



Neonatal Jaundice

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Abstract

Jaundice is the most common morbidity in the first week of life and it is the commonest cause of readmission in the neonatal period. It is a multifactorial disorder with physiological jaundice being the most prevalent cause. However a high index of suspicion should be kept for detecting the pathological forms of jaundice. The prevention, detection and management of jaundice remain a challenge because of early discharge of healthy late preterm and full term newborn infants. This review article aims to introduce jaundice in the neonatal period, its types and causes, measurement of bilirubin level (established as well as the newer methods awaiting approval), clinical approaches towards jaundice and different remedial therapeutic measures for its treatment.

Keywords: *Hyperbilirubinaemia, Jaundice, Newborn, Discharge, Phototherapy.*

Introduction

Hyperbilirubinemia is a common problem in neonates and is a cause of concern for the parents as well as for the paediatricians. Jaundice is the visible form of hyperbilirubinemia a due to the deposition of yellow orange bile pigment i.e. bilirubin ⁽¹⁾. It appears in Adult sclera at total serum bilirubin >2mg / dl and Newborn skin at total serum bilirubin >7 mg / dl⁽²⁾. Jaundice occurs in nearly 60% of term and most of preterm neonates ⁽³⁾. However, significant jaundice occurs in 6 % of term babies ⁽⁴⁾.

Physiological jaundice: Jaundice is called physiologic if it has the following characteristics:

- Appears after 24 hours

- Maximum intensity by 4th-5th day in term & 7th day in preterm
- Serum level less than 15 mg /dl
- Clinically not detectable after 14 days
- Disappears without any treatment

Pathological jaundice Characteristics:

- Appears within 24 hours of age
- Increase of bilirubin > 5 mg / dl / day or increasing by more than 0.2 mg/dL per hour
- Serum bilirubin > 15 mg / dl
- Jaundice persisting after 14 days
- Stool clay/white colored and urine staining clothes yellow
- Direct bilirubin > 2 mg / dl

Neonatal bilirubin metabolism

Hemolysis of red blood cells releases hemoglobin. Heme oxygenase degrades heme into biliverdin and carbon monoxide within the reticuloendothelial system. Biliverdin reductase reduces biliverdin to unconjugated bilirubin (indirect) which then binds to albumin and is transported to the liver. Unconjugated bilirubin can become unbound if albumin is saturated or if bilirubin is displaced from albumin by medications like ceftriaxone, streptomycin, chloramphenicol, sulfisoxazole, ibuprofen etc. UCB is lipophilic and crosses the Blood-Brain Barrier(BBB) but only free UCB crosses, albumin-bound does not.

The BBB of infants is more permeable than adults, and acidosis causes it to be even more permeable. UCB has an affinity for the basal ganglia, hippocampus, cranial nerve nuclei and it interrupts metabolism in glial cells and causes apoptosis of neurons^(5,6) Once unconjugated bilirubin bound to albumin reaches the liver, it is conjugated by uridine diphosphate glucuronosyl transferase (UGT1A1). Conjugated (direct) bilirubin is excreted into the intestine via the gallbladder and bile duct. Bacteria in the intestine can deconjugate bilirubin, allowing it to be reabsorbed into the blood. The rest of the bilirubin is excreted with the stool.^(5,6) (Figure. 1)

