
Hematologic Diseases in the Newborn

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Hematologic Diseases in the Newborn

◆ The Plan

- Normal hematopoiesis
- Erythropoiesis and Red Cells - Anemias
- Anemia of prematurity, EPO, Hemolysis
- Polycythemia - Hypervisocosity
- Newborn Platelet Disorders
- Hemostatic Abnormalities
- Neutrophil Function and Disorders

Transitions in the Newborn's Production of:

- ◆ Hemoglobin
- ◆ Red cell number
- ◆ WBC
 - Neutrophils
 - Lymphocytes
- ◆ Platelets

Globin Chain Synthesis in Fetus & Newborn

◆ Embryo

- Alpha from start throughout; Delta from wk 8; Epsilon only wks 8-12
- Delta 2 Epsilon 2
- Epsilon 4 = Gower 1
- Alpha 2 Epsilon 2 = Gower 2

◆ Fetus – wks 12-34

- Alpha 2 Gamma 2 = Hgb F (75+%)
- Alpha 2 Beta 2 = Hgb A

◆ Adult

- Hgb A
- Alpha 2 Delta 2 = Hgb A2 (<3%)

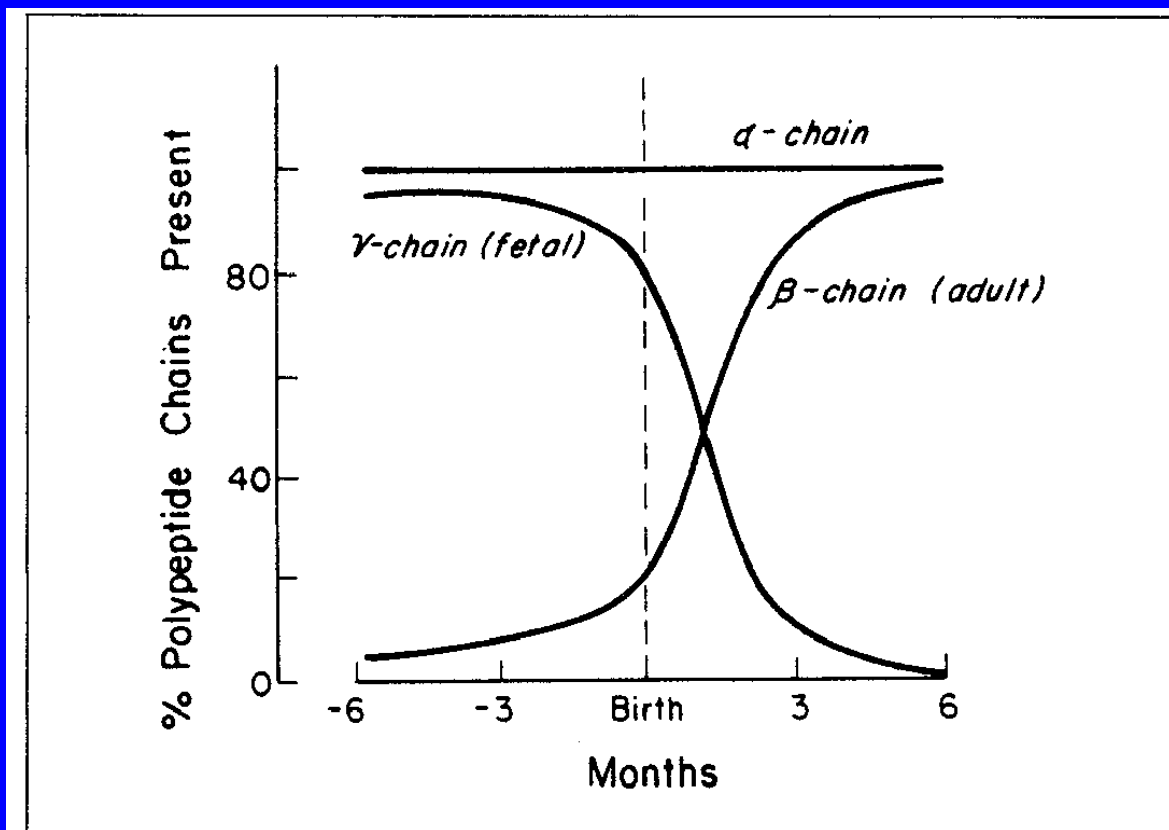


Fig. 23-4. Globin chain synthesis in the fetus and during the neonatal period. The amount of α -chain synthesis is expressed as 100%. With maturation the corresponding percentage of γ -chain synthesis decreases as production of β -chain increases, accounting for the shift from fetal to adult hemoglobin.

