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Jaundice in the Newborn

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SUMMARY

Jaundice in the newborn is a relatively common symptom. It may be physiologic or due to a pathologic cause. Determination of the serum bilirubin is followed by serial determinations to document the rate of increase. Unconjugated hyperbilirubinemia, if left untreated may reach toxic levels and cause bilirubin encephalopathy. Acceptable methods of treatment include phototherapy and exchange trnsfusion.

Jaundice is the yellow discoloration of skin, sclera and mucous membranes and may be the commonest clinical sign observed in newborn nurseries. It is a consequence of excess bilirubin in the blood and becomes visible at a level of 2 mg/dl in adults. In nerwborns however, jaundice is discernible at a level of 6-8 mg/dl. A discussion on hyperbilirubinemia can only proceed after a very clear understanding of the pathway of bilirubin synthesis, trnsport and metabolism (Fig. 1).

Bilirubin Synthesis

Bilirubin is derived from the catabolism of heme protein of which the major source is hemoglobin. Erythrocyte precursors and non-hemoglobin heme proteins (mainly cyto-chromes) are other sources and may contribute about 15-25% of the load. Hemoglobin, an iron-porphyrin complex bound to globin is converted to biliverdin by a microsomal enzyme heme oxygenase. The bridge carbon atom is converted to carbon monoxide which is excreted by the lung unchanged. The resulting linear tetrapyrrole has the structure of the ix-a isomer reflecting rupture of the methane bridge of the porphyrin ring. Biliverdin, a water-soluble pigment is rapidly reduced by the enzyme biliverdin-reductase and by nonenzymatic reducing agents in the reticuloendothelial cell to form bilirubin. The degradation of 1 gm of hemoglobin forms 34 mg of bilirubin1. In the newborn the total bilirubin production is increased severalfold as a result of a shortened circulating erythrocyte life span, (reduced to 70 to 90 days as compared with 120 days in the adult) increased heme degradation from the very large pool of hematopoietic tissue that ceases to function shortly after birth and possibly increased turnover of cytochromes.

Bilirubin Transport in Plasma

The unconjugated bilirubin released into the circulation by the reticuloendothelial cell is rapidly bound to albumin, since this nonpolar pigment is almost totally insoluble in water at pH 7.4. Each molecule of adult human albumin is capable of binding at least two molecule of bilirubin, the first more tightly bound than the second. The binding capacity in the neonate is reduced ranging from 0.5-1 mole of bilirubin per mole of albumin. A molar ratio of 1 represents about 8.5mg of bilirubin per gram of albumin. Thus a normal term neonate with a serum albumin concentration of 3.5 G/dl has a maximum binding capacity of 28mg of bilirubin/dl of plasma.

Various factors influence the binding capacity of bilirubin to albumin. These include the total serum albumin concentration, presence of organic anions, drugs, hematin, free fatty acids (bind to albumin, displacing bilirubin) and maturity of the neonate reflecting the serum albumin concentration[1].

A number of drugs are known to compete with bilirubin for albumin binding. Amongst these are the sulpha group., penicillins (oxacillin, carbenicillin, cephalothin, ampicillin), digoxin, salicylates, diuretics and sodium benzonate (used as carrier with diazepam)[3]. Increased levels of free fatty acids are seen om hypoglacemia, infection, anaemia and hypothermia. These when present in excess amy displace bilirubin from the binding site. The lowering of pH increases free circulating bilirubin by displacing it from albumin and also inrease the entry of bilirubin to cells & tissues, speciality to brain.

