NEONATAL HYPERBILIRUBINAEMIA

General recommendations

Identifying risks for significant hyperbilirubinaemia (except haemolytic)
- Previous sibling with neonatal jaundice requiring phototherapy
- East Asian race
- Gestational age < 37 weeks
- Mother’s intention to breastfeed exclusively
- Dehydration/ weight loss > 12 %
- Cephalhaematoma or significant bruising
- Combinaton of minor risk factors (maternal age ≥ 25 yrs., male, gestation 37 – 38 weeks, macrosomic infant of diabetic mother, polycythemia, 6-hour discharge)

Risks for developing bilirubin induced neurologic dysfunction (BIND)
- Serum bilirubin level greater than 340 micromol/litre in babies with a gestational age of ≥ 37 weeks gestation
- Rapidly rising bilirubin level of greater than 8.5 micromol/litre per hour
- Clinical features of acute bilirubin encephalopathy

Management of hyperbilirubinaemia

Clinical assessment and measuring bilirubin in jaundiced babies
- Examine for jaundice at every opportunity in the first 48 - 72 hours of life
- On visual inspection check the naked baby in bright and preferably natural light, examine the sclerae, gums and blanched skin across all skin tones
- Do not rely on visual inspection alone to estimate the bilirubin level in a baby with jaundice, but do not measure bilirubin levels routinely in babies who are not visibly jaundiced either
- Do not use an icterometer, umbilical cord blood bilirubin level, end-tidal carbon monoxide (ETCOc) measurement, umbilical cord blood direct antiglobulin test (DAT), albumin/bilirubin ratio and do not subtract conjugated bilirubin from total serum bilirubin

Indication for and monitoring of phototherapy
- See algorithm below and charts using serum/transcutaneous bilirubin
- Do not routinely start/continue phototherapy in babies with a gestational age of ≥ 37 weeks with jaundice above the treatment threshold lasting > 14 days or with a gestational age < 37 weeks and jaundice lasting > 21 days

Type of phototherapy to use
- Do not use sunlight as treatment for hyperbilirubinaemia
- Use conventional phototherapy if the gestational age is ≥ 37 weeks and fiberoptic or conventional phototherapy if it is < 37 weeks
- Initiate continuous multiple phototherapy if any of the following apply:
  o the serum bilirubin levels are rising > 8.5 micromol/litre per hour
  o the serum bilirubin is within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours
  o the bilirubin level fails to respond to single phototherapy (the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting single phototherapy)
- If the serum bilirubin level falls during continuous phototherapy with multiple units to a level 50 micromol/litre below the threshold for which exchange transfusion is indicated step down sequentially to single phototherapy.
• Step-up approach to continuous phototherapy with MAVI LED Phototherapy (RSCH site ONLY):
  o Use one device only set to 50 mW/cm²/nm at a distance of 40 cm between baby’s skin surface and the light for all babies above the phototherapy line
  o Use one device only set to 50 mW/cm²/nm at a distance of 40 cm between baby’s skin surface and the light plus a biliblanket/bilibed for all babies:
    1. with a serum bilirubin level rising > 8.5 micromol/litre per hour
    2. with a serum bilirubin within 50 micromol/litre below the threshold for which exchange transfusion is indicated after 72 hours
    3. with a bilirubin level failing to respond to single phototherapy (the level of serum bilirubin continues to rise, or does not fall, within 6 hours of starting single phototherapy)
  o Use two devices set to 50 mW/cm²/nm at a distance of 40 cm between baby’s skin surface and the light plus a biliblanket/bilibed for all babies above exchange line (potential risk of harm from cumulative irradiance close to 100 mW/cm²/nm justified by risk of harm from exchange transfusion, if unsuccessful)
  o Never use three devices set to 50 mW/cm²/nm at a distance of 40 cm between baby’s skin surface and the light due to questionable feasibility, effectiveness and potential harm

• If the serum bilirubin level falls during continuous phototherapy with multiple units to a level 50 micromol/litre below the threshold for which exchange transfusion is indicated step down sequentially in reverse order from described above.

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Management of Hyperbilirubinaemia

- 2 major risks or more OR
- 1 major risk and several minor risks

NO → No intervention required

YES → 6 h discharge check

YES → Mandatory visual inspection by community midwife within 48 h

NO → Review in first 24 h

YES → Visible jaundice

YES → Follow visible jaundice algorithm

NO → Review within 48 h and before discharge

Consider measuring serum or transcutaneous bilirubin
Management of Hyperbilirubinaemia

Visible jaundice

Jaundice < 24 h of life

NO

< 35 weeks gestation

NO

YES

Review within 1 h
Measure serum bilirubin

YES

Review within 6 h
Measure serum bilirubin

NO

Review within 6 h
Measure transcutaneous bilirubin

YES

Transcutaneous bilirubin > 250 micromol/l

NO

Postnatal age < 96 h

NO

Serum bilirubin above treatment threshold on chart

NO

YES

Serum bilirubin < 50 μmol/l below treatment threshold

YES

Start/continue phototherapy

NO

Consider phototherapy

NO

Stop/don’t start phototherapy

NO

Stop/don’t start phototherapy

YES

Monitor serum bilirubin 4 - 6 hourly first, then 12 hourly when stable or falling

