Jaundice in neonates

Links Pediatric cases websites

https://www.pedscases.com/neonatal-jaundice-part-1

https://www.pedscases.com/neonatal-jaundice-part-2

https://www.pedscases.com/neonatal-jaundice-part-3

Introduction :

Bilirubin level approaching exchange level or rapidly rising bilirubin level is a medical emergency prompting immediate investigation and treatment [3]

- Any clinical sign of kernicterus is a medical emergency requiring exchange transfusion

1. Bilirubin Basics

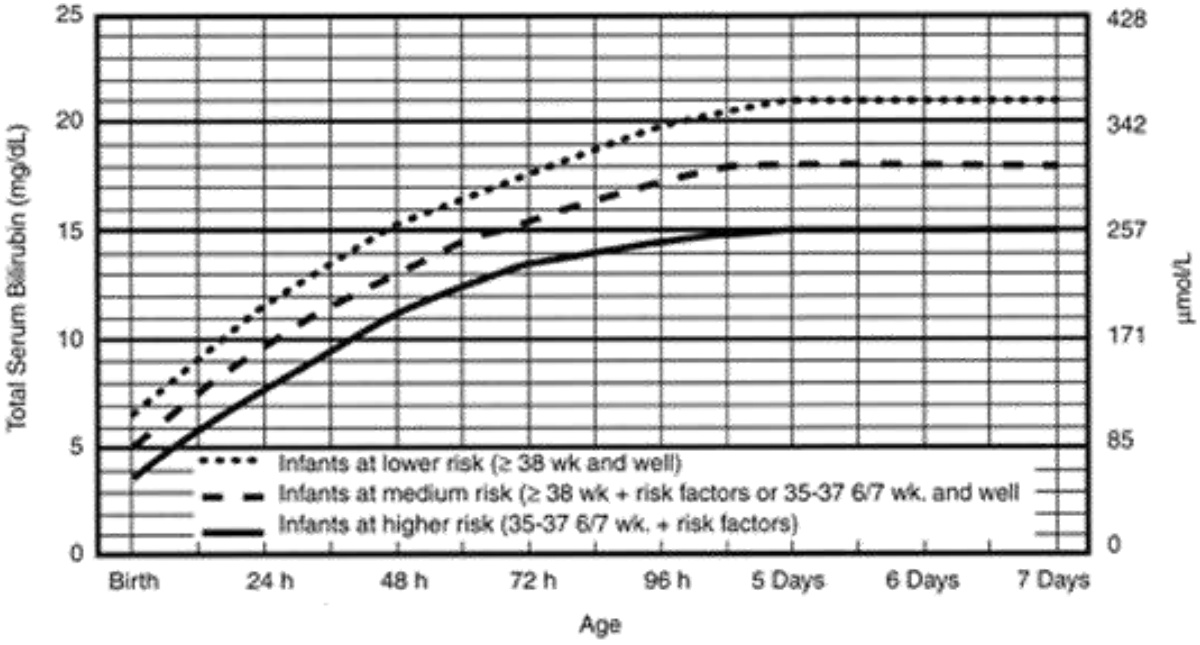
- Bilirubin is derived from proteins that contain hem
- Biggest source is breakdown of from red blood cells
- Heme is broken down to biliverdin, which is reduced to bilirubin (in the process, CO is produced)
- Measurement of exhaled CO is an indication of ongoing hemolysis

2- Bilirubin Screening

- Screening policies that are widely used do not have good evidence for predicting hyperbilirubinemia (eg. screening babies of all O+ moms)
- Total Serum Bilirubin is inexpensive (<$2) and thus has a good cost/benefit rati
- Some experts and Canadian guidelines recommend universal screening in all infants before discharge or between 24 and 72 hours of life [4]
- American Academy of Pediatrics recommends either predischarge measurement of bilirubin level or targeted screening in all infants with risk factors for severe hyperbilirubinemia [1]

- **2.1** Before discharge of new born after birth all infants should be assessed for risk factors for hyperbilirubinemia, by

- Carefully clinical assess for jaundice at 48 hours of life.
- Clinical risk factors
- Serum or transcutaneous bilirubin measurement is recommended **in all** infants with clinical signs of jaundice [3]
- Obtain a total serum bilirubin level or transcutaneous bilirubin level in all infants during the first 72 hours of life [4]
    - Plot the bilirubin level on phototherapy chart [4] [1] to determine If treatment is necessary (use phototherapy Chart)



- If total serum bilirubin level does not require immediate intervention (phototherapy) so use Bhutani charts , to determine the level of risk for severe hyperbilirubinemia and the frequency of follow-up [4]

Risk factors for sever hyperbilirubenima (Table 1)

- <u>Major risk factors:</u>

- Predischarge TSB in High Risk zone on Bhutani nomogram
- Jaundice observed in the first 24 hours
- ABO incompatibility with positive direct Coombs, other known helmolytic disease
- Gestational age 35-36 weeks
- Previous sibling received phototherapy

- Cephalohematoma or significant bruising
- Exclusive breastfeeding, especially if not nursing well and excessive weight loss
- East Asian race
- jaundice noted before discharge

- Minor risk factors:

- gestational age 37 to 38 weeks,
- jaundice in previous sibling,
- macrosomic infant of diabetic mother,
- maternal age 25 years or older
- male sex

- Overall risk increases with increasing number of risk factors

2.2 Bedside and laboratory screening tests to quantitate bilirubin concentration

Often quantitative bilirubin assessment is the only test necessary; obtain either

2.2.1 -Total serum bilirubin level

- Capillary or venous sample is acceptable; outcome data are based on total capillary blood samples [1]

- Transcutaneous bilirubinometry

- Inaccurate for levels of 14.6 mg/dL (250 µmol/L) or more or if infant is receiving phototherapy [3]
- Transcutaneous testing may resume 24 hours after discontinuation of phototherapy [3]
- Obtain serum levels to confirm any transcutaneous bilirubin measurement of 13 to 14.6 mg/dL (250 µmol/L) or more [3 5]

