Hyperbilirubinemia in Preterm Neonates

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KEYWORDS

- Bilirubin • Reactive oxygen species • Photosensitivity • BIND
- Antioxidant properties

KEY POINTS

- Preterm neonates with increased bilirubin production loads are more likely to sustain adverse outcomes due to either neurotoxicity or overtreatment with phototherapy and/or exchange transfusion.
- Clinicians should rely on expert consensus opinions to guide timely and effective interventions until there is better evidence to refine bilirubin-induced neurologic dysfunction or benefits of bilirubin.
- There are clinical approaches that minimize the risk of bilirubin neurotoxicity.

INTRODUCTION

Most preterm infants less than 35 weeks gestational age (GA) have elevated total serum/plasma bilirubin (TB) levels, which often present as jaundice, the yellowish discoloration of the skin due to bilirubin deposition. When left unmonitored or untreated in these infants, an elevated TB level (hyperbilirubinemia) can progress to silent or symptomatic neurologic manifestations. Acute bilirubin encephalopathy (ABE) is acute, progressive, and often reversible with aggressive intervention, whereas kernicterus (or chronic bilirubin encephalopathy [CBE]) is the syndrome of chronic, post-icteric and permanent neurologic sequelae that is associated with more serious and usually irreversible manifestations.[1] The current management of a preterm infant with hyperbilirubinemia, who has an increased likelihood of developing bilirubin-induced neurologic damage, is under intense scrutiny. Clinicians have been instructed to use the hour-specific TB levels (Bhutani nomogram)[2] as well as considering the concurrence with the degree of an

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infant's immaturity, illness, and/or hemolytic disease, the most common cause of increased bilirubin production, to guide the initiation of treatment. In fact, increased bilirubin production in preterm neonates adds to the risk of mortality or long-term neurodevelopmental impairment (NDI) due to bilirubin neurotoxicity[3–6] and can be manifested as the syndrome of bilirubin-induced neurologic dysfunction (BIND).[7–10] Universal screening and the prevention of Rh disease, coordinated perinatal-neonatal care, neonatal interventions with early feeding, and effective use of phototherapy has virtually eliminated the risk of kernicterus in most developed countries (ie, those with low [<5%] neonatal mortality rates).[11] Moreover, the current incidence of neurologic damage in preterm infants is also low, such that the risk-benefit spectrum for interventions should include a balance between the risk of overtreatment versus the reduction of long-term post-icteric sequelae. However, historic data attest to the increased vulnerability of the more immature neonates. In the absence of hyperbilirubinemia due to isoimmunization and without access to phototherapy or exchange transfusion (before 1955), kernicterus was reported to be 10.1%, 5.5%, and 1.2% in infants less than 30, 31 to 32, and 33 to 34 weeks GA, respectively (**Table 1**).[12] Among the infants who died due to kernicterus, 100%, 89%, 54%, and 81% were of birthweight (BW) less than 1500 g, 1500 to 2000 g, 2001 to 2500 g, and >2500 g, respectively. Overall, 60 (2.8%) of 2181 survivors of 2608 admissions to the neonatal nursery sustained kernicterus. Mortality was 73% for these 60 infants. Since 1985, phototherapy initiated at 24 ± 12 hours of life has effectively prevented hyperbilirubinemia in infants weighing less than 2000 g even in the presence of hemolysis.[12] This approach (introduced in 1985) reduced exchange transfusions from 23.9% to 4.8%. Now with 3 decades of additional experience in implementing effective phototherapy, the need for exchange transfusions has virtually been eliminated and the side effects of phototherapy in extremely low birthweight (ELBW) infants are now under active investigation. Nevertheless, bilirubin neurotoxicity continues to be associated with prematurity alone.

The ability to better predict this risk, beyond using BW and GA, has been elusive. With the known limitations of TB measurements being the ideal predictor, other biomarkers, such as unbound or "free" bilirubin (UB),[13] albumin levels, and bilirubin-albumin binding capacity (BBC), together with objective determinations of ongoing hemolysis, sepsis, and rapid rate of TB rise have been validated (**Box 1**). The individual or combined predictive utility of these measures has yet to be refined for broader

Table 1
Neonatal mortality with kernicterus among admits to neonatal nursery (by BW and GA)

GA, wk	Survivors >48 h/All NICU Admits	% Cases of Kernicterus
≥30–<31	109/264	10.1
31–32	282/356	5.7
33–34	685/801	3.2
35–36	749/792	1.1
>36	356/365	0.8
Total	2181/2608 (84%)	2.8

Abbreviations: GA, gestational age; NICU, neonatal intensive care unit.

Only sick infants >2500 g were admitted to the NICU. Neonatal risk measured in an era before the availability of phototherapy and exchange transfusion use in infants without Rh or ABO isoimmunization.

These data compare with mortality in the remainder at 23% (668/2608 NICU admissions).

Adapted from Crosse VM, Meyer TC, Gerrard JW. Kernicterus and prematurity. Arch Dis Child 1955;30:501–8.

Box 1
Historic clinical risk factors for bilirubin neurotoxicity in preterm neonates.

