Neonatal Hyperbilirubinemia

0bjectives

- At the end of the session the learner should be able to
- Define jaundice
- Describe the metabolism of bilirubin
- Classify the causes of jaundice
- Describe how to investigate and treat jaundice

Pioneers - neonatal jaundice and kernicterus

- 1785-Jean Baptiste Baumes
- 1847-Jaques Hervieux
- 1875-Johannes Orth
- 1903-Christian Schmorl

introduction

- Jaundice is the most common problem in neonate
- Most jaundiced children are perfectly normal
- Unconjugated bilirubin most common

Definition

- Hyperbilirubinemia- ↑ serum bilirubin [Neonatal 6-8mg/kg/day;Adult 3-4/kg/day]

- Jaundice – yellow discoloration of skin and mucus membranes

Formation of bilirubin

- Bilrubin is the end product of the catabolism of heme

- Major source of bilirubin is from circulating hemoglobin appr 75%

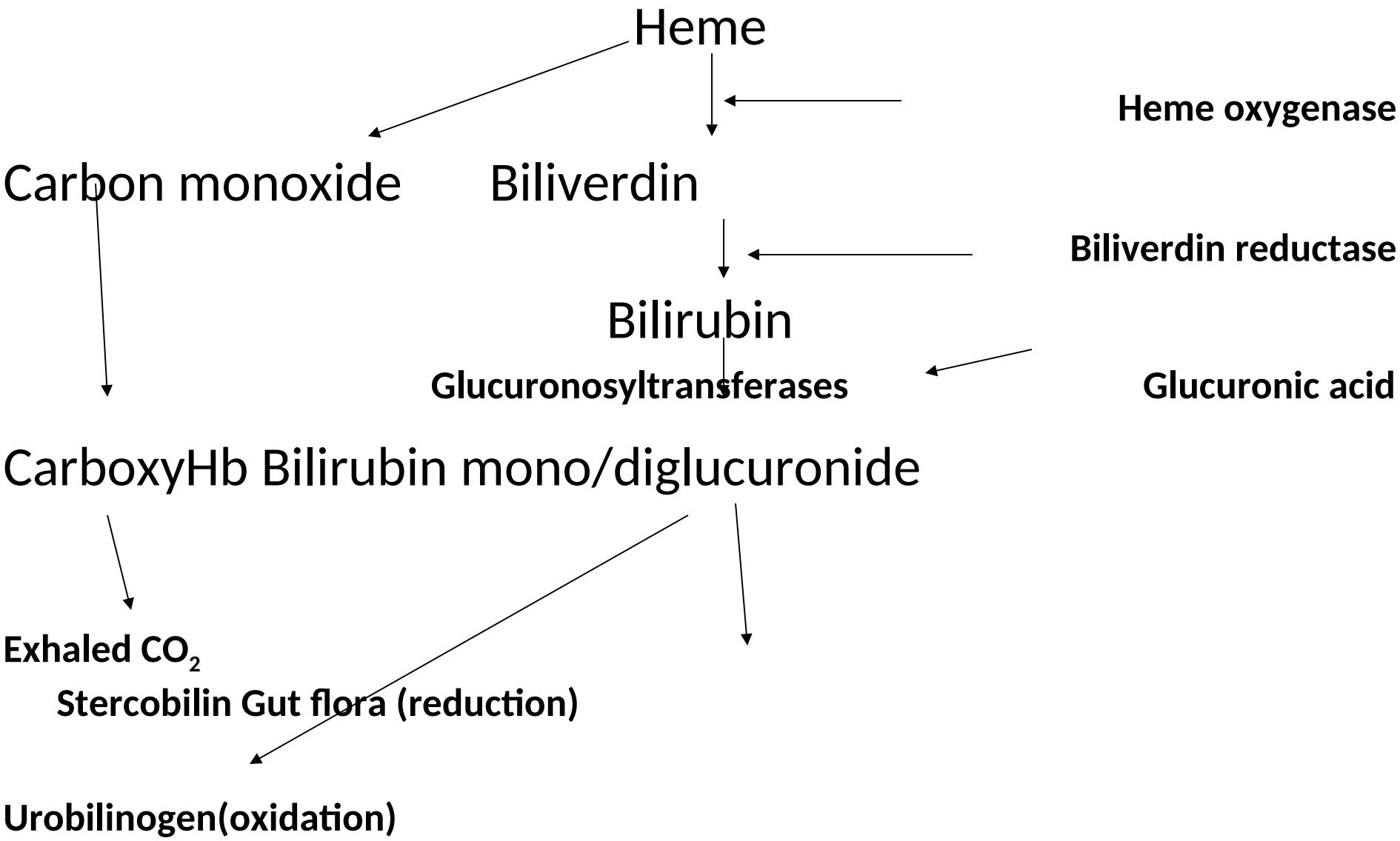
Berk, PD, Howe, RB, Bloomer, JR, Berlin, NI. Studies of bilirubin kinetics in normal adults. J Clin Invest 1969; 48:2176.