Plot transcutaneous or serum bilirubin levels of all infants on a predictive nomogram or table (based on age in hours) [19] to determine need for immediate intervention or risk of progression and need for more vigilant follow-up (eg, American Academy of Pediatrics nomogram, [1] National Institute for Health and Care Excellence table [20])

2.2.2- . Obtain ABO blood type and Rh status plus direct antiglobulin (Coombs) test for: [4]

- All infants born to mothers of blood group O and Rh negative mother
- Infants with jaundice appearing in the first 24 hours of life
- Infants whose bilirubin levels fall in high intermediate zone on predictive risk nomogram (Canadian Paediatric Society guideline, Figure 1) [4]
- Obtain ABO blood type and Rh status on all infants born to mothers who have unknown ABO or Rh status [4]

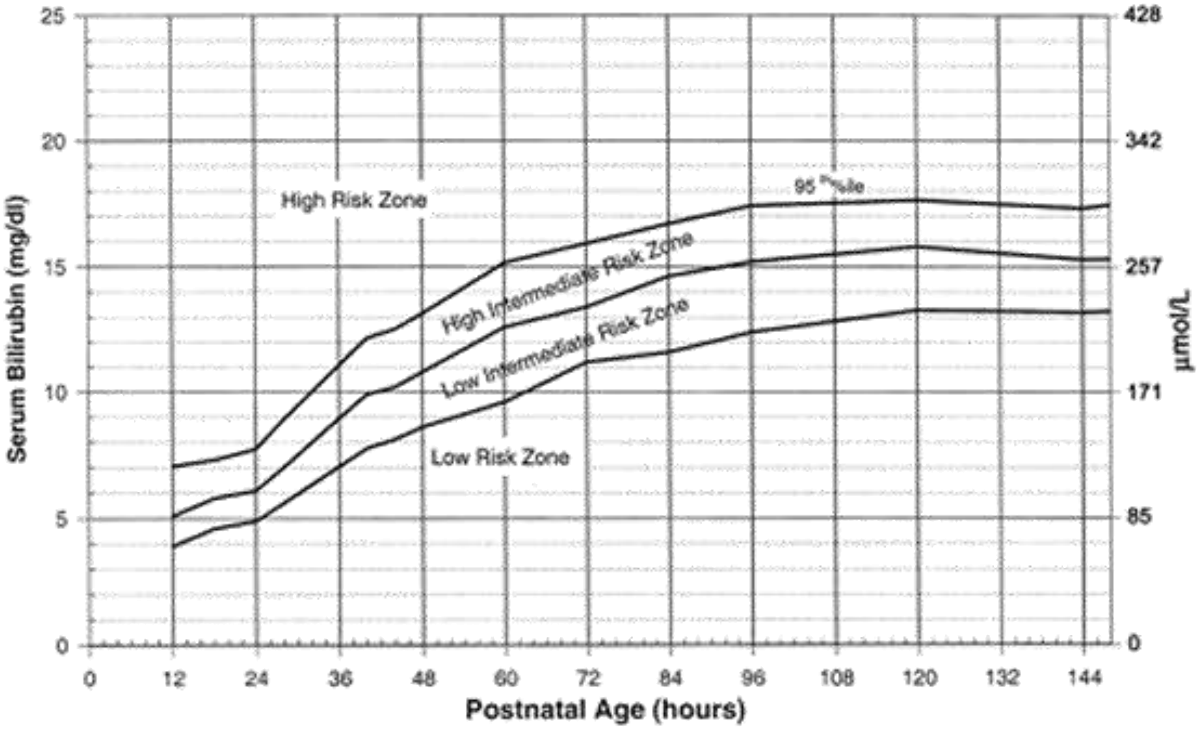
2.2.3. Obtain conjugated (direct) bilirubin level for all infants with prolonged jaundice (ie, more than 2 weeks, or 3 weeks for thriving term infants), all ill-appearing infants, and infants with hepatosplenomegaly on examination [4]

2.2.4 . – Further laboratory work-up for all infants presenting with jaundice in the first 24 hours of life or ill-appearing infants is based on history and physical examination

2.2.5. - American Academy of Pediatrics recommends laboratory investigation to determine cause of jaundice in all infants who need phototherapy [1]

2.2.6. Use of Nomograms and Guidelines

- Nomograms help assess risk for developing hyperbilirubinemia and help arrange appropriate follow-up
- There is now good data and an accepted nomogram for assessing risk based on bilirubin level (Bhutani, 1999)
- Clinical Guidelines for screening and management are available from the AAP (July 2004)
- Early jaundice (age < 24h) still has a broad differential and requires workup, despite the ease of initiating management with phototherapy



Predictive Bhtani Nomogram

3. Classification of neonatal Jaundice

Terminology

Clinical Clarification

- Clinical jaundice in neonates is visibly detectable bilirubin deposition in the skin and mucous membranes
- Physiologic jaundice is common in neonates, but significant hyperbilirubinemia distinguishes a level of jaundice requiring treatment to prevent kernicterus (irreversible bilirubin encephalopathy)

3.1 Physiologic jaundice is common in infants and is due to an immature bilirubin elimination process coupled with a relatively high bilirubin load

Usually does not require treatment outside of improving nutritional support and ensuring bilirubin elimination through adequate stool and urine output

Exclusively breastfed infants frequently have some degree of physiologic jaundice

- Threr is accumulation of unconjugated (indirect) bilirubin in the skin and mucous membranes of otherwise healthy neonates that most often does not require treatment [2]
- Present with jaundice after the first 24 hours of life in otherwise healthy and thriving infants [3]
    - Normal physiologic state in newborns, who have increased bilirubin loads and diminished physiologic capacity to eliminate bilirubin in the first week of life
- Healthy infants have an increased bilirubin load (from increased circulating RBC mass and shortened RBC lifespan) coupled with diminished ability to eliminate bilirubin in the first 1 to 2 weeks of life (glucuronosyltransferase activity of term infant is about 1% of adult activity) [7]