Clinical Risk Factors for Neurotoxicity

1. Birthweight <1000 g
2. Apgar Score <3 at 5 min of age
3. Arterial oxygen tension <40 mm Hg for >2 h
4. Arterial pH <7.15 for >1 h
5. Core temperature <35°C for >4 h
6. Serum albumin <2.5 g/dL
7. Sepsis
8. Clinical deterioration

Data from Brown AK, Kim MH, Wu PY, et al. Efficacy of phototherapy in prevention and management of neonatal hyperbilirubinemia. Pediatrics 1985;75:393–400.

clinical application. Immaturity, concurrent neonatal disease (such as cholestasis), and the use of total parenteral nutrition and lipid infusions (See Satrom K, Gourley G: Cholestasis in preterm infants, in this issue) or drugs that alter BBC may exacerbate the risk for BIND.[14] A clinician's treatment decisions need to be individualized for each infant and should, in general, reflect the consensus of experts, until definitive guidelines can be established. In this article, we review the evolving evidence for bilirubin-induced brain injury in preterm infants and highlight the clinical approaches that minimize the risk of bilirubin neurotoxicity.

NATURAL BILIRUBIN PROFILE IN PRETERM NEONATES

Previous studies suggest that preterm infants with modest TB levels can sustain long-term NDI at age 18 to 22 months,[7,15–18] and infants with high TB levels can experience increased mortality and NDI associated with auditory neuropathic or visuomotor processing disorders (now characterized as BIND).[7–10] However, some preterm infants are resistant to relatively high bilirubin loads in the absence of increased production rates because of efficient elimination of bilirubin and sufficient BBC.[19] Unnecessary or overprescription of phototherapy may compromise the ability of bilirubin to serve as a protective antioxidant from bilirubin neurotoxicity, which may occur at even very low TB levels.

Prevalence and Incidence

Poor correlation of visually apparent jaundice to assess hyperbilirubinemia and bilirubin neurotoxicity has confounded the accurate determination of the incidence of infants with jaundice and/or hyperbilirubinemia. It must be remembered that the degree of jaundice does not predict the TB level well. In addition, historical data on the incremental changes in clinical practice inform the evolving decline in the incidence of adverse outcomes. Prevention of Rh disease, starvation, prevention or early treatment of neonatal sepsis, safe use of antibiotics and drugs, and reduction of birth trauma have together contributed to a decrease in the incidence of kernicterus in preterm infants since the 1950s (see **Table 1**).[12] In the era before the routine use of exchange transfusion and availability of phototherapy, Crosse and colleagues[12] reported that 73.6% of preterm infants with kernicterus died compared with

25.6% for all infants born prematurely. The highest mortality rate was among those infants with lower BW and earlier age of onset of clinical signs. The sequelae or outcomes were dependent on the maturity of infants who survived the first 2 days after birth and are presented by GA stratification in **Table 1**. These data show the risk of mortality and kernicterus for preterm infants who are *not* actively treated with currently recommended strategies for treating hyperbilirubinemia. The current incidence of kernicterus in preterm infants is less certain because of highly variable implementation of bilirubin reduction strategies. In a retrospective postmortem neuropathological study,[20] the rate of kernicterus was reported to be 4% in 81 preterm infants (GA <34 weeks) who died after 48 hours of life and cared for after the introduction of phototherapy and universal Rh immunoprophylaxis. To date, there are no data on the prevalence of kernicterus in preterm survivors, but small case series of survivors with neurologic sequelae associated with hyperbilirubinemia have been reported.[4] Determining the incidence is also limited by the timeliness and aggressiveness of interventions, the variability and spectrum of BIND in preterm infants, presence of comorbidities (eg, sepsis, periventricular leukomalacia, and intraventricular hemorrhage), and delayed manifestations of hypertonicity. Clinically evident neurologic signs, such as the classic dystonic posture, dyskinesia, and abnormal muscle tone, may not manifest until 6 months corrected age. Since the late 1970s, the incidence of kernicterus in preterm infants has declined to the point where kernicterus is rarely seen postmortem, but a small number of cases of choreoathetoid cerebral palsy (CP) or sensorineural hearing loss associated with hyperbilirubinemia continue to be reported in preterm survivors.[4] The decreased incidence of kernicterus in preterm infants may, in part, be due to the initiation of proactive measures to reduce TB or to changes in neonatal care that have eliminated unappreciated risk factors for kernicterus. In a classic experiential example in a single neonatal intensive care unit (NICU), the discontinuance of bacteriostatic saline containing benzyl alcohol to flush intravenous (IV) lines led to a remarkable decline in the incidence of kernicterus from 31% to 0%.[21] Clearly, there have been dramatic improvements in the care of jaundiced preterm infants, but overall the data are sobering and still illustrate their vulnerability. Nonetheless, the reliance on a systems-approach in the NICU has led to tangible reductions in the use of exchange transfusions and of kernicterus in the United States.[22,23] It is also now well established that the presence of early-onset hyperbilirubinemia (<24 hours of age) is a medical emergency and that TB levels measured between ages 24 to 60 hours can predict the development of severe hyperbilirubinemia and an infant's need for phototherapy.[1,24] The recognition of clinical risk factors and the timeliness of interventions have probably had the most influence on neonatal outcomes.

Bilirubin Burden

The clinical burden of bilirubin neurotoxicity usually manifests as irreversible posticteric sequelae with the hallmark sign (usually at autopsy) of icteric (yellow) staining of the basal ganglia, specifically of the globus pallidus, which can be observed as an increased signal on MRI. BIND occurs when the TB level exceeds an infant's neuroprotective defenses, primarily in the basal ganglia; central and peripheral auditory pathways; hippocampus; diencephalon; subthalamic nuclei; midbrain; pontine; brainstem nuclei for visuomotor function; respiratory, neurohumoral, and electrolyte control; and in the cerebellum, most prominently in the vermis.[23,25–28] Acute signs can present as progressive changes in an infant's cardiorespiratory status, mental (behavioral) status, and cry, with varying degrees of drowsiness, poor feeding, hypotonia, and alternating tone followed by increasing hypertonia, especially of extensor muscles, retrocollis, and opisthotonos, first intermittent and then with increasing

severity, and finally becoming constant. Alternatively, clinical signs are nonspecific or absent; regardless, any neurologic sign needs to be investigated and may herald manifestations of ABE. Acute-stage mortality (about 7% in late preterm and term neonates) is due to respiratory failure and progressive coma or intractable seizures. Rate of progression of clinical signs depends on the rate of TB rise, duration of hyperbilirubinemia, host susceptibility, and presence of comorbidities. One of the more frequent morbidities is due to Rh disease (due to non-D antigens) and may manifest with fetal hydrops and lead to a complex neonatal course.