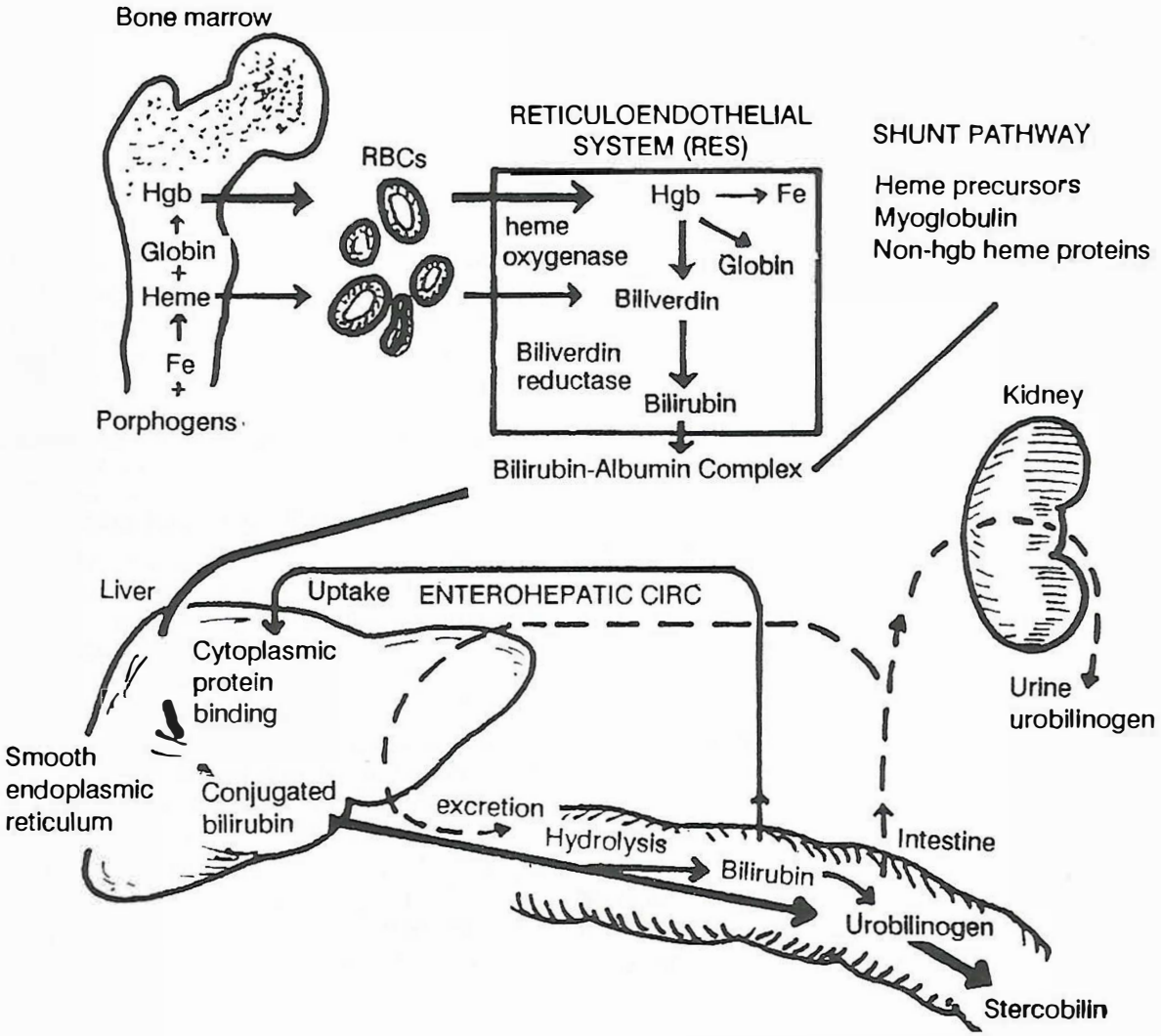

Fig. 1: The pathways of billirubin synthesis, transport, and metabolism. (From Assali, N.S: Pathophysiology of gestation, New York. 1972, Academic Press Inc.)

Hepatic Uptake of Bilirubin

The unconjugated bilirubin circulating as a bilirubin albumin complex is removed from the coirculation by the hepatocyte. Bilirubin enters the cell by a process of carrier-mediated diffsion, with ligandin (Y protein) of the liver cell cytoplasm as the major intracelluler bilirubin-binding protein. Another intracelluler protein, Z, also binds bilirubin but with a lower affinity. Bilirubin does dissociate from albumin before entering the hepatocyte.

Conjugation of Bilirubin

For bilirubin excretion to occur, it has to be converted to a more polar, water-soluble substance. This is done by conjugation of each molecule of bilirubin with two molecules of glucuronic acid by a two step conjugation process. The process accounts for about 95% of all bilirubin, the rest being conjugated with other substances or by oxidation, hydroxylation or reduction.

The enzyme UDP glucuronyl-transferase catalyzes the transfer of one glucuronic acid molecule from the activated UDP glucuronic acid to from bilirubin-monoglucuronide. The second step of conjugation involves transglucuronidase and transfers one molecule to bilirubin-monoglucuronide to another, resulting in formation of one molecule of bilirubin diglucuronide[4].

Both bilirubin monoglucuronide and diglucuronide are water-soluble and account for more

than 90% of the total bilirubin conjugates excreted in humans. Others are conjugateds with glucose, xylose, other carbohydrates, sulfates and taurine.

Bilirubin Excretion

The conversion of bilirubin to a water-soluble compound is required for excretion by the liver. The excretory process is an energy-dependent concentrative process in which bile bilirubin concentrations are approximately a hundred-fold greater than hepatocyte bilirubin concentration[5].