Red Blood Cells in the Newborn

- ◆ Hgb F - Higher O₂ affinity, less deformable, more glycolytic enzymes, greater oxidative sensitivity => 80 day life span
- ◆ Greater production rate than adult => high retic and nRBCs for first 3-4 days; high MCV
- ◆ Relative oxygen richness after birth leads to markedly decreased RBC production => physiologic anemias of infancy and prematurity

Anemia of Prematurity and EPO

- ◆ Term infant has physiologic anemia at 6-12 weeks
- ◆ Occurs earlier in premature and is shorter
- ◆ The more premature the infant, the longer the transition from fetal to adult Hgb
- ◆ VLBW infant has decreased levels of EPO
 - More dependent on liver for production of EPO
 - There is decreased EPO in oxygen environment
 - VLBW infants will increase reticulocytes with exogenous EPO
 - EPO accelerates the rate of transition to adult Hgb
 - Exogenous EPO has shorter half life and larger volume of distribution in premie – There is no common standard for dose or frequency in VLBW

Neonatal Polycythemia & Hyperviscosity

- ◆ Affects 1-5% of newborns
- ◆ Defined as > 2 SD elevation for age = Term hematocrit $\geq 65\%$
- ◆ Blood viscosity has linear relationship with hematocrit when $\leq 60\%$ but the relationship is exponential when hct $> 65\%$
- ◆ Two major causes of hyperviscosity – active and passive
 - Active – Intrapartum hypoxia, placental insufficiency, IDM, maternal hypoxemia, maternal propranolol, maternal smoking, living at high altitude, post-term, Beckwith-Wiedemann, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism, Trisomy 21, 18, or 13
 - Passive – Transfusion
- ◆ Symptoms 2-4 hours after birth
 - Cardiorespiratory – acrocyanosis, poor peripheral perfusion, tachypnea, murmur, heart failure, increased pulmonary vascular resistance, PPH
 - Neurologic – Irritability, jitteriness, poor feeding, lethargy, hypotonia, apnea
 - Jaundice, hypoglycemia, abdominal distention, hematuria, thrombocytopenia

Newborn Platelets and Coagulation Proteins

- ◆ Developmental processes and controls are similar to older child
- ◆ Generally, there are lower levels of coagulation proteins near birth
- ◆ Generally, there are lower levels of antithrombotic proteins
- ◆ => Overall normal coagulation but PT and aPTT are longer than older children

Mean and Limits for Venous Blood by Age

Screening test	Adult	Term Newborn	Preterm 1.5-2 kg	Newborn < 1.5 kg
Platelet count ($10^3/\text{cm}^3$)	300 (150)	250 (150)	250 (150)	250 (150)
Bleeding time (min)	4 (7)	4 (7)	4 (7)	4 (7)
Prothrombin Time (sec)	12 (14)	13.5 (16)	16 (19)	17 (20)
Partial Thromboplastin Time (sec)	44 (50)	65 (84)	80 (120)	108 (150)
Thrombin Time (sec)	10 (12)	14 (18)	15 (20)	15 (20)

Upper limits are in parentheses except for platelet counts are lower limits.

Effect of Gestational Age and Race on RBC Indices

(Sampling within 3 hours after delivery from dorsalis pedis or radial artery or UAC)

	23-25 weeks		26-28 weeks		29-31 weeks	
	White n = 15	Black n = 19	White n = 25	Black n = 32	White n = 50	Black n = 25
HCT	45.0 \pm 5.0	42.6 \pm 4.0	46.0 \pm 3.0	44.0 \pm 5.0	50.0 \pm 5.0	45.5 \pm 4.6
HGB	15.3 \pm 1.6	14.2 \pm 1.5	15.6 \pm 1.2	14.9 \pm 1.8	16.7 \pm 1.6	15.4 \pm 1.7
MCV	116 \pm 6	115 \pm 6	116 \pm 5	113 \pm 9	112 \pm 5	107 \pm 8
MCH	39.4 \pm 2.0	38.2 \pm 2.0	39.1 \pm 2.0	37.7 \pm 3.4	37.6 \pm 2.1	36.2 \pm 3.0
MCHC	33.8 \pm 0.5	33.0 \pm 1.0	33.7 \pm 0.6	33.5 \pm 0.6	33.6 \pm 0.6	33.8 \pm 0.9
RDW	16.0 \pm 1.0	15.7 \pm 1.9	16.2 \pm 1.0	16.7 \pm 2.4	16.3 \pm 1.4	16.3 \pm 1.4

