Neonatal hyperbilirubinaemia: a global perspective

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Hyperbilirubinaemia, presenting as jaundice, is a ubiquitous and frequently benign condition in newborn babies but is a leading cause of hospitalisation in the first week of life. In some infants jaundice can become severe, progressing to acute bilirubin encephalopathy and kernicterus with a substantial risk of neonatal mortality and long-term neurodevelopmental impairments. Severe hyperbilirubinaemia and its sequelae continue to occur in industrialised countries with functioning medical systems and a disproportionately high burden also persists in low-income and middle-income countries due primarily to delays in delivering effective treatments that are routinely available in high-income countries. In this Review we summarise up-to-date evidence on the epidemiology of neonatal jaundice including its global burden based on estimates of its prevalence, and both fatal and non-fatal health outcomes. We also discuss the management of severe hyperbilirubinaemia including the prevention of kernicterus, and highlight future directions for research.

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Introduction

Unconjugated (indirect) hyperbilirubinaemia is a ubiquitous and frequently benign condition in newborn babies that manifests in the first days of life as jaundice (icterus neonatorum)—a yellowish discolouration of the skin, sclera, and mucous membranes.[1,2] The condition is attributable to a metabolic imbalance favouring bilirubin production over hepatic-enteric bilirubin clearance.[3,4] In some babies, excessive serum bilirubin concentrations can place them at risk of acute bilirubin encephalopathy and kernicterus (chronic bilirubin encephalopathy) if not appropriately monitored and treated.[5,6] Paradoxically, bilirubin is a valuable and potent antioxidant; in vitro it can be active even at nanomolar concentrations through a cycle of oxidation–reduction between serum bilirubin and biliverdin.[7] Serum bilirubin has also been established as the most potent superoxide with peroxyl radical scavenger activity.[8] However, uncontrolled or rapidly rising hyperbilirubinaemia can reach neurotoxic concentrations with potentially lethal consequences.[5,6] Thus, the welfare of jaundiced newborn babies is dependent on striking an appropriate balance between the protective effects of serum bilirubin and the risk of bilirubin neurotoxicity. The conjugated (direct) form of hyperbilirubinaemia (cholestatic jaundice) is usually pathological and indicative of hepatic or biliary disease.[9] The condition is rarely associated with bilirubin neurotoxicity and so will not be explored further in this Review.

The UN's Sustainable Development Goals (SDGs), which encompass a robust agenda for the survival, thriving, and long-term wellbeing of all newborn babies,[10] have spurred a growing global interest in neonatal jaundice as an important health condition.[11,12] This Review seeks to summarise evidence on the epidemiology, diagnosis, and management of unconjugated hyperbilirubinaemia, including the prevention of kernicterus. We also highlight the future direction of the efforts needed to reduce disease burden, particularly in low-income and middle-income countries (LMICs).

Epidemiology

Incidence

For the identification of jaundice by visual inspection to be possible, total serum bilirubin (TSB) concentrations need to be greater than 5–6 mg/dL (85–100 µmol/L), but even experienced neonatologists might misidentify infants with concentrations much higher than this threshold.[13] Jaundice affects at least 60% of full-term and 80% of preterm neonates,[14,15] suggesting that about 84–112 million of the 140 million babies born yearly worldwide[16] will develop this condition in the first 2 weeks of life. About one in ten newborn babies are likely to develop clinically significant jaundice or hyperbilirubinaemia, requiring close monitoring and treatment. The precise TSB threshold of clinically significant jaundice is variable and influenced by postnatal age, race, comorbid prematurity, sepsis, and

Key messages

- Neonatal hyperbilirubinaemia is attributable to a metabolic imbalance favouring bilirubin production over hepatic-enteric bilirubin clearance. The condition affects 60% to 80% of newborn babies, and is a leading cause of hospitalisation in the first week of life.
- Occasionally, the serum total bilirubin could rise to dangerous levels with the potential for mortality or chronic bilirubin neurotoxicity that manifests as choreoathetotic cerebral palsy (kernicterus) or auditory dyssynchrony with or without hearing deficits.
- Important causes of bilirubin neurotoxicity worldwide are haemolytic disorders and idiopathic conditions, but the relative preponderance of G6PD-deficiency, ABO incompatibility, rhesus disease, and idiopathic and other haemolytic conditions varies across regions of the world.
- Neonatal hyperbilirubinaemia accounted for 1309 deaths per 100 000 livebirths in 2016 and ranked seventh globally among all causes of neonatal deaths in the first week of life. The disease burden is greatest in sub-Saharan Africa and south Asia.
- Delays in delivering known and effective treatments, routinely available in high-income countries, continue to account for the disproportionately high burden of severe neonatal hyperbilirubinaemia in low-income and middle-income countries.
- Initiatives to facilitate early maternal recognition, timely referral and follow-up, and the development of low-cost point-of-care tools should be regarded as global health imperatives to curtail the incidence of bilirubin-induced neurologic dysfunction and mortality, especially in resource-limited settings.

