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Background

Neonatal Jaundice is common and is usually a benign condition in the newborn affecting 50% of term infants and 80% of preterm infants in first week of life. The yellow colour usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. The physiological jaundice in term infants becomes visible on the 2nd or 3rd day, usually peaking between the 2nd and 4th days at 85-102 mmol/l and decreasing to <34mmol/l between the 5th and 7th days after birth. In premature infant visible on day 3-4, peaks on day 6-8 and starts disappearing by day 7-9. The factors related to higher susceptibility for physiological jaundice are high haemoglobin concentration, immaturity of hepatic uptake, transport and conjugation system, shorter life span of RBC compared to adults and increased level of beta-glucuronidase in the gut, releasing more unconjugated bilirubin to enterohepatic circulation.

Hyperbilirubinemia- can be caused by certain pathologic conditions or by exaggeration of the mechanisms responsible for neonatal jaundice.

Bilirubin Metabolism- In the newborn, unconjugated bilirubin (indirect bilirubin) is mostly produced by breakdown of red cells. Circulating indirect bilirubin bound with albumin is transported to the liver. In hepatocytes, the conjugation happens where uridine diphosphogluconurate glucuronosyltransferase (UGT1A1) catalyses the conjugation of bilirubin with glucuronic acid, producing water soluble mono or di glucuronides of bilirubin, also called as conjugated bilirubin(Direct bilirubin).

Conjugated bilirubin is secreted into the bile and enters the gut via biliary system. Conjugated bilirubin cannot be reabsorbed by the intestinal epithelial cells. It is broken down in the intestine by bacterial enzymes. But at birth the infant's gut is sterile and very less bacteria in the gut, so very small amount of conjugated bilirubin is reduced to urobilin. In case of not feeding, beta-glucuronidase in the intestinal mucosa, which deconjugates the conjugated bilirubin into unconjugated bilirubin. The unconjugated bilirubin then can reabsorb through the intestinal wall and recycled into the circulation, is called as enterohepatic circulation of bilirubin.

Risk Factors for Hyperbilirubinemia

- Predischarge TSB or TcB level in the high-risk zone
- History of previous sibling needing phototherapy
- Jaundice observed in the 1st 24 hr
- Blood group incompatibility(ABO ,Rh Incompatibility) with positive direct anti globulin test, other known haemolytic disease (glucose-6-phosphate dehydrogenase deficiency)
- Cephalohematoma or significant bruising
- Infant of diabetic mother
- Exclusive breastfeeding, particularly if weight loss is excessive
- Male gender
- East Asian race
Causes of Neonatal Jaundice

The cause of neonatal jaundice depends upon whether it is direct or indirect bilirubin component, but also the time of presentation. The jaundice presents with in 1st 24 hours after birth is a medical emergency. See Table 1

Physiological Jaundice

The physiological jaundice in term infants becomes visible on the 2nd or 3rd day, usually peaking between the 2nd and 4th days. It is because the haem load reaching the liver from the breakdown of RBC is transiently greater than the liver’s capacity to conjugate it.

Haemolytic Jaundice

- Maternal-foetal blood group incompatibility (rhesus, ABO, Kell, Duffy etc).
- Extravascular haemolysis - reabsorption of haematoma and petechiae.
- Congenital disorders of the red cell - congenital spherocytosis, haemoglobinopathies, glucose 6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency.

Infection

- Bacterial (generally Gram negative - E. coli, Klebsiella, Pseudomonas).
- Viral - hepatitis, herpes, cytomegalovirus, rubella, other virus infections.
- Other infections - toxoplasmosis, syphilis.

Obstructive Jaundice

- Congenital atresia of the bile ducts.
- Choledochal cyst.

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Table 1: Causes of Neonatal Jaundice

Adapted from Nelson textbook of pediatrics 20th edition
Jaundice (Hyperbilirubinaemia) and Phototherapy

- Inspissated bile or cholestasis syndrome.
- Cystic fibrosis.
- Alpha-1-antitrypsin deficiency.

**Other Causes of Neonatal Jaundice**
- Hypothyroidism.
- Galactosaemia.
- Breast milk jaundice.
- Polycythaemia.
- Drugs - sulphonamides, vitamin K and analogues (vitamin K1 excluded) novobiocin.
- Hereditary hepatic enzyme deficiencies - Crigler-Najjar hyperbilirubinemia, Gilbert’s syndrome, Dubin-Johnson syndrome, Rotors syndrome.
- Oxytocin in labour.