WBCs in the Newborn

- ◆ Neutrophil
 - Number is increased.
 - Neutrophil ingestion and degranulation are near adult levels.
 - Chemotaxis and mobility are not well studied but may be near adult levels
- ◆ Lymphocyte
 - Numbers are normal to increased
 - T and B-cell function is minimal
 - Humoral antibody production is minimal
- ◆ The infant's humoral responses are largely dependent on maternal IgG. Anything that lowers her contribution lessens protection for the child.
- ◆ Splenic removal of cells - antibody coated or not – is slower in infant than adult levels

Neonatal Jaundice

- ◆ Physiologic
- ◆ Breastfeeding
- ◆ Isoimmune hemolysis
- ◆ Autoimmune hemolysis
- ◆ Intrinsic RBC defects
 - Structural - HS, HE, Stomatocytes
 - Enzyme - G6PD, PK
 - Vitamin E deficiency
- ◆ Oxidants - Vit. K, sulfa, thiazides
- ◆ Infection
 - E. coli, Staph, GBS
 - CMV, Herpes, Hepatitis, Rubella
 - Toxoplasmosis
 - Syphilis
- ◆ Enclosed hemorrhage
- ◆ Metabolic disorders
 - Galactosemia
 - Hypothyroidism
 - Crigler-Najjar
 - Maternal hyperbilirubinemia

Maternal/Fetal Alloimmunization

- ◆ RBCs - Hemolytic Disease of the Newborn = VKDA (Vitamin K Deficiency Bleeding)
 - Rhesus complex – D >> C or E
 - ABO
 - More commonly 2nd born or greater
 - Rx – Anti-D to Rh neg mother; timing is important
 - Bililights vs exchange
- ◆ Neonatal Alloimmune Thrombocytopenia
 - PL 1a or PL 5b
 - May be first born
- ◆ Alloimmune Neonatal Neutropenia

G6PD

- ◆ Most common enzymatic disorder of RBCs
- ◆ X-linked
- ◆ Variable spectrum of hemolytic syndromes
 - Most are asymptomatic, some with episodic anemia, few with chronic hemolysis
 - WHO variant nomenclature
 - » Class I – Severe deficiency (<10% activity) – have chronic hemolytic anemia
 - » Class II – (e.g., G6PD Mediterranean) – severe deficiency but intermittent hemolysis
 - » Class III – (e.g., G6PD A-) – 10-60% activity – intermittent hemolysis
 - » Class IV (normal levels) and Class V (increased level) have no clinical significance

G6PD – Clinical Features

- ◆ Most prevalent G6PD variants are G6PD A- and G6PD Mediterranean
- ◆ Hemolysis is 2-4 days after exposure to infection, acidosis or after ingesting an oxidant
- ◆ Sudden onset of jaundice, pallor, and dark urine with or without abdominal or back pain
- ◆ Hemolysis ends in 7-10 days as the most deficient cells are destroyed and replaced with young cells with higher levels of G6PD (In G6PD A-, retics have normal levels but level declines rapidly over time – half life 13 days)
- ◆ In newborn, present with early jaundice (as early as 2 hours) that is disproportionately high – may require exchange
- ◆ The RBC destruction is no more rapid than later in life (no or mild anemia, so that the explanation for the jaundice is unclear – liver clearance?)

Pyruvate Kinase Deficiency

- ◆ Causes non-spherocytic, hemolytic anemia
- ◆ Autosomal recessive; lower frequencies than G6PD genes
- ◆ Two PK genes - Several isoforms
 - M gene – 15q22 – muscle, brain, WBC and platelets
 - » M2 isoform is most common in newborns and is replaced by M1 isoform in RBCs in first months of life
 - » M2 may persist in adults in WBC and platelets
 - L gene – 1q21 – L & R isoforms – liver and RBCs respectively; R form only in RBCs and is 33 amino acids larger than L form

