Jaundice in the Neonate

Sites where Local Guideline applies

<table>
<thead>
<tr>
<th>This Local Guideline applies to:</th>
<th>Neonatal Intensive Care Unit JHCH and post natal wards</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adults</td>
<td>No</td>
</tr>
<tr>
<td>2. Children up to 16 years</td>
<td>No</td>
</tr>
<tr>
<td>3. Neonates – less than 29 days</td>
<td>Yes, Approval gained from the Children Young People and Families Network on 27/06/2017</td>
</tr>
</tbody>
</table>

Target audience

NICU and maternity clinical staff, who provide care to neonatal patients.

Description

Guideline describing jaundice in the neonate and management of infants with jaundice.

Keywords

Bilirubin, Hyperbilirubinaemia, Jaundice, Kernicterus, Phototherapy, Rhesus disease, JHCH, NICU

Document registration number

JHCH_NICU_16.03

Replaces existing document?

Yes

Registration number and dates of superseded documents

JHCH_NICU_16.03 September 2014

Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- NSW Health Policy Directive 2014_036 Clinical Procedure Safety
- NSW Health GL2016_027 Neonatal Jaundice Identification and Management in Neonates ≥32 Weeks Gestation

Prerequisites (if required)

N/A

Local Guideline note

This document reflects what is currently regarded as safe and appropriate practice. The guideline section does not replace the need for the application of clinical judgment in respect to each individual patient but the procedure/s require mandatory compliance. If staff believe that the procedure/s should not apply in a particular clinical situation they must seek advice from their unit manager/delegate and document the variance in the patients health record.

Position responsible for the Local Guideline and authorised by

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Date authorised

This document contains advice on therapeutics

No

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27/06/2020
PURPOSE AND RISKS

This local clinical procedure has been developed to provide instruction to the health clinician and to ensure that the risks of harm to the child associated with management & treatment of jaundice are prevented, identified and managed.

The risks are:

- Kernicterus
- Weight loss due to poor feeding
- Temperature instability

The risks are minimised by:

- Clinicians having knowledge of the diagnosis and management of jaundice
- Clinicians understand the importance of accurate plotting of SBR on the gestational age appropriate chart
- Clinicians seek assistance if caring for infants with jaundice and under phototherapy lights and it is outside their scope of practice
- Following the instructions set out in the clinical procedure
- Notification and management of the complications/risks to the patient

Risk Category: Clinical Care & Patient Safety

GLOSSARY

<table>
<thead>
<tr>
<th>Acronym or Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ABO incompatability</td>
<td>Breakdown of red blood cells in baby if mother and babies blood types are incompatible and antibodies are formed</td>
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<tr>
<td>CNS</td>
<td>Central Nervous system</td>
</tr>
<tr>
<td>DAT</td>
<td>Direct antiglobulin test-(also called Coombs test)-looks for antibodies that stick to RBCs and lead to haemolysis</td>
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<tr>
<td>G6PD deficiency</td>
<td>Inherited condition where a lack of enzyme occurs that protects the red blood cell leading to haemolysis</td>
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<tr>
<td>Hyperbilirubinaemia</td>
<td>Bilirubin level above normal range</td>
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<tr>
<td>Jaundice</td>
<td>Yellow colouration of skin and mucous membranes</td>
</tr>
<tr>
<td>Physiological jaundice</td>
<td>Jaundice occurring in health newborns with no apparent cause and not requiring treatment</td>
</tr>
<tr>
<td>Severe hyperbilirubinaemia</td>
<td>Jaundice that requires investigation and treatment</td>
</tr>
<tr>
<td>SBR</td>
<td>Total serum bilirubin</td>
</tr>
<tr>
<td>TcB</td>
<td>Transcutaneous bilirubin estimation by transcutaneous bilirubinometer</td>
</tr>
<tr>
<td>T4 &amp; TSH</td>
<td>Thyroid hormones-jaundice with low levels of T4 &amp; Thyroid stimulating hormone may indicate hypothyroidism or hypopituitarism</td>
</tr>
<tr>
<td>TORCH</td>
<td>Infections, collectively grouped under the acronym TORCH for Toxoplasmosis, Other organisms (parvovirus, HIV, Epstein-Barr, herpes 6 and 8, varicella, syphilis, enterovirus), Rubella, Cytomegalovirus and Hepatitis</td>
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OUTCOMES

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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>To accurately assess jaundice in the neonate and identify risk factors</td>
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<tr>
<td>2</td>
<td>To commence phototherapy treatment utilizing the phototherapy and exchange charts</td>
</tr>
<tr>
<td>3</td>
<td>To prevent bilirubin encephalopathy and kernicterus in the neonate</td>
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</table>

Introduction

During the first week of life all newborns have increased bilirubin levels by adult standards, with approximately 60% of term and 85% of preterm babies developing jaundice.¹

Jaundice is the yellow discolouration of the skin and sclera caused by the accumulation of bilirubin in the skin and mucous membranes. Most jaundice in newborns is physiologically normal and usually benign.