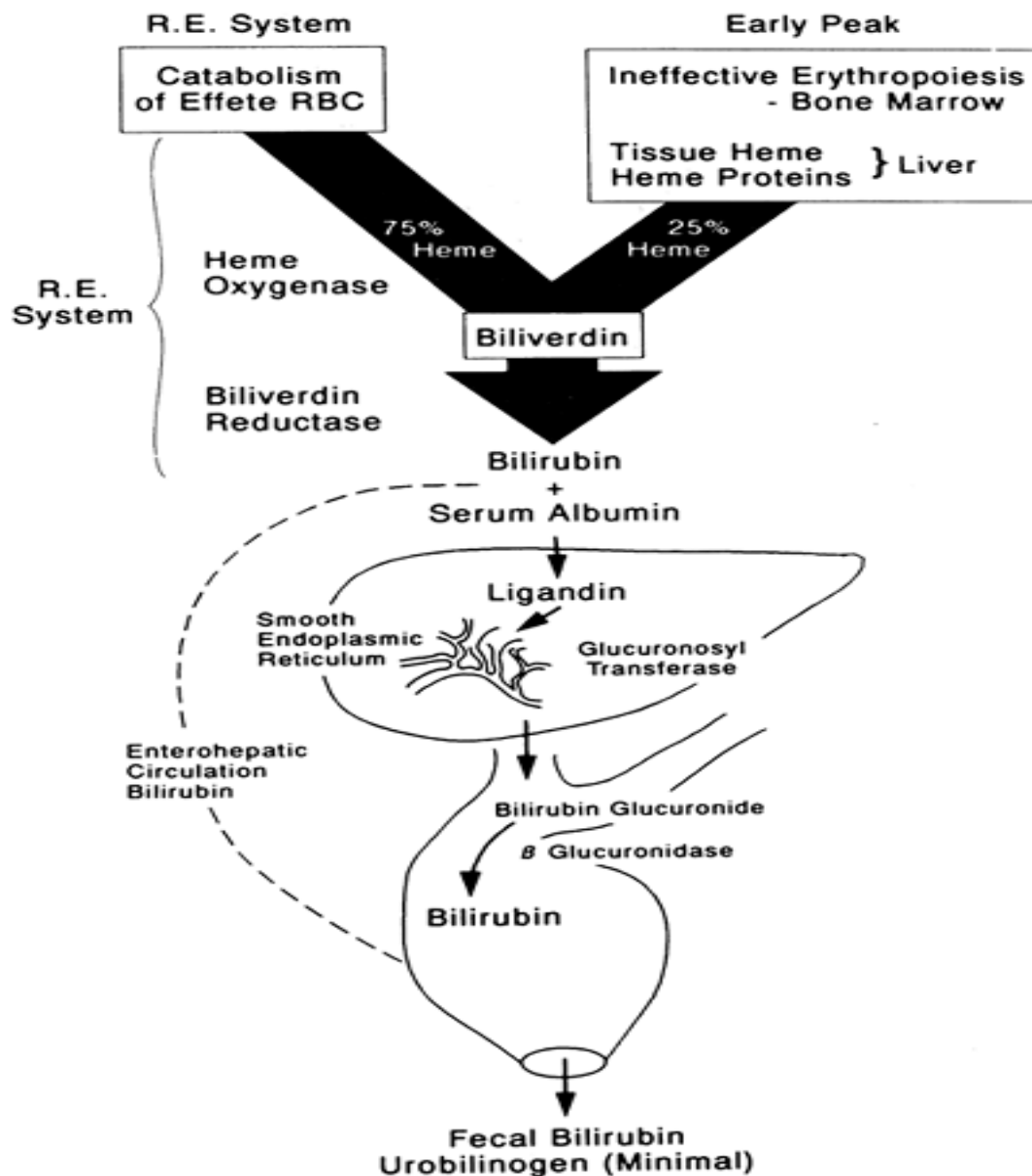


Figure 1: Bilirubin metabolism

Causes of pathological jaundice are the following:

Table1. Causes of Pathological jaundice

Appearing within 24 hours of age
Hemolytic disease of NB : Rh, ABO
Intrauterine Infections: TORCH, syphilis malaria, bacterial
Deficiency of red cell enzymes:G6PD deficiency, pyruvate kinase
Hereditary spherocytosis
Lucey-Driscoll Syndrome
Crigler_Najjar syndrome

Appearing between 24-72 hours of life : Physiological jaundice
After 72 hours of age
Sepsis
Neonatal hepatitis
Extra-hepatic biliary atresia
Breast milk jaundice
Metabolic disorders
Crigler_Najjar syndrome

Prolonged jaundice: Is defined as persistence of significant jaundice for more than 2 wk in term and more than 3 weeks in preterm babies ⁽⁹⁾.

Table 2: Causes of Prolonged indirect jaundice

Inadequacy of breastfeeding
Breast milk jaundice
Cholestasis
Ongoing hemolysis, malaria
Extravasated blood e.g. cephalhematoma
Hypothyroidism
Pyloric stenosis
Crigler Najjar syndrome

Conjugated hyperbilirubinemia

This is rare in the newborn period and is defined as a direct bilirubin level of > 2mg/dl. It is important to document cause as it is never physiological.

