Neonatal Anemia

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Red cell values at various ages: mean and lower limit of normal (22SD).

	Hemoglobin (g/dL)		Hematocrit (%)		Red cell count (10^{12}/L)		MCV (fL)		MCH (pg)		MCHC (g/dL)		Reticulocytes	
Age	Mean	22SD	Mean	22SD	Mean	22SD	Mean	22SD	Mean	22SD	Mean	22SD	Mean	22SD
Birth (cord blood)	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30	3.2	1.8
1–3 days (capillary)	18.5	14.5	56	45	5.3	4.0	108	95	34	31	33	29	3.0	1.5
1 week	17.5	13.5	54	42	5.1	3.9	107	88	34	28	33	28	0.5	0.1
2 weeks	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28	0.5	0.2
1 month	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29	0.8	0.4
2 months	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29	1.6	0.9
3–6 months	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30	0.7	0.4

Average hematological values for term and preterm infants

Gestation (weeks)	Hct (%)	Hgb (g/dL)	Retic (%)
37-40	53	16.8	3-7
32	47	15.0	3-10
28	45	14.5	5-10
26-30	41	13.4	—

Percentage of hemoglobin F & A2 in newborn & adult.

	Hemoglobin F (%)	Hemoglobin A2 (%)
Newborn	60 - 90	1.0
Adult	1.0	1.6 - 3.5

Anemia during the neonatal period can be caused by:

- **Hemorrhage:** (increased losses)
  - **Acute or Chronic**
- **Hemolysis:** (increased destruction of ery.)
  - **Congenital hemolytic anemias or due to Immune or nonimmune hemolytic anemias**
- **Hypoplasia:** (insufficient creation of ery)
  - **failure of red cell production in inherited bone marrow failure syndromes (Diamond Blackfan anemia) or Aqured**
- **Development of symptoms depends on the *speed of anemia progression***

Hemorrhage

- **Blood loss may occur during;**
  - **Prenatal ; (1/1000 births)**
    - **Transplacental**
    - **Intra placental**
    - **Retroplacental**
    - **Twin-to-twin transfusion**
  - **Intrapartum**
  - **Postnatal periods**

Prenatal blood loss

I. Transplacental fetomaternal

- Fetal red blood cells in the maternal circulation in up to 50% of pregnancies , clinically significant hemorrhage (>30 mL) is only 12% of pregnancies.
- Significant feto maternal hemorrhage is commonly seen following procedures such as;
  - Diagnostic amniocentesis
  - External cephalic version.

II. Intra placental

- Tight umbilical cord around the neck or body
- Delayed cord clamping

III. Retroplacental

- placental abruption

IV. Twin-to-twin transfusion

- **Feto maternal hemorrhage is diagnosed by demonstrating fetal red cells by flow cytometry using an antibody against HbF (fetal hemoglobin)] in the maternal circulation.**
- **Less commonly, an older, differential acid elution technique (Kleihauer Betke method) may still be used.**

- **How is Kleihauer Betke test performed?**
- **A blood sample from the mother is made into a smear on a glass slide, then the slide is flooded with acid. Maternal hemoglobin (presumably hemoglobin A as in most adults) dissolves away and the fetal hemoglobin F remains intact. Then, the slide is washed, stained, and read.**

- **Diagnosis of feto. maternal hemorrhage may be missed in situations in which red cells of the mother and infant have incompatible ABO blood groups.**

- **The optimal timing for demonstrating fetal cells in maternal blood is within 2 hours of delivery and no later than 24 hours following delivery.**

- **These techniques are not reliable when maternal HbF is raised for other reasons (maternal thalassemia, sickle cell anemia, or hereditary persistence of HbF).**

- **In the presence of these conditions, other techniques based on differential agglutination have been used, but the fetomaternal hemorrhage is usually a clinical diagnosis (a diagnosis of exclusion) in such cases.**

Twin-to-twin transfusion syndrome

- **Significant twin-to-twin transfusion occurs in at least 15% of monochorionic twins.**
- **Velamentous cord insertions are associated with increased risk of twin-to-twin transfusion.**
- **The donor twin ;**
  - **Anemic, pale**
  - **Smaller**
  - **may have evidence of oligohydramnios**
  - **evidence of congestive heart failure & shock**
- **The recipient twin;**
  - **Polycythemic**
  - **Larger**
  - **evidence of polyhydramnios**
  - **may show signs of hyperviscosity syndrome, hypoglycemia, central nervous system injury, hypocalcemia, disseminated intravascular coagulation, hyperbilirubinemia**
  - **congestive heart failure.**

Intrapartum blood loss

I. **Various obstetric accidents**

II. **Umbilical cord abnormalities**

- Rupture of normal cord
- Rupture of varix or aneurysm of cord
- Hematomas of cord or placenta
- Rupture of anomalous aberrant vessels of cord (not protected by Wharton's jelly)
- Vasa previa (umbilical cord is presenting part)
- Inadequate cord tying

