Neonatal jaundice

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Jaundice

- **Definition:**
  Jaundice = yellow coloration of skin, conjunctiva and mucosa (elevated concentration of bilirubin in intra- and extracellular spaces)

- **Hyperbilirubinemia**
  $\uparrow S$-bilirubin = 17 (25,7) umol/l
Jaundice

Incidence:
25 - 50 % of term neonates
70 - 80 % of preterm neonates

Jaundice in neonates
physiological x pathological sign
History

1876 - A. J. Pleasonton „blue glass mania“
1958 - Cremer phototherapy
(Europe, South Amerika)
1968 - Lucey phototherapy (USA)
1985 - Hegyi Minolta - transcutaneous bilirubinometry

INFLUENCE
OF THE
BLUE RAY OF THE SUNLIGHT
AND OF THE
BLUE COLOUR OF THE SKY,
IN DEVELOPING ANIMAL AND VEGETABLE LIFE;
IN ARRESTING DISEASE, AND IN RESTORING HEALTH IN ACUTE AND
CHRONIC DISORDERS TO HUMAN AND DOMESTIC ANIMALS,
AS ILLUSTRATED BY THE EXPERIMENTS OF
GEN. A. J. PLEASONTON, AND OTHERS,
Between the years 1861 and 1876.

Addressed to the Philadelphia Society for Promoting Agriculture.

"Error may be tolerated, when reason is left free to combat it." — Thomas Jefferson.
"If this theory be true, it upsets all other theories." — Richmond Whig.

PHILADELPHIA:
CLAXTON, REMSEN & HAEFFELINGER, PUBLISHERS.
1877.
Metabolism of bilirubin

Products: metabolism of haemo-proteins - cells RES (lien, hepar)

Daily production:

* adults  3 - 4 mg/kg/day
* fetal   via placenta
* neonate 6 -10 mg/kg/day

* Maxim. Daily production: 75 % bilirubin of Hb

\[
(1 \text{g} \ Hb = 34 \text{mg} = 600 \text{umol} \ \text{bilirubin})
\]

25 % myoglobin, cytochromes, uneffective

\[ \text{HEME} \rightarrow \text{biliverdin} \rightarrow \text{bilirubin} \]
Metabolism of bilirubin

Blood

- Albumin + bilirubin

Hepatocytes

- Ligandin + bilirubin
  - Glukuronyl-transferase
  - Conjugated bilirubin
    - Bile
      - Bowel, urin, blood

Bilirubin (liposolubile)

- Unconjugated x Conjugated
  - Indirect x Direct
Physiology of bilirubin metabolic Mechanisms

1. Overproduction of bilirubin

*elevated erytrocyes volume/kg BW (PT : 100 ml/kg X FT : 60 ml/kg)

*life of erytrocyes  (PT : 70 DAYS FT : 90 DAYS adults : 120 days)

2. Defective reuptake transport – conjugantion - excretion

*Immature enzymes, uptake, energy mechanisms
*Enterohaepatic circulation
Pathology of bilirubin metabolic mechanisms

1. **OVERPRODUCTION** of bilirubin
   * Hemolytic disease of fetus and neonate
   * Congenital defects of erythrocytes
   * Polycythemia
   * Extravascular haematomas
   * Enterohepatic circulation

2. **RUPTAKE transport –secretion/excretion** of bilirubin
   * Decreased conjugation of hepatic cells (PRETERM)
   * Decreased excretion: CONGENITAL, extra and intrhepatic atresia

3. Completed diseases (hypoxia, infection...) = combination 1 + 2
Bilirubin toxicity

*Toxicity of bilirubin = prevention and therapy*

• **Cytotoxicity of bilirubin**
  
  cell membrane injury, output of ions from cells, DNA synthesis defect, inhibition of enzymes of glycolysis, mitochondrial injury and injury of neurotransmitters

• **Risk factors (LAB.)**: capacity of albumin, HE-membrane, metabolic changes (ACIDOSIS)

• **Clinical syndromes (CLINICS)**: SEPSIS, IMMATURETITY, ASPYXIA
ENCEPHALOPATHY

Transport of bilirubin HE bariere transient or irreversible brain injury
typical neurotoxicity = typical necroptic yellow basal ggl. .... Last
Encephalopathy at Czech Republic 1950 (?)

