NEONATAL HYPERBILIRUBINEMIA

by:

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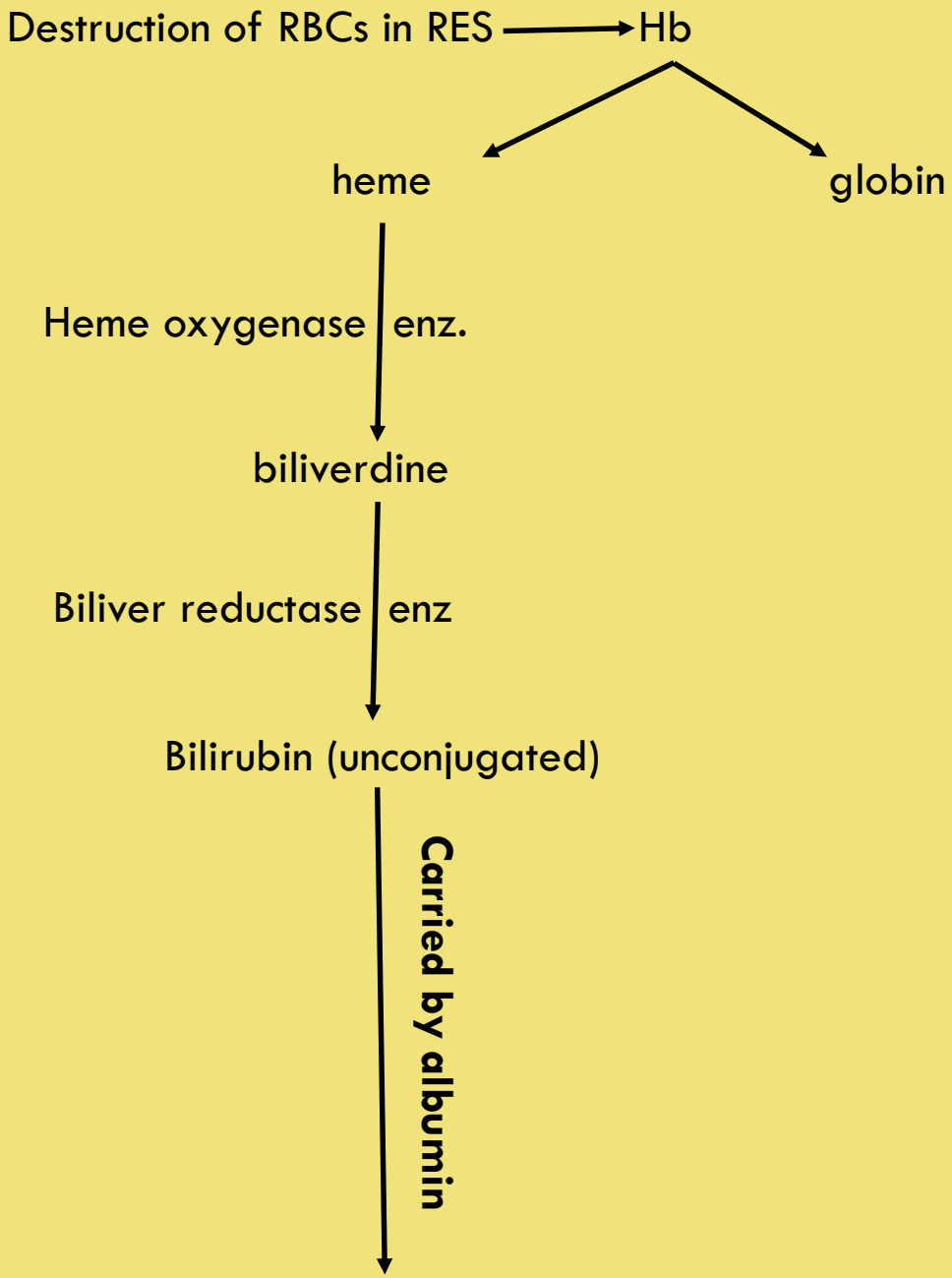
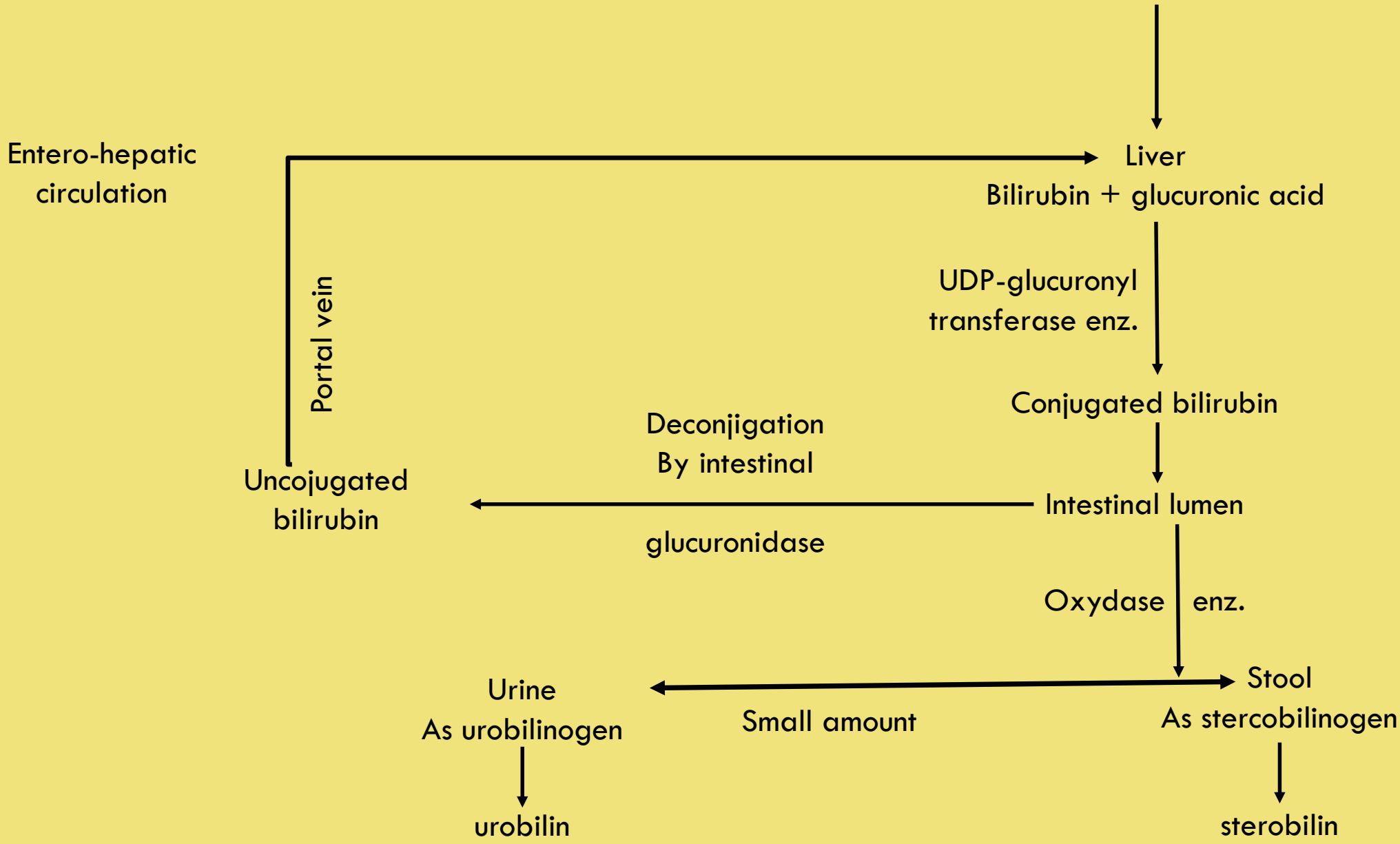
It is an accumulation of bilirubin in the serum , then its precipitation in the sclera , mucous membrane & skin to give yellow discoloration .

