Neonatal Jaundice (NNJ)

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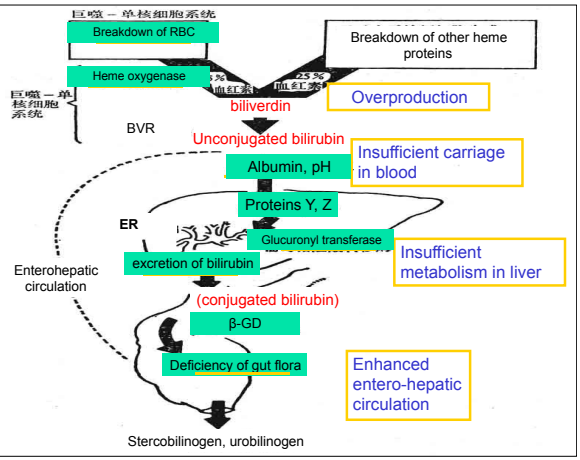
Neonatal jaundice

- Sclera, mucosa and skin becomes jaundiced because of elevated serum bilirubin.
- Jaundice is a pretty common phenomenon during neonatal phase.
- Severe and persistent jaundice may cause damage to brain and liver.

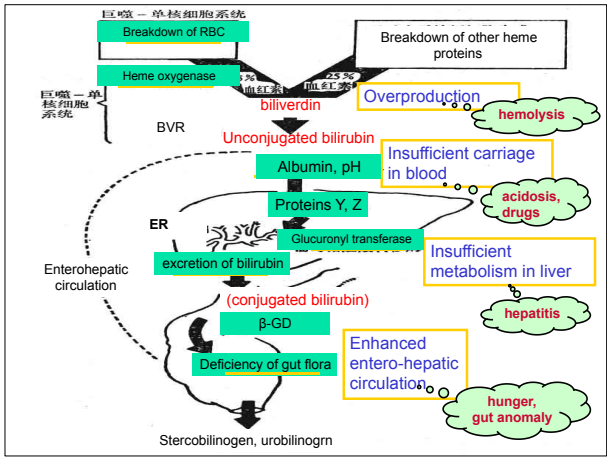
Why is jaundice so common among neonates?



Features of neonatal bilirubin metabolism

- Overproduction
- Unefficient transportation in blood
- Dysfunction of immature liver
- Enhanced entero-hepatic circulation

All the above do contribute to elevation of serum bilirubin in the first several days of life.



How to differentiate pathologic jaundice from physiologic jaundice?

Physiologic Jaundice: (all of following features)	Pathologic Jaundice: (any of following features)
Appears in 2-3d of life	Early onset: appears within first 24hours of life
Fade within 14d	Prolonged jaundice: persist >2w in term
Total serum bilirubin (TB) ≤ 12.9mg/dl (221 μmol/L)	Severe jaundice: TB >221 μmol/L and/or DB 34 μmol/L or DB/TB >20%
Normal overall condition	Rapid rising: TB increasing ≥85μmol /L/d or (8.5μmol/L/h)
	Recurrent jaundice

Because of the high susceptibility to bilirubin's neurotoxicity, neonatal jaundice of preterm babies should be treated as pathological jaundice.

A wrong opinion

☺Many people, including some clinicians, take neonatal jaundice for granted, because they consider it a physiological phenomenon.

Neonatal jaundice

- Sclera,mucosa and skin becomes jaundiced because of elevated serum bilirubin.
- Jaundice is a pretty common phenomenon during neonatal phase.
- **Severe and persistent jaundice may cause damage to brain and liver.**

How does bilirubin injure neonates?

Total serum bilirubin includs

- Unconjugated bilirubin: UB or IB
  - Fat-soluble: cross BBB
  - Deposit in brain⟶bilirubin encephalopathy
- Conjugated bilirubin: CB or DB
  - Water-soluble: excreted in feces and urine
  - Deposit in liver ⟶ hepaticcholestasis

ABE results from bilirubin neurotoxicity.

