Neonatal Hematology

Tibor ERTL

Fetal erytropoiesis

Sites of fetal erythropoiesis

- Yolk sac: 2-10. G.W.
- Liver: 10-26. G.W.
- Bone marrow: from the 18. G.W, to the 30. G.W. is the major erythropoietic organ
- At birth: almost all RBCs are produced in the bone marrow, although a low level of hepatic erythropoiesis persists through the first few days of life
- Sites of fetal erythropoiesis are occasionally reactivated in older patients with haematologic disorders

(e.g. myelofibrosis, aplastic anemia, hemolytic anemia)

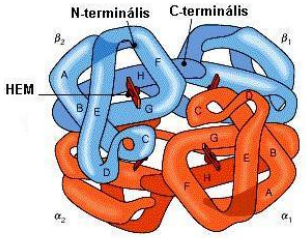
Fetal erytropoiesis
Influencing factors

- EPO: humoral erythropoietic stimulating factor produced by the kidney, controls the RBC production in extrauterin life, it's role in the fetus has not been completely defined, cc. increases directly with period of gestation – levels in term newborns are significantly higher (may reflect some degree of fetal hypoxia during late i.u. life), increased titers in placental dysfunction, fetal anemia, and maternal hypoxia
- Maternal nutritional status is not a significant factor: iron, folate and vit. B12 are trapped by the fetus irrespective of maternal stores

Fetal erytropoiesis

Time of cord clamping

- The cc. of Hb during the first few hours of life increases to values greater than those seen in cord blood: relative increase caused by reduction in plasma volume, absolute increase caused by placental blood transfusion
- The placenta contains approximately 100 ml of fetal blood (30% of the infant blood volume): 25% enters the newborn within 15 seconds of birth, and by 1 minute 50% is transfused!
- The time of cord clamping thus a direct determinant of neonatal blood volume.



Fetal erytropoiesis

Hemoglobin function

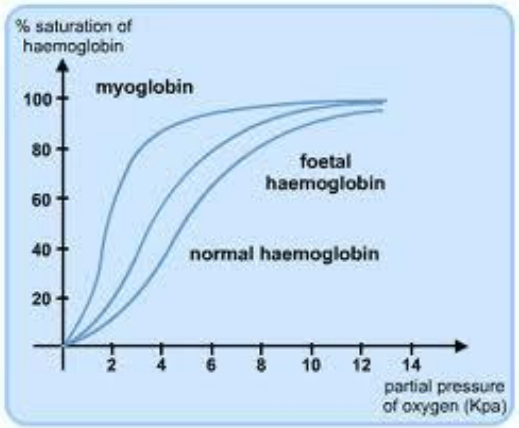
- Fetal Hb: α2γ2 – major Hb in utero

  O_2 affinity is greater than Hb A – advantageous for extractin

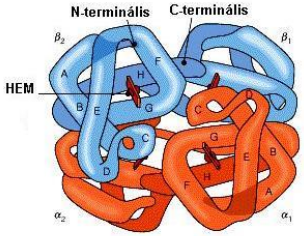
  O_2 from maternal blood within the placenta

- Adult Hb: α2β2 – normal Hb of extauterin life

  an intermediate of RBC metabolism, 2,3-diphosphoglycerate inetracts with HbA to decrease its affinity for oxygen and thereby enhance O2 release