Causes of Conjugated jaundice
Idiopathic neonatal hepatitis
Infections -Hepatitis B, TORCH, sepsis
Biliary atresia, choledochal cyst
Metabolic -Galactosemia, tyrosinemia, hypothyroidism
Total parenteral nutrition

Table 3: Causes of Conjugated jaundice

General Clinical features of neonatal jaundice:

- Yellow skin
- Yellow eyes (sclera)

- Sleepiness
- Poor feeding in infants
- Brown urine
- Fever
- High-pitch cry
- Vomiting

Major Clinical Features of Acute Bilirubin Encephalopathy

Initial Phase

Hypotonia, lethargy, high-pitched cry, and poor suck.

Intermediate phase

Hypertonia of extensor muscles (with opisthotonus, rigidity, oculogyric crisis, and retrocollis), irritability, fever, and seizures.

Many infants die in this phase. All infants who survive this phase develop chronic bilirubin encephalopathy (clinical diagnosis of kernicterus).

Advanced phase

Pronounced opisthotonus (although hypotonia replaces hypertonia after approximately 1 week of age), shrill cry, apnea, seizures, coma, and death.

- **Chronic bilirubin encephalopathy (kernicterus):** Kernicterus denotes chronic and permanent sequelae of bilirubin toxicity. Kernicterus is caused by damage to the brain centers of infants caused by increased levels of unconjugated-indirect bilirubin which is free (not bound to albumin). Clinical features of kernicterus are:
 - Athetosis
 - Complete or partial sensorineural deafness (auditory neuropathy)
 - limitation of up-ward gaze
 - Dental dysplasia
 - Intellectual deficits.

Approach to jaundiced baby

- Ascertain birth weight, gestation and postnatal age
- Assess clinical condition (well or ill)
- Decide whether jaundice is physiological or pathological

- Look for evidence of kernicterus in deeply jaundiced NB

Workup

- Maternal & perinatal history
- Physical examination
- Laboratory tests (must in all)*
- Total & direct bilirubin*
- Blood group and Rh for mother and baby*
- Hematocrit, retic count and peripheral smear*
- Sepsis screen
- Liver and thyroid function
- TORCH titers, liver scan when conjugated hyperbilirubinemia

Clinical assessment of jaundice

Visual inspection of jaundice although is not a very method but if done properly in bright day light has reasonable accuracy particularly when TSB is less than 12 to 14 mg/dL⁽⁹⁾.

Kramer's criteria

Schema for grading extent of jaundice

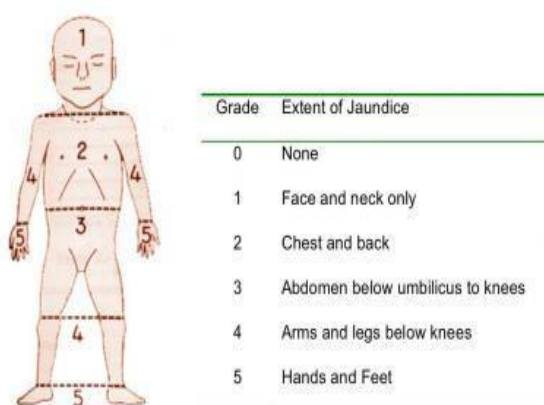


Figure 2: Kramer's criteria of Grading of jaundice based on visual inspection

Measurement of serum bilirubin

- 1) Transcutaneous bilirubinometry (TcB): It is unreliable in infants less than 35 weeks gestation and during initial 24 hr of age. It has a good correlation with TSB at lower levels, but it becomes unreliable once TSB level goes beyond 14 mg/dL. It can be used to screen for hyperbilirubinemia.⁽⁹⁾. A TcB value of greater than 12 to 14