Yes

Repeat serum bilirubin in 12 hours

NO

No further serum bilirubin monitoring

If on phototherapy, repeat serum bilirubin in 18 hours

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General care of the baby during phototherapy

- Place the baby in a supine position and ensure treatment is applied to the maximum area of skin
- Do not use white curtains, tin foil or bubble wrap routinely with phototherapy
- Give the baby eye protection and routine eye care during phototherapy, alternatively use tinted headboxes in babies with a gestational age of ≥ 37 weeks undergoing conventional ‘blue light’ phototherapy
- Monitor the baby’s temperature and maintain a thermoneutral environment
- Monitor hydration by daily weighing of the baby and assessing wet nappies
- Do not give additional fluids or feeds routinely. Maternal expressed milk is the additional feed of choice if available
- Encourage parents to interact with the baby and continue lactation/feeding support so that breastfeeding can start again when treatment stops
- During conventional ‘blue light’ phototherapy, using clinical judgement, encourage short breaks (max. 30 minutes) for breastfeeding and cares
- During the use of multiple phototherapy units do not interrupt phototherapy for feeding but continue administering intravenous/enteral feeds

Additional supporting treatment options

- Use intravenous immunoglobulin (IVIG) (see Neonatal Drug formulary) as an adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease or ABO haemolytic disease when the serum bilirubin continues to rise by > 8.5 micromol/litre per hour
- Use a double-volume exchange transfusion to treat babies with a haemoglobin of < 11 g/dl (or hct < 33 %) and/or whose serum bilirubin level indicates it is a necessity and/or with clinical features and signs of acute bilirubin encephalopathy (see Procedures Guideline)
- During exchange transfusion do not do any of the following: stop continuous multiple phototherapy, use albumin priming or routinely administer intravenous calcium
- Following exchange transfusion maintain continuous multiple phototherapy, measure serum bilirubin level within 2 hours and manage according to the treatment threshold
- Do not use any of the following to treat hyperbilirubinaemia: agar, albumin, barbiturates, charcoal, cholestyramine, clofibrate, D-penicillamine, glycerine, manna, metalloporphyrins, riboflavin, traditional Chinese medicine, acupuncture, homeopathy
- Avoid the following drugs with Glucose-6-Phosphate Dehydrogenase Deficiency: Antimalarials (Primaquine), Sulphonamides (Sulphapyridine, Sulphomaxole, Sulphamethoxypyridazine), Nitrofurans (Nitrofurantoin, Furazolidine), Antipyretics and analgesics (Acetylsalicylic acid, p-aminosalicylic acid), others (Sulfoxone, Naphelene, Methylene blue, Phenylhydrazine, Acetylphenylhydrazine, Probenecid, Vitamins ?, Fava beans

Management of Rhesus haemolytic disease & other forms of severe haemolysis

Antenatally

- Information concerning antenatal management, including in-utero transfusion, should be recorded in the paediatric notes
- Close liaison with the obstetric staff concerning timing of delivery
- Ensure appropriate neonatal medical and nursing staff are available
• Ensure availability of a pack of plasma-reduced blood for the baby prior to delivery if severe haemolysis has been identified in-utero

Immediately prior to delivery
• At least two experienced members of the neonatal staff should be present at delivery
• The neonatal staff should ensure that the standard resuscitation equipment is available and in working order and that the following are available and prepared:
  o Set up for sterile insertion of umbilical venous and arterial catheters, chest drain and pink cannulas for abdominal paracentesis
  o Blood collection tubes/syringes should be ready and labelled for cord blood samples to be taken for: haemoglobin and full blood count, serum bilirubin, direct Coomb’s test, blood grouping, cross-matching, umbilical arterial & venous gases, plasma glucose, urea and electrolytes

At delivery
• Resuscitate as per NLS (≥ 35 weeks) or local guidance (< 35 weeks)
• If adequate thoracic excursion is not achieved with IPPV improvement may be obtained by draining fluid from the intra-pleural space or from the peritoneal cavity, consider pericardiocentesis
• Insert umbilical venous catheter or other central venous line asap
• If profound anaemia (hct <15 %) is present, an immediate transfusion of blood (20 mls/kg over half an hour) should be started
• If hydrops is not present, the baby should be admitted to the neonatal unit as soon as possible following resuscitation. Blood transfusion can usually be performed as an elective procedure unless there appears to be severe anaemia causing cardiovascular compromise