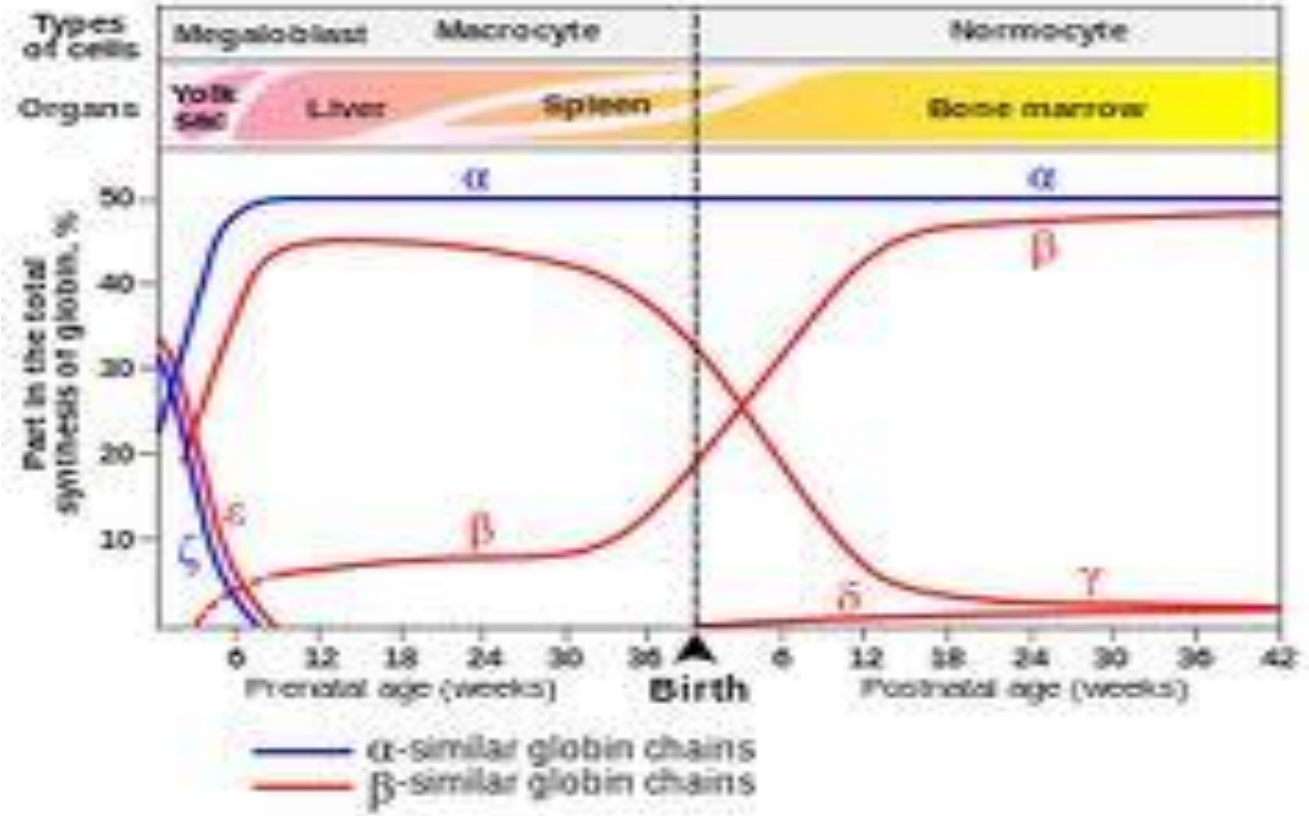


The oxygen dissociation curve



Fetal erythropoiesis

- Changes in the production of globin chains:



Fetal erythropoiesis - RBC physiology

- In utero: the fetal aortic O_2 sat. is 45% (relative hypoxia) - EPO levels are high – RBC production is rapid, signs of active erythropoiesis (nucleated RBCs, increased reticulocytes)

- After birth: O_2 sat. 95 % - EPO is undetectable – RBC production by day 7 is ≤ 1/10th the level in utero (EPO sensor is in the kidney) - nucleated RBCs disappear, reticulocytes decrease less than 1 %

- 8-12. weeks: Hb levels reach their nadir, O_2 delivery to the tissues is impaired, renal EPO production is stimulated, RBC production increases, iron strores are rapidly utilized

- After 12. weeks: Hb level decreases if iron is not supplied

Neonatal physiology

Hematology:

- Hb 17 – 19 g/dl.
- WBC 10 – 30 x 10^3 .
- Plat. 150 – 750 x 10^3.
- Coagulation (acquisition of gut flora).

Normal Values in Newborn period:

Table 5.2: Normal hematological values during the neonatal period of the term infant hemoglobin, hematocrit and RBC count

	Hb (g %)	*Hematocrit (%)*	*RBC (million/mm^3)*
Cord blood ⇦	16.2 ± 3.6	46.66 ± 5.1	4.9 ± 1.2
12-18 hours	18.79 ± 2.8	49 ± 4.8	5.3 ± 0.8
72 hours	17.38 ± 3.0	46.9 ± 5.3	5.2 ± 0.6
7 days ⇦	17.0 ± 2.4	45.0 ± 4.0	5.0 ± 1.1
15 days	16.36 ± 2.2	43.4 ± 4.1	5.01 ± 0.9
20 days	14.17 ± 2.4	42.1 ± 3.8	4.7 ± 1.0

Etiology of anemia in the neonate

- Blood loss: fetomaternal bleeding, TTTS, abruptio placentae, placenta praevia, intracranial bleeding, cephalhaematoma, ruptured liver or spleen, adrenal haemorrhage etc.
- Hemolysis: immune (RH, ABO incompatibility), hereditary RBC disorders (membrane defects, metabolic defects, hemoglobinopathies), aquired
- Diminished RBC production e.g. Blackfan-Diamond syndrome, infections, physiologic anemia, anemia of prematurity
- Vitamin E , and iron deficiency
  after 1 month!

Etiology of physiologic anemia

- 1. with the onset of respirations: more O_2 is available for binding to Hb - the Hb O_2 sat. increases to 95 % or more – switch from F Hb to A Hb synthesis – increase in blood O_2 content and tissue O_2 delivery downregulates EPO production – erythropoiesis is suppressed
- 2. dilution effect: during the postnatal rapid growth, the plasma volume increases in a higher rate, than the RBC mass.

Physiologic anemia

- **Normal venous cc. of Hb** at birth:
  - in term infants: 160-180 g/l (Htc: 55%),
  - in premature babies: 150-160 g/l (Htc: 50%).
- Shortly after birth cc. of Hb increases (caused by reduction in plasma volume), during the first week identical, than gradually decreases.
- **Nadir of Hb level:**

  in term neonates: at 2-3 months: Hb: 110-120 g/l,

  in preterm infants: 1,5-2 months: Hb: 70-90 g/l,

  in ELBW infants (<1000 g): 1-6. weeks: 65-90 g/l.
- **With the onset of respirations:** more O_2 is available for binding to Hb - the Hb O_2 sat. increases to 95 % or more – switch from F Hb to A Hb synthesis – increase in blood O_2 content and tissue O_2 delivery downregulates EPO production – erythropoiesis is suppressed
- **Dilution effect:** during the postnatal rapid growth, the plasma volume increases in a higher rate, than the RBC mass.