III. **Placental abnormalities**

- Multi lobular placenta (fragile communicating veins to main placenta)
- Placenta previa—fetal blood loss predominantly
- Abruptio placentae—maternal blood loss predominantly
- Accidental incision of placenta during cesarean section
- Traumatic amniocentesis
- Placental chorioangioma

IV. **Hemorrhagic disorders**

- Coagulation factor deficiency
- Thrombocytopenia

Postnatal blood loss

Postnatal hemorrhage may occur from a number of sites and may be internal (enclosed) or external

I. External;

- **Bleeding from umbilicus**
- **Bleeding from gut**
- **Iatrogenic (diagnostic venipuncture, post exchange transfusion)**

II. Internal;

- **Cephalohematoma**
- **Sub galeal (subaponeurotic) hemorrhage**
- **Subdural or subarachnoid hemorrhage**
- **Intracerebral hemorrhage**
- **Intraventricular hemorrhage**
- **Intraabdominal hemorrhage**
- **Retroperitoneal hemorrhage (may involve adrenals)**
- **Subcapsular hematoma or rupture of liver**
- **Ruptured spleen**
- **Pulmonary hemorrhage**

Postnatal blood loss

I. Traumatic deliveries

II. Coagulation factor deficiencies

- **Congenital**—hemophilia or other coagulation factor deficiencies
- **Acquired**—vitamin K deficiency, DIC

III. Thrombocytopenia;

- **Congenital—**Wiskott-Aldrich syndrome, Fanconi anemia, thrombocytopenia absent radius syndrome
- **Acquired—**neonatal alloimmune thrombocytopenia, maternal immune thrombocytopenia, sepsis
- **Rare causes—**neonatal adenovirus infection, fetal cytomegalovirus infection, vascular malformations

When Hg is catabolized in a resorbing hematoma, hyperbilirubinemia develop after several days.

Characteristics of acute & chronic blood loss in the newborn

Clinical & laboratory manifestations of hemorrhage depend on the Volume of the hemorrhage & Rapidity with which it occurs

	Acute blood loss	Chronic blood loss
Clinical	• Acute distress • Shallow- Rapid- Irregular respiration • Pallor • Tachycardia • weak or absent peripheral pulses • Low or absent blood pressure • No hepatosplenomegaly	• Marked pallor disproportionate to evidence of distress • occasion signs of Congestive Heart Failure may be present
Venous pressure	Low	Normal or elevated

Characteristics of Acute & Chronic blood loss in the newborn

Laboratory	Acute blood loss	Chronic blood loss
Hemoglobin concentration	May be normal initially then drops quickly during the first 24 h of life	Low at birth
Red cell morphology	Normochromic & Normo or macrocytic	Hypochromic ,Microcytic, Anisocytosis, Poikilocytosis
Serum iron	Normal at birth	Low at birth
Course	Prompt treatment of anemia & shock	Generally uneventful
Treatment	Intravenous fluids or packed red blood cells. If indicated, iron therapy	Iron therapy Packed red blood cells on occasion

Clinical & Laboratory findings of anemia due to hemorrhage

- **Anemia—pallor, tachycardia, hypotension (if severe, >20 mL/kg blood loss)**
- **Nonimmune hydrops can occur in severe anemia**
- **Liver & Spleen not enlarged** (except in chronic transplacental bleed)
- **Jaundice absent** (except after several days in entrapped hemorrhage)

- ***Laboratory findings:***
  - **a. Reduced Hg**
  - **b. Increased Reticulocyte count**
  - **c. Polychromatophilia**
  - **d. Nucleated RBCs raised**
  - **e. Fetal cells in maternal blood (in fetomaternal bleed)**
  - **f. Direct antiglobulin test (DAT) negative**

Treatment

1. Severely affected

a. **Transfusion of Packed Red blood cells**

b. **Crossmatch blood with the mother.**

If unavailable, use group O Rh-negative blood or intravenous fluids, temporarily for shock, while awaiting available blood.

