This guideline and supporting information has been prepared with reference to the following:


What is the incidence of prolonged neonatal jaundice in term and preterm newborns?
Jaundice persisting beyond 14 days of age (prolonged jaundice) can (rarely) be a sign of serious underlying liver disease (Hussein, 1991). Jaundice persists beyond 14 days in 15-40% of breastfed infants, depending on the series studied (Hannam, 2000). A prospective study of all 7139 term infants born at King's College Hospital (London) between January 1997 and June 1998 (Hannam, 2000) found 154 with prolonged jaundice, one of which had conjugated hyperbilirubinaemia (0.14 per 1000 live births). Another study of 3661 babies in Sheffield (Crofts, 1999) found 127 who were jaundiced at 28 days, of which 125 were breastfed (9.2%). Although preterm infants, whose livers are more immature, have prolonged jaundice more commonly than term infants (Fenton, 1998) there appear to be no studies of incidence in this group (Lucas, 1986).
The first large, prospective study of severe hyperbilirubinemia in UK infants in the first month of life (Manning, 2007) found an incidence of 0.7 per 1,000 live births (95% CI 0.5 – 0.8).

Evidence Level: IV

When does serum bilirubin level of a neonate fall to adult level?
High serum bilirubin levels in the first days of life “decline during the next several weeks to the values commonly found in adults” (Dennery, 2001). This time period is inexact, although 14 days is commonly accepted as a cut-off point for investigation of sustained jaundice (Fenton, 1998).

Evidence Level: V

What is the incidence of glucose-6PD deficiency in British white children?
Glucose-6PD deficiency is most common amongst Greek, Sardinian, Chinese, Jamaican and South East Asian populations (Beutler, 1994; Valaes, 1994; Singh, 1986; Doxiadis, 1961). There appear to be no epidemiological studies in British white children. The prevalence
amongst white northern European populations has been estimated as less than 1 in 1,000 (Beutler, 1995).


Singh H. Glucose-6-phosphate dehydrogenase deficiency: a preventable cause of mental retardation. BMJ 1986;292:397-8


Evidence Level: V

What is the incidence of hereditary spherocytosis presenting with prolonged neonatal jaundice only?
The incidence of hereditary spherocytosis in Northern Europeans has been estimated at 1:5,000 (Morton, 1962), although milder forms may be asymptomatic and therefore the true incidence may be higher. A recent review (Delhommeau, 2000) has taken this into consideration and suggested an incidence of 1:2,000. This condition has received little attention in the neonatal period (Delhommeau, 2000) and consequently no information can be identified concerning prolonged jaundice as the sole presenting symptom.


Evidence Level: V

What is the incidence of sickle cell anaemia in the British white population?
The first evidence-based rates for sickle-cell in the UK (Hickman, 1999) give a zero incidence in the white population. The evidence level for this is “D” which equates to “Expert advice based on unpublished data”.


Evidence Level: V

What percentage of congenital hypothyroidism is missed in the Guthrie test?
The first screening programme (Dussault, 1975) used a T4 assay alone, which had the potential for missing some babies with ectopic glands in whom T4 concentrations could be in the low-to-normal range. Later programs used TSH assay, which, although unable to detect secondary (pituitary or hypothalamic) hypothyroidism, proved extremely effective in identifying even mild cases of primary hypothyroidism (Hulse, 1980).

A report of the first 3 years of the UK national screening programme (Grant, 1988) recorded 493 cases in a total of 1,941,146 live births (incidence 1:3937). 4 cases were missed (0.8%), which was similar to the North American experience (Holtzman, 1986) of 2 missed cases for every 1 million infants screened.


Evidence Level: V

What percentage of urinary tract infection in newborns presents with jaundice only?
The association of urinary tract infection with neonatal jaundice has been well-recognised (Anon, 1971; Arthur, 1967), but no percentages can be identified for newborns presenting with jaundice alone. Most infants in published series have anaemia and/or septicaemia in addition to their jaundice (Hannam, 2000). Jaundice as the main presenting symptom of UTI appears to predominate in male infants at a ratio of 3:1 (Seeler, 1969), unlike the female preponderance generally found in paediatric UTI.