Isoimmun hemolytic anemia

Major cause of hydrops in the past
→HYDROPS: generalized edema + ascites + pericardial + pleural fluids

Etiology: maternal exposure to fetal antigens on RBCs → production of antibodies passing the placenta → immune destruction of fetal RBCs

Incidence of Rh isoimmunisation declined since the use of RhoGAM, → ABO incombatibility (O-mother + A-neonate)

Management:
- Early delivery or intrauterine transfusion
- 50% of infants with direct Commbs positivity
  require no treatment or only phototherapy
- 25% of infants present with severe anaemia,
  hyperbilirubinemia, consequent reticulocytosis

→ Early exchange transfusion

Anemia of prematurity = is an exaggeration of the normal physiologic anemia

- **Causes:** iatrogenic phlebotomy for laboratory tests, decreased RBC survival, relatively more rapid rate of growth in comparison with term infants
- **Characteristics:** normochrom, normocyter, reticulopenia, bone marrow hypoplasia, low Se EPO level, relatively full iron stores
- **Symptoms:** often asymptomatic, apnoe, tachycardia, tachypnoe, poor feeding
- **Hb value:** 60-80 g/l
- **Later:** Vitamin E deficiency, iron deficiency

Therapy of anemia = transfusion?

- Controversies: systemic O_2 transport improves, but side effects, oxidative diseases!!!
- Prophylaxis:
  - Delayad cord clamping
  - Cord „stripping”
  - Autolog placental transfusion
  - Reducing phlebotomy losses
  - Recombinant human erythropoietin therapy
  - Sufficient nutrition
  - Strict criteria for transfusion
- Volume: 15-20 ml/kg/3-4 hour

Transfusion guideline in neonates

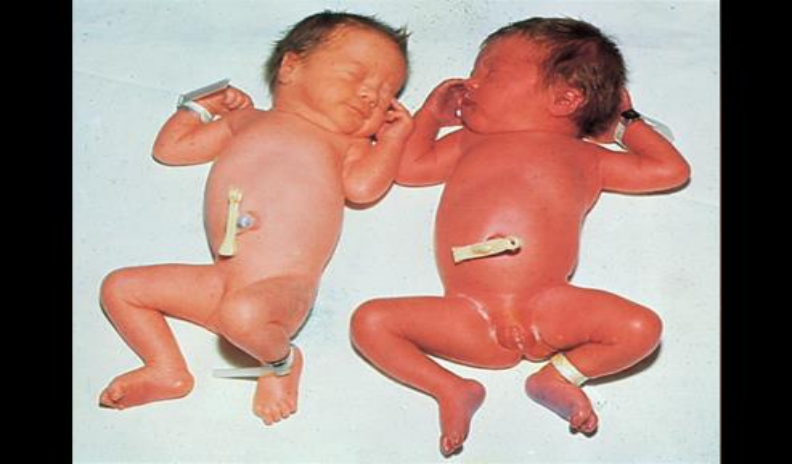
- **In case of mechanical ventilation:**
  - < 28 day, FiO_2>0,3: Hb<120g/l, Htc<40%
  - < 28 day, FiO_2<0,3: Hb<110g/l, Htc<35%
  - > 28 day: Hb<100g/l, Htc<30%
- **In case of CPAP treatment:**
  - < 28 day: Hb<100g/l, Htc<30%
  - > 28 day: Hb<80g/l, Htc<25%
- **In case of spontaneous breathing:**
  - FiO_2>0,21: Hb<80g/l, Htc<25%
  - FiO_2=0,21: Hb<70g/l, Htc<20%

Correction of hypovolaemia: urgent transfusion (20 mL/kg) of physiological saline, a "volume expander" or reconstituted blood (if available).

Correction of anaemia: (unless reconstituted blood has been used to correct the hypovolaemia, restore the haematocrit [Hct] to about 0.35 without giving more than 20 mL/kg) transfuse packed red cells (PRC) according to the following formula:

$$\text{PRC (mL)} = \frac{\text{desired Hct} - \text{observed Hct}}{\text{PRC Hct}} \times \text{NBV}$$

NBV: neonate's blood volume.



Polycythemia

- Definition: venous Htc>65%, Hb>220 g/l
- Incidence: 0,4-5,0 %, more common in SGA and post-term babies
- Pathophysiology: as the central Htc rises, there is increased viscosity and decreased blood flow, when the Htc increases to > 60 %, there is a fall in oxygen transport. Newborns RBCs are less deformable than RBCs of adults. As viscosity increases, there is impairment of tissue oxygenation and decreased glucose in plasma, and a tendency to form microthrombi.