- Breastfed infants are at 3- to 6-fold higher risk for exaggerated early physiologic hyperbilirubinemia (more than 12 mg/dL) or severe hyperbilirubinemia (more than 15 mg/dL) compared with formula-fed infants [2]
- Secondary to delayed meconium passage and lower overall fluid volume associated with breastfeeding
    - In some infants, breastfeeding may be a contributing factor

3.1.1. Breastfeeding jaundice

- Self-limited; resolves in the first week of life when maternal milk supply and infant feeding routine is established
    - Breastfeeding jaundice (BFJ)

- Begins in first 2 to 4 days of life, related to diminished caloric and fluid intake and increased enterohepatic circulation of bilirubin
- Self-limited; resolves in the first week of life when maternal milk supply and infant feeding routine is established
- Affects 13% of otherwise healthy and thriving breastfed infants

3.1.2 Breast milk jaundice

- About a third of breastfed infants have persistent physiologic jaundice beyond 2 weeks of age [3]
- Bilirubin levels associated with breastfeeding can range up to 20 mg/dL
- Phototherapy is rarely necessary
- Typically occurs after day 3 of life, peaking around days 6 to 14, and declining in the next 1 to 3 months
- Decrease in bilirubin of 2 to 5 mg/dL/day is noted if breastfeeding is interrupted owing to significant elevations in bilirubin level [5]
    - Breast milk jaundice (BMJ)
        - Begins in first 2 weeks of life
        - Normal components of breast milk (eg, β-glucuronidase) may contribute [2]
        - Genetic polymorphism may contribute example UGT1A1 gene polymorphism
        - Self-resolving by 1 to 3 months
        - Affects 2% of breastfed infants after the first week of life
-

3.1.3- Epidemiology of physiological jaundice

- **Term infant**
  - Up to 60% of infants are jaundiced in the first week of life [7]
    - Bilirubin peaks at days 3 to 5 of life, at a mean of 6 mg/dL
    - Moderate jaundice (bilirubin more than 12 mg/dL) occurs in about 12% of breastfed infants and 4% of formula-fed infants [5]
- **Preterm infant**
  - Incidence of visible jaundice: more than 80% of preterm infants [7]
    - Peaks at days 5 to 7 of life
    - Preterm infants are at higher risk for kernicterus and are treated more aggressively with phototherapy despite lower mean peak serum bilirubin levels
  - Generally not classified as having physiologic jaundice despite absence in many cases of an identifiable cause for hyperbilirubinemia (outside of preterm status)

3.2.Pathologic or severe jaundice

is jaundice with an underlying pathologic cause. Pathologic jaundice requires vigilant monitoring and treatment to prevent irreversible bilirubin encephalopathy (kernicterus). Suspect a pathologic cause for hyperbilirubinemia with:

It is secondary (table 2) to hemolysis, sepsis, extravascular blood collections, polycythemia, abnormal enterohepatic circulation, anatomic abnormalities of the liver, endocrine or metabolic disorders, or other pathologic causes [2]

- **Suspect if any of the following:** [7]
  - Jaundice presenting in the first 24 hours of life [1,5]

    - Hyperbilirubinemia in the first 24 hours of life is often a consequence of hemolysis [3]
    - Work-up is indicated
    - Potential for infant requiring treatment is high
- Bilirubin levels more than 12 to 15 mg/dL in otherwise healthy term infants [2]
- High rate of bilirubin level rise (more than 5 mg/dL in 24 hours and or >0.2-0.5mg/hr) [7]
- Bilirubin level meeting the treatment threshold on hyperbilirubinemia nomograms [4] [1]
- Severe neonatal hyperbilirubinemia
    - Bilirubin levels that place infant at risk for bilirubin encephalopathy or kernicterus by postnatal age based nomogram [1]
    - Total serum bilirubin more than 20 mg/dL [9]
    - Up to 5% of healthy term infants develop acute bilirubin encephalopathy or kernicterus with total serum bilirubin over 30 mg/dL [9]
- **Prolonged jaundice [3]**
    - Jaundice visible beyond 2 weeks of life for term infant, 3 weeks for preterm [3]
    - Most cases are accounted for by indirect hyperbilirubinemia secondary to breastfeeding (breast milk Jaundice)[3]
    - Infants who are formula fed are more likely to have a pathologic process responsible for prolonged jaundice
    - Obtain conjugated (direct) bilirubin level for all infants with prolonged jaundice (ie, more than 2 weeks, or 3 weeks for thriving term infants), [4]

- **Cholestatic jaundice** [3]
    - Conjugated jaundice: Conjugated (direct) hyperbilirubinemia (more than 1.46 mg/dL or 25 µmol/L) [3]
    - Always pathologic
    - Can be associated with clotting abnormality if secondary to hepatobiliary disease
    - Obtain conjugated (direct)

- **In all ill-appearing infants**, and infants with hepatosplenomegaly on examination [4]

4- Diagnosis

Clinical Presentation

4.1 History

- Yellow sclerae or skin may be reported by parents
  - 60% of infants develop jaundice; 2% require treatment [4]
- Output history may provide supporting information:
  - Stool frequency and color
    - Expect 3 to 4 stools daily in healthy newborns [1]
    - Slow elimination of meconium, which contains high amounts of bilirubin, increases risk for physiologic jaundice
    - Pale stools are a sign of direct (conjugated) hyperbilirubinemia
  - Urine frequency and color
    - Expect 4 to 6 episodes of urine output daily in a healthy, well-hydrated newborn [1]
    - Dark urine is a sign of direct hyperbilirubinemia
- Symptoms of very high bilirubin levels include drowsiness or lethargy and high-pitched cry
- Feeding history may include risk factors for hyperbilirubinemia (eg, inadequate intake, breastfeeding)
- Maternal prenatal history may suggest potential causes, as follows:
  - Maternal blood type, Rh factor status, and presence of minor blood group incompatibility antibody titers
    - Antibodies against antigens E, c, Kell, Kidd, Duffy, and others cause hemolytic disease of newborn [3]
    - Combination of maternal blood type O with infant blood types A, B, or AB sets up a potential for incompatibility