2 types :

1. Indirect hyperbilirubinemia : indirect bilirubin is unconjugated , lipid soluble , so it can cross the blood brain barrier(BBB) to cause neurotoxicity .
2. Direct hyperbilirubinemia : direct bilirubin is conjugated , water soluble , so it cannot pass BBB but it appears in the urine , its rise indicates a potentially serious hepatic or systemic disease.


Destruction of RBCs in RES
Hb
heme
globin
Heme oxygenase enz.
biliverdine
Biliver reductase enz
Bilirubin (unconjugated)
Carried by albumin


Entero-hepatic
circulation
Liver
Bilirubin + glucuronic acid
UDP-glucuronyl
transferase enz.
Portal vein
Conjugated bilirubin
Deconjigation
By intestinal
Uncojugated
bilirubin
Intestinal lumen
glucuronidase
Oxydase enz.
Urine
As urobilinogen
Small amount
Stool
As stercobilinogen
urobilin
sterobilin

Etiology

Indirect hyperbilirubinemia :

1. Increased load of bilirubin : hemolytic anemia, polycythemia & increased enterohepatic circulation (e.g constipation)
2. Enzyme problems :

   a. Absence of the enzyme : e.g genetic (criglar najjar syndrome & gilbrt syndrome) & prematurity.

   b. Damage or decrease activity : hypoxia, infection & hypothyroidism .

   c. Blocking or competing the enzyme by drugs.

direct hyperbilirubinemia :

1. Infection &/or inflammation : sepsis , TORCH infection , idiopathic neonatal hepatitis.
2. Obstruction: biliary atresia , choledochal cyst , inspissated bile syndrome following sever hemolysis.
3. Metabolic : galactosemia , frucosemia , tyrosinemia , alpha -1- anti –trypsine deficiency & cystic fibrosis.

Clinical manifestations

The jaundice appears at birth or later on according to the cause , it appears with cephalocaudal progression from above downward (roughly , by dermal pressure at face 5 mg/dl chest 5-10 mg/dl abdomen 15 mg/dl sole 20mg/dl

Transcutaneous measure (by special equipment) is for screening . While it is confirmed by serum measure as total serum bilirubin (TSB) , then can be differentiated into direct & indirect

indirect	direct
1. Skin : orangish – yellow. 2. Stool : normal colored. 3. Urine : normal (contains urobilinogen)	1. Skin : greenish – yellow. 2. Stool : clay (white) colored. 3. Urine : tea colored (contains bile pigment)

Differential diagnosis

The 1st question in taking the history is the onset of jaundice

- Within the 1st 24 hr of life : erythroblastosis fetalis, concealed hemorrhage , congenital infaction and Grigler najjar
- Within 2-3 days of life : physiological jaundice , familial non –hemolytic jaundice (G. N. & G. syndromes) & breast feeding jaundice .
- After 3rd day – end of 1st week : UTI and bacterial sepsis .
- After the 1st week : breast milk jaundice , hypothyroidism , pyloric stenosis , morphological abnormalities (e.g. spherocytosis) or enzyme deficiency of RBCs (e.g. G6PD deficiency) & causes of direct hyperbilirubinemia .

. Causes of jaundice after the two weeks and may persist in and beyond 1st month may lead to what is called prolonged jaundice

Physiological jaundice

It is a common cause of neonatal hyperbilirubinemia , it is due to transient immaturity of the hepatic conjugating mechanism .

In full term : indirect bilirubin is normally 1-3 mg/dl in the blood of umbilical cord , because of physiological jaundice it will be increased at a rate of less than 5 mg/dl/day to be visible at 2-3 day of life , peaking at 3-4 day (not more than 12 mg/dl) then decreased to less than 2mg/dl at 5^{th}-7^{th} day .

in preterm : slower & longer duration , peaked at 4^{th} -7^{th} day of life (not more than 14mg/dl) & it is infrequently seen after 10^{th} day .

Its diagnosis is of exclusion made after careful evaluation to rule out other causes of jaundice.

Physiological jaundice can occur at ranges out of the above & this is called exaggerated physiological jaundice , it has many risk factors to occur: maternal DM, polycythemia ,male downs syndrome ,cuteneous bruising ,breast feeding , dehydration ,caloric deprivation ,delayed bowel motion , family history , oxytocin infusion & race(Greeks , Asian & Native American)

Prolonged jaundice causes include

- Hemolysis
- Hypothyrodism
- Hereditory glucuronyl transferase deficiency
- Breast milk jaundice
- Intestinal obstruction (pyloric stenosis)
- Idiopathic neonatal hepatitis
- Cholestasis
- TORCH
- Galactossaemia
- Biliary atresia
- Inspissated bile syndrome follow hemolytic anemia

