# Prolonged Neonatal Jaundice

<table>
<thead>
<tr>
<th>Title of Guideline</th>
<th>Guideline for the assessment and management of prolonged neonatal jaundice</th>
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|------------------------------------|--------------------------------------------------------------------------------|
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Paediatrics |
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| Guideline Number | 1940 |
| Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis) | Infants with prolonged jaundice arising in the neonatal period  
Excludes Management in first 14 days of life which is covered by neonatal guideline 1752  
Detection and Management of Jaundice in Newborn Infants |
| Abstract | This guideline describes the assessment, investigation and management of prolonged neonatal jaundice in infants. |
| Key Words | Paediatrics, Children, Jaundice, neonatal, hyperbilirubinaemia, biliary atresia |
| Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues? | The evidence base is drawn from the research evidence included in the recent NICE guidance and subsequent cohort studies. The majority of the research pertaining to prolonged neonatal jaundice is level 3 evidence. |
| Evidence base: (1-5) | |
| 1a | meta analysis of randomised controlled trials |
| 1b | at least one randomised controlled trial |
| 2a | at least one well-designed controlled study without randomisation |
| 2b | at least one other type of well-designed quasi-experimental study |
| 3 | well–designed non-experimental descriptive studies (i.e. comparative / correlation and case studies) |
| 4 | expert committee reports or opinions and / or clinical experiences of respected authorities |
| 5 | recommended best practise based on the clinical experience of the guideline developer |
| Consultation Process | Departmental Clinical Guidelines Meeting  
Neonatal Unit Clinical Guidelines |
| Target audience | Medical and nursing staff caring for infants with prolonged neonatal jaundice |

This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.
Document Control

Document Amendment Record

<table>
<thead>
<tr>
<th>Version</th>
<th>Issue Date</th>
<th>Author</th>
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<tbody>
<tr>
<td>V1</td>
<td>Feb 2013</td>
<td>Dr Louise Wells, Consultant Paediatrician&lt;br&gt;Dr Damian Wood, Consultant Paediatrician</td>
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Summary of changes for new version:

- Updated references
Prolonged Neonatal Jaundice

Introduction
Prolonged neonatal jaundice (hyperbilirubinaemia) is defined as:

- visible jaundice persisting beyond day 14 in term neonates
- visible jaundice persisting beyond day 21 in preterm infants (born at less than 37 completed weeks gestation).

Causes of Prolonged Jaundice
There are many causes of prolonged jaundice in neonates. The commonest is breast milk jaundice which resolves spontaneously over time. The main reason for prolonged jaundice screening is to pick up biliary atresia as early as possible. Below is a list of some of the other causes:

<table>
<thead>
<tr>
<th>Unconjugated/Mixed</th>
<th>Conjugated</th>
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<tbody>
<tr>
<td>• Breast milk jaundice</td>
<td>• Decreased excretion (conjugated)</td>
</tr>
<tr>
<td>• Haemolysis</td>
<td>- Obstruction</td>
</tr>
<tr>
<td>– Coombs positive</td>
<td>• Biliary atresia</td>
</tr>
<tr>
<td>• Rhesus incompatibility</td>
<td>• Choledochal cyst</td>
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<tr>
<td>• Anti-Kell, anti-Duffy</td>
<td>• Spontaneous bile duct perforation</td>
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<td>• ABO incompatibility</td>
<td>• Hepatoblastoma, haemangioma, neuroblastoma</td>
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<tr>
<td>– Coombs negative</td>
<td>– Infection</td>
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<tr>
<td>• Red cell membrane defects e.g. spherocytosis</td>
<td>• Septicaemia, UTI</td>
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<tr>
<td>• Red cell enzyme defects e.g. G6PD, pyruvate kinase deficiency</td>
<td>• TORCH infections, syphilis</td>
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<tr>
<td>– Haemoglobinopathy</td>
<td>• Hepatitis, Varicella zoster, HIV and other viral</td>
</tr>
<tr>
<td>– Sepsis</td>
<td>– Inherited/metabolic/endocrine</td>
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<tr>
<td>– Disseminated intravascular coagulation</td>
<td>• a1-antitrypsin deficiency</td>
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<tr>
<td></td>
<td>• Alagille's syndrome</td>
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<tr>
<td>• Increased enterohepatic circulation</td>
<td>• Cystic fibrosis</td>
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<td>– Pyloric stenosis</td>
<td>• Galactosaemia, fructosaemia</td>
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<tr>
<td>– Intestinal obstruction</td>
<td>• Glycogen storage diseases</td>
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<tr>
<td>• Decreased conjugation (unconjugated)</td>
<td>• Tyrosinosis</td>
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<tr>
<td>– Crigler–Najjar syndrome</td>
<td>• Hypermethioninaemia</td>
</tr>
<tr>
<td>– Gilbert's disease</td>
<td>• Hypopituitarism/ hypoadrenalism</td>
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<tr>
<td>– Hypothyroidism</td>
<td>• Myochoondrial cytopathies</td>
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<td>– Prematurity</td>
<td>• PFIC syndromes</td>
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<td></td>
<td>– Chromosomal disorders</td>
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<td></td>
<td>• Turner's syndrome</td>
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<td></td>
<td>• Trisomy 13, 18, 21</td>
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<td></td>
<td>– Toxic/drugs</td>
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<td></td>
<td>• Fetal alcohol syndrome</td>
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<tr>
<td></td>
<td>• Idiopathic neonatal hepatitis</td>
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<td>– TPN / PN</td>
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2. Referrals from Primary Care