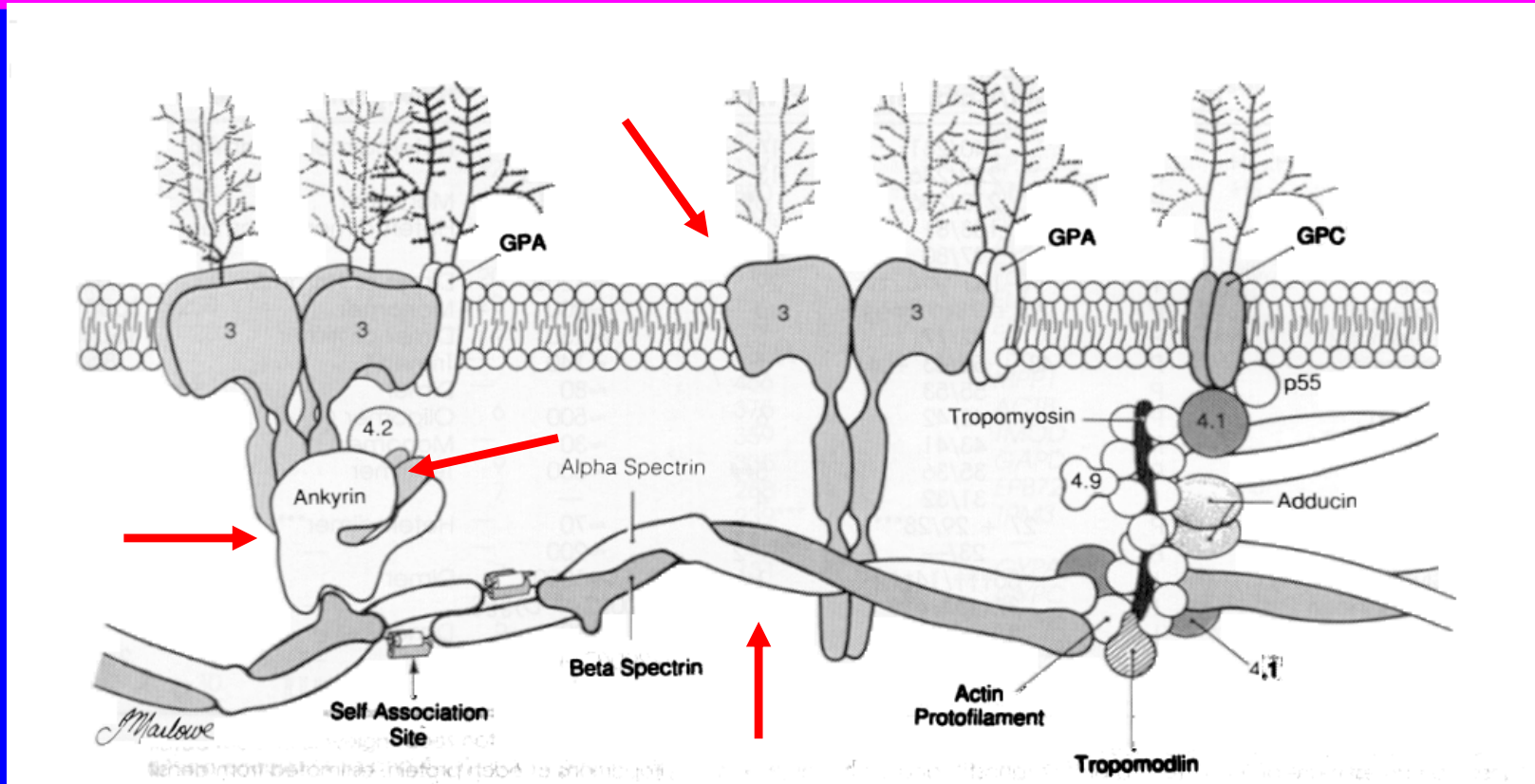
Pyruvate Kinase - continued

- ◆ Clinical PK deficiency is R isoform with impact on RBCs with normal levels in WBCs
- ◆ Mechanism for hemolysis is not clear
- ◆ RBC survival is shortened and maturation of splenic RBC precursors is impaired resulting in apoptosis => a double effect on RBC # and survival. Greater role for splenectomy to attain transfusion independence.
- ◆ Severity of hemolysis is variable – hydrops to mild, fully compensated hemolysis
- ◆ Typically present with jaundice, pallor and splenomegally
- ◆ Haptoglobin and LDH may not be helpful since hemolysis is mainly extravascular.
- ◆ Gallstones are more frequent at age 10 or older.

