Treatment Of Indirect Hyperbilirubinemia

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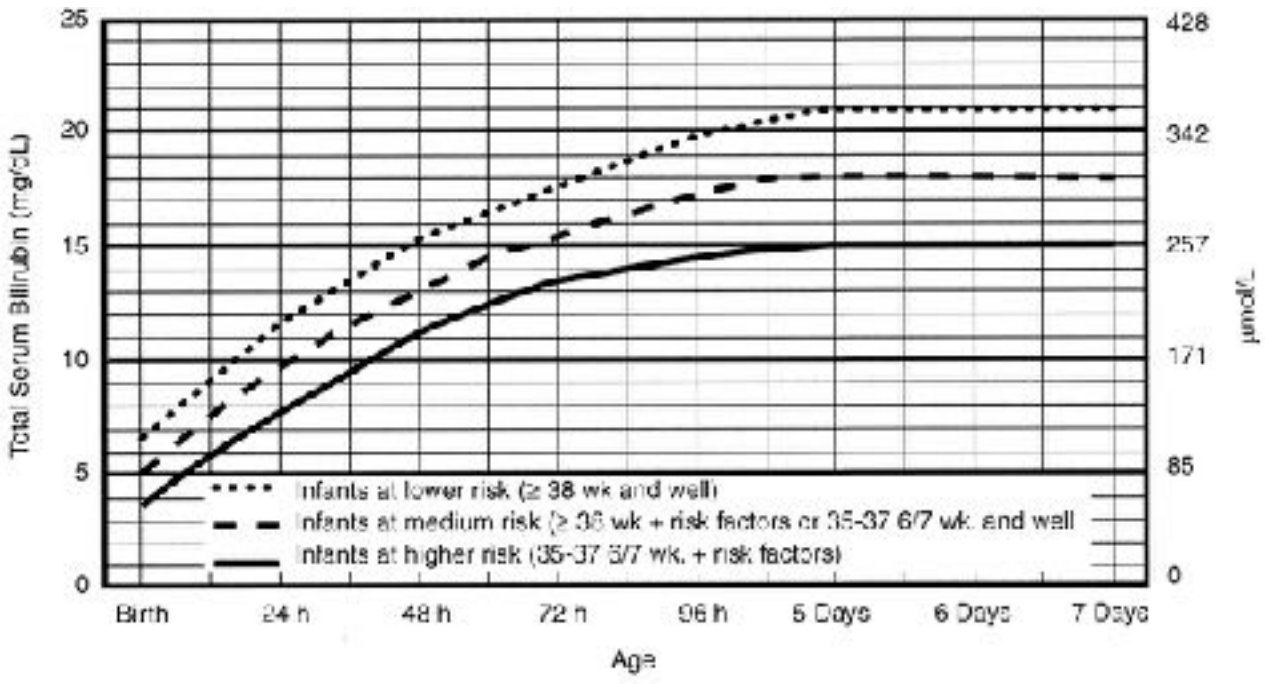
- Approach should be to prevent development of severe hyperbilirubinemia and treat using a structured systematic approach. As if not treated in a timely manner, they are at risk of developing severe hyperbilirubinemia and possibly bilirubin induced neurologic dysfunction (BIND).
- The aim of treatment is to ensure that serum bilirubin is kept at safe level and brain damage is prevented.

- **The three interventions use to reduce bilirubin level are;**
  1) Enhanced Enteral Nutrition.
  2) Phototherapy.
  3) Exchange Blood Transfusion.

Management

1. AAP criteria should be used for deciding need for phototherapy or exchange blood transfusion.



- 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.

Interpretation of AAP chart for phototherapy:

- Determine the need for phototherapy
- Infant age on X axis and TSB on Y axis (do not deduct direct from TSB)
- Choose appropriate curve based on gestation and risk factors
- The three curves on AAP charts indicate:
    a. Top curve: Infants at lower risk (> 38 weeks and well)
    b. Middle curve : Infants at medium risk (> 38 weeks + risk factors, or 35-37 6/7 week)
    c. Lower curve : Infants at higher risk : (35-37 6/7 + risk factors)
- Risk factors include : Isoimmune haemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis or albumin < 3.0 g/dL
- For preterm and LBW babies NICE guidelines are used for phototherapy.

2. **Phototherapy:**

Phototherapy, using light of specific wavelengths and doses, is considered a safe and effective intervention to reduce total serum or plasma bilirubin (TB) levels PT remains the mainstay for treating hyperbilirubinemia in neonates.