- Combination of maternal Rh-negative status with infant Rh-positive status sets up a potential for incompatibility
- Family history
  - Inherited disorders
    - G6PD deficiency
    - Thalassemia
    - Spherocytosis
  - Sibling with history of neonatal jaundice, phototherapy, or exchange transfusion

4.2 Physical examination

- General signs of hyperbilirubinemia that will require treatment
  - Signs of anemia
    - Pallor
  - Signs of very high bilirubin level
    - Lethargy or drowsiness
    - Ill appearance
    - Hypotonia, poor sucking, or sluggish Moro reflex
- Jaundice
  - Becomes visually apparent in the newborn at bilirubin levels of 5 to 7 mg/dL [6]
    - Visual estimation of specific bilirubin levels is inaccurate [6]
  - Yellow discoloration of sclerae and gums; blanched skin
    - Inspection of these areas requires special care in dark-skinned and preterm infants, in whom signs of jaundice may be more difficult to see [3]
    - Scleral icterus may be the only sign of jaundice in dark-skinned infants
    - Jaundice appears in a cephalocaudal progression as bilirubin levels rise [6]

- Jaundice of face and chest only is predictive of a bilirubin level less than 12 mg/dL [6]
- Palms and soles are last areas to be involved
- In general, involvement of palms and soles correlates with higher levels of jaundice, although estimation of specific levels is inaccurate [2]
  - In hospital after birth, ensure that neonates are assessed for visible jaundice by an experienced practitioner at least every 8 to 12 hours [1]

4..3 Laboratory investigation

- **Laboratory measurements**

- Early-onset jaundice requiring treatment [3]

  - Initial/primary tests to obtain in all infants [18]

    - Fractionated bilirubin (total/direct)
    - Blood group and direct antiglobulin test
    - Hematocrit or CBC
    - Peripheral smear

- Secondary optional investigations to consider [18]

    - G6PD deficiency screen
    - Albumin level
    - Reticulocyte count if there are concerns about anemia and appropriate bone marrow response (eg, in hemolysis)

- Additional laboratory tests for ill-appearing infants, for those with bilirubin level not responding to phototherapy, or for those in whom exchange transfusion is indicated

    - RBC enzyme studies [3] and hemoglobin electrophoresis [7]
    - Infection screen if indicated by history and physical examination [3]
    - CBC and blood culture, urinalysis and urine culture, cerebrospinal fluid analysis and culture, stool for virology
    - Serology for congenital infections if indicated
    - Urine test for cytomegalovirus

- Type and cross-match blood

- Prolonged jaundice [3]
    - Obtain fractionated bilirubin in all infants with prolonged jaundice beyond 2 to 3 weeks of life
        - Screening can be postponed in thriving term infants until 3 weeks [3]

- Other studies to consider when clinically indicated (on the basis of history and physical examination,) include:
    - CBC with peripheral smear
    - Direct antiglobulin test plus ABO blood type and Rh status if maternal type and Rh status are unknown
    - Urinalysis and urine culture
    - Urine copper sulfate test (eg, Clinitest) for reducing substances
    - Check newborn screening results for congenital hypothyroidism and galactosemia
    - G6PD level (in Jordan)

Secondary other tests to consider as indicated on the basis of clinical course, family history, physical examination findings, and prenatal and maternal history thay include include:

- Erythrocyte galactose 1-phosphate uridyltransferase activity
- Liver function tests
- $Alpha_1$-antitrypsin assay and phenotype
- Immunoreactive trypsin
- Cystic fibrosis DNA screen
- Plasma cortisol level

        - Serum amino acid screen
        - Thyroid studies
    - Conjugated hyperbilirubinemia [3] [21]
    - Additionally initial laboratory tests to obtain include
        - Urinalysis and urine culture to evaluate for urinary tract infection
            - Consider sepsis evaluation
        - Liver function test and PT/PTT to evaluate for hepatic disease and Vitamin K deficiency
        - Electrolytes and glucose to screen for metabolic disorders
    - Obtain liver ultrasonography to evaluate for hepatocellular disease and biliary obstruction amenable to surgical correction
    - Obtain hepatobiliary excretion imaging to evaluate for biliary obstruction
    - Further work-up is determined by findings on initial evaluation; further work up for other causes (eg, genetic, metabolic, infectious) may be indicated

Available guidelines to aid in the diagnostic process include (reference for investigations)