Sources of bilirubin

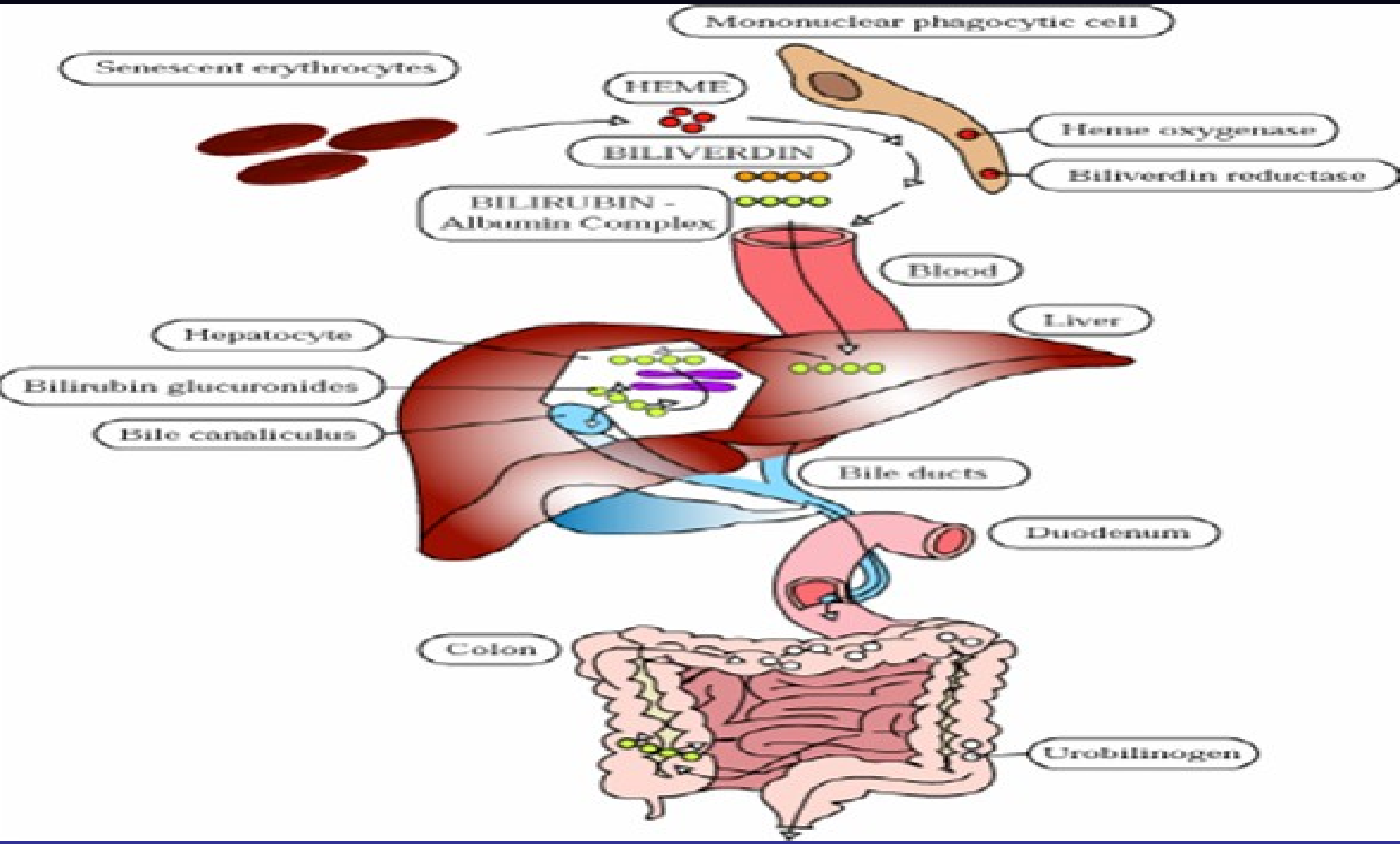
1. Erythrocytic-Hemoglobin -80% [250-400mg adults]

2. Non erythrocytic
   - Myoglobin
   - Cytochromes
   - Catalase
   - Peroxidase
   - Tryptophan pyrrolase

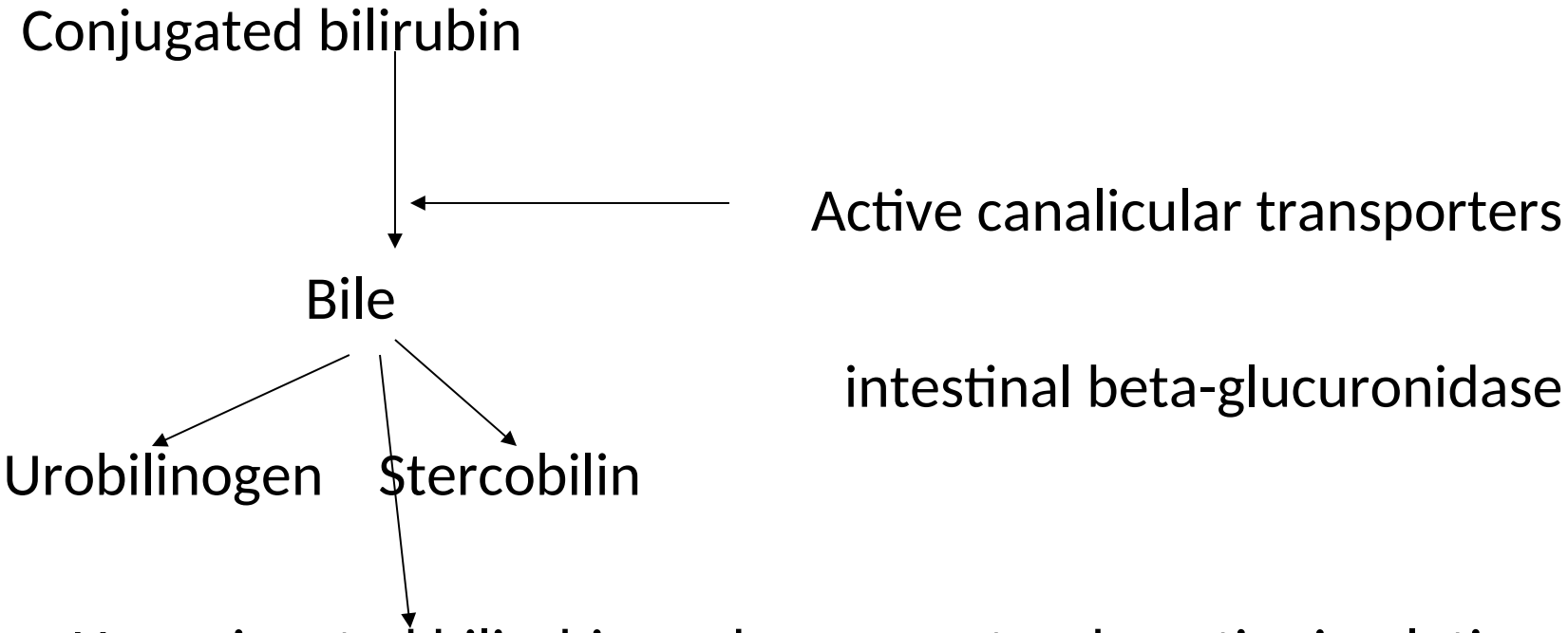
Bilirubin metabolism



Bilirubin Metabolism



Biliary excretion



Enterohepatic circulation

- Bilirubin conjugates are unstable and are easily hydrolyzed to none conjugated bilirubin within intestinal lumen