- Unconjugated bilirubin:
  - Fat-soluble,
  - Free (exceed the albumin-binding capacity)
- Higher permeability of BBB: immature
- Risk factors: susceptible to bilirubin neurotoxicity
  - Preterm baby, esp. GA<34wks and BW<1500gm
  - Serious illness: hemolytic diseases, infectious diseases, hypoxia, hypothermia or hyperthermia.

bilirubin encephalopathy (ABE, kernicterus)

Alert phase (12-24hrs): reversible damage

Convulsion phase (24-48hrs)
Recovery phase (10ds-2wks)
Sequelae phase

} Irreversible damage

bilirubin encephalopathy (ABE: acute bilirubin encephalopathy)

transient disturbance

Alert phase (12-24 hrs):

- ✓**Drowsy**
- ✓**Poor feeding**
- ✓**Decreased muscle tone**
- ✓**Decreased primitive reflex, eg. Moro reflex**

bilirubin encephalopathy (kernicterus)

Catastrophic damage to brain

Convulsion phase (24-48 hrs) (about 1/3-1/2 die):

✓Staring, hypertonia, lie on arched back (opisthotonos), seizure (trosion spasm)

Recovery phase (10 ds-2 wks): pseudo-normalize

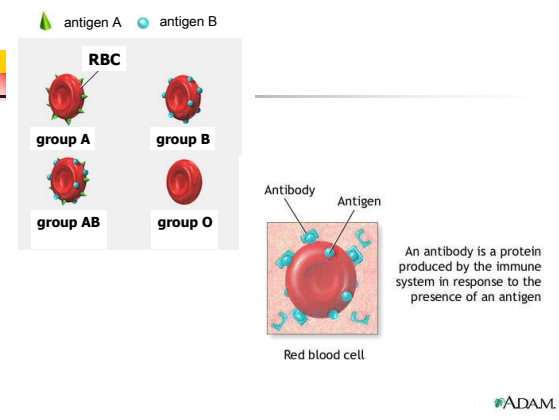
✓recovery in muscle tone and reaction

Sequaele phase (post-neonatal):

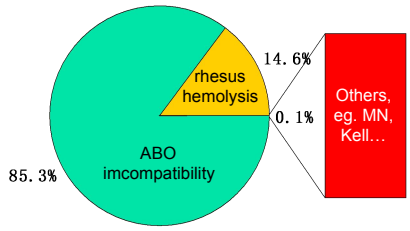
✓Mental retardation, choreoathetoid CP, epilepsy, learning difficulties, sensorineural deafness

Pathological jaundice: etiology

- Neonatal jaundice
  - Non-infectious jaundice
    - Hemolytic diseases
      - Immune hemolysis
      - RBC defects
        - G-6PD deficiency
        - Spherocytosis
        - Thalassemia
    - Others
      - Bile duct obstruction
      - Breast milk jaundice
  - Infectious jaundice
    - Neonatal hepatitis
    - Neonatal septicemia



Constituent ratio of neonatal hemolysis

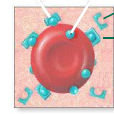


Neonatal hemolysis: pathogenesis

Mother: produce Ab specific to Ag on fetal RBC

Placenta barrier → IgG

Fetus : free hemolysin (blood)



Bound hemolysin (sensitized fetal RBC)

Hemolysis

Neonatal hemolysis: clinical features

- Unconjugated hyperbilirubinemia
- Early onset and rapid rise
- Anemia in different degree
- Hepatosplenomegaly
- Hydrops
- Cholestasis: conjugated hyperbilirubinemia and "bronze baby" syndrome
- Bilirubin encephalopathy

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G-6-PD deficeincy

- Hemolytic disorder:
  - Unconjugated hyperbilirubinemia
  - Kernicterus, anemia
- Common inherited disease in south China
- X-linked, partial dominant
- Male infant, family history
- Tests of G-6-PD activity and gene

Pathological jaundice: etiology

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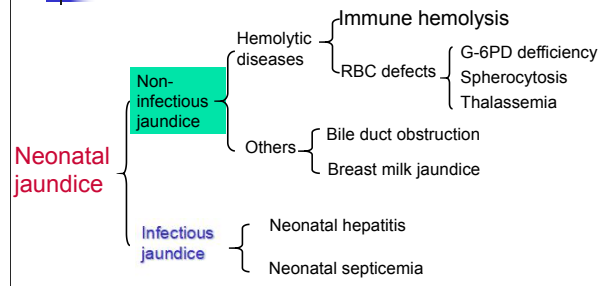
Bile duct obstruction

