NEONATAL JAUNDICE

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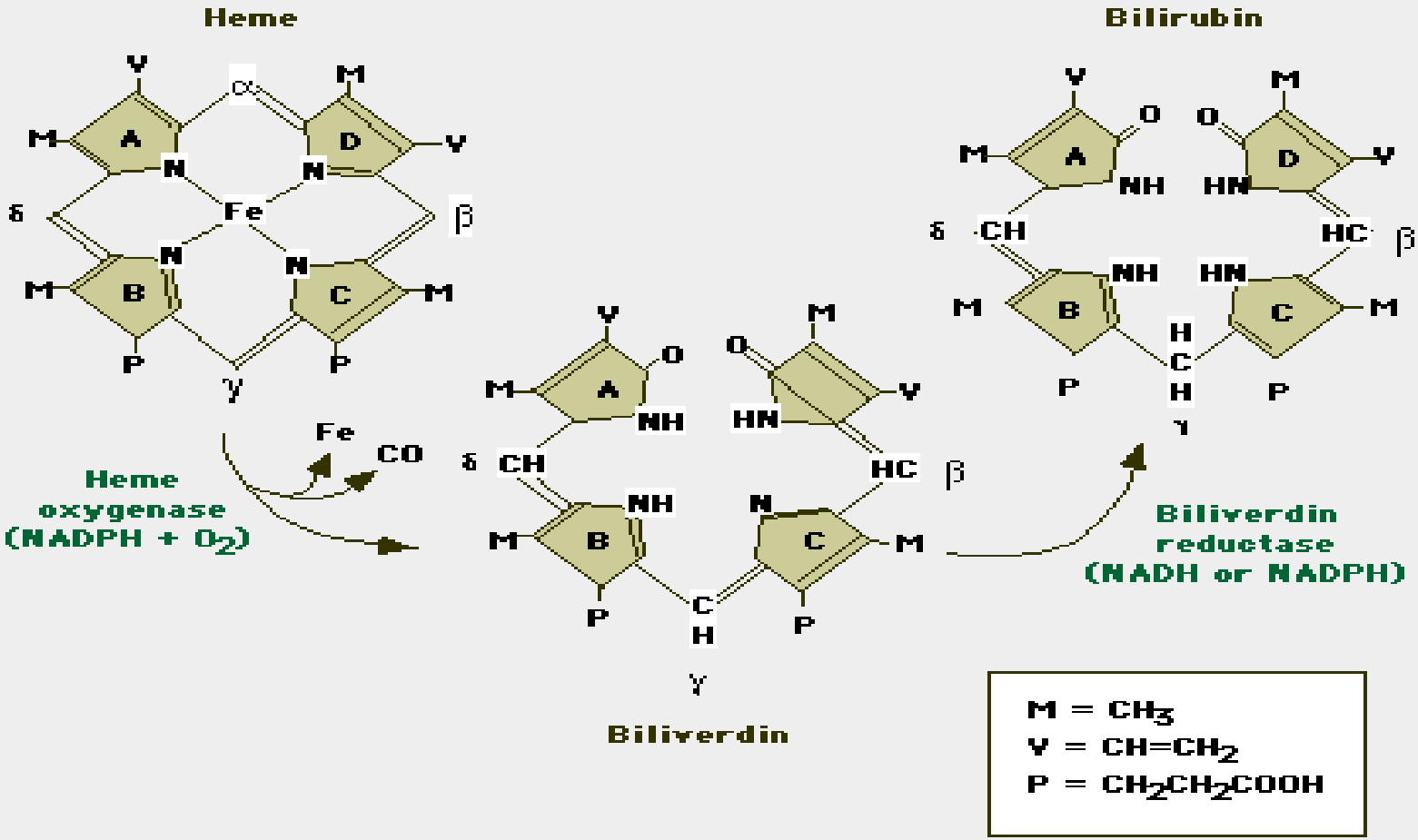
Overview

- Neonatal Hyperbilirubinemia
- Bilirubin Production & Metabolism
- Etiologies & Types
- Diagnosis
- Management
- Complications

Neonatal Hyperbilirubinemia

- Definition = Total serum bilirubin (TSB) > 5 mg/dL
- Significance
  - Present in up to 60% of term newborns
  - Severe complications possible

Where does Bilirubin Come From?