- Bacterial Beta glucoronidase enzyme is responsible for deconjugation

- Enzyme ativity high with introduction of enteral feeding

- After hydrolysis the bilirubin can be reabsorbed across the intestinal mucosa to return to the liver via portal circulation

Fetal bilirubin metabolism

- Bilirubin detected in amniotic fluid 12/40
- Always unconjugated and excreted across placenta
- Disappears by 36-37weeks
- Uridine Diphosphoglucoronosyl transferase enzyeme activity is 0.1% adult levels17- 30/40

Birth changes

- Newborns rarely jaundiced at birth except in severe hemolytic disease

- ↑ bilirubin at birth independent of gestation

Daily neonatal bilirubin production

- 75% ←senescent RBC destruction

- 25% ← other sources

1. Non-erythropoeitic component

2. Erythropoieteic component

Physiological jaundice

- Mild unconjugated hyperbilirubinemia
- Develop in normal newborn
- Usually during 1-2weeks of life
- 5 to 6 mg/dL (86 to 103 µmol/L) but not >17 to 18 mg/dL (291 to 308 µmol/L)
- Develops 72-96hrs after birth

Causes:

1. Increased RBC turnover-large vol of mature and immature erythrocytes precusors

2. decreased RBC lifespan 70-90 days compared to 120 days in adults

*Maisels,MJ. Neonatal Hyperbilirubinemia. In: Care of the High-Risk Neonate, 5th ed, Klaus, MH, Fanaroff, AA (Eds), WB Saunders, Philadelphia 2001. p.324

3. immature UDPGT and transporter systems-enzyme level less than 0.1% in the first 10 days

4. ↑ beta-glucuronidase activity – reabsorption due to presence of bacteria in the gut

Physiological jaundice

4. Defective hepatic intake-less binding protein.it reaches adult levels by day 5

5. Variations in thymine-adenine repeats***

6. Mutation in UDPGT gene(Gly71Arg) in Asians****

**Halamak,LP, Stevenson,DK. Neonatal jaundice and liver disease. In: Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant, 7th ed, Fanaroff, AA,Martin,RJ (Eds), Mosby, St. Louis 2002. p.1309.

***Beutler, E, Gelbart, T, Demina, A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism?. Proc Natl Acad Sci U S A 1998; 95:8170.

****Akaba, K, Kimura, T, Sasaki, A, et al. Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. Biochem Mol Biol Int 1998; 46:21.

Risk factors

- Maternal-
- Perinatal –
- Neonatal

Maternal factors

- Race/ethnicity-Asian,Native Americans,Greek Islanders

- Runs in families- with previous risky baby the higher the risk

- Pregnancy complications- diabetis mellitus-
  - –large babies have increased erythropoiesis therefore high bilirubin
- Maternal drugs eg oxytocin,diazepam- drugs may reduce enzyme activity

Perinatal factors

- Birth trauma-SVD have high total serum bilirubin than C/S
  - Cephalohematoma
  - echymosis
  - Delayed cord clamping
  - Forcep delivery

- Infection
  - Viral -HIV
  - Bacterial-streptococcus,hemophilus,treponema
  - Protozoal-malaria