- Conjugated hyperbilirubinemia
- Later onset, and slowly rise or prolonged
- Pale color of feces
- May be associated with intrauterine infection
- Liver function and ultrasound testing
- Intervention ASAP for better outcome

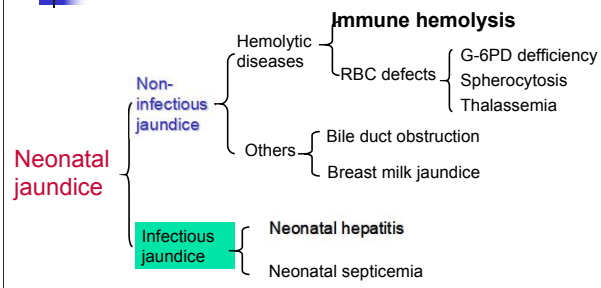
Pathological jaundice: etiology



Breast milk jaundice

- Unconjugated hyperbilirubin
- Gradually rise, and then fade
- Pure breast-feeding
- Overall condition is good
- Other conditions should be excluded
- Do not recommend to discontinue breast-feeding

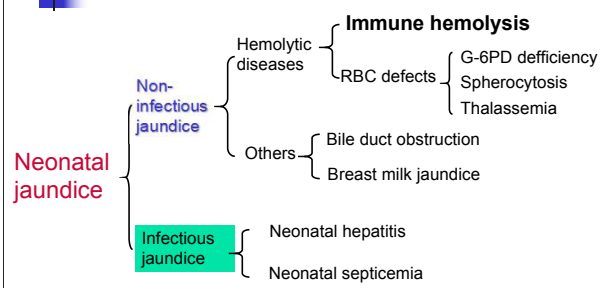
Pathological jaundice: etiology



Neonatal hepatitis

- Conjugated hyperbilirubinemia
- Later onset, and slowly rise or prolonged
- May be associated with intrauterine infection: TORCH
- Abnormal hepatic function and/or ultrasound image

Pathological jaundice: etiology



Neonatal septicemia

- Usually unconjugated hyperbilirubinemia
- Existence of risk factors
- Be aware:
  - Jaundice may be the unique sign in the early phase of sepsis
- Common pathogen in China:
  - E.coli, staphylococcus
- Blood culture and routine test

How to diagnose neonatal jaundice?

- Clinical features
- Laboratory tests
- Complications:
  - Bilirubin encephalopathy
  - Damage to heart and liver

Clinical features

- Age at onset: guide to the likely cause
- Progress speed:
  - hemolysis>septicemia>hepatitis
- Color of urine and feces
- Family history, pregnancy history
- Physical exam:
  - jaundice, anemia, hepatosplenomegaly
  - signs of central nervous systems

Age of onset is a useful guide to likely cause of jaundice.

Age of the onset	Unconjugated bilirubin	Conjugated bilirubin(>15%TB)
<24hrs	Hemolytic disorders	Congenital infection
24hrs-2wks	Physiological, Breast milk, hemolysis……	Infection???
>2wks(persistent/ prolonged)	Breast milk, Infection, Hemolysis, Hypothyroidism	Hepatitis, Bile duct obstruction

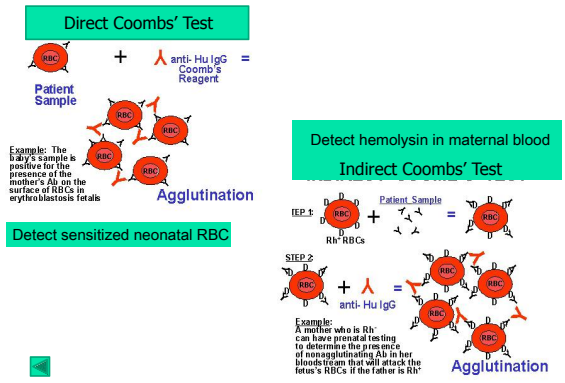
Laboratory tests

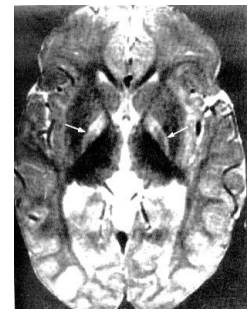
- Complete Blood Counting, blood film
- Serum bilirubin: TB, DB
- Others:
  - immunological tests for hemolysis
  - G-6-PD activity and gene detect,
  - liver function test and belly ultrasound,
  - serological test of intrauterine infection
  - Nervous system:
    - brain-stem auditory evoked potential (BAEP),
    - cranial images(ultrasound, CT,MRI),
    - neuro-behavior neonatal assessment (NBNA)

