Jaundice is a common and mostly benign condition in neonates but because of the potential toxicity of bilirubin, neonates must be monitored to identify those who might develop severe hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy or kernicterus. Over 60 percent of term and 80 percent of preterm babies develop clinical jaundice during the first week of life. Clinical jaundice, in neonates appears first on the face at a serum bilirubin concentration of 5 mg per dl in contrast to adults who appear jaundiced when the serum bilirubin is greater than 2 mg per dl. The yellowish discoloration is usually the result of deposition of unconjugated, nonpolar, lipid soluble indirecely reacting bilirubin present in the skin formed from enzymatic and non enzymatic degradation of haemoglobin while a part of this discoloration can be attributed to deposition of the pigment after it has been converted in the liver by uridine diphosphoglucouronic acid (UDP)-glucuronyl transferase to the polar, water soluble direct reacting ester glucuronide of bilirubin. Severe untreated unconjugated hyperbilirubinemia is potentially neurotoxic and conjugated hyperbilirubinemia indicates a serious hepatic or systemic disease. In the present chapter, we would be mainly concentrating over unconjugated hyperbilirubinemia for all practical purposes.

ASSESSMENT OF SEVERITY OF JAUNDICE
This can be done by various techniques like clinical assessment, by icterometer, by transcutaneous bilimeter and laboratory estimation of serum bilirubin level.

Clinical Assessment: The assessment of jaundice must be performed in a well lit room, or preferably, in daylight with the infant naked. It utilizes the principle that clinical jaundice has a cephalocaudal progression as it increases in intensity. The pulp of the finger or thumb is pressed on the baby's skin, preferably on a bony part, till it blanches. The underlying skin is noted for the yellow colour which gives a rough estimate of serum bilirubin. Krammer's criteria is used to estimate clinical jaundice as given below-

<table>
<thead>
<tr>
<th>Area of body discoloured</th>
<th>Range of bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>4 - 8 mg/dl</td>
</tr>
<tr>
<td>Upper trunk</td>
<td>5 - 12 mg/dl</td>
</tr>
<tr>
<td>Lower trunk &amp; thighs</td>
<td>8 - 16 mg/dl</td>
</tr>
<tr>
<td>Arms &amp; lower legs</td>
<td>11 -18 mg/dl</td>
</tr>
<tr>
<td>Palms &amp; soles</td>
<td>more than 20 mg/dl</td>
</tr>
</tbody>
</table>

By experience and concerted efforts, the clinical assessment can be enhanced to within +/- 2 mg/dl. After phototherapy, the skin gets bleached and clinical assessment of severity by this method becomes unreliable. Nevertheless, one has to rely on estimation of the serum bilirubin level in any case for clinical decision making and management.

Icterometer: Assessment is done by matching the skin colour with the colour codes depicted on the plastic strip. This method can be used by health workers for screening.

Transcutaneous Bilimeter: Works on the principle of computerized spectro-photometry and provide digital display of total bilirubin. The photoprobe is pressed against the forehead or sternum to take the reading.

Laboratory assessment of serum bilirubin: This is usually done by the Vanden Berg test and with the help of the bilimeter. It needs to be emphasised that blood samples used for bilirubin estimation should be protected
from light, otherwise photo degradation of haemoglobin may lead to erroneously high level of serum bilirubin. The inter laboratory variation in the levels of serum bilirubin range between 10 - 20 percent for total bilirubin and up to 25 percent for conjugated bilirubin. The bilimeter needs a micro centrifuged sample of blood in a capillary tube and provides an instant digital read out of the total bilirubin, which by and large is equivalent to unconjugated fraction during the first week of life for practical purposes.

**Clinical settings predictive of significant hyperbilirubinemia:**

The following are the clinical settings in which one can anticipate significant hyperbilirubinemia-

- Rh negative and O group mothers.
- Certain maternal medications e.g. large doses of vitamin K, salicylates, oxytocin etc
- Family h/o hyperbilirubinemia.
- Maternal illness suggestive of intrauterine infection viz febrile illness within 2 weeks of delivery, fever with rash in the early antenatal period.
- A cord blood bilirubin level of more than 2.5 mg/dl.
- Nomogram charting of bilirubin levels for risk designation of term and near term well newborns with y axis showing total serum bilirubin (mg/dl) and x axis showing age in hours.