Neonatal factors

- Prematurity
-
- breech, lowbirth weight, male,

- Decreased leads to increased enterohepatic circulation

Neonatal factors

4. Polycythemia

5. Drugs-streptomycin,CAF,benzyl alcohol,sulfisoxazole

6. Early onset breastmilk jaundice

PATHOLOGICAL Unconjugated hyperbilirubinemia

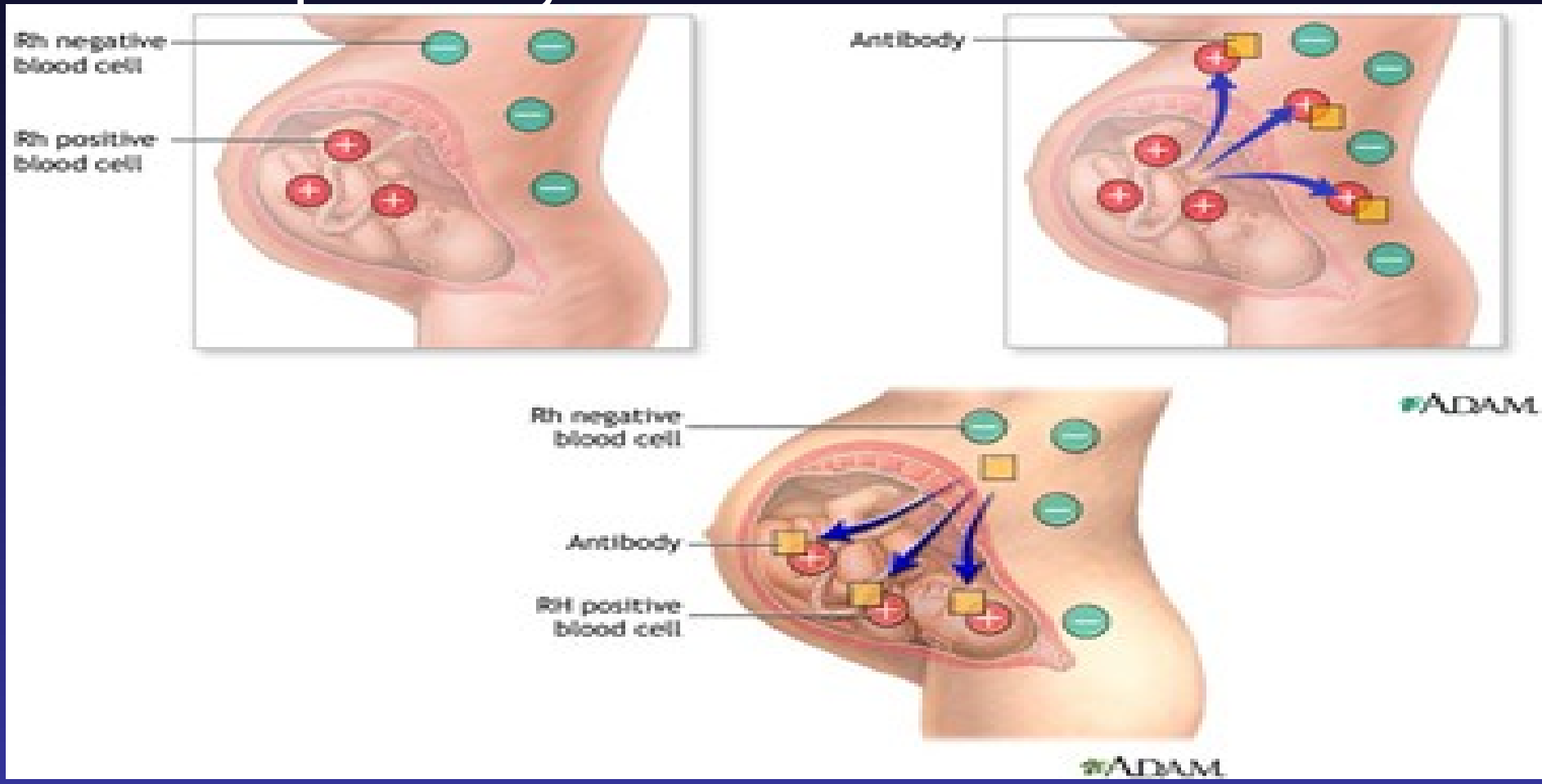
- ↑ bilirubin load metabolized by liver
- Damaged/ ↓ transferase enzyme activity
- Competition and blocking transferase enzyme

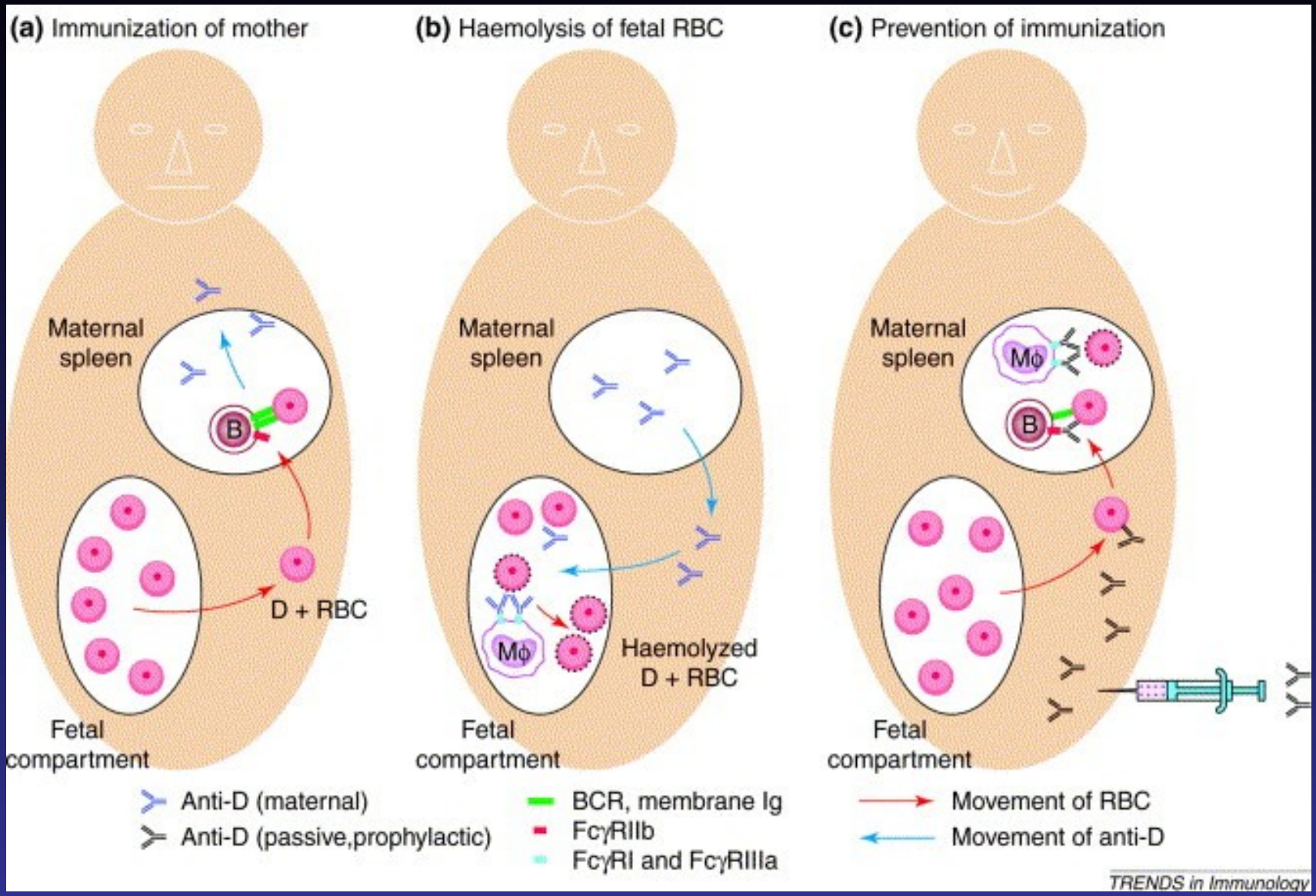
↑bilirubin load

- A) Hemolytic anemia
  - -immune-
    - Rhesus isoimmunization
      - Most severe degree of hyperbilirubinaemia
      - First baby is not affected
      - Develops within the first few hours of life
      - Rise of bilirubin occur rapidly within 48 hours
      - Cholestasis may occur due to congestion of the liver from extramedullary erythropoisis,heart failure and from tissue hypoxia due to decreased blood supply and anaemia
      - High risk of encephalopathy
      - RX-phototherapy,exchange transfusion,anti D to mother