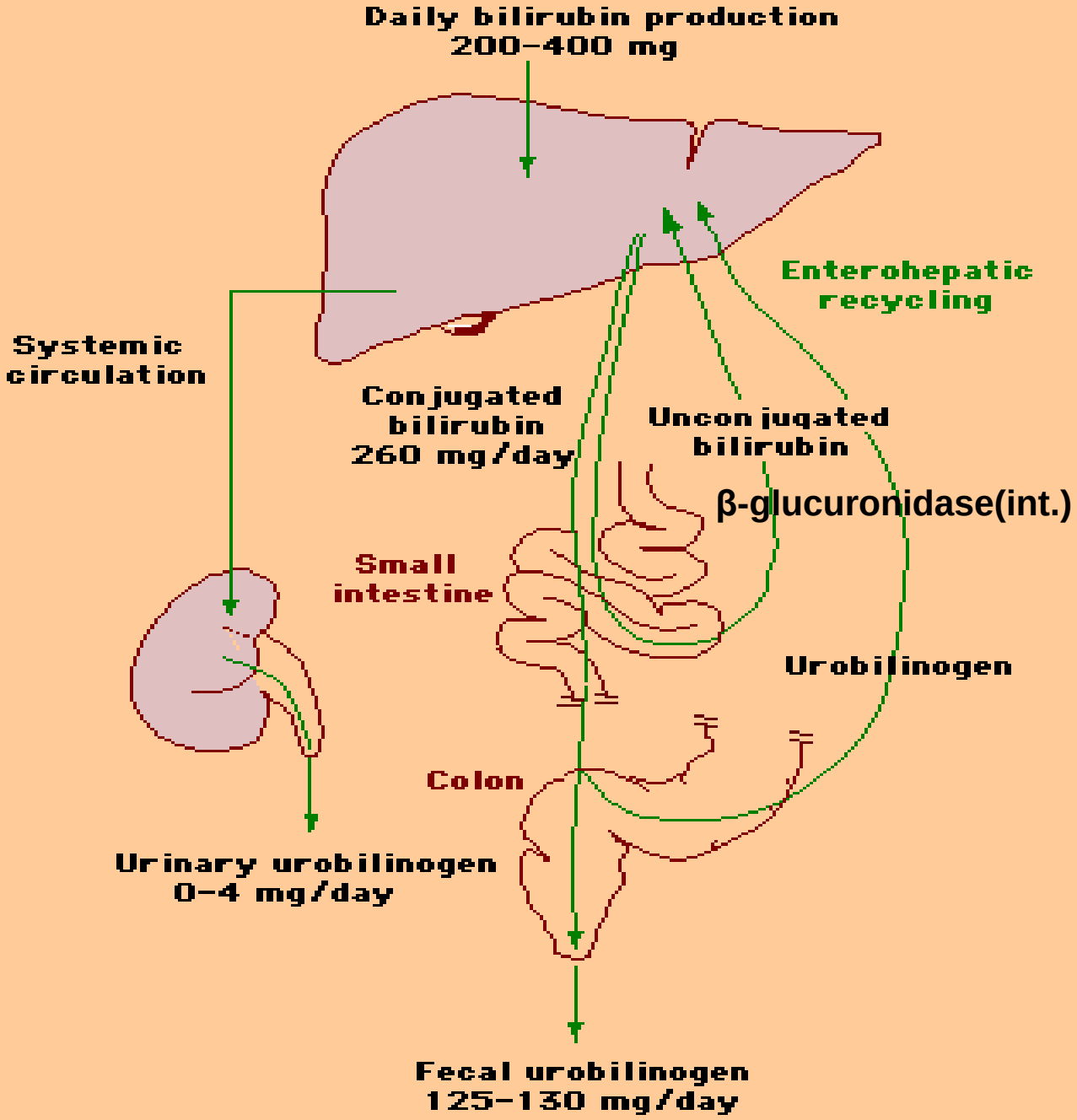


Bilirubin synthesis Conversion of heme to biliverdin and then bilirubin. Heme ring-opening at the alpha-carbon bridge of heme is catalyzed by heme oxygenase, resulting in the formation of biliverdin. This is followed by reduction of biliverdin to bilirubin in a reaction catalyzed by biliverdin reductase.

How do we get rid of bilirubin?

- Unconjugated Bilirubin (In Plasma)
  - Not water soluble - Bind to Albumin
  - Not excretable - Not polar
  - Associated with toxic effects of bilirubin Crossing BB Barrier
  - InDirect reaction to Diazo (diazo sulfanilic acid)
- Bilirubin conjugation (In Bile)
  - Occurs in liver - Polar
  - Makes bilirubin water soluble and excretable
  - Achieved by adding glucuronic acid to bilirubin
  - Enzyme is UDP-Glucuronyl transferase
  - Not crossing BB Barrier
  - direct reaction to Diazo

Enterohepatic and Systemic Circulation of Bilirubin and its Metabolites in Adults



Etiologies

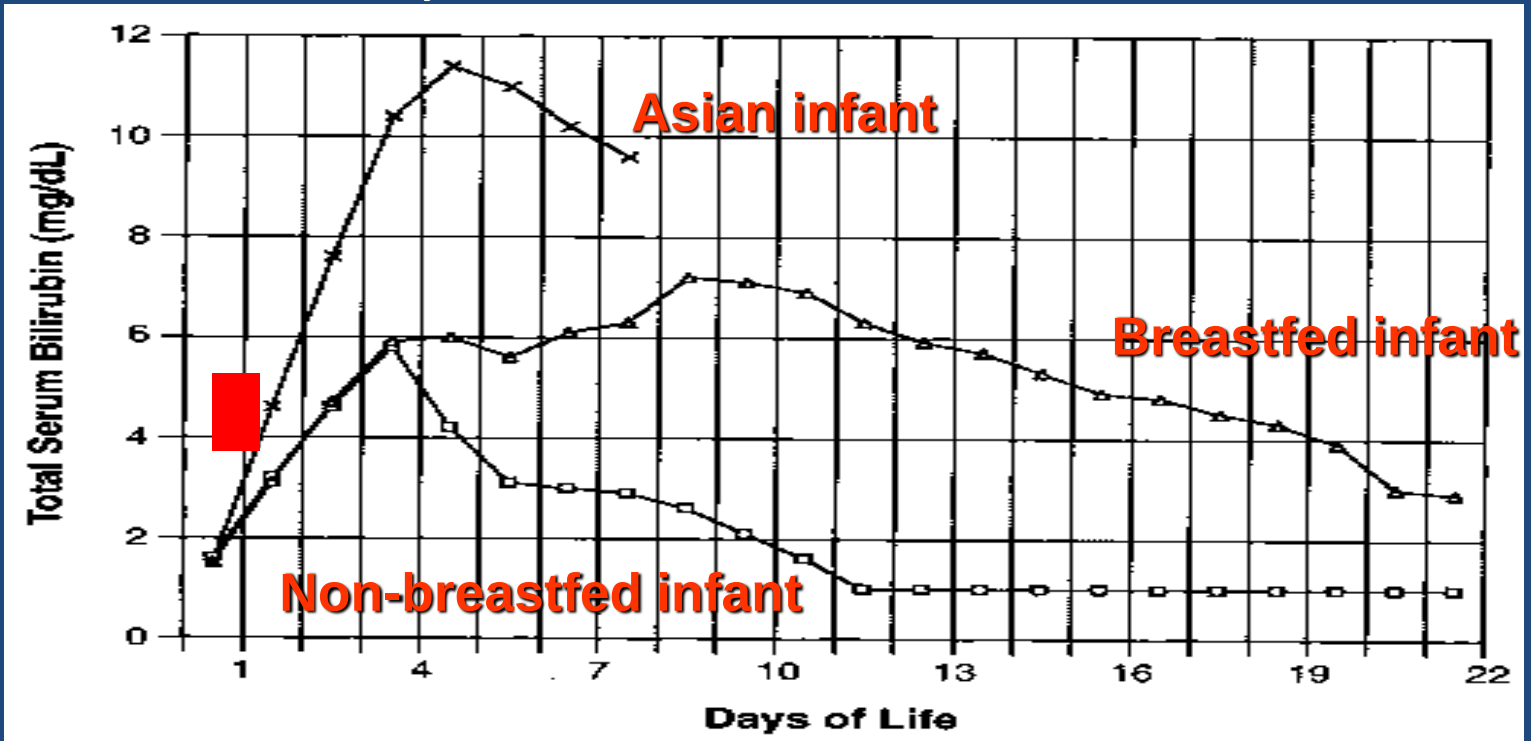
- Benign
  - Physiologic
  - Breast Milk
  - Breastfeeding
- Pathologic
- NON Hemolytic
- Hemolytic
  - ……
  - ……
  - ……
- NON Hemolytic
  - ……
  - ……
- Hemolytic
  - ……
  - ……

