Rebound Hyperbilirubinemia in Neonates after Phototherapy

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Abstract: Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st week of life in approximately 60% of term infants and 80% of preterm infants. Neonatal hyperbilirubinemia is defined as a total serum bilirubin level above 5 mg per dl (85 µmol per L) is a frequently encountered problem. Jaundice is an important problem in the first week of life. It is a cause of concern for the physician and a source of anxiety for the parents. High bilirubin levels may be toxic to the developing nervous system and may cause neurological impairment even in term newborns. Nearly 60% of term newborns become visibly jaundiced in the first week of life. In most cases it is benign and no intervention is required. Approximately 5-10% of them have clinical significant hyperbiliubinemia mandating the use of phototherapy. Hyperbilirubinemia is either unconjugated (which is potentially toxic but may be physiological or pathological) or conjugated (not toxic but always pathological).

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Introduction

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st week of life in approximately 60% of term infants and 80% of preterm infants **(Ambalavanan and Carlo, 2012)**.

Neonatal hyperbilirubinemia is defined as a total serum bilirubin level above 5 mg per dl (85 µmol per L) is a frequently encountered problem. Jaundice is an important problem in the first week of life. It is a cause of concern for the physician and a source of anxiety for the parents. High bilirubin levels may be toxic to the developing nervous system and may cause neurological impairment even in term newborns. Nearly 60% of term newborns become visibly jaundiced in the first week of life. In most cases it is benign and no intervention is required. Approximately 5-10% of them have clinical significant hyperbiliubinemia mandating the use of phototherapy **(Mishra et al., 2008)**.

Hyperbilirubinemia is either unconjugated (which is potentially toxic but may be physiological or pathological) or conjugated (not toxic but always pathological) (**Sun et al., 2007**).

The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin **(Mitra S et al.,2017).**

Epidemiology:

Neonatal hyperbilirubinemia is extremely common. Incidence figures are difficult to compare because authors of different studies do not use the same definitions for significant neonatal hyperbilirubinemia or jaundice **(Hansen, 2011)**.

Sixty percent of term infants and 80% of preterm infants have clinical jaundice **(Gomella et al., 2009)**.

Over the years, it has been documented that there is an increase in this incidence from around 4-6 percent to around 8 -10 percent. This increase could be due to more awareness, better laboratory methods and increase in incidence of breast feeding. The incidence of jaundice is much higher in preterm neonates **(Hansen, 2011).**

Mechanism of bile formation

Introduction

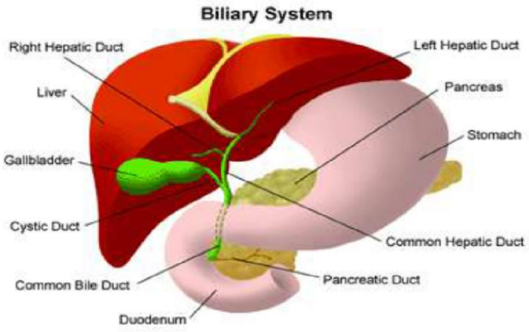

Figure (1): Anatomy of biliary system **(Bismuth, 1999)**.

Bile is a bitter yellow, blue and green fluid produced by hepatocytes in the liver, draining through the many bile ducts that penetrate the liver. During this process, the epithelial cells add a watery solution

that is rich in bicarbonates and that dilutes and increases alkalinity of the solution. Bile then flows into the common hepatic duct, which joins with the cystic duct from the gall bladder to form the common bile duct. The common bile duct in turn joins with the pancreatic duct to empty into the duodenum **(Suchy and Ananthanarayanan, 2006)**.

Constituents of bile:

Bile has various components, some of which are produced by hepatocytes in the liver. The main components include:-

- Water.
- Cholesterol.
- Bile pigments.
- Bile acids (glycocholic and taurocholic acid).
- Phospholipids (mainly lecithin).
- Bicarbonate and acids.

(Fuchs, 2003).

Physiological functions of bile:

Five major physiological functions of bile acids are now wellestablished. **First** and most important is the eliminationof cholesterol. Bile acids eliminate cholesterol from the body by converting it to bile acid and by micellarsolubilizationof cholesterol in bile, enabling cholesterol to move from thehepatocyte to the intestinal lumen, ultimately leading to eliminationvia the fecal route. Inborn defects in the conversion of cholesterolto bile acids can cause severe hepatic or systemic disease **(Hofmann and Hagey, 2008)**.

Second is lipid transport in the form of mixed micelles. Inthe small intestine, bile acids promote dietary lipid absorptionby solubilizing dietary lipids and their digestion productsas mixed micelles. Such mixed micelle formation acceleratesdiffusion through the unstirred layer, greatly acceleratinglipid absorption. Unless bile acids are present in micellarform, fat-soluble vitamins (A, D, E and K) will not be absorbed, and a deficiency will occur **(Hofmann and Hagey, 2008)**.

The **Third** and **Fourth** functions of bile acids are stimulationof bile flow and stimulation of biliary phospholipid secretion. Bile acids are actively transported into the biliary canaliculibetween hepatocytes and induce bile flow by their osmotic properties. Bile acids promote the transfer of phospholipids from the canalicularmembrane into bile. The presence of phospholipids in bile resultsin a greater fraction of bile acids existing in the form ofmixed micelles and a lower monomer concentration of bile acids, thereby preventing bile acids from damaging the bile duct epithelium **(Monte, 2009)**.

Fifth is negative feedback regulation of bile acid and cholesterolbiosynthesis. The concentration of bile acids in the hepatocyteseems to act as a signal; when high, bile acid synthesis islow; when low, bile acid synthesis increases up to 15 folds. Because bile acids are synthesized from cholesterol, cholesterolsynthesis undergoes a parallel increase **(Monte, 2009)**.

Bilirubin metabolism

Bilirubin is produced by the catabolism of hemoglobin. Compared with older children and adults, newborns have a high rate of hemoglobin catabolism and bilirubin production because of their elevated hematocrit and red blood cell volume per body weight, and their shorter life span of red blood cells (70 to 90 days). Although bilirubin production is elevated in newborns, conjugation and clearance of bilirubin can be slow. Immaturity of hepatic glucuronyltransferase and inadequate milk intake can cause delayed clearance of bilirubin **(Ambalavanan and Carlo, 2012)**.

Within the reticuloendothelial system, heme is broken down into biliverdin and carbon monoxide. Biliverdin is reduced to bilirubin by biliverdinreductase. At this initial stage, bilirubin is lipid soluble and unconjugated (indirect-reacting). Unconjugated bilirubin binds to albumin. If the albumin-binding sites are saturated, or if unconjugated bilirubin is displaced from the binding sites by medications (e.g., sulfisoxazole, streptomycin, vitamin K), free bilirubin can cross the blood-brain barrier. Free, unconjugated bilirubin is toxic to the central nervous system **(Gowen, 2006)**.

When unconjugated bilirubin reaches the liver, it is conjugated with glucuronic acid by glucuronyltransferase to bilirubin diglucuronide (conjugated or direct-reacting), which is water soluble and easily excreted by the liver and biliary tract. In the intestine, some bilirubin may be converted back to its unconjugated form by a glucoronidase and reabsorbed by the intestine. Breast milk increases bilirubin reabsorption through this enterohepatic absorption **(Gowen, 2006)**.

Newborn infants who do not feed adequately probably have increased enterohepatic circulation of bilirubin, because fasting causes increased accumulation of bilirubin in animals **(Kumral et al., 2009)**.

Since increasing the number of oral feedings allows for more rapid excretion of bilirubin. Early, frequent nursing or supplemental feedings with formula may be effective in reducing serum bilirubin concentrations in breast-fed infants who are undergoing phototherapy. In contrast, supplementation with water or dextrose may disrupt the mother's production of milk, resulting in higher serum bilirubin concentrations **(Kumral et al., 2009)**.