Enteric Bilirubin Absorption

Bilirubin monoglucuronides and diglucuronides are relatively unstable conjugastes and may be hydrolyzed to unconjugated bilirubin enzymatically by the enteric mucosal enzyme, B-glucuronides. Unless rapidly eexcreted this unconjugated bilirubin returns to the liver via the portal circulation. As much as 25% of the total bilirubin excreted into the intestine may be reabsorbed through this enterohepatic circulation. Of the total, about 10% of bilirubin is excreted unaltered, whereas the remaining pigment is coverted to urobilinoids, the majority being excreted in stool and a small portion by the kidney (urobilinogen).

A. Physiological Jaundice of the Newborn

In the full term, physiologic jaundice is characterized by a gradual rise in serum unconjugated bilirubin concentration to a level of 6-8 mg/dl between 72 and 90 hours of age, followed by a fall to 2 mg/dl by the fifth day of life. Further fall in the level is more gradual, reaching 1 mg/dl by the tneth day. The jaundice in premature infants is more severe, with peak concentrations reaching 10-12 mg/dl by the fifth day of life with persistence of visible jaundice into the second week[6].

Facotrs responsible in the pathogenesis of physiologic jaundice include the following:-

1. Increased load of bilirubin presented to the liver. It isestimated that the rate of production is 6-8 mg/Kg/24 hours and results from the larger RBC mass and shortened life span (70-90 days).
2. Deficient binding of unconjugated bilirubin to serum albumin.
3. Deficient conjugation of bilirubin resulting from insufficient enzyme synthesis and inhibition of enzymatic activity by naturally occuring substances.
4. Developmental deficiencies of intracellular-binding (Y) protein.
5. Sluggish canalicular exerction of organic anions.
6. Significant enterohepatic circulation. The absence of anaerobic intestinal flora, the presnce of B-glucuronidase acitivity contribute.
7. Persistant patency of ductus venous, diverting blood from the liver.
8. Removal of placental mechanism for bilirubin removal and detoxification.

Bilirubin Transport in the Fetus

Only small amounts of bilirubin are excreted by the fetal liver into a sluggish bile flow, most of bilirubin being accumulated by meconium. The bilirubin is transfered across the placenta into the maternal circulation and excreted by the maternal liver. Occasionally unconjugated bilirubin may be transfered from the maternal circulation into the fetus, conjugated bilirubin not being transferable.

B. Pathological States of Unconjugated Hyperbilirubnemia

Keeping the pathway of bilirubin production, transport and metabolism in mind, it is not difficult to formulate reasons for exaggerated hyper-bilirubinemia i.e. I) Overproduction of Bilirubin II) Undersecretion or III) A combination (Table I).

A brief description of important causes follows:-

I. Overproduction

a. Isoimmunization

Upon delivery of her first Rh positive child, the Rh-negative mother receives a small transfusion of Rh-positive fetal cells. As a response, the maternal immune system develops an antibody to the foreign Rh-positive red cell antigen. Further exposure, either during the same pregnancy or during the next, prompts an increase in the maternal IgG antibody titre against the cells of her fetus. Maternal anti-Rh 1gG antibodies then cross the placenta to the fetus and cause destruction of the Rh-positive fetal cells. The intrauterine hyperbilirubinemia and hemolytic anaemia may cause, in the more sevee cases a high-output cardiac failure, anasarca and hydrops fetalis. Replacement of red-cell mass, treatment of cardiac failure and occasionally ventilatory support may be required. The widespread use

Table 1: Cause of neonatal hyperbilirubinemia.

Overproduction

A. Hemolytic disorders

1. Fetomaternal blood group Incompatiablity, ABO Rh, others
2. Genetic causes of hemolysis
   a) Hereditary spherocytosis
   b) Enzyme defects -G6PD. Pyruvate kinase, others
   c) Hemoglobinopathies
      a Thalassemia
      b Thalassemia, other
      d Galactosemia
3. Drug induced Hemolysis-vitamin K

B. Extravascular blood-petechiae, hematoma, pulmonary and cerebral hemorrhage, swallowed blood

C. Polycythemia

1. Chronic fetal hypoxia
2. Maternal-fetal or fetofetal transfusion
3. Placental transfusion (cord stripping)

D. Exaggerated Enterohepatic Circulation

1. Mechanical obstruction
   a) Atresia and stenosis
   b) Hirschsprung's disease
   c) Meconium ileus
   d) Meconium plug syndrome
2. Reduced peristalsis
   a) Fasting or underfeeding
   b) Drugs (hexamethoniums, atropine)
   c) Pyloric stenosis

Undersecretion

E. Decreased hepatic uptake of bilirubin

1. Persistent ductus venosus shunt
2. Cytosola receptor protein (Y) blocked by:
   a) Drugs
   b) Abnormal human milk inhibitor (? NEFA ? may belong in D or F).

