Jaundice and Kernicterus in the Moderately Preterm Infant

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KEYWORDS

• Kernicterus • Bilirubin-induced neurologic dysfunction • Jaundice
• Hyperbilirubinemia • Bilirubin encephalopathy • Newborn jaundice
• Moderately preterm

KEY POINTS

- Moderately preterm infants remain at increased risk for adverse outcomes, including acute bilirubin encephalopathy (ABE) relative to term infants. Evidence-based guidelines for the management of hyperbilirubinemia in moderately preterm infants, however, are lacking.
- High concentrations of unconjugated bilirubin can cause permanent neurologic damage in infants, known as chronic bilirubin encephalopathy or kernicterus.
- There is growing concern that exposure to even moderate concentrations of bilirubin may lead to subtle but permanent neurodevelopmental impairment (NDI), known as bilirubin-induced neurologic dysfunction (BIND).
- Clinical manifestations of ABE in preterm infants are similar to, but often more subtle than, those of term infants.
- This article provides clinical strategies to operationalize the thresholds for the management of hyperbilirubinemia in moderately preterm infants, based on recently published consensus-based recommendations.

INTRODUCTION

The American Academy of Pediatrics published guidelines for management of hyperbilirubinemia in infants greater than or equal to 35 weeks' gestational age (GA) in 2004.[1] This management protocol, based on available evidence, has been widely

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accepted as standard practice and has been successfully implemented for late preterm infants.[2] Similar guidelines in the United States for infants less than 35 weeks' GA have been elusive due to absence of a rigorous standard of evidence and the practical inability to test the hypothesis of bilirubin-induced injury in vulnerable infants. As a result, management of hyperbilirubinemia in moderately preterm infants ($28^{0/7}$ to $34^{6/7}$–wk GA) varies greatly among neonatal intensive care units (NICUs).[3–5] A consensus-based recommendation was recently proposed for use of phototherapy and exchange transfusion in preterm infants less than 35 weeks' GA.[6] These practical recommendations are based on expert consensus because there are insufficient data to establish evidence-based guidelines.

Posticteric complications are infrequent, with liberal and effective use of phototherapy in current clinical practice. The risk is not zero, however, and several recent studies have shown that even moderate or low total serum/plasma bilirubin (TB) levels can lead to development of kernicterus in sick premature infants.[7–10] Furthermore, recent population studies suggest that moderate elevations in TB may be associated with NDI,[10,11] although additional studies failed to identify increased risk of NDI with moderate TB elevation.[12,13] Studies of extremely low birth weight (ELBW) infants have been informative. A recent randomized controlled trial showed that aggressive phototherapy in ELBW infants reduced NDI and hearing loss among surviving infants versus those receiving conservative phototherapy. A post hoc statistical analysis reported, however, a 5% higher mortality among those infants weighing 501 g to 750 g in the aggressive phototherapy group, although the CI included 1.0.[14] This subcohort of the smallest of infants with translucent and fragile skin was exposed to light irradiance that lowered their concentration of plasma bilirubin (a powerful antioxidant).

There is extensive literature on phototherapy guidelines for full-term and ELBW infants; however, management of hyperbilirubinemia in infants less than 35 weeks' GA has not been subject to similar scientific rigor. This review outlines clinical strategies that would operationalize the management of hyperbilirubinemia in moderately preterm infants to meet the recently published consensus-based recommendations[6] and examines the scope of the problem of hyperbilirubinemia in moderately preterm infants, the mechanism of brain injury, clinical manifestations of untreated and progressive hyperbilirubinemia, and the spectrum of BIND.

SCOPE OF THE PROBLEM

Infants 30 to 35 weeks' GA constitute almost one-third of all NICU admissions.[15] This moderately preterm population is more vulnerable to adverse outcomes at lower TB concentrations, including ABE, relative to term infants.[15–17]

The prevalence of hyperbilirubinemia among preterm infants 30 to 34 weeks' GA is difficult to quantify. The thresholds for excessive hyperbilirubinemia in this group are not standardized by GA, and clinicians often utilize lower TB thresholds to intervene with decreasing GA.[18] As a result, the exact prevalence of BIND and kernicterus in preterm infants who survive to discharge is not known.[19]

The consequence of hyperbilirubinemia in premature infants is more severe than in term infants, with mean peak TB levels approaching 10 to 12 mg/dL (171–205 μmol/L).[17] Premature infants face higher bilirubin burdens due to increased bilirubin production, decreased hepatic uptake, decreased uridine-diphosphoglucuronate glucuronosyltransferase (UGT) activity, and increased enterohepatic circulation. Disorders in binding of bilirubin to albumin augment the vulnerability of both sick and healthy preterm infants. Furthermore, preterm infants are at higher risk for ABE due to their immature and developing nervous systems.[20–22]