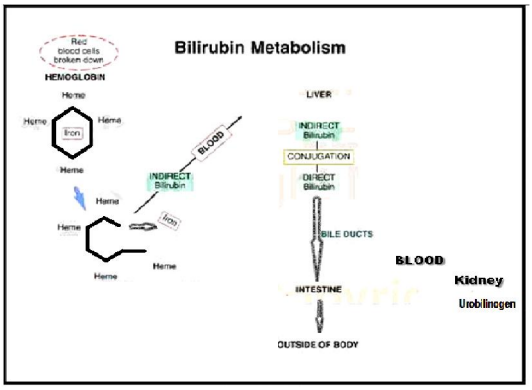

Figure (2): Schematic diagram showing liver physiology and bilirubin metabolism (Bhutani et al., 2008).

Community healthcare professionals should be aware that differential diagnosis of neonatal hyperbilirubinemia is broad.

Physiologic Jaundice:

Results from increased erythrocyte breakdown and immature liver function. It presents at two or three days old, begins to disappear towards the end of the first week and resolves by day 10. The bilirubin level does not usually rise above 12-13 mg/dl and the baby remains well. However the bilirubin level may go much higher if the baby is premature**(Kuzniewicz et al.,2014).**

The accepted upper limit of physiologic jaundice is 12.9 mg/dl for term babies and 15 mg/dl for preterm babies, with less than 2 mg /dL of the conjugated form **(Bhat, 2005)**.

Causes of neonatal hyperbilirubinemia:

Table (1): Differential diagnosis of neonatal hyperbilirubinemia **(Gowen, 2006)**.

(I) Unconjugated hyperbilirubinemia:	
Increased production of unconjugated bilirubin from heme:	Hemolytic diseases (Rh incompatibility, ABO incompatibility), Congenital spherocytosis, Erythrocyte enzyme defects, Hemoglobinopathy (Sickle cell anemia, Thalassemia), Polycythaemia.
Decreased bilirubin uptake across hepatocyte membrane:	Breast milk jaundice, Hypothyroidism, Hypoxia, Acidosis.
Decreased biotransformation (conjugation):	Physiologic neonatal jaundice, Hereditary Crigler-Najjar syndrome, Gilbert disease.
Enterohepatic recirculation:	Intestinal obstruction (Ileal atresia, Hirschsprung disease, Cystic fibrosis, Pyloric stenosis).
(II) Conjugated hyperbilirubinemia:	
Infectious:	Viral hepatitis (Hepatitis B, Cytomegalovirus, Rubella virus), Toxoplasmosis, Urinary tract infection.
Metabolic:	Tyrosinemia, Galactosemia, α_1-Antitrypsin deficiency, Hypopituitarism, Hypothyroidism.
Toxic:	Sepsis.
Intrahepatic diseases:	Idiopathic neonatal hepatitis, Alagille syndrome, Progressive familial intrahepatic cholestasis.
Extrahepatic diseases:	Biliary atresia, Choledochal cyst.

Neonatal physiologic jaundice results from simultaneous occurrence of the following 2 phenomena:

1. Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened life span of fetal erythrocytes and the higher erythrocyte mass in neonates **(Christensen RD et al,.2015).**

2. Hepatic excretory capacity is low both because of low concentrations of the binding protein ligandin in the hepatocytes and because of low activity of glucuronyltransferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble **(Woodgate P et al,.2015)**.

Table (2): Possible mechanisms involved in physiologic Jaundice

➢	Increased bilirubin load on liver cell.
➢	Increased erythrocyte volume.
➢	Decreased erythrocyte life span (70-90 days).
➢	Increased load from ineffective erythropoiesis.
➢	Increased enterohepatic circulation of bilirubin.
➢	Defective hepatic uptake of bilirubin from plasma
➢	Decreased ligandin.
➢	Binding of Y and Z protein by other anions.
➢	Defective bilirubin conjugation.
➢	Decreased uridinediphosphoglucuronyltransferase activity.
➢	Defective bilirubin excretion.

(Bhat, 2005).

Factors Which Exaggerate or Contribute to Physiologic Jaundice Could be Genetic, Ethnic or Familial Factors.

Maternal factors: Maternal diabetes and drugs administrated to the mother like oxytocin and diazepam, can increase risk of jaundice.

Neonatal factors: Neonatal polycythemia, delayed cord clamping, breast feeding, low birth weight and prematurity can increase the risk of hyperbilirubinemia. These factors can independently cause jaundice and exaggerate physiologic jaundice **(Maisels et al., 1999)**.

Pathologic Jaundice

(Non-physiologic Jaundice)

The term pathologic Jaundice implies that jaundice is due to non-physiological factors and these babies may have unconjugated or conjugated hyperbilirubinemia **(Bhat, 2005)**.

Criteria to suspect pathologic Jaundice:

a. Clinical jaundice in the first 24 hours of life.

b. T.S.B concentration increasing by more than 0.2 mg/dl per hour or 5 mg/dl per day.

c. T.S.B concentration exceeding the 95th percentile for age in hours (based on a nomogram for hour-specific serum bilirubin values).

d. Direct serum bilirubin concentration exceeding 1.5-2 mg/dl.

e. Clinical jaundice persisting for more than 2 weeks in full-term infants.

All neonates who fulfill any of the above criteria should be investigated for jaundice and will most often require therapeutic intervention **(Madan et al., 2005)**.

a) Early neonatal jaundice (onset less than 24 hours)

Causes:

- Haemolytic disease: The most common causes of hemolytic jaundice include:

(a) Rh hemolytic disease.

(b) ABO incompatibility.

(c) Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and minor blood group incompatibility.

- Infection: congenital (e.g. toxoplasmosis, rubella, cytomegalovirus (CMV), herpes simplex, syphilis) or postnatal infection.
- Increased haemolysis due to haematoma.
- Maternal autoimmune haemolyticanaemia: e.g. systemic lupus erythematosus (SLE).
- Crigler-Najjarsyndrome,Dubin-Johnson syndrome and Gilbert syndrome.

b) Prolonged jaundice (jaundice lasting for longer than 14 days in term infants and 21 days in preterm infants)

Causes:

- Infection, e.g. urinary tract infection.
- Hypothyroidism, hypopituitarism.
- Galactosaemia.
- Breast milk jaundice: baby is well and the jaundice usually resolves by six weeks but occasionally continues for up to four months.
- Breast feeding jaundice.
- Gastrointestinal (GI): biliary atresia, choledochal cyst, neonatal hepatitis. **(Kuzniewicz et al. 2014)**.

Causes of Pathological Unconjugated Hyper-bilirubinemia:

1-Breast Milk Jaundice

Transient nonhemolytic unconjugated hyperbilirubinemia is observed in some breast-fed babies of mothers whose breast milk contains pregnane-3α, 20β diolbut not in their bottle-fed counterparts. In other cases, jaundice may result from inadequate calorie provision by breast milk and from enhanced intestinal absorption of bilirubin. Kernicterus has not been reported in this setting, probably because severe jaundice does not develop until the 7th to 10th day of life **(Sato H et al,.2013).**

2-Hypothyroidism

Congenital hypothyroidism can be accompanied by prolongedhyperbilirubinemia (unconjugated), presumably because of a delay in maturation of the bilirubin-conjugating enzymes **(Bongers et al., 2005)**.

Several mechanisms may be involved in this process, because only some of these hypothyroid patients with jaundice demonstrate rapid resolution of the problem after hormonal therapy. The prolonged jaundice associated with congenital hypothyroidism may stem from a delayed maturation of the ability of the liver to conjugate bilirubin because of the hormone-dependent variations in uridinediphosphateglucuronyltransferase (UDPGT) activity. Reports also suggest that the thyroid hormones cause changes in protein expression, rather than enzyme latency although some coordinated regulation of glucuronidationand levels of cytochrome P-450 also has been hypothesized **(Bongers et al., 2005)**.

3. Inherited Disorders of Bilirubin Metabolism

A. Crigler-Najjar syndrome:

Crigler-Najjar syndrome is a rare disorder of bilirubin metabolism resulting in familial,congenital non- hemolytichyperbilirubinemia. This often results in neonatalkernicterus. It is divided into two types: type **I** and type **II** (sometimes called Arias syndrome)**.** It was first described in 1952 **(Ambrosino et al., 2005)**.