2. Mild anemia due to chronic blood loss

a. **Ferrous sulfate** (4 - 6 mg elemental iron/kg body weight per day) **for 3 months**

Hemolytic anemia

- **Acquired erythrocyte defects;**
- ***May be due to immune (DAT positive) or nonimmune (DAT negative) causes***

I. Immune

- **Maternal autoimmune hemolytic anemia; Rare in neonate**
- **Isoimmune hemolytic anemia: Rh disease, ABO, minor blood groups (M, S, Kell, Duffy, Luther)**

II. Nonimmune

- **Infections**
  (CMV, toxoplasmosis, herpes simplex, rubella, adenovirus, malaria, syphilis, bacterial sepsis)
- **Toxic exposure (drugs, chemicals)**
- **Vitamin E deficiency**
- **Metabolic disease (galactosemia, osteopetrosis)**

- **Congenital erythrocyte defect;**
  - **Memranophaty**
  - **Enzymopathy**
  - **Hemoglubinopathy**

Hemolytic anemia

- **Congenital Erythrocyte Defects;**
  - **Hemolytic anemia** (low hemoglobin, Reticulocytosis, increased NRBC, morphologic changes)
  - **Unconjugated Hyperbilirubinemia**
  - **DAT negative**

I. Membrane defects ;

- **Hereditary spherocytosis-Hereditary elliptocytosis-Hereditary stomatocytosis-Hereditary xerocytosis-Infantile pyknocytosis-Hereditary pyropoikilocytosis**

II. Hemoglobin defects;

- **α-Thalassemia syndromes- γ β-Thalassemia- Unstable hemoglobins (Hb Ko¨ ln, Hg Zu¨ rich, HbF Poole, Hb Hasharon)**

III. Enzyme defects;

- **Glycolytic pathway (Pyruvate kinase deficiency - Glucose phosphate isomerase deficiency)**
- **Hexose-monophosphate shunt (G6PD deficiency)**

Acquired erythrocyte defects;

1- Maternal autoimmune hemolytic anemia

- Autoimmune hemolytic anemia (AIHA) is a rare condition that can cause potentially serious complications in pregnant women & newborns.
- Presentation was less common in the first pregnancy (34%); most cases presented in the second or third trimester (83.3%)
- Presentation in first or second trimester in pregnancy & lower Hb nadir were significantly associated with adverse pregnancy outcomes.

- Steroids& blood transfusions were needed in most patients
- Hemolysis persisted on average for 6 weeks postpartum.
- Coombs negativity was associated with shorter duration of postpartum hemolysis.

- Preterm labor & stillbirth were observed in 33.3% of pregnancies.

Acquired erythrocyte defects;
2- Immune hemolytic anemia
Rh isoimmunization

- ***Clinical features;***
- **Anemia,** mild-to-severe (if severe, may be associated with hydrops fetalis).
- **Jaundice** (unconjugated hyperbilirubinemia).
  a. presents during first 24 hours.
  b. Kernicterus may occur if the bilirubin level in full-term infants rises to, or exceeds, 20 mg/dL
- **Hepatosplenomegaly**—varies with severity.
- **Petechiae** (only in severely affected infants)—Hypo regenerative Thrombocytopenia & Neutropenia
- **Hydrops fetalis**, stillbirth, or death in utero
- **Late hypo regenerative anemia** with decreased reticulocyte count—this may occur during the second to the fifth weeks and is due to diminished population of erythroid progenitors (EPO) is low & the marrow numbers of erythroid precursors are not elevated

Rh isoimmunization

- ***Laboratory findings;***
- **Serologic abnormalities**
  - **(positive DAT in the infant.)**
  - **(positive indirect antiglobulin test due to antibodies in the mother's serum)**
- **Decreased hemoglobin level, elevated RETIC , smear: increased NRBC,polychromasia, anisocytosis**
- **Raised indirect Bili. Level**

- ***Severity of disease is predicted by:***
  - **History indicating the severity of hemolytic disease of the newborn in previous infants**
  - **Type of RBC antigen mismatch (Rh mismatch is generally more severe than ABO mismatch)**
  - **Maternal antibody titers**
  - **Fetal ultrasonography**
  - **Percutaneous fetal blood sampling**

Rh isoimmunization

- ***Management;***
- **In Antenatal Mothers , screened at first antenatal visit for anti-D & other Ab.**
- **If a likely pathogenic antibody is detected in the mother's serum, management includes the following:**
- **Detailed past obstetric history & outcome of previous pregnancies**
- **History of prior blood transfusions**
- **B.G .& indirect antiglobulin test Blood group and indirect antiglobulin test (to determine the presence and titer of irregular antibodies).**
- **Determination of zygosity of the father (homozygous or heterozygous)**
- **Screening for severe fetal anemia using Doppler ultrasonography to measure peak systolic velocity in the middle cerebral artery of the fetus (MCA-PSV). This more accurate and noninvasive method**
- **MCA-PSV values are used to determine need & timing for fetal blood sampling**

Rh isoimmunization

- **Need for intrauterine transfusion should be made by multidisciplinary teams**
- **intravenous immunoglobulin (IVIG)**
- **Despite intrauterine transfusion, there is an approximately 20% risk of premature delivery and most will need exchange transfusion to prevent kernicterus.**
- **Multiple intrauterine transfusions are associated with suppression of erythropoiesis in the newborn & late or prolonged postnatal anemia that requires transfusion support.**