Infants with prolonged jaundice should be seen in the next prolonged jaundice clinic unless:

- They are unwell (fever, difficulty breathing, pallor, vomiting)
- They have pale stools or dark urine
- They have bleeding or bruising

in which case they should be seen urgently

Community midwives and / or health visitors should contact the on call paediatrician to discuss the baby. If they are well, have normal stools and urine and no bleeding or bruising they should be booked into the next prolonged jaundice clinic by contacting the ward clerk on D33 at Nottingham Childrens Hospital (0115 924 9924 X 69033).

The babies name, date of birth and NHS number along with mother’s name and a telephone contact number should recorded at the time of referral and a date and time for a jaundice clinic appointment provided by the ward clerk on D33 at Nottingham Childrens Hospital.

3. Initial Assessment at the prolonged jaundice clinic.

Identify Life Threatening Features

Remember prolonged jaundice can be caused by conditions which can be associated with severe infection (galactosaemia) and cardiac problems (haemolytic anaemia, Alagille’s syndrome). Assess Airway, Breathing, Circulation and Disability to identify potential life-threatening features. If you are concerned that the baby has immediately life threatening features call for senior medical and nursing assistance and institute initial management as per the Cardiopulmonary resuscitation guideline.

History

For every baby with prolonged jaundice the following information should be obtained:

- Method of feeding and weight gain (include birth weight and current weight)
- Urine colour/recent wet nappies
- Colour of stool/delayed passage of meconium
- Lethargy and sleep/wake/feed behaviour
- Seizures and abnormal movements
- Bleeding/bruising
- Family history
  - Blood /liver and metabolic disorders
  - Cystic fibrosis
- Antenatal history
  - Maternal drug history / infection / USS and blood group
Examination
Check the observations (temp, HR, CRT, BP) and the information in the Child Health Record (red book). Plot available weights on a growth chart (the majority of healthy infants have regained their birth weight by 14 days of age). Examine for

- Jaundice
- Pallor
- Hydration status
- Dysmorphic features
- Cataracts
- Hepatosplenomegaly
- Hypotonia and encephalopathy
- Petechia/purpura
- Look in the nappy – colour of stool and urine
- Examine for features suggestive of congenital heart disease

Investigations
Carry out the following investigation in babies with prolonged jaundice (that is, persisting more than 14 days in term babies and more than 21 days in preterm babies):

- visual inspection of stool and urine look for pale chalky stools and/or dark urine which stains the nappy
- total and conjugated bilirubin
- full blood count
- blood group determination (mother and baby) and DAT (Coombs’ test)
- ensure that routine metabolic (heel prick) screening (including screening for congenital hypothyroidism) has been performed.

Results

- **Conjugated bilirubin above 25 μmol/L or greater than 20% of the total bilirubin** should be referred immediately for further management by the paediatric gastroenterology team. (see section 5)
- **Total bilirubin greater than 350 μmol/L (Conjugated bilirubin below 25 μmol/L)** should be repeated in one week if the baby is well and other tests normal
- **Haemoglobin**: If the haemoglobin in less than 10g/dl then repeat the haemoglobin in 1 week to ensure the levels are not dropping rapidly. Consider iron and folic acid supplementation
- **Neutrophil count**: If the neutrophil count is
  - > 1.0 it does not need repeating
  - 0.5-1.0 repeat in children’s outpatients in 4 weeks
  - <0.5 repeat in children’s outpatients in 2 weeks
Parents should be sent a form, date and time to come to children’s outpatients for repeat bloods. The form should have the hot week consultants code on it and be labelled for COPD. The result will then come back to the relevant consultant.

- **Other abnormal results** should be discussed with the hot week consultant
- **In those who have**
  - Total bilirubin less than 350,
  - conjugated bilirubin less than 25 micromol/l
  - Normal Hb
  - Normal neutrophil count

no further assessment is needed unless new concerns. The parental advice sheet should be given, and letter sent to primary care team

5. Investigation and Management of Conjugated Hyperbilirubinaemia

Refer immediately for further management by the Consultant Paediatric Gastroenterologist.