Crigler-Najjar Type I

In CN syndrome type I, UGT1A1 mutations result in a complete or near-complete loss of UGT1A1 enzyme activity. In CN syndrome type I, jaundice is

apparent from the first days of life. It increases progressively, and the risk of kernicterus (bilirubin encephalopathy) is high **(Watchko et al,.2013).**

Table (3): Risk factors for development of severe hyperbilirubinemia in infants 35 or more weeks' gestation.

Major risk factors
• Predischarge TSB or TcB level in the high risk zone.
• Jaundice observed in the first 24hs.
• Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated ETCO.
• Gestational age 35-36 weeks.
• Previous sibling received phototherapy.
• Cepalhematoma or significant bruising.
• Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive.
Minor risk factors
• Predischarge TSB or TcB level in high intermediate –risk zone.
• Gestational age 37-38 weeks.
• Jaundice observed before discharge.
• Previous sibling with jaundice.
• Macrocosmic infant of a diabetic mother.
• Maternal age ≥ 25 years.
• Male gender.
Decreased risk
• TSB or TcB level in low-risk zone.
• Gestational age ≥ 41 weeks.
• Exclusive bottle-feeding.
• Black race.
• Discharge from hospital after 72 hours.

(Kaplan et al.;2015).

Treatment of CN syndrome type I in the neonate consists of exchange transfusions to maintain serum bilirubin levels below the threshold for kernicterus plus phototherapy for 12 hours a day. Phototherapy transforms bilirubin into colorless water-soluble derivatives and isomers that are secreted into bile without conjugation and are more easily excreted into urine than bilirubin itself. Isolated hepatocyte transplantation has been used experimentally in a few patients but is not sufficient to correct CN syndrome type I **(Ambrosino et al., 2005)**.

Crigler-Najjar Type II

Crigler-Najjar syndrome type **II**, or Arias disease, is more common but more difficult to recognize in the first week of life. Children with type II disease excrete small amounts of bilirubin glucuronides into bile. The hyperbilirubinemia experienced by these patients is less severe than in type **I** disease, with levels ranging from 8 to 25 mg/dl, with less risk of kernicterus. Treatment of CN syndrome type II consists of lifelong phenobarbital therapy **(Canu, Get al,.2013).**

B. Gilbert's Syndrome:

Mild unconjugatedhyperbilirubinemia that usually occurs in young adults. Patients sometimes describe right upper abdominal discomfort or dyspepsia, but the relationship with hyperbilirubinemia is unclear. Except for jaundice when apparent, clinical findings are normal, as is liver histology when performed **(Madan et al., 2005)**.

Fasting increases serum bilirubin levels, while phenobarbital, a microsomal enzyme inducer, lowers serum bilirubin levels, often to normal values. Treatment with this drug is rarely necessary, and the prognosis is excellent **(Memon N et al,.2016).**

Kernicterus

Kernicterus by its strict definition, includes only the neurologic changes that are characterized by pigment deposition in specific regions of the brain, specially the basal ganglia, pons and cerebellum. Of all infants with kernicterus 50% die and the survivors may have choreoathetoid cerebral palsy, high frequency auditory nerve deafness and mental retardation. The term bilirubin encephalopathy is correctly applied to the clinical manifestations of the effects of bilirubin on the central nervous system; a broad spectrum of neurologic signs is attributed to bilirubin, ranging from subtle behavioral changes such as lethargy and irritability to seizures, hearing deficits, mental retardation and death **(Newman et al., 2006)**.

The prevention of kernicterus remains a serious clinical concern for neonatal caregivers worldwide **(Bhutani et al.,2013).**

Table (4): Clinical Severity of acute bilirubin-induced neurologic dysfunction (BIND Score).

Parameter	Finding	Score	ABE
Mental status	Normal.	0	None
	Sleepy but arousable; decreased feeding.	1	Subtle
	Lethargy, poor suck and/or irritable/jittery with strong suck.	2	Moderate
	Semi-coma, apnea, unabletofeed, seizures, coma.	3	Advanced
Muscle tone	Normal.	0	None
	Persistent mild to moderate hypotonia.	1	Subtle
	Mild to moderate hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation.	2	Moderate
	Persistent retrocollis and opisthotonos bicycling or twitching of hands and feet.	3	Advanced
Cry pattern	Normal.	0	None
	High pitched when aroused.	1	Subtle
	Shrill, difficult to console.	2	Moderate
	Inconsolable crying or cry weak or absent.	3	Advanced

(Johnson et al., 2004).

BIND, bilirubin-induced neurological dysfunction; ABE, acute bilirubin encephalopathy; TSB, total serum bilirubin.

Minimum score = 0, Maximum score = 9

Score of 7–9: represent advanced ABE: urgent, prompt and individualized interventions are recommended to prevent further brain damage, minimize severity of sequelae and possibly reverse acute damage.

Score of 4–6: represent moderate ABE and are likely to be reversible with urgent and prompt bilirubin reduction strategies.

Score of 1–3: are consistent with subtle signs of ABE in infants with hyperbilirubinemia. An abnormal ABR or 'referred' automated ABR is indicative of likely bilirubin neurotoxicity and would be suggestive of moderate ABE. In infants with these non-specific signs (score 1–3), a failed ABR hearing screen supports a diagnosis of moderate ABE. Serial ABR may be used as an objective measure of progression, stabilization or reversal of acute auditory damage and could interpret effectiveness of bilirubin reduction strategies **(Johnson et al., 2004).**

Table (5): Staging of BIND score.

Stage of BIND	Features
IA	Minimal signs, totally reversible with therapy.
IB	Progressive signs but reversible with therapy.
II	Irreversible signs but severity decreased with prompt and aggressive therapy.

(Johnson et al., 2004)

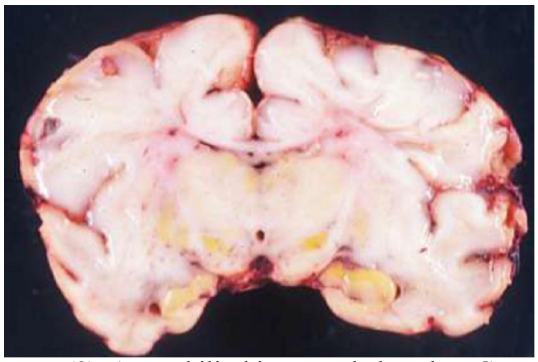

Figure (3) Acute bilirubin encephalopathy. Coronal section through parietotemporal lobes show yellow discoloration in the hippocampus and subthalamicnuclei. Thalamus and globuspallidus are focally stained. (**Kaplan et al.;2015**)

Management of indirect hyperbilirubinemia

Any infant who appears jaundiced should have bilirubin levels measured right away. Experience with implementation of the AAP 2004 clinical practice guideline on the management of hyperbilirubinemia in the newborn at 35 or more weeks' gestation coupled with several subsequent clinical studies led to a 2009 update with clarifications. The update was notable for recommending universal predischarge birth hospitalization bilirubin screening using TSB or transcutaneous (TcB) measurements to help assess the risk for subsequent severe hyperbilirubinemia. The

predischarge bilirubin measurement combined with the gestational age of the infant make up a particularly predictor of subsequent severe hyperbilirubinemia that is consistent with the importance of immaturity as a risk factor for jaundice. Studies consistently demonstrate that implementation of routine predischarge bilirubin screening is associated with significantly reduced numbers of infants with extreme or hazardous hyperbilirubinemia **(Kuzniewiczet al.,2014).**

➢ **Investigations**

Usually, a total serum bilirubin level is the only testing required in a moderately jaundiced infant who presents on the second or third day of life and is otherwise well. Further investigations are essential for any baby who is also unwell, presents in the first 24 hours or has prolonged jaundice (after 10 days) (**Moerschel et al., 2008**).

Futher Laboratory assessment:-

- Total Serum Bilirubin (T.S.B) is sufficient in most cases.
- Unconjugated & conjugated fractions in specific conditions as prolonged jaundice.
- Infant's and maternal blood group & Rh.
- Direct Coomb's test.
- G6PD status.
- Full blood count.
- Reticulocyte count.
- Peripheral blood film (if hereditary spherocytosis is suspected).
- Blood culture, urine microscopy and culture (if infection is suspected) **(Bhutani et al., 2006)**.
- Reducing substance in urinefor galactosaemia.
- Thyroid function tests.