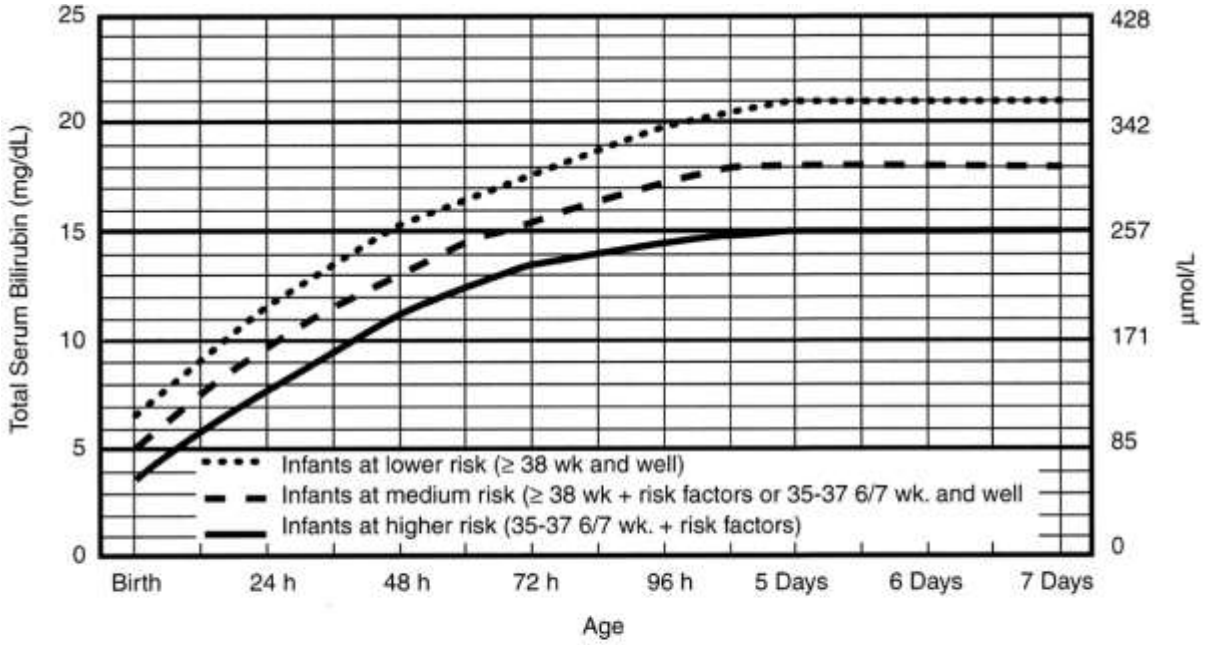
- NICE guidelines updated 2016 [20]
- Canadian guidelines 2007 [4]
- American Academy of Pediatrics guidelines 2004 [1]
- Norwegian guidelines 2011 [22]

- **Key therapeutic options for hyperbilirubinemia include:** [5]

5.1.Phototherapy (specific guidelines are based on nomogram [1] [4]

- Based on American Academy of Pediatrics guideline Figures [1] or Canadian Paediatric Society guideline Figures [4]
- Phototherapy nomogram incorporates risk factors (for bilirubin neurotoxicity) to determine need for treatment [1]

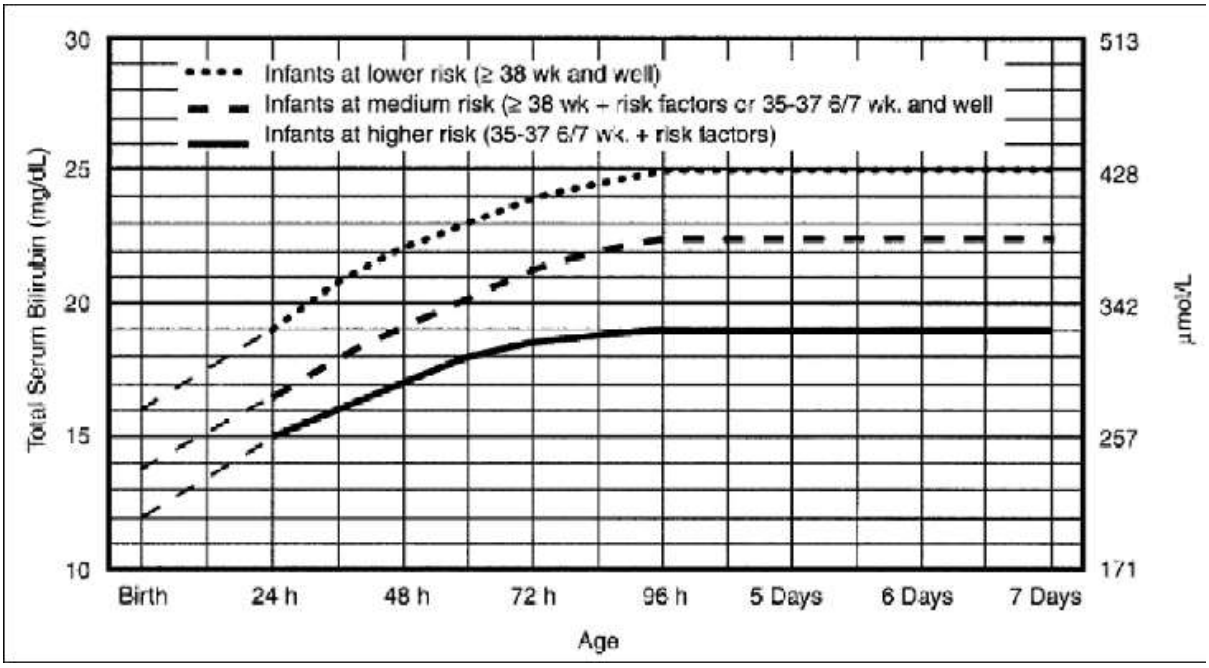
6.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

.5.2. Exchange transfusion (specific guidelines are based on nomogram [1] [4])

- Packed RBCs are exchanged for equal infant blood volume. They must be type O Rh negative (or crossmatched to infant), irradiated, cytomegalovirus negative, warm, and free of offending antigen

7. 