As per this nomogram developed by Bhutani et al, the total serum bilirubin estimated at 24-36 hours after birth is plotted on the nomogram. If the total serum bilirubin level at this age falls in the high risk zone i.e. more than 95th percentile, then chances of subsequent hyperbilirubinemia is around 40% whereas, if it falls in the low risk zone i.e. less than 40th percentile, there is no measurable risk.

**Risk Assessment Pre discharge:**

At the time of discharge or even before that, all newborns should be assessed for risk factors predictive of severe hyperbilirubinemia. As more than 80 % of deliveries still occur at the community level, timely and appropriate referral of a newborn predictive of severe hyperbilirubinemia based on the factors given below to a centre where necessary care facilities are available, makes a huge difference. The more are the risk factors, the greater is the risk of significant hyperbilirubinemia and vice versa.

1. Primipara mother.
2. Jaundice visible on the first day of life.
3. Gestational age less than 38 week.
4. H/O neonatal jaundice or anaemia requiring treatment in previous siblings.
5. ABO/ Rh incompatibility.
7. Weight loss at discharge, more than 3% per day or more than 7% cumulative weight loss.
8. Presence of signs of underlying illness like vomiting/lethargy/poor feeding/temperature instability/apnea.
10. Cephalohaematoma or bruising (central hematocrit more than 65%).
11. East Asian/ Mediterranean / Native American heritage.
12. Newborn's trunk is distinctly yellow stained with yellow tinge of palms and soles.
13. Persistence of neonatal jaundice beyond 10 days in term and 14 days in preterm baby.
Is there any measurable serum bilirubin level to allay fear of neurological damage:

Kernicterus or bilirubin encephalopathy can occur due to different serum bilirubin levels in different clinical scenarios. Studies on global basis have shown bilirubin encephalopathy is unlikely to occur if-

1. Serum bilirubin is less than 20 mg/dl in neonates with haemolytic disease i.e. newborns with ABO/Rh incompatibility, G-6-PD deficiency, pyruvate kinase deficiency, hereditary spherocytosis.
2. Serum bilirubin is less than 25 mg/dl in healthy term newborns with non haemolytic unconjugated hyperbilirubinemia.
3. Serum bilirubin levels up to 18 mg/dl during the first 3 days in exclusively breast fed babies.
4. In preterm babies, the bilirubin level is maintained below 1mg/dl for every 100 grams weight of the newborn. Entry of bilirubin into the brain occurs as free (unbound) or as bilirubin bound to albumin in the presence of a disrupted blood brain barrier. 1 gram of albumin binds with 8.5 mg of bilirubin. The low bilirubin kernicterus reported in preterms was largely due to factors other than bilirubin alone viz intracranial haemorrhage, exposure to drugs that displace bilirubin from albumin, and conditions that can disrupt the blood brain barrier like hyper osmolarity, anoxia, hypercarbia, and sepsis and lead to increased deposition of bilirubin in brain. Acidosis affects the solubility of bilirubin and its deposition into brain tissue.

Management:

Lab investigations to be done when there is pathological hyperbilirubinemia:

1. Blood grouping ABO and Rh of infant and mother.
2. Total and direct serum bilirubin levels in baby's blood.
3. Direct Coomb's Test (cord blood or infant's blood).
4. Antibody screen in mother after delivery (Indirect Coomb's Test).
5. Reticulocyte count, peripheral blood smear and hematocrit.
6. Normal haemoglobin range in newborn varies from 13.7 to 20.1 gm/dl with a mean value of 16.8 gm/dl in term newborns. An increased reticulocyte count of more than 6% accompanied by a haemoglobin less than 13 gm/dl is suggestive of haemolysis.
7. G-6-PD screen of male baby when other causes are not present.