(Bhutani et al., 2006).

Table (6): Bilirubin /albumin (B/A) ratio at which exchange transfusuion should be considered.

Risk Category	B/A ratio
Infants > 38 0/7 wks	8
Infants 35 0/7- 36 6/7 wks & well (or) Infants > 38 0/7 wks if higher risk or isoimmune hemolytic disease or G6PD deficiency	7.2
Infants 35 0/7 – 37 6/7 wks if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8

- B/A ratio = TSB (total serum bilirubin) in mg/dl / Albumin in g/dl.
- Bilirubin level refers to the total bilirubin. Direct bilirubin is not subtracted from the total unless it constitutes more than 50 % of the total bilirubin. **(American Academy of Pediatrics, 2004)**

Prevention of Complications of Neonatal Jaundice

1. Primary prevention:

Numerous policy statements, recommend breast feeding for all healthy term and near term newborns, since increasing the number of oral feedings allows for more rapid excretion of bilirubin. Early, frequent nursing may be effective in reducing serum bilirubin concentrations in breast-fed infants **(Kumral, 2009)**.

In contrast, supplementation with water or dextrose may disrupt the mother's production of milk, resulting in higher serum bilirubin concentrations **(Gourley et al., 2005)**.

Prevention of Rh Hemolytic Disease

The current standard is to administer RhIG to all unsensitized Rh-negative women at 28 weeks' gestation with an additional dose administered soon after birth if the infant is Rh-positive, irrespective of the ABO status of the baby. It is also administered to unsensitized Rh-negative women after any event known to be associated with transplacental hemorrhage. The standard dose of RhIG is 300µg and is increased (300µg for every 25 ml of fetal blood in maternal circulation) based on the amount of fetomaternal hemorrhage. Most physicians resort to the indirect Coombs' test in the mother to assess the adequacy of RhIG dose in a woman with significant fetomaternal hemorrhage. The indirect Coombs' test result should become positive in a woman with a prior negative test result, suggesting the presence of excess antibody in circulation **(Moise, 2008)**.

2. Secondary Prevention:

Clinicians should perform ongoing systematic assessments during the neonatal period for the risk of an infant developing severe hyperbilirubinemia which includes:

- Blood typing.
- Clinical assessment and detection of risk factors before discharge (beyond 24 hours) along with an assessment of individual risk factors for jaundice such as gestational age, race, method of feeding, presence of polycythemia, blood group incompatibility or bruising **(Madan et al., 2005)**.
- Laboratory evaluation including predischarge measuring of TcB or T.S.B and comparing it with the hour specific bilirubin nomogram, can help in timing of follow-up examination of a selected group of infants **(Madan et al., 2005)**.
- Follow-up assessment **(American Academy of Pediatrics, 2004)**.

Recommendations for prevention of neonatal hyperbilirubinemia:

- Promote and support breastfeeding.

- Establish nursery protocols for identifying and evaluating hyperbilirubinemia.
- Measure bilirubin levels in all infants with jaundice in the first 24 hours after delivery.
- Recognize that visual estimation of bilirubin levels is inaccurate.
- Interpret all bilirubin levels according to the infant's age in hours.
- Identify preterm (i.e., less than 37 weeks), breastfed infants and provide close monitoring.
- Perform a thorough risk assessment for all infants.
- Provide parents with written and verbal information about newborn jaundice.
- Treat newborns, when indicated, with phototherapy or exchange transfusion.

(American Academy of Pediatrics, 2004).

Treatment

The child will need treatment if the bilirubin level is too high or is rising too quickly. The baby is kept well hydrated with breast milk or formulae. Frequent feedings (up to 12 times a day) encourage frequent bowel movements, which help remove bilirubin through the stools (**Bhutani et al., 2008**).

Lines of treatment

- Treatment of the underlying cause.
- Increase fluid intake - usually oral but may require intravenous fluids depending on the cause and well-being of the baby.
- Phototherapy.Exchange transfusion.
- Pharmacological treatment. (**Tan, 2001**).

Phototherapy

Phototherapy has remained the standard of care for the treatment of hyperbilirubinemia in infants for four decades. Phototherapy is the most widely used form of therapy for the treatment and prophylaxis of neonatal unconjugated hyperbilirubinemia. In nearly all neonates, phototherapy reduces or blunts the rise of TSB concentrations (regardless of maturity, the presence or absence of hemolysis, and the degree of skin pigmentation) (**Kaplanet al.;2015**).

The formation of lumirubin, a water-soluble compound, is the rate-limiting step in the elimination of bilirubin by phototherapy. Two factors determine the rate of lumirubin formation: the spectrum and the total dose of light delivered. Because bilirubin is a yellow pigment, it is likely to absorb blue light (with a wave-length of approximately 450 nm). Thus, blue lamps are most effective in reducing hyperbilirubinemia, but eye can't detect cyanosis in neonates when we using this blue lamps, so they are not common in hospitals. Longer (green) wavelengths penetrate the skin more deeply and may interact more effectively with albumin-bound bilirubin, but fluorescent white light is the most common form of phototherapy (**Tan, 2001**).

- **Photochemical reactions of phototherapy:**

When bilirubin absorbs light, three types of photochemical reactions occur:

1. Photoisomerization: occurs in the extravascular space of the skin. The natural isomer of UCB (4Z,15Z) is rapidly converted to a less toxic polar I somer (4Z, l5E) that diffuses into the blood and is excreted into the bile without conjugation. However, excretion is slow, and the photoisomer is readily converted back to UCB, which is resorbed from the gut if the baby is not having stools**.** After approximately 12 hours of phototherapy, the photoisomers make up approximately 20% of total bilirubin. Standard tests do not distinguish between naturally occurring bilirubin and the photoisomer, so bilirubin levels may not change much although the phototherapy has made the bilirubin present less toxic. Photoisomerization occurs at low-dose phototherapy.

2. Structural isomerization: is the intramolecularcydization of bilirubin to lumirubin. Lumirubin makes up 2% to 6% of serum concentration of bilirubin during phototherapy and is rapidly excreted in the bile and urine without conjugation. Unlike photoisomerization, the conversion of bilirubin to lumirubin is irreversible, and it cannot be reabsorbed. It is the most important pathway for the lowering of serum bilirubin levels and is strongly related to the dose of phototherapy used in the range of 6 to 12 JJ. W/cm2/nm.

3. The slow process of photo-oxidation converts bilirubin to small polar.

products that are excreted in the urine. It is the least important reaction for lowering bilirubin levels **(Cloherty et al., 2012)**.

The dose delivered, or irradiance, depends on the power of the light and its distance from the infant. For standard phototherapy, eight fluorescent white bulbs are used to deliver 6 to 12 µW per square centimeter of body-surface area exposed per nanometer of wavelength. Fiberoptic blankets have a small effective surface area but generate heat and can therefore be positioned nearer the infant, providing up to 50 µW per square centimeter per nanometer. A new device that uses high-intensity gallium nitride light-emitting diodes can generate more than 200 µW per square centimeter per nanometer, resulting in high rates of photodegradation of bilirubin in vitro (**Vreman et al., 2008**).

An infant being treated with phototherapy is placed (preferably naked) under a bank of lights (eight fluorescent bulbs), and the eyes are shielded. Temperature and hydration status should be monitored. When dehydration is suspected, intravenous fluids are infused. Otherwise, the infant

receives only oral fluids. Phototherapy can be discontinued for periods of one to two hours to allow family visits and feeding (**Yetman et al., 2008**).

The time at which phototherapy is initiated varies according to the infant's gestational age and the cause of the jaundice. Full-term infants with no evidence of hemolysis should be treated according to the guidelines of the American Academy of Pediatrics. No guidelines have been published for preterm infants, but we suggest following the published recommendations that are based on gestational age, birth weight, and relative health. Phototherapy can be discontinued once the serum bilirubin concentration has been reduced by about 4 to 5 mg per deciliter (68 to 86 μmol per liter). Phototherapy may not reduce the serum bilirubin concentration in breast-fed infants as rapidly as in bottle-fed infants, because the former may have greater degrees of enterohepatic recirculation, but supplementing breast-feeding with formula reduces recirculation and allows for continued breast-feeding even in infants with severe hyperbilirubinemia (**Tan, 2008**).