- **Efficacy:**

Effective phototherapy results in a decline of TB of at least 2 to 3 mg/dL (34 to 51 micromol/L) within four to six hours.

- **Dosing:**
    - Under standard phototherapy, an infant is exposed to an irradiance between 8 to 10 microW/cm2/nm consistent with the 2004 American Academy of Pediatrics (AAP) Guideline primarily focused on preventing hyperbilirubinemia.
    - In infants with TB >20 mg/dL (342 micromol/L), rapidly rising TB levels or if TB >25 mg/dL (428 micromol/L), intensity of phototherapy is increased (irradiance of 30 to 35 microW/cm2/nm), by adding additional light sources to increase BSA exposure, or increasing the intensity of the light source.

- **Mechanism of action :**
    1. Structural isomerization to Lumirubin
    2. Photooxidation to polar molecules

3. Photoisomerization to less toxic bilirubin isomer

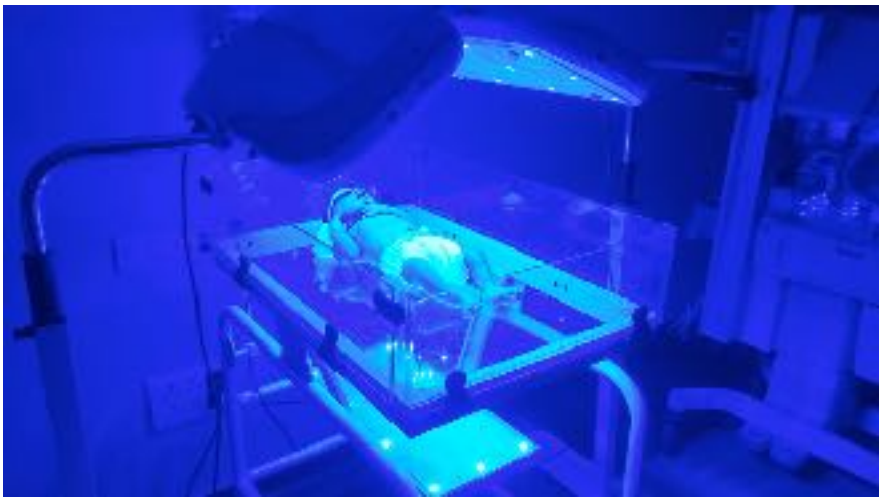
- **Light sources and devices:**

  Fluoroscent tubes or Halogen bulbs

  Blue LEDs

  Fiberoptic blankets or pads

  - Blue light are best as spectrum of blue is best absorb by bilirubin. Most commonly Blue Fluorescent Lamp (CFL) High intensity lights emitting diodes (LED) are used. Blue LED lights are used commonly and have advantage of long life and capable of delivering higher irradiance. Blue LED lights have become more affordable leading to wide spread acceptability.



- **Intensive Phototherapy (Crash cart phototherapy)**

  - It is given when there is poor response to standard phototherapy, when total bilirubin levels close to exchange transfusion threshold or during interim time period is needed to set up exchange transfusion.

- Intensive phototherapy uses higher levels of irradiance (usually 25 microW/cm2/nm, although up to 35 microW/cm2/nm can be used in term infants [gestational age (GA) ≥37 weeks]) with exposure to maximal BSA. Light should be delivered to as much of an infant's BSA as possible with a combination of available devices, and/or in combination with a fiberoptic pad/mattress, blue LED pad/mattress, or special blue lights placed below the infant. Another option is the use 360° phototherapy, but more studies are needed to confirm that it provides increased efficacy

- **Monitoring:**
  - During phototherapy, the dose of phototherapy (irradiance) and the infant's temperature, hydration status (intake and output), time of exposure, and TB should be monitored daily.
  - Excessive fluid loss may be associated with phototherapy, which may increase insensible skin fluid loss.
  - LED-based devices emit lower levels of heat than other light sources, and thus fluid loss due to hyperthermia is less of a concern when using these types of devices

- **Response to phototherapy:**
  - A decline in TB levels is a positive response to phototherapy. The frequency of measuring TB levels depends upon the initial and the first subsequent TB value.

  - ***For infants who have been readmitted for phototherapy***, TB measurements should be repeated two to three hours after initiation of phototherapy to assess its effectiveness.

- ***For infants who required phototherapy during the birth hospitalization***, TB levels should be measured after 4 to 6 hours following the start of phototherapy.

