

JAUNDICE

Supporting Information

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

Anon. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114:297-316

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).

Crofts DJ, Michel VJ, Rigby AS, et al. Assessment of stool colour in community management of prolonged jaundice in infancy. *Acta Paediatr* 1999;88:969-74

Fenton TR, Gastrointestinal problems and jaundice of the newborn. In: Campbell AG, McIntosh N, (eds). *Forfar and Arneil's Textbook of pediatrics*, 5th ed. New York: Churchill Livingstone, 1998. p219

Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. *Acta Paediatr* 2000;89:694-7

Hussein M, Howard ER, Mieli-Vergani G, et al. Jaundice at 14 days of age: exclude biliary atresia. *Arch Dis Child* 1991;66:1177-9

Lucas A, Baker BA. Breast milk jaundice in premature infants. *Arch Dis Child* 1986;61:1063-7

Evidence Level: V

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).

Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med* 2001;344:581-90

Fenton TR, Gastrointestinal problems and jaundice of the newborn. In: Campbell AG, McIntosh N, (eds). *Forfar and Arneil's Textbook of pediatrics*, 5th ed. New York: Churchill Livingstone, 1998. p214

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).

Beutler E. Glucose-6-phosphate dehydrogenase deficiency and other enzyme abnormalities. In: Beutler E, Lichtman MA, Coller BS, et al (eds). Williams Hematology, 5th ed. New York, McGraw-Hill, 1995. p572

Beutler E. G6PD deficiency. Blood 1994;84:3613-36

Doxiadis SA, Fessas P, Valaes T. Glucose-6-phosphate dehydrogenase deficiency: a new aetiological factor of severe neonatal jaundice. Lancet 1961;i:297-301

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

Valaes T. Severe neonatal jaundice associated with glucose-6-phosphate dehydrogenase deficiency: pathogenesis and global epidemiology. Acta Paediatr Suppl 1994;394:58-76

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.

Delhommeau F, Cynober T, Schischmanoff PO, et al. Natural history of hereditary spherocytosis during the first year of life. Blood 2000;95:393-7

Morton NE, MacKinney AA, Kosower N, et al. Genetics of spherocytosis. Am J Hum Genet 1962;14:170

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”.

Hickman M, Modell B, Greengross P, et al. Mapping the prevalence of sickle cell and beta thalassaemia in England: estimating and validating ethnic-specific rates. *Br J Haematol* 1999;104:860-7

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.

Dussault JH, Coulombe P, Laberge C, et al. Preliminary report on a mass screening program for neonatal hypothyroidism. *J Pediatr* 1975;86:670-4

Grant DB, Smith I. Survey of neonatal screening for primary hypothyroidism in England, Wales, and Northern Ireland 1982-4. *BMJ* 1988;296:1355-8

Holtzman C, Slazyk WE, Cordero JF, et al. Descriptive epidemiology of missed cases of phenylketonuria and congenital hypothyroidism. *Pediatrics* 1986;78:553-8

Hulse JA, Grant DB, Clayton BE, et al. Population screening for congenital hypothyroidism. *BMJ* 1980;280:675-8

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

Arthur AB, Wilson BD. Urinary infection presenting with jaundice. *BMJ* 1967;i:539-40

Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. *Acta Paediatr* 2000;89:694-7

Seeler RA, Hahn K. Jaundice in urinary tract infection in infancy. *Am J Dis Child* 1969;118:553-8

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, 1994) 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 $\mu\text{mol/l}$ (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 $\mu\text{mol/l}$ ”. The AAP (Anon, 1994) recommends exchange transfusion and intensive phototherapy when serum bilirubin is $\geq 430 \mu\text{mol/l}$ if age 25-48 hours or $\geq 510 \mu\text{mol/l}$ if >48 hours. Standard phototherapy should begin at 257 $\mu\text{mol/l}$ or 308 $\mu\text{mol/l}$ for the same age bands, in the term or near term infant.