There is a common belief that the discontinuation of phototherapy is associated with rebound hyperbilirubinemia. In a recent study, 264 healthy newborns who weighed 1800 g or more had lower serum bilirubin concentrations as long as 30 hours after the discontinuation of phototherapy than they did immediately after discontinuation, suggesting that rebound hyperbilirubinemia is rare. Whether this finding can be extrapolated to smaller preterm infants or infants with hemolysis is not clear. Overall, phototherapy is an effective way to decrease serum bilirubin concentrations (**Yetman et al., 2008**).

Figure (4): Newborn infant undergoing phototherapy to treat neonatal jaundice (Cremer et al., 2008).

Phototherapy works through a process of isomerization that changes trans-bilirubin into the water-soluble cis-bilirubin isomer (**Stokowski, 2006**).

In phototherapy, blue light is typically used because it is more effective at breaking down bilirubin. Two matched groups of newborn infants with jaundice were exposed to intensive green or blue light phototherapy. The efficiency of the treatment was measured by the rate of decline of serum bilirubin concentration after 6, 12 and 24 hours of light exposure. A more rapid response was obtained using the blue lamps than the green lamps. However, a shorter phototherapy recovery period was noticed in babies exposed to the green lamps. Green light is not commonly used because exposure time must be longer to see dramatic results. Ultraviolet light therapy may increase the risk of skin moles in childhood. While an increased number of moles is related to an increased risk of skin cancer, it is not ultraviolet light that is used for treating neonatal jaundice. Rather, it is simply a specific frequency of blue light that does not carry these risks (**Titus-Ernstoff et al., 2005**).

Conventional phototherapy

Involves exposing a maximum area of skin to an irradiance of 6 to 12μW/cm2/nm using banks of lights, whereas fiberoptic light systems contain optical fibers in blanket that is wrapped around the infant **(Dennery et al., 2001)**.

The fiberoptic light systems expose greater surface area to light. They are convenient to use, and less disruptive to parents-child bonding **(Mills and Tudehope, 2006).**

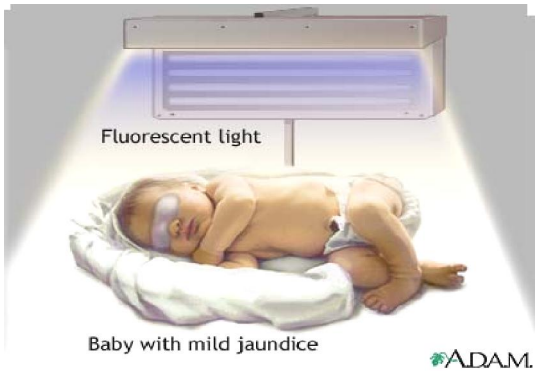

Figure (5): neonate on conventional phototherapy (Mills and Tudehope, 2006).

Double phototherapy or (double surface phototherapy DSP)

A number of systems have been developed to provide phototherapy above and below the infant. It was documented that treatment with double phototherapy is more effective in reduction of TSB levels with no long-term complications **(Madan et al., 2005).**

Indications for intensive phototherapy

When an infant's serum bilirubin is rising rapidly or approaching exchange transfusion level, intensive phototherapy must be instituted at maximal spectral power. This entails delivering high levels of irradiance

(usually 30 [mu] W/cm2/nm or higher) to as much of the infant's surface area as possible (**Vreman et al., 2004**).

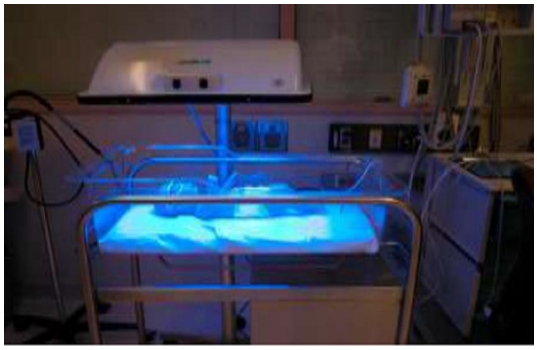

Figure (6): Double surface phototherapy, a newborn baby undergoing treatment of neonatal jaundice by double phototherapy. (Madan et al., 2005).

❖ **Indications for phototherapy in infant of 35 or more weeks' gestation**

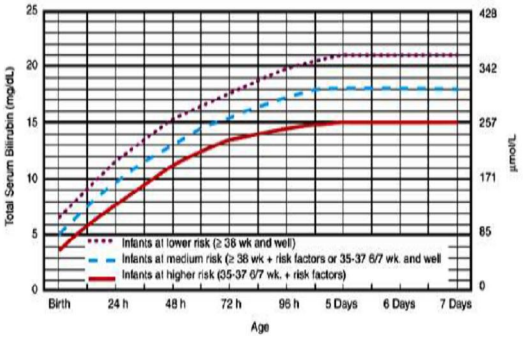

Figure (7): Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation (AAP2004).

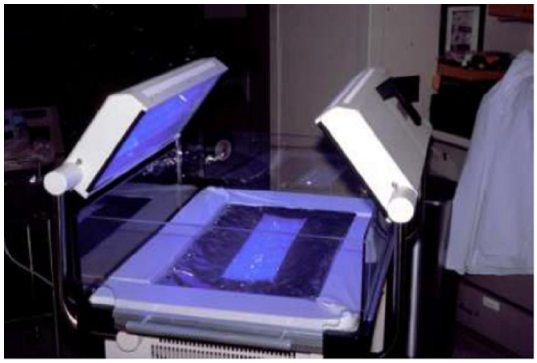

Figure (8): Intensive phototherapy using triple surface phototherapy (Madan et al.,2005).

The most efficient phototherapy units available should be used, and they should be positioned for maximum skin coverage. In these situations, additional surface-area exposure can be achieved by removing the infant's diaper and lining the sides of the bassinet, incubator, or radiant warmer with light-reflecting material such as aluminum foil or white linens (**Djokomuljanto et al., 2006**).

Intensive phototherapy can produce a decline in serum bilirubin of as much as 10 mg/dL within a few hours in severely hyperbilirubinemic infants (**Hansen, 2011**).

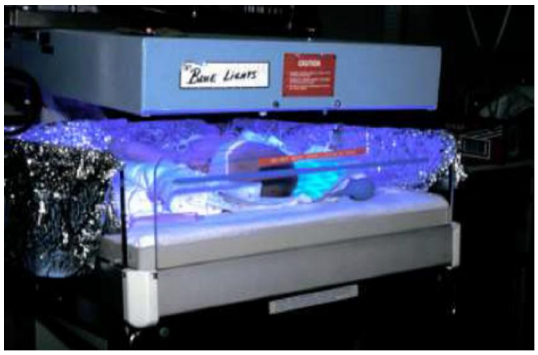

Figure (9): Warmer lined with aluminum foil or white material will increase the surface area of the infant exposed and increase the efficacy of phototherapy (Djokomuljanto et al., 2006).

❖ **Adverse Effects of Phototherapy**

1. Skin complications: The most noticeable clinical complication of phototherapy is "bronze baby syndrome," a grayish-brown discoloration of the skin that occurs exclusively in infants with cholestatic jaundice **(AAP, 2004).** Bronze baby syndrome is believed to occur when the brown photoproducts of porphyrins, especially copper porphyrins, accumulate in the skin and their excretion is impaired by cholestasis **(Wong et al., 2006).**

2. Eye damage: Because light can be toxic to the retina, the eyes of infants receiving phototherapy should be protected with appropriate eye patches **(Madan et al., 2005)**.