Clinical findings of polycythemia/hyperviscosity

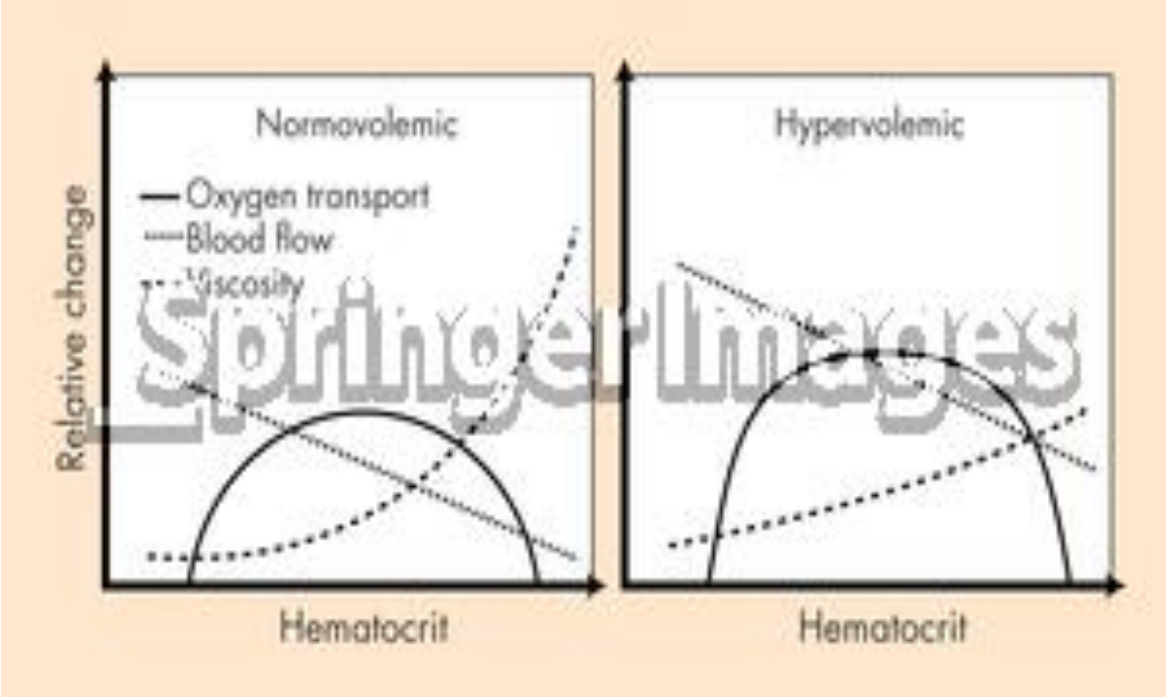
- Often asymptomatic
- Common, non-specific symptoms:
  - **CNS:** apnoe, tremors, seizures, poor feeding, hypotonia, cerebral venous thrombosis
  - **Cardiorespiratory:** tachypnoe, cyanosis, heart murmurs, elevated pulm. vasc. resist., cong. heart failure
  - **Renal:** decreased glomerular filtration, renal vein thrombosis
  - **Other:** hypoglycemia, hypocalcemia, NEC, tctpenia, hyperbilirubinemia

Causes of polycythemia

- Placental RBC transfusion: delayed cord clamping, cord stripping, TTTS, materno-fetal tr., holding the baby below the mother at delivery etc.
- Placental insufficiency: (increased fetal erythropoiesis secondary to chronic i.u. hypoxia): SGA, maternal hypertension syndromes, postmature infants, smoking, infants born to mothers with chr. hypoxia
- Other conditions: IDM, LGA, Down syndrome, maternal drugs e.g. propranolol, dehydration

Hyperviscosity

- The relationship between Htc and viscosity is nearly linear below a Htc of 60%, but viscosity increases exponentially at a Htc of 70 % or greater.



Management of polycythemia

- Symptoms + venous Htc ≥ 65 %: partial exchange transfusion
- Asymptomatic infants+ venous Htc 60-70%: increasing fluid intake (infusion) and repeating the Htc in 4 to 6 hours
- Asymptomatic infants + Htc ≥ 70%: partial exchange transfusion?
- Partial exchange transfusion: with normal saline or 5 % albumin, goal: Htc: 55-60%
- Volume of exchange in ml: 15-20 ml/kg
  blood volume (ml) x (actual Htc-desired Htc)/actual Htc

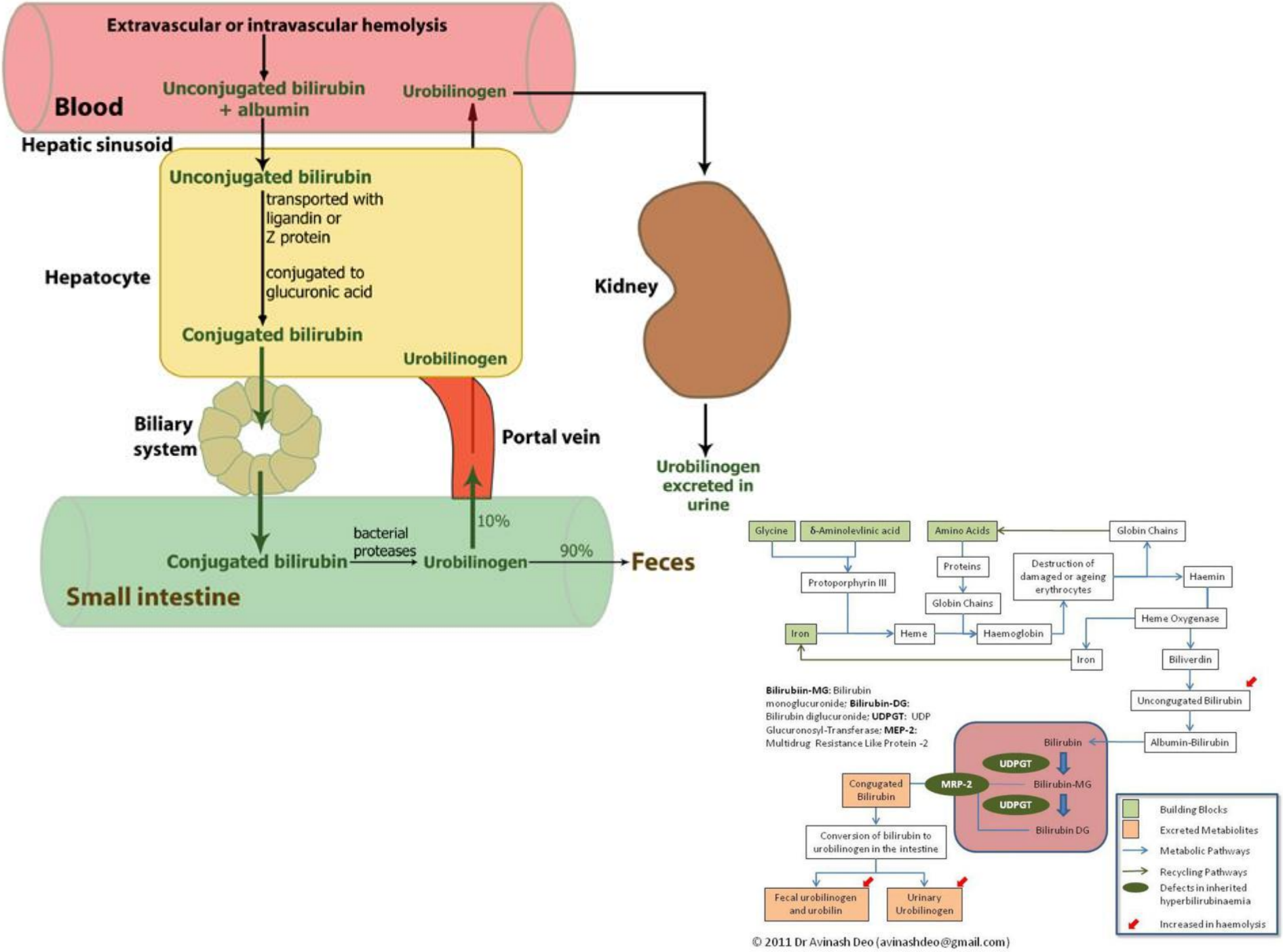
  (blood volume = 80-100 ml/kg)