Kernicterus, often used interchangeably with CBE, is reserved for irreversible classic sequelae diagnosed in infants who survive ABE. Diagnosis is primarily dependent on presence of dystonia, athetoid CP, paralysis of upward gaze, and sensorineural hearing loss of varying degrees of severity. Cognition is usually spared to a striking degree. BIND is a wider spectrum of disorders that excludes classic (chronic) kernicterus.[8,29] Clinical evidence of damage confined to more narrow neural pathways may result in isolated, less severe clinical signs, such as auditory or visual deficits. Auditory neuropathy (or auditory "dys"-synchrony) defined by characteristic clinical criteria and distinctive findings on the auditory brainstem-evoked response (ABR) and normal cochlear function (normal cochlear microphonic, normal otoacoustic emissions [OAE]) without severe hearing loss or by similar auditory neuropathy associated with minimal fine and/or gross motor disability. Subtle neurologic manifestations of BIND include signs of awkwardness, minimal fine and gross motor incoordination, gait abnormalities, fine tremors, exaggerated extrapyramidal reflexes, and perhaps auditory learning and behavioral problems. These subtle signs are difficult to diagnose because of delayed clinical expression and their nonspecificity.

CLINICAL PROFILE OF SUBTLE POSTICTERIC SEQUELAE

As summarized by Johnson and Bhutani,[8] pilot studies conducted in the prephototherapy era for neonates cared for in 1965 to 1966, identified altered pyschometric, audiologic, speech, language, and visuomotor disorders. Their reanalysis of 4-year and 7-year follow-up studies showed a consistent, significant correlation of low bilirubin binding reserve, with suspicious and abnormal ratings for the psychometric and audiologic examinations. An abnormal bilirubin-albumin molar ratio (BAMR) appeared to predict changes in ABR. The BAMR may serve as an approximate surrogate for UB levels, and can be used as an additional factor in determining the need for exchange transfusion in neonates of 35 or more weeks GA. Preterm infants are likely to have lower serum albumin levels, and it has been suggested that the BAMR would be a good measure of the risk for bilirubin toxicity based on BW. However, its usefulness may be limited, as other factors (eg, acidosis, use of multiple drugs, elevated free fatty acids, and bilirubin photoisomers) may interfere with bilirubin-albumin binding or binding of bilirubin to sites other than albumin.[30,31]

Auditory Dysfunction

In preterm infants, the relationship between hyperbilirubinemia and hearing loss is significant and can be modulated by other risk factors.[32] Preterm infants with high TB levels ($\geq$14 mg/dL), and those with BW less than 1500 g have a higher risk of deafness than their healthy counterparts with BW more than 1500 g. Furthermore, among high-risk patients, the mean duration of hyperbilirubinemia was significantly longer in deaf infants, who appeared to have a greater number of acidotic episodes while they were hyperbilirubinemic. Hyperbilirubinemia appears to cause selective damage to the brainstem auditory nuclei and may also damage the auditory nerve and spiral

ganglion.[25] In contrast, the organ of Corti and thalamocortical auditory pathways appear to be unaffected by bilirubin. Clinically, a common form of hearing loss caused by hyperbilirubinemia is auditory neuropathy spectrum disorder (ANSD).[33,34] Thus, tests of auditory transduction and outer hair cell function within the cochlea, such as the cochlear microphonics and OAEs, may be normal while ABR testing is abnormal. Some experts believe that ANSD is associated with a more subtle neurologic manifestation (BIND).[33,34] Diagnosis of ANSD is difficult due to delayed clinical onset and nonspecificity. In a study of 260 patients with ANSD, historical risk of hyperbilirubinemia was 47.7% in premature infants, and 20.3% in those who received exchange transfusion.[33] A Polish study of 9419 infants whose hearing ability was uncertain or who had risk factors for hearing loss, 352 were diagnosed with sensorineural hearing loss.[35] Of these, 18 (5.1%) were diagnosed with ANSD associated with prematurity and low BW (n = 5), pharmacologic ototoxicity (n = 8), and hyperbilirubinemia (n = 7), and 4 had no risk factors. Whether these effects are transient and have no impact on speech and language development has to yet be proven.

Visuocortical Dysfunction

Aside from the classic visuo-oculomotor manifestations of kernicterus, preliminary data have demonstrated a number of interesting and potentially worrisome findings when the visual cortex function in healthy, bilirubin-exposed infants was studied.[36] By using a quantitative measure of neural activity, the swept parameter visual-evoked potential (sVEP) response functions over a wide range of contrast, spatial frequency, and vernier offset sizes in 16 full-term infants with high TB levels (>10 mg/dL) and 18 age-matched infants with no visible neonatal jaundice, Hou and coworkers[36] compared sVEP thresholds and suprathreshold response amplitudes in all enrolled infants at 14 to 22 weeks postnatal age. Infants who had hyperbilirubinemia showed lower response amplitudes ($P<.05$) and worse or immeasurable sVEP thresholds compared with control infants for all 3 measures ($P<.05$). sVEP thresholds for vernier offset were correlated with TB levels ($P<.05$), but spatial acuity and contrast sensitivity measures in the infants with neonatal hyperbilirubinemia were not ($P>.05$). The effect of neonatal bilirubinemia on vernier acuity, which is a close surrogate for Snellen or optotype acuity, appears to be dose related. The effect of bilirubin on the visual cortex lasts well beyond the period of exposure and more than one type of vision is affected, suggesting widespread effect of bilirubin on the visual cortex.