3. DNA damage: Although irradiation of cells with light intensities similar to those used in phototherapy can produce DNA damage, no change in growth, or infant behavior have been reported in long term follow up studies of infants who have received phototherapy **(Madan et al., 2005).**

4. Phototherapy can damage red-blood-cell membranes, increasing their susceptibility to lipid peroxidation and hemolysis. These effects may contribute to the pathogenesis of disorders common in the very low-birth-weight infant, including bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis**(Vreman et al., 2004).**

5. Phototherapy has been associated with patency of the ductusarteriosus and ileus in very low-birth-weight infants, as well as retinopahty of

prematurity. Recent evidence also suggests that phototherapy impairs immune system function through alterations of cytokine production **(Xiong et al., 2011).**

6. Phototherapy has been linked to the development of abnormal melanocytic nevi when the children become older. The evidence for this association is not definitive and has been debated, but at this time, this possible effect cannot be ruled out**(Brewster et al., 2010).**

Although it is not always possible to separate the effects of phototherapy from the effects of hyperbilirubinemia itself, recent research has implicated phototherapy as a risk factor for childhood asthma **(Aspberg et al., 2010).**

Other rare side effects include purpura and bulbous eruptions, which can occur in infants with elevated direct bilirubin. Phototherapy is contraindicated in infants with congenital erythropoietic porphyria, because blistering and photosensitivity can result **(Wong et al., 2006)**.

Limitations of home phototherapy and sunlight

The irradiance and surface area exposure produced by home phototherapy units are lower than those produced by typical hospital units making them less efficient at lowering the serum bilirubin level. Whether a valid indication for home phototherapy exists is questionable; current guidelines state that a bilirubin high enough to warrant treatment should be managed in the hospital **(AAP, 2004).**

Exchange Transfusion

Exchange transfusion was the first successful therapy for severe neonatal jaundice. This technique rapidly eliminates bilirubin from the circulation. Exchange transfusion is especially beneficial in infants who have ongoing hemolysis from any cause**.** One or two central catheters are placed, and small aliquots of blood are removed from the infant and replaced with similar aliquots of red cells from a donor, mixed with plasma. This procedure is repeated until twice the blood volume has been replaced. During the procedure, serum electrolytes and bilirubin should be measured periodically. The amount of bilirubin removed from the circulation varies according to both the amount of bilirubin stored in tissues that reenters the circulation and the rate of hemolysis. In some cases, the procedure needs to be repeated to lower the serum bilirubin concentration sufficiently. Infusion of salt-poor albumin at a dose of 1 g per kilogram one to four hours before exchange transfusion increases the mean amount of bilirubin removed from 8.7 to 12.3 mg per kilogram of birth weight, demonstrating the importance of albumin in binding bilirubin **(Odell et al., 2002).**

Indications of exchange transfusion

Exchange transfusion should be considered in cases of hemolysis in which intensive phototherapy has failed to decrease the TSB levels by 1 to 2 mg/dl in 4 to 6 hours or when the rate of rise of TSB indicates that the level will reach 25mg/dl within 48 hours. It also should be performed in infants with high TSB concentrations and early signs of kernicterus and in cases of hemolysis with anemia and hydrops **(Madan et al., 2005).**

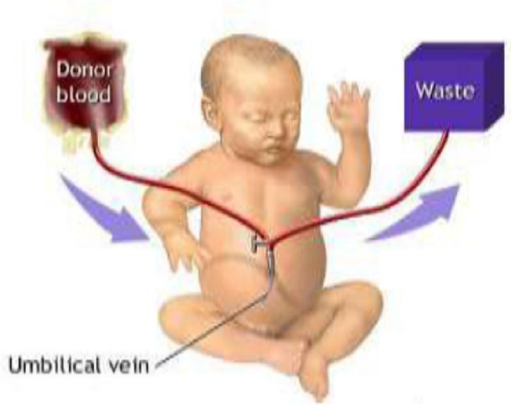

Figure (10): Exchange transfusion in a jaundiced neonate (Odell et al., 2002).

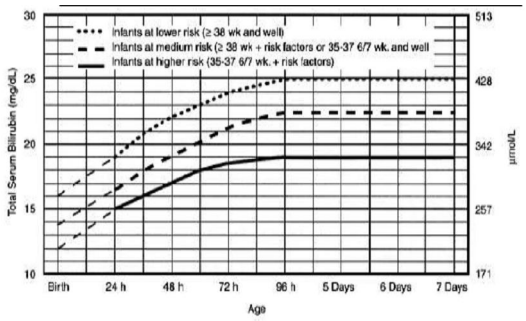

Figure (11): Guidelines for exchange transfusion in infants 35 or more weeks' gestation (American Academy of Pediatrics2004)

Exchange Volume

- A "two volume" exchange is usually performed: Blood volume estimate: 85 cc/kg in term infants. 100 cc/kg in prematures less than 1000 gm. 84-88% of sensitized red blood cells can be removed with a 2 volume exchange but only approximately 45% of plasma bilirubin can be removed because the later re-equilibrates between intravascular and extravascular spaces.
- Infants with aggressive hemolytic disease may require more than one exchange transfusion before an accepted bilirubin concentration is achieved **(Madan et al., 2005)**.

Blood typing and preparation

- Blood should be fresh (less than 72 hrs old), blood stored for more than 4 days has excessive potassium levels. Such blood requires erythrocyte washing and resuspention in compatible plasma**.**
- Rh incompatibility: O negative, or ABO group of baby and Rh negative blood.
- ABO incompatibility: O, Rh of the baby.
- Cross-match to mother in alloimmune disease, and to recipient.
- Other blood group incompatibility: for other hemolytic diseases (eg, anti-Rh-c, anti-Kell, anti-Duffy), blood must be cross-matched to the mother's blood to avoid the offending antigens**.**
- O neg blood with AB plasma is optimal for emergency transfusions (e.g., at delivery).
- Adjust hematocrit to 50% if possible.
- Screen for infectious agents such as CMV.
- Irradiation of blood will prevent graft versus host disease.
- Warm blood to 34-35 deg C. **(Madan et al., 2005)**.

Exchange Rate

- Syringe volume should be less than 5 ml/kg.
- Infuse/withdraw slowly over about 2 min.
- Too rapid infusion or removal of blood results in transient changes in blood pressure and heart rate and may contribute to necrotizing enterocolitis in XTs performed within the portal vein.
- A slow XT and/or a 30-minute break between the first and second volume exchange increases total bilirubin removed **(Rubaltelli and Griffith, 2002).**
- In some cases, particularly in infants with hemolytic disease, the procedure may need to be repeated to lower the TSB concentration sufficiently **(Madan et al., 2005).**

Drug Supplementation during exchange transfusion:

1. Albumin:

- (0.5-1.0 gm/kg) infused over 5-10 min 30 min before the ET.
- May increase the shift of bilirubin from tissues, including brain (duration of ET probably more important).
- May be useful in symptomatic infants while awaiting ET.
- Albumin will acutely increase blood volume, and should be used judiciously in patients with heart failure (e.g., hydrops) **(Peterec, 2005).**

2. Intravenous immunoglobulin:

The use of intravenous immunoglobulin in adose of 500 mg/kg/dose over 2 hours may reduce the chance for repeat exchange transfusion **(Ambalavanan and Carlo, 2012)**.

3. The anticoagulant of choice in the blood being infused is citrate phosphate-dextrose. Citrate chelates calcium ions, so there may be a need for calcium gluconate infusion during the course of the exchange **(Madan et al., 2005)**.

Table (7): American Academy of Pediatrics guidelines for management of indirect hyperbilirubinemia in term newborn.

Serum Total Bilirubin Level (Mg/Dl)				
Age (h)	**Consider phototherapy**	**Phototherapy**	**Exchange Transfusion**	**Exchange transfusion+ intensive phototherapy**
25-48	≥12	≥15	≥20	≥25
49-72	≥15	≥18	≥25	≥30
>72	≥17	≥20	≥25	≥30

(AAP, 2004)

Table (8): Bilirubin level and management guidelines in LBW babies based on birth weight.

Weight In Gm	Phototherapy At Bilirubin Level	Exchange Transfusion At Bilirubin Level
<1000	Prophylactic	10-12
1000-1500	5-8	13-16
1500-1999	8-12	16-18
2000-2499	11-14	18-20

(American Academy of Pediatrics, 2004)

Post Exchange Monitoring

- Measure blood pH, electrolytes, Mg, Ca, Hct or Hgb, and bilirubin following exchange transfusion. Measure rebound bilirubin, WBCs, platelets 4 hrs post exchange transfusion **(Madan et al., 2005).**

Complications of exchange transfusion

Many complications of exchange transfusions have been reported, including thrombocytopenia, portal-vein thrombosis, necrotizing enterocolitis, electrolyte imbalance, graft-versus-host disease, and infection (**Jackson, 2007**).