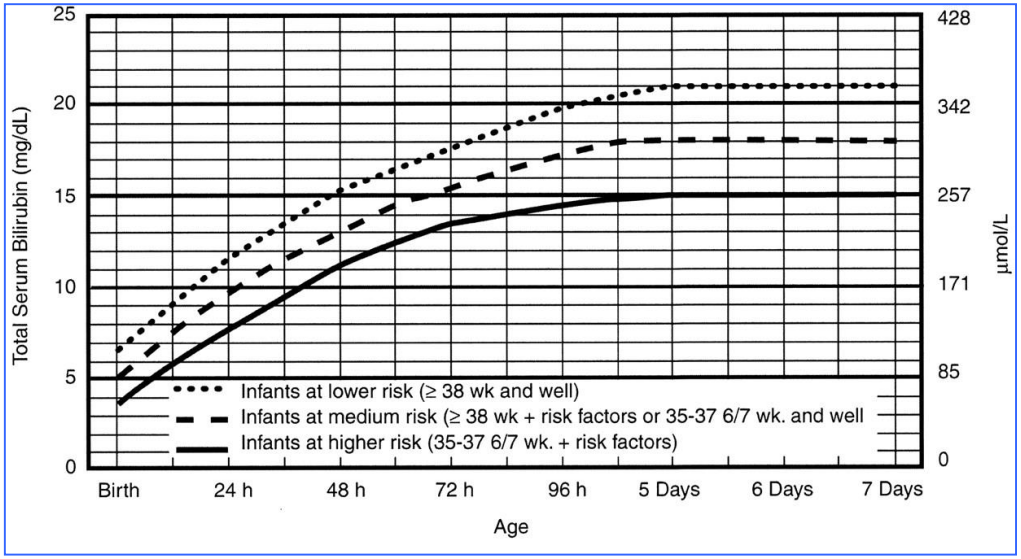
Jaundice

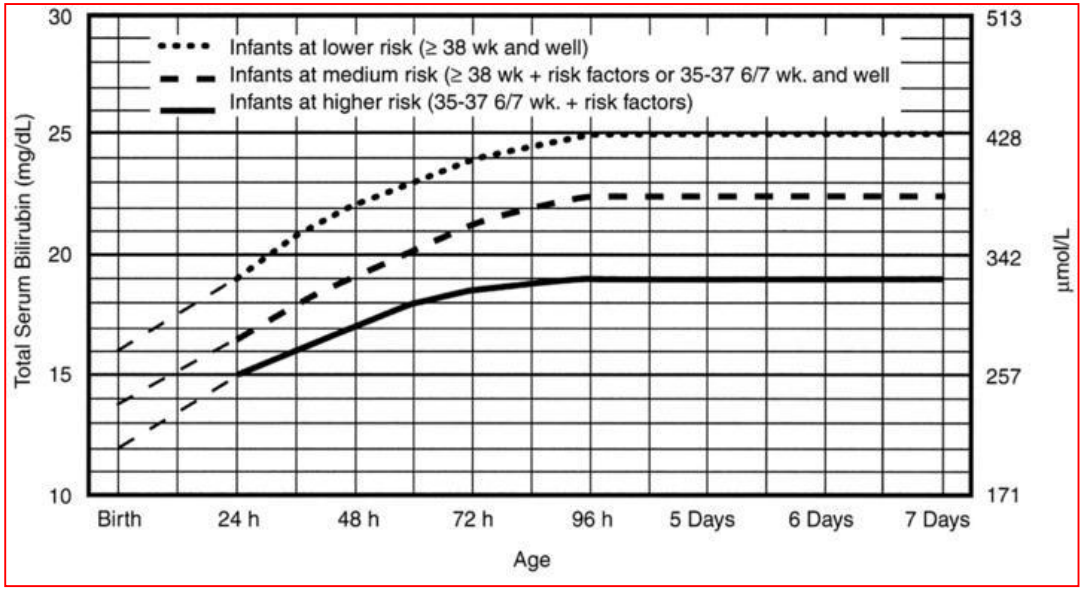
> 7mg/dl serum bilirubin level
Physical examination is not reliable!
→ transcutanous
→ laboratory measurement
progresses in cephalocaudal direction

Physiologic hyperbilirubinemia

- ≤ 12 mg/dl (204 umol/l)
- Starts to fall on day 4
- Causes: increased bilirubin production
  defective uptake
  defective conjugation
  decreased hepatic excretion
- No intervention needed!