Investigations to be done for newborns born to Rh negative mother:

1. ABO & Rh grouping of baby
2. Direct Coomb's test
3. Reticulocyte count
4. Hematocrit
5. Peripheral blood smear
6. Cord blood bilirubin

Investigations to be done for babies born to O positive mothers:

1. ABO & Rh grouping of baby
2. Direct Coomb's test to be done if there is-
   - significant jaundice
   - baby is to be discharged early
   - follow up is not possible
Investigations for baby with prolonged unconjugated jaundice:

Jaundice persisting beyond 14 days in a term baby and 21 days in a preterm is usually considered to be pathologically prolonged. The various causes for prolonged jaundice are as given below-

- Breast milk jaundice
- Extravasated blood e.g. cephalohematoma
- G-6-PD deficiency
- Persistence of haemolysis.
- Hypothyroidism
- Functional or organic intestinal stasis.
- Infection e.g. UTI, septicaemia
- Malaria
- Congenital Hypertrophic Pyloric Stenosis
- Criggler Najjar Syndrome Type II

As per American Academy of Pediatrics (AAP) practice guidelines, baby with prolonged hyperbilirubinemia should be investigated after 3 weeks provided -

- they are not ill.
- there is no abnormal physical examination.
- no dark urine or light coloured stools i.e. no evidence of cholestasis.

The investigations to be sent in such a baby includes-

1. CBC; CRP; Procalcitonin; Peripheral smear- all for evidence of sepsis.
2. Total serum bilirubin and direct bilirubin.
3. Urine analysis and urine culture (for ruling out UTI).
4. Urine for reducing substances (to rule out galactosemia).
5. Malaria parasite.
6. Thyroid Profile (T3, T4, TSH).

Investigations to be sent in a sick jaundiced newborn:

All the investigations listed under the heading of prolonged jaundice need to be sent in a sick jaundiced newborn.

Treatment Modalities:

The goal of therapy is to prevent the concentration of unconjugated bilirubin from reaching the levels at which neurotoxicity may occur. Phototherapy and exchange transfusion are the two treatment modalities which have been recommended for this purpose a part from other treatment modalities like -

1. Phenobarbitone - It is given in the dose of 5 to 8 mg/kg/day to increase conjugation in indirect hyperbilirubinemia in Criggler Najjar syndrome type II and direct hyperbilirubinemia associated with total parenteral nutrition. If given ante nataly, can also lower serum bilirubin levels in erythroblastotic infants.
2. Substances blocking bilirubin reabsorption viz oral agar in a dose of 500 mg/kg can be used to augment the efficacy of phototherapy. It acts by decreasing the entero hepatic circulation. It is as effective as phototherapy even when it is used alone, but experience is limited.
3. Substances inhibiting bilirubin production- Tin protoporphyrin acts by inhibiting the conversion of biliverdin to bilirubin by hemoxygenase. A single intramuscular dose on anticipation of jaundice e.g. G-6-PD
deficiency, may reduce the need of phototherapy. More data about the efficacy and toxic effects is necessary for its recommendation as therapy.

4. Agents inhibiting haemolysis: Intravenous immunoglobulin (IVIg) in a dose of 500 to 750 mg/kg/dose over a 2-4 hours period given 12 hourly for 3 doses is shown to be effective in reducing bilirubin in Coomb's positive haemolytic anaemia. The immunoglobulin could act by occupying the Fc receptors of the reticulo endothelial cells, thereby preventing them from taking up and lysing antibody coated RBCs.

MANAGEMENT GUIDELINES:

Hemolytic Disease of Newborn: It includes Rh incompatibility, ABO incompatibility, haemolytic disease due to other causes like G-6-PD deficiency, hereditary spherocytosis, minor blood group incompatibilities, homozygous alpha thalassemia, congenital intrauterine infection.

Rh incompatibility: Intensive phototherapy should be started immediately after birth and cord blood sent for haemoglobin and serum bilirubin and monitored for necessity of exchange transfusion. Intensive phototherapy implies the use of high levels of irradiance in the 430-490 nm band (usually 30microwatt/sq cm/nm or higher) delivered to as much of the infant's surface area as possible. If the total serum bilirubin does not decrease or continues to rise in an infant who is receiving intensive phototherapy, this strongly suggests the presence of ongoing haemolysis and need for exchange transfusion.