Potential complications of exchange transfusion include the following:-

- **Cardiac**: Arrhythmia, volume overload, congestive failure and arrest.

- **Hematological:** Over-heparinization, thrombocytopenia, neutropenia and graft versus host disease.
- **Infectious**: Bacterial, viral (CMV, HIV, hepatitis).
- **Metabolic:** Acidosis, hypocalcaemia, hypoglycemia, hyperkalemia and hypernatremia.
- **Vascular:** Embolization, thrombosis, necrotizing enterocolitis, and perforation of umbilical vessel.
- **Systemic:** Hypothermia. **(Ip et al., 2004)**

Table (9): Exchange transfusionguidelines in LBW infantsbased on TSB mg/dL and B/A Ratio (mg/g).

	<1250 G	1250-1499G	1500-1999G	2000-2499G
Standard risk				
TSB	13	15	17	18
B/A ratio	5.2	6.0	6.8	7.2
High risk				
TSB	10	13	15	17
B/A ratio	4	5.2	6	6.8

Risk factors: Apgar <3 at five minutes; PaO_2< 40 mm Hg ≥ 2 h; pH ≤ 7.15 ≥ 1hr; birth weight < 1,000 g, hemolysis; clinical or central nervous system deterioration; total protein ≤ 4 g/dl or albumin ≤ 2.5 g/dL. **(Ahlfors, 2004)**

Table (10): Management of extremelowbirthweight newbornswithjaundice (Protocol for NICHHD trial of phototherapy and exchangetransfusion).

	Total bilirubin (mg/dl)				
	Birth weight	Phototherapy	Exchange	Phototherapy	Exchange
Aggressive managment	501-750g	ASAP after enrollment	≥13mg/dL	≥8mg/dL	≥13mg/dl
Conservative managment	751-1000g	ASAP after enrollment	≥15mg/dL	≥10mg/dL	≥15mg/dL

(Arnold C et al., 2014).

Pharmacological therapies

Phenobarbital: used in Crigler-Najjar syndrome type II disease to reduced TB concentrations, phenobarbital administration to pregnant mothers and their offspring was shown to reduce, by about 50%, peak TB concentrations caused by physiologic jaundice. The major effect of this therapy is to increase hepatic UGT activity and the conjugation of bilirubin. It also may enhance hepatic uptake of bilirubin in the newborn. The administration of phenobarbital to newborns at the time jaundice is first observed or even immediately after delivery is much less effective than its administration to the mother during pregnancy for at least 2 wk before delivery. The drug is much less effective in premature neonates **(Kaplan et al.;2015).**

Phenobarbital is potentially addictive, may lead to excessive sedation of the newborn, and has other potent metabolic effects in addition to those on bilirubin metabolism. For these reasons, its use has not achieved wide application but has been reserved largely for specific high-risk populations. Phenobarbital is also useful in the differentiation of Crigler-Najjar syndromes type I and type II. Combining phenobarbital treatment with phototherapy has no advantage, the effect being no greater than that of phototherapy alone **(Kaplanet al.;2015**).

Unconjugated bilirubin is metabolized by **bilirubin oxidase**. When human or rat blood is passed through a filter containing bilirubin oxidase, more than 90 percent of the bilirubin is degraded in a single pass. This procedure may prove useful in the treatment of neonatal hyperbilirubinemia, but it has not yet been tested in clinical trials. Moreover, it may pose a risk of allergic reaction because the enzyme is derived from a fungus (**Mullon et al., 2009**).

Synthetic metalloporphyrins in which the central iron is replaced by other metals limit the production of bilirubin by competitively inhibiting hemeoxygenase (**Martinez et al., 2009**).

Reduction of bilirubin in the enterohepatic circulation by miscellaneous Agents

Frequent milk feeding (cow or human) may slow the rise of TB levels and enhance the bilirubin-reducing effect of phototherapy. Oral administration of nonabsorbable substances that bind bilirubin in the intestinal lumen and presumably reduce enteric absorption of bilirubin may reduce peak TB concentrations in physiologic jaundice.

Orlistat has been used to increase fecal fat excretion, thereby enhancing bilirubin elimination and

decreasing the serum unconjugated bilirubin concentrations in Crigler-Najjar syndrome.Feeding breastfed newborns **β-glucuronidase inhibitors** (L-aspartic acid or enzymatically hydrolyzed casein) during the first week reduced jaundice without affecting breastfeeding deleteriously. **Activated charcoal** has been used, but is effective only when administered during the first 12 hours of life. **Agar** has also been shown to be effective. Further study of this type of therapy is needed before recommendations can be made regarding clinical applications. These pharmacologic agents may be no more effective than frequent milk feeding (every 2 hours) (**Kaplanet al.;2015**).

Intravenous immunoglobulin (IVIG)

Intravenous immunoglobulin reduces bilirubin concentrations in newborns with rhesus hemolytic disease and other immune hemolytic jaundice. It acts as a competetive inhibitor for those antibodies which cause red cell destruction that releases hemoglobin causing jaundice **(Watchko,2005).**

Rebound hyperbilirubinemia

Definition

Significant post-phototherapy rebound hyperbilirubin- emia was defined as bilirubin increase of more than 2 mg/dl or the 95th percentile. The rebound hyperbilirubinemia should not necessarily be equated with danger nor with a decision to reinstitute phototherapy. The significant rebound, does not necessarily mean the failure of phototherapy or presence of underlying pathology, but it can be the normal trend of bilirubin in a neonate, with or without therapy **(Firoozeh Nili et al.,2014)**.

According to Kaplan's study, rebound is defined as more than 120% bilirubin increase, bilirubin discontinuation or more than 14 mg/dl, and phototherapy does not resume until bilirubin level reaches 15 mg/dl **(Kaplan et al., 2006)**.

Incidence

In contrast to the initiation of treatment for neonatal jaundice, specific guidelines for discontinuation of phototherapy and subsequent management of the infants are lacking **(Bansal et al., 2010).**

Risk Factors for rebound hyperbilirubinemia

- Predischarge TSB or TcB level in the high risk zone.
- Jaundice observed in the first 24hs (pathological jaundice).
- Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency).
- Gestational age 35-36 weeks.
- Previous sibling received phototherapy.
- Cepalhematoma or significant bruising.
- Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive.
- East Asian race.
- Macrocosmic infant of a diabetic mother.
- Maternal age ≥ 25 years.
- Male gender.
- Down syndrome.
- Evidence of infection (**Michael Kaplanet al.;2015**).

Pathophysiology of rebound hyperbilirubinemia

Rebound hyperbilirubinemia after complete phototherapy session is not common in term neonates. However, newborns having an early onset of jaundice within 48 hours, requiring immediate phototherapy had more chance to develop rebound phenomenon **(Manutham et al., 2007).**

Hospital discharge does not need to be delayed for observation for rebound. However, in the presence of hemolytic disease or low-birth-weight infants, such reassurance may not be warranted. Because hemolysis or other processes responsible for increased bilirubin production may continue, the rebound in these cases depends not only on the effectiveness of phototherapy but also on the severity of bilirubin production **(Kaplan et al., 2006).**

Continuation of phototherapy until significant decrease in bilirubin level is observed– has no effect on decreasing rebound during the 24 hr after discontinuation of therapy. It is still more preferable to measure bilirubin levels after discontinuation of phototherapy in neonates who have risk factor/s. It is optional to keep the infant hospitalized during this monitoring process. It is important to know that rebound may occur after 24 hr; therefore, parents should be provided with necessary warnings at discharge. The time at which phototherapy is initiated varies according to the infant's gestational age and the cause of the jaundice. Phototherapy can be discontinued once the serum bilirubin concentration has been reduced by about 4 to 5 mg per deciliter (68 to 86 μmol per liter). **(Al-Saedi, 2002)**.