Scenario 2

Pathological Jaundice Secondary to Rh Incompatability




(a) Immunization of mother
(b) Haemolysis of fetal RBC
(c) Prevention of immunization
Maternal spleen
B
D + RBC
Fetal compartment
Mϕ
Haemolyzed D + RBC
Anti-D (maternal)
Anti-D (passive,prophylactic)
BCR, membrane Ig
FcγRIIb
FcγRI and FcγRIIIa
Movement of RBC
Movement of anti-D
TRENDS in Immunology

- ABO incompatibility
  - Milder and more brief
  - Rarely causes kernicterus
  - Occur even in first born
  - Common in blood group O mother and group A baby

– Inheritable –

- RBC membrane defects
  - e.g hereditary spherocytosis,elliptocytosis
- RBC enzyme deficiences
  - » -glucose 6 phosphate deficiencies,pyruvate kinase deficiency
- hemoglobinophathies

- Others
  - Sepsis—infection increases RBC destruction and hepatocellular damage
  - Extravasation of blood-hematoma, pulmonary haemorrage –this slows bilirubin release as macrophages gradually converts heme to bilirubin

- B) increased enterohepatic circulation
  - Breast milk jaundice
    - –develops in an estimated 2% of breast-fed term infants
    - –after the 7th day of life, with maximal concentrations as high as 10–30 mg/dL
    - – reached during the 2nd–3rd week.

- If breast-feeding is continued, the bilirubin gradually decreases
- may persist for 3–10 wk at lower levels.
- Phototherapy may be of benefit.

- etiology of breast-milk jaundice is not entirely clear

- may be attributed to the presence of glucuronidase in some breast milk.

Breastfeeding jaundice

- occur in the 1st week of life
- Hyperbilirubinemia (>12 mg/dL) develops in 13% of breast-fed infants in the 1st wk of life

Aetiology

- may be due to
  - » decreased milk intake with dehydration
  - »and/or reduced caloric intake.

- Giving supplements of glucose water to breast-fed infants is associated with higher bilirubin levels,
  - » in part because of reduced intake of the higher caloric density of breast milk.

Prevention

- Frequent breast-feeding (>10/24 hr)
- rooming-in with night feeding
- discouraging 5% dextrose or water supplementation
- lactation support

Grunebaum, E, Amir, J, Merlob, P et al. Breast milk jaundice: natural history, familial incidence and later neurodevelopmental outcome of the infant. Eur J Pediatr 1991; 150:267.

**Gourley, GR, Arend, RA. beta-Glucuronidase and hyperbilirubinaemia in breast-fed and formula-fed babies. Lancet 1986; 1:644.

- Intestinal disorders-
  - »Pyloric stenosis
  - »Small or large bowel obstruction
  - »Reduces clearance of bilirubin due to increased enterohepatic circulation

- If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal levels within a few days.

- With resumption of breast-feeding, bilirubin levels seldom

- C) decreased clearance
  - prematurity
  - congenital atresia of the bile ducts.
    - **Jaundice persisting for more than 2 wk**
    - **associated with acholic stools and dark urine**
  - inspissated bile syndrome.

D) Metabolic disorders

- Hypothyroidism- prolonged jaundice occurs in 10% of cases
- Results from depressed metabolism or dependance of maturition of hepatic pathways on thyroxine
- Hypopituitarism

E) In born errors of metabolism

galactosemia

tyrosinemia

Damaged / ↓ transferase enzyme activity

- Genetic deficiencies→ absent /deficient enzymes

Genetic

1. Familial disorders of conjugation

e.g.

Gilbert's syndrome-

- affect enzyme encoding
- autosomal dominant and recessive
- Usually mild

Criglar-Nagger I-

- inherited
- Autosomal recessive
- Infants have a complete absence of UDPGT
- Develop severe jaundice

- RX liver transplant

- Crigler najjar type ii
  - Autosomal dominant
  - Less severe
  - Neonates with reduced enzyme activity
  - Respond to phenobarbitone

1. Enzymatic defects-G6PD;pyruvate kinase;hexokinase; congenital erythropoietic porphyria

2. Erythrocyte structural defects-spherocytes;elliptocytes

- Hypoxia
- Hypothermia-decreased enzyme activity

Competition and blocking transferase enzyme

- Drugs and other substances requiring glucuronic acid oxidation

Clinical features

- Jaundice may be present at birth

- or may appear at any time during the neonatal period, depending on etiology.

- Jaundice usually becomes apparent in a cephalocaudal progression

- starting on the face and progressing to the abdomen and then feet, as serum levels increase.

- Dermal pressure may reveal the anatomic progression of jaundice

❖(face, = 5 mg/dL;

❖mid-abdomen, = 15 mg/dL

❖soles, = 20 mg/dL

clinical examination cannot be depended on to estimate serum levels.

- Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange

- jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast.

