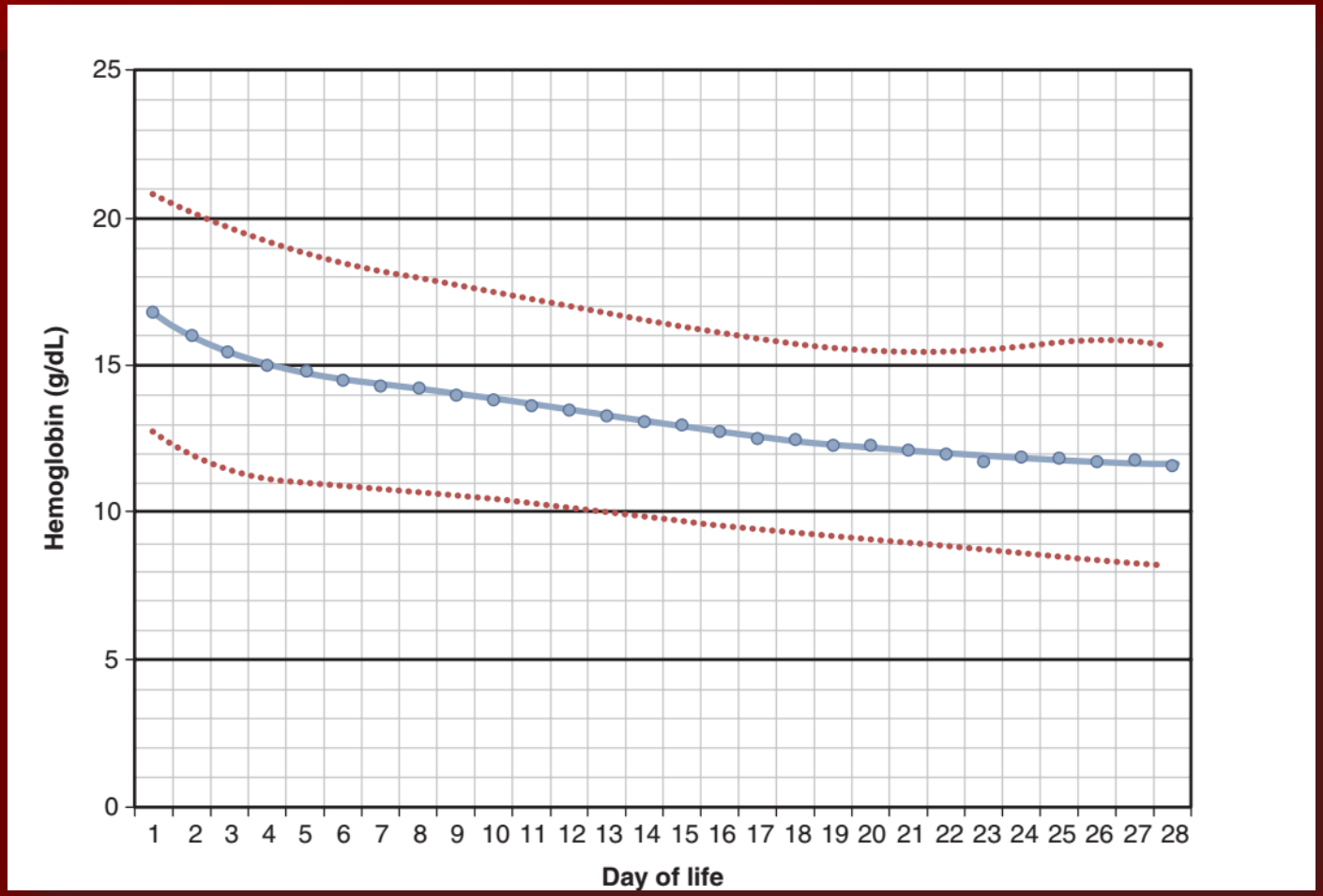
Blood hemoglobin concentration over the first 28 days of life for neonates born at 35 to 42 weeks' gestation.

(Henry E, Christensen RD. Reference intervals in neonatal hematology. Clin Perinatol. 2015;42:486)



Blood hemoglobin concentration over the first 28 days of life for neonates born at 29-34 weeks' gestation.

(Henry E, Christensen RD. Reference intervals in neonatal hematology. Clin Perinatol. 2015;42:486.)



Defining Anemia

- Anemia that is present at birth or appearing during the first weeks of life can be broadly classified into categories of anemia caused by
  - Blood loss
  - Hemolysis
  - Abnormal red cell production
- A systematic approach to evaluating anemia can narrow the differential diagnosis and provide guidance on which individuals warrant more detailed hematologic evaluation.

Defining Anemia

- Term infants are born with a relative increase in their hemoglobin caused by low oxygen saturation in the fetus. After birth, hemoglobin concentrations decrease, reaching a nadir around 9 weeks of age, known as the physiologic nadir of infancy.
- Preterm infants are born with lower hemoglobin levels, have shorter RBC survival, and a relative impairment in erythropoietin production caused by liver immaturity. The result is an exaggerated physiologic nadir that occurs earlier and is more significant than in term infants, known as anemia of prematurity.
- Consideration of sex: differences in causes of anemia in neonates and infants are primarily related to the possibility of X-linked disorders manifesting in boys.

Nonimmune Anemias

- **History:**
  - **Pregnancy/birth history: details regarding bleeding during pregnancy or delivery, and inspection of the placenta for any evidence of abnormalities, including placental or umbilical cord tear or abruption.**
  - **Family history: family history must include a detailed history of anemia in biological mother, father, and siblings as well as history of anemia within the extended family.**
  - **Inquiry regarding a prior history of jaundice, gallstones (cholecystectomy), and/or splenomegaly should be obtained.**
    - **Given the increased red cell turnover in hemolytic anemias and inherited anemia.**

Nonimmune Anemias

- **Physical Examination**
  - **A detailed physical examination should include careful inspection of the facies, eyes, skin, chest, and abdomen with attention to any dysmorphisms that may be related to an underlying syndrome also associated with anemia and/or marrow failure.**
  - **In addition, patients should be evaluated for jaundice, scleral icterus, hepatomegaly, splenomegaly, or skin findings possibly consistent with extramedullary hematopoiesis.**

Nonimmune Anemias

- **HEMOLYTIC ANEMIAS**
  - **Hemolytic anemia involves the increased destruction of erythrocytes, typically with a compensatory increase in erythrocyte production leading to increased reticulocyte levels in the peripheral blood. Most infants with hemolytic anemia have accompanying Hyperbilirubinemia.**
    - **Inherited Red Blood Cell Membrane Defects**
    - **Red Blood Cell Enzymopathies**
    - **Hemoglobin Abnormalities**

Nonimmune Anemias

- HEMOLYTIC ANEMIAS (Inherited Red Blood Cell Membrane Defects)
- Mutations in the genes encoding the RBC membrane cytoskeleton, including ankyrin, spectrin, band 3, and protein 4.2, can result in inherited hemolytic anemias, careful attention to the family history of anemia, gallstones, splenomegaly, and cholecystectomy, is important.
- Hereditary spherocytosis:
  - HS is the most common inherited nonimmune hemolytic anemia and typically has an autosomal dominant inheritance
  - Approximately 75% of cases with AD inheritance, 20%–25% are sporadic mutations, and <5% are autosomal recessive), occurring in approximately 1 in 1500 to 1 in 5000 live births.
  - The pathophysiology is related to an intrinsic red cell defect in the membrane, leading it to be inefficiently tacked to the cytoskeleton and resulting in poor deformability as red cells pass through the spleen and red cell removal.
  - This condition results in a hemolysis with variable degree of anemia based on mutation (with approximately 15% of patients with compensated hemolysis without anemia)
  - Key features in the neonatal period include neonatal jaundice in the first 24 hours of life and exacerbation of anemia during the newborn nadir, although 40% to 50% of neonates do not develop significant neonatal jaundice with mild HS.

Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Inherited Red Blood Cell Membrane Defects)**
  - **Hereditary Spherocytosis:**
    - **Anemia and reticulocytosis**
    - **Increases in bilirubin and lactate dehydrogenase levels.**
    - **An increase in the mean corpuscle hemoglobin concentration (>36 g/dL caused by relative cellular dehydration) often solidifies the diagnosis in older children; however, an increased MCHC is less reliable in neonates and infants compared with older children.**
    - **Classically, the diagnosis is made using osmotic fragility testing for lysis of RBCs suspended in solutions of decreasing osmolality, with increased hemolysis noted in hypotonic saline.**
    - **Because of the poor sensitivity of this testing in young infants, flow cytometry has aided in the diagnosis of HS in infants.**
    - **Treatment includes serial monitoring of blood counts and transfusion as needed based on the trajectory of anemia.**
    - **The need for phototherapy, or rarely exchange transfusion.**
    - **Infants with more significant anemia (typically related to a genetic mutation conferring more significant baseline hemolysis), may need to be transfused episodically, especially in the first year of life, but often transfusion needs decline thereafter.**

Nonimmune Anemias

- HEMOLYTIC ANEMIAS (Inherited Red Blood Cell Membrane Defects)
- Hereditary Elliptocytosis:
  - Elliptocytosis occurs in approximately 1 in 4000 live births, with increased incidence in some populations, including those of African descent.
  - Severity of disease range widely, from being asymptomatic in neonates and infants to causing intrauterine death.
  - Almost all forms of hereditary elliptocytosis are autosomal dominant
  - Elliptocytosis is further subcategorized as follows:
    - Heterozygous hereditary elliptocytosis, hereditary elliptocytosis with hemolysis, spherocytic hereditary elliptocytosis, south east Asian ovalocytosis
  - Diagnosis is solidified with evaluation of characteristics elliptocytes on review of the peripheral blood smear
  - Neonates and infants with elliptocytosis rarely require serial transfusion unless there is a family history of more significant phenotypic anemia

Nonimmune Anemias

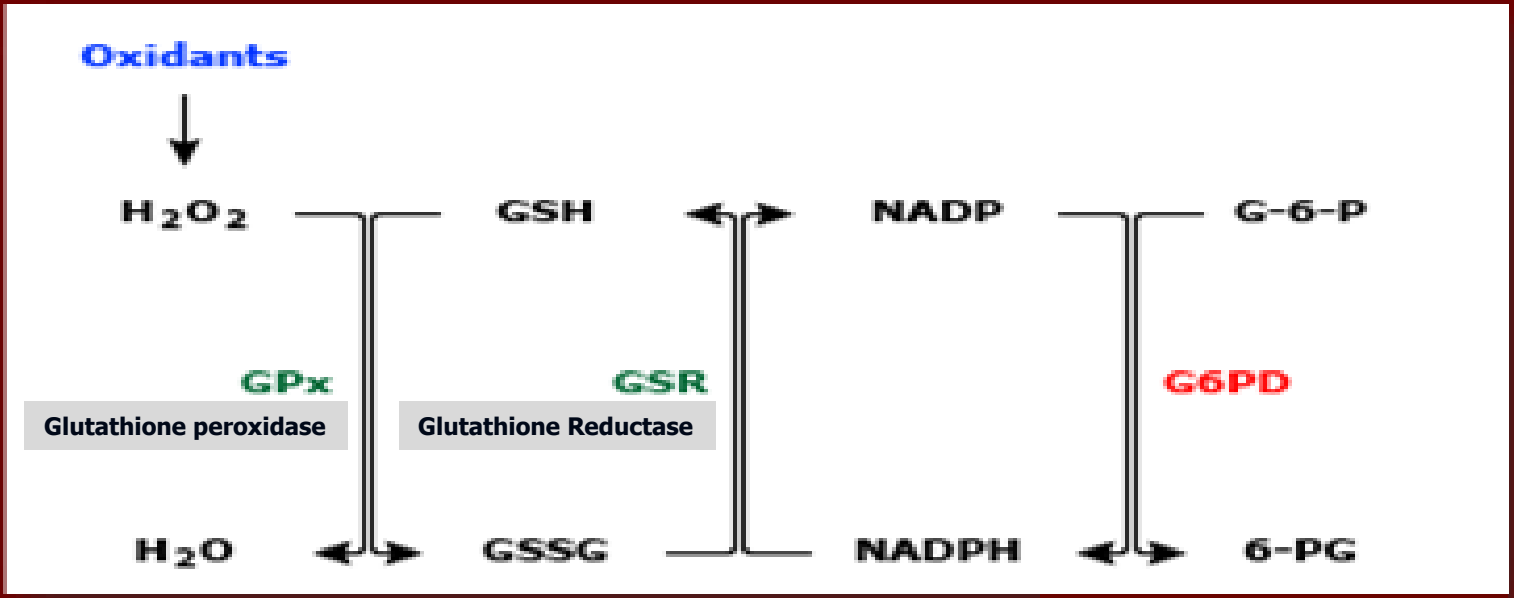
- **HEMOLYTIC ANEMIAS (Inherited Red Blood Cell Membrane Defects)**
- **Hereditary Pyropoikilocytosis:**
  - **This is a rare cause of severe hemolytic anemia in newborns/infants and has a strong association with hereditary elliptocytosis.**
  - **HPP is autosomal recessive**
  - **Most patients have severe hemolysis in infancy and then typically more mild symptoms later in life.**
  - **Key features include significant anemia in the neonatal period with reticulocytosis**
  - **The diagnosis can be solidified by review of a well-prepared blood smear, which shows:**
    - **Red cells with bizarre shapes and sizes (Anisopoikilocytosis)**
    - **Red cell fragmentation**
    - **Microspherocytes**

Nonimmune Anemias

- HEMOLYTIC ANEMIAS (Red Blood Cell Enzymopathies)
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency:
  - The most common red cell enzyme disorder is G6PD deficiency, which affects millions of individuals worldwide.
  - This disease is inherited usually in an X-linked recessive fashion; females are thought to be affected secondary to the Lyon hypothesis.
  - It is more common among people of South Asian, Mediterranean, and African descent. This is likely due in part to the protection it offers against malaria.
  - Individuals with A-negative blood type are also seen to have G6PD deficiency

Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Red Blood Cell Enzymopathies)**
- **Glucose-6-phosphate dehydrogenase (G6PD) deficiency:**
  - **G6PD in the pentose phosphate pathway make NADPH, which can be used to make energy for the RBC, NADPH is also responsible for reducing glutathione, the source of antioxidant used by the RBC.**