F Decreased bilirubin conjugation

1. Congenital reduction in glucuronyl transferase activity
   a) Famillal nonhemolytic jaundice (type I & II)
   b) Gilbert's syndrome*
2. Enzyme inhibitor
   a) Drugs and hormones-novobicon, ? pregnanediol
   b) Galactosemia (early)
   c) Lucey -Driscoll syndrome
   d) Abnormal human milk

G. Impaired transport of conjugated Bilirubin out of hepatocyte

1. Congenital transport Defect-->Dubin-Johnson and Rotor's syndromes
2. Hepatocellulur demage secondary to metabolic disorders
   a) Galactosemia (late)
   b) a-I-Antitrypsin deficiency*
   c) Tyrosinemia
   d) Hypermethioninemia
   e) Hereditary fructose intolerance*
3. Toxic obstruction (IV allementation

(Cont....)

H. Obstruction to bile flow

1. Biliary atresia
2. Choledochal cyst*
3. Cystic fibrosis*
4. Extrinsic obstruction (Tumor or band).

Mixed

I. Prenatal infection

1. Toxoplasmosis
2. Rubella
3. Cytomegalovirus (CMV)
4. Herpesvirus hominis
5. Syphilis
6. Hepatitis
7. Others

J. Postnatal infections (sepsis)

K. Multisystems disorders

1. Prematurity + RDS
2. Infants of diabetic mothers.
3. Severe erythroblastosis

of anti Rh-immune-globulin during the third trimester or immediately after delivery has reduced the incidence of Rh hemolytic disease.

b. ABO-Hemolytic Disease

More common and less serios, ABO incompatibility is another cause of hemolysis. When the mother is of group O and the infant is group A or B, re-formed maternal A or anti-B antibodies of the 1gG class are passively transfered to the infant late in pregnancy. Although ABO incompatibility occurs in 20-25% of pregnancies, hemolytic disease develops in only 10%. Most cases are mild, with jaundice as the manifestation. Liver and spleen are not enlarged. Rarely it may be a cause of severe anemia and jaundice, prompting treatment[7].

c. Polycythemia

A larger than normal mass of red blood cells leads to an increased rate of bilirubin production even at normal rates of destruction8. Chronic fetal hypoxia may be the underlying cause of polycythemia, although a maternal-fetal trans-placental hemorrhage may be suspected. Fetofetal transfusion in twins, specially when discordant is another reason.

d. Exaggerated Enterohepatic Circulation

As mentioned earier, jaundice is often a consequence of increased enterohepatic circulation.

Starving a newborn or under-feeding are relatively common causes in our society. Delayed passage of meconium as a consequence of meconium plug is often a contributing etiology9. Weisman et al10 demonstrated that infants given a suppository passed the first meconium stool earlier than the control group and showed lower bilirubin levels measured over the first 3 days.

II. Undersecretion

a. Decreased Hepatic Uptake of Bilirubin

Uptake of bilirubin by the liver may be affected by the reduction of portal blood through the liver sinuosoids (persistence of flow through ductus venous) as seen in hypoxia and prematures or a deficiency of itracellular bilirubin binding proteins (Y and Z). These proteins may be saturated by steroids, free fatty acids, chloramphenicol, thyroxine and BSP dye and thus compete with bilirubin for binding[11].

b. Decreased Bilirubin Cconjugation

Criggler Najjar Syndrome

Two genetically and functionally distinct disorders due to lack of hepatic glucuronyl transferase activity in the liver cells have been descibed.

Type I is the rare and more severe form. The enzyme deficency is complete and the hyperbilirubinemia more severe (levels in excess of 25 mg/dl). It is inherited as an autosomal recessive disorder, appears in the first 3 days of life and is generally associated with kernicterus. Repeated exchange transfusion may be required. Phototherapy has been found to be beneficial.