**Investigate the Following Jaundice**

- **Appearing in the First 24 Hours of Life**
  - This is always important and must be investigated. It will most likely be due to haemolytic disease either associated with ABO incompatibility, rhesus isoimmunisation or due to one of the other rare antigens. If the infant shows evidence of skin haemorrhages such as petechiae, then a non-bacterial trans-placental infection such as cytomegalovirus, toxoplasmosis, herpes or rubella is a possibility. Syphilis should also be considered.
- **Occurring After the First Day**
  - Jaundice occurring on the second or third day of life is most likely to be due to physiological jaundice of the newborn. However, if the infant appears sick in any way, then other causes must be considered. Physiological jaundice is a diagnosis only arrived at by exclusion of more serious conditions.
- **Occurring Beyond the Fourth or Fifth Day of Life**
  - Generally this is not due to haemolytic disease so one must be on the lookout for bacterial infection particularly of the urinary tract or septicaemia. Again prenatally acquired infections should be considered. Jaundice due to drug interference is a possibility, and in infants of Asian or Mediterranean parents, glucose 6-phosphate dehydrogenase deficiency should be considered.
- **Persisting Beyond the First Two Weeks of Life**
  - If bilirubin is mainly in the unconjugated form and the above mentioned conditions have been excluded then breast milk jaundice, hypothyroidism, Galactosaemia and some of the other less common causes of jaundice should be considered.
- **Conjugated Hyperbilirubinaemia**
  - If the total bilirubin level contains a high conjugated level (> 20% of the total serum bilirubin) is always pathological, then an anatomical obstruction or neonatal hepatitis is the most likely cause. This must always be investigated.
Clinical Assessment of the Jaundiced Infant

Jaundice can be readily detected in the newborn when the serum level is 80-90 mmol/L. A simple and useful method of assessing the degree of jaundice is Kramer’s rule (Kramer 1969).

<table>
<thead>
<tr>
<th>KRAMER’S RULE</th>
<th>AVERAGE SERUM INDIRECT BILIRUBIN (PER UMOL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZONE</td>
<td>JAUNDICE</td>
</tr>
<tr>
<td>1</td>
<td>Limited to head and neck</td>
</tr>
<tr>
<td>2</td>
<td>Over upper trunk</td>
</tr>
<tr>
<td>3</td>
<td>Over lower trunk and thighs</td>
</tr>
<tr>
<td>4</td>
<td>Over arms, legs, below knee</td>
</tr>
</tbody>
</table>

Use this rule to assess if investigations are required. Calculate age of infant in hours, do not use hospital days but work out age from date and time of birth. If the “estimated Kramer level” suggests that high levels of hyperbilirubinaemia may develop, if the rate of rise is maintained, then investigations are indicated. The age at which jaundice is first present is important.

Transcutaneous Bilirubin Measurement

Transcutaneous measurement of bilirubin in this hospital uses a JM-103 bilirubinometer. TcB measurements may be performed as an initial screen for jaundice in the well, term infant who is greater than 24 hours of age. Infants in whom jaundice presents less than 24 hours of age, or where other risk factors are present (e.g. preterm, maternal antibodies, possible sepsis, G6PD risk, etc.) should have an SBR performed in the first instance.

Criteria for use

- Well babies (no set-up for sepsis)
- Babies > 24hrs of age
- Babies > 34weeks
- Babies > 2000gm
- Babies who have not started phototherapy and
- Babies ordered bloods which includes an SBR

<table>
<thead>
<tr>
<th>Jaundice onset</th>
<th>TcB</th>
<th>Action</th>
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<tr>
<td>&lt; 24 hours</td>
<td>_____</td>
<td>Perform SBR</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>&gt; 140 µmol/L</td>
<td>Perform SBR</td>
</tr>
<tr>
<td>48-72 hours</td>
<td>&gt;200 µmol/L</td>
<td>Perform SBR</td>
</tr>
<tr>
<td>&gt; 72 hours</td>
<td>&gt;260 µmol/L</td>
<td>Perform SBR</td>
</tr>
</tbody>
</table>

Note: The trans-cutaneous bilirubin is unreliable following the commencement of phototherapy, unless a skin patch has been applied prior to starting lights and this area is used exclusively for TcB measurement (not routinely done at KEMH).

- An SBR should be performed to track progress once lights are instigated. The frequency with which monitoring should occur varies with the absolute SBR, the expected or actual rate of change of serum bilirubin level, and risk factors present.
- In general, high risk infants should be monitored 4-6 hourly initially.
• Low risk infants can be monitored daily.