6-Phosphogluconolactone

Nonimmune Anemias

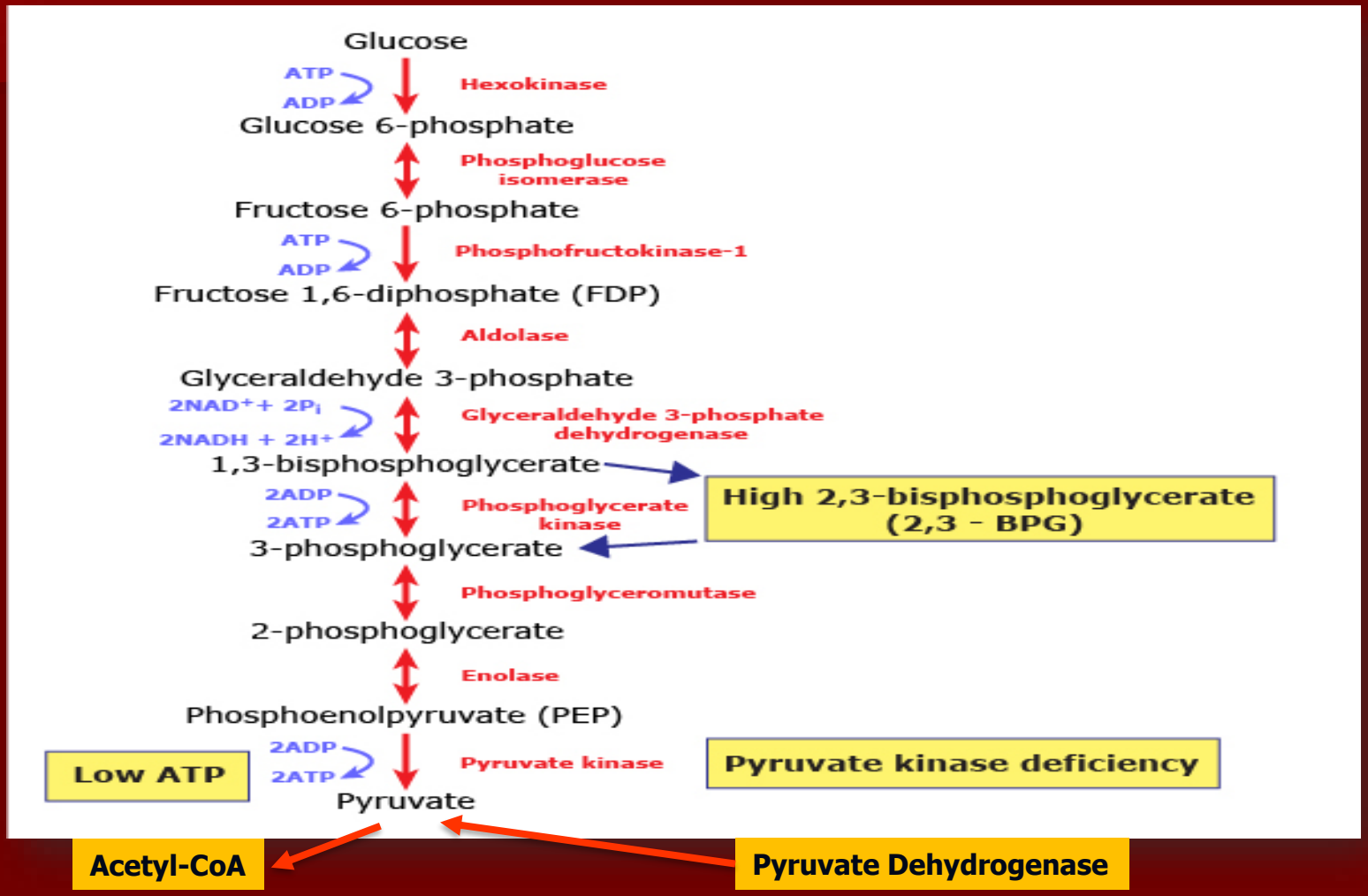
- **HEMOLYTIC ANEMIAS (Red Blood Cell Enzymopathies)**
- **Glucose-6-phosphate dehydrogenase (G6PD) deficiency:**
  - **Hemolysis occurs in response to oxidative stress in the setting of infection, medications, and certain dietary and environmental exposures.**
  - **Depending on the specific mutation, anemia can be low grade and chronic or more acute after exposure to an oxidant.**
  - **G6PD deficiency can be detected on newborn screen and confirmed with a quantitative level.**
  - **Review of peripheral blood smear can reveal red cell inclusions, known as Heinz bodies, which are denatured hemoglobin, as well as blister cells.**

Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Red Blood Cell Enzymopathies)**
- **Pyruvate kinase deficiency**
  - **Pyruvate kinase deficiency is the second most common RBC enzymatic defect.**
  - **It is usually inherited in an autosomal recessive fashion, but autosomal dominant inheritance has also been observed. It is common among individuals of Northern European descent.**
  - **Pyruvate kinase is used in the last step of glycolysis in the RBC.**
  - **PKD resulting in RBCs with less adenosine triphosphate (ATP) availability; this affects energy-driven pumps in the cell membrane, eventually affecting the shape of the membrane and targeting the cell for destruction.**

Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Red Blood Cell Enzymopathies)**
- **Pyruvate kinase deficiency (pyruvate kinase is used in the last step of glycolysis in the RBC)**

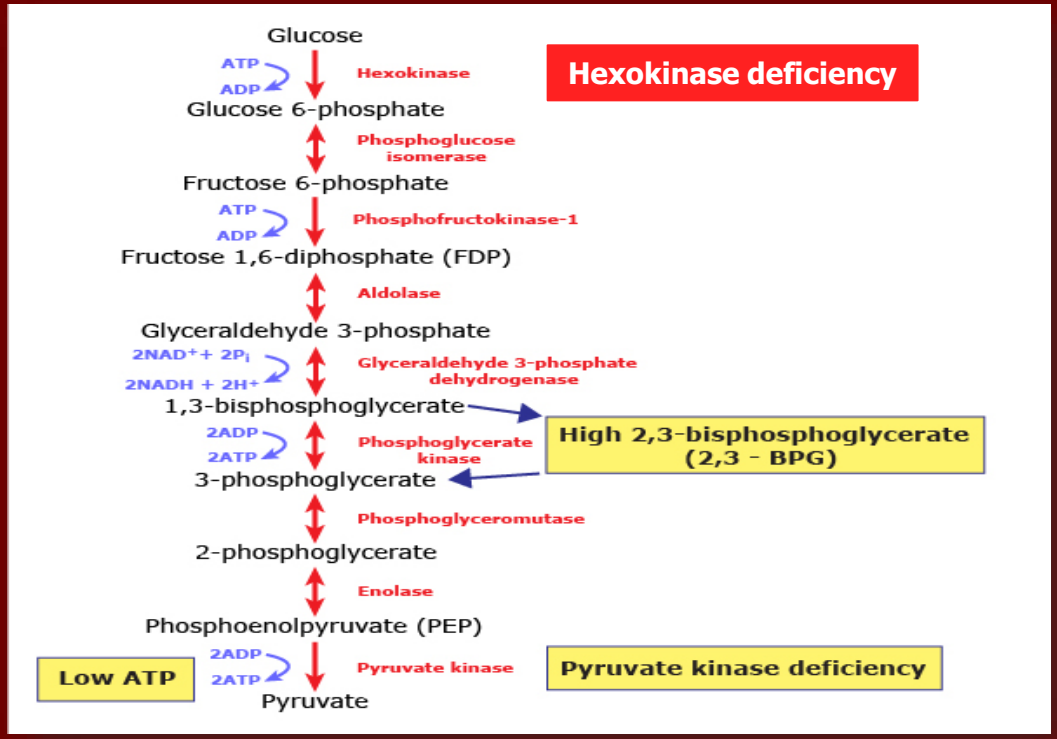


Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Red Blood Cell Enzymopathies)**
- **Pyruvate kinase deficiency**
  - **The severity of hemolysis in PK deficiency is highly variable, although it is similar within families.**
  - **PK deficiency is the commonest cause of a chronic hemolytic anemia from an RBC enzyme deficiency.**
  - **PK deficiency is asymptomatic in the heterozygous state, but can lead to severe neonatal hemolysis and severe hyperbilirubinemia in the homozygous state.**
  - **The diagnosis of PK deficiency can be made through determination of PK levels in red cells as well as DNA sequencing.**