Pathological jaundice

Jaundice is considered pathological if the time of appearance duration or pattern of rising vary significantly from that of physiological jaundice or the course is compatible with physiological j. but other reason exits to suspect that the infant is at risk , so it includes :

1. j. appears in the 1st 24-36 hr of life
2. S. bilirubin is increased at a rate of more than 5mg/dl/day .
3. S. bilirubin is more than 12mg/dl in full term , or 14mg/dl in preterm baby(especially with absence of the above risk factors).
4. If j. persists after 10-14day of life .
5. Direct bilirubin is at any time more than 2mg/dl with more than 20% of the total serum bilirubin .
6. Presence of symptoms and sings of hemolysis ,sepsis , kernicterus , cholestasis , or family history of hemolytic disease.

In any of these condition , a search to determine the cause is mandatory.

Breast milk jaundice

Occurs in about 2% of breast fed babies , occur after 7th day . Max. elevation is 10-30 mg/dl ,although kernicterus is uncommon but it can occur, the cause is unclear , maybe due to the presence of glucuronidase in some breast milk which increase enterohepatic circulation , or it may contains an inhibitors of bilirubin conjugation .

Therapeutic & diagnostic way is by interruption of breast milk for 1-2days , this will decrease the jaundice and seldom returns to previous high level . It should be recognized from breast feeding jaundice which occur in the 1st wk of life in about 13% due to decreased milk intake with dehydration &/or decreased caloric intake , some give glucose water and this will more exaggerate the condition because it affect the intake of high density breast milk , treatment is with frequent feeding (more than 10 times /day) , and stopping of glucose water intake .

Erythroblastosis fetalis

Maternal Ab passes through the placenta to cause fetal RBCs destruction. More than 60 antigenic systems can cause this problem , but the most common is Rh & ABO blood groups , while the others are rare (kell , duffy , M, Kidd……)

Rh incompatibility

Rh antigens are C,D,E., about 90% the disease is due to D antigen . It occur if the mother's Rh –ve & the baby's Rh +ve , if small amount of blood (usually more than 1 ml) of Rh +ve blood pass to Rh –ve maternal circulation sensitization to form Abs against D antigens of the passed blood . Once sensitization has taken place , then only small doses of Rh +ve blood will stimulate Ab increment which is IgM but later on will replaced by IgG which can pass through the placenta to cause hemolysis in the fetus or baby after birth.

Blood can pass from the fetus to the mother in the following conditions :

Delivery , abortion , abdominal trauma in pregnancy , ectopic pregnancy ,amniocentesis & chorionic villous biopsy , or by medical error.

The disease is rarely to occur during the 1st pregnancy because transfer of fetal blood occur mostly at delivery (unless by other means mentioned above than delivery) , so the time is not enough for sensitization to occur but the next pregnancy will be affected & the risk increased with successive pregnancy .

Clinical manifestations

The severity ranges from mild (only laboratory evidence) to severe hemolysis leading to compensatory hyperplasia of the erythropoitic tissue (HSM) to overcome the anemia , if this compensatory mechanism is inadequate , anemia will occur which later on will lead to cardiac decompensation (cardiomegaly & fetal distress) , massive anasarca (hydrops fetalis) , & circulatory collapse . Failure to initiate breathing due to pul . Edema or pleural effusion will cause asphyxia . Thrombocytopenia can occur due to decreased productions or concurrent DIC ; also hypoglycemia may occur as a result islet hyperplasia of pancreas .

jaundice is usually absent at birth because of placenta clearance unless severe hemolysis , generally it appearse at 1st 24 hr & may rapidly increased in cause kernicterus , most of cases are normal at birth , but after delivery the hemolysis started with anemia & jaundice &this may lead to shock &/or kernicterus.