- ***If TB levels have effectively declined***, subsequent measurements can be obtained every 8 to 12 hours. Changes in phototherapy dosing are made based on the subsequent measurements with intensifying dosing with inadequate reduction or allowing interruption of phototherapy for feeding with an adequate response.

- ***If, despite intensive phototherapy, TB levels are at or approach the threshold for exchange transfusion***, blood should be sent for immediate type and cross-match. In addition, if exchange transfusion is being considered, serum albumin levels should be measured so that the serum (or plasma) bilirubin/albumin (B/A) ratio can be calculated and used in conjunction with the TB level and other factors to determine the need for exchange transfusion.

- **Hydration:**
  - There is no evidence that intravenous (IV) fluid supplementation provides significant additional benefit beyond adequate oral hydration.
  - However, IV hydration is a potential option to correct for dehydration, hypovolemia, and/or hypernatremia in infants with significant volume depletion whose oral intake is inadequate

- **Breastfeeding:**
  - Breastfed infants whose intake is inadequate, who have excessive weight loss (>10 percent of BW), or who have evidence of hypovolemia should receive supplementation with human milk either expressed maternal milk (preferred) or pasteurized donor milk.
  - Formula may be used if these preferred sources of human milk are not available. If breastfeeding is interrupted, it should be resumed as soon as possible.

- **Discontinuation of phototherapy**
  - Stop phototherapy when the TB has fallen to, or below the age specific cut off.

- **Rebound**
  - Check for rebound hyperbilirubinemia, 18 to 24 hours after stopping the phototherapy.

- Check rebound after 8 to 12 hours in neonates with gestational age < 35 weeks, birth weight < 2kg's, G6PD deficiency/ haemolytic diseases.

- **Role of sunlight**
  - Direct exposure to unfiltered sunlight for phototherapy is not recommended.

- **Filtered sunlight**
  - Data is insufficient to support or refute use of the filtered sunlight for phototherapy..
  - Data from a resource-limited center has shown that filtered sunlight phototherapy using commercial window tinting films (which remove harmful UV and IR light rays) is a safe and efficacious method for reducing TB levels and can provide similar results to that of conventional phototherapy.

- **Rebound hyperbilirubinemia**
  - Rebound hyperbilirubinemia is defined as increase in total bilirubin level, following discontinuation of phototherapy, is due to rise in rate of bilirubin production, that exceeds natural elimination process.
  - However rebound level is still typically lower than total bilirubin value, before the initiation of phototherapy. Rebound hyperbilirubinemia occurs in at-least 5% of infants.
  - Risk factor for Rebound Hyperbilirubinemia -- includes gestational age < 38 weeks, asian ethnicity, breast feeding, positive DCT (Direct Coombs Test), use of early phototherapy (Initiated within 72 hours of birth).

3. **Exchange transfusion**

- **Indication:**
  - Indication for double volume exchange transfusion at birth in infants with Rh Iso-immunisation – cord bilirubin is 5 mg/dl or more or cord Hemoglobin is 10 gm/dl or less or if TSB levels reach age specific cut off for exchange transfusion as shown in figure 4.

- **Pre -procedure management:**
  - Exchange transfusions should be performed only by trained personnel in a neonatal or pediatric intensive care unit (NICU/PICU) equipped with full monitoring and resuscitation capabilities. Initiation of intensive (crash-cart) phototherapy.

- During the time interval needed to set up an exchange transfusion, infants should receive intensive phototherapy.
- In some cases, effective phototherapy may effectively reduce TB so that exchange transfusion can be avoided.

- **Efficacy:**
  - After a successful double-volume exchange transfusion, TB typically falls to approximately one-half to three-quarters of the pre-exchange value.
  - Triple-volume exchange transfusion could reduce TB levels by 95 percent
  - TB subsequently increases to approximately two-thirds of that of the pre-exchange concentration because of re-equilibration between extravascular and vascular bilirubin.

- **Post procedure management**:
  - TB is measured within two hours following the procedure and management decisions are made dependent on the level of TB.