On admission to the neonatal unit
• Insert umbilical arterial catheter or other arterial line asap
• Critically ill babies do not tolerate exchange transfusions as well as others and the exchange volume at this stage should be limited to 50-100 % of the circulating blood volume - i.e. 40-80 ml/kg
• Subsequently, when the baby has been stabilised, with normal blood gases, a double-volume exchange will usually be required - i.e. 160 ml/kg
• Further management will be guided by plasma bilirubin and haemoglobin levels (see above)

Subsequent management
• Babies with severe haemolytic disease will need to have their haemoglobin concentration checked at regular intervals, both before and after discharge, until the level is clearly rising; the frequency of these checks will depend upon the absolute haemoglobin concentration and the rate of change (discuss with Registrar or Consultant)
• All babies with haemolytic disease of the newborn should receive folic acid, from 14 days of age or on discharge until weaned onto a mixed diet, in the following doses - 100 micrograms/day (first 1 month), then 1 mg/kg/week
• All babies who require exchange transfusion should be followed up ensuring that adequate hearing checks have been carried out.

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Formal assessment for underlying disease and differential diagnoses

Potential causes of hyperbilirubinaemia
• Overproduction of bilirubin
  o Haemolytic disorders (foetomaternal blood group incompatibility, e.g. ABO, Rhesus; hereditary spherocytosis, red cell enzyme defects, e.g. G-6-PD, pyruvate kinase; haemoglobinopathies)
  o Extravasation of blood (external bruising, internal haemorrhage)
  o Polycythaemia (twin to twin transfusions, delayed clamping of the cord, small for dates babies)
  o Increased entero-hepatic circulation (paralytic ileus, dehydration, congenital mechanical gut obstruction)
• Impaired hepatic clearance of bilirubin
  o Congenital hypothyroidism
  o Inborn errors of metabolism (e.g. galactosaemia)
  o Decreased bilirubin conjugation (deficiency of glucuronyl transferase, i.e. Crigler-Najjar Syndrome; enzyme inhibited by progesterone derivative in breast milk, i.e. breast milk jaundice)
• Obstruction of bile flow (high level of conjugated bilirubin)
  o Biliary atresia, choledochal cyst, cystic fibrosis, α-1-antitrypsin deficiency
• Mixed
  o Prematurity, prenatal infections (TORCH, Syphilis, etc.), postnatal sepsis

Baseline investigations
• Serum bilirubin, FBC, blood group (mother and baby), DAT (Coombs’ test, interpret the result taking account of the strength of reaction, and whether mother received prophylactic anti-D immunoglobulin during pregnancy)

Additional tests
• Depending on the suspected aetiology full blood count and examination of blood film, blood glucose-6-phosphate dehydrogenase levels (taking account of ethnic origin), microbiological cultures of blood, urine and/or cerebrospinal fluid (if infection is suspected) are indicated
• Eosin-5-maleimide (EMA) binding test for hereditary spherocytosis. Contact Dr. May-Jean King (Membrane Biochemistry, International Blood Group Reference Laboratory, NHS Blood and Transplant, North Bristol Park, Northway, Filton, Bristol BS34 7QH, UK. May-jean.king@nbs.nhs.uk). Tel.: 0117-991-2111, FAX 0117-959-1660. Use email to communicate with Dr King. 500 microlitres of blood in an EDTA bottle and a 3ml EDTA maternal sample to act as a control required. The samples must be sent either on wet ice or with freezer blocks, but if these are used the samples must be protected by wrapping in paper tissue to stop them from freezing. The samples must arrive within 24 hours. The parcel must indicate: Urgent for Biochemistry in Filton, storage condition at 4 º only, local contact details. For further information and a copy of the request form please see this document: http://ibgrl.blood.co.uk/ReferenceServices/UserGuides/UG02-06%20Memb%20biochem%20user%20guide.pdf

Care of babies with prolonged jaundice
• Definition: > 20 % of total conjugated and/or conjugated bilirubin > 20 μmol/l
• Look for pale chalky stools and/or dark urine that stains the nappy
• Measure conjugated bilirubin and perform routine metabolic screening and additional tests (see investigation proforma below)
• Seek expert advice (King’s College Paediatric Hepatology)
### INVESTIGATION OF CONJUGATED HYPERBILIRUBINAEMIA

<table>
<thead>
<tr>
<th>INVESTIGATION</th>
<th>DATE PERFORMED</th>
<th>SPECIMEN REQUIRED</th>
<th>RESULT</th>
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<tr>
<td><strong>INFECTIVE CAUSES</strong></td>
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<tr>
<td>Urine Culture</td>
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<td>Blood Culture</td>
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<tr>
<td>Urine for CMV PCR</td>
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<td>Urine specimen in sterile pot</td>
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<td>Hepatitis C Serology</td>
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<tr>
<td>G-I-P-U-T</td>
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<td>Urine reducing substances</td>
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<td><strong>OTHER CAUSES</strong></td>
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<tr>
<td>Ophthalmology</td>
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<td>Cataract/retinitis/optic atrophy/posterior emryotoxon</td>
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