If the baby is born with hydrops, the baby should be first stabilized with correction of acidosis and given partial exchange transfusion to correct circulatory overload, later followed by intensive phototherapy as described above.

ABO incompatibility: ABO incompatibility is thought to exist when newborn with blood group A or B is born to O blood group mother. The screening for early detection of ABO haemolytic disease can be done by the following ways:

1) ABO grouping and DCT in cord's blood and follow up of the babies on the basis of serum bilirubin levels.
2) Estimation of serum bilirubin at 12 hours of age in all newborns born to group O mothers.
3) Clinical observation of jaundice.

Babies born with ABO incompatibility are considered to have haemolysis if they have anaemia (hematocrit less than 45%), an abnormal blood smear (3 to 4 spherocytes) or if reticulocyte count is 4.5% or higher in the first 24 hours or if reticulocyte count is more than 1 to 2 % in the first 1 to 2 weeks.

In term babies with ABO incompatibility with no medical problem, phototherapy should be started at serum bilirubin of 10mg/dl at 12 hours, 12 mg/dl at 18 hours, 14 mg/dl at 24 hours or 15 mg/dl at any time after birth.

Haemolytic disease due to other causes (exemplified above):

Intensive phototherapy should be started immediately after birth and cord blood sent for haemoglobin and serum bilirubin and monitored for necessity of exchange transfusion.

Indications for Exchange transfusion: The following are the broad indications of exchange transfusion, irrespective of the cause of haemolytic disease.

1) Cord blood bilirubin level is more than 4.5 mg/dl and cord blood haemoglobin level is less than 11 gm/L.
2) Bilirubin level is rising over 1 mg/dl/hour despite phototherapy.
3) The haemoglobin level is between 11 and 13 gm/L and the serum bilirubin levels are rising over 0.5 mg/dl/hour, even the serum bilirubin level is below the exchange transfusion level.
4) Presence of progressive anaemia despite adequate control of serum bilirubin by phototherapy.
FOR NEONATES BORN AT LESS THAN 35 WEEKS OF GESTATION:

<table>
<thead>
<tr>
<th>B.Wt (gm)</th>
<th>PT (S. Bilirubin mg/dl)</th>
<th>ET (Bilirubin mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy infant</td>
<td>Sick infant</td>
</tr>
<tr>
<td>Less than 1000</td>
<td>5 to 7</td>
<td>4 to 6</td>
</tr>
<tr>
<td>1001-1500</td>
<td>7 to 10</td>
<td>6 to 8</td>
</tr>
<tr>
<td>1501-2000</td>
<td>10 to 12</td>
<td>8 to 10</td>
</tr>
<tr>
<td>2001-2500</td>
<td>12 to 15</td>
<td>10 to 12</td>
</tr>
</tbody>
</table>

PT = Phototherapy ; ET = Exchange transfusion

FOR NEONATES BORN AT MORE THAN 35 WEEK OF GESTATION (BEYOND 24 HOURS)

Total serum bilirubin levels (mg/dl)

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 wk &amp; well</td>
<td>38 wk &amp; risk factors* or 35-37 6/7 wk &amp; 35-37 6/7 wk &amp; well</td>
<td>risk factors* Age(hours)</td>
</tr>
<tr>
<td>PT IPT ET</td>
<td>PT IPT ET</td>
<td>PT IPT ET</td>
</tr>
<tr>
<td>24 9 12 19</td>
<td>7 10 17</td>
<td>5 8 15</td>
</tr>
<tr>
<td>48 12 15 22</td>
<td>10 13 19</td>
<td>8 11 17</td>
</tr>
<tr>
<td>72 15 18 24</td>
<td>12 15 21</td>
<td>10 13 18.5</td>
</tr>
<tr>
<td>96 17 20 25</td>
<td>14 17 22.5</td>
<td>11 14 19</td>
</tr>
<tr>
<td>Above 96 18 21 25</td>
<td>15 18 22.5</td>
<td>12 15 19</td>
</tr>
</tbody>
</table>

* Risk factors include isoimmune haemolytic disease, G-6-PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis or serum albumin less than 3gm/dl.