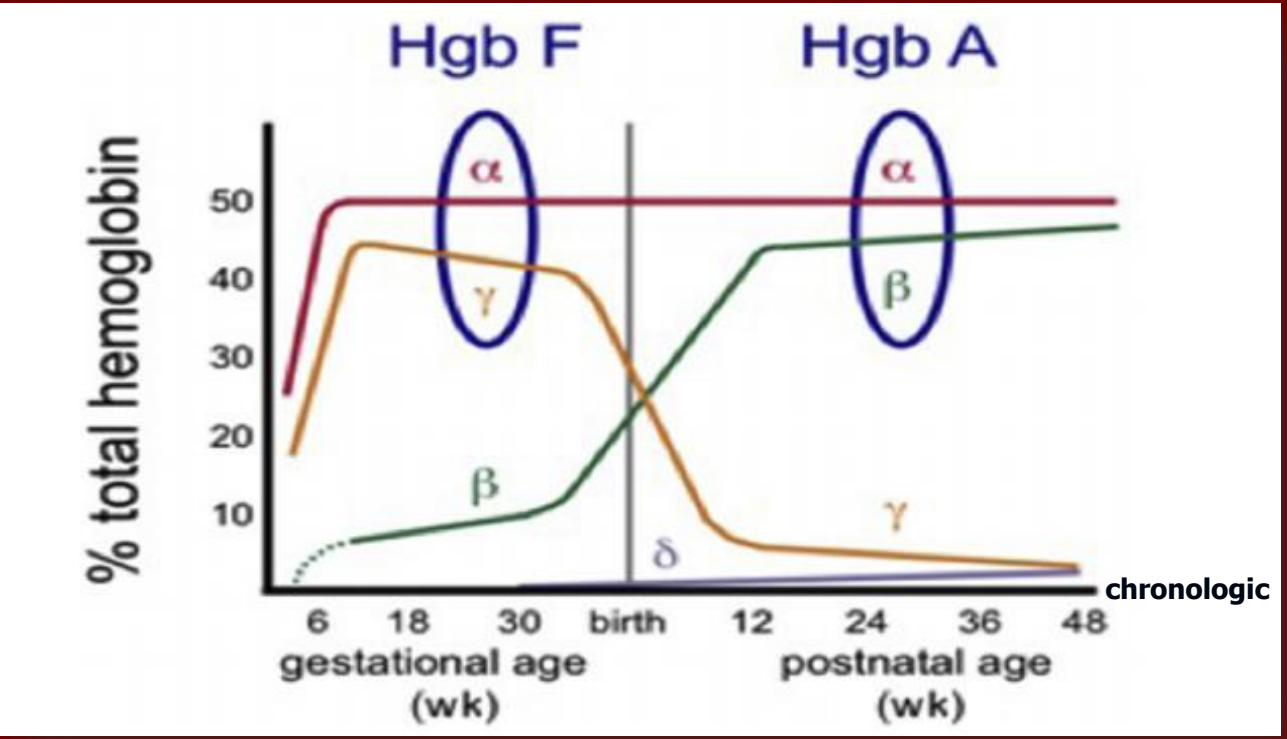
Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Red Blood Cell Enzymopathies)**
- **Other deficiencies in enzymatic pathways (such as hexokinase deficiency) can also cause hemolytic anemia.**
  - **However, they occur rarely can lead to intermittent or persistent hemolysis.**
  - **When unexplained hemolytic anemia exists, evaluation for these disorders through testing of enzyme levels and/or DNA sequencing in a dedicated laboratory offering testing for rare red cell disorders can aid in the diagnosis**



Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Hemoglobin Abnormalities)**
- **Hemoglobin abnormalities can be classified as those that involve decreased globin production resulting in thalassemia, structural hemoglobin changes resulting in qualitative abnormalities of hemoglobin (including the sickling syndromes), and changes in heme and globin binding leading to unstable hemoglobinopathies. Some hemoglobin abnormalities manifest during infancy.**



Nonimmune Anemias

- HEMOLYTIC ANEMIAS (Hemoglobin Abnormalities)
- Decreased Globin Production
  - Alfa-thalassemia is caused by 1 or more a chain mutations, which are most typically gene deletions.
  - With abnormal alfa-globin production, gamma-globin genes form a tetramer known as hemoglobin Barts.
  - Alfa-thalassemia can be detected on newborn screen by the presence of Hemoglobin Barts.
  - Individuals with alfa-thalassemia have persistent microcytic anemia.
  - Work-up to determine the cause of microcytic anemia can include hemoglobin electrophoresis and genetic testing to identify common genetic mutations in a gene.

Nonimmune Anemias

- HEMOLYTIC ANEMIAS (Hemoglobin Abnormalities)
- Decreased Globin Production
  - Beta-thalassemia is cause by 1 or more typically point mutations in the Beta-globin genes.
  - Although hemoglobin A usually constitutes less than 30% of the normal hemoglobin at birth, under certain circumstances, such as intrauterine blood loss, this can be greater.
  - Beta-thalassemia is classified depending on the severity of symptoms; thalassemia major (Cooley anemia), thalassemia intermedia, and thalassemia minor.
  - Signs and symptoms of anemia appear within the first 2 years of life, and typically within the first year, when hemoglobin A production typically predominates.

Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Hemoglobin Abnormalities)**
- **Decreased Globin Production**
  - **Gamma-thalassemia: given the production of g-globin in utero to form fetal hemoglobin, mutations in this gene can lead to gamma-thalassemia, which can be apparent in fetuses or newborns.**
  - **Gamma-Thalassemia results in transient microcytic hemolytic anemia, which may mimic hemolytic disease of the newborn.**
  - **Treatment includes supportive transfusion given that anemia is transient and improves after beta-globin production increases, leading to increasing concentrations of hemoglobin A.**

Nonimmune Anemias

- **HEMOLYTIC ANEMIAS (Hemoglobin Abnormalities)**
- **Structural hemoglobinopathies: Genetic mutations exist that confer qualitative abnormalities in hemoglobin.**
  - **The most widely known include those that cause decreased solubility, including hemoglobin S and hemoglobin C.**

Interpretation and recommendations based on hemoglobin findings on newborn screen

Pattern	Interpretation	Recommendation
FA	Normal	None
F only	Premature infant, β-thalassemia major	Repeat testing if persistent only F, confirmatory testing and hematology referral
AF	Likely after blood transfusion	Repeat testing
FS	Hemoglobin SS, sickle β-thalassemia, sickle HPFH	Hematology referral
FSA	Sickle β-thalassema	Hematology referral
FAS	Sickle cell trait, sickle β-thalassemia	Repeat testing at 3 mo to rule out sickle β-thalassemia
FSC	Hemoglobin SC disease	Hematology referral
FC	Hemoglobin C disease, hemoglobin C β-thalassemia	Hematology referral
FE	Hemoglobin E disease	Hematology referral
FA + variant	Hemoglobin variant trait	Education and genetic counseling
FA Barts	Silent α-thalassemia carrier, α-thalassemia trait, hemoglobin H disease, hemoglobin H Constant Spring	If Barts <10%, patient needs education and genetic counseling; if Barts >10%, patient needs further testing for evaluation of hemoglobin H (hematology referral)

Nonimmune Anemias

- HEMOLYTIC ANEMIAS (Fragmentation Syndrome)
- Hallmark of the disorder include red cell fragmentation (schistocytes) and thrombocytopenia:
  - In newborn, TTP is almost always related to a genetic mutation that prevent from normal cleavage of Von Willebrand factor (VWF).
    - Without ADAMTS13 (metalloprotease), ultralarge multimers of VWF exist that can induce platelet thrombosis and microthrombi in the vasculature, leading to red cell shearing and destruction. Hallmarks of this disorder include anemia and thrombocytopenia, as well as renal dysfunction, fever, and possible mental status changes.
  - DIC is characterized by coagulopathy, anemia, bleeding, renal dysfunction, hepatic dysfunction, and possible thromboembolism.
    - Key differentiators between DIC and TTP include normal coagulation studies PT and PTT in TTP given there is no consumption of clotting factors with TTP.
    - Differentiating DIC versus liver disease, factor VIII levels are normal or increased in liver disease, whereas they are decreased because of consumption in DIC.
  - Cavernous hemangioma or hemangioendothelioma/Renal artery stenosis/Severe coarctation of the aorta

Nonimmune Anemias

- Disorders of Impaired Red Cell Production
- Failure of the bone marrow to produce RBCs; some conditions have other cytopenias at the time of diagnosis, whereas others have predominant anemia; some disorders are associated with congenital anomalies.
  - Diamond-Blackfan Anemia: DBA is a congenital red cell aplasia that typically presents in infancy.
    - Genetic mutations in ribosomal protein genes have been implicated with wide genetic heterogeneity among those with a similar phenotype.
    - An estimate 25% of patients with DBA have evidence of anemia at birth.
      - Hemoglobin values as low as 9.4 g/dL along with low reticulocyte count may be seen in the first days of life.