Transcutaneous jaundice meter

Minibilirubin Mornitor

Serum bilirubin test





Magnetic resonance image of 21-month-old with kernicterus. Area of abnormality is the symmetric high-intensity signal in the area of the globus pallidus (arrows). *Courtesy of M.J. Maisels.*

How to treat neonatal jaundice?

Phototherapy* * *

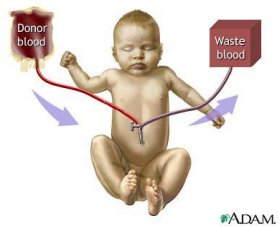
Exchange transfusion* *

Assistant treatment with drugs

Aims of intervention

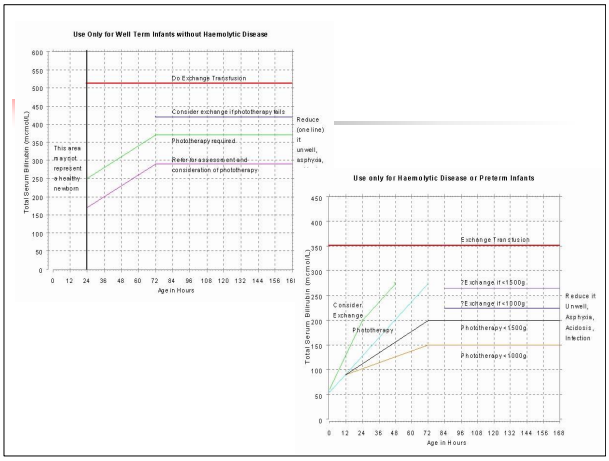
- To decrease serum **uncongugated** bilirubin level ASAP, so to prevent bilirubin damage to brain!

Phototherapy and ECT(exchange transfusion)



Treatment

- No specific bilirubin level is definitely safe or toxic for all infants.
- Low levels in a sick infant may be more detrimental than high levels in a well infant.
- There is no consensus among pediatricians on the bilirubin levels at which phototherapy and exchange transfusion should be performed.



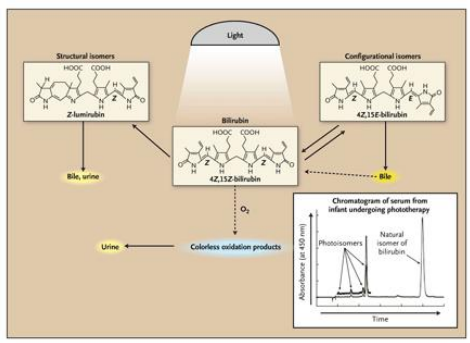
General guidelines of phototherapy

- Term well infants >24 hours old
  - phototherapy when uSB >12.9 mg/dl (221 μmol/l)
- Preterm well infants >24 hours old
  - phototherapy when uSB >8 mg/dl (120 μmol/l)
- Lower threshold for phototherapy if unwell

- **Prophylactic phototherapy if**
  - **uSBR > 6mg/dl (100 μmol/l) <24 hours old**
  - **evidence of hemolysis**
  - **extensive bruising**

Phototherapy

- Photoisomerization
  - converts bilirubin to a less toxic isomer
  - conversion is rapid
  - reabsorbed into blood stream and excreted in bile
  - re-conversion to uSB occurs in the gut
  - clearance is slow
- Other mechanisms exist