Type II is transmitted as an autosomal recessive disorder and associated with a partial defciency of the enzyme. appearing during the first 3 days also, the level of bilirubin in a range compatable with physiologic jaundice. Phenobarbitone, with its induction of hepatic enzyme activity is effective in treatment and there is no risk of kernicterus[12].

c. Hypothyroidism

Hypothyroidism is also a cause of prolonged unconjugated hyperbilirubinemia although the mechanism is not clear[13].

d. Breast Milk Jaundice

The mean bilirubin concentrartion is slightly higher, the duration of jaundice is slightly longer and the incidence of clinically detectable hyperbilirubinemia during the first week is more frequent in breast fed infants. Also, appro-ximately 2% of breast-fed infants develop a prolonged (from 2-8 weeks) course of hyperbilirubinemia. Various factors considered in the etiology of this Breast Milk Jaundice include a) the presence of 3, alpha-20-beta-pregenediol, inhibitor of glucuronyl transferase, b) free fatty acids of breast milk, which bind competitively with albumin and c) the presence of B-glucuronidase in breast milk 14. Breast milk jaundice is a diagnosis of exclusion, to be considered in protracted unconjugated hyperbilirubnemia. A therapeutic test of discontinuation of breast feeding for 36-48 hours (fall of bilirubin of 2-4 mg/dl) confirms the diagnosis. However, even if feeding is continued, the level does fall gradually on its own. Simple reassurance is all that is required.

e. Impaired Transportation of Conjugated Bilirubin

A primary defect in the active transport of conjugated bilirubin out of the hepatocyte is seen in Dubin-Johnson's (autosomal recessive) and Rotor's syndrome (autosomal dominant)[15].

Genetic-metabolic diseases such as galactosemia, hereditary fructose intolerance, tyrosinemia and cystic fibrosis cause hepatocellular injury and hepatic fibrosis.

f. Obstruction to Bile flow

Defects in the hepatocellular phase of excretion or in canalicular or ductal function or from loss of patency of these structures results in a rise in the direct-reacting fraction of serum bilirubin[16].

Biliary atresia is a pathologic entity with obliteration of some portion of the extrahepatic bile ducts. The disease is panductular i.e. both extrahepatic and intrahepatic ducts are involved, with early occlusion in the extrahepatic and if left uncorrected, intrahepatic biliary obstruction. It carries an incidence of 1:15,000 live births, with a slight female preponderence. It manifests with jaundice at 3 to 6 weeks of age in otherwise healthy, thriving infants . Stools are acholic and as many as 15-30% of infants may have associated defects such as polysplenia, cardiovascular anomalies and malrotation of the intestines. The precise initiating event for the disease is unknown,

but circumstantial evidence of an intrauterine reovirus type 3 infection has been presented[17].

Diagnosis is aided by ultrasound evaluation of the presence of bile ducts, but the standard test remains the 99M Tc-iminodiacetic acid (IDA) hepatobiliary scan. Given intravenously, uptake by liver is rapid but no excretion occurs into the intestine in case of biliary atresia.

III. Combined Overproduction and Undersecretion

Intrauterine infections such as toxoplasmosis, rubella, cytomegalovirus disease, herpes simplex, syphilis and hepatitis are an example of this group. These neonates present with growth retardation, hepatosplenomegaly, hemolytic anemia, thrombocytopenia and hepatocellular injury. In addition, microcephaly or hydrocephalus may be found.

Intrahepatic cholestasis, giving rise to elevated levels of conjugated bilirubin may also occur in newborn infants with sepsis. The combination of polycythemia and increased enterohepatic circulation may contribute to jaundice in infants of diabetic mothers, though there may be other factors.

Bilirubin Toxicity

High circulating levels of unconjugated bilirubin are toxic to the central nervous system and cause a form of encephalopathy. Although the basal ganglia are the most vulnerable, there is often evidence of injury throughout the CNS as alluded to earlier. Determinants of bilirubin neurotoxicity include concentrtions of bilirubin and albumin, the albumin binding capacity for bilirubin, the blood-brain barrier and neuronal uptake and the neuronal sus-ceptibility to bilirubin toxicity.

Epidemiologic surveys of bilirubin encephalopathy showed that clinical signs of bilirubin encephalopathy were occasionally encountered when the serum indirect bilirubin reached or exceeded 20 mg/dl, but that, in most proven cases, the serum bilirubin exceeded that level considerably, often approaching 30 mg/dl. Premature infants, especially those under 1500 grams and others with sepsis or metabolic complication of asphyxia, acidosis and hypothermia may be vulnerable to bilirubin toxicity at lower levels, even as low as 10 mg/dl[18]. It is primarily the alteration in blood brain barrier that plays a role in the genesis of bilirubin encephalopathy[19]. The earliest symptoms are poor sucking and hypotonia with a weak moro response. Vomiting and high pitched cry may be followed by seizues and death[20]. Chronic encephalopathy is characterized by hypotonia, athetosis, chorea, balismus, gaze abnormalities, and auditory disturbances[21].