DG:

**Acute (acute encephalopathy):** 1week
1. stadium - hypotonia, lethargy, central crying
2. stadium - opisthotonus, seizures, ascendent paralyse
dead 1st week after birth

**Chronic (basal ganglia jaundice):** 4M - 1year
3. stadium - hypertonus
4. stadium - late spasticity, athetoic, PMR S-N morbidity, hearing lose
Pre-term newborn 35.wks of GA
ELBW - newborn 24.wks of GA
**DF DG:**

Clinical assessment

*S* - bilirubin (jaundice)

1. Dynamics
2. Timing of jaundice primary / secondary symptoms?

HYPERBILIRUBINAEMIA

Un-conjugated
- Physiologic
- NON-Physiologic

Conjugated
- NON-PHY>20% of total S-bilirubin
Manifestation of jaundice

S - bilirubin  70 - 85 umol/l
Assessment of the newborn

• **History** (RH, ABO): **HAEMOLYSIS?**
• **Physical examination:** **PRIMARY SIGN?**
• **General + neurological**
• **Skin color**
• **RESPRATION**
• **HAEMODYNAMICS**
• **Abdomen** (bowel distension, **stool**, vomiting, hepathomegaly)
ELBW - newborn 24.wks of GA
Characteristics of physiological jaundice

* umbilical S-bilirubin: max. 50 umol/l
  - after 1st day
  - MAXM. 4(5th) day
  - physiologic neonatal estimation

- optimal dynamics of S-bilirubin peak 300 umol/l (FT), 220 umol/l (PT)

* no therapy (90%) (10% PT)
Characteristics of pathological jaundice

* umbilical S-bilirubin: > 60 umol/l
- before 24 hours of life and after 8 days FT, 14 days PT

- rapidly S-bilirubin elevation 100 umol/l/6H
- Pathologic symptoms: act. weight, lethargy, thermolability,
- direct bili > 20% of total bilirubin

* Therapy in about 90% of neonates (10% without therapy)
Clinical types of unconjugated hyperbilirubinaemia

1. Physiologic jaundice

2. Pathological jaundice
   a) haemolysis (Rh, ABO), hereditary spherocytosis
   b) sepsis + TORCH adnate infection
   c) haematomas
   d) congenital metabolic defects (hypothyreosis, galactosaemia…)
   e) polycythemias
   f) congenital enzymes defects (Criggler-Najar)
   d) jaundice of breast fed neonates (early), jaundice from mother milk
      (late) – physiological type but pathological from intensity or timing
   e) neonates of diabetic mother
   g) praematurity
Clinical types of conjugated / combined / hyperbilirubinaemia

1. **HAEMOLYSIS**

   RH incompatibility. ABO

2. **Hepatic cells injury** (conjug + unconjug)

   - syndrom neonatal hepatitis (big cells idiopathic, bacterial, TORCH)
   - toxic injury (endotoxin, drugs toxicity)
   - congenital metabolic defects - galactosemia, glycogenosis,

3. **Cholestasis** (typical conjug)

   - extrahepatic (extrahepatic atresia of biliary ductus)
   - intrahepatic (intrahepatic atresia of biliary ductus)
   - syndrom of inspiss. bile by sever hemolysis
Laboratory tests

**Physiological jaundice:**
S – Bilirubin (once daily)

**Pathological jaundice:**
- Mother – Child Blood Group
- Coombs tests (direct, indirect CT, CT), incompl. Ab
- bili total, direct, indirect
- liver enzymes, blood count, CRP
- urinanalysis (biochemistry)
- abdomen sonography

**Df. dg.:** erythrocytes morphology, TORCH, IMD
RH incompatibility/isoimmunisation

• RH incompatibility- anti D
  1. phase: 1st pregnancy
  immunization of mother
  Mother x Child
  BG RH neg x Rh positive

  DG: Coombs tests+++++
  (population 15 % d/d)