However, if unconjugated serum bilirubin levels get too high, bilirubin can cross the blood brain barrier into the brain where it is neurotoxic, particularly to the auditory nerve and basal ganglia. Brain injury and lifelong disability can result. Because of this, it is important to identify those babies at risk of the rare complication of acute bilirubin encephalopathy and kernicterus.¹,²,³,⁴

The clinical challenge is to identify the minority of babies with pathological neonatal jaundice from the majority with benign physiological jaundice. There are clues that jaundice may be pathological.³

Classification of Jaundice in the Newborn:

It is clinically useful to classify jaundice according to the age of the baby when he/she becomes visibly jaundiced. Other methods of classifying jaundice are in Appendix z

Onset less than 24 hours of age (uncommon)
- Nearly always pathological
- Usually due to haemolysis
  - Rhesus disease
  - ABO incompatibility
  - Other blood group incompatibilities
  - Rarer, red cell enzyme defects (e.g. G6PD deficiency)
  - Rarer, red cell membrane defects (e.g. spherocytosis, elliptocytosis)
- Can be but uncommonly due to sepsis

Onset between 24 hours and 10 days (very common)
- Physiological jaundice
- Haemolysis
- Breakdown of a high haemoglobin load
  - Cephalhaematoma
  - Severe bruising
  - CNS haemorrhage
- Breast milk jaundice
- Increased enterohepatic circulation which may be due to
  - inadequate feeding
  - gut obstruction
- Sepsis

Onset greater than 10 days (uncommon) or Prolonged Jaundice
- Breast milk jaundice (commonly persistent from earlier period)
• Haemolysis
  - Rhesus disease
  - ABO incompatibility
  - Other blood group incompatibilities
  - Rarer, red cell enzyme defects (e.g. G6PD deficiency)
  - Rarer, red cell membrane defects (e.g. spherocytosis, elliptocytosis)
• Hypothyroidism
• Sepsis particularly in urinary tract
• Galactosaemia
• Conjugated hyperbilirubinaemia due to:
  - idiopathic neonatal hepatitis
  - infections (Hepatitis B, TORCH, sepsis)
  - congenital malformations (biliary atresia, choledochal cyst, bile duct stenosis)
  - metabolic disorders (galactosaemia, hereditary fructose intolerance, Alpha-1 antitrypsin deficiency, tyrosinaemia, glycogen storage disease type IV, hypothyroidism)

**Risk Factors for Developing Severe Hyperbilirubinaemia:**

**Major risk factors**

• Blood group incompatibility with positive Coombs test
• Gestation less than 35-36 weeks
• Jaundice observed in the first 24 hours
• Previous sibling received phototherapy
• Cephalhaematoma or significant bruising
• Exclusive breastfeeding, especially if not feeding well and excessive weight loss
• East Asian race

**Minor risk factors**

• Pre-discharge SBR or TcB in in high intermediate risk zone on Bhutani nomogram
• Gestation 37-38 weeks
• Jaundiced before discharge
• Previous sibling with jaundice
• Macrosomic infant of diabetic mother
• Maternal age >25 years
• Male gender

A common pneumonic for risk factors for hyperbilirubinaemia is JAUNDICE:
  J – jaundice within the first 24 hours of birth
  A – a sibling who required phototherapy as a baby
  U – unrecognised haemolysis
  N – non-optimal sucking/feeding
  D – deficiency of G6PD
  I – infection
  C – cephalhaematoma or bruising
  E – Ethnicity (Asian heritage)

**Bilirubin Toxicity**

Prolonged high levels of bilirubin can cause brain damage displayed clinically as an encephalopathy, pathologically as kernicterus and in the long term as neuro-sensory deficits such as deafness and cerebral palsy.
**Bilirubin encephalopathy**
This clinical syndrome presents initially as
- lethargy
- hypotonia
- poor feeding
- high pitched cry
Progression of symptoms may occur to
- Hypertonia with opisthotonus or retrocollis
- Seizures
- Impaired consciousness
- Death
Late sequelae in survivors (chronic bilirubin encephalopathy)
- Extrapyramidal abnormalities (facial grimacing, drooling, dysarthria, athetosis, dystonia, spasticity) most commonly diagnosed as athetoid cerebral palsy
- Gaze abnormalities
- Sensorineural hearing loss
- Dental dysplasia
The cerebral cortex is relatively spared and intelligence is believed to be close to normal.