Intensive phototherapy in neonatal hyperbilirubinemia rapidly decreases serum total bilirubin below the threshold for treatment. However, underlying alteration in bilirubin production and excretion may persist and cause bilirubin rebound after stopping phototherapy **(Bansal et al., 2010).**

Exposing infants to high levels of colored light changes trans-bilirubin to the more water soluble cis-form which is excreted in the bile. When bilirubin absorbs light, three types of photochemical reactions occur: Photoisomerization, Structural isomerization andphoto-oxidation. Photoisomerization of bilirubin occurs in the extravascular space of the skin. The natural isomer of unconjugated bilirubin is rapidly converted to a less toxic polar isomer that diffuses

into the blood and is excreted into the bile without conjugation. However, these reaction is reversible and photoisomer excretion is slow. So in infant with increased enterohepatic circulation or those with constipation the photoisomer is readily converted back to unconjugated bilirubin, which is resorbed from the gut if the baby is not passing stools properly**.** After approximately 12 hours of phototherapy, the photoisomers make up approximately 20% of total bilirubin. On the other hand, Structural isomerization of bilirubin lead to formation of lumirubin makes up 2% to 6% of serum concentration of bilirubin during phototherapy and is rapidly excreted in the bile and urine without conjugation. photo-oxidationis a slow process which considered the least important reaction for lowering bilirubin levels **(Cloherty et al., 2012)**.

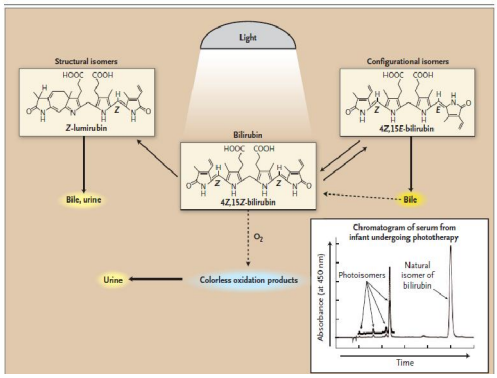

Figure (12): Mechanism of phototherapy (Maisels and McDonagh., 2008).

Feedings invoke the gastrocolic reflex, and bilirubin is excreted in stool before most of it can be deconjugated and reabsorbed. However in many neonates, the unconjugated bilirubin is reabsorbed and returned to the circulation from the intestinal lumen (enterohepatic circulation of bilirubin). Increased enterohepatic bilirubin circulation occurs in infants who are exclusively breastfed and not feeding well, and who have low levels of intestinal bacteria preventing conversion of bilirubin into a non-reabsorbable form **(Hanoudi, 2013).**

The total serum bilirubin level at the time of discontinuation of phototherapy is a significant factor associated with a need to start phototherapy again in jaundiced babies, especially if treatment is stopped before five days of life when the total serum bilirubin usually peaks **(Maisels and Kring, 2002).**

Preventive strategies of rebound hyperbilirubinemia

The serum bilirubin level should be obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95thpercentile (high-risk zone) (**Bhutani & Johnson, 2009**).

Table (10): Follow-up after discharge:

Infant Discharge	**Should Be Seen By Age**
Before age 24h	**72h**
Between 24 and 47.9h	**96h**
Between 48 and 72h	**120h**

(American Academy of Pediatrics, 2004)

Nomogram for hour-specific bilirubin values:

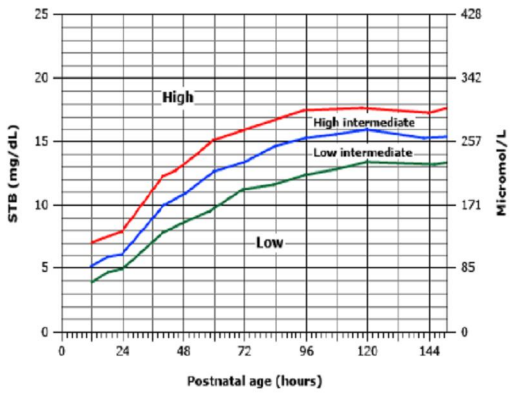

Figure (13): Nomogram for designation of risk in well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values **(American Academy of Pediatrics, 2004).**

This is a useful tool for predicting, either before or at the time of hospital discharge, which infants are likely to develop high serum bilirubin values. Infants identified in this manner require close follow-up monitoring and repeated bilirubin measurements. The predictive ability has been shown both for bilirubin values measured in serum and for values measured transcutaneously **(Schutz et al.,2010).**

Consider follow up total serum bilirubin level measurement within 12 - 24 hours after discharge. Another bilirubin level may be checked a few days later to make sure that the bilirubin level (if it increased from the previous level) has started to stabilize or decline. If the bilirubin level shows

stabilization or if the level is decreasing, no further checks will be needed if baby is otherwise doing well with feedings **(Kaplan et al., 2006)**.

Follow up should be provided within 2-3 days of discharge to all neonates discharged earlier than 48hr after birth. Early follow up is particularly important for infants <38 week gestation. The need for and timing of a repeat TcB or TSB measurement will depend on the zone in which the TSB falls. It is recommended that information be given to parents at the time of discharge. Parents should be advised to contact a doctor if:

- Baby's jaundice is worsening.
- Jaundice is persisting beyond 14 days.
- Mothers of jaundiced breastfed babies should be encouraged to breastfeed frequently, and the baby woken to feed if necessary.

Follow up assessment must include:

- Baby's weight and percentage change from birth weight.
- Adequacy of intake.
- Voiding and stooling pattern.
- Clinical judgement to determine the need for total serum bilirubin level measurement.
- **(Queensland Maternity and Neonatal Clinical Guidelines Program 2012)**

The goal of hyperbilirubinemia treatment is to avoid bilirubin concentration that may result in kernicterus. Phototherapy remains an effective therapeutic intervention that decreases bilirubin concentration **(Cloherty et al., 2012)**.

After discontinuing phototherapy the bilirubin level often rises slightly, a phenomenon known as rebound. Rebound hyperbilirubinemia is usually an elevation of 1 to 2 mg/dL (17 to 34 μmol per liter) and occasionally more can occur after phototherapy is discontinued. However, postphototherapy rebound to clinically significant levels can occur. It is usually unnecessary to keep an infant in the hospital to check for rebound **(American academy of pediatrics, 2004)**.

The processes instrumental in the pathogenesis of the hyperbilirubinaemia may not yet have resolved by the time phototherapy is discontinued. As a result, a serum bilirubin measurement obtained 24 hours after discontinuation of phototherapy will detect rebound hyperbilirubinemia **(Kaplan et al., 2006)**.

Another bilirubin level may be checked a few days later to make sure that the bilirubin level (if it increased from the previous level) has started to stabilize or decline. If the bilirubin level shows stabilization or if the level is decreasing, no further checks will be needed if baby is otherwise doing well with feedings **(Kaplan et al., 2006)**.

The rebound of bilirubin level after termination of phototherapy in otherwise healthy term infants is minimal; thus measurement of serum bilirubin is not required after termination of phototherapy and adds unnecessary expense, prolongs hospitalization or both **(Al-Saedi, 2002)**.

Newborn completing phototherapy for hyperbilirubinemia before the age of 2 weeks, who are cured, do not require a follow up test in the second day to check for rebound hyperbilirubinemia. So we can decrease the laboratory and nurses charges, the time of hospital admission and money cost **(Al-Mardeny et al., 2005)**.

Infants at greatest risk for significant postphototherapy rebound in serum bilirubin levels requiring closer follow-up include the following:

* Premature infants.
* Infants with ongoing hemolysis.
* Infants treated before 72 hrs of age. **(Kaplan et al., 2006)**.

Rebound hyperbilirubinemia after complete phototherapy session was not common in term neonates. However, newborns having an early onset of jaundice within 48 hours, requiring immediate phototherapy had more chance to develop rebound phenomenon **(Manutham et al., 2007)**.

Data available are inadequate to formulate recommendations for or against post-phototherapy bilirubin testing. Significant bilirubin rebound is rare and therefore, measurement of bilirubin rebound is not needed. In addition, routine measurement of bilirubin rebound may increase workload, add to expenses and prolong the hospital stay **(Bansal et al., 2010).**

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