mg/dL should be confirmed by TSB measurement⁽⁹⁾

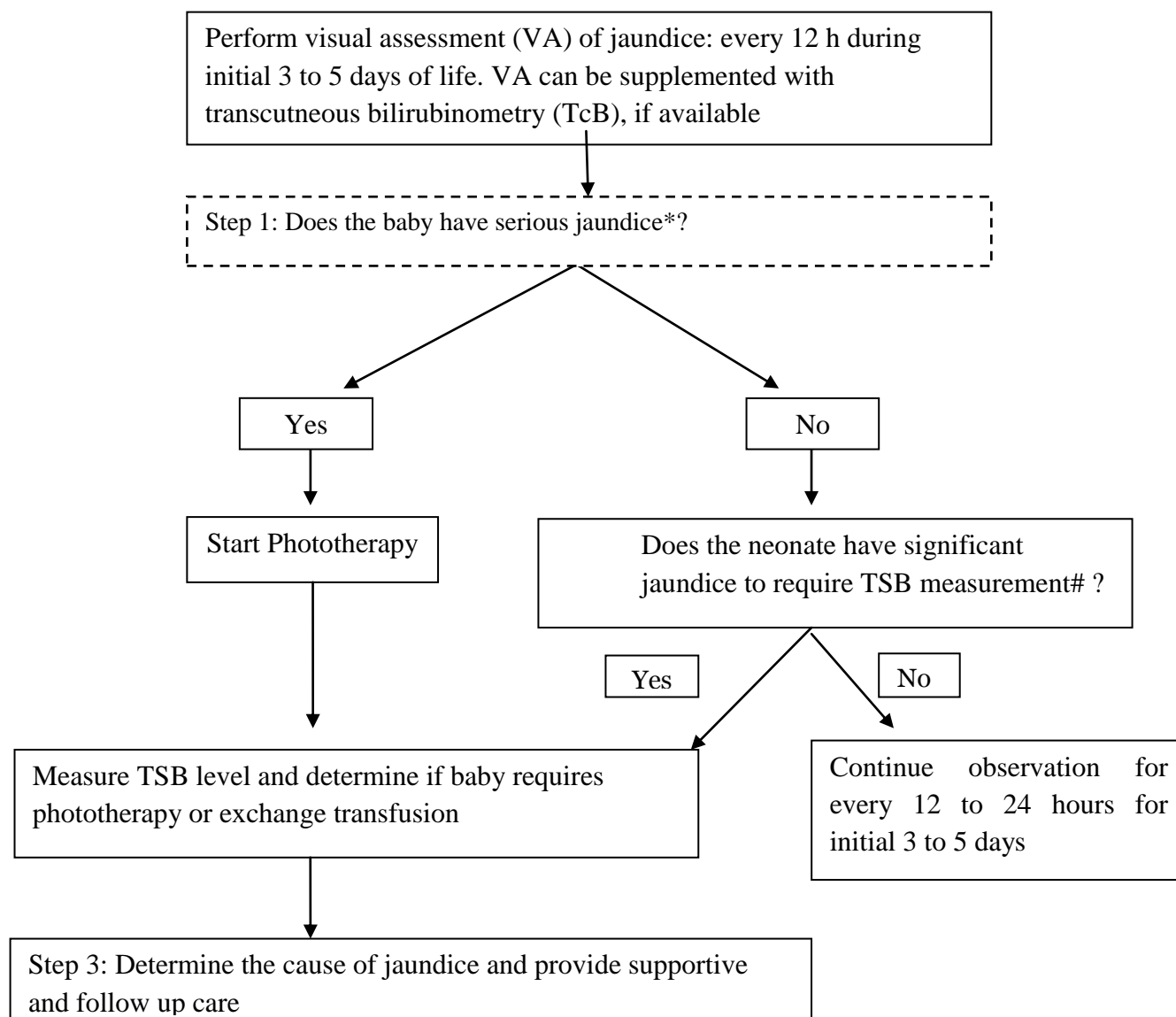
2) Measurement of TSB:

Indication of TSB measurement:

- Jaundice in first 24 hour
- Beyond 24 hr: if visually assessed jaundice is likely to be more than 12 to 14 mg/dL (as beyond this TSB level, visual assessment becomes unreliable) or approaching the phototherapy range or beyond.
- If you are unsure about visual assessment
- During phototherapy, for monitoring progress and after phototherapy to check for rebound in select cases (such as those with hemolytic jaundice)

Methods of TSB measurements

- Biochemical: High performance liquid chromatography (HPLC) remains the gold standard for estimation of TSB.
- Micro method for TSB estimation: It is based on spectrophotometry and estimates TSB on a micro blood sample

Approach to jaundice ⁽⁹⁾:**Figure 3:** Approach to jaundice. ⁽⁹⁾

*serious jaundice: present in first 24 hours; affecting palms and soles; Signs of acute bilirubin encephalopathy or kernicterus; TcB value more than 95th percentile as for age specific nomogram
 #Measure serum bilirubin if: jaundice in first 24 hours; beyond 24 hours: if likely to be more than 12 to 14 mg/dl or approaching phototherapy range

Management

The rationale is to reduce level of serum bilirubin and prevent bilirubin toxicity. The various opinions available for reduction of bilirubin levels beyond a certain threshold are: phototherapy, exchange transfusion and drugs.