The late effects of moderate levels of jaundice on extremely preterm infants are unknown, although it is generally accepted they are more at risk than term infants for the same SBR level.

**Kernicterus**
At autopsy, babies display evidence of bilirubin staining of the basal ganglia and brain stem nuclei, neuronal necrosis and scarring known as kernicterus.

**Risk Factors for Kernicterus**
Once a baby develops severe jaundice, the risk of progressing to kernicterus is increased by the following:
- Isoimmune haemolytic disease
- G6PD deficiency
- Acidosis (pH<7.2)
- Proven sepsis
- Asphyxia (Sarnat stage 2 or more)
- A generally unwell neonate - temperature instability, significant lethargy

**Approach to the Jaundiced Neonate**
The jaundiced neonate needs to be assessed for
1. Wellbeing
2. History for risk factors
3. Level of jaundice
4. Investigation for cause of jaundice
5. Risk factors for earlier phototherapy and exchange transfusion

1. **Well Being**
Signs of being unwell such as marked lethargy, poor responsiveness, temperature instability, poor feeding, cyanosis, apnoea, bradycardia, mottled skin suggest sepsis, metabolic disturbances or other serious disorders that need to be ruled out. A generally unwell neonate is at risk of kernicterus at a lower level of bilirubin and should be started on phototherapy at the lower line.
(Phototherapy with Risk Factors) on the treatment graphs. Examination findings of bruising, pallor, plethora may offer clues to causation.

2. **History for Risk Factors**
Factors that may be significant in causation in the maternal history include blood group, antibodies, and maternal infections in pregnancy. In labour and delivery use of epidural analgesia is a risk factor. Intention for exclusive breast feeding and a family history of siblings needing phototherapy are risk factors. A baby’s feeding history with significant weight loss or poor weight gain suggest inadequate milk intake.

3. **Level of Jaundice**
The level of jaundice can be estimated by clinical examination of colour or measurement by a transcutaneous bilirubin meter and definitively by measuring blood bilirubin level in the NICU gas machine or serum bilirubin in the laboratory.

**Colour**
Always assess jaundice in a well-lit room or in daylight at a window by blanching the baby’s skin with a finger and observing the underlying skin colour. Jaundice appears first in the face and progresses caudally to the trunk and extremities.\(^1\)\(^,\)\(^2\)\(^,\)\(^6\) Kramer recognised the cephalo-caudal progression of jaundice with increasing total serum bilirubin levels and visually divided the baby into 5 zones, with a total serum bilirubin level measurement associated with each zone. This is known as Kramer’s rule (see Figure 1) and has traditionally been used to visually assess the severity of jaundice.\(^7\)

<table>
<thead>
<tr>
<th>Zone</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Head and neck</td>
<td>Upper trunk</td>
<td>Lower trunk and thighs</td>
<td>Arms and lower legs</td>
<td>Palms and soles</td>
</tr>
<tr>
<td><strong>Bilirubin (micromol/L)</strong></td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>&gt;250</td>
</tr>
</tbody>
</table>

Kramer’s rule is unreliable on a baby who has already commenced phototherapy.\(^1\) Visual estimation of bilirubin levels can lead to errors especially in darkly pigmented babies. A total serum bilirubin level (SBR) should be used to assess response to phototherapy and may be necessary if clinical assessment is difficult in babies with darker skins. In darker skinned babies rubbing and visualizing the gums can assist in assessing the level of jaundice.
Transcutaneous bilirubin level (TcB)

Bilirubin levels can be measured transcutaneously by a Transcutaneous Bilirubinometer. Available devices differ in accuracy; safe use of this device requires knowledge of the accuracy of the particular device being used. See separate guideline on the use of Bilirubinometer in NICU or Maternity and Newborn: Transcutaneous Bilirubinometer for the Detection of Neonatal Jaundice HNELHD G and P 14_16.

A formal SBR is required if the TcB level is within 50 micromol/L of the threshold for phototherapy OR a term baby’s TcB level is > than 250 micromol/L.

Transcutaneous bilirubin levels are inaccurate on a baby who has already commenced phototherapy. Do not use a bilirubinometer on a baby that has received phototherapy within the last 72 hours. The DRÄGER JAUNDICE METER JM-105 is used in NICU and can be used on babies as young as 24 weeks.

