Hyperbilirubinemia in Preterm Neonates

Vinod K. Bhutani, MD*, Ronald J. Wong, BS, David K. Stevenson, MD

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

Author Disclosure: None of the authors have financial relationships relevant to this article to disclose. None of the authors have conflicts of interest to disclose.
Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford Children's Health, Lucile Packard Children's Hospital, Stanford University School of Medicine, Stanford, CA, USA
* Corresponding author. Department of Pediatrics, Stanford University School of Medicine, 750 Welch Road, Suite #315, Palo Alto, CA 94304.
E-mail address: bhutani@stanford.edu

Clin Perinatol 43 (2016) 215–232
http://dx.doi.org/10.1016/j.clp.2016.01.001 **perinatology.theclinics.com**
0095-5108/16/$ – see front matter

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 $\pm$ 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.