Evaluation of the Jaundiced Infant

Despite the development of physiologic jaundice of some degree in nearly every newborn, only about half of all neonates are visibly jaundiced during the first week of life. This is because visible cutaneous and scleral jaundice in the newborn is usually noted when the serum level exceeds 7 to 8 mg/dl. There is no indication therefore for routine serum bilirubin in the newborn.

Unconjugated hyperbilirubinemia implies an excessive level of bilirubin and is defined as an elevation of the indirect-reacting serum bilirubin concentration to greater than 1.0 or 1.5 mg/dl. Conjugated hyperbilirubinemia is an elevation of the direct-reacting fraction in the vanden Bergh reaction to greater than 1.5 mg or 2.0 mg/dl or when this fraction accounts for more than 10% of the total serum bilirubin (upto 10% of the unconjugated pigment will behave as direct reacting in the van-den Bergh reaction).

Classification of hyperbilirubinemia as conjugated or unconjugated requires performance of a determination of serum bilirubin concentration that distingushes between direct and indirect-reacting pigments. The proto-type of all such methods is the van-den-Bergh test, a modification of the Ehrlich diazo reaction.

During the first few days of postnatal life, most neonates exibit levels of bilirubin far in excess of the upper limits of normal for adults. This is termed physiologic hyperbilirubinemia and considered developmental. Maisels and Gilford found that 6.1% of 2,416 normal, asymptomatic term infants had serum concentrations of more than 12.9 mg/dl[22].

Hyperbilirubinemia therfore is a frequent observation in the nursery, asnd the term implies that the level of jaundice observed is greater than expected. Generally however, when the level exceed 12 mg/dl, one may term it as "exaggereted hyperbilirubinemia" with the implication that pahtological causes need to be ruled out.

Generally, it is best to examine the baby undressed, in daylight or adequate light. Visible inspection of skin, sclera and brief compression of skin wil help in detection of clinical jaundice. Skin reflection with a transcutaneous bilirubinometer[23] is

another method although correlation with serum bilirubin is much better in whites. As a rough guide, scleral and facial jaundice becomes visible at 6-8 mg/dl., of the shoulders and trunk at 8-10 mg/dl, lower body at 10-12 mg/dl and all over at 12-15 mg/dl. Another point to remember is that visible jaundice on the first day needs evaluation. Once detected, a detailed scrutiny of maternal and neontal records and clinical examination for weight, maturity, general, condition, evidence of hematomas, hepatosplenomegaly needs to be carried out. This is folowed by a workup detailed in Table 2. Estimation of liver function, total serum albumin or G-6-P-D levels may need to be done some circumtances. The workup is done primiarily to answer the question-Is it physiologic or is there a pathologic cause? The age at first presentation of cliniucal jaundice and the subsequent rate of increase in serum bilirubin levels will often help in differentiating the two. A normal full term infant, without any hemolytic component manifests a rise of about 0.2 mg/dl/hour or about 5 mg/dl per day of bilirubin. Visible jaundice on the first day or a rate of increase of more than 0.2 mg/dl/hour is not physiologic and requires workup as detailed above. When the direct fraction is more than 1.5 mg to 2.0 mg/dl, appropriate investigations are in order for causes of conjugated hyperbilirubinemia.

Table 2: Suggested workup of jaundice.

1. Hemoglobin, TLC, DLC, Platelet count
2. Peripheral count
3. Reticulocyte count
4. Blood group, Rh of mother and neonate
5. Bilirubin level - total and direct
6. Coombs test

Treatment of Unconjugated Hyperbilirubinemia

Severe unconjugated hyperbilirubinemia may be associated with the risk of bilirubin encephalopathy and this forms the basis of therapy. Current acceptable methods for treatment include the use of phototherapy and exchange transfunction. Both of these modalities are directed towards disposing of the excess bilirubin after it has already been formed. A standard treatment protocol as used by Shaikh Zayed Hospital is given in Figure 2.

Phototherapy

Gremer, Perryman and Richard's observation in 1958 that jaundice occured less frequently in a well-lighted nursery led to the use of fluorescent light to lower bilirubin levels[24]. In the present setup, the dose applied to the skin is 5 to 10 U/W cm2/nm in the spectral range of 400 to 500 nm[6,25,31]. This converts unconjugated bilirubin to its isomers through light-induced formation of configurational and structural changes. These isomeric forms of bilirubin are more water-soluble than the parent compound and are therefore excreted through the liver more rapidly[1,31,33]. The excreted of these photo-isomers may however be rate-limiting for the dose response. Also, unless this photo-bilirubin in the intestine is rapidly exerted, some may be reconverted to bilirubin ix-a through the enterohepatic circulation. Feeding with its inherent stimulus of peristalsis and colonization should thus be encourged.