Nonimmune Anemias

- **Disorders of Impaired Red Cell Production (DBA)**
  - **Compared with other bone marrow failure syndromes, DBA typically has anemia/red cell aplasia without other abnormalities in the blood counts.**
  - **Congenital abnormalities are present in approximately 40% of patients, including:**
    - **Thumb abnormalities (bifid thumb, hypoplastic thenar eminence)**
    - **Craniofacial dysmorphisms (microcephaly, hypertelorism, cleft palate)**
    - **Cardiac defects**
    - **Genitourinary abnormalities**
  - **Key features in addition to anemia with reticulocytopenia include macrocytosis, increased fetal hemoglobin level, increased adenosine deaminase level in the blood.**

Nonimmune Anemias

- **Disorders of Impaired Red Cell Production**
  - **Pearson syndrome is a cause of impaired red cell production**
    - **That may manifest in the neonatal period.**
    - **The syndrome is thought to be related to mitochondrial DNA deletion, and is characterized by sideroblastic anemia and vacuolization of the bone marrow precursor cells.**
  - **Congenital dyserythropoietic anemia is a rare inherited disorder hallmarked by ineffective erythropoiesis resulting in decreased red cell production**
    - **There are 3 major forms of CDA, with CDA type I having severe macrocytic anemia that presents in the neonatal period, often accompanied by a history by intrauterine growth restriction.**
  - **Other bone marrow failure syndromes include Fanconi anemia, Dyskeratosis Congenital, and Reticular Dysgenesis.**
    - **These syndromes do not classically cause anemia in the newborn period but typically manifest with cytopenias in infants and older children**

Immune-Mediated Hemolytic Anemia

- As many as 50 antigens present on the RBC may cause this antibody mediated response.

NON-RhD ANTIBODIES AND ASSOCIATED HDFN

Antigen system	Specific antigen	Antigen system	Specific antigen	Antigen system	Specific antigen
			Frequently associated with severe disease		
Kell	−K (K1)				
Rhesus	−C				
			Infrequently associated with severe disease		
Colton	$-CO^a$	MNS	$-Mt^a$	Rhesus	−HOFM
	−Co3		−MUT		−LOCR
Diego	−ELO		−Mur		−Riv
	$-Di^a$		$-M^v$		−Rh29
	$-Di^b$		−s		−Rh32
	$-Wr^a$		$-s^o$		−Rh42
	$-Wr^b$		−S		−Rh46
	$-Fy^a$		−U		−STEM
Duffy	$-Js^a$		−Vw		−Tar
Kell	$-Js^b$	Rhesus	$-Be^a$	Other antigens	−HJK
	−k (K2)		−C		−JFV
	$-Kp^a$		−Ce		−JONES
	$-Kp^b$		$-C^w$		−Kg
	−K11		$-C^x$		−MAM
	−K22		−ce		−REIT
	−Ku		$-D^w$		−Rd
	$-Ul^a$		−E		
Kidd	$-Jk^a$		$-E^w$		
MNS	$-En^a$		−Evans		
	−Far		−e		
	−Hil		−G		
	−Hut		$-Go^a$		
	−M		−Hr		
	$-Mi^a$		$-Hr_o$		
	−Mit		−JAL		
			Associated with mild disease		
Dombrock	$-DO^a$	Gerbich	$-Ge^2$	Scianna	−Sc2
	$-Gy^a$		$-Ge^3$	Other	−Vel
	−Hy		$-Ge^4$		−Lan
	$-JO^a$		$-Ls^a$		$-At^a$
Duffy	$-Fy^b$	Kidd	$-Jk^b$		$-Jr^a$
	$-Fy^3$		$-Jk^3$		

Immune-Mediated Hemolytic Anemia

- The Rhesus system includes the C, D, and E antigens.
  - Approximately 20% of white women are RhD negative, (1.5% of Asian women and 3% to 5% of black American women)
  - CDC estimates that Rh sensitization currently affects 6.7 newborns per 1000 live births.
  - Anti-D–associated disease is the most common and most severe immune-mediated hemolytic disease.
  - The D antigen is highly antigenic (50 times more than the other Rh antigens)
  - the incidence of a primary immune response to the D antigen is 15% after inoculation with 1 mL and 70% to 90% after exposure to 250 mL of fetal blood.
- Fetal cells may be found in the maternal circulation in about half of all pregnancies
- Volume is 0.5-40 mL; in 1% of pregnancies exceeds 40 mL

Immune-Mediated Hemolytic Anemia

- The Rhesus system includes the C, D, and E antigens.
  - It is estimated that less than 0.1 mL of fetal blood is needed to immunize the mother and produce a secondary immune response (IgG3 driven).
  - Rhesus c disease is also noted to be potentially severe.
  - Rhesus E disease may present with mild anemia and jaundice.
  - Exposure to the remainder of the Rhesus groups (e and C) uncommonly results in HDFN.
  - The combination of incompatibilities in Rhesus antigens can be severe and potentially fatal.

Immune-Mediated Hemolytic Anemia

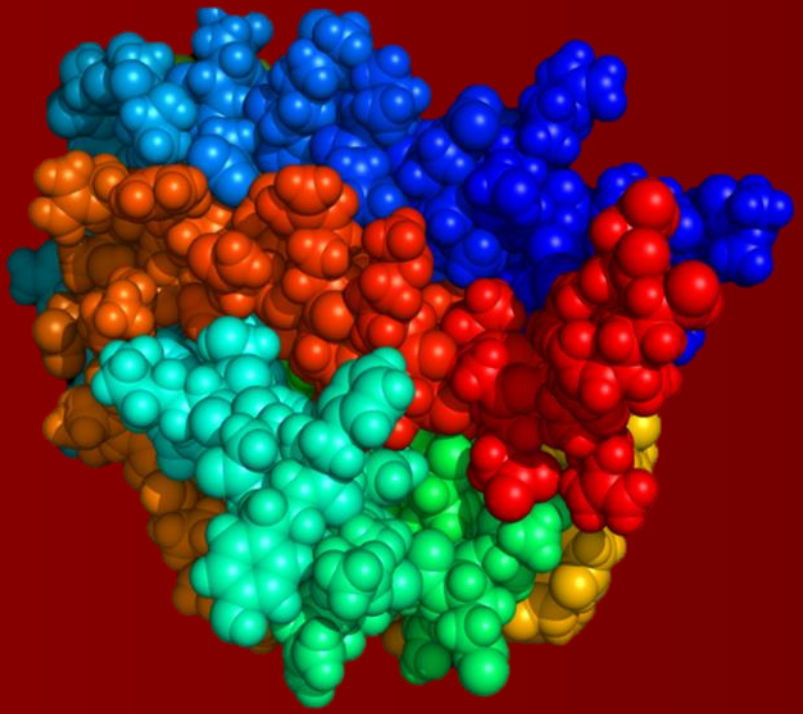
- **ABO**
  - Although 15%-20% of all pregnancies have ABO discrepancies between fetus and mother, only a small number of pregnancies are affected by hemolytic disease (disease develop in only 0.3-2.2% of live births)
  - Most cases of ABO incompatibility are noted in blood type O mothers, because they produce enough IgG antibodies against the A and B antigens that cross the placenta.
  - In the United States, 45% of white American and 49% of black Americans are blood type O
  - ABO incompatibility does not present with the same degree of anemia and complications as are seen with RhD incompatibility.
    - This is thought to be related in part to the presence of the A/B antigen on multiple cell types in the fetus.
    - Additionally, fetal A and B antigens are not fully developed on the red cell surface compared with adult red cells.
  - Hallmark of ABO HDN is microspherocytes in PBS
  - Unlike Rh disease, ABO incompatibility usually does not lead to a more severe phenotype with each subsequent pregnancy.

Immune-Mediated Hemolytic Anemia

- **Kell**
  - **After Rhesus and ABO disease, anti-Kell1 antibodies leading to IMHA are the next most common reason for disease.**
  - **Ninety-one percent of the white American population is Kell1 negative.**
  - **Of Kell1-positive people, only a small proportion are homozygous for Kell1 (0.2%), leading to delivery of Kell1-positive infants (4.5% of Kell1-negative mothers).**
  - **Maternal sensitization is usually due to maternal blood transfusion with Kell1-positive blood, although previous pregnancy with a Kell1-positive infant can also lead to an immune response.**
  - **Anti-Kell antibodies are usually IgG in class.**
  - **Kell antigens are present on RBC progenitor cells.**
    - **Because progenitor cells lack hemoglobin, a marked increase in bilirubin is not observed in the fetus or newborn.**

Immune-Mediated Hemolytic Anemia

- Other minor blood group incompatibilities (Duffy system, Kidd, and MNS antibodies) are unusual in clinical practice.
- The Duffy antigens (Fy[a] and Fy[b]) have been implicated in transfusion reactions.
  - However, only Fy(a) has been associated with severe HDFN.
  - A recent study reported the presence of anti-Fy(a) antibodies during pregnancy at between 0.01% and 0.54%; this may account for the rarity of Duffy-related HDFN as reported
- Of the MNS system (M, N, S, s, U), anti-M, anti-S, anti-s, and anti-U have been associated with severe anemia in the fetus.
  - Anti-N remains IgM in nature and has not been associated with HDFN.
- The Kidd antigens (Jk[a], Jk[b], Jk[3]) are difficult to detect in serum.
  - Antibodies may be IgG or IgM in nature.
  - Antibodies to all three Kidd antigens have been rarely associated with severe HDFN
- No reports have described HDFN associated with Lewis and P system antibodies.