Rh isoimmunization

- **Postnatal;**
- **For the hydropic infant at birth;**
  - **Phototherapy**
  - **Adequate ventilation**
  - **Drainage of pleural effusions & Ascites**
  - **Resuscitation fluids and drugs, Surfactant, Glucose infusions to counteract Hyper insulinemic hypoglycemia**
  - **Partial exchange transfusion may be necessary to correct severe anemia**
  - **Double-volume exchange transfusion may be required later**
  - **Hyperbilirubinemia is the most frequent problem & can be managed by exchange transfusion.**

Rh isoimmunization

- ***Other current Guidelines ;***
- **Exchange transfusion should be performed for any signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry).**

- **Exchange transfusion is recommended when the total serum bilirubin exceeds limits on age-specific nomograms despite intensive phototherapy.**

- **Exchange transfusion should be considered when the bilirubin-to-albumin ratio exceeds cutoff values based on gestational age and comorbidities such as G6PD deficiency and isoimmune hemolytic anemia.**

Rh isoimmunization

- **Blood for Ex.Tr. should be ABO compatible & for anti-D hemolytic dis. of newborn, D neg.**
- **If mother is alloimmunized to Ag. other than D, blood should not have that Ag.**
- **Crossmatch compatible with the mother's serum**
- **Leukocyte depleted & negative for Kell antigen**
- **If the initial Ex. Tr. is carried out O neg. , any further Ex. transfusions should use O neg.**
- **Graft-versus-host disease occurs rarely after Ex.Tr., so blood must be irradiated**

Rh isoimmunization

- ***Prevention of Rh hemolytic disease;***
- **Use of Rh immunoglobulin, which is indicated in the following circumstances:**
  - **For all D-negative or partial D-negative mothers who are unimmunized to D.**
  - **Rh immunoglobulin is given as a single large dose at 28 weeks' gestation**
  - **or as 2 smaller doses at 28 and 34 weeks' gestation, and within 72 hours of delivery of D-positive newborn. .**

- **For all unimmunized D-neg. mothers ;**
  - **spontaneous (1.52% risk of sensitization)**
  - **Induced abortion (5% risk of immunization)**

- **The D antigen is detectable on embryonic red cells by 38 days after conception**
- **Rh immunoglobulin should be given beyond the 7^{th} or 8^{th} wks. of gestation**

2-ABO isoimmunization

- **ABO incompatibility is milder than hemolytic dis. of newborn caused by other antibodies.**

- ***Clinical features***
  1. **Jaundice (indirect hyperbili.) usually within first 24 hrs.; rarely, to cause kernicterus.**
  2. **Anemia at birth is usually absent or moderate & late anemia is rare.**
  3. **Possible hepatosplenomegaly.**

ABO isoimmunization

- ***Diagnosis;***

1. **Hemoglobin decreased**
2. **Smear:**
   Spherocytosis in 80% of infants, Retic, marked Polychromasia
3. **Elevated indirect Bili.**
4. **Demonstration of incompatible blood group**
   a. Group O mother & an infant who is group A or B.
   b. Rarely, mother may be A & baby B or AB or mother may be B & baby A or AB.

5. **DAT of infant's red cells often positive**
6. **Demonstration of antibody in infant's serum**
7. **Demonstration of antibodies in maternal serum**

ABO isoimmunization

- ***Treatment***
- ***In ABO hemolytic disease, unlike Rh disease, antenatal management or premature delivery is not required.***

- **After delivery;**
  - **Controlling hyperbilirubinemia**
  - **Phototherapy**
  - **Exchange transfusion.**
  - **The principles & methods are the same as those described for Rh hemolytic disease**
  - **Group O blood of the same Rh type as that of the infant should be used. Whole blood or**
  - **Reconstituted red blood cells in fresh frozen plasma can be used to permit maximum bilirubin removal by albumin.**

Clinical and laboratory features of immune hemolysis caused by Rh and ABO incompatibility

Feature	Rh disease	ABO incompatibility
Clinical evaluation		
Frequency	Rare (since the use of Rh-Ig)	Common
Occurrence in first born	5%	40-50%
Predictably severe in subsequent pregnancies	Usually	No
Stillbirth and/or hydrops	Occasional	Rare
Pallor	Marked	Minimal
Jaundice	Marked	Minimal (occasionally marked)
Hepatosplenomegaly	Marked	Minimal
Incidence of late anemia	Common	Uncommon

Clinical and laboratory features of immune hemolysis caused by Rh and ABO incompatibility