Diagnosis

After birth

- Rh of mother & baby
- CBP : Hb may be as low as 3-4 mg/dl , high retie ,count & thrombocytopenia in severe cases.
- Blood film : polychromasia & increased nucleated RBCs .
- Indirect bilirubin may increased with the time especially early hrs of life conjugated bilirubin may also increased.
- Coombs testis strongly +ve (direct & indirect)

Antenatal diagnosis

- History of Rh –ve mother.
- Fetal Rh by getting fetal cells or DNA (plasma) from maternal circulation.
- Measurement of maternal titer of IgG to D Ag around 15 , 30 & 36 weeks of gestation .presence of measurable Ab titer at the beginning . Rapid rise ,or a titer of 1:64 or more will indicate fetal monitoring by ultrasonography (organomegaly ,signs of hydrops, or fetal distress by Doppler ultrasound) if any of these finding is present then amniocentesis or percutaneous umbilical blood sampling (PUBS) should be done.

PUBS is take fetal blood to check Hb , while amniocentesis is to know the level of bilirubin.

Treatment

2 goals

1- prevent intra-uterine or extra-uterine death from severe anemia.

2- avoid neurotoxicity

Unborn infant :

Intrauterine transfusion (through umbilical vein under ultrasound guide) to transfuse packed RBCs for hydrops or if PCV is less than 30% (to achieve 45-55%) and repeated every 4 wks.

Live born :

Prophylactic phototherapy .

Monitoring of hemolysis (by Hb & s. bilirubin) every 4-6 hr initially , then according to the condition .

Exchange transfusion is done according to the levels of Hb and s. bilirubin .

Indications of immediate exchange transfusion are :

1- cord Hb equal or less than 10 gm/dl.

2- cord TSB equal or more than 5 mg/dl.

3- other factors are considered : if cord retic .count is more than 15% , prematurity , previous exchange or kernicterus in sibling . Type of the blood for exchange is fresh , Rh –ve compatible with maternal & baby blood .

Prevention

I. M. injection of 300 mg of human anti-D (1ml) within 72 hrs of the above conditions to destruct the passed fetal RBCs before sensitization .

ABO incompatibility

It is the most common cause of hemolytic anemia in neonate , occurs due to natural maternal Abs against A & B antigens of the baby RBCs . It occurs significantly if the mother is O & the baby is A or less commonly B blood groups.
Those Abs are IgM & cannot pass the placenta except anti-A which may be IgG , so it can cross & cause hemolysis in the 1st pregnancy , while the others can pass by the same mechanism mentioned in Rh incompatibility (by sensitization)

Clinical manifestations

Most cases are mild j. may the only manifestation ,pallor & hydrops are rare, & liver & spleen are not greatly enlarged if at all . J. appears at the 1st day , rarely become sever to cause kernicterus.

Diagnosis

- History : blood groups of the baby & mother.
- CBP : Hb may be normal or as low as 10-20 gm/dl , increased retic count.
- Blood film : extensive polychromasia nucleated RBCs with spherocytes (DDX:spherocytosis)
- Weak – moderate +ve direct Coombs test.
- TSB in about 10-20% reaches 20 mg/dl or more unless phototherapy is used.

Treatment

- Phototherapy light in blue range (420 – 470 nm) , light source distance from infant is 45cm.
- In some cases exchange transfusion with type O blood of the same Rh of the infant is needed.
- Slowly progressive hemolysis may lead to anemia later on which need packed RBCs transfusion , so post discharge monitoring of Hb is indicated .

Kernicterus (bilirubin encephalopathy)

It is a neurological syndrome resulting from deposition of unconjugated bilirubin in the basal ganglia & brain stem nuclei when indirect bilirubin level exceeding the binding capacity of albumin (normally in term baby 20 mg/dl of bilirubin can bind to albumin) . Neurotoxicity of hyperbilirubinemia is increased in :

1- decreased retention of bilirubin in the circulation : hypoproteinemia, displacement of bilirubin from albumin by competitive drugs (e.g. sulfisoxazole , moxalactam) acidosis & hypoglycemia .

2- increased permeability of BBB & neural susceptibility injury by asphyxia prematurity hyperosmalarity & infection .

There is no precise level of indirect bilirubin can cause kernicterus but it is rare to occur in healthy term baby when his s. bilirubin is below 25 mg/dl , while there is evidence suggest a low serum level below 25 mg/dl may affect IQ of healthy term baby , the more premature infant the greater susceptibility to kernicterus, it can develop in very immature neonate weighing less than 1000 gm when the serum bilirubin is less than 10 mg/dl.