The convertion of a portion of the circulating bilirubin to water-soluble isomers which are less likely to cross the blood brain barrier is a potential advantage. The mechanism of phototherapy should not change criteria for exchange transfusion.

Phototherapy is most effective when used in the prevention and therapy of coombs negative hyper-bilirubinemia. It may also be used prophylactically specially in prematures and clinical trials have been extended to its use in hemolytic hyperbilirubinemia. Phototherapy is indicated for the infant with an increasing bilirubin level that is approaching the level at which exchange transfusion is dicated. It is begun when bilirubin concentration is 5 mg/dl less than the transfusion level.

Although conventionally, continuous photo-therapy is used, intermittent use has also been found effective. The neonate must be undressed and eyes protected. Generally safe, side effects do include skin rahes, diarrhoea, lactose intolerance, skin burns, hemolysis, increased losses of body fluid, poor weight gain, mild fever and occasionally bronze dis-coloration of skin[34]. It remains thus an effective and safe method of management of hyperbilirubinemia.

Exchange Transfusion

Although performed earlier, it was in 1948 that Diamond et al described the technique of exchanging blood via the ubmilical vein that made the procedure prac-tical[35]. It remains an effective method to lower indirect serum bilirubin levels, thus preventing

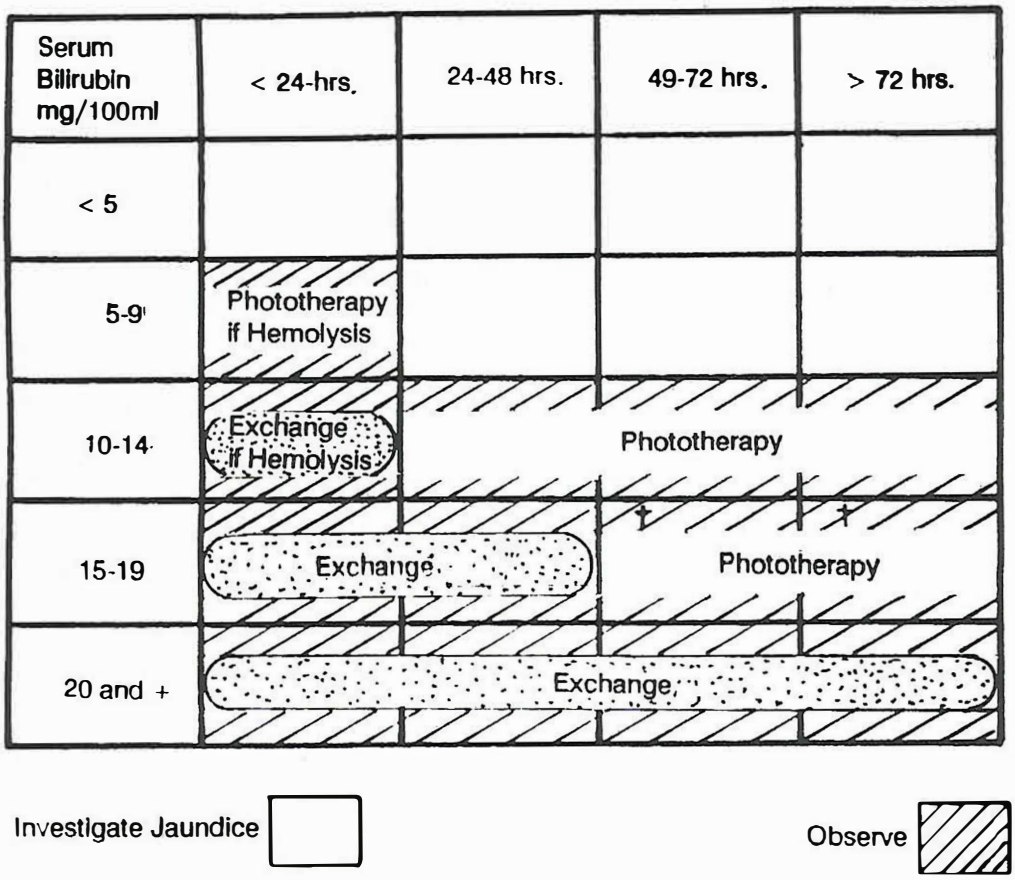

Fig. 2: Consider immediate phototherapy but exchange if bilirubin continues to rise consider exchange, particularly if previous phototherapy not effective.

kernicterus. With this technique, approximately 85% of the circulating red blood cells will be replaced when a double volume (160/Kg body weight) is used in aliquots not to exceed 10% of the total blood volume.