Panel 1: **Categories of clinically significant hyperbilirubinaemia**[18,19]

Significant hyperbilirubinaemia

- Unconjugated bilirubin concentration requiring treatment with phototherapy that varies with postnatal age and cause of the condition (typically total serum bilirubin [TSB] ≥12 mg/dL or 205 μmol/L)

Severe hyperbilirubinaemia

- Bilirubin concentrations at or near exchange transfusion threshold based on postnatal age and cause of the condition (typically TSB ≥20 mg/dL or 342 μmol/L) or any elevated TSB associated with the early signs of mild acute bilirubin encephalopathy

Extreme hyperbilirubinaemia

- Bilirubin concentrations at exchange transfusion threshold (typically TSB ≥25 mg/dL or 428 μmol/L) or any elevated TSB associated with signs of mild to moderate acute bilirubin encephalopathy

Hazardous or critical hyperbilirubinaemia

- Bilirubin concentrations at exchange transfusion threshold (typically TSB ≥30 mg/dL or 513 μmol/L) or any elevated TSB associated with signs of moderate to severe acute bilirubin encephalopathy

Bilirubin encephalopathy

- Abnormal neurological signs caused by bilirubin toxicity to the basal ganglia and various brainstem nuclei
- Progressing from an acute phase to the chronic form as kernicterus

Acute bilirubin encephalopathy

- Acute manifestations of bilirubin toxicity seen within 14 days of birth
- Signs of acute bilirubin encephalopathy are typically classified as mild (poor feeding, lethargy, and tone abnormalities), moderate or intermediate (high-pitched cry, irritability, and increasing hypertonia), or severe or advanced (deep stupor, fever, apnoea, inability to feed, retrocollis, opisthotonos, and obtundation)

Chronic bilirubin encephalopathy (or kernicterus)

- Permanent or chronic neurological damage, including choreoathetoid cerebral palsy, enamel dysplasia, paralysis of upward gaze, and hearing impairments, including auditory neuropathy spectrum disorders

haemolytic disorders.[14,17] However, the degree of jaundice in late-preterm and term infants can be classified roughly by TSB concentrations as significant, severe, extreme, or hazardous (panel 1).[18,19] In a systematic review,[20] the overall incidence of severe jaundice globally was reported as 99 cases per 100 000 livebirths (95% CI 28–356). The highest incidence of 6678 cases per 100 000 livebirths (95% CI 6033–7385) was reported in Africa and the lowest of 37 cases per 100 000 livebirths (95% CI 17–80) in Europe. A major observation was the paucity of population-based data, especially from LMICs. Hospital-based data have shown that severe jaundice is a leading cause of hospitalisation in the first week of life and accounts for up to 35% of hospital readmissions in the first month of life.[21–23] The incidence of kernicterus ranges from about 0·2 to 2·7 cases per 100 000 livebirths.[24,25]

Global disease burden

To address the dearth of population-based data and the limitations of systematic reviews in showing that neonatal jaundice is an important cause of neonatal mortality and morbidity, mathematical modelling tools can be used to estimate fatal and non-fatal health outcomes of diseases for policy decisions.[26,27] Bhutani and colleagues[28] were perhaps the first to model the global burden of severe jaundice. They estimated that about 18% (or 24 million) of the 134 million liveborn babies in 2010 developed clinically significant jaundice and 481 000 late-preterm and term neonates developed extreme hyperbilirubinaemia (TSB >25 mg/dL), with 114 000 deaths and more than 63 000 survivors who had moderate or severe long-term neurological impairments. Data from the Global Burden of Disease study[12,29] in 2016 showed that neonatal jaundice accounted for 1309·3 deaths per 100 000 livebirths (95% uncertainty interval [UI] 1116·8–1551·3) and ranked seventh globally among all causes of neonatal deaths in the early-neonatal period (0–6 days). The burden of jaundice was highest in south Asia (seventh leading cause of neonatal mortality) and sub-Saharan Africa (eighth leading cause of neonatal mortality). Additionally, jaundice was the 13th leading cause of neonatal mortality in North America and ninth in western Europe. In the late-neonatal period (7–27 days) jaundice accounted for 187·1 deaths per 100 000 (95% UI 156·7–225·6) and ranked ninth globally. The condition ranked seventh in south Asia and 12th in sub-Saharan Africa, compared with 15th in western Europe and 21st in North America; it was the 16th leading cause of mortality in children younger than 5 years among over 100 causes of child mortality globally.

Because survivors of severe jaundice are frequently at substantial risk of life-long neurodevelopmental disabilities,[5,30,31] examining the burden of this condition by use of disability-adjusted life-years (DALYs) can be useful. DALYs are the sum of the years of life lost as a result of premature mortality and the years lived with disability.[32] Conceptually, this metric combines mortality and morbidity outcomes for any condition. 1 DALY represents 1 year of healthy life lost because of the condition at the population level. Globally, neonatal jaundice accounted for 113 401 DALYs (95% UI 96 728–134 352) in 2016 and ranked seventh as the leading cause of DALYs in the early neonatal period. However, in the late neonatal period, the condition dropped to ninth with 16 214 DALYs (95% UI 13 581–19 543) and was the 17th leading cause of DALYs among children under 5 years globally.[12]