Anon. Urinary tract infection presenting as jaundice. BMJ 1971;iii:546-7

Evidence Level: V

At what level of total serum bilirubin (TSB) does kernicterus occur in a) the term baby b) the preterm baby of 32 weeks? At what level should phototherapy be started in the term baby?
The American Academy of Pediatrics (Anon, 2004) states that “It is not known at what bilirubin concentration...significant risk of brain damage occurs or when the risk of damage exceeds the risk of treatment.” Cases of kernicterus have occurred at TSB levels below 200 micromol/l (Gustafson, 1995). This level of uncertainty persists (Wennberg, 2006): “There are insufficient published data to precisely define sensitivity and specificity (of TSB) in determining risk for acute bilirubin neurotoxicity or chronic sequelae (kernicterus).”

One authority (Ives, 1999) suggests that the threshold lies “somewhere between 400 and 650 micromol/l”. The AAP (Anon, 1994) recommends exchange transfusion and intensive phototherapy when serum bilirubin is >/= 430 mmol/l if age 25-48 hours or >/= 510 mol/l if >48 hours. Standard phototherapy should begin at 257 micromol/l or 308 micromol/l for the same age bands, in the term or near term infant.

Data from the Pilot Kernicterus Registry (Johnson, 2002) showed that the median total serum bilirubin (TSB) concentration of infants on readmission to hospital with kernicterus was 600 micromol/l (350 mg/l).

The most recent information on this subject (Bhutani, 2004) indicates that TSB concentrations of >342 micromol/l (>200 mg/l) should be a cause for concern and that values >/= 513 micromol/l (>300 mg/l) should be considered “dangerous”.

TSB concentrations are, however, poor predictors of bilirubin toxicity in the sick or preterm infant (Bhutani, 2004). Although “free” or unbound bilirubin may provide a more accurate measure, no tests for this have been validated to date (Bhutani, 2004).

A sliding scale has been suggested, based on infant weight, to indicate when intensive phototherapy should be started, but exchange transfusion is recommended when TSB >190 mL/kg (Bhutani, 2004).


Evidence Level: V

Can gamma-glutamyl transpeptidase (GGTP) be useful in distinguishing neonatal hepatitis (NH) from extrahepatic biliary atresia (EHBA)?

A study in 132 patients (Arora, 1992) found that serum GGTP at a cut-off level maintaining 100% sensitivity for EHBA (< 150 IU L(-1)), used in conjunction with non-excreting 99mTc-mebrofenin IDA scans, reduced the false positivity of individual tests. In this series, operative cholangiograms would have been avoided in 21 patients having both tests, vs 9 when only IDA scan was performed.

A study in 47 infants with EHBA, 10 with NH and 130 age-matched healthy controls (Yamagiwa, 1996), noted significant differences in GGTP levels between the EHBA and NH infants at 6 weeks of age (314 +/- 232 IU/L vs 69 +/- 58 IU/L).

A much earlier study in 17 infants aged 5-16 weeks (Wright, 1960) found that the mean maximal GGTP level in NH patients (183 +/- 54 IU/L) was significantly lower than that found in EHBA patients (760 +/- 492 IU/L).

Evidence Level: IV

What is the optimal dose and duration of treatment in total parenteral nutrition (TPN) related cholestasis?

“To date, there is no universally accepted treatment for intractable TPN-associated cholestasis” (Al-Hathlol, 2006).

BNF for Children advises ursodeoxycholic acid (UDCA), 10 mg/kg 3 times a day.

Most studies have included very small numbers of patients. A pilot study in 7 children (Spagnuolo, 1996) found that UDCA took 4-8 weeks to normalise biochemical markers of cholestasis. Another, in 13 infants (Al-Hathlol, 2006) used a dose of 15-20 mg/kg/day and found that although patients responded from the second week of therapy, about four months of treatment were needed before normalisation occurred.

An alternative treatment is cholecystokinin, which needs to be administered intravenously for 3-5 days in a dose of 2-4 IDU/kg (Teitelbaum, 1997; Teitelbaum, 1995; Rintala, 1995).


Evidence Level: IV

**What is the threshold for home phototherapy in patients with criggler najar?**
No firm evidence has been identified with which to answer this question, but case reports mention a threshold serum bilirubin concentration of 15 mg/dL (0.833 mmol/L) (O'Reilly, 1988; Shevell, 1987). Home phototherapy is a relatively recent service in the UK, the first such service being reported in 2004 (Walls, 2004).


Evidence Level: V

**What are the most appropriate tests to be ordered for prolonged jaundice?**
A prospective study in 144 infants (Hannam, 2000) concluded that “the number of investigations may safely be reduced to: a total and conjugated bilirubin, packed cell volume, glucose-6-phosphate dehydrogenase level (where appropriate), a urine for culture and inspection of a recent stool sample for bile pigmentation”.


Evidence Level: IV

Last amended June 2008