Hereditary Spherocytosis

- ◆ Epidemiology:
 - Occurs in all racial groups
 - 1:5000 in N. Europe
- ◆ Genetics:
 - AD 75%
 - AR 25%
- ◆ Etiology:
 - Membrane Skeletal Protein Defects

Red Cell Skeleton and HS



HS Defects

1. Ankyrin
2. Spectrin
3. Protein 4.2
4. Band 3

Spectrin defects cause hereditary elliptocytosis

HS Pathophysiology and Clinical Manifestations

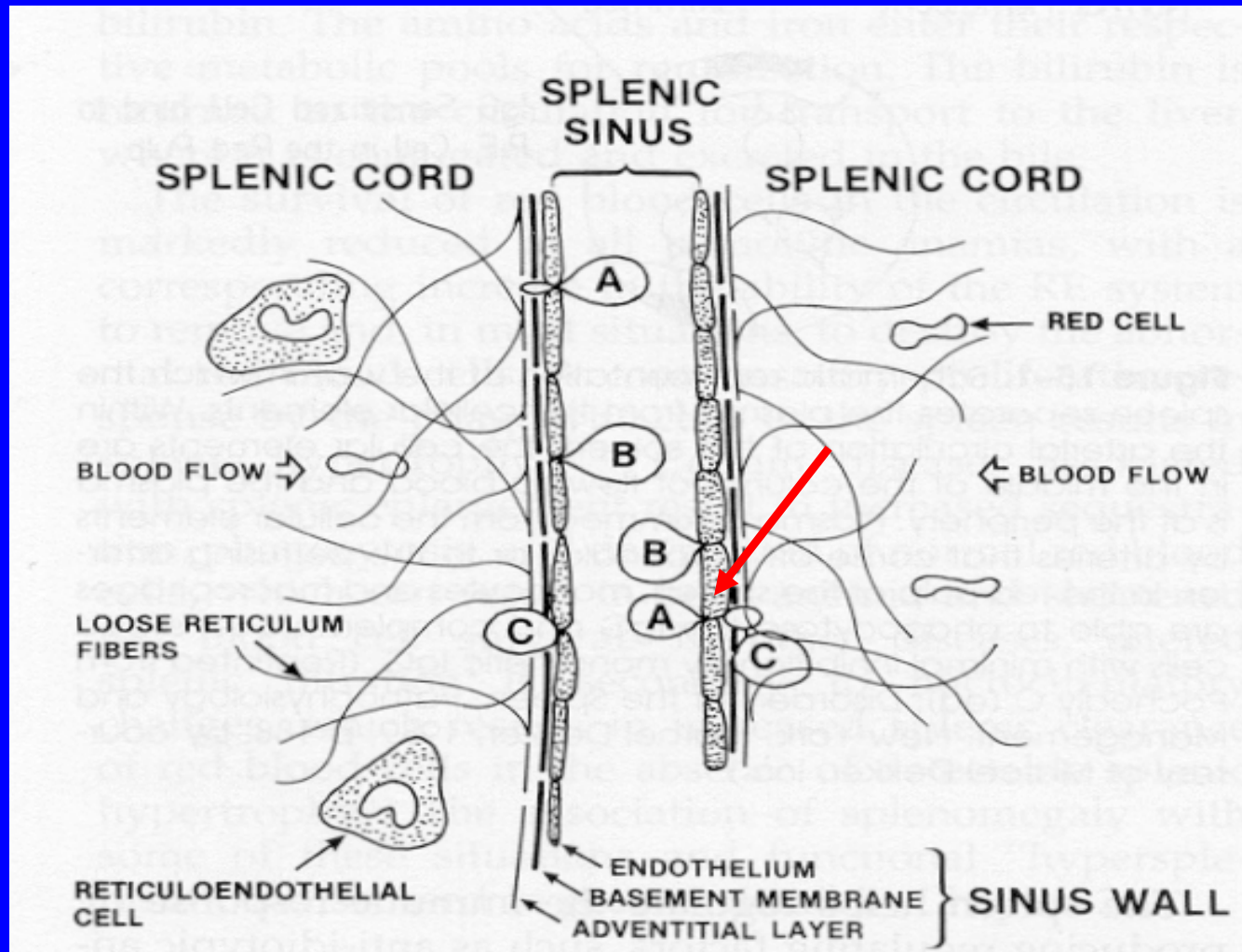
◆ Pathophysiology

- Membrane loss
- Loss of Cellular Deformability
- Splenic Trapping
 - » Physical Trapping (Splenic Cords)
 - » Oxidative Stress through Erythrostasis
- Autohemolysis