Feature	Rh disease	ABO incompatibility
laboratory		
Blood type, mother	Rh negative O	(occasionally A or B)
Blood type, infant	Rh positive	A or B or AB
Direct antiglobulin test	Positive	Usually positive
Indirect antiglobulin test	Positive	Usually positive
Hemoglobin level	Moderately or severely low	Mildly or moderately low
Serum bilirubin	Markedly elevated	Variably elevated
Red cell morphology	Nucleated RBCs, polychromasia, spherocytes	Spherocytes, variable polychromasia

Clinical and laboratory features of immune hemolysis caused by Rh and ABO incompatibility

Treatment	Rh disease	ABO incompatibility
Need for antenatal management	Yes	No
Exchange transfusion	Often needed	Uncommonly needed
Donor blood type	D-negative group specific, when possible	Rh same as infant group O only

Late-onset anemia in immune hemolytic anemia

- **Severe anemia during the first 6 weeks of life that can last to 4 - 6 months of life**
  - **I. Infants with hemolytic anemia of the newborn due to isoimmunization**
  - **II. Particularly in infants who have severe isoimmunization treated with IUT**
  - **III. Infants who do not require Ex.T for hyperbili. following immune Hemolytic Anemia**
- **Etiology;**
  - **Due to persistent maternal IgG that clear circulating RBC & Reticulocytes**
  - **Suppression of erythropoiesis due to intramedullary destruction of erythroblasts**
  - **Hg & Retic counts should be monitored regularly for <u>4- 6weeks,</u>**
  - **or until evidence of resolution, which can take <u>several months.</u>**
- ***Treatment with EPO or darbepoetin may be needed to decrease the need for transfusion***

Vitamin E deficiency

- **Premature infants (<36 weeks gestation or weighing <2000 g) are susceptible to vitamin E deficiency because of decreased absorption of the vitamin.**
- **With improvement in infant formulas recognizing this propensity, this condition has virtually disappeared.**
- ***Clinical findings;***

I. **Hemolytic anemia & Reticulocytosis**

II. **Thrombocytosis**

III. **Pyknocytes (acanthocytes), small number of spherocytes, fragmented red cells**

IV. **Peripheral edema**

V. **Neurologic signs:**

a. Cerebellar degeneration

b. Ataxia

c. Peripheral neuropathy

Vitamin E deficiency

- ***Diagnosis***
- ***Peroxide hemolysis test:***
- **Red cells are incubated with small amounts of hydrogen peroxide & amount of hemolysis is measured.**

- **This test is not readily available as a clinical assay and has been replaced by**
- **Measurement & interpretation of *serum tocopherol* levels in the context of consistent clinical and laboratory features.**

Hemoglobinopathies

- **Anemia due to *gamma-hemoglobinopathies* resolves spontaneously, Rarely, marked in utero and neonatal hemolysis can occur. Some variants can be identified during newborn screening.**

- ***beta hemoglobinopathies* are clinically inapparent at birth and manifest only after a few months.**
- **Anemia from *alpha hemoglobinopathies* can occur throughout life (prenatal and postnatal)**

Infantile pyknocytosis

- **The cause of this has not been clearly defined**
- ***Causes of pyknocytes in the blood have been excluded*** **such as G6PD deficiency, pyruvate kinase deficiency, microangiopathic hemolytic anemia, neonatal hepatitis, vitamin E deficiency, neonatal infections, hemolysis caused by drugs and toxic agents.**
- **It is a congenital , but it is not an ongoing, lifelong,**

- **Infantile pyknocytosis is characterized by:**
  - **Hemolytic anemia—DAT negative (nonimmune)**
  - **Distortion of as many as 50% of red cells dense, contracted cells (pyknocytes) with several to many spiny**
  - **projections (up to 6% of cells may be distorted in normal infants).**
  - **Disappearance of pyknocytes &hemolysis by the age of 6 months.**
  - **This is a self-limiting condition.**
  - **Hepatosplenomegaly**

Failure of red cell production (Hypoplasia)

- **Congenital :**
  - **Diamond-Blackfan anemia (pure red cell aplasia)**
  - **Fanconi anemia**
  - **Mitochondriopathies (Pearson syndrome)**
  - **Sideroblastic anemia**
  - **Congenital dyserythropoietic anemia**

- **Acquired;**
  - **Viral infection (hepatitis, HIV, CMV, rubella, syphilis, parvovirus B19)**
  - **Malaria**
  - **Anemia of prematurity**

Diamond-Blackfan anemia (pure red cell aplasia)

- DBA is a rare, predominantly red cell aplasia presenting in 90% of the patients within the first year of life.
- Macrocytic anemia ,Reticulocytopenia ,Normocellular bone marrow with a selective paucity of erythroid precursors
- Autosomal dominant inheritance
- Median age at presentation of anemia is 2 months
- Median age at diagnosis of DBA is 3 -4 months.
- Physical anomalies;
  - Short stature, are found in half of the patients.
  - Face and head (microcephaly, cleft palate, ear and eye anomalies)
  - Upper limb & hand (thumb deformity, triphalangeal thumb, duplication of thumb, bifid thumb)
  - Genitourinary
  - Cardiac Anomali

