JAUNDICE
Supporting Information

This guideline has been prepared with reference to the following:

Fawaz R, Baumann U, Ekong U et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2017;64:154-68

https://www.naspghan.org/files/documents/pdfs/position-papers/Guideline_for_the_Evaluation_of_Cholestatic.23.pdf

NICE. Jaundice in newborn babies under 28 days. 2016. London. NICE

https://www.nice.org.uk/guidance/qs57

What is the incidence of prolonged neonatal jaundice in term and preterm newborns?
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).
The first large, prospective study of severe hyperbilirubinaemia 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).

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

Manning D, Todd P, Maxwell M, et al. Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland. Arch Dis Child Fetal Neonatal Ed 2007;92:F342-6
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675352/

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).

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?
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

Evidence Level: V

What is the incidence of hereditary spherocytosis presenting with prolonged neonatal jaundice only?
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
http://www.bloodjournal.org/content/95/2/393.long?sso-checked=true

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Evidence Level: V

What percentage of congenital hypothyroidism is missed in the Guthrie test?
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.

Grant DB, Smith I. Survey of neonatal screening for primary hypothyroidism in England, Wales, and Northern Ireland 1982-4. BMJ 1988;296:1355-8
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2545827/

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

Evidence Level: V

What percentage of urinary tract infection in newborns presents with jaundice only?
A study in 102 infants with asymptomatic, unexplained indirect hyperbilirubinaemia in the first two weeks of life (Bilgen, 2006) found UTI in 8 cases (8%). The authors concluded that urine culture should be considered in the bilirubin work-up of infants older than three days of age with an unknown etiology.

Bilgen H, Ozek E, Unver T et al. Urinary tract infection and hyperbilirubinemia. Turk J Pediatr 2006; 48:51–5

Evidence Level: IV

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?
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).
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. Although “free” or unbound bilirubin may provide a more accurate measure, no tests for this have been validated to date. Bhutani et al suggest using a sliding scale, based on infant weight, to indicate when intensive phototherapy should be started, but exchange transfusion is recommended when TSB >190 mL/kg.

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
http://www.clinchem.org/content/50/3/477.long

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

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, 2001) 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).

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

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?

A small study of 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.

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

Evidence Level: IV

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

Evidence Level: IV

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