  2. phase: hemolysis Ab II.
  pregnancies
  a) fetal type:
  anemia - hypoxia - hydrops +
  b) neonatal type:
  Jaundice-anaemia

• ABO incompatibility
  1. phase = 2. phase

  Mother x Child
  O x A, B

  Dg:
  Ab ani A- anti B
  S- bilirubin
Mother produced IgG /one of the five types of the antibodies/

- **Fetus** IgG passed through the placenta include ones attack the red blood cells in the fetal circulation
- Red cells are broken down
- The fetus can develop reticulocytosis and anaemia
- Mild to very severe disease – erythroblasts are present in the foetal blood
• **Serological diagnoses**
  
  • **ABO system**
    
    – **[ABO hemolytic disease of the newborn](#)** can range from mild to severe, but generally it is a mild disease.
    
    • anti-A antibodies
    
    • anti-B antibodies
  
  • **Rhesus system (the Rh d antigen and Rh d antibodies do not exist)**
    
    – **[rhesus D hemolytic disease of the newborn](#)** (often called Rh disease) is the most common form of severe HDN. The disease varies from mild to severe.
    
    – **[rhesus E hemolytic disease of the newborn](#)** is a mild condition
    
    – **[rhesus c hemolytic disease of the newborn](#)** can range from a mild to severe disease - is the third most common form of severe HDN
    
    – rhesus e hemolytic disease of the newborn - rare
    
    – rhesus C hemolytic disease of the newborn - rare
    
    – antibody combinations (ie anti-Rhc and anti-RhE antibodies occurring together) - can be severe
  
  • **Kell system**
    
    – **[anti-Kell hemolytic disease of the newborn](#)**
      
      • anti-K 1 antibodies - disease ranges from mild to severe - over half of the cases are caused by multiple blood transfusions - is the second most common form of severe HDN
      
      • anti-K 2 ,anti-K 3 and anti-K 4 antibodies - rare
  
  • **Other blood group antibodies (Kidd, Lewis, Duffy, MN, P and others).**
• **Diagnosis**
• The *diagnosis* of HDN is based on history and laboratory findings:
• **Blood tests done on the newborn baby**
• Biochemistry tests for *jaundice*
• Peripheral blood *morphology* shows increased *reticulocytes*. *Erythroblasts* (also known as nucleated red blood cells) occur in moderate and severe disease.
• Positive *direct Coombs test* (might be negative after fetal interuterine blood transfusion)
• **Blood tests done on the mother**
• Positive *indirect Coombs test*
**Direct Coombs test / Direct antiglobulin test**

Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient’s washed RBCs are incubated with anti-human antibodies (Coombs reagent).

RBCs agglutinate: anti-human antibodies form links between RBCs by binding to the human antibodies on the RBCs.

**Legend**
- Antigens on the red blood cell’s surface
- Human anti-RBC antibody
- Anti-human antibody (Coombs reagent)

**Indirect Coombs test / Indirect antiglobulin test**

Recipient’s serum is obtained, containing antibodies (Ig's).

Donor’s blood sample is added to the tube with serum.

Recipient’s Ig’s that target the donor’s red blood cells form antibody-antigen complexes.

Anti-human Ig’s (Coombs antibodies) are added to the solution.

Agglutination of red blood cells occurs, because human Ig’s are attached to red blood cells.
Therapy PRIMARY JAUNDICE

• **Prenatal period :**
  A) prevention high risk pregnancy Anti D gammaglobulin - Rhega Ig to mother below 72 h after birth
  B) therapy (RH incompatibility) - ransfusion in utero. Albumin 20%, IVIG

• **Postnatal period :**
  DRUGS- PT - ET
Phototherapy
“Hodr’s graph”

- Light 425 - 475 nm (blue light) - photodegradation of bilirubin nontoxic isomers of bilirubin without way of hepatic conjugation

- **a) photoisomers** - excretion to bile *isomer of bilirubin*
- **b) intramolecular cyclisation** - excretion to bile *lumirubin*