Because of differences in reliability of measurement between individual babies, trend of TcB measurements are more reliable than those made on a single value as the basis for clinical decision making.

Total Serum Bilirubin (SBR)

The SBR remains the ‘gold standard’ measurement for treatment decisions regarding jaundice. Venous and capillary SBR levels should be treated the same. The total serum bilirubin as opposed to just the unconjugated fraction is used for judging treatment thresholds. SBR can be measured either in the laboratory on a serum sample or in NICU on the gas machine.

A blood sample in preference to TcB measurement should be used for SBR in the following clinical situations:
- visible jaundice in the first 24 hours.
- jaundiced baby whose mother has rhesus or other red blood cells antibodies.
- if a TcB level is within 50 micromol/L of the threshold for phototherapy.
- term baby with estimated serum bilirubin levels or TcB level is greater than 250 micromol/L.
- any baby, if there is clinical doubt about the degree of jaundice.
- any unwell baby with jaundice.
- any baby with clinical signs of obstructive jaundice (pale stool and dark urine).
- prolonged jaundice greater than 2 weeks in term babies and greater than 3 weeks in preterm babies.
- In the 72 hours after phototherapy ceases.

Repeated Assessment of Jaundice Level

Jaundiced babies require repeated assessment of jaundice level until the clinician is confident the bilirubin level is decreasing. This may be done by any of the methods mentioned above i.e. Clinical judgment by Kramer’s Rule, TcB by bilirubinometer or SBR. Blood sample SBR must be used in babies who have had or are having phototherapy.

For babies having or just completed phototherapy see Monitoring and Stopping Phototherapy.

4. Investigations for Cause of Jaundice

Investigation for a cause of neonatal jaundice should be considered in the following situations:
- Any baby that is clinically unwell.
- Early onset jaundice (first 24 hours).
- Total SBR above phototherapy threshold at any time.
- Rapidly rising bilirubin level (>8 micromole/L/hour).
• Suggested investigations include:
  Clinically unwell baby
  • Workup for sepsis – FBC and film, blood culture, +/-urine culture, +/-blood gas,
  • Review mother’s blood group and antibody status
  • Blood group and DAT
  • Other investigations indicated from clinical situation and findings e.g. consideration for metabolic investigations

Early onset jaundice
• Review mother’s blood group and antibody status
• Blood group and DAT
• FBC and film
• Glucose-6-phosphate dehydrogenase (G6PD) deficiency screen in babies with high risk family history or ethnic/geographic origin (Mediterranean, Middle Eastern, African, Asian)
• Consider need for workup for sepsis
• Other investigations indicated from clinical situation and findings

Late onset or prolonged jaundice
• Central to the management of late onset or prolonged jaundice is whether the hyperbilirubinaemia is conjugated or unconjugated. If the conjugated bilirubin is over 30 micromol/L then it is a conjugated hyperbilirubinaemia which is always significant and serious. It needs urgent investigation and management and often referral to a gastroenterologist. The list of possible causes of conjugated hyperbilirubinaemia is very long (see appendix x). Unconjugated hyperbilirubinaemia is nearly always benign.

Investigations should include
• Review for history suggestive of obstructive jaundice e.g. acholic pale stools and dark urine that stains the nappy.
• Total and direct (conjugated) bilirubin

For unconjugated hyperbilirubinaemia
• Review mother’s blood group and antibody status
• Blood group and DAT if not already done, (interpret the result taking account of the strength of reaction, and whether mother received prophylactic anti-D immunoglobulin during pregnancy)
• Full blood count
• Urine culture
• Ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed.
• Free T4 and TSH

Total SBR approaching exchange transfusion thresholds (see Exchange Transfusion Guideline)
As blood collected after an exchange transfusion is of no value for investigating many of the rarer causes of severe hyperbilirubinaemia, these investigations should be considered before performing exchange transfusion.¹
• serum albumin level. Low albumin levels may be a risk factor for kernicterus.
• liver function tests (LFT)
• conjugated bilirubin
• Newborn screening card
• G6PD testing (not just screening)
• Blood for microarray
• **Assessment of Risk Factors for early Phototherapy and Exchange transfusion**

The risk factors are listed in an earlier section [Risk Factors for Kernicterus](#). The presence of a risk factor should prompt use of the lower thresholds for phototherapy and exchange transfusion on the graphs.

**Treatment of Neonatal Jaundice**

Severe hyperbilirubinaemia can be treated with:

- phototherapy
- exchange transfusion
- pharmacological agents

Treatment should include general management of hydration in babies with excess weight loss (more than 10% of birth weight) and treatment of any underlying illnesses that may be causing jaundice (e.g. infection).