Anemia of Prematurity

Anemia of prematurity

- In term infants, the hemoglobin level typically reaches an average nadir of 11 g/dL at approximately 8 to 12 weeks after birth
- Anemia of prematurity (AOP) typically occurs at 3 to 12 weeks after birth in infants less than 32 weeks gestation.
- The onset of AOP is inversely proportional to the gestational age at birth.
- Many infants are asymptomatic despite having hemoglobin values less than 7 g/dL
- The anemia typically resolves by three to six months of age.

Anemia of prematurity

- Peripheral blood smear demonstrates normocytic and normochromic red blood cells.
- The reticulocyte count is low, and red blood cell precursors in the bone marrow are decreased.
- Serum concentrations of erythropoietin (EPO) are low in preterm infants during the first postnatal month compared with adults (9.7 versus 15.2 mU/mL) and remain inappropriately low for the extent of anemia through the second postnatal month

In the US annually 77000 birth under 32 weeks of GA

- **Life-threating complications:**
  - **IVH**
  - **NEC**
  - **ROP**
  - **Anemia**
    - **PENUT (preterm Epo Neuroprotection) trial**

Ohis RK, Kamath-Rayne BD, Christensen RD, et al. Cognitive outcomes of preterm infants randomized to darbepoetin. Pediatrics, Vol. 133, No. 6, 2014.

Anemia of prematurity

- multifactorial
  - Sharp elevation at partial pressure of oxygen
  - No appropriate response to hypoxia by liver
  - Increased Epo clearance
  - Increased RBC clearance
  - Increased hemoglobin clearance (HO-1 isoform high activity)
  - Phlebotomy
    - Laboratory phlebotomy losses 15% to 30% of total blood volume in the 1st 6 wks after birth at ELBW infant
      Semin Perinatol. 2012; vol. 36, No. 4

It is estimated that approximately 90% of ELBW infants will required at least one transfusion *NeoReviews Vol. 16, No. 5, May 2015*

- **Transfusion Complications:**
  - **Immunologic complications**
    - **Transfusion Reactions**
    - **Hemolytic Transfusion Reactions**
    - **Febrile Nonhemolytic Reactions**
    - **Allergic Transfusion Reactions**
    - **GVHD**
    - **Transfusion-Related Acute Lung Injury**
    - **T-Antigen activation**
  - **Transfusion-Associated Dyspnea**

It is estimated that approximately 90% of ELBW infants will required at least one transfusion *NeoReviews Vol. 16, No. 5, May 2015*

- **Transfusion-Transmitted infections**
  - **Bacterial contamination**
  - **Hepatitis A, B, C, ….**
  - **HIV-1, HIV-2**
  - **CMV**
  - **HTLV-1, HTLV-2**
  - **WNV**
  - **T. cruzi**
  - **Syphilis**
  - **Malaria**
  - **Babesia microti**
  - **Creutzfeldt-Jakob**

Adverse outcome associated with transfusion in the preterm infant

Bronchopulmonary Dysplasia

Valieva OA, Strandjord TP, Mayock DE, Juul SE. Effects of transfusions in extremely low birth weight infants: a retrospective study. J Pediatr. 2009;155(3):331-337.e331.

- **RBC storage lesion**
  - **Iron-mediated oxidative stress**
  - **Free radical damage**

ETTNO (Effect of Transfusion Thresholds on neurocognitive outcome of ELBW) trial
TOP (Transfusion Of Premature) trial
PINT (Premature Infants in need of transfusion) trial

- **NEC**
  - Described premature infants who developed NEC during 48 hours after transfusion
- **IVH/PVL**
  - Infants who experience restrictive-transfusion guidelines less likely to have grade III or IV IVH and PVL
- **ROP**
  - The ARIPI trial addresses the meaningful correlation between age of RBC and development of ROP

Guidelines & Protocols

- Limiting the amount of blood drawn
- Restrictive policy for red cell transfusions
- Reduce the number of donor exposures
  - Use of satellite packs, which allow for repeated transfusions from the same donor to the individual infant
- Majority of VLBW infants are at risk for excessive iron stores due to transfusion; when serum ferritin levels is >350 ng/mL, iron supplement should be withheld. (Preterm infants administered ESA (Erythropoiesis-Stimulating Agents) during their NICU stay show fewer need for transfusions, higher cognitive scores, and a lower incidence of neurodevelopmental impairment. *Ohls RK, Kamath-Rayne BD, Christensen RD, et al. Cognitive outcomes of preterm infants randomized to darbepoetin, erythropoietin, or placebo. Pediatrics 2014;133:1023–30.)*

Guidelines & Protocols

Table 1. Red Cell Transfusion Guidelines From the United States Recombinant Human Erythropoietin Trial (26)

Do not transfuse for blood out alone
Do not transfuse for low hematocrit (Hct) alone
Transfuse at Hct ≤35% (0.35) for infants who are:
• Receiving >35% oxygen • Receiving continuous positive airway pressure or mechanical ventilation with mean airway pressure of 6 to 8 cm H_2O
Transfuse at Hct ≤30% (0.30) for infants who are:
• Receiving any supplemental oxygen • Receiving continuous positive airway pressure or mechanical ventilation with mean airway pressure <6 cm H_2O • Having significant episodes of apnea and bradycardia (>9 episodes in 12 h or 2 episodes in 24 h requiring bagging while receiving therapeutic doses of methylxanthines) • Experiencing heart rates >180 beats/min or respiratory rates >80 breaths/min for 24 h • Experiencing weight gain <10 g/d over at least 4 days while receiving 100 kcal/kg per day • Undergoing surgery
Transfuse at Hct ≤20% (0.20) for infants who are:
• Asymptomatic, with absolute reticulocyte count $<100\times10^3$/mcL (100×10^9/L)

Table 2. Canadian Paediatric Society Recommendations for Red Cell Transfusions (28)

Red cell transfusions should be considered in neonates in the following specific clinical situations:
• Hypovolemic shock associated with acute blood loss • Hematocrit between 30% and 35% (0.30 and 0.35) or hemoglobin between 10 and 12 g/dL (100 and 120 g/L) in extreme illness for which red cell transfusion may improve oxygen delivery to vital organs • Hematocrit between 20% and 30% (0.20 and 0.30) or hemoglobin between 6 and 10 g/dL (60 and 100 g/L), and the infant is severely ill and/or receiving mechanical ventilation with compromised oxygen delivery • Hematocrit falling below 20% (0.20) or hemoglobin falling below 6 g/dL (60 g/L), with absolute reticulocyte count of 100 to 150×10^3/mcL (100 to 150×10^9/L) or less, suggesting low plasma concentration of erythropoietin, with the presence of the following clinical signs: poor weight gain, heart rate >180 beats/min, respiratory distress and increased oxygen needs, and lethargy