Integrity of Brainstem Function and Structure

The frequency and distribution of periodic breathing apnea events of more than 20 seconds requiring positive pressure ventilation have been described by Amin and colleagues[37] as signs of intractable apnea and possible signs of BIND. Classic brain magnetic resonance findings for kernicterus have been reported, almost exclusively descriptive of term infants, and demonstrating vulnerability of the basal ganglia.[25] Initially, within days of a hyperbilirubinemia-related insult, T1-weighted brain imaging shows hyperintensity of the globus pallidus with or without abnormal signal in the subthalamic nuclei. Weeks or months later, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images become hyperintense, and hyperintensity is no longer seen on T1-weighted images. A normal image does not eliminate the possibility of bilirubin-related brain injury; serial images may reveal an early abnormal pattern, followed by apparent resolution, then later, an abnormal T2-weighted pattern at a time that can be variable. Similarly distinctive findings have been described in a series of preterm infants of less than 30 weeks estimated gestational age (EGA).[38] In these infants, BAMRs, but not TB levels, were reported above the exchange transfusion

thresholds recommended in the 1990s,[39] although all had evidence of clinical instability during their hospitalization. Therefore, it has been hypothesized that this constellation of findings may be underrecognized among preterm infants. Importantly, the bilirubin-related injury pattern can be differentiated from the most common type of preterm brain injury of white matter injury alone.[40,41]

BENEFICIAL ROLE OF BILIRUBIN

Tissue injury from a biological, chemical, or traumatic insult usually results in a cascade of adaptive response to protect against further injury possibly through restoring vascular integrity that may include endogenously elevated TB (See Stevenson DK, Wong RJ, Arnold CC, et al. Phototherapy and the risk of photo-oxidative injury in extremely low birth weight (ELBW) infants, in this issue). Mildly elevated TB may be associated with lowered morbidity and related mortality, which could be attributed to the antioxidant properties of bilirubin. The highly inducible, anti-inflammatory, antioxidant, and antiapoptotic protein, heme oxygenase-1 (HO-1) is one of the more robust mechanisms. Catalysis of the pro-oxidant heme to equimolar iron, carbon monoxide (CO), and bilirubin (converted from biliverdin) is responsible for beneficial effects of HO-1 expression to the cytoprotective properties of these by-products of the reaction. Bilirubin, generally regarded as a potentially cytotoxic, lipid-soluble waste product, is now known to exhibit potent antioxidant properties preventing the oxidative damage triggered by a wide range of oxidative stressors.[42] Therefore, the idea of a physiologic role for bilirubin in cytoprotection against short-lasting and long-lasting oxidant-mediated cell injury, such as chronic inflammatory rheumatoid arthritis, has been proposed.[43] Elevated TB levels also have been shown to be protective against stroke, atherosclerosis, and vasculitis. Earlier studies have reported negative association with coronary artery disease and possibly favorable coronary collateral growth in patients with coronary total occlusion. In another clinical example, chronic renal disease, which is associated with systemic inflammation and oxidant stress, is a strong and independent risk factor for cardiovascular disease.[44,45] Many clinical studies indicate a negative relationship of coronary artery disease as well as related mortality in patients on chronic dialysis.[46–48] A low TB concentration is associated with accelerated progression of chronic renal disease over an approximately 8-year follow-up period, indicating that bilirubin could be an independent predictor of progression.[49] Hyperbilirubinemic (>1.24 mg/dL) patients had a reduced incidence of end-stage kidney disease,[50] and that mildly elevated TB concentrations (>0.8 mg/dL) are associated with improved estimated glomerular filtration rates.[51] A negative correlation between TB concentrations and common carotid intima media thickness was reported in children who had undergone kidney transplantation and peritoneal dialysis, suggesting bilirubin may protect from vascular complications.[52] Bilirubin is also regarded as an in important multipoint inhibitor of atherosclerosis[50,53,54] and may protect from vascular damage via its antioxidant properties, thus protecting from free radical–induced damage to lipids and proteins.[55–57] Yet another example is of individuals with Gilbert syndrome who have unconjugated hyperbilirubinemia ($\geq$1 mg/dL or 17.1 μmol/L) and whose reduced oxidative stress and inflammatory status might prevent glomerular dysfunction and vascular complications.[58] Further investigations are needed to study the protective antioxidant properties of bilirubin in sick and preterm newborns.