- signs of kernicterus rarely appear on the 1st day
- affected infants may present with lethargy and poor feeding
- without treatment, can progress to acute bilirubin encephalopathy

- Laboratory Evaluation of the Jaundiced Infant of 35 o
  More Weeks' Gestation

- ❑ *Jaundice* in first 24 hr
  - ❑ Measure TcB and/or TSB
- ❑ Jaundice appears excessive for infant's age
  - ❑ Measure TcB and/or TSB

- Infant receiving phototherapy or TSB rising rapidly and unexplained by history and physical examination
    - Blood type and Coombs test,
    - Complete blood count and smear
    - Measure direct or conjugated bilirubin
    - It is an option to perform reticulocyte count
    - Repeat TSB in 4–24 hr depending on infant's age and TSB level

- TSB concentration approaching exchange levels or not responding to phototherapy
    - Perform reticulocyte count,
    - G6PD
    - albumin

- Elevated direct (or conjugated) bilirubin level
    - Do urinalysis
    - urine culture.
    - Evaluate for sepsis if indicated by history and physical examination

- Jaundice present at or beyond age 3 wk, or sick infant
  - Total and direct (or conjugated) bilirubin level
  - If direct bilirubin elevated, evaluate for causes of cholestasis
  - Check results of newborn thyroid and galactosemia screen
  - evaluate infant for signs or symptoms of hypothyroidism

kernicterus

DEFINITION

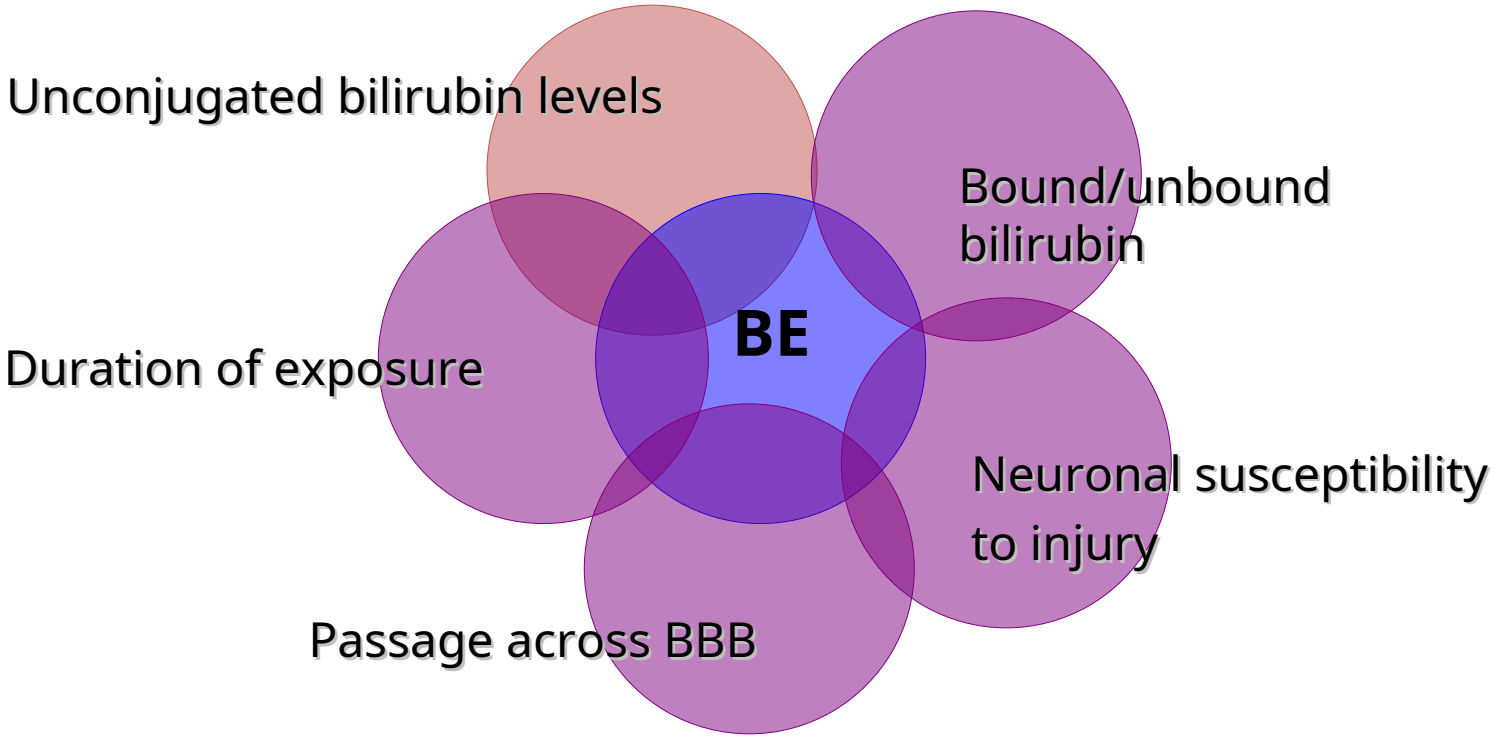
- Neurological syndrome resulting deposition of unconjugated bilirubin in the basal ganglia and brainstem nuclei

- Kernicterus ≡ Bilirubin encephalopathy

- **pathogenesis**
- multifactorial
- involves an interaction between
  - unconjugated bilirubin levels,
  - albumin binding
  - unbound bilirubin levels
  - passage across the blood-brain barrier,
  - neuronal susceptibility to injury.

Pathogenesis

Multifactorial involvement



Bilirubin toxicity-

- Factors that Increases permeability of BBB or nerve cell membranes to bilirubin or
- **Disruption of the blood-brain barrier**

1. Asphyxia
2. Prematurity
3. Hyperosmolality
4. Infection

Mechanism of toxicity

- Unclear but several postulations

1. Inhibits mitochondrial enzymes interfering with DNA synthesis
2. Induces DNA strand breakage
3. Inhibits protein synthesis and phosphorylation

Critical levels

- Precise level of the bilirubin at which Kernicterus occurs unknown

- Encephalopathy develops >30mg/dL in term healthy infants without hemolysis (21-50mg/dL)

Critical levels

- All infants with hemolysis have risk directly proportional to the serum bilirubin levels
- VLBW infants 8-12mg/dL associated with Kernicterus
- The less mature the infant the greater the susceptibility to Kernicterus

Clinical forms

signs and symptoms usually appear

- 2-5 days after birth in term infants
- and as late as 7th day in premature

Early sign not indistiguishable from

- **Sepsis**
- **asphyxia**
- **hypoglycemia**
- **intracranial hemorrhage**

Acute form - 3 phases

1. Phase 1-1-2days;
   - poor suckling;
   - ↓mororeflex+deep tendon reflexes;
   - lethargy;seizures;
   - respiratory distress
   - stupor