In exchange transfusion, fresh whole blood or reconsitituted acid citrate dextrose (ACD) anti-coagulated blood should be used. For Rh incompatibility, ABO compatablke Rh negative cells are recommended while type O Rh-specific cells are used in ABO incompatibility alongwith a low titre of anti-A and Anti-B antibody plasma. In the severely affected, hydropic or nonhydropic erythroblastic infant, a partial exchange using packed red blood cells coupled with reduction in blood volume is the therapy of choice. The advantages of exchange transfusion include replacement of fetal cells with compatiable adult red blood cells, remioval of free maternal antibodies, removal of bilirubin and provision of albumin for further binding bilirubin. The guidelines for exchange transfusion are as in Table 3. Although a relatively safe procedure it carries a mortality risk of 0.1% to 1% and a significant morbidity (Table-4).

Table 3: Indications for exchange transfusion.

A. Neonates with hymolytic disease
1. Cord bilirubin > 5 mg/dL
2. Cord hemoglobin < 10 g/dL
3. Anemia (hemoglobin 10-12g/dL).
4. Bilirubin level rising more than 1 mg/dL/hr.

B. Neonates with or without hemolytic disease
1. Serum bilirubin level > 20 mg/dL
2. Clinical factors that mamy suggest exchange transfusion at lower serum bilirubin levels such as:
   a) Prematurity
   b) Sepsis
   c) Hypoxia and acidosis
   d) Hypoproteinemia
   e) Use of drugs that compete with bilirubin binding sites.

Table 4: Complications of exchange transfusion.

System	Problem
Vascular	Embolization (air thrombus) Thrombosis of portal vein Necrotizing enterocolitis Perforation of vessel Uncontrollable hemorrhage
Cardiac	Arrythemia Cadiac arrest Heart failure (volume oveload)
Electrolyte	Hyperkalemia Hypernatremia Hypocalcemia Acute hypercalcemia Acidosis Alkalosis
Coagulation	Hemorrhagic disorder caused by overheparinization Thrombocytopenia Microembolization with intravascular Hemolysis
Infections	Bactereremia Hepatitis B Cytomegalovirus
Immunologic	Transfusion mismatch reaction
Miscellaneous	Mechanical injury to donor cells Hypothermia

Adapted from Odell, G.B. and others, Pediatr, Clin. North Am 1962 : 9: 605.

No infant should be allowed to develop a hyperbilirubinemia of more than 20 mg/dl during the first 28 days of life. For purposes of exchange, direct-reacting biirubin dose not enter the CNS and does not in itself enter CNS, yet it may partially displace unconjugated bilirubin from albumin-binding sites to increase the risk of keranicterus.

Pharmacological Management

Phenobarbital is one of a large group of drugs that stimulate protein synthesis in general and hepatic glucuronyl transferase and hepatic ligandin synthesis specifically. It is used primarily for infants with type II Crigler Najjar syndrome, in a dose of 5 mg/Kg/day, and the inspissated bile syndrome[36].

The drug is potentially addicting, may lead to sedation of the newborn and has other potent metabolic effects besides those on bilirubin metabolism and its use therefore needs to be discouraged except in the above mentioned specific indication.

Newer Trends

Recently, the administration of metalloporphyrins to treat hyperbilirubinemia has been suggested 37. Tin-porphyrin is a synthetic heme-analogue that is a potent competitive inhibitor of heme-oxygenase, the initial and rate-limiting enzyme in the sequence of heme degradation and bilirubin production. The potential advantage is that it treats hyperbilirubinemia before the bilirubin is formed. Although preliminary studies with the use of this drug are encouraging, the meabolism of tin-portoporphyrin in the newborn and its long-term effects on he developing infant require further investigation before widespread use of the drug can be recommended.

Figure 2 Guidelines for the management of hyperbilirubinemia. Phototherapy should be used after any exchange transfusion. Hyperbilirubinemia should be treated as though it were in the next higher catogery in the presence of the following: 1) Perintal asphyxia, 2) respiratory distress, 3) metabolic acidosis (pH 7.25 or below), 4) hypothermia (temprature below 35°C), 5) low serum protein (< 5gm/dl) 6) birth weight less than 1500gm, 7) signs of clinical or central nervous system deterioration, 8) sepsis, 9) rapid hemolysis, or 10) the presence of anything that might interfere with the binding of bilirubin to albumin (e.g. sulfisoxazole, sodium benzoate). (From M.J. Maisels, Neonatal Jaundice. In G.B. Avery (ed.), Neonatalogy (2nd ed._. Philadelphia: Lippincott, 1981).

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