Although the AAP document is under review (Anon, 2001), no updated guidance is as yet available.

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 $\mu\text{mol/l}$ (350 mg/l).

The most recent information on this subject (Bhutani, 2004) indicates that TSB concentrations of $>342 \mu\text{mol/l}$ ($>200 \text{mg/l}$) should be a cause for concern and that values $\geq 513 \mu\text{mol/l}$ ($\geq 300 \text{mg/l}$) 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 $>190 \text{mL/kg}$ (Bhutani, 2004).

Anon. Practice parameter: Management of hyperbilirubinemia in the healthy term newborn. *Pediatrics* 1994;94:558-65

Anon. Neonatal jaundice and kernicterus. *Pediatrics* 2001;108:763-5

Bhutani VK, Johnson LH. Urgent clinical need for accurate and precise bilirubin measurements in the United States to prevent kernicterus. *Clin Chem* 2004;50:477-80

Gustafson PA, Boyle DW. Bilirubin index: a new standard for intervention? *Med Hypotheses* 1995;45:409-16

Ives NK. Neonatal jaundice. In: Rennie JM, Robertson NR, eds. *Textbook of neonatology*, 3rd ed. Edinburgh, Churchill Livingstone, 1999. p721

Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. *J Pediatr* 2002;140:396-403

Wennberg RP, Ahlfors CE, Bhutani VK, et al. Toward understanding kernicterus: a challenge to improve the management of jaundiced newborns. *Pediatrics* 2006;117:474-85

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).

Arora NK, Kohli R, Gupta DK, et al. Hepatic technetium-99m-mebrofenin iminodiacetate scans and serum gamma-glutamyl transpeptidase levels interpreted in series to differentiate between extrahepatic biliary atresia and neonatal hepatitis. *Acta Paediatr* 2001;90:975-81

Wright K, Christie DL. Use of gamma-glutamyl transpeptidase in the diagnosis of biliary atresia. *Am J Dis Child* 1960;135:134-6

Yamagiwa I, Iwafuchi M, Obata K, et al. Pre-operative time course changes in liver function tests in biliary atresia: its usefulness in the discrimination of biliary atresia in early infancy. *Acta Paediatr Jpn* 1996;38:506-12

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).

Al-Hathlol K, Al-Madani A, Al-Saif S, et al. Ursodeoxycholic acid therapy for intractable total parenteral nutrition-associated cholestasis in surgical very low birth weight infants. *Singapore Med J* 2006;47:147-51

Rintala RJ, Lindahl H, Pohjavuori M. Total parenteral nutrition-associated cholestasis in surgical neonates may be reversed by intravenous cholecystokinin: a preliminary report. *J Pediatr Surg* 1995;30:827-30

Spagnuolo MI, Iorio R, Vegnente A, et al. Ursodeoxycholic acid for treatment of cholestasis in children on long-term parenteral nutrition: a pilot study. *Gastroenterology* 1996;111:716-9

Teitelbaum DH. Parenteral nutrition-associated cholestasis. *Curr Opin Pediatr* 1997;9:270-5

Teitelbaum DH, Han-Markey T, Schumacher RE. Treatment of parenteral nutrition-associated cholestasis with cholecystokinin-octapeptide. *J Pediatr Surg* 1995;30:1082-5

Evidence Level: IV

What is the threshold for home phototherapy in patients with crigler najjar?

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).

O'Reilly C, Dixon R. Crigler-Najjar syndrome: treatment at home with phototherapy. *Scott Med J* 1988;33:335-6

Shevell MI, Bernard B, Adelson JW, et al. Crigler-Najjar syndrome type I: Treatment by home phototherapy followed by orthotopic hepatic transplantation. *J Pediatr* 1987;110:429-31

Walls M, Wright A, Fowle P, et al. Home phototherapy in the United Kingdom. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F282

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".

Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. *Acta Paediatr* 2000;89:694-7

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