This is defined as a conjugated bilirubin above 25 μmol/L. Percentage values may be falsely reassuring in cases of high total values. In babies with conjugated hyperbilirubinaemia the priorities are to:

- establish the diagnosis (particularly early diagnosis of biliary atresia)
- prevent intracranial haemorrhage by identifying and correcting clotting abnormalities which reflect underlying impaired synthetic liver function

**Investigation**

Ask parent/carer and nursing staff to keep a sample from every stool to show gastroenterology team

In cases of **conjugated** hyperbilirubinaemia perform the following investigations

- Liver function tests
- Coagulation screen
- Blood glucose
- Full blood count
- TORCH screen / Hepatitis serology
- Alpha-1-Antitrypsin level (Li. Hep.) and genotype (EDTA)
- Gal-1-Put – discuss with Clinical Chemistry if the child received prior blood transfusion
- Thyroid Function Tests (XTFT)
• Cortisol (<420 is abnormal and needs d/w endocrine team)
• Plasma amino acids
• Serum iron and ferritin or ZPP
• Urine metabolic screen
• Abdominal ultrasound (looking for evidence of a choledochal cyst and the presence of a visible gallbladder)

Further management should be by the Paediatric Gastroenterology Team

• Prescribe oral Phenobarbital 5mg/kg once daily (immediately if stools acholic) to maximise hepatic excretion in preparation for a HIDA scan.

More specialized investigations will include:
• HIDA Scan after enzyme induction for five days with Phenobarbital (5mg/kg once daily before scan and stopped after scan)
• Abdominal Ultrasound (before next feed but do not starve due to risk of hypoglycaemia)
• CXR (butterfly vertebrae)
• Eye examination (posterior embryotoxin) via referral to the consultant paediatric ophthalmologist
• Liver biopsy (after correction of coagulopathy)
• Echocardiography (pulmonary stenosis)
• Sweat test

Biliary Atresia

Biliary atresia occurs in 1:14,000 live births and is characterised by progressive obliteration of extra-hepatic bile ducts. Affected infants have a conjugated hyperbilirubinaemia. The aetiology of biliary atresia is unknown. In some, it may be a developmental anomaly although meconium is of normal colour in nearly all cases indicating at least initial patency of the biliary tree, but there is a higher incidence of associated cardiovascular, gastrointestinal and genitourinary anomaly (10–20%) – for example:
• situs inversus
• polysplenia
• absent inferior vena cava
• malrotation

Affected infants may grow normally for first months and 1/3rd have normal stools.

Idiopathic Neonatal Hepatitis Syndrome

Neonatal Hepatitis Syndrome is the collective name given to a varied group of disorders that result in a combination of:
• conjugated hyperbilirubinaemia
• decreased or absent bile flow
• dark urine
• pale acholic stools
Neonatal hepatitis syndrome occurs in one in 2500–3000 live births and whilst there is a particular emphasis placed on early diagnosis of biliary atresia in as many as one-third of cases no specific cause is identified, thus leaving a group collectively known as ‘idiopathic neonatal hepatitis’. These idiopathic cases generally have a good prognosis with 90% showing full recovery within the first year of life.

6. Investigation and Management of significant Unconjugated Hyperbilirubinaemia (Greater than 350 μmol/L)

Haemolytic Jaundice

There are number of haemolytic disorders which may result in jaundice and anaemia. They often cause early onset jaundice (jaundice visible before 24hrs of age). The hyperbilirubinaemia is unconjugated and there may be other evidence of haemolysis including hepatosplenomegaly. In cases of haemolytic jaundice the haemoglobin level and reticulocyte should be monitored to detect anaemia and the blood film examined along with testing for blood group incompatibility and red cell disorders. If a haemolytic disorder is the likely cause of the prolonged neonatal jaundice then further discussion with the paediatric haematology team is recommended.

Breast Milk Jaundice

The majority of infants with prolonged jaundice will turn out to have breast milk jaundice a diagnosis of exclusion. The jaundice is more marked and prolonged jaundice than in those babies who are purely formula-fed and is thought to be due to a number of factors:

- Lower breast milk volume
- Slower gut transit
- Enhanced enterohepatic circulation of bilirubin
- Breast milk of b-glucuronidase unconjugates bilirubin enabling it to re-enter the circulation
- Altered bacterial colonisation results in a decrease in the conversion of bilirubin glucuronides to urobinoloids

Breast milk jaundice occurs in up to 1/3rd of breastfed babies and peaks at 2–3 weeks. Resolution can take 2–3 months.

A mixed picture of raised unconjugated and conjugated bilirubin may be seen in the following and appropriate investigations done in this case:

- Neonatal hepatitis (LFTs)
- intrauterine infections (TORCH screen)
- bacterial sepsis (urine culture and blood culture if unwell)
• Galactosaemia (gal-1-PUT)
• Aminoacidaemias (plasma amino acids)
• congenital hypopituitarism (TFTS)
• Haemolytic anaemia (DCT)
• Breast Milk Jaundice
• Physiological Jaundice

Advice for Parents

For well infants whose investigations have been completed:

• Provide the parents with a copy of the Parent Information Sheet
• Inform the Primary care team and parents of normal screening results by letter
References

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