Mechanism of Phototherapy: Photoisomerization

Suitable Wavelength

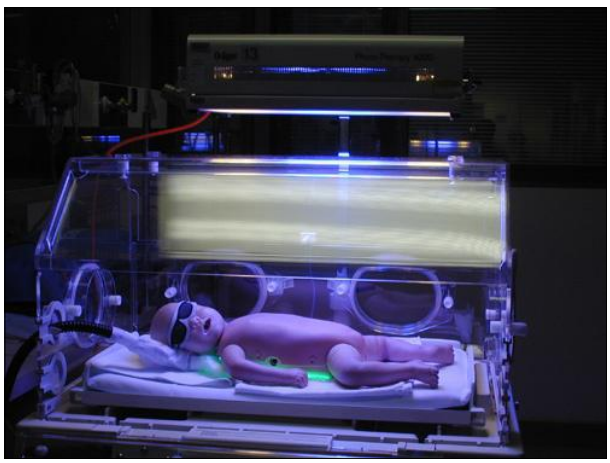
- Light source with output range between 280-700 nm (bilirubin adsorbs light in 400-500 nm range)
- Blue lamps peak output: 425-475 nm
- Cool white lamps peak output: 550-600 nm

Techniques

- Adequate skin exposure
- Eye protection
- Temperature control
  - cots, heat shields, incubators
- Monitor hydration eg.weight measurements
- Blue/white light versus biliblanket

Side effects

- ↑ insensible water loss
- Diarrhoea
- Retinal damage (in animal experiment)
- 'Bronze baby' syndrome
- Degradation of amino acid solutions in TPN



Exchange Transfusion

Principles of Exchange Transfusion

- Removes bilirubin from extravascular space
- Removes red cell antibodies
- Removes sensitized red cells
- Correction of anemia
- Single-volume exchange removes 63% of infant's blood volume
- Double-volume exchange removes 87%

Exchange transfusion

- Indications:
  - Hemolytic disease: cord Hb <11 gm/dl and cord uSB >4.5 mg/dl (75μmol/l)
  - uSB rising over 1mg/dl/hr (17μmol/l/hr) despite intensive phototherapy
  - uSB >20 mg/dl (340μmol/l) in term infants. Lower if symptomatic
  - Progressive anemia

Practicalities

- Fresh blood
- Double volume exchange (160 ml/kg) + dead space
- Warm blood to 37^{0}C
- Restrain infant

- Keep warm (radiant warmer)
- Heart rate and blood pressure monitoring
- Reliable arterial/venous access
- Base line FBC, SB, glucose, pH, electrolytes, calcium
- Gentle push-pull technique, 10-20 mls aliquots depending on infant's condition

- Repeat FBC, SB, glucose, pH, electrolytes, calcium measurements mid way and at end of exchange
- Continue with phototherapy
- Purse string suture around umbilical vein before removal of UVC
- Beware of rebound and need for further exchange

Complications

- Vascular
  - embolization (air or clots)
  - vasospasm
  - thrombosis
  - infarction
- Cardiac
  - arrhythmias
  - volume overload

- Electrolyte imbalance
  - Hyperkalemia(hypokalemia)
  - Hypoglycemia(hyperglycemia)
  - hypernatremia
  - hypocalcemia
  - acidosis

- Bleeding
  - thrombocytopenia
  - deficient clotting factors
- Infections: hepatitis
  - CMV,HIV
- Others
  - NEC
  - hypo- or hyperthermia
  - Blood group mismatch

Assistant drugs

- Alkalization of blood:
  - transfusion of sodium bicarbonate
- Supplement of albumin
- Inhibition of immune hemolysis:
  - a large dose of IVIG
- Decreasing of entero-hepatic circulation:
  - Enough feeding if permission
  - Intake of probiotics

Assistant drugs

- Chinese traditional herb?
- Sn-mesoporphyrin?
  - no DB, RCT yet
  - reports showed effective in lowering max SB and need for phototherapy and exchange transfusion
  - 6 μmol/kg given IM
  - not yet approved by FDA

Prophylaxis of RhD hemolysis

- Introduction of prophylactic anti-D immunoglobulin for rhesus negative mother:
  - When rhesus negative mother carrying rhesus positive fetus, 300μg anti-D immunoglobulin should be given by intramuscular route when GA is 28wks, 32wks, and <72hrs after delivery and abortion.

TAECHING REQIREMENTS

- 1. difference between pathological jaundice and physiological jaundice of neonates.
- 2. common causes of neonatal jaundice in China.
- 3. common pathogens of neonatal sepsis in China.
- 3. clinical features of neonatal haemolysis.
- 4. laboratory investigations about neonatal haemolysis .
- 5. treatment of neonatal jaundice.