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Barring the limitations associated with statistical modelling of disease burden in general,[27–29,32] the available data suggest that neonatal jaundice is an important cause of neonatal mortality and morbidity even though it is less prevalent than the more fatal events such as preterm birth and intrapartum complications, including birth asphyxia, infections, and congenital anomalies.[11]

Risk factors

A summary of the demographic, biological, laboratory, and clinical risk factors for severe jaundice, including acute bilirubin encephalopathy and kernicterus, is shown in panel 2. The knowledge of these risk factors and their epidemiological profile in different racial populations is helpful for the early detection and effective management of infants with, or at risk of, severe jaundice. The most prevalent of these factors are probably prematurity, haemolytic disease, perinatal infection, and exclusive breastfeeding.[2,14,33,34]

Preterm infants (<37 weeks gestational age) have a higher risk of severe jaundice with or without bilirubin-induced neurotoxicity than do full-term infants (≥37 weeks), mainly because of increased bilirubin production, hepatic immaturity in the uptake and conjugation of bilirubin, and increased enterohepatic circulation of bilirubin due to intestinal immaturity and delayed enteral feeding.[35,36] Although this risk decreases with increasing gestational age, even late-preterm (34–36 weeks) and early-term (38 weeks) newborn babies have a higher risk of severe jaundice and neurotoxicity than do full-term newborn babies.[37] For example, of the 125 newborn babies reported in the voluntary US Kernicterus Registry, 30 (24%) had a gestational age of 35 or 36 weeks.[38] Of the five babies who died within the first postnatal week, four had a gestational age of less than 37 weeks.

Haemolysis can present as a pathological shortening of the lifespan of red blood cells due to a wide range of genetic and non-genetic disorders such as isoimmune haemolytic disease (blood group incompatibility), glucose-6-phosphate dehydrogenase (G6PD) deficiency, and hereditary spherocytosis.[39] Exposure to oxidant substances such as sulfonamide products, methylene blue, naphthalene, or fava beans eaten by nursing mothers, triggers or exacerbates haemolysis in G6PD deficient newborn babies. Rhesus disease has been virtually eliminated in high-income countries but is still an important cause of haemolytic hyperbilirubinaemia.[28,34,40] G6PD deficiency, which was once thought to be limited to the geographical regions to which it is indigenous, can now be found worldwide because of migration patterns and ease of travel.[41]

Sepsis predisposes individuals to severe jaundice because of a combination of excess destruction of red blood cells and hepatocellular dysfunction, including intrahepatic biliary stasis.[42] The contribution of infections to severe jaundice or kernicterus has been reported to vary from 14% in Africa to 31% in Asia, compared with 2% in Europe and North America.[14] Pooled data from a later systematic review[34] showed that infants diagnosed with sepsis in LMICs were independently at increased risk of severe hyperbilirubinaemia compared

Panel 2: **Risk factors for severe neonatal hyperbilirubinaemia**

Genetic factors
- Gilbert's syndrome
- Crigler–Najjar syndrome
- Alagille's syndrome
- β thalassaemia
- Glucose-6-phosphate dehydrogenase deficiency
- Bilirubin glucuronosyltransferase polymorphism
- Pyruvate kinase deficiency
- Erythrocyte structural defects (including hereditary spherocytosis and elliptocytosis)
- Galactosaemia

Maternal factors
- Race or ethnic group (Asian or black race)
- Family history of severe jaundice
- Primiparity
- Teenage pregnancy
- Diabetes
- Rhesus incompatibility
- ABO incompatibility
- Use of drugs during labour (including oxytocin, promethazine, and bupivacaine)
- Exclusive breastfeeding

Perinatal factors
- Mode of delivery (breech *vs* vertex, instrumentation)
- Birth trauma (cephalohematoma or substantial bruising, extravasation)
- Birth asphyxia
- Delayed cord clamping
- Congenital infections (including cytomegalovirus and syphilis)
- Sepsis

Neonatal factors
- Male sex
- Prematurity or low birthweight and small-for-gestational age
- Hypothyroidism
- Polycythaemia
- Hypoglycaemia
- Low intake of breast milk, dehydration, or weight loss
- Breast milk jaundice

Other risk factors and markers
- Previous sibling received phototherapy or exchange transfusion
- Pre-discharge total serum bilirubin or transcutaneous bilirubin concentration in the high-risk zone
- Use of haemolytic agents (eg, naphthalene or menthol-based products) in glucose-6-phosphate dehydrogenase deficient population groups
- Folate deficiency
- Aflatoxins
- Hypothermia
- Birth outside of a health-care facility

Adapted from Dennery et al,[2] National Institute for Health and Care Excellence guidelines,[14] American Academy of Pediatrics guidelines,[33] and Olusanya et al.[34]

with infants in high-income countries (odds ratio [OR] 9·15, 95% CI 2·78–30·1, p<0·0001).