Phototherapy: Phototherapy remains the mainstay of treating hyperbilirubinemia in neonates.

Principle of phototherapy

The initial and most rapid reactions occurring as a result of phototherapy produce configurational isomers. The most prominent of these configurational isomers is called 4Z,15E bilirubin (native bilirubin being 4Z,15Z bilirubin). The second most rapid photochemical reaction leads to the formation of structural isomers, the most prominent known as lumirubin. But because lumirubin is cleared from the serum much more

rapidly than the 4Z,15E isomer, it is likely that lumirubin formation is mainly responsible for the phototherapy induced decline in serum bilirubin in the human infant. 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 level⁽¹⁰⁾.

Factors That Affect the Dose and Efficacy of Phototherapy

- Wavelength: Bilirubin absorbs light primarily around 400 to 500 nm . The most effective lights for phototherapy are those with high energy output near the maximum absorption peak of bilirubin (450–460 nm).
- Irradiation level: *Conventional phototherapy should deliver spectral irradiance at the infant's level of 8 to 10 $\mu\text{W}/\text{cm}^2/\text{nm}$. Intensive phototherapy delivers at least 30-40 $\mu\text{W}/\text{cm}^2/\text{nm}$.*
- Distance: Distance should be kept at distance of 45 cm and *can be reduced to 15-20* to provide more effective or intensive phototherapy. .
- Nature and character of the light source: Special blue lamps with a peak output at 425 to 475 nm are the most efficient for phototherapy.

Bilirubin concentration

Monitoring & stopping phototherapy

Monitoring of temperature of the baby should be done every 2 to 4 hr. Weight record done daily (small infants weighed twice daily) .TSB level is measured every 12 to 24 hours and phototherapy is discontinued once two TSB values 12 hr apart fall below current age specific cut offs. The infant should be then monitored clinically for rebound bilirubin rise within 24 hours after for babies with hemolytic disorders.

Exchange Transfusion

With this technique, the equivalent of two neonatal blood volumes (160 mL/kg of body

weight) is replaced in aliquots not to exceed 10% of the total blood volume. This results in the replacement of approximately 85% of the circulating RBCs. In the push–pull method, blood is removed in aliquots that are tolerated by the infant⁽¹⁰⁾.

Choice of blood for exchange blood transfusion

ABO incompatibility: Use O blood of same Rh type, ideal O cells suspended in AB plasma

Rh isoimmunization: Emergency O -ve blood , Ideal O -ve suspended in AB plasma or baby's blood group but Rh –ve

Other situations (G6PD deficiency, non-hemolytic, other isoimmune hemolytic jaundice): Baby's blood group.

American Academy of Paediatrics (AAP) criteria should be used for making decision regarding phototherapy or exchange transfusion in jaundiced newborn⁽⁷⁾. AAP provides two age-specific nomograms- one each for phototherapy and exchange transfusion. The nomograms have lines for three different risk categories of neonates: One each for lower risk babies (38 wk or more and no risk factors), medium risk babies (38 wk or more with risk factors, or 35 wk to 37 wk and without any risk factors) and higher risk (35 wk to 37 wk and with risk factors)⁽⁷⁾. Risk factors are isoimmune hemolytic anemia, asphyxia, temperature instability, G6PD deficiency, significant lethargy, acidosis, hypothermia, sepsis and hypoalbuminemia.

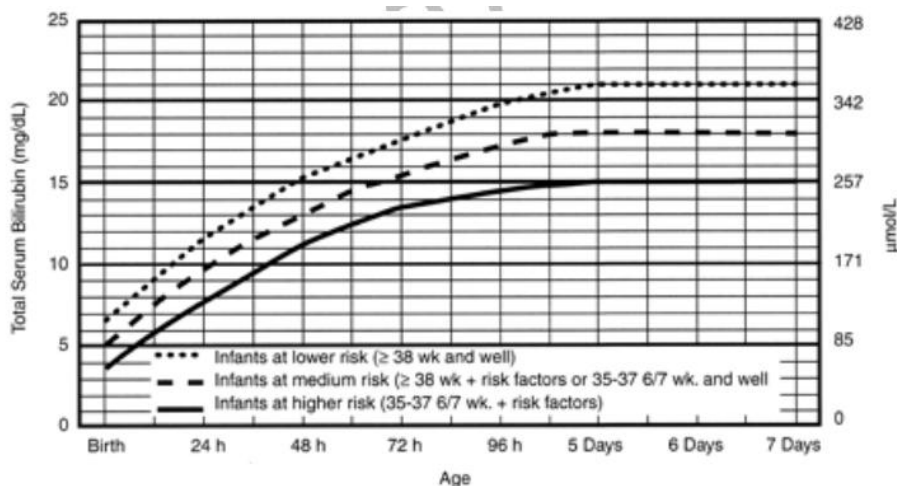


Figure 4: AAP nomogram for phototherapy in hospitalized infants of 35 or more weeks' gestation ⁽⁷⁾