Physiological Jaundice

- Affects nearly all newborns
- Factors responsible:
  - Increased Bilirubin production
    - Due to bulky breakdown of fetal RBCs
    - Limited ability for Enz. conjugation in NB liver
    - Shorter life span of fetal RBCs
- Jaundice may be seen by 48-96 hrs (2^{nd} – 4^{rd} day)
- Peak level typically 10-12 mg/dl……./
- Does not exceed 17-18 mg/dl

Physiologic Jaundice

- Risk factors that exaggerates Phy. jaundice:
  - ❑ Breast Feeding - Weight Loss
  - ❑ Family H/o jaundice - Delayed BM
  - ❑ Prematurity



Breast Feeding Jaundice

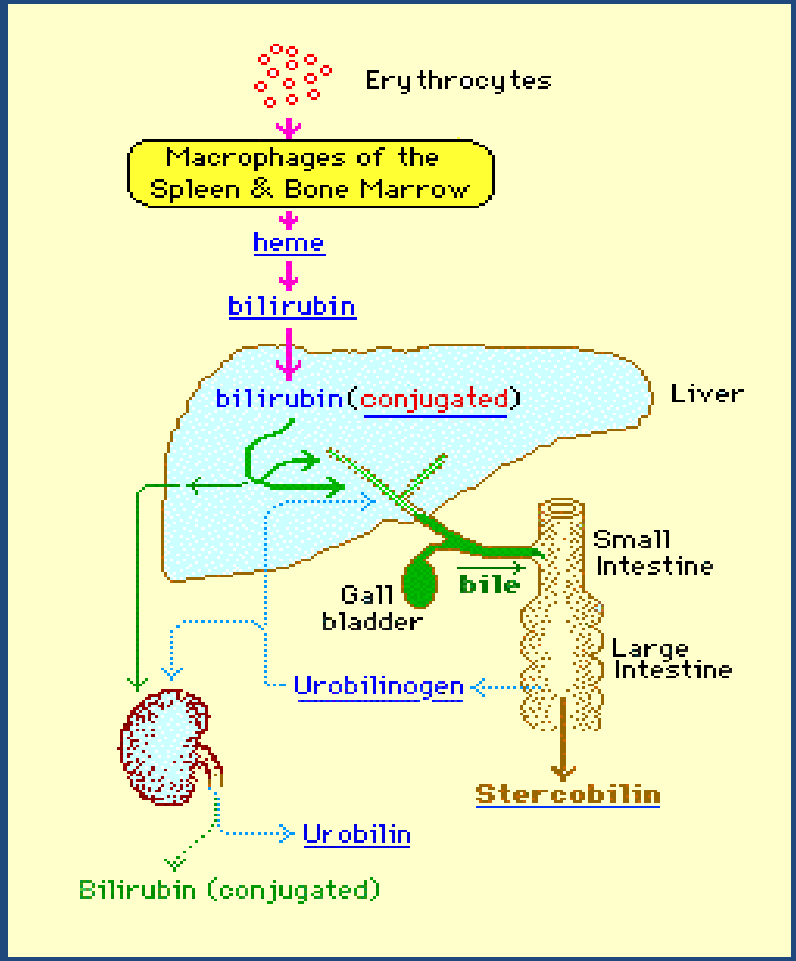
- Gradual increase in bilirubin
  - Presentation toward end of first week of life
- Clues are all in the feeding history
- No reported case of kernicterus(?) in healthy term infants
  - Even with levels of up to 30
  - **However, you must treat!?**

Breast Milk Jaundice

- Elevated unconjugated Bilirubin
- Prolongation of physiologic jaundice
    - 66% of breastfed babies jaundiced into 3rd week of life
    - May persist up to 3 months
- Average max TSB = 10-12 mg/dL
- TSB may reach 22-24 mg/dL
- ?Milk factor

Pathologic Jaundice

- Features
  - **Jaundice in 1st 24 hrs**
  - Rapidly rising TSB (> 5 mg/dL per day)
  - TSB > 17 mg/dL
- Categories
  - Increased Bilirubin load
  - Decreased conjugation
  - Impaired Bilirubin excretion



Increased Bilirubin Load

- Elevated unconjugated bilirubin

❑ Hemolytic Disease

elevated reticulocytes, decreased Hgb (smear)

– Coomb's (+) Rh incompatibility, ABO incompatibility, minor antigens

– Coomb's (-) G6PD, spherocytosis, etc.