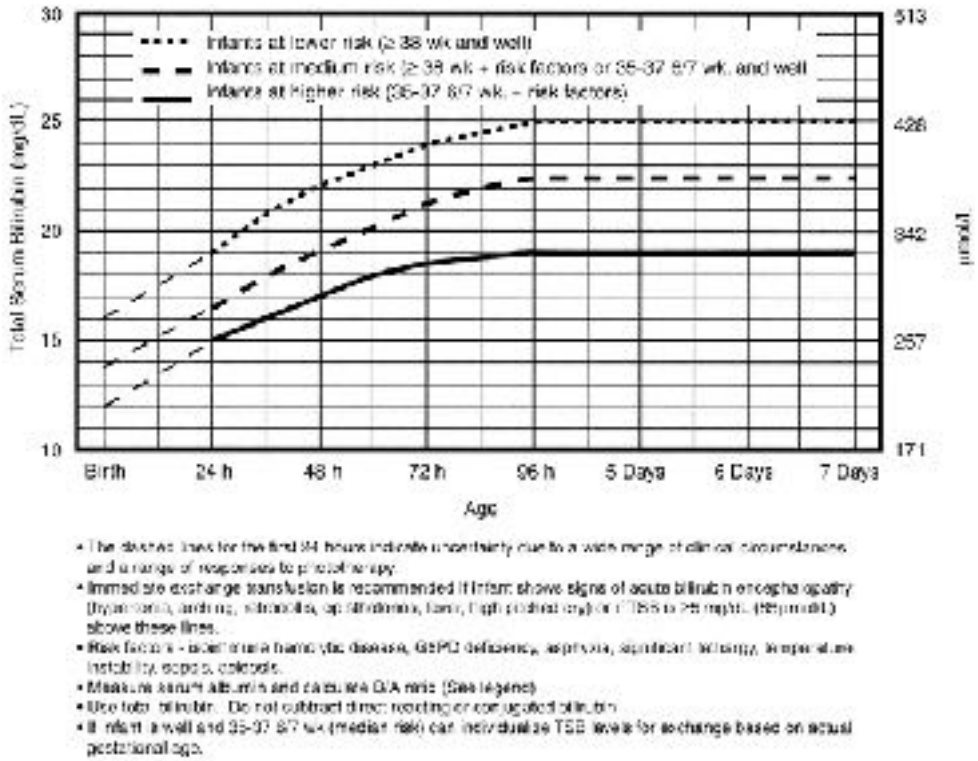


Table 1. Choice of Blood Group for Donor Blood (ABO and Rh Typing)

Maternal group	Infant group	Donor blood group
O	O or A OR B or AB	O
A or B or AB	O or A or B or AB	Baby blood group or O group
Rh negative	Rh positive or negative	Rh negative

- **Role of IV immunoglobulins:**
  - In infants with Rhesus (Rh) isoimmune hemolytic disease, administration of intravenous immune globulin (IVIG; dose 0.5 to 1 g/kg over two hours) is suggested if the TB level is rising despite phototherapy or is within 2 or 3 mg/dL (34 to 51 micromol/L) of the threshold for exchange transfusion
  - The dose may be repeated in 12 hours if necessary.

- **Subthreshold (prophylactic) phototherapy :**
  - Subthreshold phototherapy not to be used in the routine care of newborns when good follow-up is arranged, as it unnecessarily exposes many infants to phototherapy (and its potential adverse effects), prolongs birth hospitalization, and increases hospital costs.

- **Phenobarbitone**
  - It is not recommended to used routinely to treat neonatal unconjugated hyperbilirubinemia.

- **Infants with hyperbilirubinemia**
  - Jaundice occurs in most newborn, most jaundice is benign, but because of potential toxicity of bilirubin, when treated appropriately, the outcome is excellent, with minimal/ no additional risk for adverse neurodevelopmental sequelae.

- **Preventive and supportive measures**
  - Hydration should be maintained and hypoglycaemia should be prevented by early breast feeding. Early feeding augments colonisation of gut and reduces entero-hepatic circulation.

- **Treatment of sepsis**

- When sepsis is suspected, appropriate antibiotic should be started with blood culture

Practice Points

Aggressive phototherapy is the cornerstone for severe jaundice. Ensure adequate feeding while baby is under phototherapy.
Do not depend on TCB (Transcutaneous Bilirubin) or clinical estimation when baby is on phototherapy.
Monitor the progress of jaundice while under phototherapy with frequent TSB measurements.
Expose maximum body area and keep the baby under phototherapy as much as possible.
All management of jaundice is based on TSB and not on unconjugated bilirubin.

No role in the management of jaundice

Prophylactic phototherapy
Sunlight
Albumin infusion
Routine IV calcium for ET
Supplementation of water, dextrose feeds
Stopping breast feeding in breast milk jaundice
Routine phenobarbitone
Herbal remedies
Steroids

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