- ***Diagnostic criteria for Diamond Blackfan anemia;***
- **Normochromic, usually macrocytic anemia**
- **Reticulocytopenia**
- **Normocellular marrow with selective paucity of erythroid precursors**
- **Age less than 1 year**
- ***Definitive but not essential***
- **Presence of mutation described in classical DBAa**
- **Major**
- **Positive family history**
- **Minor**
- **Congenital abnormalities described in classical DBA**
- **Macrocytosis**
- **Elevated fetal hemoglobin**
- **Elevated erythrocyte adenosine deaminase activity**

Acquired B.M.F

- ***Viral diseases***
- **Viral medullary toxicity (CMV & HIV) with fetal haematopoiesis may cause anaemia, leukopenia & thrombocytopenia in the newborn, sometimes with evidence of extramedullary hematopoiesis**

Physiologic anemia

- Hg. level falls to 11.4+/- 0.9 g/dL at 8-12 weeks (physiologic anemia)
- In utero the O2 sat. of the fetus is 70% (hypoxic levels) , stimulates EPO, produces a Reticulocytosis & Increases RBC production causing a high hemoglobin at birth
- **ETIOLOGY;**
  - After birth the oxygen saturation is 95%, EPO is undetectable, & RBC production by day 7 is 10% of the level in utero
  - Short RBC lifespan–40 to 60 days, compared to 120 days in adults
  - Rapid postnatal growth inducing a dilution effect on Hb secondary to the increased circulating volume
- Infants born prematurely experience a more marked decrease in Hg. concentration that may start earlier & last longer than full-term infants
- Premature infants weighing <1500 g have a Hg. level of 8 g/dL at age 4 -8 weeks

Anemia of prematurity

- ***The low hemoglobin concentration is due to:***
  - **Preterm infants deprived of 3th trimester hematopoiesis & iron transport**
  - **Decreased marrow erythroid elements & red cell production**
  - **Shorter red cell lifespan**
  - **Impaired EPO production**
  - **Increased blood volume with growth**
  - **Marked blood loss from phlebotomy to monitor problems related to prematurity**
  - ***It may be compounded by folic acid, vitamin E, & Iron availability, frequent blood sampling.***

Anemia of prematurity

- **Nadir of Hg. level is at 4 - 8 weeks & is 8 g/dL in infants weighing <1500 gr.**

- ***Clinical features;***
  - **Anemia Normocytic & Normochromic**
  - **Tachycardia**
  - **Increased apnea**
  - **Increased oxygen requirement**
  - **Poor weight gain**

Transfusion guidelines

- **Guidelines for RBC transfusions differ worldwide & are based mainly on expert opinion.**
- **After that period the indication for transfusion should not be based on hemoglobin concentration alone but on available *tissue oxygen* which is determined by:**
  - **Hemoglobin concentration**
  - **Position of the oxyhemoglobin dissociation curve (usually inferred or guessed, but it can be measured in some laboratories)**
  - **Arterial oxygen saturation**
  - **Gestational age at birth**
  - **Postnatal age at time of transfusion**
  - ***Infant's clinical condition that includes:***
    - **Mainly focusing on the degree of respiratory failure**
    - **Weight gain**
    - **Fatigue during feeding**
    - **Tachycardia**
    - **Tachypnea**
    - **Evidence of hypoxemia by an increase in blood lactic acid concentration**

Transfusion guidelines

- ***Single donor;***
- **The use of single donor products for RBC transfusions for preterm infants is currently widespread in several developed countries**
- **An adult unit of RBC can be divided in up to 4 or 5 smaller units of 50 ml, so called pedipacks, which can be reserved for one specific neonate**
- **All transfusions should be provided from *a single donor*, be *less than 7-10 days old* and be *leukodepleted***

Transfusion guidelines

- ***RBC storage***
- **Concerns have been raised about the transfusion of ‘older’ RBCs, that is, stored for a longer period before being transfused**

- **Long storage may theoretically:**
  - **Increase the risk of infection due to immunomodulatory effects**
  - **Decrease the oxygen delivery to organs & tissue**
  - **Induce a greater inflammatory response**

- **Significant differences were found between the groups of infants transfused with RBCs stored <7 days old compared with RBCs stored >7 days**

- ***What volume should we transfuse?***

- **Transfusion volume (ml)=**
- **Pa. wt** (kg) **x EBV**(ml/kg) **x (desired Hb** (g/l)**–pa. Hb** (g/l) **/ Hb of donor unit)**

- **EBV is 100–120 ml/kg in extremely pre-term infants**
- **EBV is 80–85 ml/kg in term infants**