BENCH EVIDENCE OF BILIRUBIN NEUROTOXICITY IN PRETERM NEONATES

In a recent review, Brites and Brito[59] outlined the mechanisms of dysfunction and demise of neurons by unconjugated bilirubin (UCB) derived from excitotoxicity,

oxidative stress, alterations in neuronal arborizations, synaptotoxicity, and apoptosis mediated by alterations in mitochondria dynamics and caspase activation, ultimately leading to cell demise. UCB decreases the expression of presynaptic proteins and was shown to cause presynaptic degeneration in the Gunn rat, an animal model of hyperbilirubinemia. Neurogenesis and proliferating neural stem cells and young neurons show increased susceptibility to UCB as compared with mature and old ones, thus explaining the increased vulnerability of premature infants. Neurons damaged by UCB seem less able to recover. Hippocampal neurons have shown a particular susceptibility to UCB when compared with those from cortex and cerebellum. Moreover, the addition of proinflammatory cytokines, such as tumor necrosis factor-α plus interleukin-1β, to UCB increasingly activate intracellular signaling pathways that culminate in the demise of immature neurons, providing supportive evidence for the higher risk of hyperbilirubinemia when associated with inflammation and prematurity. Hansen[60] and Watchko and Tiribelli[61] recently summarized the clinical, scientific evidence, and mechanism(s) of bilirubin neurotoxicity. These indicate that bilirubin kills specific neurons by causing necrosis; in vitro studies show that it induces apoptosis and support in vivo observations in older literature showing neuro-anatomic changes consistent with apoptosis. Evidence also suggests that bilirubin interferes with intracellular calcium homeostasis through alterations in the function and expression of calcium/calmodulin kinase II, by selectively decreasing calcium-binding proteins in susceptible brainstem areas and increasing intracellular calcium in cultured neurons, and by sensitizing the cell to other injuries or triggering apoptosis. Bilirubin also may be cytotoxic by causing neuronal hyperexcitability, perhaps via excitatory amino acid neurotoxicity, or it may have other membrane of neurotransmitter effects. Finally, it may act by interfering with mitochondrial respiration and energy production. Thus, interventions that reduce bilirubin exposure to the neonatal brain have been shown to prevent bilirubin neurotoxicity.

Prematurity in the presence of concurrent inflammatory responses in the preterm developing brain can lead to myelination delay. The initial impact on the microglial cells reacting to perinatal brain injury is by releasing proinflammatory cytokines and enhancing phagocytic potential. Thus, microglia operating during synapse formation and maturation may be dysfunctional and worsen the long-term effects on neural circuitry. In addition, astrocytic and microglial activation have been implicated in increased susceptibility to seizures, and to neurologic effects in adulthood of early-life seizures. In recent years, activated microglia have been implicated in the pathogenesis of white matter injury, such as periventricular leukomalacia.[59]

MARGINS OF CLINICAL SAFETY

Management of hyperbilirubinemia in preterm infants varies among institutions, with little evidentiary support for these differences in management.[62] Because of the limited specificity of TB as a predictor for neurotoxicity, the margin of safety is narrow and unpredictable. Thus, interventions are primarily for prevention rather than for rescue. Interventions include the following: (1) alterations of preterm gut physiology and enterohepatic circulation by early initiation of feeds to alter luminal milieu and promote gastrointestinal motility; (2) use of effective phototherapy, including irradiance and light source, as well as method and risks of exchange transfusion (not reviewed here and have been the subject of several recent reports); and (3) acute reduction of bilirubin load. Chemoprevention remains a potential option, but is limited by evidence of safety and efficacy.[63]

Recent recommendations for management of hyperbilirubinemia presented in this article (**Fig. 1**) are consensus-based. Long-term follow-up data and future randomized

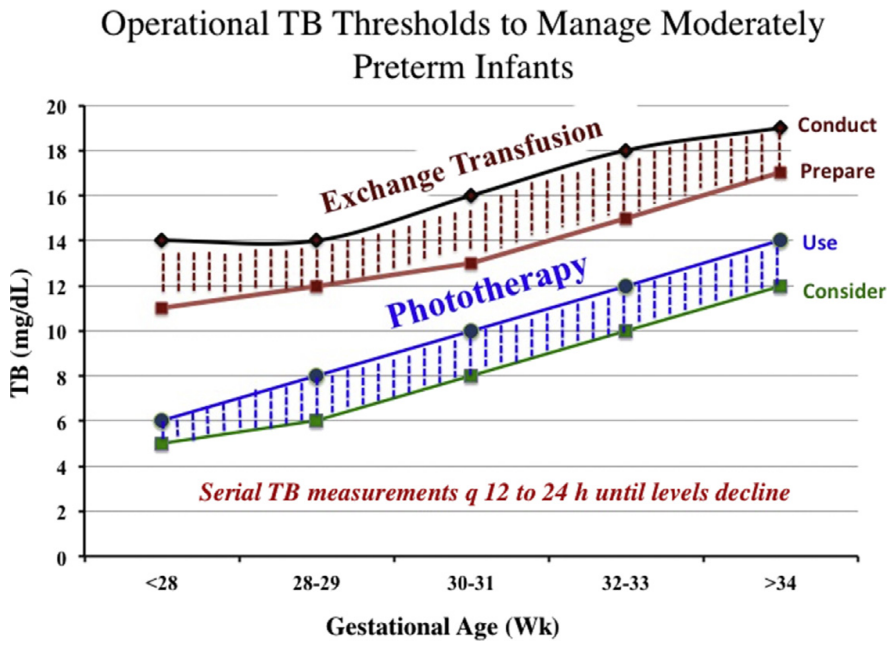

Fig. 1. Suggested use of phototherapy and exchange transfusion in preterm infants less than 35 weeks GA. The operational thresholds have been demarcated by recommendations of an expert panel. The shaded bands represent the degree of uncertainty. Recommended thresholds to prepare for exchange transfusion assume that these infants are already being managed by effective phototherapy. Increase in exposure of body surface area to phototherapy may inform the decision to conduct an exchange transfusion based on patient response to phototherapy. (*Adapted from* Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol 2012;32:660–4; with permission.)

controlled clinical trials may help to determine if these guidelines produce the best outcomes for preterm infants. There is a delicate balance between risk of BIND and overtreatment (and possibly, mortality) in the setting of reducing the potential antioxidant properties of bilirubin that needs more study. In the meantime, continued assessment of best practices would be helpful to minimize overtreatment or unintended consequences of bilirubin reduction strategies.