◆ Clinical Manifestations

- Anemia
- Splenomegaly
- Neonatal Jaundice
- Intermittent Hemolysis
- Aplastic Crises
- Gallstones

Splenic Trapping of RBCs



HS Diagnosis and Treatment

◆ Diagnosis:

- Characteristic Morphology
- Red Cell Indices (increased MCHC)
- Osmotic Fragility Test
- AGLT
- Autohemolysis Test
- Molecular Diagnosis
- Rapid flow cytometry – could become a screening tool

◆ Treatments

- Transfusion
- Splenectomy
- Cholecystectomy
- Folate

◆ Ongoing issues

- » Aplasia - hypoplasia
- » Hemolysis

Anemia in a newborn

◆ Critical history

- Pregnancy and birth, IDM
- Mother/Baby ABO and Rh
- Familial anemia – Ask about splenectomy and gall bladder

◆ Critical features of infant exam

- Bruising or hematomas
- Anomalies or hemangiomas
- Signs of infection or ill appearing

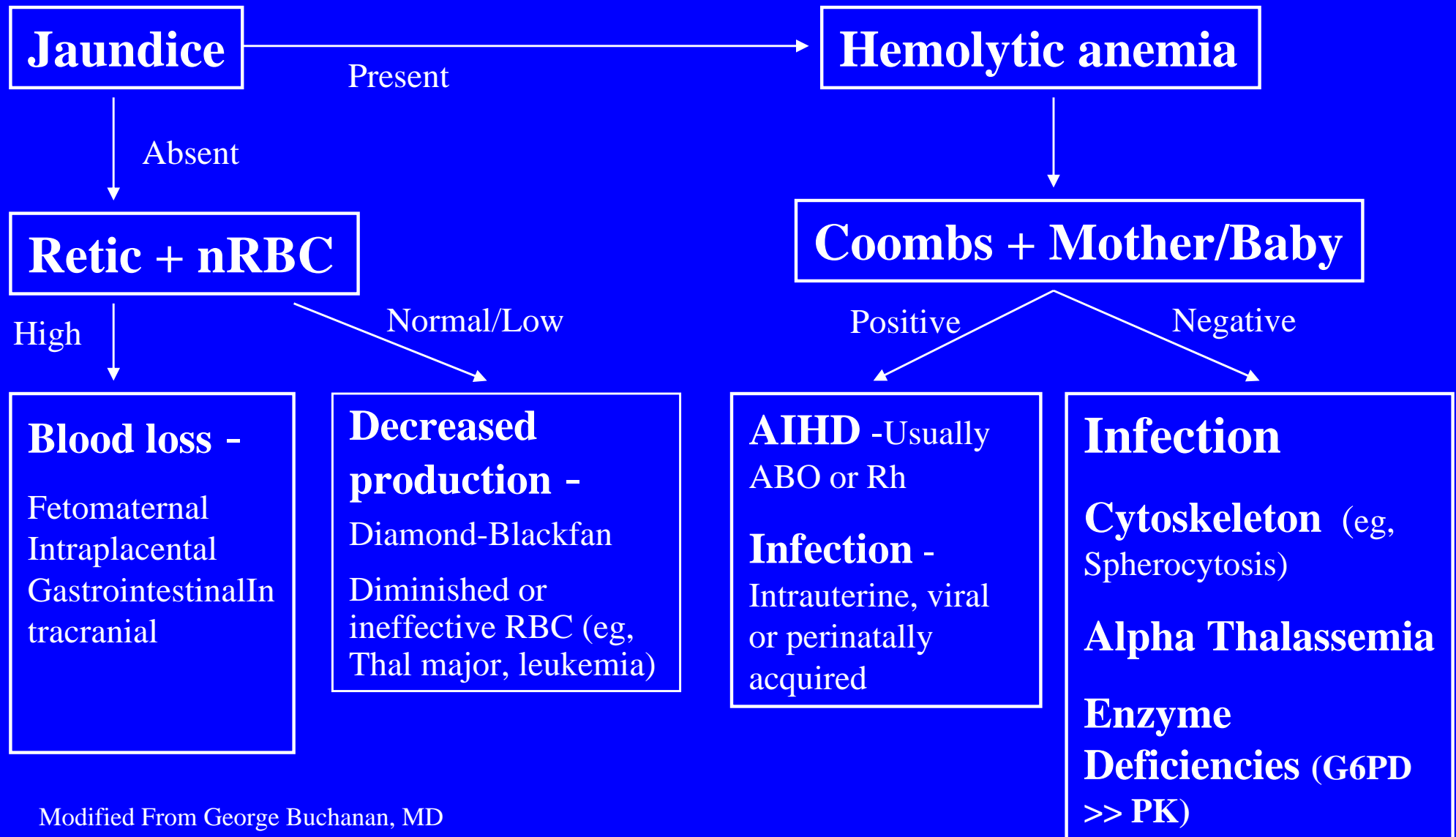
Anemia in a Newborn

- ◆ Acute blood loss - most common
- ◆ Hemolytic anemia - next most common - ABO, Rh, infection, cell defects, enzyme defects => all produce jaundice
- ◆ Decreased production - least common in newborn – Sepsis, Maternal drugs - Normal nadir in RBC is at 6-12 wk
- ◆ Hypoplasia or Aplasia are rare in newborns

Causes of Hydrops or Early Neonatal Anemia

- ◆ IDM
- ◆ Acute Blood Loss
- ◆ Hemolytic Anemia
 - Alloimmune (ABO, Rh, etc)
 - Alpha Thalassemia Major
 - G-6-PD
 - Pyruvate Kinase
- ◆ Cardiac disease
 - Arrhythmias
 - Mechanical (eg VSD, subaortic stenosis)
 - Hypoplastic left heart
- ◆ Vascular accidents
- ◆ Chest masses
 - Diaphragmatic hernia
 - Sequestered lung
- ◆ Vascular malformation
 - Of placenta or cord
 - Hemangiomata - liver, other sites, Kasabach-Merritt
- ◆ Infections
- ◆ Trisomy 18, 21, XXX
- ◆ Osteogenesis Imperfecta
- ◆ Marrow infiltration
- ◆ Diamond-Blackfan

Diagnostic Approach to Anemia in the Newborn



Modified From George Buchanan, MD

Bleeding in a Newborn

- ◆ Critical history
 - Pregnancy and delivery
 - Maternal health
 - Given vitamin K?