Early initiation of breastfeeding within the first hour of life and exclusive breastfeeding in the first 6 months of life are widely promoted for newborn babies in both developed and developing countries through the Baby-friendly Hospital Initiative.[43,44] However, not all breastfed infants will receive optimal milk intake during the first few days of life. As a result, as many as 10–18% of exclusively breastfed newborn babies in the USA lose more than 10% of birthweight.[44] Starvation or suboptimal caloric intake in breastfed infants beyond age 5 days could result in increases in TSB concentrations due to increased intestinal re-absorption of unconjugated bilirubin.[44] Breastfeeding jaundice should be distinguished from breastmilk jaundice, which is commonly associated with prolonged unconjugated bilirubin, with typical onset after the fifth day of life and persisting beyond 2 weeks.[44]

Additionally, delayed cord clamping for 30–60 s in term infants is widely recommended in many countries and is supported by WHO because it increases haemoglobin levels at birth and improves iron stores in the first few months of life, besides other benefits.[45,46] However, a delay of 1 min before cord clamping could raise the newborn baby's haemoglobin concentration substantially and precipitate the need for phototherapy.[46] Therefore, this practice should be carefully monitored.

Long-term sequelae

Long-term neurodevelopmental disabilities frequently associated with severe jaundice with or without a diagnosis of bilirubin encephalopathy include choreoathetoid cerebral palsy,[47–49] auditory spectrum disorders,[37,50–53] and general developmental delays.[30,54] A growing number of studies are exploring the risk of bilirubin-induced neurotoxicity in infants with jaundice on the basis of unbound bilirubin rather than serum or plasma bilirubin.[37,53] Few studies have found an association between severe jaundice and epilepsy,[30,55] although the association with autism[56–59] and childhood asthma[60–62] remains a subject of ongoing investigation and debate. In a rare longitudinal study[63] in Finland, the long-term effect of severe hyperbilirubinaemia (TSB ≥20 mg/dL or 342 µmol/L) on educational, occupational, and social functioning (n=128 *vs* 82 controls) over a 30-year period was investigated; 45% of infants who had experienced jaundice had cognitive abnormalities in childhood and into adulthood. This finding was reflected in academic achievement (p<0·0001) and the completion of both secondary (p<0·0001) and tertiary (p<0·004) education. Childhood symptoms of hyperactivity or impulsivity (p<0·0001) and inattention (p<0·02) were more common in the group that experienced jaundice than the control group.

The available evidence underscores the need for a long-term perspective for survivors of severe jaundice, especially in LMICs, where health, educational, social, and vocational support services are generally scarce. Systematic interventions could address the delays seen in seeking, accessing, and receiving timely and appropriate care in many LMICs.[12,31] In high-income countries, such delays, as well as system failures in health-care delivery, are not uncommon post-discharge in infants born in hospitals, at home, or in small birthing units.[38]

Management of neonatal hyperbilirubinaemia

The pathophysiology of bilirubin metabolism is outside the scope of this Review but is well described in the literature.[3,4,64–68] The primary goal for the management of neonatal hyperbilirubinaemia is to avoid bilirubin-induced mortality and neurotoxicity in otherwise healthy newborn babies by preventing serum bilirubin from reaching potentially neurotoxic concentrations. A summary of consensus-based clinical guidelines for the management of severe jaundice in late-preterm and term infants in high-income countries and LMICs is available in the literature;[19,69] the most widely cited is the 2004 statement of the American Academy of Pediatrics (AAP),[33] which has been adopted with modifications in many national guidelines. Additional considerations have also been recommended for preterm infants who have a higher risk of bilirubin-induced neurotoxicity at lower concentrations of TSB (low bilirubin kernicterus) than late-preterm or term infants.[14,70,71] An overview of the key issues addressed in several guidelines, especially for high-burden LMICs, is presented in panel 3.

Primary prevention

Jaundice is a naturally occurring condition that cannot and probably should not be prevented in newborn babies. In the subset of infants at risk of severe jaundice it is important to ensure, as far as practicable, that this risk is promptly recognised and controlled. Education of mothers and health-care practitioners on the difficulty of differentiating jaundice that is innocuous from jaundice that is dangerous to the baby is required. An awareness of the potential risks of severe jaundice with concomitant exposure to home-based haemolytic triggers, such as menthol and naphthalene substances, in populations with a high frequency of G6PD deficiency is also essential.[72] Because bilirubin concentrations in infants with physiological jaundice peak between the third and fifth day of life when most affected babies would have been discharged from hospital, mothers are usually the first to observe the onset of severe jaundice. Assessing the risk of severe jaundice before discharge for infants born in hospitals or other birthing units is an important aspect of primary prevention.[33] Risk factors include jaundice in the first 24 h of life, a history of neonatal jaundice in older siblings, a family history of haemolytic disease, evidence of haematomas or other sequestered blood, birth more than 2–3 weeks before term, and exaggerated postnatal weight