CLINICAL CARE STRATEGIES

Timing of Interventions to Reduce Excessive Bilirubin Load

The timing of bilirubin reduction strategies impacts the outcome of preterm infants at risk for excessive hyperbilirubinemia. Early implementation of strategies to rapidly and effectively reduce the excessive bilirubin load before the onset of neurologic signs, in all likelihood, could prevent chronic posticteric sequelae or kernicterus. The initial evidence for this approach, using phototherapy, was demonstrated by a National Institute of Child Health and Development (NICHD) Neonatal Research Network trial to test the efficacy of phototherapy as compared with exchange transfusion alone.[64] This study showed that phototherapy initiated at 24 ± 12 hours effectively prevented hyperbilirubinemia in infants weighing less than 2000 g even in the presence of hemolysis and reduced exchange transfusions from 23.9% to 4.8% (**Table 2**). Now, with 3 decades of experience in implementing and refining effective phototherapy, the need for exchange transfusions has virtually been eliminated. Once the clinical signs of bilirubin neurotoxicity are evident, emergent intervention to reduce the bilirubin load is the only known recourse in clinical practice. To date, exchange transfusion coupled

Table 2
Estimated risk thresholds for UB (using peroxidase assay) and calculated BBC (% saturation)

Study: (Duration/Exposure Not Measured)	UB, nM	% Saturation of BBC, Calculated
Hypothetical model[19]	*20*	*67*
Historical review[77]	17–23	63–69
Clinical: ABR changes[78]	19–33 (23)	66–77 (69)
Transient ABR changes[79]	>8.5	>46
Overt BIND[79]	>17	>63
Kernicterus present[80]	>27	>73
Kernicterus absent[80]	<13	<57
Kernicterus present[81]	>18	>65
Kernicterus absent[81]	<11	<52

Abbreviations: ABR, auditory brainstem-evoked response; BBC, bilirubin-albumin binding capacity; BIND, bilirubin-induced neurologic dysfunction; UB, unbound bilirubin.

with a "crash-cart" phototherapy remains the only known clinical option. Even though there is no predictive evidence that a specific TB level will or will not cause neurotoxic damage, the critical TB level is influenced by postnatal age, maturity, duration of hyperbilirubinemia, and rate of TB rise.

Triage for a Jaundiced Preterm Newborn with Suspicious Clinical Neurologic Signs

The triage process should be guided by ongoing staff education and development and sharing local protocols and plans of action:

1. Supplies
   Ready access to devices, equipment, and transport isolettes to manage cardiorespiratory deterioration. Specific devices include phototherapy equipment, irradiance meters specific for the device that is being used, and protective gear for the baby including opaque eye masks and filters to exclude ultraviolet light exposure. Infants with hydrops secondary to isoimmunization will likely require intensive resuscitation, stabilization, correction of anemia, and possible preparation for exchange transfusion.
2. Testing
   Transcutaneous bilirubin testing, clinical and rapid neurologic examination, and "STAT" laboratory studies (total and conjugated bilirubin and serum albumin measurements, blood typing, and cross-matching). Calculated BAMR may be assessed for additional insight to plan interventions in moderately preterm infants (**Fig. 2**). Serial bilirubin levels will need to be monitored to assess the rate of TB rise (mg/dL/h) to concurrent interventions.
3. Advise parents of the medical emergency and seek informed consent, as needed.
4. Transfer to facility that specializes in care of sick preterm neonates or commence treatment with effective phototherapy as soon as possible (crash-cart approach).

Emergency Interventions for Rapid Reduction of Bilirubin Concentrations

Rapid bilirubin reduction strategies to reverse the rapid rate of TB rise include effective phototherapy (nearly the entire body surface area [>80%]), double-volume blood exchange transfusion, and occasional need for pharmacologic agents often used in

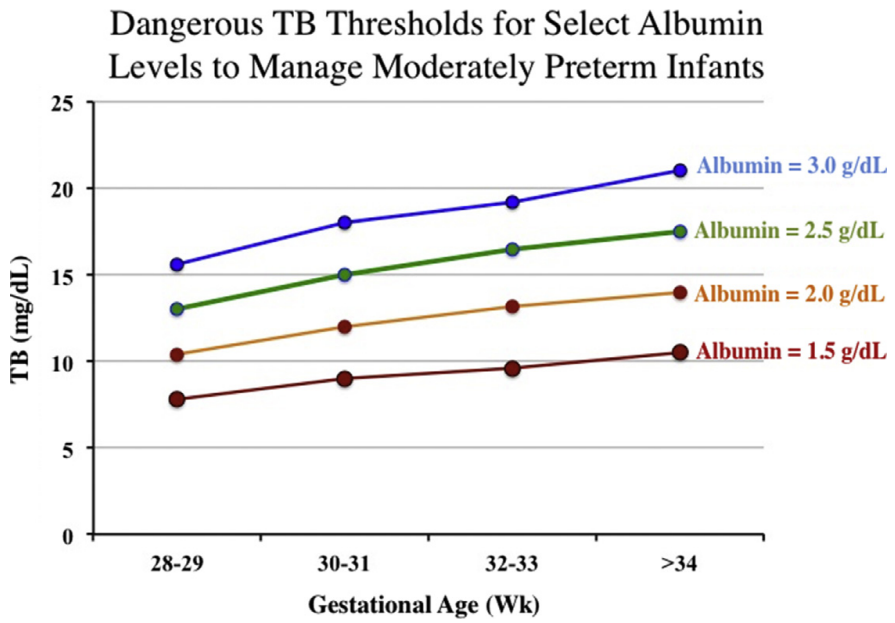

Fig. 2. Recommended use of BAMR for initiation of exchange transfusions. BAMR values have been calculated to bilirubin (mg/dL)/albumin (g/dL). Values above the thresholds for select serum albumin values of 1.5, 2.0, 2.5, and 3.0 g/dL are presented as bands above which bilirubin is likely to be displaced and may be neurotoxic. (*Data from* Ahlfors CE. Criteria for exchange transfusion in jaundiced newborns. Pediatrics 1994;93:488–94.)