- ◆ Critical features of exam
 - Is the child ill?
 - Heart, lung and abdominal exam
- ◆ What does the CBC show?

Bleeding in the Newborn

◆ Baby is well

- Swallowed maternal blood
- Vitamin K Deficiency
- Local vascular lesion (GI, abdomen)
- Immune thrombocytopenia
- Hemophilia
- Infection - rubella, CMV, EBV
- Leukemia, marrow aplasia

◆ Baby is sick

- DIC
- Mechanical destruction (Bacterial infection, NEC, pulmonary or heart disease)
- Immune thrombocytopenia
- Liver disease
- Local vascular lesion (ICH - especially in premature)

Hemorrhagic Disease of the Newborn

- ◆ Occurs because of acquired Vitamin K deficiency
 - Vitamin K crosses placenta poorly
 - Begins at 3-5 days of age
 - Is associated with absence of oral feeding and failure to use prophylaxis
 - May be associated with breastfeeding mother who is taking anticonvulsants or anticoagulants (earlier onset)
 - Can occur in children with malabsorption syndromes including NEC, short gut
- ◆ Commonly is mucosal, skin or GI bleeding. May be renal or intracranial (30-60% of HDN have intracranial bleeding)

Thrombosis in the Newborn

- ◆ Coagulation proteins are made by 5-6 weeks gestation
- ◆ At birth,
 - K-dependent factors are 70% of adult values (II, VII, IX, X)
 - Fibrinogen, V, VIII, XIII, and vWF antigen are 170% of adult values
 - Protein C, Protein S, antithrombin III levels are decreased (more variable but 60-80% of adult values)

Thromboses in Newborns

- ◆ Account for the majority of thromboses in children
 - 90% are catheter related – be sure to consider renal vein and portal vein involvement
 - Cerebral and Sinovenous thromboses are next most common
- ◆ LMWH is preferred over unfractionated heparin
 - Superior bioavailability, longer half-life, dose independent clearance, less risk of bleeding or osteoporosis
- ◆ Coumadin is not recommended
 - Variability in K stores, low levels of K-dependent factors already, variable K intake, greater need for frequent testing