- ***Hb content of RBCs can vary; in general, each 10–15 ml/kg transfused is expected to increase the infant's Hb level by approximately 10–20 g/l***

- ***Some suggest a volume of 15 ml/kg for infants less than 32 weeks GA or ≤1500 g because an association between a greater total volume of infused blood & transfusion-related NEC is reported in VLBW infants***

Transfusion guidelines

- ***Leukocyte filtration***
- ***The transmission of latent intracellular viruses, such as CMV, can be greatly diminished by leukocyte depletion using filtration***
- ***An additional method is the selection of CMV antigen-negative donors***
- ***CMV-safe RBCs are often indicated in case of intrauterine blood transfusions & for very preterm infants***

Transfusion guidelines

- ***Irradiation;***
- **To prevent graft-versus-host disease in immune compromised hosts, irradiation of cellular blood products, such as RBCs, is often advised for *all intrauterine transfusions.***

- **For postnatal transfusions, irradiation guidelines differ worldwide & range from irradiation of all products for *infants in the first year of life* to no irradiation needed at all**

Neonatal red blood cell transfusion

- ***Blood transfusions are associated with;***
  - **Infectious**
  - **Non-infectious serious hazards of transfusion (NISHOTs)**
    - **Necrotizing enterocolitis(NEC)**
    - **Bronchopulmonary dysplasia (BPD)**
    - **Retinopathy ofprematurity (ROP)**
    - **Intraventricular haemorrhage (IVH)**
    - **Long-term abnormal neurodevelopment**
  - **Complications specific to premature neonates(cytomegalovirus)**

- **Prestorage leucoreduction & use of CMV-negative donor blood decrease but does not completely eliminate CMV transmission**

Use of Erythropoietin

- **EPO could potentially be beneficial for decreasing later RBC transfusions**
- ***But the early need for RBC transfusions in the first week of life will not be diminished***

- ***Recombinant human EPO (rHuEPO) ;***
  - **Increase reticulocyte counts**
  - **Raise hemoglobin**
- **Darbepoetin can be used instead(**darbepoetin alfa (long-acting EPO-stimulating agent))

- **A potential advantage of rHuEPO is the associated right shift in the oxyhemoglobin dissociation curve ,due to *increased erythrocyte 2,3-BPG content***

- **Reduction in need for transfusions in premature infants who receive rHuEPO early (before day 8 of life) or late (between days 8 and 28 of life),**

- **Incidence of *NEC, intraventricular hemorrhage, periventricular leukomalacia* has been shown to be lower in very-LBW infants treated with rHuEPO, but whether this impacts the controversial is neurodevelopmental outcomes**

- ***To prevent development of iron deficiency, especially in combination with rHuEPO.***

  - **Supplemental oral iron in a dose of at least 2 mg/kg/day**
  - **or intravenous iron supplementation**

  - **Intake of folate, vitamin E, protein are important to support erythropoiesis**

- ***Iron supplementation***
- **Iron is transported across the placenta from mother to child particularly during the last trimester of pregnancy**
  - **Infants delivered *prematurely* have a smaller supply of iron**
  - **In addition, preterm infants have an increased need for supplemental iron due to increased risk of iatrogenic blood loss related to frequent laboratory testing.**
- *Most guidelines advise the use of extra iron (2–3 mg/kg) in preterm infants, starting early in life (when 100 ml/kg enteral feeding is tolerated).*

- ***Preventative measures***
  - ***Delaying cord clamping for 30-60 seconds in infants who do not require immediate resuscitation can be considered to reduce the severity of anemia of prematurity***