Clinical manifestation

Acute stage

Phase 1 (1st 1-2 days) : the early signs are subtle & undistinguished from sepsis , hypoglycemia , intracranial bleeding or other acute illness , these are lethargy , poor feeding , loss of Moro reflex , then loss of tendon reflexes & respiratory distress.

Phase 2 (middle of 1st wk) : opisthotonos , bulging fontanels , seizure , high pitch cry.

Phase 3 (after 1st wk) hypertonia .

After the acute stage many infants die & the survivors are seriously damaged, but later on appear recovered & at 2-3 mo show only few abnormalities.

Chronic stage

1st year : hypotonia , active tendon reflexes , obligatory tonic neck reflexe.

2nd year : the above signs diminish & the typical syndrome starts to appear.

3rd year : complete neurological syndrome : bilateral chorioethetasis , seizure , mental retardation , dysarthria speech , squint , sensorineural deafness & enamel dysplasia with discoloration .

Pathology

The surface of the affected parts of the brain appears pale yellow , on section , certain regions stained yellow while others are not , there is neural loss , gliosis & atrophy at later stages .

Prevention & treatment

It may be prevented by avoiding excessively high indirect bilirubin by good management & by avoiding conditions or drugs that exaggerate the condition . Very early signs of kernicterus occasionally may be reversed by immediate exchange transfusion but it cannot be treated if well developed but we must do exchange transfusion , at least , to stop more progression .

Treatment of jaundice

phototherapy

It is an effective & relatively safe to reduce indirect bilirubin , done by exposure of the neonate to ultraviolet light it is many types (white , blue , super blue & green) it is maximally effective at blue range of wave length (420- 470 nm)fluid intake should increase by 10-20% due to over heating .

The mechanism of action is by converting the isomer of native (natural) bilirubin to new isomers one is easily excreted in biliary tract without conjugation & the other is highly water soluble (so can be excreted by kidneys in urine easily).

Its indicated at lower levels than that of exchange transfusion , but when exchange transfusion is indicated , there is no alternative .

Metalloporphyrin

This acts by inhibition of the formation of biliveridine by heme oxygenase , used as single intramuscular injection at the 1st day if the jaundice is anticipated , e.g. ABO incompatibility , G6PD deficiency .

IVIG

0.5 – 1 g/kg 1 dose repeat in 12 hr reduces the need for exchange transfusion in both ABO & RH hemolytic anemia .

Exchange transfusion:

Double volume exchange transfusion if intensive phototherapy has failed

Complications

- **Acut comp. hypoglycaemia , hypoxia acidosis , transient bradycardia , hypocalcimia , cyanosis , vasospasm , thrombosis , apnea , NEC , thrombocytopenia , volume over load , arrhythmia , death 0,3%**
- **Late comp. cholestasis , infection (CMV , Hepatitis , HIV) , late anaemia , mild graft versus host reaction , inspissated bile syndrome portal vein thrombosis and portal hypertension**

Note:

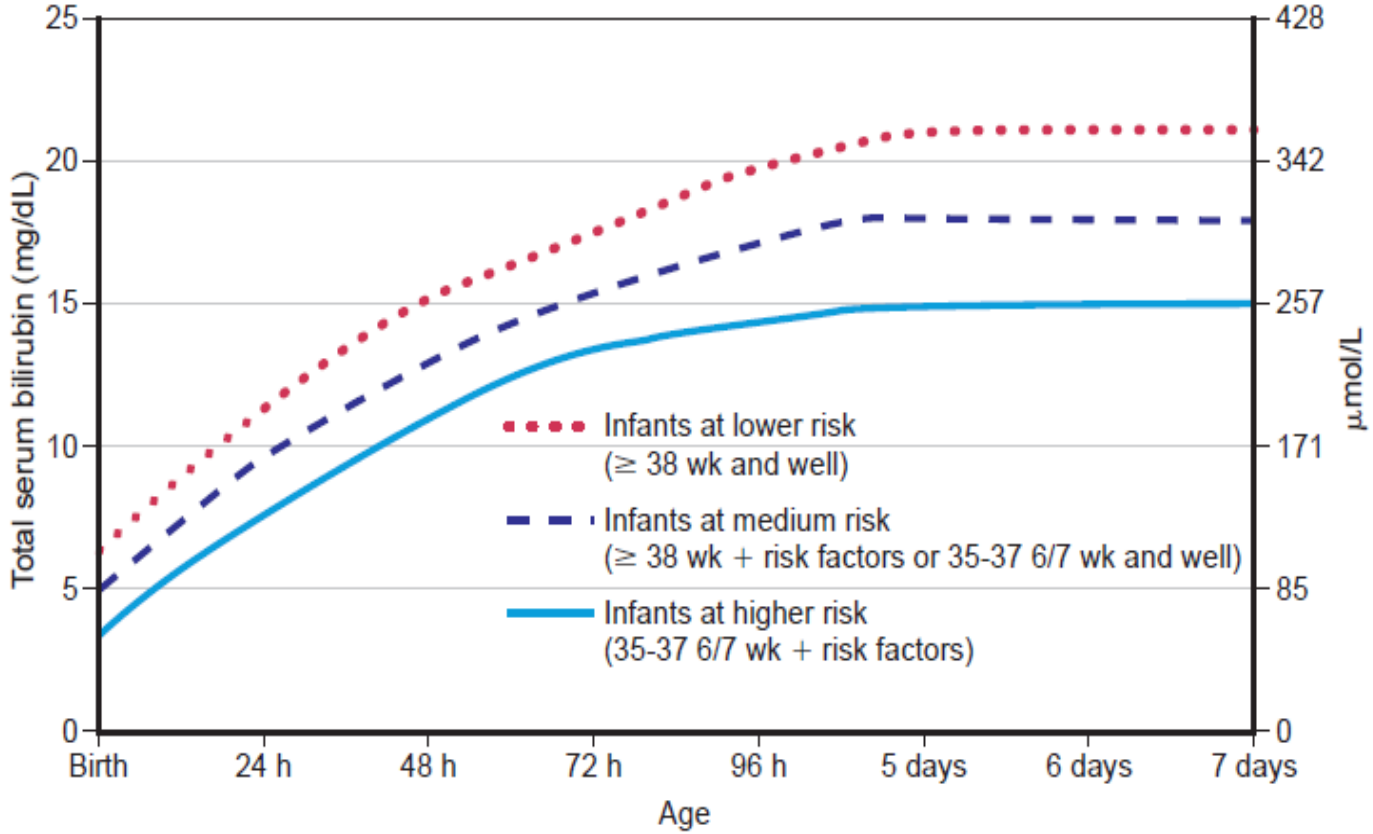
Signs suggesting Kernicterus is an indication for exchange transfusion.

Strategies for treatment of indirect hyperbilirubinemia in infants 35 or more weeks