5.3 Promotion of bilirubin excretion through urine and stool (by augmentation of breastfeeding)

- Feeding and nutritional support are important early on to prevent worsening of jaundice, especially with breastfeeding mother-infant pairs
- Interruption of breastfeeding is discouraged as part of general hyperbilirubinemia treatment [4]
- Breastfeeding jaundice and breast milk jaundice generally do not require phototherapy
  - Main treatment is to increase breastfeeding frequency [5]
  - Interruption of breastfeeding results in a rapid decline in bilirubin levels, but this practice is controversial and not routinely recommended [1 5]
  - Some recommend holding breastfeeding (while mothers continue to pump) for formula supplementation for 24 hours [5]
  - Bilirubin levels will rapidly decline at a rate of about 3 mg/dL/day if jaundice is secondary to breast milk [2]
  - Alternatively, parenteral fluids can be given to augment bilirubin removal through urine in severe cases [18]

- Occasionally formula supplementation, parenteral fluids, or both are indicated in infants with inadequate oral intake/output, excessive weight loss, or clinical signs of dehydration

  Treatment of newborn jaundice is based on cause of jaundice and level of bilirubin

- Treatment thresholds for bilirubin are determined by plotting total bilirubin level against a nomogram (eg, American Academy of Pediatrics guideline nomogram) [1] or table (eg, National Institute for Health and Care Excellence guideline table) [20] based on age and presence of risk factors for progression or severe disease

5.4 **IV immunoglobulin** in cases of isoimmune hemolytic anemia
5.5 May be indicated for isoimmune hemolytic disease of the newborn if bilirubin is rising despite intensive phototherapy or if the bilirubin level is within 2 to 3 mg/dL of exchange level [1]

6 **Critical elements in kernicterus prevention include**: [6]

6.3.1 Support of breastfeeding

6.3.2 Measurement of bilirubin level when jaundice appears clinically and universal screening level at discharge (more than 18 hours after birth)

6.3.3 Hyperbilirubinemia risk assessment

6.3.4 Appropriate follow-up

6.3.5 Effective and timely treatment of hyperbilirubinemia with phototherapy and exchange transfusion

6.3.6 Monitor all infants closely during the first week of life until feeding is well established and bilirubin levels are falling

6.3.7 Prognosis is good for any infant with physiologic jaundice or when bilirubin levels are maintained below 20 mg/dL. [7] Kernicterus is likely with a bilirubin

level more than 30 mg/dL [5] and carries 30% mortality and 70% long-term morbidity [8]

Pitfalls

- Determining bilirubin level based on degree of jaundice on physical examination is inaccurate. Obtain a bilirubin measurement if jaundice is noted on physical examination
    - In dark-skinned infants, jaundice is especially difficult to detect on physical examination, and use of physical examination alone may lead to missed hyperbilirubinemia
- In infants who are discharged in the first 24 hours of life, arrange clinical assessment for jaundice between days 2 and 3 of life and again after the first week to assess for hyperbilirubinemia and excessive weight loss

FREQUENTLY ASKED QUESTIONS ABOUT PHOTOTHERAPY

WHAT WAVELENGTH OF LIGHT IS USED?

Phototherapy lights emit light in the blue-green spectrum (wavelengths 430-490nm). It is NOT ultraviolet light.

WHAT'S THE DIFFERENCE BETWEEN "CONVENTIONAL" AND "INTENSIVE" PHOTOTHERAPY?

"Intensive phototherapy" means the irradiance of the light is at least 30μW/cm2 per nm as measured at the baby's skin below the center of the phototherapy lamp. A hand-held radiometer can be used to measure the spectral irradiance emitted by the light. Because measurements taken directly under the lights will be higher, measurements should ideally be made at several locations and averaged. The appropriate radiometer will vary based on the phototherapy system used, so manufacturer recommendations should be followed.

With "Conventional phototherapy" the irradiance of the light is less, but actual numbers vary significantly between different manufacturers. In general, it is not necessary to rountinely measure irradiance when administering phototherapy, but units should be checked periodically to ensure that the lamps are providing adequate irradiance, according to the manufacturer's guidelines.

WHY ARE THE BABY'S EYES COVERED?

In adults, prolonged exposure to blue light can cause retinal damage. Although retinal damage from phototherapy has not been reported, eye covers for newborns are standard prophylaxis.

WHAT ARE THE RISKS OF PHOTOTHERAPY?

A rare complication (bronze baby syndrome) occurs in some infants with cholestatic jaundice when treated with phototherapy. With exposure to phototherapy lamps, these infants develop a dark, gray-brown discoloration of skin, urine, and serum. Although the exact etiology is not understood, this effect is thought to be the result of an accumulation of porphyrins and other metabolites.

Another possibility is the development of purpura or bullae in infants with cholestatic jaundice or congenital erythropoietic porphyria. Because the photosensitivity and blistering can be severe in infants with porphyria, infants who have this diagnosis or a positive family history for this disorder, have an **absolute contraindication for phototherapy**.

DOES PHOTOTHERAPY POSE ANY RISK TO CAREGIVERS?

No, although some people who are around blue lights for prolonged periods will feel nauseated. Yellow plastic placed on the outside of the isolette may mitigate this effect.

HOW LONG IS PHOTOTHERAPY USUALLY NEEDED?

There are no specific guidelines for when to discontinue phototherapy. Evidence of hemolysis and age of the infant will impact the duration. In some cases, phototherapy will only be needed for 24 hours or less, in some cases, it may be required for 5 to 7 days. The AAP Guidelines suggest that an infant readmitted for hyperbilirubinemia, with a level of 18 mg/dL or more, should have a level of 13 - 14 mg/dL in order to discontinue phototherapy. In general, serum bilirubin levels should show a significant decrease before the lights are turned off.

Physical examination for jaundice is *not* helpful once treatment has started as the yellow color of the skin is temporarily "bleached" by the phototherapy.

HOW CAN PHOTOTHERAPY BE MAXIMIZED?

The effectiveness of phototherapy is determined largely by the distance between the lamps and the infant, so phototherapy can easily be intensified by bringing the

lamps closer to the infant. Because a closed isolette does not allow the lamps to be moved in close, if there is a concern about the effectiveness of phototherapy, an isolette should not be used.

With the infant in an open bassinet, it is possible to bring the lamps to within 10 cm of the infant. An undressed term infant with not be overheated with this arrangement, however, is is important that halogen spotlights NOT be used. Halogen lights can get hot, and burns may result if used this way. Special blue, regular blue, and cool white lights are all acceptable alternatives.