Use of TcB in the late preterm infant: Several studies have investigated the use of transcutaneous bilirubin measurement in preterm infants. De Luca et al obtained a correlation coefficient of 0.795 (p < 34 weeks or birthweight < 2000 grams will be admitted to SCN. Data pertaining to the use of TcB in preterm infants suggests a high level of correlation between TcB and SBR measures; however, these infants are also at higher risk. Therefore, infants < 34 weeks or birthweight < 2000 grams should have a SBR performed if clinical jaundice is evident.

Clinical Management of Jaundice (Hyperbilirubinaemia)

1. Management is aimed at risk assessment, recognition and appropriate treatment of hyperbilirubinemia to prevent the development of severe hyperbilirubinemia and the possibility of bilirubin encephalopathy. (see Flow chart)

2. Plot the level on phototherapy graph according to Gestational age, Postnatal age in hours to determine the need for phototherapy

Guidelines for Phototherapy (Infants > 35 Weeks)

The birthweight-based/gestation age graphs and guidelines of the American Association of Paediatrics should be taken as a guide. See Appendix 2.

• All infants considered to have clinically significant jaundice must be assessed appropriately with thorough physical examination and careful history taking. Jaundice due to specific conditions such as infection, drug interference etc. must be managed according to the diagnosis.
• If phototherapy indicated determine if TSB is within 50μmol/L of the exchange transfusion line on Exchange Transfusion Graph. If yes, then discuss with Senior registrar or Consultant.

• **There are no generally accepted total serum bilirubin levels at which to treat infants < 35 weeks.** In the case of infants < 35 weeks, or infants with haemolysis, sepsis, dehydration or haemodynamic instability discuss each case with the neonatal consultant or senior registrar.

• Phototherapy should be used to avoid Exchange Transfusion in situations where this may become necessary. Infants born at 35-37 weeks gestation have been noted to be at risk for sequelae from severe hyperbilirubinaemia at total serum bilirubin levels lower than those of more mature infants.

• In using the guidelines for phototherapy and Exchange Transfusion listed, the direct reacting (or conjugated) bilirubin should not be subtracted from the total. In unusual situations where the direct bilirubin level is 50% or more of the total, there are no good data to provide guidance for therapy. Treatment in these cases should be discussed with the consultant neonatologist.

### Guidelines for Phototherapy (Preterm Infants < 35 Weeks)

<table>
<thead>
<tr>
<th>Age</th>
<th>Wt. &lt; 1500g (Mmol/l)</th>
<th>Wt. 1500 – 2000g (Mmol/l)</th>
<th>Wt. &gt; 2000g (Mmol/l)</th>
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<tbody>
<tr>
<td>&lt; 24 hours</td>
<td>&gt; 70 Bili Level</td>
<td>&gt; 70 Bili Level</td>
<td>&gt; 85 Bili Level</td>
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<tr>
<td>24-48 hours</td>
<td>&gt; 85</td>
<td>&gt; 120</td>
<td>&gt; 140</td>
</tr>
<tr>
<td>49-72 hours</td>
<td>&gt; 120</td>
<td>&gt; 155</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>&gt; 72 hours</td>
<td>&gt; 140</td>
<td>&gt; 170</td>
<td>&gt; 240</td>
</tr>
</tbody>
</table>

### Phototherapy

• The aim of this treatment is to lower the bilirubin level and to avoid exchange transfusion. In commencing phototherapy one must consider the age of the infant in hours, risk factors, and the rate of rise of serum bilirubin.

• **Mechanism:** Bilirubin absorbs light maximally in the blue range (420-470 nm). Bilirubin in the skin absorbs light energy, causing several photochemical reactions. There are two major product from phototherapy is a result of a reversible photoisomerization reaction converting the toxic native unconjugated 4Z,15Z-bilirubin into an unconjugated configurational isomer, 4Z,15E-bilirubin, which can then be excreted in bile without conjugation. The other major product from phototherapy is lumirubin, which is an irreversible structural isomer converted from native bilirubin that can be excreted by the kidneys in the unconjugated state.

• Once phototherapy commences then repeat estimations of the bilirubin are essential, as the skin colour will no longer be a guide to the level.

• **Use clinical judgment considering Risk Factors, response to therapy and level of TSB to determine patient specific timing of repeat level (4 - 24 hourly)**

• Early feeding assists the elimination of meconium, reducing the available bilirubin for reabsorption and thus interfering with the enterohepatic circulation.
- Infants under phototherapy require additional fluid as a result of the increased insensible water losses. Total fluids should therefore be increased by 10-15%.
- **Complications** of phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyriemia, overheating, dehydration, hypothermia from exposure, and a benign condition called bronze baby syndrome (very rare complication, which occurs in the presence of direct hyperbilirubinemia).