Panel 3: Management of neonatal hyperbilirubinaemia

Primary prevention

- Education of existing and expectant mothers, families, and health-care providers on:
  - The transient nature of neonatal jaundice and the likelihood that it could become very pronounced and potentially harmful in a few babies.
  - The avoidance of haemolytic substances including camphor or naphthalene balls, menthol-containing powder, creams, balms, and eucalyptus oil.
  - The benefits of early detection accompanied by timely and appropriate treatment in health facilities adequately equipped for the care of newborn babies.
  - Discouraging traditional therapies and indiscriminate use of self-prescribed medications (eg, ampicillin-cloxacillin).
  - Recognition of acute bilirubin encephalopathy and bilirubin-induced neurologic dysfunction.
  - The value of a hygienic environment during birth to prevent or minimise the risk of infection (sepsis).
- Referral to secondary or tertiary centres of all preterm babies (<35 weeks gestation) and surveillance for full-term infants with history of medically treated jaundice in a sibling presenting at primary health centres.
- Promotion and support for successful breastfeeding.
- Screening of expectant mothers for the risk of blood group incompatibilities by use of routine ABO and rhesus testing with counselling on the importance of rhesus immunoglobulin and ensuring availability when indicated.
- Judicious use of oxytocin during labour.
- Identification of babies with extensive bruises, cephalohaematomas, and fractures, and babies at risk for concealed haematomas (eg, babies that had difficult deliveries).
- Request blood tests to rule out glucose-6-phosphate dehydrogenase deficiency in high-risk populations.
- Early phototherapy for infants with haemolytic diseases.

Early detection, diagnosis, and monitoring

- Routine examination of all newborn babies within 24 h of birth and the next 48 h for possible jaundice.
- Monitoring of infants who had delayed cord clamping at birth.
- If jaundice is suspected, examine the infant naked in a well lit room or preferably in natural daylight near a window guided by Kramer's chart; recognise that estimation of the degree of hyperbilirubinaemia on the basis of visual signs of jaundice can lead to errors, particularly in darkly pigmented infants; blanching of the gum could be more reliable in dark-skinned babies.
- If jaundice is visible, measure the total serum bilirubin (TSB) or transcutaneous bilirubin concentration. Transcutaneous bilirubin values above 12 mg/dL (205 µmol/L) should be cross-checked if possible with TSB measurement.
- Establish if the infant has early signs of acute bilirubin encephalopathy or qualifies as high risk, including possible haemolytic diseases, hypothermia, hypoglycaemia, or sepsis.
- Refer to actionable concentrations for measured TSB or transcutaneous bilirubin in a relevant clinical guideline for the population.
- Ensure follow up of infants discharged before 48 h after delivery, especially babies with established risk factors within 1–2 days of discharge (take advantage of the earliest routine immunisation visit and any other times infants younger than 2 weeks are seen).

Treatment

- Refer to recommended age-specific actionable concentrations of TSB or transcutaneous bilirubin (in the absence of TSB) for the population.
- When indicated, particularly in the presence of isoimmune haemolytic diseases, ensure early treatment of newborn babies with intensive phototherapy to minimise the need for exchange transfusion.
- Ensure that the irradiance (light intensity) of phototherapy units are periodically monitored and the recommended specifications are strictly followed.
- Be familiar with simple and inexpensive adjustments that can substantially improve the effectiveness of phototherapy devices.
- Maximise irradiance by placing the units as close as possible to the infants without overheating (usually 10–20 cm above the baby by use of cool lights [unless specified otherwise by the manufacturer], with white reflecting materials on all sides of cots, exposing as much of the baby as possible (thereby maximising spectral power [irradiance multiplied by the size of irradiated area]); change fluorescent tubes according to manufacturer's recommendations (if available) or periodically (every 8–12 weeks) if unable to measure irradiance levels; when blue tubes are not available, use ordinary daylight fluorescent tubes.
- Ensure that the infant's eyes are covered but keep the cover small to maximise skin surface available for phototherapy.
- Ensure that male genitals are covered with small nappies unless the infant's concentrations of bilirubin are nearing those eligible for exchange transfusion.
- Ensure that babies are placed in cots not incubators when under phototherapy unless they are hypothermic.
- Ensure that blood samples for relevant investigations are collected and refrigerated before initiating exchange transfusion and any blood samples are protected from light, including the phototherapy light. In infants admitted with extreme jaundice or signs of acute bilirubin encephalopathy, the start of phototherapy should not be delayed while waiting for lab specimens to be drawn.

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(Panel 3 continued from previous page)

- Ensure that an infant with clinical signs of moderate–severe acute bilirubin encephalopathy receives exchange transfusion promptly. Place the infant under the best phototherapy device available while preparing for the exchange transfusion. While waiting for blood to be prepared for an exchange, intravenous immune globulin (0·5–1 G/kg) could help to stop the rise in TSB, especially in ABO hetero-specific newborn babies. Intravenous immune globulin might need to be repeated after the exchange transfusion.
- Ensure that the infant remains adequately hydrated and is breastfeeding or feeding well.
- Avoid drugs that compete for albumin binding such as sulfonamides, ceftriaxone, and acetylsalicylic acid.
- Ascertain the risk of bilirubin rebound after phototherapy or exchange transfusion before hospital discharge.

Follow up assessment

- Assess non-jaundiced infants on days 3 and 5 after birth.
- Assess jaundiced infants regularly in the first 7–10 days of life or until jaundice is clearly resolved, even after receiving treatment.
- Educate parents on the need for a follow-up neurodevelopmental assessment of all infants treated for severe hyperbilirubinaemia with intensive phototherapy or exchange transfusion, or with a history of such treatment at age 3–6 months.
- Ensure that, at the minimum, developmental assessment includes auditory brainstem response audiometry, language processing and development, and clinical assessment of abnormalities of tone, posture, and movements for infants with signs of acute bilirubin encephalopathy or bilirubin-induced neurologic dysfunction (who had exchange transfusion) and infants with a bilirubin level of ≥20 mg/dL.
- Disseminate information on the local providers of age-appropriate developmental assessment of infants and young children to the affected parents on discharge or during any subsequent clinical consultations.