- **c) photooxidative reactions** - urin elimination
- **!: syndrome of bronze baby** !! lumirubin - bilifuscin
Graph (Hodr, Poláček)
Pre-term newborn 35.wks of GA
<table>
<thead>
<tr>
<th></th>
<th>≥ 37 weeks of GA</th>
<th>≤37 weeks GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh</td>
<td>ABO</td>
<td>other</td>
</tr>
<tr>
<td>V.</td>
<td>ET</td>
<td>ET (PT) ET (VT) ET</td>
</tr>
<tr>
<td>IV.</td>
<td>ET (PT) PT</td>
<td>PT ET</td>
</tr>
<tr>
<td>III.</td>
<td>PT B 2x</td>
<td>B 2x ET (PT)</td>
</tr>
<tr>
<td>II.</td>
<td>B 2x B 2x</td>
<td>- ET</td>
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AAP - Subcommitee on Hyperbilirubinemia (1994) :
www.aap.org./family/jaundicefaq.htm

* redukovat incidenci hyperbilirubinemie a encefalopatie
* motivace kojící matky
* definovat riziko propuštění a follow up
* léčbou u novorozence předcházet vzniku jádrového ikteru
* cost benefit

www.pediatrics.org
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www.pediatrics.org
ET = exchange transfusion

1. **ICU – monitoring!**

2. **Indication**: Elimination of bilirubin + defected erythrocytes and Ab
   Steps: Group incompatibility DG and Verified Treatment
   * BG mother, neonate
   * BG incompatibility = sole cause indication of ET

3. **Proceeding:**
   Erythrocytes transfusion x plasma Rh - compatible transfusion
   *RH incomp.:
   ORh neg/ O Rh positive child  (Treatment: O BG Rh negative)/ G A.B of child  (RH negative transfusion)
   *ABO incomp.: O mother /A child  (Treatment : O BG but Rh of child)
Complications:

I. dysbalances
   glu, K, Ca, ABE

II. Infection (umbilical catheter)

III. GVH reaction

IV. Thrombembolic complication

V. Haemodynamic instability

VI. Course of ET: blood volume 160-200ml/kg of BW : 90 - 120 min.
   Prevention of: FOR every 50 ml/ blood, + 0.5 ml 10% Ca gluconicum
   (antidotum = citrate) + 5-10 ml 10% Glucose sol. Every course repeated:
   blood Volume 5-10 (PT) - 20 ml (FT)
Newborn DG: MODF
QUIZ ?????????????????? DG???

• \( \geq 24 \text{ H} \)
• TERM NEONATE
• JAUNDICE - 2nd DAY
• \( \uparrow\uparrow \) JAUNDICE – 6 th DAY
• DISCHARGE HOME

• \( \leq 24\text{H} \)
• PRETERM (35w)
• \( \uparrow \)JAUNDICE
• S- bilirubin (2nd DAY) + Tax 38.0 C
• S-bilirubin=280 umol/l
• (PT)
• NO HISTORY of RH
Screening: CH+PKU+GAL+CAH
Single intradermal BCG - injection of the deltoid
Physiologic Neonate

• ≥ postnatal age : 72 H (resp. 96 H)

• Assessment +

• Feeding +
• Neonatal screening + hearing + catarracta
• BCG +
• Vitamines prophylaxis
## Tab: Total bilirubin values dependent on age

**Total - bili:**

<table>
<thead>
<tr>
<th>Age</th>
<th>koncentrace umol/l</th>
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<tbody>
<tr>
<td>0 – 1 den</td>
<td>34 – 103</td>
</tr>
<tr>
<td>0 – 2 dny</td>
<td>103 – 171</td>
</tr>
<tr>
<td>3 – 5 dní</td>
<td>68 – 137</td>
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<tr>
<td>1 – 15 R</td>
<td>3,4 – 17,1</td>
</tr>
<tr>
<td>15 – 99 R</td>
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**Conjugated-bili:**

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<tr>
<td>0 – 99 R</td>
<td>≤3,4</td>
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Tab.1: Rozmezí hodnot S-bili s ohledem na populaci

<table>
<thead>
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Celkový bilirubin:

Konjugovaný bilirubin:

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