**Phototherapy Units**

Phototherapy units available have differing energy outputs. The energy output is influenced by the age and type of the lights and is marked on each individual unit in microwatts per cm² (μW/cm²). The higher the ‘μW/cm²’ the more efficient the unit is. Phototherapy light source degrades with use, and stated values below are nominal and assume new units.

- **Microlite:** ~1450-1700 μW/cm².
- **Medela (blue/white light):** ~1400 μW/cm².
- **Bili blanket (fibre optic/LED):** large and small pad sizes are available ~ 40-50 μW/cm².

The higher the SBR the more energy output will be required for successful treatment. When selecting a phototherapy unit or Bili blanket consider the following:
- LED is a cold light source therefore less likely to overheat the infant.
- Direct contact provides the most efficient form of phototherapy treatment therefore choose the appropriate size pad.

**Procedure**

1. Take baseline temperature. Temperature regulation initially may be a problem and therefore needs to be closely monitored until stable. Maintain a NTE that is appropriate for the infant’s age and gestation.
2. Weigh baby daily and monitor urine and stool output.
3. Completely cover the eyes with appropriate size eye pad without applying excessive pressure and taking care not to occlude the nares. Remove every 4 hrs to permit evaluation of infant’s eyes and leave off whenever phototherapy unit is off, i.e., parents visits, feeding, care times. Replace pads 24 hourly or as needed. Eye toilets with N/Saline and sterile cotton wool may be required.
4. Adjust fluids as ordered. Usually fluid volumes > 10-15% to account for increased insensible water loss. Check urine SG, PGL, U&Es etc. as ordered.
5. Check unit height - 40 cms away from infant (excluding Bili blanket).
6. Document start time and type of unit in use on MR489/491.
7. Supportively position infant utilising positional aids. Reposition/cares as appropriate for gestation.
8. Check repeat SBR levels as ordered. Remember to turn off unit when taking blood.
9. Encourage parenteral contact and involvement. It is rarely necessary to cease suck feeds.
10. If diarrhoea develops maintain skin integrity with good hygiene.

**Ceasing Phototherapy**

Phototherapy is ceased when the following criteria are met:
- SBR is low enough to eliminate the risk of kernicterus.
• The infant is old enough to handle the bilirubin load.
• Document the cessation of lights in the relevant notes.

**Risk Assessment before Discharge**

Assessment of the risk of severe hyperbilirubinemia should be made on all infants prior to discharge. Infants discharged before 72 hours are likely to still have a rising total serum bilirubin level. The best documented method for assessing the risk of subsequent hyperbilirubinemia is to measure total serum bilirubin and plot it on a nomogram, see Appendix 1.

• Infants in the low risk zone are at very low risk of developing severe hyperbilirubinemia.

• Infants in the high risk zone and those, whose total serum bilirubin level is crossing centiles upwards, should have their management discussed with the consultant neonatologist or senior registrar.

Follow-up assessment of an infant’s level of jaundice after discharge by either a doctor or a visiting midwife would be appropriate when a rise in jaundice levels into the high risk zone is considered possible.
Appendix 1

Nomogram for Management of Jaundice (Hyperbilirubinemia) in the Term Infant


Nomogram for designation of risk in 2840 well newborns at 36 or more weeks’ gestational age with birth weight of 2000 grams or more, or 35 or more weeks’ gestational age and birth weight of 2500 grams or more based on the hour-specific serum bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone).
Appendix 2

Nomogram for Phototherapy in Hospitalised Infants of 35 or More Weeks Gestation


Guidelines for phototherapy for infants of 35 of more weeks of gestation

- Use total bilirubin
- Risk factors = isoimmune haemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temp instability, sepsis, acidosis.

Date/Time

Age in hours

TSB level
Appendix 3

Nomogram for Exchange Transfusion in Infants’ > 35 Weeks Gestation


- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is > 5 mg/dL (85 µmol/L) above these lines.
- Risk factors - isoimmune haemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis and acidosis.
- Measure serum albumin and calculate B/A ratio
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 week (medium risk) can individualise TSB levels for exchange based on actual gestational age.
Jaundice (Hyperbilirubinaemia) and Phototherapy

References

9. UpToDate, Pathogenesis and aetiology of unconjugated hyperbilirubinemia in the newborn(assessed on November 2018)

Related WNHS policies, procedures and guidelines

Neonatal Clinical Guidelines - Exchange Transfusion

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