Adapted from National Institute of Health and Care Excellence 2010 guidelines,[14] Olusanya et al,[19] and American Academy of Pediatrics guidelines.[33]

loss or inadequate weight recovery. Empowering mothers to seek timely and appropriate referral is a crucial first step in the prevention of potentially hazardous jaundice.[31,73] Among mothers who give birth outside hospitals and who do not have the services of community health visitors after birth, this step is even more important. Simple-to-use and cost-effective tools such as customised icterometers and smart phone apps to assist mothers with the detection of jaundice in their newborn babies in home-settings well before the early symptoms of acute bilirubin encephalopathy are currently being developed in LMICs.[74–76] Routine screening and monitoring for G6PD deficiency and rhesus disease sensitisation should be emphasised, especially in LMICs where rhesus disease still occurs.

Early detection and diagnosis

Prompt identification of infants with jaundice in and out of hospital should be incorporated into the care of newborn babies, especially because jaundice could easily be overlooked in settings with an overwhelming burden of more fatal neonatal illnesses. The cost-effectiveness of universal bilirubin screening remains a subject of debate because of the quality of the available evidence. For example, the AAP guidelines recommend universal pre-discharge bilirubin screening by measuring TSB or transcutaneous bilirubin concentrations to assess the risk of subsequent severe hyperbilirubinaemia.[33] However, the US Preventive Services Task Force has stated that the available evidence was insufficient to make such a recommendation.[77] This statement was corroborated by another evidence review in the UK.[14] Nevertheless, universal pre-discharge bilirubin screening is currently implemented in several settings in high-income countries. Evidence suggests that although this programme could be costly because of the high number of infants tested and treated, it was likely to be a good predictor of infants requiring treatment if the screening used postnatal age-adjusted TSB or transcutaneous bilirubin combined with clinical risk factors, especially gestational age.[15,78] The prospects in LMICs remain uncharted as the detection of infants with jaundice largely relies on visual assessment by clinicians in many settings.

Although TSB is a poor predictor of neurotoxicity compared with unbound bilirubin,[79] it is still the diagnostic tool of choice and the measure for instituting and monitoring treatment efficacy because tools for evaluating unbound bilirubin are not yet routinely available.[80,81] The use of the ratio of bilirubin to albumin as a surrogate for plasma free bilirubin does not improve prediction of acute bilirubin encephalopathy or residual encephalopathy over TSB alone.[82,83] The gold standard method for measuring TSB in serum samples is high performance liquid chromatography because it is not subject to interference from haemoglobin or lipaemia.[84] However, this method is labour-intensive and not practical for routine use; in most clinical settings TSB is measured by the Diazo (Jendrassik-Gróf-based) reaction method or direct spectrophotometry.[84,85]

The use of transcutaneous bilirubin as a proxy or pre-screening tool for TSB to reduce the amount of unnecessary and painful blood draws in newborn babies is not uncommon.[14,25,33] Transcutaneous bilirubin devices are non-invasive and convert the colour of the baby's skin into a bilirubin value by use of specific algorithms. The devices

are simple-to-use and less costly than TSB bilirubinometers and the measurements are highly associated with TSB regardless of gestational age.[86] However, in individual patients, discrepancies between transcutaneous bilirubin and TSB measurements across racial populations could have clinically significant implications for decision making.[87,88] For example, approximately one in three black African neonates with hyperbilirubinaemia could be prone to transcutaneous bilirubin overestimation (≥3 mg/dL), resulting in unnecessary treatments when confirmatory TSB is not readily available.[88] The reliability of transcutaneous bilirubin decreases rapidly at increased bilirubin concentrations (typically >12 mg/dL or 205 µmol/L), and most commercially available transcutaneous bilirubin devices cannot measure bilirubin concentrations above approximately 20 mg/dL (340 µmol/L).[88,89] Transcutaneous bilirubin is also not a reliable alternative for an unbound bilirubin assay,[90] and its use for evaluating the need for phototherapy or monitoring treatment efficacy remains controversial.[91,92] Low-cost and minimally invasive point-of-care tools for plasma and serum bilirubin measurements,[89,93] a smartphone application that uses digital images to estimate bilirubin concentrations,[94] and a rapid G6PD screening technology that uses digital microfluidic fluorescence[95] are under development and hold promise for LMICs.