❑ Non-hemolytic Disease

– Features: normal reticulocytes

– Extra vascular sources – I.e. Cephalhematoma Polycythemia - Exaggerated enterohepatic circulation – I.e. CF

Differential Dx for Pathologic Indirect Hyperbilirubinemia

- **Hemolytic disease**
  - Rh & Blood group incompatibility
  - Red cell membrane defects (her.spherocytosis etc)
  - Enzyme defects (G6PD)
- **Infection**
  - Sepsis or UTI
- **Cephalhematoma/Bruising**

Differential Dx for Pathologic Indirect Hyperbilirubinemia

- **Polycythemia**
  - Infant of diabetic mother
  - Fetal transfusion
  - Delayed cord clamping

- **Miscellaneous**
  - Hypothyroidism
  - Hypoxia (Birth asphyxia)
  - Acidosis

Differential Dx for Pathologic Indirect Hyperbilirubinemia

- **Decreased Conjugation**
  - Criggler Najjar, Gilbert Disease
    - Deficiency of UGT (UDP Glucuoronyltransferase)
- **Breast Milk Jaundice**
- **Congenital infection (TORCH)**

Recommended work up for Hyperbilirubinemia

- Total and Direct Bilirubin
- Baby Blood group and Coombs test
  - to determine risk of incompatibility
- Mother Blood group
- Serum albumin (optional)
  - Low level may lower threshold for intervention
- CBC with diff
  - **Anemia**/ Polycythemia , signs of infection
  - Urine exam. & C/S

Recommended work up for Hyperbilirubinemia (Diagnosis)

- **Smear for red cell morphology**
  - Membrane defects
  - ABO incompatibility

  } Spherocytes in PBS

- **Reticulocyte count**
  (Evidence of red cell destruction)

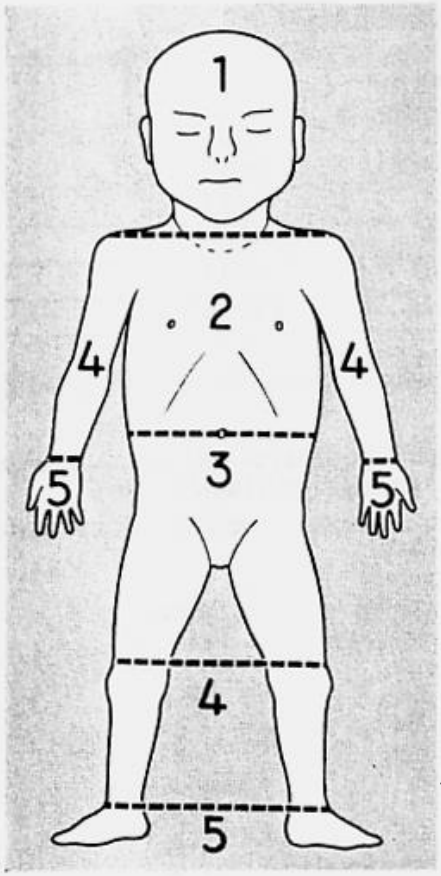
- **G6PD (enzyme level)**
  - if suggested by ethnic background
  - or poor response to Photo.

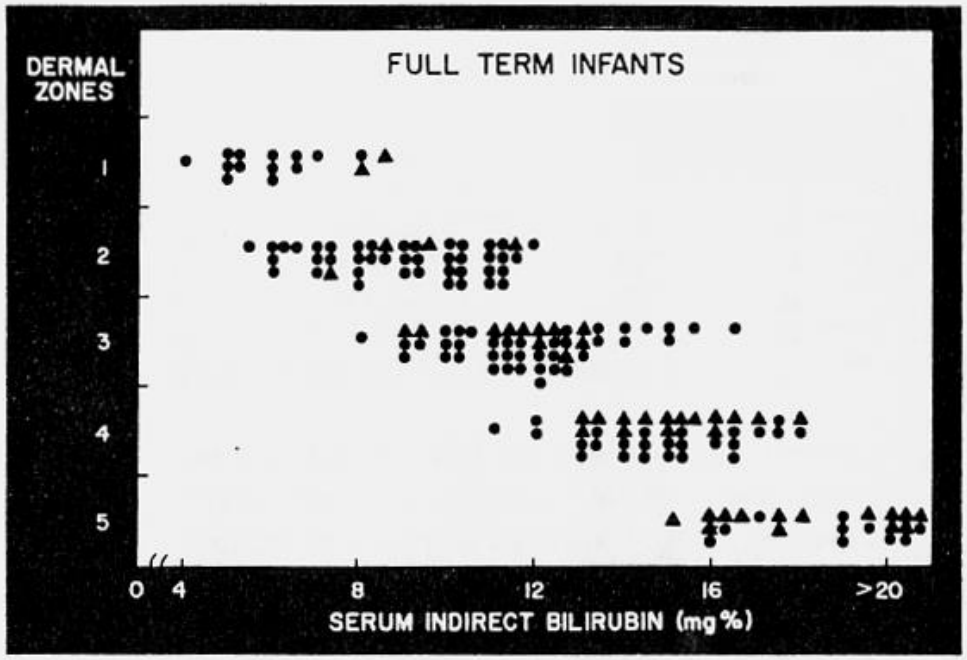
Evaluation of Hyperbilirubinemia

- Feeding history critical
- Assess breastfeeding by
  - Sucking, swallowing, satisfaction, decrease in breast size
  - Stools (color and frequency)
  - Urine output
  - Weight loss (<10% at 5-7 days)

Evaluation of Hyperbilirubinemia

- Head to Toe progression: Is it reliable?





LI Kramer. AJDC. 1969;118:454-458

Indications for Work up of Jaundice

- **Jaundice in 1st 24 hrs**
- **Jaundice excessive for pt's age**
- **Infant receiving PTX or bili rising rapidly and unexplained by history**
- **Jaundice present at or beyond 3 wks, or sick infant**

- Bili approaching exchange levels or not responding to PTX

Prolonged Neonatal Jaundice

- Jaundice persists more than 3 weeks
- Causes:
  - Breast milk jaundice
  - UTI
  - Hypothyroidism
  - crigler-najjar syndrome
  - Conjugated Hyperbilirubinemia

ABO Incompatibility

- **Hemolytic Disease** Usually Mild
  - ABO antigens not fully developed on red cells at birth
  - Antigens similar to A and B are present on other tissues that neutralize the anti A and B Abs.
  - Infant's HB level is normal or slightly reduced
  - No Hepatosplenomegaly
  - Peaks in the first 12-72 hours
  - Coomb's test negative or weakly positive