Total Serum Bilirubin (mg/dL)
25
20
15
10
5
0
428
342
257
171
85
0
µmol/L
Infants at lower risk (≥ 38 wk and well)
Infants at medium risk (≥ 38 wk + risk factors or 35-37 6/7 wk. and well
Infants at higher risk (35-37 6/7 wk. + risk factors)
Birth
24 h
48 h
72 h
96 h
5 Days
6 Days
7 Days
Age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24 h
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96 h
5 Days
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7 Days
Age

Nonphysiologic hyperbilirubinemia

- Onset of jaundice before 24 hours of age
- Any elevation in serum bilirubin levels requiring phototherapy
- Rapid elevation of serum bilirubin
- Signs of underlying illness
- Persisting jaundice

Examination:
- family history (hemolytic anemia, liver disease)
- physical examination
- blood tests: →blood type
  direct Coombs, antibody screen
  peripheral smear, reticulocyte number
  hematocrit
  cultures

Classification of Neonatal Hyperbilirubinemia Based on Mechanism of Accumulation

Increased bilirubin load

Hemolytic causes

- Characteristics: increased unconjugated bilirubin level, >6 percent reticulocytes, hemoglobin concentration of <13 g per dL (130 g per L)
- Coombs' test positive: Rh factor incompatibility, ABO incompatibility, minor antigens
- Coombs' test negative: red blood cell membrane defects (spherocytosis, elliptocytosis), red blood cell enzyme defects (G6PD deficiency, pyruvate kinase deficiency), drugs (e.g., sulfisoxazole acetyl with erythromycin ethylsuccinate (Pediazole), streptomycin, vitamin K), abnormal red blood cells (hemoglobinopathies), sepsis

Nonhemolytic causes

- Characteristics: increased unconjugated bilirubin level, normal percentage of reticulocytes
- Extravascular sources: cephalohematoma, bruising, central nervous system hemorrhage, swallowed blood
- Polycythemia: fetal-maternal transfusion, delayed cord clamping, twin-twin transfusion
- Exaggerated enterohepatic circulation: cystic fibrosis, ileal atresia, pyloric stenosis, Hirschsprung's disease, breast milk jaundice

Decreased bilirubin conjugation

- Characteristics: increased unconjugated bilirubin level, normal percentage of reticulocytes
- Physiologic jaundice
- Crigler-Najjar syndrome types 1 and 2
- Gilbert syndrome
- Hypothyroidism
- Breast milk jaundice

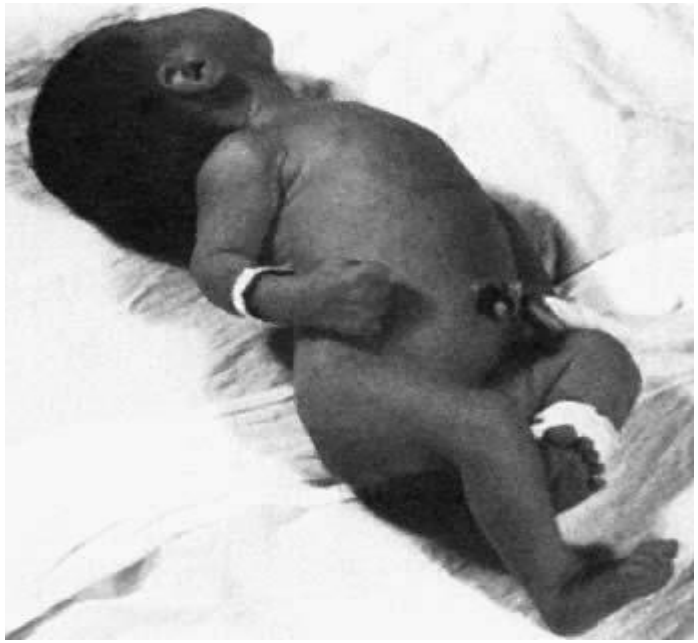
Impaired bilirubin excretion

- Characteristics: increased unconjugated and conjugated bilirubin level, negative Coombs' test, conjugated bilirubin level of >2 mg per dL (34 µmol per L) or >20% of total serum bilirubin level, conjugated bilirubin in urine
- Biliary obstruction: biliary atresia, choledochal cyst, primary sclerosing cholangitis, gallstones, neoplasm, Dubin-Johnson syndrome, Rotor's syndrome
- Infection: sepsis, urinary tract infection, syphilis, toxoplasmosis, tuberculosis, hepatitis, rubella, herpes
- Metabolic disorder: $alpha_1$ antitrypsin deficiency, cystic fibrosis, galactosemia, glycogen storage disease, Gaucher's disease, hypothyroidism, Wilson's disease, Niemann-Pick disease
- Chromosomal abnormality: Turner's syndrome, trisomy 18 and 21 syndromes
- Drugs: aspirin, acetaminophen, sulfa, alcohol, rifampin (Rifadin), erythromycin, corticosteroids, tetracycline