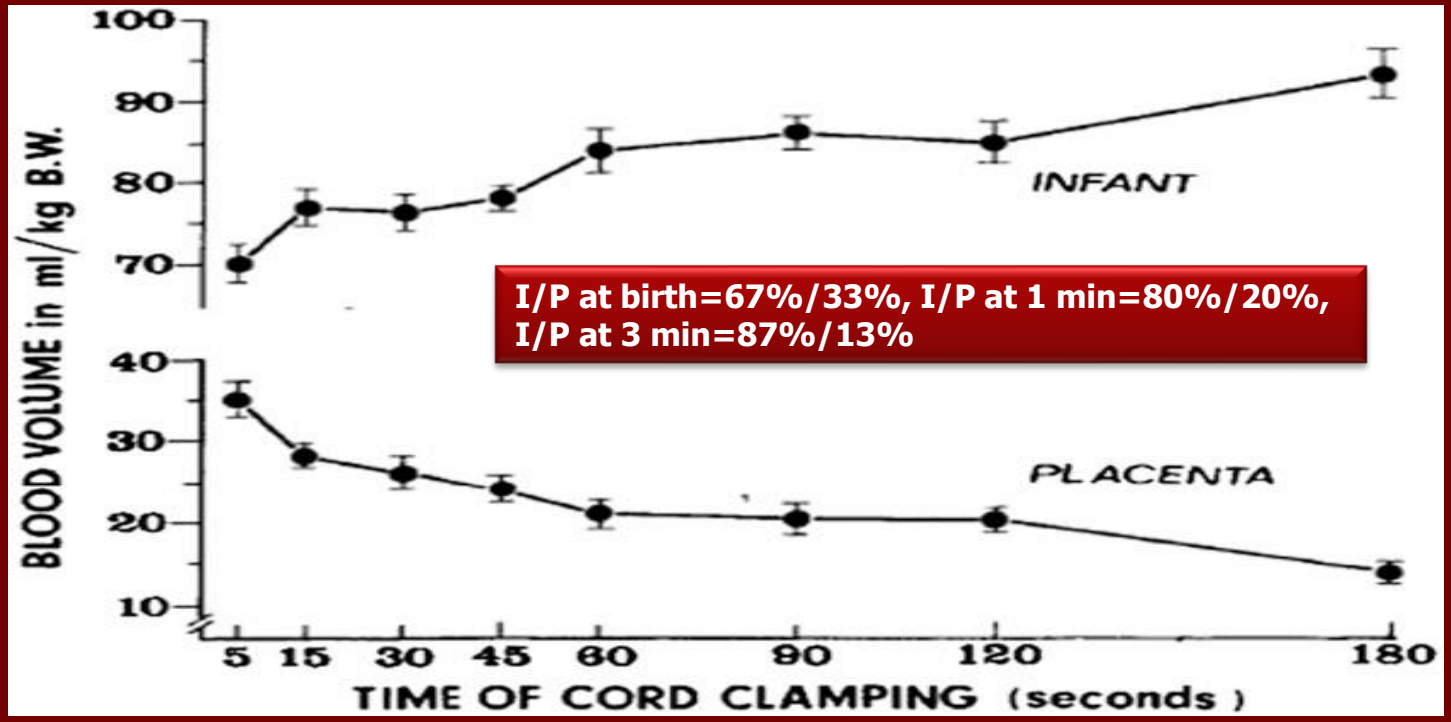
Detection of tissue hypoxia

- NIRS
  - $rSO_2 = SaO_2 - TOFE.SaO_2$
- VEGF (Vascular Endothelial Growth Factor)
  - levels > 140 pg/mL

Near InfraRed Spectroscopy	
GA	Brain FTOE (Tissue O_2 Fraction Extraction)
30-31	0.09
32-33	0.05
34-35	0.10
36-37	0.21
38-39	0.22
40-41	0.19

Preventions

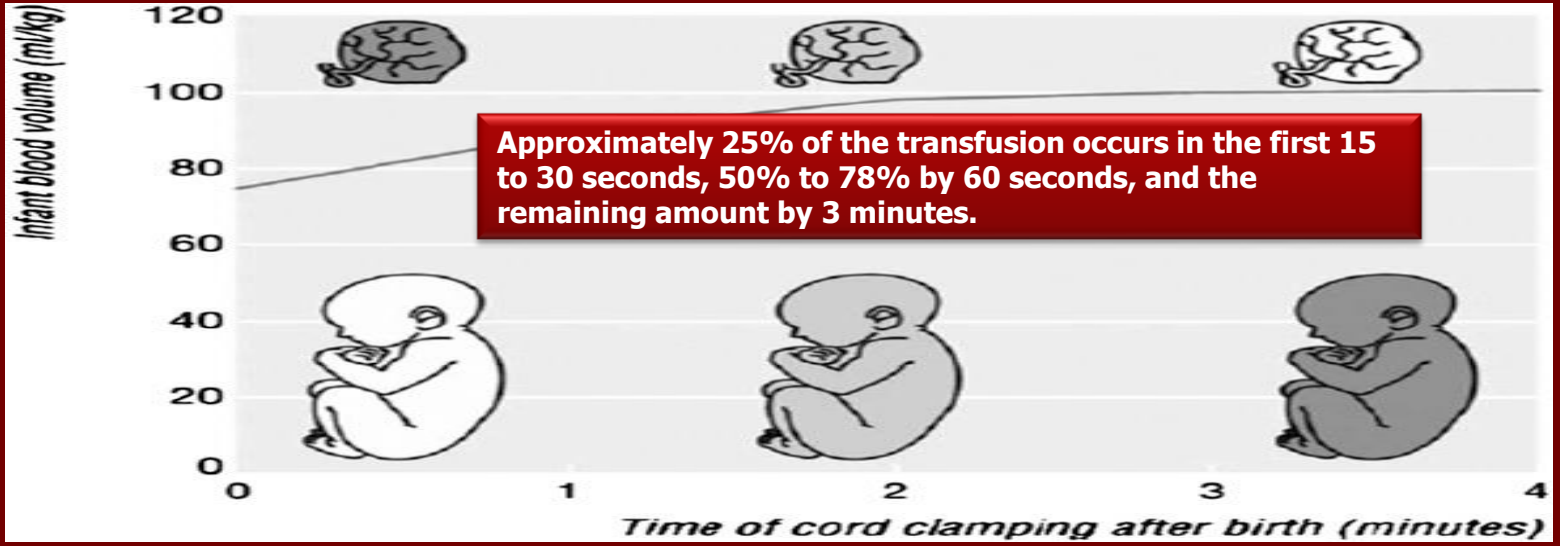
- During fetal life, only approximately 10% of cardiac output is sent to the lungs, whereas more than 50% of cardiac output is sent to the placenta, after birth pulmonary blood flow until approximately 50% of neonatal cardiac output.
- The total amount of whole blood in the fetal-placental circulation throughout gestation is estimated to be 110 to 115 mL/kg of fetal body weight, with approximately 30 mL/kg of this volume in the placenta at any one time.



Another thing very injurious to the child, is the tying and cutting of the navel string too soon; which should always be left till the child has not only repeatedly breathed but till all pulsation in the cord ceases. (Erasmus Darwin)

Physiologic Changes during Neonatal Transition and the Influence of Respiratory Support. Clin Perinatol 48 (2021) 697–709

- **It is believed that the arteries constrict flow rapidly diminishing during the first 20 to 25 seconds and negligible by 40 to 45 seconds, this prevents the loss of blood from the infant back into the placenta, the umbilical vein remains open, allowing flow for up to 3 minutes to facilitate transfusion of blood from placenta to the infant. After 3 minutes, flow is insignificant, and placental circulation absolutely ceases by 5 minutes in 95% of infants.**
- **In the first 5 minutes after birth while the cord was left intact found that the mean transfusion of blood was 81 mL, or 25 mL/kg, predicting that placental transfusion could account for 24% to 40% of the total potential blood volume at birth.**



DCC (Delay Cord Clamping) Vs ECC (Early Cord Clamping)

- ***Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev. 2012;8(8):CD003248***
  - ***results of 7 trials (n=392) revealed that fewer infants received transfusions and the overall number of transfusions was less in the DCC groups***
  - ***There was a decreased risk of IVH at DCC***
- ***Bhatt S, Alison BJ, Wallace EM, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm infant. J Physiol. 2013;591(pt 8):2113–2126***
  - ***The DCC exhibited no significant change in heart rate after delivery and had a less severe decrease in right ventricular output***
  - ***Infants who received DCC of 4 minutes exhibited larger left ventricular end-diastolic diameters on day 3 after birth***
  - ***Higher mean blood pressure (P < .01) through the first 4 hours after delivery reported among infants in the DCC group***
  - ***cerebral regional tissue oxygenation was better at both 4 and 24 hours after delivery in infants receiving DCC***
  - ***DCC appears to provide hemodynamic stability that may reduce fluctuations in cerebral blood flow and blood pressure that contribute to IVH.***