Increasing the skin surface area exposed to phototherapy will also maximize treatment. Commonly, an overhead phototherapy unit is combined with a bili blanket that can be place under the infant. Some of these blankets or pads are rather small, so 2 or 3 of these units may be needed to supply more complete coverage from below. Lining the sides of the bassinet with white blankets or aluminum foil can also increase the effectiveness of phototherapy.

Key massages

- Breastfeeding jaundice and breast milk jaundice [5]
    - *Breastfeeding jaundice* is the conventional term for jaundice in the first week of life associated with a healthy breastfed infant with no other abnormalities on physical examination
    - *Breast milk jaundice* is the conventional term for self-resolving jaundice in an otherwise healthy breastfed infant exhibiting prolonged, nonpathologic, unconjugated hyperbilirubinemia after the first week of life
    - Hemoglobin level is normal, with no signs of hemolysis on peripheral smear, normal reticulocyte count, and no blood group incompatibility
    - Breastfeeding jaundice and breast milk jaundice are considered physiologic processes, and phototherapy is rarely necessary
    - If diagnosis is in question, breastfeeding can be interrupted for 24 to 48 hours; a decrease in bilirubin levels of 2 to 5 mg/dL/day is consistent with breastfeeding jaundice and breast milk jaundice [5]
    - Hemolytic disease of newborn (Related:) [5]Hemolytic disease of the newborn
    - Early severe jaundice due to hemolysis from maternofetal blood group incompatibility (from ABO, Rh, or minor blood group antigens)
    - Most infants at risk are identified by prenatal maternal antibody screening for blood group incompatibilities
    - Primarily indirect bilirubin is elevated; conjugated hyperbilirubinemia is occasionally observed

- Infants have high reticulocyte count, anemia with hemolysis on peripheral smear, rapidly rising bilirubin level, and usually a positive direct antiglobulin test result

- Infants who lose more than 10% of their birth weight or have inadequate output may be candidates for formula supplementation [4]

- Exclusively breastfed infants normally lose 6% to 8% of their birth weight by days 3 to 4 of life [4]

- Encourage mothers to nurse (breastfeed)infants 8 to 12 times a day, with pumping after feedings to stimulate milk supply [18]

- Normal urine output is 4 to 6 wet diapers/day [1]

- Normal stool output is 3 to 4 stools/day through day 4 of life [1]

- Phototherapy : Provide eye protection for infants receiving phototherapy

- Symptomatic bilirubin encephalopathy (eg, hypertonia, retrocollis, opisthotonos, fever, high-pitched cry) is an absolute indication for immediate exchange transfusion [3]

- Death : 90% of neonates with bilirubin level more than 35 mg/dL will die or develop severe cerebral palsy [5]

- Chronic bilirubin encephalopathy

    - Clinical sequelae of acute bilirubin encephalopathy with cerebral palsy, seizures, developmental delay, hearing deficit, oculomotor disturbances, dental dysplasia, and intellectual disability

    - Incidence: about 1 per 50,000 to 100,000 live births [4]

    - Mild bilirubin encephalopathy [5]

    - Learning difficulties and cognitive dysfunction

Table 1: Risk factors and/or associations for significant Hyperbilirubinemia		
	INCREASE RISK	***DECREASED RISK 1***
Age	Neonate	Discharge from hospital after 72 hours
Sex	Affects boys more than girls [4]	
Ethnicity/race	Asian, Native American, or Greek descent [5]	Black race
Genetics	Sibling with neonatal hyperbilirubinemia or phototherapy requirement Rh, minor blood group, or ABO antigen incompatibility Inherited disorders G6PD deficiency (OMIM #300908) [11] Phenylketonuria (OMIM #261600) [12] Galactosemia (OMIM #230400) [13] Alpha$_1$-antitrypsin deficiency (OMIM #613490) [14] Cystic fibrosis (OMIM #219700) [15] Gilbert disease (OMIM #143500) [16] Crigler-Najjar syndrome (OMIM #606785) [17]	
Gestation Age	Prematurity (gestation less than 38 weeks) [5]	Gestational age 41 weeks or older
Birth weight	Low birth weight [5]	
Feeding	Excessive weight loss after birth [5] Exclusive breastfeeding [5]	Exclusive bottle feeding

Others	Visible bruising or cephalhematoma Delayed meconium passage [5] Polycythemia [5] Neonatal infection [5] Premature rupture of membranes [5] Maternal age older than 25 years Maternal gestational diabetes [2] Maternal medications [5] Oxytocin Promethazine hydrochloride	

Table 2 Causes Pathologic processes	
Causes of unconjugated (indirect) hyperbilirubinemia	Causes of conjugated (direct) hyperbilirubinemia
Hemolysis Isoimmune hemolytic disease of newborn Rh antigens ABO antigens Minor blood group antigens Spherocytosis and other erythrocyte membrane defects G6PD deficiency Pyruvate kinase deficiency Sepsis Disseminated intravascular coagulation Thalassemia P**olycythemia** Small-for-gestational-age development Twin-twin transfusion Delayed cord clamping	Hepatocellular disease Intrauterine infections TORCH: toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex virus Parvovirus B19 Hepatitis viruses Perinatal asphyxia/hepatic ischemia Prolonged parenteral nutrition [10] Progressive familial intrahepatic cholestasis [10] Biliary tree abnormalities Biliary atresia; most common cause of infantile obstructive cholangiopathy [10 10] Choledochal cyst [10]