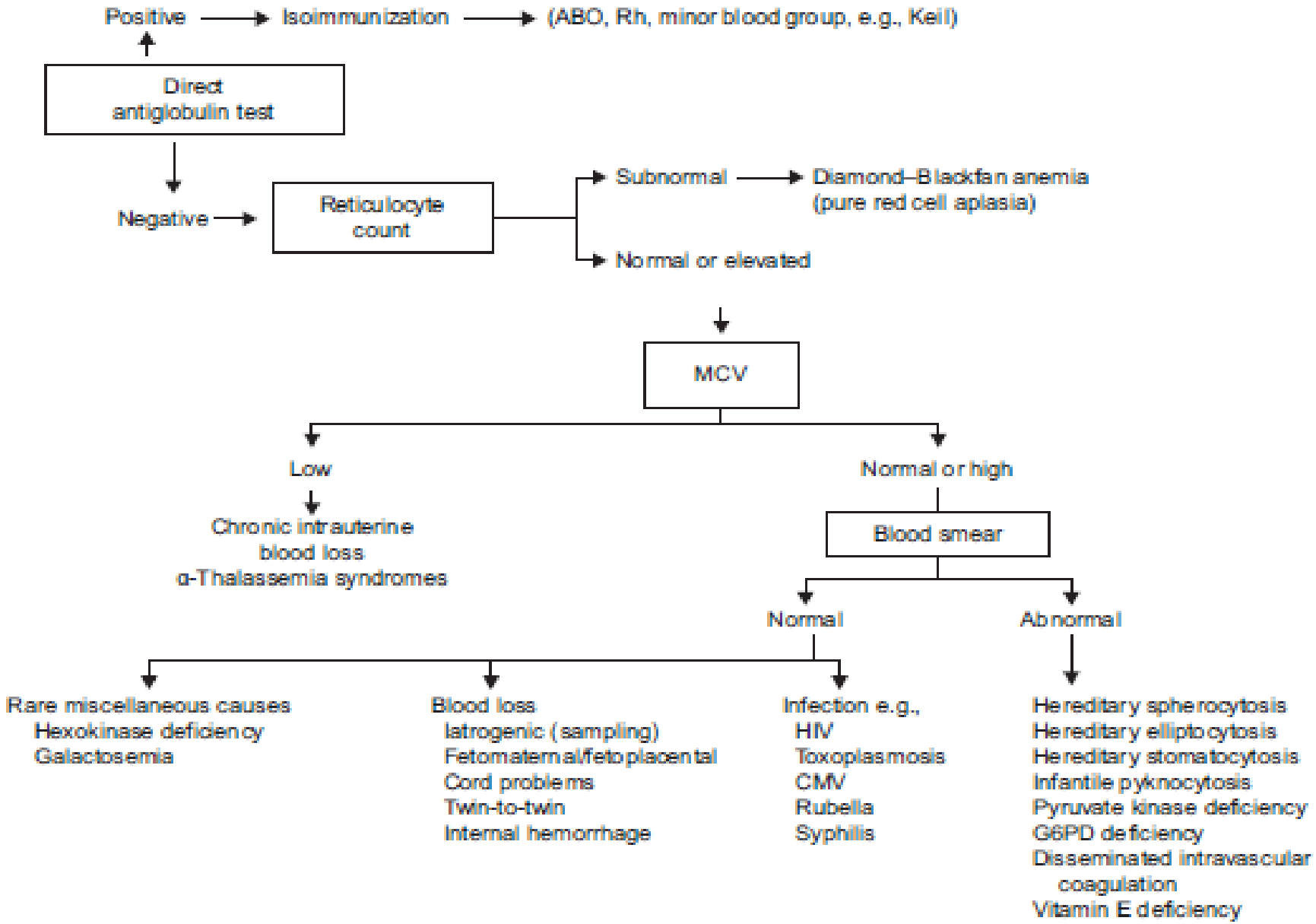
  - ***Delayed cord clamping (DCC)***
    - **DCC implies waiting at least 30 s (up to a max. of 2–3 min after birth) before clamping the umbilical cord**
    - **improved circulatory stability & a reduction in the rate of IVH & NEC**
    - **DCC in preterm infants is with a higher concentration of peak Bili , without an increased need for phototherapy**
    - **DCC leads to a higher Hb level at birth & improved iron status at 3–6 months of age**
    - **Milking the umbilical cord massaging the cord and thus umbilical cord blood toward the infants two to four-times before clamping**

  - **Reduction of iatrogenic blood loss**
    - **use of microanalysis, smaller amounts of blood for diagnostic testing**

- ***Protein Supplementation***
- **Substantial evidence indicates that inadequate protein intake is an important contributor to anemia in preterm infants.**
  - (protein intake 3.5 to 3.6 g/kg compared with those who receive intakes of only 1.8 to 1.9)
- **Amount of protein intake needed for optimal body growth is related to body size and the level of maturity, with the smallest infants requiring the greatest daily protein intakes per kilogram of body weight.**

- ***Vitamin Supplementation***
- **Because preterm infants have limited body supplies of the water-soluble vitamins & higher protein requirements, adequate intake *of vitamin B12 & folate* may be important in preventing anemia**

Diagnostic approach to anemia in the newborn



Clinical and laboratory evaluation in anemia in the newborn.

- ***HISTORY***
  - **Obstetric history**
  - **Family history**
- ***PHYSICAL EXAMINATION***
- ***LABORATORY TESTS***
  - **CBC**
  - **Retic. count**
  - **Blood smear**
  - **Antiglobulin test (direct and indirect)**
  - **Blood type of baby & mother**
  - **Bilirubin level**
  - **Flow cytometry of maternal blood (fetal red cells in maternal blood)**
  - **Studies for neonatal infection**
  - **Ultrasound of abdomen and head (if indicated)**
  - **Red cell enzyme assays (if clinically indicated)**
  - **Bone marrow (if clinically indicated)**

Thank you for your attention