DCC (Delay Cord Clamping) Vs ECC (Early Cord Clamping)

- Kaempf JW, Tomlinson MW, Kaempf AJ, et al. Delayed umbilical cord clamping in premature neonates. Obstet Gynecol. 2012;120(2, pt 1):325–330
  - Infants in the DCC group were significantly less likely to have blood culture proven late-onset sepsis during their neonatal intensive care unit stay.
  - Among pooled data Rabe et al found a decreased risk of NEC
  - Found that preterm infants who received 60 to 90 seconds of DCC had lower risk of respiratory distress syndrome compared with those receiving ECC.
- Mercer JS, Vohr BR, Erickson-Owens DA, Padbury JF, Oh W. Seven-month developmental outcomes of very low birth weight infants enrolled in a randomized controlled trial of delayed versus immediate cord clamping. J Perinatol. 2010;30(1):11–16
  - Reported decreased rates of IVH and late-onset sepsis among infants randomized to DCC.
  - They found trend toward better Bayley Scales and motor scores in boys who received DCC

Alternatives to DCC: UCM (Umbilical Cord Milking) UCM Vs ECC

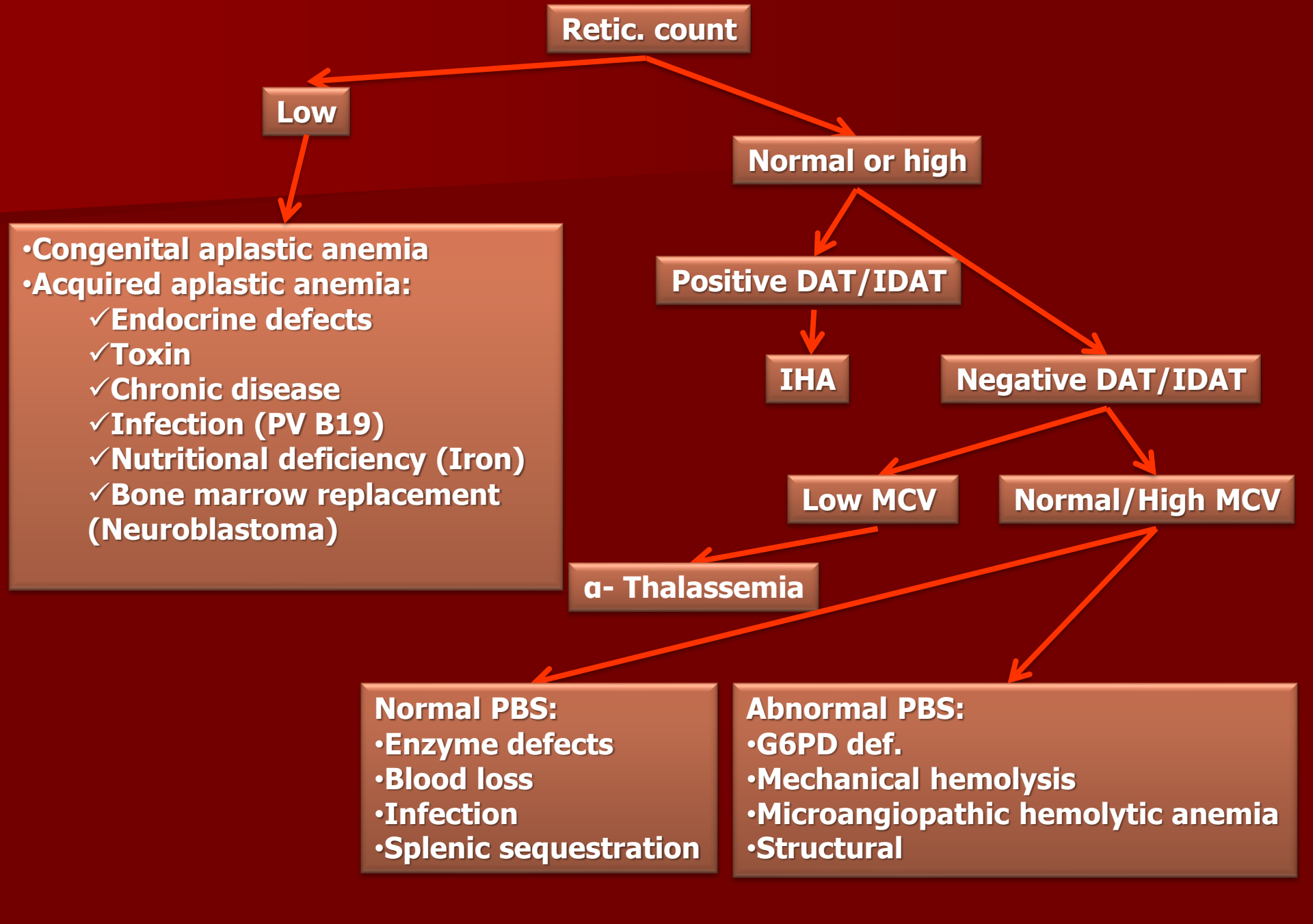
- Takami T, Suganami Y, Sunohara D, et al. Umbilical cord milking stabilizes cerebral oxygenation and perfusion in infants born before 29 weeks of gestation. J Pediatr. 2012;161(4): 742–747.
- Upadhyay A, Gothwal S, Parihar R, Garg A, Gupta A, Chawla D, Gulati IK. Effect of umbilical cord milking in term and near term infants: randomized controlled trial. Am J Obstet Gynecol. 2013;208(2):120-126.
  - They found umbilical vein contains 15-20 mL of blood
  - They found that infants in the UCM group were more likely not to have needed red blood cell transfusions and had a decreased number of red blood cell transfusions.
  - They found that those infants in the UCM group had significantly higher systolic and diastolic blood pressures in the first 12 hours after birth, as well as significantly higher urine output in the first 72 hours after birth.
  - They also found that left ventricular end-diastolic dimension, left ventricular cardiac output, and superior vena cava flow were higher in the milked group compared with
  - Cerebral oxygenation and perfusion measured by near-infrared spectroscopy.

Classification of the Anemia According to MCV

Macrocytic Anemia	Microcytic Anemia	Normocytic Anemia
Reticulocytosis	Iron deficiency	Low Retic.
Folic acid deficiency	Lead poisoning	Infection
B12 deficiency	Thalassemia	Parvovirus B19
MMA	Chronic infection	TEC
Diamond-Blackfan		Chronic disease
Fanconi		Immune HA
Acquired aplastic anemia		Mechanical HA
Drugs		Drugs
		Leukemia
		Hemoglobinopathy
		Unstable Hg
		Normal or high Retic.
		Blood loss
		Sequestration
		RBC enzyme defect

Morphologic Findings on PBS

Morphologic Finding	Etiologies
Hypochromia	Iron def., Thalassemia, Lead poi.
Target cells	Hgb C, S, E; Thalassemia, Liver dis., Abetalipoproteinemia
Sickle cells	Hgb S dis.
Basophilic stippling	Iron def.; Lead poi.; Hemolytic anemia; Thalassemia
Heinz bodies	Normal; Enzymatic defect (HA)
Howell-Jolly bodies	Splenic hypofunction
Spherocytes	Immune HA (ABO more common than Rh); G6PD def. Structural
Eliptocytes	Structural
Schistocytes	Microangiopathic HA
NRBC	Normal; HA; Semi acute blood loss
Polychromasia	Normal; Proliferative response to anemia


Retic. count
Low
Normal or high
•Congenital aplastic anemia
•Acquired aplastic anemia:
✓Endocrine defects
✓Toxin
✓Chronic disease
✓Infection (PV B19)
✓Nutritional deficiency (Iron)
✓Bone marrow replacement (Neuroblastoma)
Positive DAT/IDAT
IHA
Negative DAT/IDAT
Low MCV
Normal/High MCV
α- Thalassemia
Normal PBS:
•Enzyme defects
•Blood loss
•Infection
•Splenic sequestration
Abnormal PBS:
•G6PD def.
•Mechanical hemolysis
•Microangiopathic hemolytic anemia
•Structural