Rh Hemolytic Disease

- Rh_o is the same as "D"
- Don't ignore: C, c, E, e, Duffy, Kell, Lewis…
- Rapid rate of rise:
  - **Jaundice in the first 24 hours is abnormal**
  - Bilirubin level >10 in first 24 hours is abnormal
  - Rate of rise > 0.5 mg/dL / h
- **Coombs test positive**
  - Detects IgG antibodies on the baby's RBCs
- **Must keep bilirubin <20**

Rh Disease (= HDN)

- In infants with detectable anti D Abs
  - 50% unaffected or mildly affected]
  - 30% moderate neonatal disease]
  - 20% severely affected in utero] **Hydrops**
- RH disease less severe in ABO incompatible fetuses **(= O Neg. with B Pos.)**
  - ABO Antibodies in maternal serum destroy fetal cells before maternal immune system reacts to D antigen

Rh Hemolytic disease

Features of moderate to sever disease

- Sever Anemia or rapidly increasing Anemia
- Early and rapidly increasing jaundice
- Hepatosplenomegaly
- Hypoglycemia
- Hydrops fetalis in sever cases
- Thrombocytopenia
- Early phototherapy sonst exchange transfusion

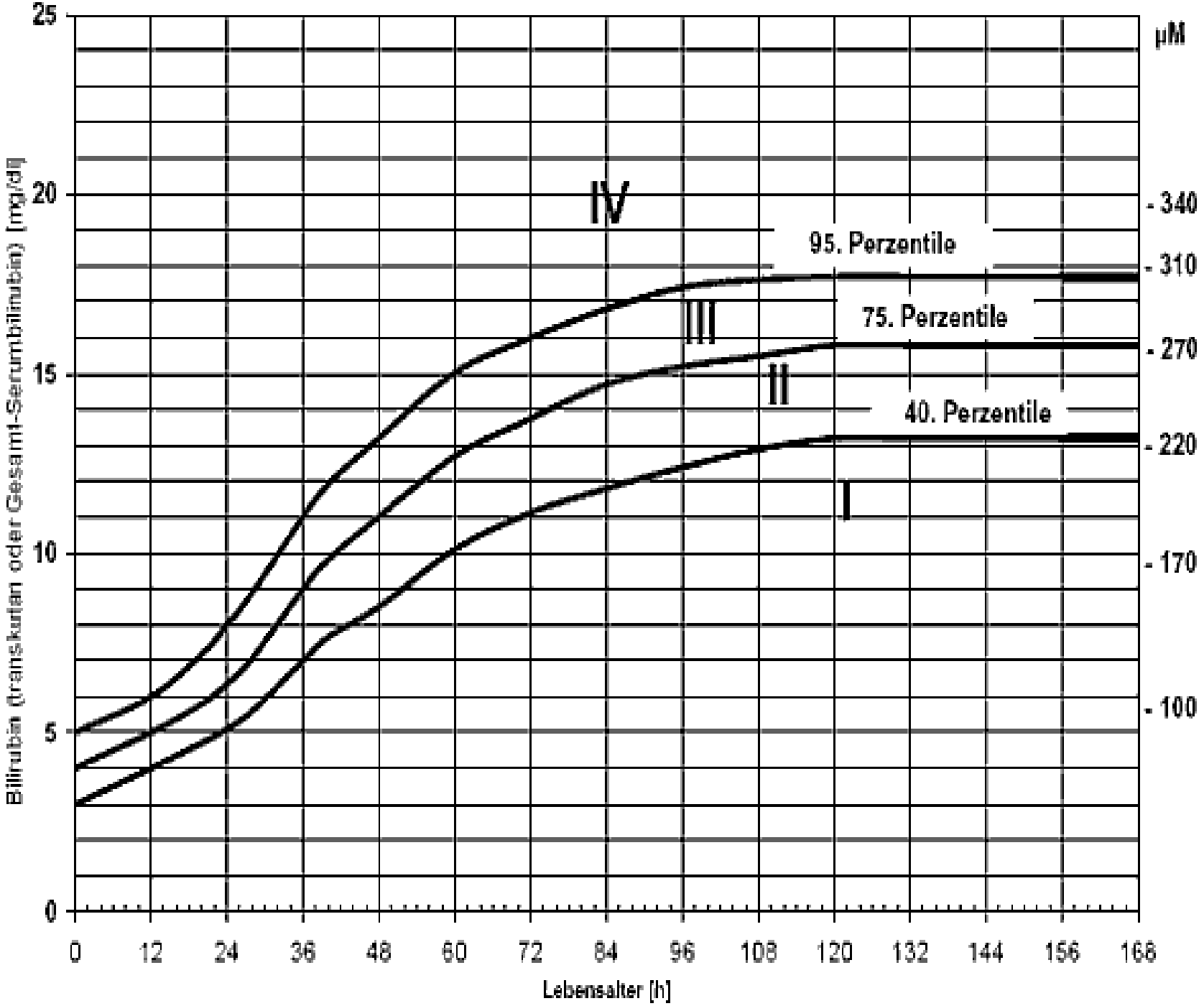
RHIG (RhoGAM) Anti D

- Rate of Hemolytic Disease of the Newborn declined from 40.5 to 10.6 cases/ 10,000 births after introduction in 1980