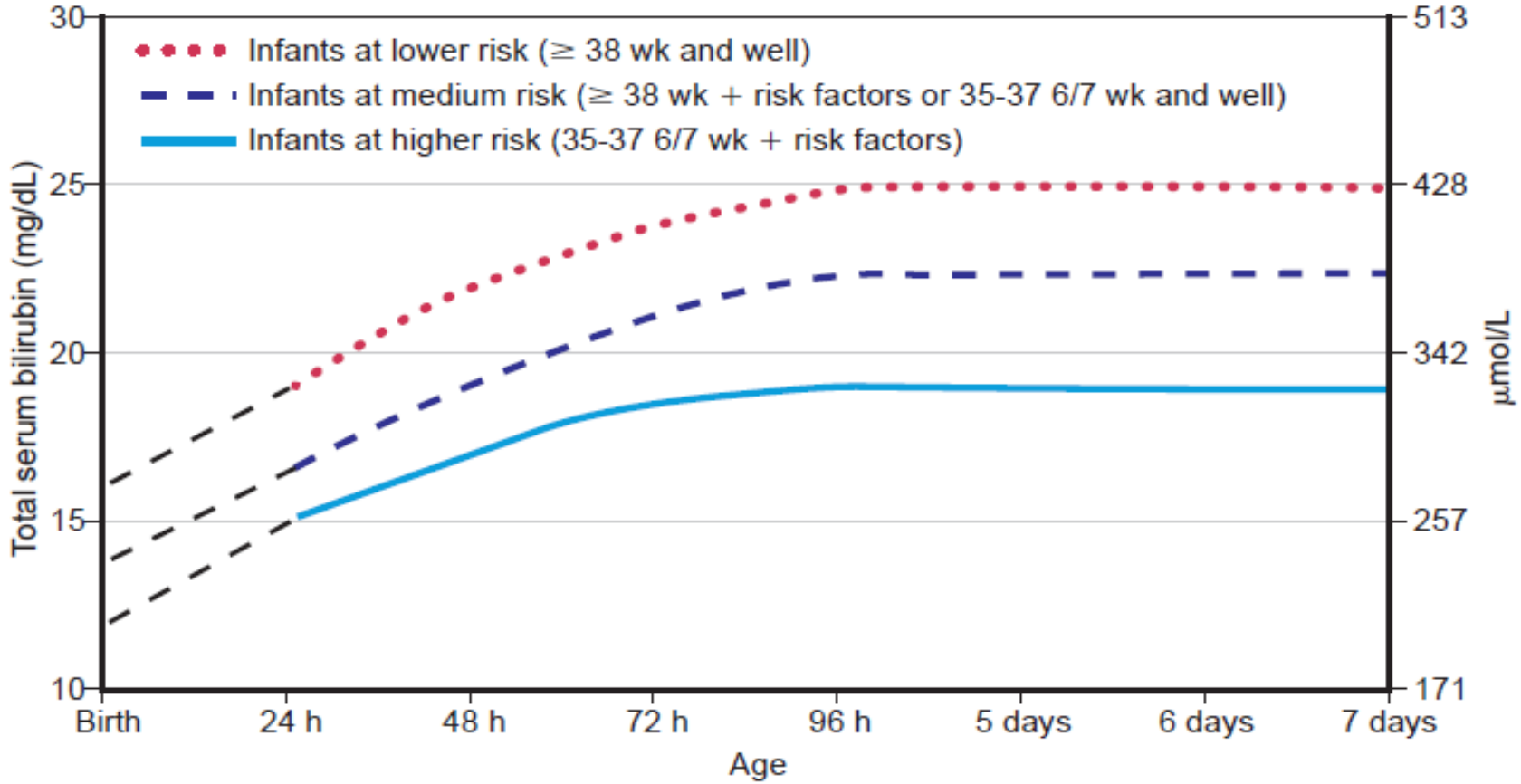
Use agraph for guidelines of intensive phototherapy and exchange transfusion level in hospitalized infants 35 or more weeks gestation which depend on

- TSB level
- Age in hours and days
- Gestational age
- Infant condition and presence of risk factors that increase risk of kernicterus at lower bilirubin level as

✓ Isoimmune hemolytic anemia , G6PD deficiency
✓ Asphyxia , IVH
✓ Lethargy , tempt. Instability
✓ Sepsis , meningitis
✓ Acidosis , hypoalbuminemia , hypoglycaemia



Guidelines for phototherapy in hospitalized infants of ≥35 wk of gestation. *Note:* These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the total serum bilirubin (TSB) exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood–brain barrier, and the susceptibility of the brain cells to damage by bilirubin. "Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths approximately 430-490 nm) of at least 30 µW/cm^2/nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's skin surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system. If TSB levels approach or exceed the exchange transfusion line , the sides of the bassinette, incubator, or warmer should be lined with aluminum foil or white material, to increase both the surface area of the infant exposed and the efficacy of phototherapy. The presence of hemolysis is strongly suggested if the TSB does not decrease or continues to rise in an infant who is receiving intensive phototherapy. Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin value (cholestatic jaundice) may inconsistently have the bronze-baby syndrome. G6PD, glucose-6-phosphate dehydrogenase. *(From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation,* Pediatrics *114:297–316, 2004.)*



Guidelines for exchange transfusion in hospitalized infants of ≥35 wk of gestation. *Note:* These suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin (TSB) rises to these levels despite intensive phototherapy. In a readmitted infant, if the TSB level is above the exchange level, TSB measurement should be repeated every 2-3 hr; exchange transfusion should be considered if the TSB remains above the levels indicated after intensive phototherapy for 6 hr. The following B:A (bilirubin:albumin) ratios can be used together with, but not in lieu of, the TSB level as an additional factor in determining the need for exchange transfusion. G6PD, glucose-6-phosphate dehydrogenase. *(From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation,* Pediatrics *114:297–316, 2004.)*

Thank you...