combination. Effective phototherapy is the current "drug" of choice to reduce the severity of neonatal unconjugated hyperbilirubinemia (regardless of etiology) in a matter of 2 to 4 hours. Optimum use of phototherapy has been defined by specific ranges of TB thresholds that have been correlated to an infant's postnatal age (in hours) and their potential risk for bilirubin neurotoxicity (see previously). Effective phototherapy implies its use as a drug with specific light wavelengths at a specific narrow peak (460 nm, blue) and a range of emission spectrum (that is minimized from the traditional range of 400–520 nm), preferably in a precise (narrow) bandwidth that is delivered at an irradiance (dose) of greater than or equal to 25 to 30 $\mu W/cm^2/nm$ (measured specifically for the selected light wavelength) to 80% of an infant's body surface area.[65,66] There are several commercial devices and delivery methods for phototherapy for use at both the hospital and home. Blue light-emitting diodes in the 425 to 475 nm range should be easily and rapidly accessible, and periodically inspected and maintained to ensure proper functioning. Shadows with multiple lights should be avoided. The efficacy is additionally influenced by the following: (1) optimization of light administration to achieve a minimum distance between the device and the patient such that the footprint of light covers maximum surface area with minimal physical barriers; (2) infant characteristics, such as the severity of jaundice, surface area proportions, as well as dermal thickness, pigmentation, and perfusion; and (3) the duration of treatment to a specific TB threshold.[65,66]

Exchange transfusion is a critical and invasive procedure that can significantly reduce TB levels in a matter of 1 to 2 hours. Trained personnel in neonatal/pediatric intensive care facilities with full monitoring and resuscitation capabilities should perform this procedure. Exchange transfusion should be considered and anticipated when there are any neurologic signs even if TB is falling, or there are significant concerns of neurotoxicity. Concerns for neurotoxicity in term infants are heightened in an asymptomatic infant when (1) TB level exceeds 25 mg/dL; (2) intensive

phototherapy fails to produce a significant TB reduction in an infant with severe hyperbilirubinemia (a progressive TB decline of at least >0.5 mg/dL per hour or >2 mg/dL drop in 4 hours should be expected) without onset of neurologic signs; or (3) an infant who had an earlier successful hearing screen and fails an automated ABR screen. Before an exchange transfusion is initiated, the health care team should review the risks and benefits of the procedure with the parents, so parents can provide informed parental consent (see later in this article). The adverse effects of an exchange transfusion include neonatal morbidities such as apnea, anemia, thrombocytopenia, electrolyte and calcium imbalances, risk of necrotizing enterocolitis, hemorrhage, infection, complications related to the use of blood products, and catheter-related complications.[67] Exchange transfusion also carries the risk of neonatal mortality, especially in sick infants. Exchange transfusion is ideally performed as an isovolumic procedure, preferably with concurrent withdrawal from an arterial line and infusion through a venous line. Double-volume exchange (170 mL/kg) is preferable, but in the event of technical difficulties, a single-volume exchange transfusion may be adequate if supplemented with intensive phototherapy. The entire process should be accomplished within 4 to 6 hours of the identification of the medical emergency.[1] Pharmacologic options and chemoprevention strategies have been reviewed in recent articles,[63,68] but have a limited role in the emergency room management of a sick infant.

Albumin Infusion

At times, an albumin infusion (1 g/kg) has been suggested before an exchange transfusion, especially if serum albumin is low (<3.0 g/dL).[69] However, there is no current evidence to support this practice. In the preterm infant, there is concern for increased intravascular volume, increased alveolar leak, and cardiopulmonary compromise.

Intravenous Gamma Immunoglobulin

Intravenous gamma immunoglobulin (IVIG) may be administered when the hyperbilirubinemia is attributed to isoimmunization. IVIG has been shown, anecdotally, to reduce the need for exchange transfusions in Rh and ABO hemolytic diseases.[1,70,71] Although data are limited, there is no evidentiary basis for its use and there are concerns for significant side effects in preterm neonates.

Phenobarbital

Phenobarbital can accelerate bilirubin excretion by increasing hepatic clearance.[71] However, this drug is no longer recommended, as it has no clinical effect when administered to infants of less than 32 weeks GA and is ineffective when given before 12 hours of age. The adverse effects of this therapy include sedation, risk of hemorrhagic disease, and the potentially addictive nature of phenobarbital.[72] This drug has a slow onset of effect (usually several days) and a long duration of action (1–2 weeks) after its discontinuation. For all of these reasons, the use of phenobarbital is no longer recommended.

Metalloporphyrins

Synthetic heme analogs or metalloporphyrins can inhibit HO, the rate-limiting enzyme in the bilirubin production pathway.[73] Some have been noted to cause photosensitization (especially during exposure to intense fluorescent light). These drugs are being investigated in clinical pharmacologic and toxicologic studies and have been shown

to reduce TB levels.[63,74] The Food and Drug Administration has not yet approved their use in the United States.

