Management of neonatal jaundice

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Abstract

Jaundice is the most common clinical sign in neonatal medicine, but only rarely is it associated with bilirubin neurotoxicity or the harbinger of significant underlying disease. Cases of kernicterus, which should be a never event, are still occurring. Delays in the diagnosis of pathological causes of prolonged jaundice, such as biliary atresia are still resulting in life long morbidity. These are salutary reminders that healthcare professionals should never take neonatal jaundice for granted. Phototherapy remains the mainstay of treatment of significant unconjugated hyperbilirubinaemia, and its optimal use will usually prevent the need for exchange blood transfusion. In cases of antibody-mediated haemolysis high-dose immunoglobulin is indicated if the serum bilirubin is continuing to rise despite multiple phototherapy. For babies with prolonged jaundice investigation should be directed towards making a timely diagnosis and avoiding secondary complications.

Keywords conjugated hyperbilirubinaemia; exchange blood transfusion; kernicterus; phototherapy; prolonged jaundice; unconjugated hyperbilirubinaemia

Introduction

With relaxation of treatment thresholds for jaundice over the past two decades a 'kinder, gentler approach' to clinical management in healthy full-term newborns has evolved. Earlier postnatal discharge, shortcomings in community surveillance and translation of the more relaxed approach to therapy in the term baby to that in the late preterm or near term infant were all likely factors in a resurgence of kernicterus. There is a requirement to identify which babies are at greatest risk of developing levels of significant jaundice. The 2010 United Kingdom NICE Guideline on Neonatal Jaundice emphasized review within 48 hours of birth of babies with known risk factors, and mandates measurement rather than visual estimation of the bilirubin level in all babies presenting with clinical jaundice.

Premature infants are more prone to bilirubin encephalopathy and should be managed with thresholds adjusted accordingly. The baby with a serum bilirubin level approaching or above the exchange transfusion threshold is a neonatal emergency. The prompt use of multiple phototherapy and timely availability of blood for an urgent exchange transfusion will avoid chronic neurological sequelae in the majority of cases. Symptomatic bilirubin encephalopathy remains an absolute indication for exchange transfusion, irrespective of the bilirubin level. High-dose immunoglobulin is an accepted adjunct to therapy in cases of antibody-mediated haemolysis, but the use of metalloporphyrins to suppress haem catabolism and modify the pattern of neonatal jaundice has yet to enter clinical practice.

Up to one-third of breastfed babies remain clinically jaundiced beyond two weeks of age, and they represent the overwhelming majority presenting for a prolonged jaundice screen. The discovery of an underlying pathology in cases of conjugated jaundice involves a sequence of investigations that may need to be guided by supra-regional paediatric hepatology services. This article will review the current guidelines and make recommendations to enable adherence to best practice.

Prevention

Identifying the newborn at risk of bilirubin encephalopathy

The 2010 NICE Guidance in the UK has emphasized an additional clinical review within 48 hours of birth of babies with the following risk factors for significant hyperbilirubinaemia:

- gestational age under 38 weeks
- a previous sibling with neonatal jaundice requiring phototherapy
- mother's intention to breastfeed exclusively
- visible jaundice in the first 24 hours of life

Clinical jaundice is more difficult to recognize in babies with dark skin tones and can be missed without close examination of the sclerae, gums and blanched skin. These babies fall into a heightened risk category if they are not examined properly. In cases of doubt a low threshold should be adopted for checking the transcutaneous or serum bilirubin.

The bilirubin/albumin ratio

The bilirubin/albumin ratio reflects the free unbound bilirubin level, and correlates with abnormal auditory brainstem responses in jaundiced infants. An exchange transfusion threshold has been proposed at a bilirubin/albumin ratio of 0.8 in the healthy term newborn, 0.72 in a sick term infant and as low as 0.4 for the sick premature infant of less than 1250 g. This ratio has not gained widespread clinical acceptance, but may help to inform the decision as to whether or not to perform an exchange transfusion in borderline cases. (Note that when calculating the bilirubin/albumin ratio, values for serum albumin concentration in g/litre need to be converted to SI Units of μmol/litre using the factor 15.15).