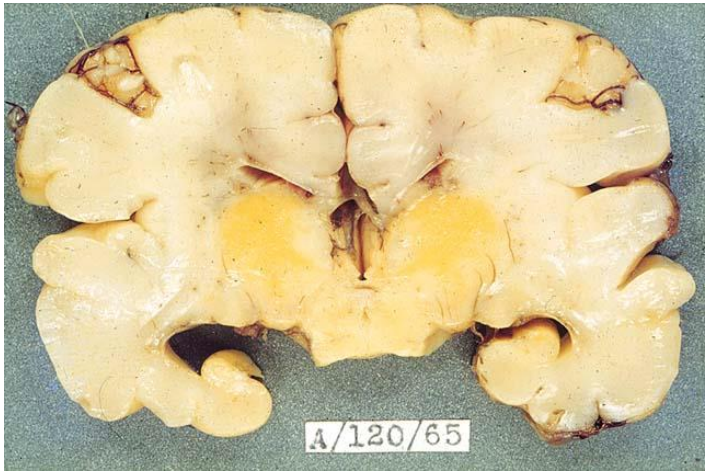
Bilirubin toxicity

Effects of Bilirubin Toxicity in Newborns

Early	Late	Chronic
Lethargy	Irritability	Athetoid cerebral palsy
Poor feeding	Opisthotonos	High-frequency hearing loss
High-pitched cry	Seizures	Paralysis of upward gaze
Hypotonia	Apnea	Dental dysplasia
	Oculogyric crisis	Mild mental retardation
	Hypertonia	
	Fever	



KERNICTERUS



Therapy of unconjugated hyperbilirubinaemia

Irradiation with light near the maximum

adsorbtion peak of bilirubin (450-460 nm)

→unconjugated bilirubin is turned into watersoluble byproducts, which can be excreted with the urine

Side effects:

insensible water loss
redistribution of blood flow
watery diarrhea (bile salts in stool)
tanning, „bronze-baby” syndrome
retinal damage

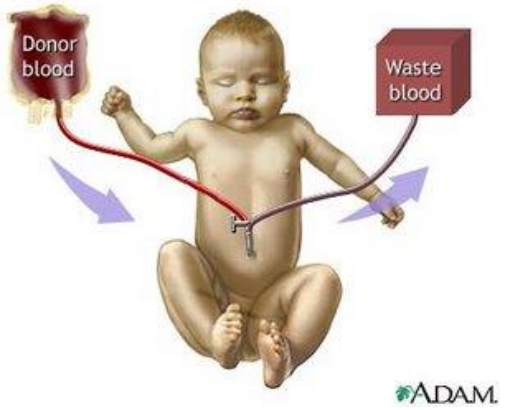
Further therapy – Exchange transfusion

Removal of partially hemolyzed
+ antibody coated RBCs
+ unattached antibodies
+ bilirubin.
Replacement of uncoated RBCs.

Indication
→ phototherapy ineffective
→ to correct anemia
→ stop hemolysis by removing antibodies

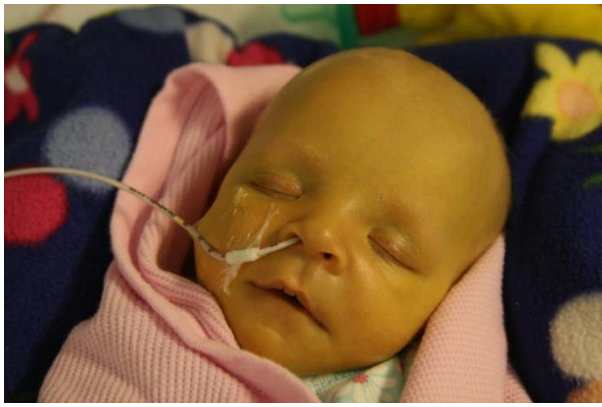
Exchange transfusion is usually performed with the double volume of the infants blood.
2x 80ml/kg irradiated reconstituted whole blood

Complications:
- changes of glucose and electrolyte levels
- cardiovascular complications
- bleeding, infection