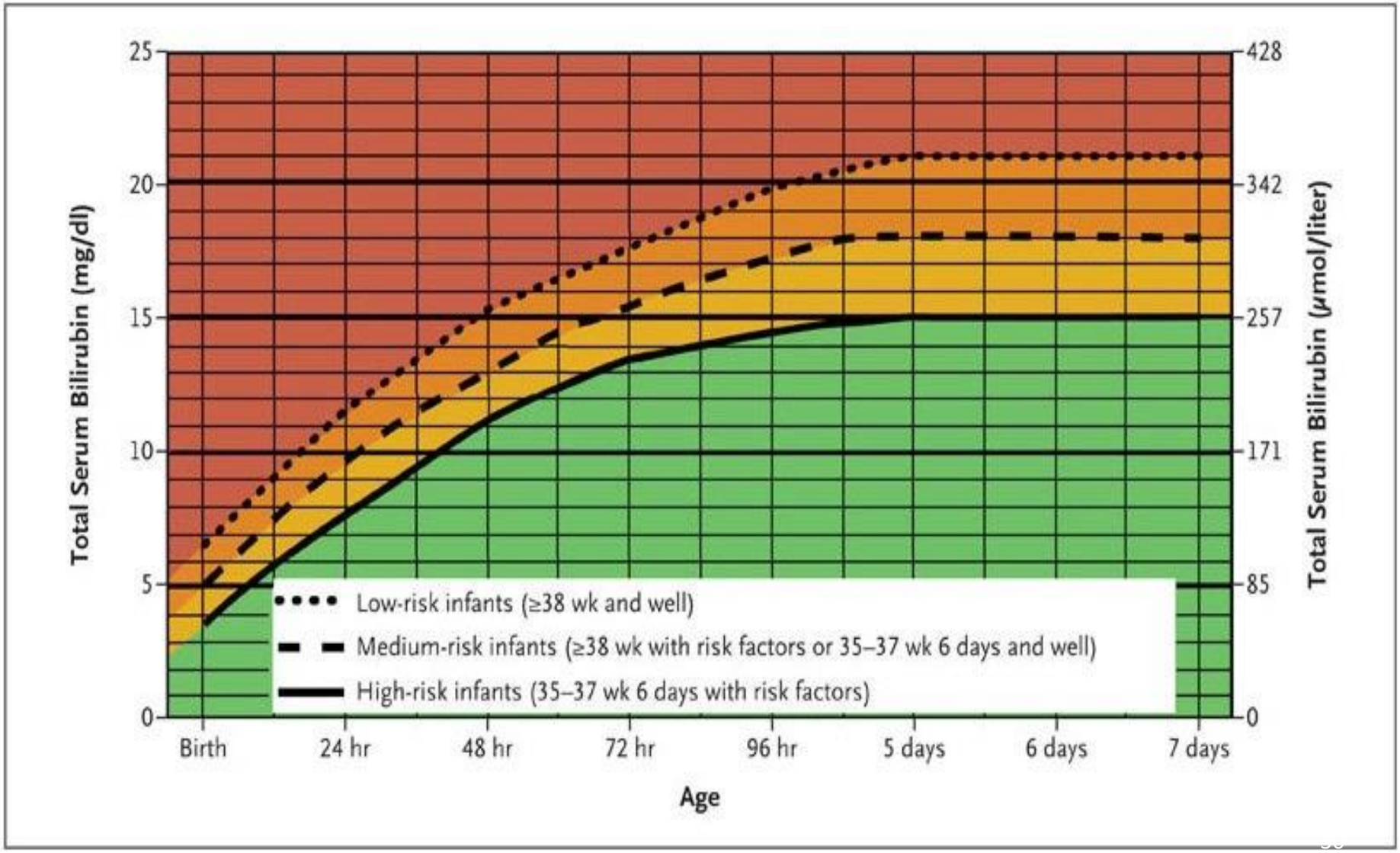
- Only helps protect against development of antibodies to Rh
- Works by
  - Destroying fetal cells in maternal circulation
  - Coating antigens on fetal cells
  - Activating inhibitory intracellular signally pathways to decrease antibody production

Management of Hyperbilirubinemia

- Improve feeding
- Phototherapy
- Exchange Transfusion


Bilirubin (transkutan oder Gesamt-Serumbilirubin) [mg/dl]
25
20
15
10
5
0
µM
- 340
- 310
- 270
- 220
- 170
- 100
IV
95. Perzentile
III
75. Perzentile
II
40. Perzentile
I
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Lebensalter [h]

Bilirubin w. risk factors



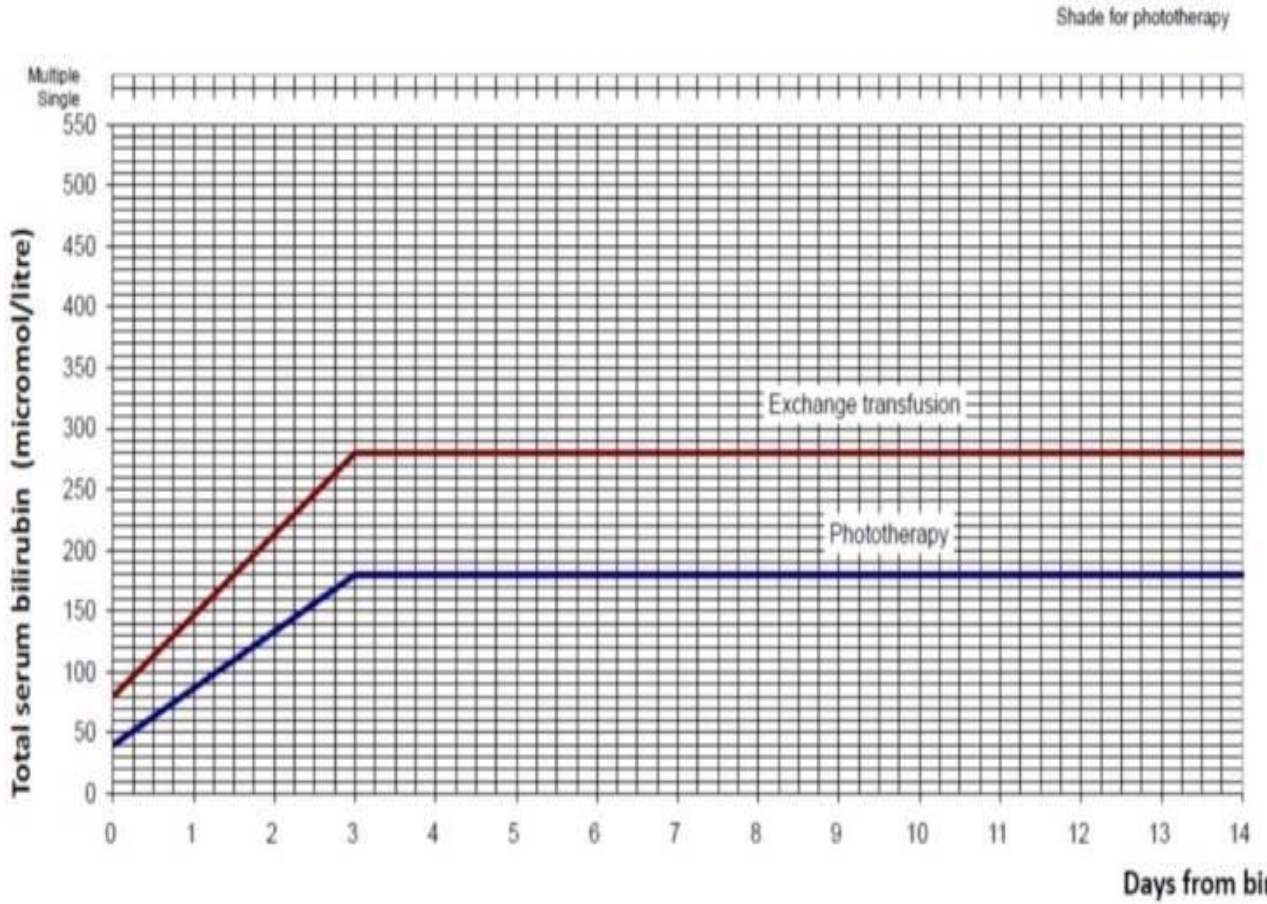
Risk factors requiring exchange transfusion