**Phototherapy**

The graphs below are the 3 graphs in use in NICU JHCH. These graphs have been agreed to by the neonatologists after reviewing available evidence and practice in other units.
Any jaundice in the first 24 hours of life needs urgent investigation and management.

High Risk refers to high risk factors for kernicterus - see over page.
Information on the reverse side of each 3 phototherapy charts

**Risk Factors for Kernicterus**
- Rapidly rising bilirubin level (>8 micromol/L/hour)
- Isoimmune haemolytic disease
- G6PD deficiency
- Acidosis (pH<7.2)
- Proven sepsis
- Asphyxia (Sarnat stage 2 or more)
- A generally unwell neonate - temperature instability, significant lethargy

**Bilirubin Results in the first 24 hours**
If a SBR in the first 24 hours is over 80 micromol/L then a repeat bilirubin should be done in 4 to 6 hours and the jaundice guideline consulted for further advice. If still in doubt consult the neonatologist.

**Bilirubin Results from Gas Machine and Laboratory**
If concurrent samples have been obtained, action according to the laboratory result (regarded as the gold standard)
If concurrent results are widely discrepant repeat the test on a venous sample
Any jaundice in the first 24 hours of life needs urgent investigation and management.
Any jaundice in the first 24 hours of life needs urgent investigation and management.
Phototherapy
Phototherapy is the first line treatment for neonatal jaundice and is effective in most babies in stabilising or reducing SBR level. Phototherapy should be initiated when the SBR (laboratory or blood gas machine) is above the phototherapy threshold shown on the graph appropriate to the baby’s gestation at birth and postnatal age. Assess the baby for Risk Factors for Kernicterus. If any are present use the lower phototherapy line and lower exchange transfusion lines on the graphs as a guide to management. TcB measurements can be plotted on the graphs to follow the progress of jaundice but are not used for initiating phototherapy. Such plots should be annotated as ‘TcB’. Also note if collected from the blood gas machine.

When administrating phototherapy there are four key points to consider achieving effective treatment and decreasing the time of treatment. These are:
- Intensity of the light
- Spectral qualities of the light source
- Distance between the light and the infant’s skin
- Body surface area exposed

**WARNING for preterm infants ≤ 1000g**

NeoBLUE LED Phototherapy systems, comprising of Natus Neoblue LED lights and Natus Neo blue mini lights can deliver an irradiance of >30 μW/cm²/nm which may not be appropriate for all infants.

See ‘Phototherapy in NICU and Post Natal Wards JHCH_NICU_16.04’ CPG for specific details of phototherapy equipment use as well as Appendix 2 in Phototherapy CPG ‘Warning: neoBLUE LED Phototherapy System for preterm infants≤1000g’.

Be aware that phototherapy can cause side effects to the infant including:
- Loose stools
- Dehydration
- Hyperthermia
- Lethargy
- Skin rashes
- Eye damage
- Bronze baby syndrome

**Bilirubin Measurement after Starting Phototherapy**

After initiating phototherapy measure serum bilirubin again 6-8 hours later. This measure is to ensure phototherapy is being effective and to gauge the rate of any continued rise in bilirubin level.

**Ongoing Monitoring and Stopping Phototherapy**

**Repeat Bilirubin after Starting Phototherapy**

After initiating phototherapy measure SBR in 6 to 8 hours. This measure is useful in determining if the bilirubin level is continuing to rise and the rate of rise under phototherapy.
Further Monitoring
Repeat SBR measurements are based on level, rate of rise of bilirubin, cause of jaundice and clinical situation. A suggested guide is below:

- If SBR is less than 30 above the line measure SBR again in 24 hours.
- If SBR is more than 30 above the phototherapy line and rising but more than 30 below exchange transfusion line measure SBR in 12 hours.
- If SBR is within 30 of the exchange transfusion line measure SBR again in 6 hours.
- Continue to measure SBR until level is more than 50 below phototherapy threshold.

Ceasing Phototherapy
Stop phototherapy when the SBR is more than 50 below the phototherapy line in use.
A rebound in total serum bilirubin levels can occur after phototherapy is discontinued. Babies at increased risk of clinically significant rebound are those:

- born at less than 37 weeks gestation
- with haemolytic disease

Repeat the SBR measurement 12 – 24 hours after stopping phototherapy.

Restarting Phototherapy
Before restarting phototherapy the level should be at least 25 micromol/L above the phototherapy line.