Treatment

Phototherapy and exchange transfusion are the mainstay treatments for severe hyperbilirubinaemia. Considerations for optimising these therapies are shown in panel 3. Phototherapy is always the first line of treatment,[14,33] regardless of side-effects including interference with mother–child bonding, imbalance of thermal environment, and water loss.[96] Phototherapy is required even when exchange transfusion is indicated and is used while awaiting preparation of the blood for transfusion. The goal of the intervention is to reduce the concentration of circulating bilirubin or keep it from increasing. The therapy works by use of photons that interact with the predominant bilirubin IXα (Z,Z) isomer and change its structure, converting it to isomers that have increased polarity (photoisomers) and that can be excreted in urine and bile without the need for conjugation. Therefore, the bilirubin products produced after phototherapy bypass the inadequate conjugation mechanisms in newborn infants thereby accelerating elimination.[96]

An effective phototherapy device should produce specific blue-light wavelengths (peak emission: 430–470 nm), preferably in a narrow bandwidth, applied to as much of an infant's skin surface area as possible.[97] Conventional phototherapy should have an irradiance of at least 8–10 µW/cm²/nm, and intensive phototherapy should have an irradiance of 30 µW/cm² per nm or greater (either from single or multiple phototherapy units).[33] Various phototherapy devices are available that use different light sources including fluorescent tubes, halogen lamps, and light emitting diodes (LEDs). In areas where special blue phototherapy lamps are not available or affordable, conventional white fluorescent lamps or green light can also achieve a good therapeutic outcome.[14] LED devices are more power efficient and portable, weigh less, have a longer life span, and produce less heat than fluorescent bulbs, making them more suitable for intensive phototherapy.[97,98] Regular monitoring of the irradiance from phototherapy devices is necessary to ensure that it remains within the therapeutic range. In remote tropical locations, where access to conventional treatment is not assured, heliotherapy (eg, with specially filtered canopies) might be considered in order to minimise the risk of kernicterus.[99] Evidence to support the use of clofibrate in combination with phototherapy[100] and fluid supplementation for infants who require phototherapy are inconclusive.[101]

Intravenous immune globulin has been shown to substantially reduce the need for exchange transfusion in infants with rhesus or ABO incompatibility in some settings.[25,102] Notably, Huizing and colleagues[102] used intravenous immune globulin effectively as a rescue therapy for infants who had crossed, or were about to cross, the intervention threshold for exchange transfusion. Because most infants with blood group isoimmunisation can be managed well with phototherapy only, intravenous immune globulin treatment for all infants with blood group isoimmunisation would be wastefully expensive and could even lead to a misconception about the utility of intravenous immune globulin among health-care professionals.[25]

Immediate exchange transfusion is warranted when phototherapy has failed to effectively reduce the rate of bilirubin rise and the TSB or transcutaneous bilirubin measurement is near or exceeding exchange concentrations, or if the infant has any signs of moderate to advanced acute bilirubin encephalopathy.[14,19,33] This invasive procedure reduces the TSB concentration by removing circulating bilirubin. Secondary advantages include removal of antibody coated red blood cells in haemolytic disease (eg, in rhesus and ABO sensitisation) or red blood cells that have become vulnerable because of G6PD and other red blood cell enzyme deficiencies.[103] Adverse events associated with exchange transfusion, which can be fatal, include sepsis, electrolyte imbalance, air embolism, portal vein thrombosis, cardiac overload, thrombophlebitis, thrombocytopenia, necrotising enterocolitis, as well as the transmission of blood-borne diseases, even in settings with advanced clinical care.[103] Ineffective phototherapy among severely jaundiced infants who present late in hospitals could increase the risk of repeat exchange transfusions in poorly resourced settings.[104] Exchange transfusion with G6PD-deficient donor blood should be avoided because it could prolong time under phototherapy and result in repeat exchange transfusions. Similarly, blood should be screened for HIV and hepatitis. Rhesus-negative blood should be used for neonates with

rhesus-isoimmunisation and group O blood should be used for neonates with ABO incompatibility.

The evidence in support of the use of pharmacotherapies such as D-penicillamine, phenobarbital, bile salts, laxatives, and bilirubin oxidase is inconclusive.[105] Additionally, traditional herbs or medications used to treat newborn jaundice in many LMICs are generally not recommended in clinical settings because of the scarce evidence on their efficacy, safety, and long-term effects. The therapeutic benefits of infant massage on neonatal hyperbilirubinaemia are still debated. Inadequate breastfeeding under the Baby-friendly Hospital Initiative for exclusive breastfeeding continues to pose ethical dilemmas between providing the best form of nutrition and reducing the risk of severe jaundice caused by inadequate caloric intake, especially in poorly resourced settings where people have little access to timely and effective treatment.

Follow-up and neurodevelopmental assessment

Clinically significant bilirubin rebound can occur, for example, in neonates at more than 37 weeks gestational age, those with a positive direct Coombs test, and those who received phototherapy before the first 72 h of life.[106] Such high-risk neonates should have a repeat bilirubin test about 24 h after cessation of phototherapy, although they do not have to remain hospitalised.[33] Many cases of kernicterus reported in industrialised countries have occurred in infants who had been discharged as healthy from their birth hospitalisation.[38] Several cases that had shown clinical signs of acute bilirubin encephalopathy but that were rescued by immediate and aggressive therapeutic intervention (a so-called crash-cart approach), had a prior history of having been discharged then readmitted with extreme jaundice.[38,107] A system in which the responsibility for follow up of jaundice in neonates during the first 2 weeks of life is placed with the birth hospital, can succeed in establishing an exceptionally low incidence of kernicterus (eg, 1:600 000 in Norway).[25] This approach suggests that the management of neonatal jaundice with a goal to avoid kernicterus cannot be limited to the design of treatment charts and improvement in the quality control of phototherapy but should encompass post-discharge follow up as mandated in several national guidelines. Removing barriers to admission and re-admission, and emergent management of infants who develop jaundice at home, are also important.[25,38,107,108]