Isovolumetric
push-pull etchnique

Direct hyperbilirubinemia



Definition: CB> 2mg/dl or >15% of TB

Symptoms: greenish jaundice, hepatosplenomegaly, dark urine and pale stools

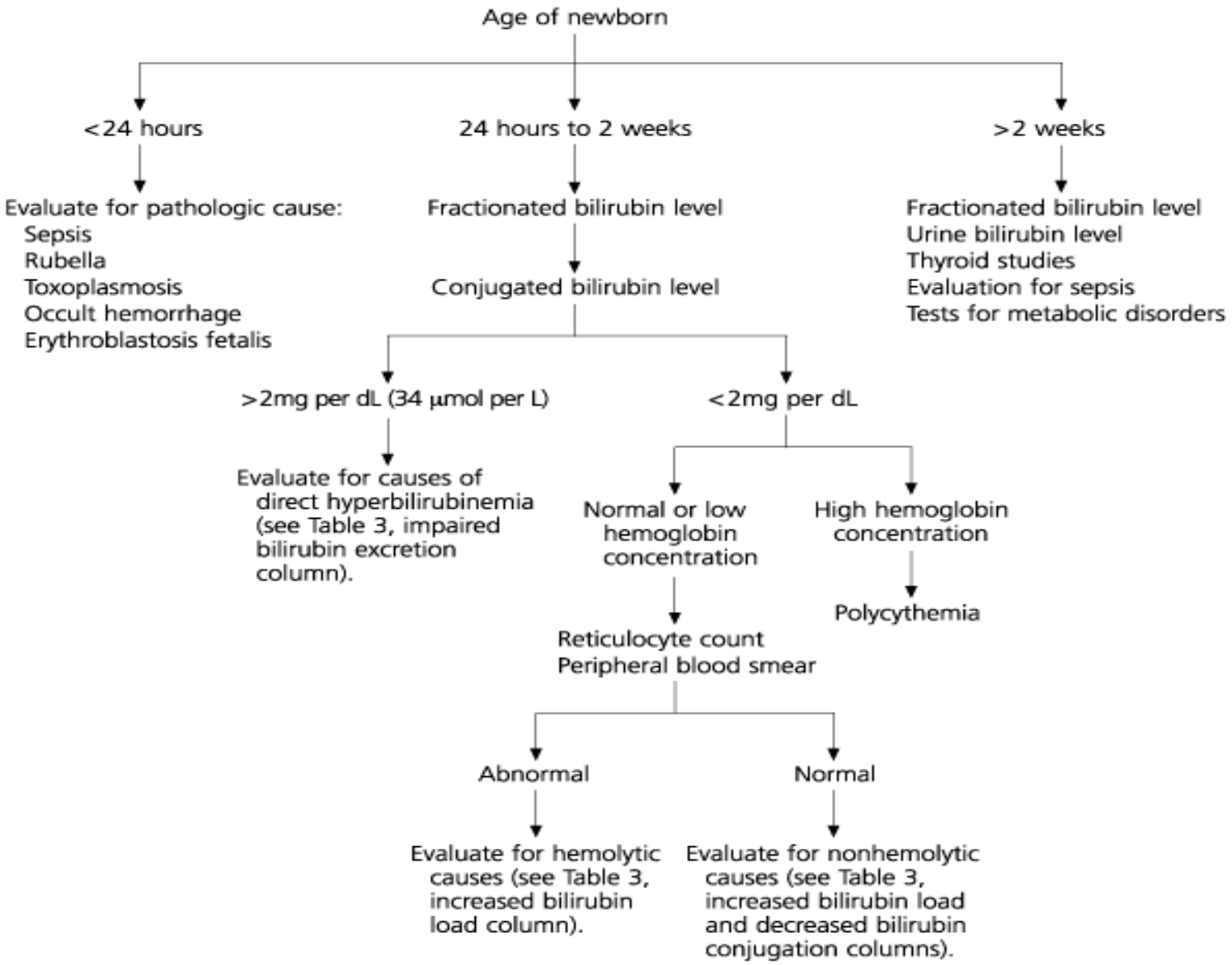
Pathogenesis:

Liver cell injury:	- intravenous hyperalimnetation - viral, bacterial or parasitic infection - metabolic disorders
Bile flow obstruction:	- extrahepatic - intrahepatic

Further evaluation:

- laboratory tests
- ultrasound
- laparotomy / biopsy

Evaluation of nonphysiologic hyperbilirubinaemia



Bleeding

- Transitory deficiency of the vit. K –depenedent factors (II., VII., IX., and X.) = Haemorrhagic disease of the newborn
- Disturbances of clotting e.g. DIC due to infection, sepsis, asphyxia, hypoxia
- Inherited abnormalities of clotting factors

Haemorrhagic disease of the newborn

= neonatal transitory vitamin K deficiency

- Newborn infants are born with few amount of vit. K, because of negligible placacental transport.
- The blood levels of procoagulant vit. K - dependent factors (II, VII, IX, X) decrease to the 5-8% of normal value in a few days.
- By day 2 or 3 bleeding can occur if the babies are not supplemented with vit. K.

Haemorrhagic disease of the newborn

„Early” type

- Symptoms: 2-3 days of age bleeding after vein puncture, bleeding of the umbilicus, growing cephalhematoma, melaena, hematemesis, rarely intracranial haemorrhage
- Bleeding in the first 24 hours: if the mother received vit. K antagonist drugs e.g. phenytoin, phenobarbital, salycilates
- Differential dg.: melaena spuria, GI tract malformations
- Prophylaxis: at birth: term infants: 2 mg Konakion (vit. K1) orally, premature infants: 1 mg Konakion iv.
- Treatment: 2-5 mg Konakion iv., FFP (replaces the clotting factors immediately), in case of melaena oral feeding holding up!

Haemorrhagic disease of the newborn
„Delayed”

- At 2-12 weeks of age
- In breast-fed infants, who are not receiving supplementation
- In case of enterocolitis, broad-spectrum antibiotic treatment and infants with malabsorption (liver disease, CF)
- Prophylaxis: 2 mg Konakion orally/week

IDIOPATHIC THROMBOCYTOPENIA

Idiopathic thrombocytopenic purpura (ITP) is seen in approximately 1 to 2 per 1000 live births and is an immune process in which antibodies are directed against platelets.

Platelet-associated IgG antibodies can cross the placenta and cause thrombocytopenia in the fetus and newborn.

The severely thrombocytopenic fetus is at increased risk for intracranial hemorrhage.

IDIOPATHIC THROMBOCYTOPENIA

Postnatal management involves observation of the infant's platelet count.

For infants who have evidence of hemorrhage, single- donor irradiated platelets may be administered to control the bleeding.

The infant may benefit from an infusion of intravenous immunoglobulin. Neonatal thrombocytopenia usually resolves within 4 to 6 weeks.