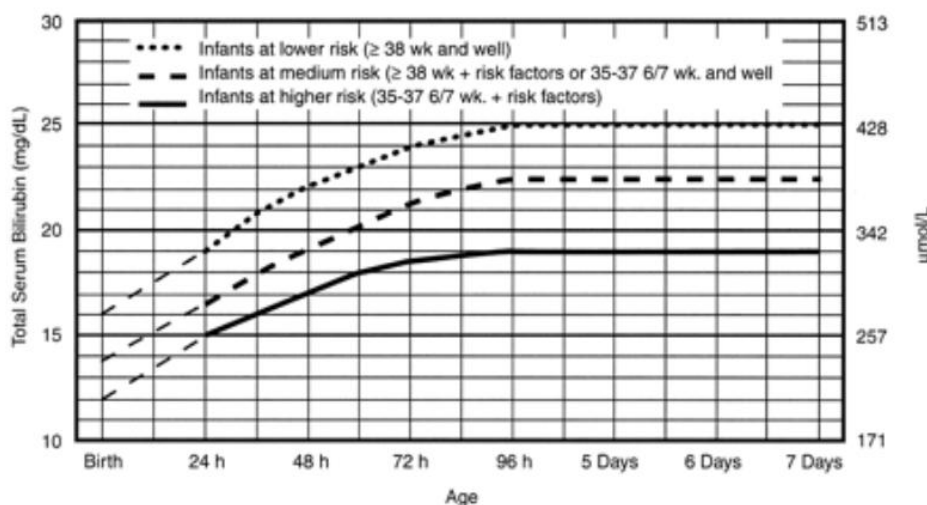


Figure 5: AAP nomogram for exchange transfusion in infants 35 or more weeks' gestation ⁽⁷⁾

Table 4 . Phototherapy and exchange transfusion cut-offs for preterm babies ⁽⁸⁾

BIRTH WEIGHT	Total serum bilirubin (mg/dl)			
	Healthy baby		Sick baby	
	Phototherapy	Exchange transfusion	Phototherapy	Exchange transfusion
<1000 gm	5-7	11-13	4-6	10-12
1001-1500 gm	7-10	13-15	6-8	11-13
1501-2000 gm	10-12	15-18	8-10	13-15
2001-2500 gm	12-15	18-20	10-12	15-18

Pharmacologic Treatment

Phenobarbital

Phenobarbital is a potent inducer of microsomal enzymes, ligandin and glucuronyl transferase (UDPGA) thus increasing bilirubin uptake, conjugation and excretion. Phenobarbitone in a single dose of 10 mg/kg intramuscular or 5mg/kg/day in two divided doses orally for 3 days is indicated in infants with Cord serum bilirubin more than 2.5 mg/dl ,Early onset of jaundice due

to any cause, Difficult or instrumental oxytocin-induced delivery with bruising and cephalhematoma, G-6-PD deficiency, Type 2 Crigler – Najjar syndrome

Intravenous Immunoglobulin

In both RH and ABO hemolytic disease of newborn, the hemolysis of neonatal red blood cell coated by transplacentally acquired antibodies is mediated by Fc receptor bearing cells within the reticuloendothelial system. IVIG acts by blocking Fc receptors thereby inhibiting hemolysis and

reducing formation of bilirubin. IVIG is given in a dose of 0.5-1g/kg as slow infusion over 2 hours.