- Isoimmune hemolytic disease
- G6PD
- Asphyxia
- Significant lethargy
- Temperature instability
- Acidosis
- Sepsis
- prematurity

Bilirubin thresholds for phototherapy and exchange transfusion in babies with hyperbilirubinaemia

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ 28 weeks gestation



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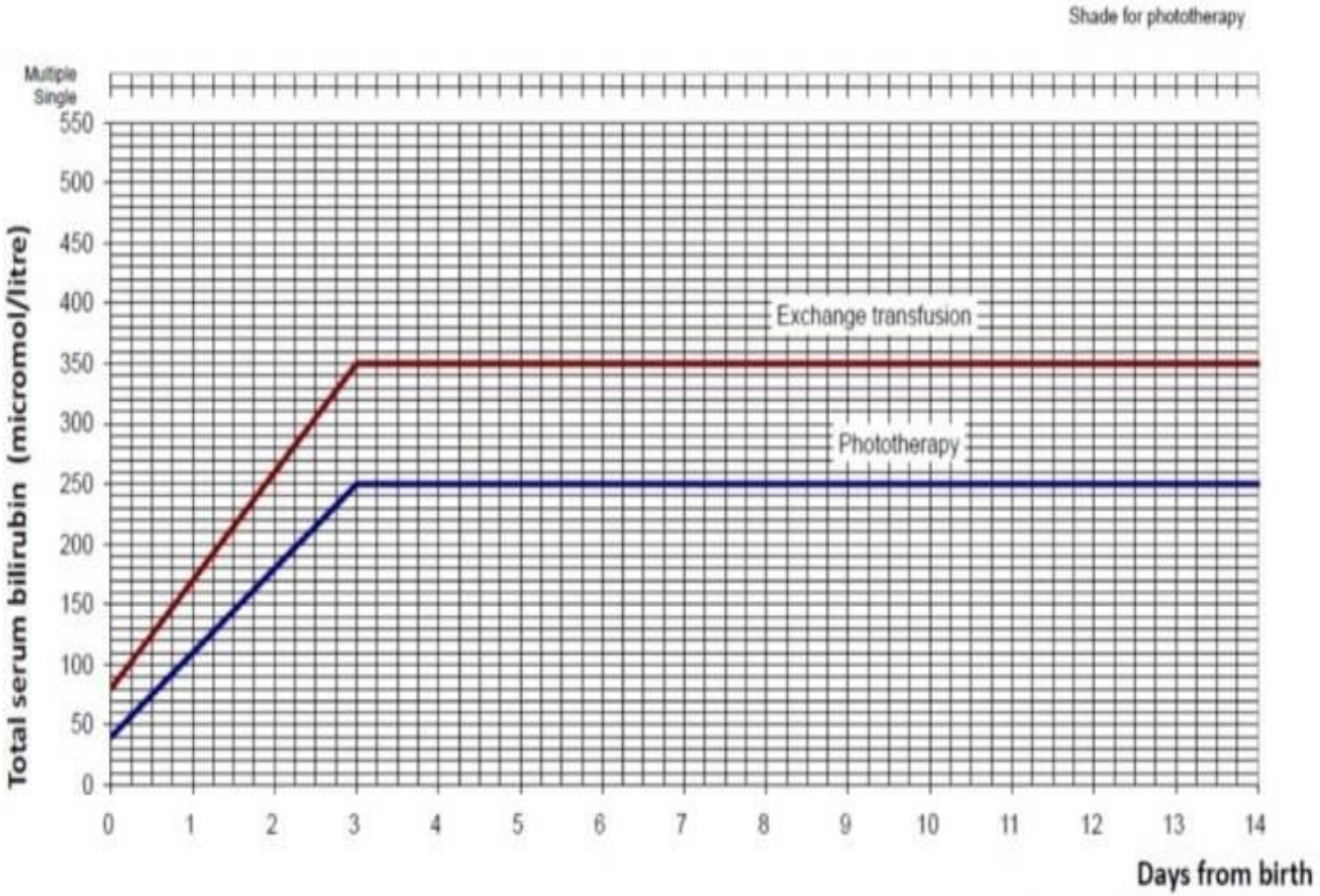
Baby's blood group _____ Mother's blood group _____

Bilirubin thresholds for phototherapy and exchange transfusion in babies with hyperbilirubinaemia

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ 35 weeks gestation



Baby's blood group _____ Mother's blood group _____

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Treatment of Hyperbilirubinemia in the Healthy Term Newborn

Age in hours	Bili mg/dL	Bili mg/dL	Bili mg/dL	Bili mg/dL
	Consider Photo.	**Phototherapy.**	**Exchange Trans. (if Intensive Photo fails)**	**Exchange trans. and Intensive Photo.**
≤24	--	--	--	--
25-48	≥12	≥ 15	≥ 20	≥ 25
49-72	≥ 15	≥ 18	≥ 25	≥ 30
>72	≥ 17	≥ 20	≥25	≥30