Exchange Transfusion
A total serum bilirubin level at or above the exchange transfusion level should be considered a medical emergency. Commence intensive (multiple light) phototherapy immediately\(^1,2\) and discuss further care with a Neonatologist.

It is preferable to anticipate the need for exchange transfusion prior to SBR reaching the threshold level, particularly in a baby with known haemolysis. So, consider exchange transfusion where SBR levels are rising faster than 17 micromol/L per hour despite intensive phototherapy in a baby with known haemolysis.

Babies with known rhesus sensitisation are a special case and cord blood should be tested for group and DAT, haemoglobin and SBR. Cord haemoglobin less than 100 gram/l and/or SBR above 120 micromol/L should lead to consideration of early exchange transfusion.

Consider exchange in well, non-haemolytic babies only after rehydration and a period of intensive phototherapy (4-6 hours).

Adjunct pharmacological therapy

Intravenous Immunoglobulin (IVIG)
IVIG may reduce bilirubin concentrations in babies with rhesus haemolytic disease and other immune haemolytic jaundice.\(^1\) Babies with a positive DAT who have predicted severe disease based on antenatal investigation or have an elevated risk of progressing to exchange transfusion based on the postnatal progression of total serum bilirubin levels, may be considered for IVIG.\(^11\)

The dose required is 1 g/kg given intravenously over 2 hours.

A systematic review of earlier trials did show effect of IVIG, two recent trials do not support the use of IVIG in rhesus disease to prevent exchange transfusion.
Intravenous albumin
The rationale for albumin supplementation is empirical; there is no high quality evidence to support its effectiveness. Consider administering 20% albumin (1 to 2g over 1 hour) as a rehydration fluid for babies with acute bilirubin encephalopathy or those approaching the level for exchange transfusion where there may be co-existent dehydration and particularly when the serum albumin level is low.³

Discharge planning for the jaundiced baby
All newborns that are visibly jaundiced in the first 24 hours of life should be investigated as per guideline and must not be discharged until cause is known and jaundice is settling.

Never discharge a baby with a conjugated jaundice without attempting to find the cause and making appropriate referral and follow up arrangements.

All babies should be assessed for risk of developing severe hyperbilirubinaemia at hospital discharge.² This assessment is particularly important if discharge occurs before 72 hours of age, as these babies are likely to still have a rising total serum bilirubin level. Kramer’s rule has traditionally been used to visually assess the severity of jaundice.⁷ Visual estimation of bilirubin levels can lead to errors, especially in darkly pigmented babies and in infants who have received phototherapy. Transcutaneous bilirubinometers (see section above) may be useful to more accurately assess bilirubin levels.

Parental Advice at Discharge
It is recommended that information be given to parents at the time of discharge. Parents should be advised to contact a healthcare professional if:
- their baby becomes jaundiced
- baby’s jaundice is worsening
- jaundice is persisting beyond 14 days
- their baby is passing pale stools

Mothers of jaundiced breastfed babies should be encouraged to breastfeed frequently, and the baby woken to feed if necessary.

APPENDICES
1. Causes of Neonatal Hyperbilirubinaemia according to Mechanism
2. Classification of Hyperbilirubinaemia
3. Causes of Conjugated Hyperbilirubinaemia
4. Differential Diagnosis of Neonatal Cholestasis