Assessing the level of serum bilirubin

Visual inspection

Clinical jaundice becomes apparent visually at serum bilirubin levels of 80–90 μmol/litres. It is more difficult to detect in preterm infants and can be missed without close inspection in babies with darker skin tones. Visual assessment can be unreliable under artificial light, and once phototherapy has started. Healthcare professionals and parents can be taught to recognize clinical jaundice, but studies show that they are unable to assess its severity. Accuracy is not enhanced by the use of icterometers or assessment of the cephalocaudal progression of dermal jaundice. For these reasons, whenever a baby is visibly jaundiced, the bilirubin level must be measured to inform appropriate clinical management.

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Transcutaneous bilirubinometry

The use of non-invasive transcutaneous bilirubinometry is established in the USA and has increased in UK practice following NICE guidance. Transcutaneous bilirubinometers measure bilirubin in the skin of the forehead or overlying the sternum. They reduce the requirement for blood sampling, but accuracy decays at levels more than 250 μmol/litre. Validation of the use of transcutaneous bilirubinometry in preterm babies is limited. The current UK NICE guidance recommends that a serum sample should be obtained at transcutaneous bilirubinometer readings more than 250 μmol/litre.

Phototherapy removes bilirubin from the skin, which precludes the use of transcutaneous bilirubinometry to monitor the progress of treatment 'under the lights', but testing can resume accurately some 24 hours after 'coming out of lights'. Researchers at the University of Washington are evaluating an 'App' known as the 'BiliCam', which it is hoped will enable primary healthcare workers and parents to screen a baby's jaundice level using a smartphone.

Invasive blood sampling

A bilirubinometer employing direct spectrometry is used in many neonatal units to provide point of care testing of total serum bilirubin. Such instruments reflect the sum value of all species of bilirubin, conjugated and unconjugated, including photoisomers. Whole blood bilirubin assay is a facility on some blood gas analysers. Regular instrument quality control and calibration are necessary. Measurement should be accurate to within ±20–30 μmol/litre, and the limitations of any analyser should be known when measuring very high values.

Diagnostic approaches

Defining the severity of jaundice

The terms 'physiological' and 'pathological jaundice' lead to confusion and are best avoided; as are adjectives, such as extreme or hazardous, used by some to grade the severity of jaundice. Defined more simply 'hyperbilirubinaemia' denotes a raised level of bilirubin in the blood, 'clinical jaundice' describes visually detectable jaundice, and 'significant hyperbilirubinaemia' distinguishes a level of jaundice requiring treatment. Regardless of the level, jaundice in the first 24 hours of life and rates of rise in serum bilirubin consistent with haemolysis add urgency to investigation and treatment.

Jaundice with a pathological cause

Clinical features that suggest a pathological cause of jaundice and prompt further investigation are as follows:

- jaundice appearing in the first 24 hours of life
- aundice in a sick neonate
- rapidly rising serum bilirubin
- prolonged jaundice more than14 days in term infants; more than 21 days in preterm infants
- conjugated serum bilirubin more than 25 μmol/litre
- pale, chalky stools and dark urine

The more common causes of unconjugated and conjugated hyperbilirubinaemia arising from an underlying pathology are listed in Boxes 1 and 2. Unless there are diagnostic pointers to the more rarely encountered causes of neonatal jaundice, stepwise investigation should aim to identify the more common ones first (Box 3).

Early-onset jaundice

Jaundice within the first 24 hours of life is commonly the result of significant haemolysis. This is a neonatal emergency and a serum bilirubin measurement should be obtained within 2 hours. An urgent medical review should be conducted to establish the

Causes of unconjugated jaundice in the newborn

Haemolysis

- Isoimmunization
  - Rhesus
  - ABO
  - Minor blood groups
- Other
  - Spherocytosis and other red cell abnormalities
  - G-6PD deficiency
  - Pyruvate kinase deficiency and other enzyme defects
  - Sepsis*
  - Disseminated intravascular coagulation

Polycythaemia

- Small for dates infant
- Twin–twin transfusion syndrome
- Delayed cord clamping
- Maternofetal transfusion
- Infant of diabetic mother

Extravasated blood

- Bruising, e.g. cephalhaematoma
- Pulmonary haemorrhage
- Cerebral haemorrhage
- Intra-abdominal haemorrhage

Increased enterohepatic circulation

- Pyloric stenosis
- Bowel obstruction
- Swallowed blood

Endocrine/metabolic

- Hypothyroidism*
- Hypopituitarism*
- Hypoadrenalism*
- Glucuronosyl transferase deficiency (Crigler–Najjar Syndrome)
- Galactosaemia*
- Tyrosinaemia*
- Hypermethioninaemia*

*Conjugated jaundice often coexists

Box 1