PT= Phototherapy ; IPT = Intensive Phototherapy ; ET = Exchange Transfusion

Facts about various available treatment modalities:

PHOTOTHERAPY:

Phototherapy remains the main stay for treating neonatal indirect/ unconjugated hyperbilirubinemia. Exposure of the jaundiced skin of the newborn to the light source of wavelength 460-490 nm used in phototherapy causes the photo isomerisation of the insoluble bilirubin into the soluble isomers that are readily excreted into the bile without any prior need of conjugation and finally excreted in baby's urine and faeces.

Indication:

Phototherapy is indicated only in the treatment of unconjugated/ indirect hyperbilirubinemia. If indirect bilirubin level is high in the presence of conjugated hyperbilirubinemia, exchange transfusion is the treatment of choice.

Factors deciding effectiveness of phototherapy:

The effectiveness of phototherapy increases with the following:

- Blue light (460 - 490 nm).
- Intensity of the light (30 microwatt/cm2/nm or more, can be checked with light intensity meter).
- The greater the surface area of the skin exposed.
- The closer the light source to the baby (limited by the risk of overheating the baby).

Good quality light source should not need to be closer than 30 cm. Phototherapy alone is rarely effective with severe haemolytic causes of jaundice where the bilirubin concentration can rise rapidly and continue to rise despite aggressive phototherapy.
In breastfed infants who require phototherapy, breastfeeding should continue. There is no evidence to support the administration of additional fluids to jaundiced infants as such, but 10-20% extra fluid over the usual requirements is required for the babies placed under aggressive phototherapy to compensate for the increased insensible water loss.

**Surface area:**
In most circumstances, it is not necessary to remove the infant's diaper, but when the serum bilirubin levels approach the exchange treatment range, the diapers should be removed until there is clear evidence of a significant decline in the bilirubin level.

**Monitoring during phototherapy:**
During phototherapy infants require ongoing monitoring for:
- adequacy of hydration and nutrition.
- temperature.
- clinical improvement in jaundice: In infants with haemolytic disease or those with toxic levels of bilirubin, serum bilirubin and hematocrit should be estimated 6 to 8 hours after starting phototherapy, thereafter every 12 hourly. Monitoring should continue for at least 24 hours after cessation of phototherapy in babies with haemolytic disease to detect rebound hyperbilirubinemia.
- potential signs of bilirubin encephalopathy.

**Ceasing Phototherapy:**
Phototherapy should be given until serum bilirubin comes down to safe level i.e. below 10 mg/dl or baby is old enough to handle increased levels of serum bilirubin i.e. 10.7 +/- 1.2 mg/dl by 7th day in pre term and 13 +/- 0.7 mg/dl by 4th day in term babies. Rechecking the bilirubin level after cessation of phototherapy is not usually required unless increased risk of significant rebound is there as in the below mentioned scenarios:
- haemolytic disease.
- gestational age is less than 37 weeks.
- cessation of phototherapy at less than 72 hours of life.

In these circumstances, a bilirubin level is to be checked 12 hours after cessation of phototherapy.

**TYPES OF PHOTOTHERAPY:**
**Intermittent Vs Continuous Phototherapy:**
In most circumstances, phototherapy does not need to be continuous. Phototherapy may be interrupted during feeding or brief parental visits. Individual judgement should be exercised. If the infant's bilirubin level is approaching the exchange transfusion level, phototherapy should be administered continuously until a satisfactory decline in the serum bilirubin level occurs or exchange transfusion is initiated.

**Intensive Phototherapy:**
Intensive phototherapy is recommended for those with "higher risk" based on age specific nomograms. It implies the use of high levels of irradiance in the 430 to 490 nm band (usually 30 microwatt/cm2/nm or more) with the aid of two or more light sources (combination of overheads, spots, biliblankets) delivered to as much of infant's surface area as possible. The overheads should be placed as close as to the baby as possible without causing hyperthermia or burn. Normally, bilirubin should decline by 1-2 mg/dl within 4-6 hours of intensive phototherapy and continue to decline and remain below the threshold level for exchange transfusion. Failure of
intensive phototherapy is said to occur and hence an indication for exchange transfusion when this predicted normal fall in serum bilirubin does not occur.