Other strategies that warrant further investigations and clinical trials are use of agents that interrupt the enterohepatic circulation and bilirubin accumulation from the continued action of β-glucuronidase. Chemoprevention with use of casein supplements or other agents, such as L-aspartic acid, could decrease intestinal reabsorption of bilirubin and may play a potential preventive or adjunctive clinical role.[75]

FOLLOW-UP OF PRETERM INFANTS AT RISK FOR BILIRUBIN-INDUCED NEUROLOGIC DYSFUNCTION

Posticteric sequelae are often unrecognized, mislabeled, or misdiagnosed in preterm infants. These errors have led to prolonged diagnostic and health-seeking odysseys for families. Follow-up studies of infants enrolled in the NICHD trial of 1979 to 1985 demonstrated the challenges of follow-up in this population as well as the residual morbidities identified at late childhood and in adults. Oh and colleagues,[16] through a retrospective observational analysis in infants with BW less than 1000 g, noted that TB concentrations during the first 14 days of birth are directly correlated with death, NDI, sensorineural hearing loss, and other physical impairments. Confounding effects of modest hyperbilirubinemia or potential toxic effects of phototherapy could not be excluded.[16] These have been supplemented by similar concerns for adverse outcomes at age 16 to 22 months for preterm infants weighing less than 1000 g.[76] Infants with TB levels that approach thresholds for an exchange transfusion should be followed through infancy until school age for awkwardness, gait abnormality, failure of fine stereognosis, gaze abnormalities, poor coordination, and exaggerated extrapyramidal reflexes. Follow-up should include neurologic and neurodevelopmental evaluation, neuroimaging with magnetic resonance, and ABRs.

SUMMARY

Bilirubin, a powerful antioxidant, also can act as a powerful but silent neurotoxin at the most vulnerable stage of preterm life. The impact is long-lasting with both functional and structural neurologic injury that alters the processing of afferent input and leads to disordered efferent function. Moreover, these perturbations can potentially arrest or retard the natural neural maturation and/or lead to disordered clinical extrapyramidal function, sensory processing of hearing, visual responses, and learning. At a cellular level, development of neurogenic niches and maturation of both vascular endothelial cells and glial cells are significant in the immediate postnatal period, which may be amplified by the concomitant stresses that can accompany these exposures, such as prematurity, inflammation/sepsis, and oxidative stress. Innovative rehabilitation techniques during early follow-up may promote plastic compensation for loss of function. Functional recovery would depend on the ability of the maturing brain to reestablish neuroplasticity as with most preterm neonates at risk for developmental sequelae. In the future, advances in neuroimaging techniques, comprehensive evaluation for the integrity of auditory and visual responses, and specific testing for extrapyramidal neuromotor performances may contribute to the increased recognition of bilirubin-related neurologic sequelae. In the meantime, as better predictive biomarkers are validated, individualized clinical judgment is the key to balance the risks and benefits of preventive, effective, and timely interventions.

Best practices

What is the current practice?

To reduce the bilirubin load and use of exchange transfusion in preterm infants.

Current practices include the following:
- Early onset of enteral feeding
- Proactive use of effective phototherapy
- Clinical reliance on TB levels to assess bilirubin load
- Identification of vulnerable infants with hemolysis, sepsis, or hypoalbuminemia

Best practice recommendations

- Use consensus and expert recommendations for initiation and use of phototherapy until predictive evidence is validated in prospective studies
- Minimize, based on clinical judgment, exposure to phototherapy in ELBW infants who may be more vulnerable to side effects of photo-oxidant injury, yet more at risk for developing bilirubin-related neurotoxicity if left untreated
- Aggressive reduction of bilirubin load if there is onset of any neurologic signs
- Be informed of hypoalbuminemia or any concurrent conditions that may alter bilirubin binding to albumin and increase the potential risk of BIND

What changes in current practice are likely to improve outcomes?

- Research regarding proven predictive biomarkers of BIND
- Early recognition of rate of rise in TB levels that could overwhelm the bilirubin binding to albumin in preterm neonates
- Consistent use of blue light-emitting diode devices to deliver phototherapy and implement the American Academy of Pediatrics guideline
- Develop quality improvement measures that promote use of phototherapy as a "drug"

Is there a clinical algorithm?

- See **Figs. 1** and **2** algorithms that guide interventions using expert recommendations.

Summary statement

Hyperbilirubinemia in preterm infants is related to increased bilirubin production and/or concurrent delayed bilirubin elimination. Clinical burden of hyperbilirubinemia is confounded by an infant's prematurity, delayed enteral feeding, presence of neonatal sepsis, use of drugs that impede bilirubin binding to albumin, and cholestasis that is often attributed to prolonged use of parenteral nutrition. A higher risk of mortality, long-term neurologic injury, and risk of subtle sequelae (BIND) have been more evident in preterm as compared with term neonates. Evaluation of bilirubin load includes determination of TB, rate of rise of TB for age in hours, serum albumin levels, UB, and BBC, as well as measures of bilirubin production (such as end-tidal carbon monoxide, corrected for ambient CO (ETCOc) or carboxyhemoglobin, corrected for ambient CO [COHbc]). Early enteral feeding and optimization of narrow-band light wavelength phototherapy are the current ways to prevent and treat progressive hyperbilirubinemia in newborns less than 35 weeks of GA. Effective and widely accessible phototherapy has resulted in rare occurrences of ABE and CBE as well as the infrequent need for exchange transfusion. However, recently there are more reports of potential for photo-oxidant injury in the management of ELBW infants exposed to phototherapy.

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