Maternofetal transfusion Maternal diabetes (gestational or chronic) **Extravascular blood** Bruising or cephalhematoma Pulmonary, cerebral, or intra-abdominal hemorrhage Swallowed maternal blood **Increased enterohepatic circulation** Pyloric stenosis Bowel obstruction Cystic fibrosis Hirschsprung disease **Endocrine or metabolic disorders** Hypothyroidism Hypopituitarism Hypoadrenalism **Genetic** Galactosemia, tyrosinemia, or hypermethioninemia Glucuronosyltransferase defect Gilbert disease Crigler-Najjar syndrome **Drugs that displace bilirubin from albumin** **Sulfonamides** Erythromycin Ceftriaxone Moxalactam Ibuprofen	Spontaneous bile duct perforation Idiopathic neonatal cholestasis Alagille syndrome of intrahepatic biliary hypoplasia [10] Metabolic disorders $Alpha_1$-antitrypsin deficiency [10] Cystic fibrosis [10] Galactosemia, tyrosinemia [10], or hypermethioninemia Other Bacterial sepsis [10] Severe hemolysis Drugs Aspirin Corticosteroids Some conditions can cause both direct and indirect hyperbilirubinemias Hypothyroidism Hypopituitarism Cystic fibrosis Severe hemolysis Galactosemia, tyrosinemia, or hypermethioninemia Drugs Erythromycin Sulfisoxazole

Table 3:Additional causes of indirect Hyper bilirubinemia	
Hemplysis	
Spherocytosis [5]	RBC structural defect that can present in the neonatal period with indirect hyperbilirubinemia and hemolysis Family history may be positive for early gallstones, anemia, or spherocytosis Splenomegaly is extremely common CBC shows markedly elevated mean cell hemoglobin concentration and red cell distribution width; peripheral smear shows characteristic uniform spherocytes Definitive diagnosis is confirmed by osmotic fragility test; glucose administration corrects the autohemolysis
G6PD deficiency	Family history may be positive for G6PD deficiency; more common in males than in females; associated with African, Middle Eastern, Asian, or Mediterranean ethnicity Hyperbilirubinemia can be due to hemolysis in the neonatal period, but it is usually not associated with a hemolytic process in the newborn with jaundice and G6PD deficiency Bite or blister cells characteristically seen on peripheral smear; anemia is rare Quantitative measurement of total percentage of G6PD enzymatic activity during quiescent period is gold standard to diagnose
Thalassemia	α-thalassemia can result in neonatal hemolysis, severe indirect hyperbilirubinemia, and hydrops fetalis Thalassemias have a wide array of clinical presentations Can result in a milder neonatal jaundice picture May remain asymptomatic in the newborn period Family history may be suggestive; condition is more common in those with Southeast Asian, Middle Eastern, or Mediterranean ethnicity Peripheral smear shows a hypochromic, microcytic anemia with a large number of circulating nucleated RBCs Definitive diagnosis of thalassemia is confirmed by hemoglobin electrophoresis

Sepsis in neonates	Sepsis can present as a mixed indirect and direct hyperbilirubinemia in newborns Jaundice is rarely the only manifestation of bacteremia or sepsis [5] Children are more ill appearing and present with temperature instability Septic work-up, including cultures of blood, urine, and cerebrospinal fluid, confirms diagnosis
Urinary tract infection	Classically presents with mostly conjugated hyperbilirubinemia Typically other signs of illness are present (eg, poor feeding, fussiness, vomiting, temperature instability) Patients have abnormal urine test results and culture results positive for infection
Sequestration [5]	Extravascular blood from cephalhematoma or excessive bruising can result in an indirect hyperbilirubinemia Occult hemorrhage (eg, intracranial, pulmonary, intestinal) and swallowed maternal blood can also present with jaundice History and physical examination findings differentiate these causes from physiologic jaundice Apt test or high-performance liquid chromatography on infant stool or gastric contents detects swallowed maternal blood [5]
Polycythemia [5]	Increase in RBC mass can produce indirect hyperbilirubinemia Polycythemia in the neonate can be secondary to maternofetal transfusion, twin-to-twin transfusion, delayed cord clamping, intrauterine hypoxia, and some maternal diseases (eg, diabetes mellitus) Blood test results are normal except for elevated hemoglobin level and hematocrit
[5]Gilbert disease	Common, benign, inherited disorder of bilirubin conjugation affecting about 3% to 7% of humans, with autosomal dominant or recessive transmission [5] Males show more clinical manifestations Except for an increase in unconjugated bilirubin, results of liver function tests and other blood tests are normal Infants are predisposed to severe or prolonged hyperbilirubinemia especially in combination with other clinical disorders (eg, G6PD deficiency, β-

	thalassemia, hereditary spherocytosis, pyloric stenosis) Genetic testing is available if the diagnosis of this chronic unconjugated hyperbilirubinemia is in question
Crigler-Najjar syndrome	Rare inherited disorder of nonhemolytic, indirect jaundice caused by defects in hepatic glucuronidation (bilirubin conjugation) Degree of bilirubin rise (15-45 mg/dL) in infants and adults can lead to kernicterus if not appropriately treated Exchange transfusions may be necessaryExcept for an increase in unconjugated bilirubin, results of liver function tests and other blood tests are normal Results of evaluation for other causes of severe neonatal jaundice are negative; if diagnosis is under consideration, DNA testing can help establish diagnosis Administration of phenobarbital diminishes bilirubin level in most patients with autosomal dominant type II Crigler-Najjar syndrome Type I Crigler-Najjar syndrome is autosomal recessive and leads to more severe hyperbilirubinemia Clinical course differentiates Crigler-Najjar syndrome from other causes of severe neonatal hyperbilirubinemia because it is a lifelong disorder requiring phototherapy until definitive treatment by liver transplant
Disorders of enterohepatic circulation that are responsible for increased indirect hyperbilirubinemia	Any condition that prolongs passage of meconium (eg, meconium ileus, meconium plug syndrome, Hirschsprung disease) History and physical examination findings differentiate these disorders from physiologic jaundice

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7 **(Assess risk factors)**