1. Phase 2-mid 1st wk-
   - ❑ hypertonia of extensor muscles
   - ❑ opisthotonous
   - ❑ bulging fonatnelles
   - ❑ high pitched cry
   - ❑ Twitching
2. Phase 3-after wk1-
   - ❑ hypertonia
   - ❑ Spasms
   - ❑ Convulsions
   - ❑ posturing

Clinical forms

Chronic form

Year 1-opisthotonus;

- hypertonia;
- active deep tendon reflexes;
- obligatory tonic neck reflexes;
- delayed motor skills;
- rigidity and convulsion

- After year 2-movt disorders e.g.
  - bilateral choreoathetosis;
  - ballismus;
  - tremors
  - Seizures
  - mental deficiency;
  - disarthric speech;
  - sensorineural hearing loss;
  - upward gaze abnormalities

Pathology

- Generalized yellow staining of the brain which later localizes to:-

1. Corpus subthalamicum
2. Hippocampus
3. Olfactory area
4. Striate bodies
5. Thalamus
6. Globus pallidus
7. Inferior clivus
8. Putamen
9. Cerebellar and cranial nerve nuclei

Treatment Options

- Phototherapy
- Exchange transfusion
- Drugs
- Alkalinization of plasma

treatment

- Assess for jaundice in bright, natural light if possible, check the eyes, blanched skin on nose and the sole of the foot

- Always measure serum bilirubin if age < 24 hours and if clinically moderate or severe - Any jaundice if aged <24hrs needs further investigation and treatment

- **Refer early if jaundice in those aged <24hrs and facility cannot provide phototherapy and exchange transfusion**

- Indications of phototherapy:
  - In a well baby with jaundice easily visible on the sole of the foot
  - In a preterm baby with ANY visible jaundice
  - In a baby with easily visible jaundice and inability to feed or other signs of neurological impairment ***and consider immediate exchange transfusion***

Mechanism of action of phototherapy

- Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to a high intensity of light in the visible spectrum.

- Bilirubin absorbs light maximally in the blue range (420–470 nm).

- .

- Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels
- Bilirubin in the skin absorbs light energy, causing several photochemical reactions.

Mechanism of action of phototherapy

structural isomerisation:

phototherapy refers to the use of light to convert bilirubin molecules in the body into water soluble isomers that can be excreted by the body.

The main structural isomer of bilirubin is Z-lumirubin.

structural isomerization is irreversible.

structural isomers of bilirubin are less lipophilic than normal bilirubin and can be excreted into bile without undergoing glucuronidation in the liver

Structural bilirubin isomers, like Z-lumirubin, can also be excreted in the urine.

- configurational isomerisation:.
- converting the toxic native unconjugated 4Z, 15Z-bilirubin into an conjugated configurational isomer 4Z,15E-bilirubin, which can then be excreted in bile without conjugation.

Configurational isomerization is reversible,

the configurational of bilirubin are less lipophilic than normal bilirubin and can be excreted into bile without undergoing glucuronidation in the liver.

Some of the configurational isomers of bilirubin, however, revert back to the native form after excretion into bile and can be reabsorbed via enterohepatic circulation in the gut.

Photooxidation :

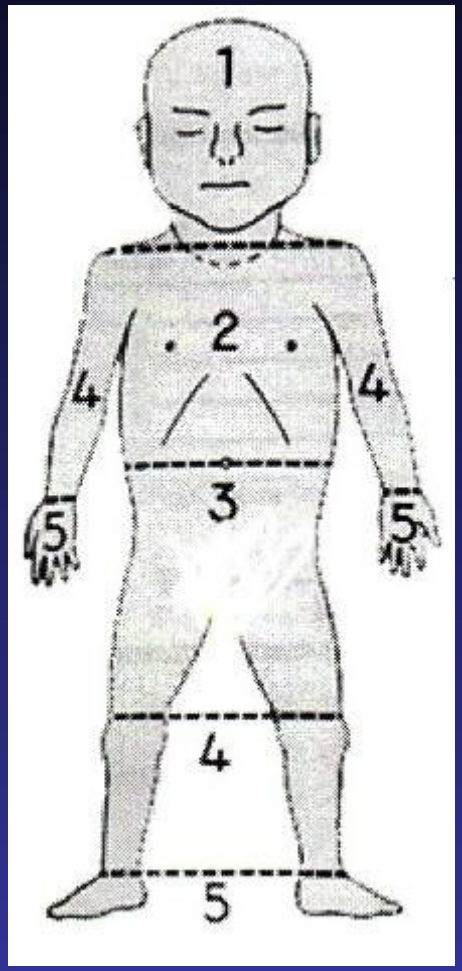
The absorptions of light by bilirubin also results in the generation of excited-state bilirubin molecules that react with oxygen to produce colorless oxidation products, or photooxidation products.

This process occurs more slowly than configurational or structural isomerization.

Photooxidation products are primarily excreted in the urine.

Kramer's rule

Clinically jaundiced when the bilirubin level reaches 80-120 µmol/L



Zone	1	2	3	4	5
SBR (umol/L)	100	150	200	250	>250

- **Stop phototherapy** – when bilirubin 50 micromol/L **lower** than phototherapy threshold for the baby's age on day of testing

Phototherapy and Supportive Care - Checklist

- ***Shield the eyes with eye patches.*** **–**
  - Remove periodically such as during feeds

- ***Keep the baby naked***

- ***Place the baby close to the light source***
  - – 45 cm distance is often recommended
  - but the more light power the baby receives the better the effect so closer distances are OK if the baby is not overheating especially if need rapid effect.