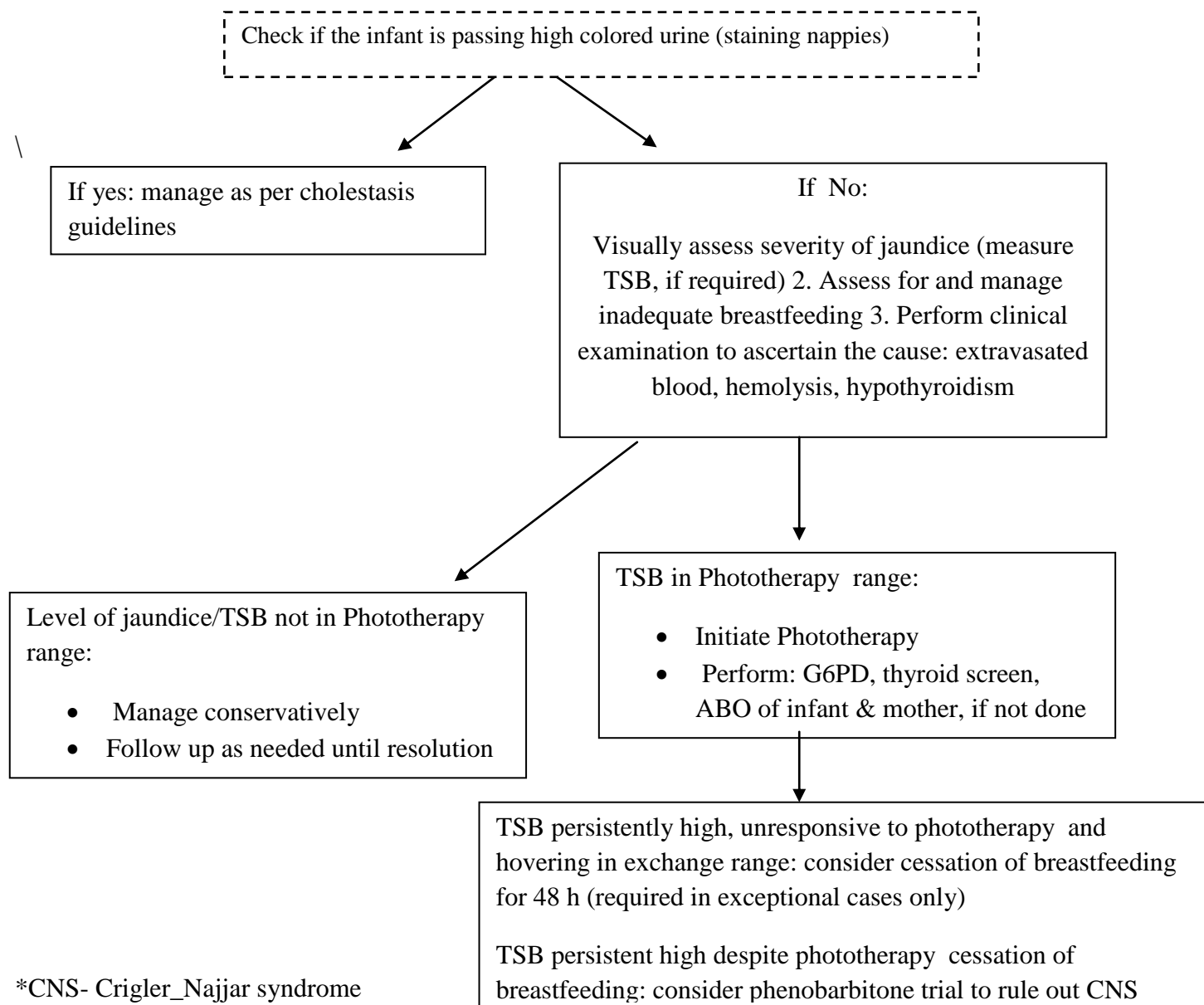
IV hydration

Infants with severe hyperbilirubinemia and evidence of dehydration (e.g. excessive weight loss) should be given IV hydration.

Others

Tin Mesoporphyrin, Orotic acid, Inhibiting the Enterohepatic Circulation of Bilirubin (Charcoal, Agar and Orlistat), Zinc bis glycol porphyrin, Clofibrate

Approach to prolonged jaundice:



*CNS- Crigler_Najjar syndrome

Figure 6: Approach to prolonged jaundice

Recent Advances in jaundice

- Hour-specific bilirubin nomograms have been constructed based on routine pre-discharge bilirubin assessment
- Newer modalities of bilirubin testing: BILIRUBIN: ALBUMIN RATIO (B: A),

Free bilirubin, Bilirubin Binding Capacity (BBC), Free bilirubin: TSB (proposed), Role of ETCO in hemolytic jaundice are being investigated.

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