**Contraindications:**
- Conjugated hyperbilirubinemia.
- Liver disease.
- Congenital Porphyrias
- Photosensitizer drugs in usage by the baby.

**Complications:**
Possible complications include:
- overheating
- increased insensible water loss
- diarrhoea
- ileus (pre term infant)
- rash (no specific treatment required)
- retinal damage (theoretical)
- parental anxiety/ separation
- bronzing of infants with conjugated hyperbilirubinemia.

**EXCHANGE TRANSFUSION:**

**Indications:**
It can be divided under two broad heads- Rh incompatibility and others.

**Rh incompatibility:**
Exchange transfusion should be considered in infants with Rh incompatibility who:
- have not received blood transfusion in utero.
- have cord blood haemoglobin less than 10 gm/dl.
- have cord blood bilirubin level more than 4.6 mg/dl.
- are visibly jaundiced within 12 hours of birth.

The effects of intrauterine transfusions are unpredictable, but haemolysis is usually less severe because more of the baby’s blood is Rh negative donor blood.

**Others:**
- Indications in well term infants are:
  - Failure of phototherapy to prevent rise of serum bilirubin to toxic levels.
  - see the threshold graphs
- In pre term or sick infants, lower concentration of bilirubin may warrant exchange transfusion.
- Infants manifesting the signs of intermediate to advanced stages of acute bilirubin encephalopathy, even if the bilirubin level is falling.
An early exchange transfusion is indicated in the presence of-
- Hydrops
- H/O previously severely affected infants
- a known sensitized infant.
An early exchange transfusion removes sensitized RBCs before haemolysis and removes bilirubin before it is distributed to the extra vascular space.

**Volume and type of blood used for exchange transfusion and after process monitoring:**

A double volume i.e. 160 ml/kg body weight whole blood is usually used for contemplating one cycle of exchange transfusion. It is said that one double volume whole blood exchange transfusion removes 87% of infant’s blood volume and lowers the bilirubin level to about 45-50% of the pre exchange levels. However, it increases to 60% of the pre exchange values within half an hour due to rapid influx of the bilirubin from the extra vascular space to the vascular space. It should be noted that higher the pre exchange values, higher is the rebound. This is the main reason for continuation of intensive phototherapy after exchange transfusion.

Blood for exchange transfusion is modified whole blood cross matched against the mother and compatible with the newborn.

The bilirubin level is measured after 30 minutes and then after every 4-6 hours of exchange transfusion. Blood glucose and haemoglobin levels have also to be monitored as ongoing haemolysis may result in significant anaemia leaving the baby still needing a number of top up simple blood transfusions.

**THINGS TO CONSIDER BEFORE EXCHANGE TRANSFUSION:**

- Hypoxia, acidosis and hypoalbuminemia, if present, should be corrected prior to exchange transfusion.
- Sick infants who are anaemic (hematocrit less than 35%) should be given a partial exchange transfusion with packed RBCs (25-80 ml/kg) to raise hematocrit to 40% before further exchange can be performed for hyperbilirubinemia.

**RISKS OF EXCHANGE TRANSFUSION:**

Risks of exchange transfusion, although uncommon, include:

- apnea
- air embolism
- bradycardia
- cyanosis
- necrotising enterocolitis
- portal vein thrombosis
- septicemia
- umbilical sepsis
- vasospasm
- death (rarely)

These risks are higher in sick, pre term infants.

**ROLE OF INTRAVENOUS IMMUNOGLOBULIN (IVIG):**

In isoimmune haemolytic disease, administration of intravenous immunoglobulin in the dosage of 0.5 to 1 gm/kg over 2 hours is recommended if the total serum bilirubin is rising despite intensive phototherapy or the total serum bilirubin level is within 2 to 3 mg/dl of the exchange level. If necessary, this dose can be repeated in 12 hours.
REFERENCES