Neutropenia in a newborn

◆ Critical history

- Pregnancy and birth - infection risk
- Maternal illness
- Familial neutropenia

◆ Critical features of exam

- Signs of infection or ill appearing
- Limbs, skin, nails, hair

Differential Diagnosis of Neutropenia in the Newborn

Disorder	Relative Frequency	Associated Features
Severe Bacterial Infection	Common	Relative excess of bands and immature forms
Transient – Related to maternal factors	Common	Maternal hypertension or birth asphyxia
Congenital – Ethnic variation Familial benign Kostmann Reticular dysgenesis Cartilage-hair hypoplasia Dyskeratosis congenita	Common Uncommon Uncommon Rare Rare Rare	ANC lower in blacks AD, Differentiate from other forms AR, Low ANC only newborn sign Thymic agenesis, low Ig AR, Short limbs, fine hair, ANC mild X-L, incr pigment, nails, ANC mild
Isoimmune	Rare	Maternal Ab to NA1, NB1; Persists 3-9 months

Thrombocytopenia in the Newborn

- ◆ Uncommon in the NBN - <1% of healthy infants have <150k/cmm in first week of life
- ◆ Common in the NICU – 18-35% will have platelets <150k/cmm
- ◆ More common in ELBW infants –

Christensen RD et al; *J Perinatology* 2006;26:348-353

Platelet Count	Occurrence	Mortality
0-20k/cmm	9%	16.7%
21-50k/cmm	38%	16.4%
51-100k/cmm	77%	19.7%
101-149k/cmm	23%	14.6%

Thrombocytopenia in a Newborn

◆ Critical history

- Pregnancy and birth - infection risk
- Maternal illness and drug history
- Familial thrombocytopenia or other

◆ Critical features of exam

- Hepatosplenomegally
- Anomalies

Causes of Thrombocytopenia in 208 ELBW Infants

Factors identified	Number with	In first 3 days	After DOL 3
Unexplained/Undiagnosed	101	50	51
SGA or PIH	76	55	21
DIC	40	32	8
Bacterial Infection	36	23	13
Fungal Infection	12	7	5
NEC	11	1	10
Genetic *	2	2	0
Thrombus **	1	0	1

* One trisomy 18 and one TAR

** Right atrial thrombus from central catheter

From Christensen RD et al; *J Perinatology* 2006;26:348-353

Causes of Newborn Thrombocytopenia

◆ Decreased production

- TAR
- Megakaryocytic hypoplasia
- Fanconi's anemia
- Leukemia, NB, Histiocytosis
- Wiskott-Aldrich
- X-linked or AR TP

◆ Increased destruction

- Maternal ITP or SLE
- Isoimmune
- Maternal drugs -Thiazudes

- Giant hemangioma (Kasabach-Merritt)
- DIC
- May-Hegglin (AD, giant plts)
- Bernard-Soulier (AR, large plts)

◆ Both decreased production and increased destruction

- Infection - TORCH, HIV
- Osteopetrosis

Immune Thrombocytopenia in the Newborn

	Maternal ITP	Isoimmune TP
Usual Offending Antigen Specificity	“Public Antigens – eg, glycoprotein IIb – IIIa complex	Platelet specific antigen – PLA-1a, 1b or 5a – absent from mother’s platelets
Maternal Platelet Count	Usually reduced but may be normal	Always normal
Therapy with Maternal Platelets	Not indicated	Treatment of choice for symptomatic or bleeding infants

Newborn Platelet Goals

<i>Diagnosis</i>	<i>Bleeding</i>	<i>Desired Count</i>
Term infant	None	>30,000
Premature		
> 34 weeks	None	>30,000
	Oozing	>50,000
< 34 weeks	None	>50,000
	Oozing	>75,000
Ill or septic	None	>75,000
	Oozing	100,000
Post Major Surgery	Gen oozing	100,000

Platelet Transfusion - Factors Affecting Target Platelet Count

- ◆ Patient's baseline platelet count
- ◆ Clinical factors affecting platelet function
 - Acidosis
 - Infection
 - Cardiac or pulmonary disease
 - Giant hemangioma
 - Fever
 - DIC
 - Splenomegally
- ◆ Is patient bleeding?
- ◆ Recent/impending surgery?

Hematologic Diseases in the Newborn

- ◆ Remember transitions in Hgb production
- ◆ Consider mechanical and other issues external to the neonate
- ◆ Responses are mostly for low numbers but don't forget about hyperviscosity
- ◆ Be aware of the high use of EPO by our neonatologists