Healthy = not ill appearing, otherwise healthy, no evidence of hemolysis

In all situations, use intensive PTX if bili fails to decline with conventional PTX

Phototherapy

- By Photoisomerization converts indirect Bilirubin to water soluble Bili. (**Lumirubin)**
- Intensive Phototherapy (cylinder photo)
  - Multiple lights for surface coverage
  - With a light blanket
  - Put lights close to baby for high radiance
- Intensive phototherapy failing to lower the Bilirubin level suggests:
  - Hemolytic disease
  - Some other pathologic process / Weak lights

Complications of PHT

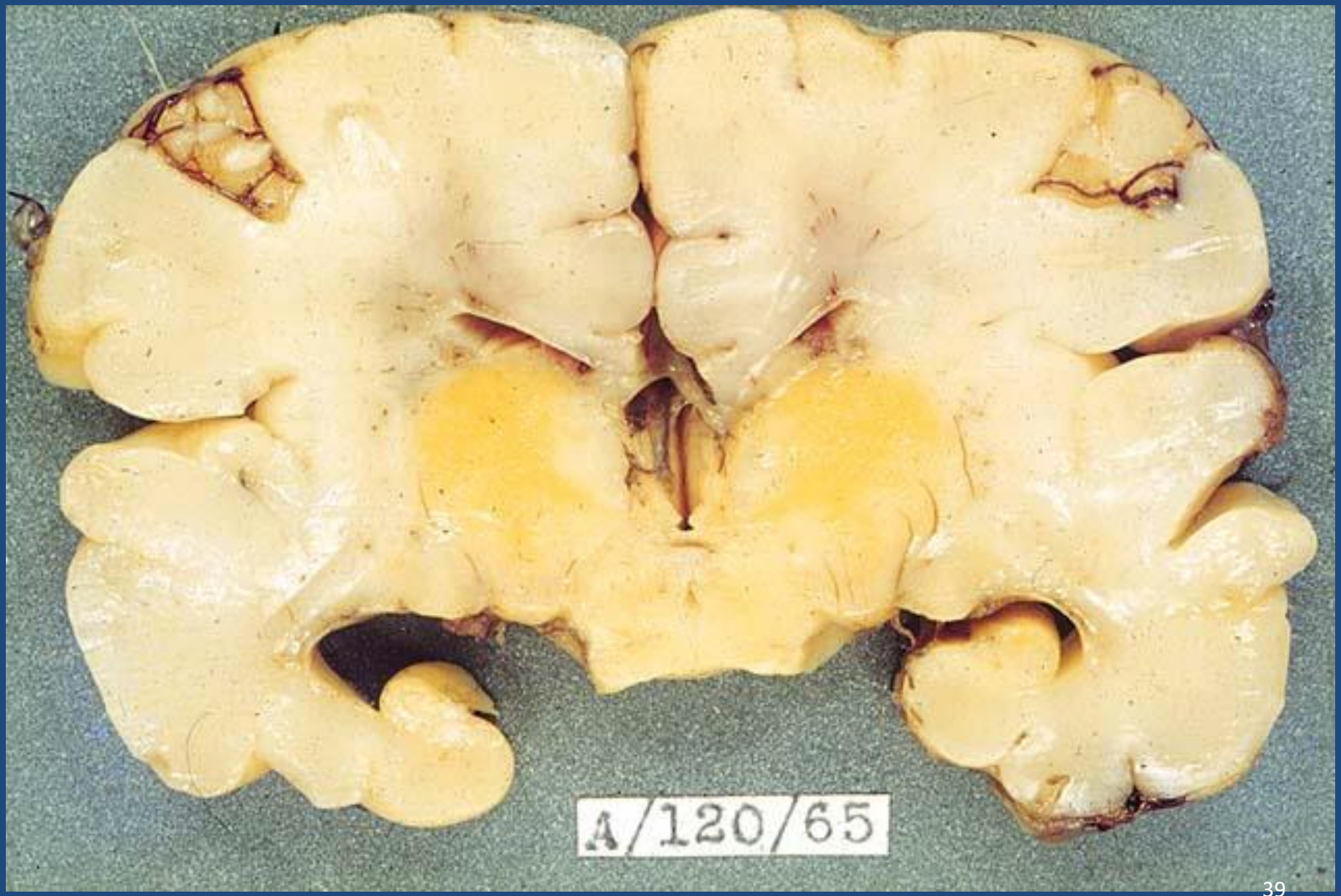
- Loose stools
- Skin rash
- Damage to the eyes
- Hyperthermia
- Bronze baby syndrome
- dehydration

Exchange Transfusions

- **Complications:**
  - Death 3/1000
  - Significant Morbidity 50/1000 (5%)
    - Apnea
    - Bradycardia/arrhythmia
    - Vasospasm
    - Thrombosis
    - Necrotizing Enterocolitis
    - Thrombocytopenia/coagulopathy
    - Hypocalcaemia
  - All Risks of Blood transfusion (infection, GVHD etc)

Toxic effects of bilirubin

- **Kernicterus**
  - Originally a pathologic diagnosis
  - Bilirubin staining of Cerebellum and Brainstem Nuclei
  - Term may be used interchangeably with chronic bilirubin encephalopathy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Clinical Features of Acute Kernicterus

- Acute
  - **Phase 1** (first 1-2 days): poor sucking, hypotonia, lethargy
  - **Phase 2** (mid first week): Hypertonia of extensors, Opisthotonus, fever, irritability, high pitched cry

Acute Bilirubin Encephalopathy

- **Advanced Phase (3)** – after the first week

  Nervous system damage probably ***irreversible***

  - Shrill cry
  - No feeding
  - Apnea, deep stupor
  - Seizure, coma, death

Chronic Bilirubin Encephalopathy

- Occurs during the first year

  Hypotonia, active DTRs, obligate tonic neck reflex, delayed motor skills
- Athetoid Cerebral Palsy
- Auditory Dysfunction **(Hearing loss)**
- Dental enamel dysplasia
- Paralysis of Upward gaze
- Intellectual and other handicaps (less common)

Thank you