REFERENCES


3. RPA Newborn Care Guideline: Jaundice November 2011.


Appendix 1

Causes of Neonatal Hyperbilirubinaemia according to Mechanism

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Increased enterohepatic circulation</td>
<td>Breast milk (breast milk jaundice)</td>
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<tr>
<td></td>
<td>Breastfeeding failure (breastfeeding jaundice)</td>
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<td></td>
<td>Drug-induced paralytic ileus (Mg sulfate or morphine)</td>
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<td></td>
<td>Fasting or other cause for hypoperistalsis</td>
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<td></td>
<td>Hirschsprung's disease</td>
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<td></td>
<td>Intestinal atresia or stenosis, including annular pancreas</td>
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<td></td>
<td>Meconium ileus or meconium plug syndrome</td>
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<td></td>
<td>Pyloric stenosis*</td>
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<td></td>
<td>Swallowed blood</td>
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<td>Overproduction</td>
<td>Breakdown of extravascular blood (e.g., hematomas; petechiae;</td>
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<td></td>
<td>pulmonary, cerebral, or occult hemorrhage)</td>
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<td></td>
<td>Polycythemia due to materno-fetal or feto-fetal transfusion or delayed</td>
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<td></td>
<td>umbilical cord clamping</td>
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<tr>
<td>Overproduction due to hemolytic anemia</td>
<td>Certain drugs and agents in neonates with G6PD deficiency (e.g.,</td>
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<tr>
<td></td>
<td>acetaminophen, alcohol, antimalarials, bupivacaine, corticosteroids,</td>
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<tr>
<td></td>
<td>diazepam, nitrofurantoin, oxytocin, penicillin, phenothiazine,</td>
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<td></td>
<td>sulfonamides)</td>
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<td></td>
<td>Materno-fetal blood group incompatibility (e.g. Rh, ABO), RBC enzyme</td>
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<tr>
<td></td>
<td>deficiencies (e.g. of G6PD or pyruvate kinase)</td>
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<tr>
<td></td>
<td>Spherocytosis</td>
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<tr>
<td></td>
<td>Thalassemias (α, β-γ)</td>
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<tr>
<td>Under secretion due to biliary obstruction</td>
<td>α1-Antitrypsin deficiency*</td>
</tr>
<tr>
<td></td>
<td>Biliary atresia*</td>
</tr>
<tr>
<td></td>
<td>Choledochal cyst*</td>
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<tr>
<td></td>
<td>Cystic fibrosis* (inspissated bile)</td>
</tr>
<tr>
<td></td>
<td>Dubin-Johnson syndrome and Rotor's syndrome*</td>
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<td></td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td>Tumor or band* (extrinsic obstruction)</td>
</tr>
<tr>
<td>Under secretion due to metabolic-endocrine</td>
<td>Crigler-Najjar syndrome (familial non-hemolytic jaundice types 1 and 2)</td>
</tr>
<tr>
<td>conditions</td>
<td>Drugs and hormones</td>
</tr>
<tr>
<td></td>
<td>Gilbert syndrome (see Gilbert Syndrome)</td>
</tr>
<tr>
<td></td>
<td>Hypermethioninemia</td>
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<tr>
<td></td>
<td>Hypopituitarism and anencephaly</td>
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<td></td>
<td>Hypothyroidism</td>
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<td></td>
<td>Lucey-Driscoll syndrome</td>
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<td></td>
<td>Maternal diabetes</td>
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<tr>
<td></td>
<td>Prematurity</td>
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<td></td>
<td>Tyrosinosis</td>
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<tr>
<td>Mixed overproduction and under secretion</td>
<td>Asphyxia</td>
</tr>
<tr>
<td></td>
<td>Intrauterine infections</td>
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<tr>
<td></td>
<td>Maternal diabetes</td>
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<tr>
<td></td>
<td>Respiratory distress syndrome</td>
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<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Severe erythroblastosis fetalis</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>TORCH infections</td>
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</table>

*Jaundice may also occur outside the neonatal period.
TORCH = toxoplasmosis, other pathogens, rubella, cytomegalovirus, and herpes simplex.
Appendix 2
Classification of Hyperbilirubinaemia

Non Conjugated Hyperbilirubinaemia

Hemolytic
Intrinsic causes of hemolysis
- Membrane conditions
  - Spherocytosis
  - Hereditary elliptocytosis
- Systemic conditions
  - Sepsis
  - Arteriovenous malformation
- Enzyme conditions
  - Glucose-6-phosphate dehydrogenase deficiency (also called G6PD deficiency)
  - Pyruvate kinase deficiency
- Globin synthesis defect
  - sickle cell disease
  - Alpha-thalassemia, e.g. HbH disease

Extrinsic causes of hemolysis
- Alloimmunity (The neonatal or cord blood gives a positive direct Coombs test and the maternal blood gives a positive indirect Coombs test)
  - Hemolytic disease of the newborn (ABO)
  - Rh disease
  - Hemolytic disease of the newborn (anti-Kell)
  - Hemolytic disease of the newborn (anti-Rhc)
  - Other blood type mismatches causing hemolytic disease of the newborn

Non-hemolytic causes
- Breast milk jaundice
- Cephalohematoma
- Polycythemia
- Urinary tract infection
- Sepsis
- Hypothyroidism
- Gilbert's syndrome
- Crigler-Najjar syndrome
- High GI obstruction

Conjugated (Direct) Hyperbilirubinaemia

Hepatic causes
- Infections
  - Sepsis
  - Hepatitis A
  - Hepatitis B
  - TORCH infections
- Metabolic
  - Galactosaemia
  - Alpha-1-antitrypsin deficiency, which is commonly missed, and must be considered in DDx
  - Cystic fibrosis
  - Dubin-Johnson Syndrome
  - Rotor syndrome
- Drugs
- Total parenteral nutrition
- Idiopathic