  - May use white cloth to reflect light back onto the baby making sure these do not cause overheating

- ***Do not place anything on the phototherapy devices*** –
  - lights and baby need to keep cool so do not block air vents / flow or light.
    - Also keep device clean – dust can carry bacteria and reduce light

- ***Promote frequent breastfeeding.***
    - Unless dehydrated, ***supplements or intravenous fluids are unnecessary***.
    - Phototherapy use can be interrupted for feeds; allow maternal bonding.

Periodically change position supine to prone –

- Expose the maximum surface area of baby to phototherapy;
- may reposition after each feed.

- ***Periodic (12 to 24 hrs) plasma/ serum bilirubin test***.
  - Visual testing for jaundice or transcutaneous bilirubin is unreliable.

- m***ake sure that each light source is working*** and emitting light.

  - Fluorescent tube lights should be replaced if:
    - More than 6 months in use (or usage time >2000 hrs)
    - Tube ends have blackened
    - Lights flicker.

- **Complications**
- loose stools
- erythematous macular rash
- purpuric rash associated with transient porphyrinemia
- overheating
- dehydration (increased insensible water loss, diarrhea)
- hypothermia from exposure
- benign condition called *bronze baby syndrome*..

- Contraindication
- presence of porphyria.

Intravenous Immunoglobulin.

- is an adjunctive treatment for hyperbilirubinemia due to isoimmune hemolytic disease

- Its use is recommended when serum bilirubin is approaching exchange levels despite maximal interventions including phototherapy.

- Intravenous immunoglobulin (0.5–1.0 g/kg/dose; repeat in 12 hr)

- has been shown to reduce the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis.

Exchange Transfusion.

- **Introduction**
- An exchange transfusion involves removing aliquots of patient blood and replacing with donor blood in order to remove abnormal blood components and circulating toxins whilst maintaining adequate circulating blood volume.

- It is primarily performed to
  - remove antibodies
  - excess bilirubin in isoimmune disease
- the incidence of exchange transfusion is decreasing
  - secondary to the prevention
  - improved prenatal management of alloimmune haemolytic disease
  - improvements in the management of neonatal hyperbilirubinaemia

- **Indications**
- 1. Alloimmune haemolytic disease of the newborn
- Remove circulating bilirubin to reduce levels and prevent kernicterus
- Replace antibody-coated red cells with antigen-negative red cells

- Severe hyperbilirubinaemia secondary to alloimmune haemolytic disease of the newborn is the most common reason for exchange transfusion in the neonatal intensive care unit.
- A total serum bilirubin level at or above the exchange transfusion level should be considered a medical emergency and intensive phototherapy (multiple light) should be commenced immediately.

- 2. Significant unconjugated hyperbilirubinaemia with risk of kernicterus due to any cause when intensive phototherapy is unsuccessful
- 3. Severe anaemia (where there is normal or increased circulating blood volume)
- 4

- . Antibodies in maternal autoimmune disease
- 5. Polycythaemia (to reduce haematocrit, usually accomplished with partial exchange transfusion using normal saline replacement)
- 6. Severe disturbances of body chemistry

- Double volume exchange transfusion is performed
  - if intensive phototherapy has failed to reduce bilirubin levels to a safe range
  - if the risk of kernicterus exceeds the risk of the procedure.

procedure

- Done in neonatal ICU
- Use one way or 2 way catheter
- May use umbilical vein up to inferior vena cava or atrium
- Blood type rhesus negative blood group of blood withdraw over 2 minutes infuse slightly faster

- Blood volume for infusion

- 85mls/kg body weight and give double volume thus 170mls/kg body weight
- One volume removes 65% of babies RBC
- Double volume removes 88% of babies RBC

- **Complications**
    - Air embolus
    - metabolic acidosis
    - electrolyte abnormalities-
        - Hyperkalemia
        - hypernatremia
        - hypoglycemia
- hypocalcemia**Complications**
- The most commonly reported adverse events during or soon after exchange transfusion:
- Catheter related complications; air emboli; thrombosis; haemorrhage
- Haemodynamic (related to excess removal of injection of blood): hypo or hypertension, intraventricular haemorrhage (preterm)
- Hypo or hyperglycaemia
- Hypocalcaemia, hyperkalaemia, acidaemia

- Potential complications related to exchange transfusion:
- Arrhythmias
- Bradycardia
- Neutropenia, dilutional coagulopathy
- Feed intolerance, necrotizing enterocolitis
- Septicaemia, blood born infection
- Hypo or hyperthermia

- **Preparation of the Infant**
- Medical staff should discuss the procedure with

- thrombocytopenia
- volume overload
- arrhythmias
- NEC
- infection
- graft versus host disease
- death.
- Anaemia/polycythemia

- Coagulopathy
- Blood transmited infections

Pre-exchange specimens

- Arterial blood gases
- Electrolytes sodium, pottasium, calcium, blood glucose
- Full blood count ,differentials
- Urea,creatinine
- Bilirubin total and direct
- Blood group,mothers blood group

During the procedure

- Blood gas analysis
- Electrolyte
- Blood glucose

Post-exchange specimens

- Arterial blood gases analysis
- Electrolytes sodium, potasium, calcium, blood glucose
- Full blood count ,differentials
- Urea,creatinine
- Bilirubin total and direct
- Blood group,mothers blood group

Clinical monitoring

Baseline

- Axilla Temperature
- Heart rate
- Respiratory rate
- Blood pressure
- Oxygen saturation

continously

Baseline

- skin Temperature
- Heart rate
- Respiratory rate
- Blood pressure
- Oxygen saturation

Post transfusion

- Axilla Temperature every 15minutes
- Record blood in and blood out
- Monitor vitals every 2 hours post transfusion

- NOTE:
  - This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range

prognosis

- Overt neurologic signs have a grave prognosis;
  - more than 75% of such infants die
  - 80% of affected survivors
    - have bilateral choreoathetosis
    - involuntary muscle spasms
    - Mental retardation
    - deafness
    - spastic quadriplegia

conclusion

- **POCKET BOOK OF Hospital care for children** GUIDELINES FOR THE MANAGEMENT OF COMMON CHILDHOOD ILLNESSES
- **Second edition**