In most settings, clinicians still regard survival as the endpoint of successful treatment for acute neonatal illnesses. In some infants with acute bilirubin encephalopathy immediate reversal of the presenting symptoms after treatment could mask underlying long-term neurological and developmental sequelae that subsequently manifest in early childhood. The SDGs mandate a child health framework that incorporates survival and thriving for the wellbeing of all children.[11,109] Routine follow up and assessment of survivors of severe hyperbilirubinaemia for potential neurodevelopmental sequelae, including objective assessment for auditory impairments, is therefore necessary to facilitate early detection and intervention for affected infants.[30] Such a follow up should be an integral part of any clinical protocol for the management of infants who have been treated for severe hyperbilirubinaemia. The follow up is equally relevant for the new nurturing care framework for disability-inclusive early childhood development recommended by WHO, UNICEF, and the World Bank.[110]

Future directions and conclusions

Despite 2018 marking the 60th anniversary of the discovery of phototherapy,[111] and the fact that exchange transfusion had been used for another decade before that,[112] many aspects of neonatal jaundice remain enigmatic. For example, the search for the putative basic mechanism of bilirubin neurotoxicity continues 71 years after Richard Day published the first study in rats, which included both in-vivo and in-vitro experiments.[113] The topic has been extensively reviewed by several researchers and all seem to have their favourite theory.[4,6,36,114,115] Agreement on the basic mechanisms would allow planning of further studies to assess how the mechanisms could be manipulated to reduce the vulnerability of the brain to bilirubin toxicity.

Mechanisms that have been proposed that could be targeted with pharmacological or other interventions include inflammation and the role of glial cells,[115] and blood–brain barrier transport molecules (flippases).[114] Attention has also been focused on bilirubin photoisomers and their solubility characteristics relative to passage through the blood–brain barrier.[4] Hypothetically, photoisomers of bilirubin, because of their increased polarity, should have reduced ability to cross the blood–brain barrier since polar molecules appear to need specific transporters to gain entry into the brain. Although no such molecule capable of transporting bilirubin into the brain has been described, ABC transporters can reduce bilirubin entry into the brain.[114] Despite multiple attempts by several groups, the perfect model to test the hypothesis of bilirubin photoisomers and brain entry has yet to be devised.[4]

Further research is also required into the prediction of the development of severe neonatal jaundice. In industrialised countries, kernicterus is rare and so other aspects of bilirubin disease are used to predict the development of severe jaundice including rate of readmission for hyperbilirubinaemia or TSB concentrations exceeding a predetermined threshold. Therefore, countries where kernicterus occurs relatively frequently would be more suitable than industrialised countries to pursue research into the use of early clinical signs of acute bilirubin encephalopathy (eg, bilirubin-induced neurologic dysfunction scoring system) as a predictive tool. Multiple enzymes and pathways are involved in bilirubin metabolism. Therefore, in addition

Search strategy and selection criteria

We identified original research and review articles in English published in PubMed and the Cochrane Library between Jan 1, 2005, and Dec 31, 2017, using the search terms "neonatal jaundice", or "neonatal hyperbilirubinaemia" AND "epidemiology", "pathophysiology", "risk factors", "sequelae" or "management". We also considered commonly referenced and highly regarded papers published before 2005. Relevant articles including book chapters from the reference lists of the publications identified by the search strategy were also reviewed. The start year of 2005 was chosen to capture relevant publications after the release of the landmark guidelines for neonatal hyperbilirubinaemia in 2004 by the American Academy of Pediatrics.

to delineating clinical risk parameters, the use of the principles of pathway genetic load has been proposed to improve prediction abilities.[116]

Furthermore, recognising that achieving these goals will take time, the acute management of infants with extreme hyperbilirubinaemia and signs of acute bilirubin encephalopathy should also be prioritised. Acute bilirubin encephalopathy could be reversible, at least in some cases, if treated aggressively.[107] Therefore, admission procedures for such infants should be streamlined to reduce the time between identification and the start of treatment. Diagnostic approaches include end-tidal carbon monoxide measurement with a non-invasive, bedside device to establish the presence of haemolysis associated with a high risk of severe hyperbilirubinaemia and neurotoxicity. A therapeutic method that is hoped to become available in the near future is metalloporphyrin—a drug capable of blocking haem oxygenase, thereby preventing bilirubin production.[105]

In conclusion, neonatal hyperbilirubinaemia is associated with fatal and non-fatal health outcomes globally with potentially devasting long-term consequences in some survivors. Community-oriented interventions to reduce the incidence of haemolytic jaundice, ensure timely access to effective treatment, and provide appropriate follow up for all newborn babies with, or at risk of, severe hyperbilirubinaemia, should be prioritised. This approach will contribute to the health and wellbeing of the many beneficiaries of global investments towards reducing child mortality, especially in LMICs, as recommended in the SDG agenda.

Contributors

BOO drafted the manuscript. MK and TWRH critically reviewed and revised the manuscript for intellectual content. All authors approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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