Identification of Neonates at Risk for Hazardous Hyperbilirubinemia: Emerging Clinical Insights

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KEYWORDS

- Jaundice • Kernicterus
- Glucose-6-phosphate dehydrogenase deficiency
- Late preterm gestation • Breast milk feeding
- East Asian ethnicity

Hyperbilirubinemia is the most common condition requiring evaluation and treatment in neonates, but for most newborns, it is a benign postnatal transitional phenomenon of no overt clinical significance. In a select few, however, the total serum bilirubin (TSB) may rise to hazardous levels that pose a direct threat of brain damage. Advanced phases of acute bilirubin encephalopathy may ensue, frequently evolving into chronic bilirubin encephalopathy (kernicterus), a devastating, disabling condition classically characterized by the clinical tetrad of choreoathetoid cerebral palsy, high-frequency central neural hearing loss, palsy of vertical gaze, and dental enamel hypoplasia as the result of bilirubin-induced cell toxicity.[1,2]

Originally described in newborns who had Rh hemolytic disease, kernicterus has been reported in apparently healthy term and late preterm gestation breastfed infants who do not have documented hemolysis.[3–5] Published reports of kernicterus in the United States[3–5] and abroad[6–8] have increased since the mid- to late-1980s. In the United States, a striking and sustained increase in breastfeeding prevalence[9] coupled with a concurrent progressive decline in birth hospitalization length of stay[10] appear to have unmasked a previously underappreciated potential to develop extreme levels of

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hyperbilirubinemia in some neonates (**Fig. 1**), the biologic basis of which is often multifactorial.[11,12] This article highlights selected demographic, environmental, and genetic risk factors that may contribute to a neonate's predisposition to marked hyperbilirubinemia. It is meant not to be comprehensive in scope but to define among the myriad of potential contributors the salient ones that may merit special clinical attention and provide updated details regarding their possible etiopathogenic roles.

Although each selected factor holds the potential to be a singularly important, even sole, contributor to an infant's marked hyperbilirubinemia, risk factors are more often observed in combination with others.[11,12] In infants who had peak TSB levels of 25 mg/dL (428 μmol/L) or higher, 88% had a least two and 43% had three or more identified risk factors in one recent report,[11] and 58% who had peak TSB levels of 20 mg/dL (342 μmol/L) or higher had at least two risk factors in another report.[12] Data derived from risk instruments that incorporate several factors support the potential multifactorial etiopathogenesis of marked hyperbilirubinemia, albeit genetic contributors may go undetected and individual factors confer different degrees of risk.[11,13] These risk instruments further highlight the clinical importance of two specific risk factors in particular, namely late preterm gestational age and exclusive breastfeeding.[11,13,14] These two contributors are reviewed first, followed by six others of notable clinical impact: glucose-6-phosphate dehydrogenase (G6PD) deficiency, ABO hemolytic disease, East Asian ethnicity, jaundice observed in the first 24 hours of life, cephalohematoma or significant bruising, and history of a previous sibling treated with phototherapy.[15] Each contributor is characterized as a major risk factor for the development of severe hyperbilirubinemia in infants of 35 or more weeks' gestation in the 2004 American Academy of Pediatrics (AAP) clinical practice guideline on hyperbilirubinemia management (**Box 1**).[15] Also summarized is the emerging evidence that combining risk factors with predischarge TSB or transcutaneous bilirubin (TcB) levels improves hyperbilirubinemia risk prediction.[13,14,16] Practitioners

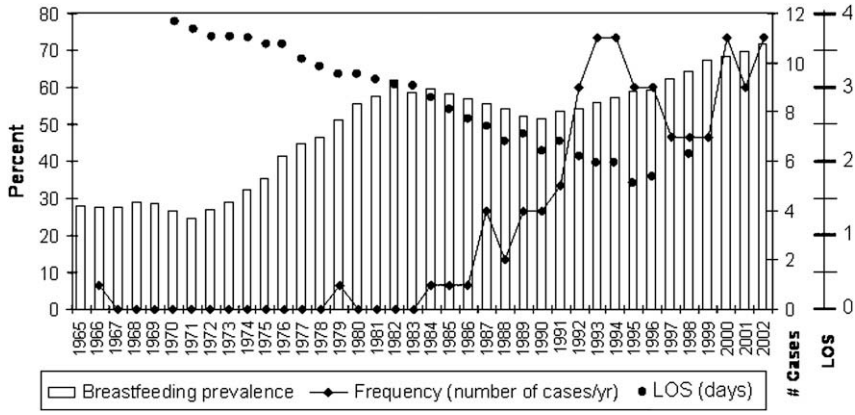

Fig. 1. Number of reported kernicterus cases by birth year from 1965 to 2002 (*solid diamonds*)[4] in relation to annual prevalence of breastfeeding at birth hospitalization (*open bars, as percentage*)[9] and birth hospitalization length of stay (*solid circles, in days*).[10] An increase in reported cases of kernicterus is seen in conjunction with a sustained resurgence of breastfeeding initiation prevalence during birth hospitalization and concurrent decreased birth hospitalization length of stay (LOS). (*From* Watchko JF. Kernicterus and the molecular mechanisms of bilirubin-induced CNS injury in newborns. Neuromolecular Med 2006;8:515; with permission.)