Post-hepatic
- Biliary atresia or bile duct obstruction
  - Alagille syndrome
  - Choledochal cyst

Non-organic causes
Breastfeeding failure jaundice
Appendix 3

Causes of Conjugated Hyperbilirubinaemia

1. Presentation with acute liver failure (unwell neonate)
   - Galactosaemia
   - Tyrosinaemia
   - Congenital and acquired infection
     - Bacterial, Herpes virus,
     - Coxsackie virus
     - ECHO virus, Hepatitis B,
     - Adenovirus, CMV,
     - Toxoplasma. *Treponema pallidum*
   - Neonatal haemochromatosis
   - Mitochondrial diseases
   - Familial haemophagocytic lymphocytic histiocytosis

2. Well-term neonate
   i) Intrahepatic causes
   - Alpha-1 antitrypsin
deficiency
   - Cystic fibrosis
   - Progressive familial intrahepatic cholestasis
   - Alagille syndrome
   - Endocrine causes
     - Hypothyroidism
     - Hypopituitarism
   - Storage diseases
     - Zellweger's syndrome
     - Wolman's syndrome
     - Niemann Pick type C
     - Gaucher's disease
   - Neonatal hepatitis
   - Bile acid oxidation defects
   - PN associated liver disease
   - Other systemic causes
     - Urinary tract infection
     - Trisomy 13 or Trisomy 18
     - Ischaemia ('shock liver')
   ii) Extrahepatic causes
   - Biliary atresia
   - Choledochal cyst
   - Inspissated bile syndrome
Appendix 4

Differential Diagnosis of Neonatal Cholestasis

1) Idiopathic neonatal hepatitis

2) Infections
   Viral:
   Cytomegalovirus
   Rubella
   Reovirus3
   Adenovirus
   Coxsackie virus
   Human herpes virus 6
   Varicella zoster
   Herpes simplex
   Parvovirus
   Hepatitis B and C
   Human immuno-deficiency virus
   Bacterial:
   Sepsis
   Urinary tract infection
   Syphilis
   Listeriosis
   Tuberculosis
   Parasitic:
   Toxoplasmosis
   Malaria

3) Bile duct anomalies
   Biliary atresia
   Choledochal cyst
   Alagille syndrome
   Non syndromic bile duct paucity
   Inspissated bile syndrome
   Caroli syndrome
   Choledocholithiasis
   Neonatal sclerosing cholangitis
   Spontaneous common bile duct perforation

4) Metabolic disorders
   α₁-antitrypsin deficiency
   Galactosaemia
   Glycogen storage disorder type IV
   Cystic fibrosis
   Hemochromatosis
   Tyrosinaemia
   Arginase deficiency
   Zellweger’s syndrome
   Dubin-Johnson syndrome
   Rotor syndrome
   Hereditary fructosaemia
   Niemann Pick disease, type C
   Gaucher’s disease
   Bile acid synthetic disorders
   Progressive familial intrahepatic cholestasis
   North American Indian familial cholestasis
   Aagenaes syndrome
   X-linked adreno-leukodystrophy

5) Endocrinopathies
   Hypothyroidism
   Hypopituitarism (Septo-optic dysplasia)

6) Chromosomal disorders
   Turner’s syndrome
   Trisomy 18
   Trisomy 21
   Trisomy 13
   Cat-eye syndrome
Donahue’s syndrome (Leprechauns)

7) Toxic
   Parenteral nutrition
   Fetal alcohol syndrome
   Drugs

8) Vascular
   Budd-Chiari syndrome
   Neonatal asphyxia
   Congestive heart failure

9) Neoplastic
   Neonatal leukaemia
   Histiocytosis X
   Neuroblastoma
   Hepatoblastoma
   Erythrophagocytic lymphohistiocytosis

10) Miscellaneous
    Neonatal lupus erythematosus
    ‘Le foie vide’ (infantile hepatic non regenerative disorder)
    Indian childhood cirrhosis

IMPLEMENTATION, MONITORING COMPLIANCE AND AUDIT

The level of implementation, monitoring or compliance and audit will be based on the risk rating of the document. Owners/developers must detail how:

1. the document will be communicated via email notification on message board on the Neonatal Hub and implemented when approved by CQ&PCC;
2. education will be provided to staff at arranged in-service times as well as bedside teaching by Education staff
3. the document will be monitored for effectiveness and compliance by reviewing the SBR charts and irradiance levels

FEEDBACK

Any feedback on this document should be sent to the Contact Officer listed on the front page.