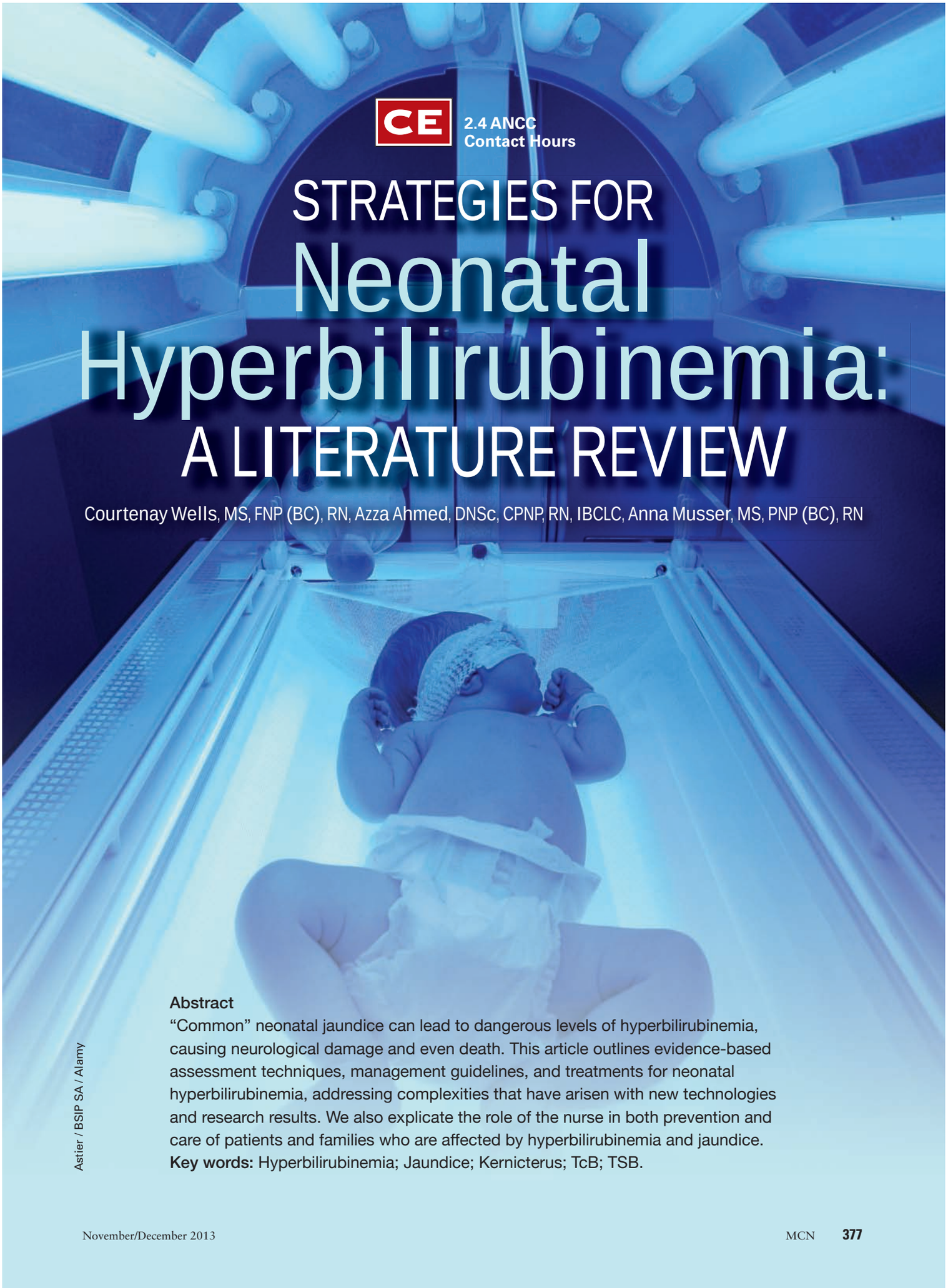

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STRATEGIES FOR Neonatal Hyperbilirubinemia: A LITERATURE REVIEW

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Abstract

"Common" neonatal jaundice can lead to dangerous levels of hyperbilirubinemia, causing neurological damage and even death. This article outlines evidence-based assessment techniques, management guidelines, and treatments for neonatal hyperbilirubinemia, addressing complexities that have arisen with new technologies and research results. We also explicate the role of the nurse in both prevention and care of patients and families who are affected by hyperbilirubinemia and jaundice.

Key words: Hyperbilirubinemia; Jaundice; Kernicterus; TcB; TSB.

Astier / BSIP SA / Alamy

Prevention of a Tragic "Never-Event"

Kernicterus—the permanent, debilitating neurophysiological result of bilirubin toxicity in neonates—has been likened to a plane crash (Bhutani & Johnson, 2009a): it is enormously tragic, it is a systems failure, and it is preventable (American Academy of Pediatrics (AAP), 2004; Bhutani & Johnson, 2009b; Lazarus & Avchen, 2009). Prevention attempts have been hampered by parental lack of awareness of hyperbilirubinemia (Lazarus & Avchen, 2009) perhaps because there has been success in treating jaundice caused by abnormally high serum bilirubin in recent decades, and the general public therefore hears little about its long-term effects and danger. It can also be a hidden problem because no national registry officially monitors numbers or victims (Lazarus & Avchen, 2009), and guidelines designed to prevent and manage jaundice may not be followed by a majority of healthcare providers (Bhutani & Johnson, 2009b). This article outlines evidence-based assessment techniques, management guidelines, and treatments for neonatal hyperbilirubinemia and explains the role of the nurse in handling, managing, and preventing this healthcare problem.

Development of Hyperbilirubinemia in the Neonate

Hyperbilirubinemia describes an imbalance between bilirubin production, conjugation and elimination (Colletti, Kothari, Jackson, Kilgore, & Barringer, 2007). Red blood cell and hemoglobin break down results in the buildup of unconjugated bilirubin (Maisels, 2006), which binds to albumin and is carried to the liver (Moerschel, Cianciaruso, & Tracy, 2008). Unconjugated bilirubin is conjugated by the liver, making it water soluble and easily eliminated from the body through stool (Moerschel et al., 2008). Accumulation of unconjugated bilirubin in the system causes jaundice and a yellow skin tint (Maisels, 2006). Unconjugated bilirubin can cross the blood–brain barrier where it produces toxic effects on the central nervous system that can have serious short- and long-term consequences (Moerschel et al., 2008).

Most neonates experience lag time before their own livers can effectively begin conjugating bilirubin, so they may manifest a transient condition known as physiologic jaundice (Maisels, 2006), which peaks at around 3 to 5 days postpartum and resolves after 1 to 2 weeks (Lazarus & Avchen, 2009). Though usually self-limiting, physiologic jaundice requires continued assessment.

Toxic effects of hyperbilirubinemia for infants can include acute bilirubin encephalopathy, involving retrocollis-opisthotonos (hyperextension of the neck and arching and stiffening of the back), a shrill cry, inability to feed, apnea, seizures, and death (AAP, 2004; Kaplan, Bromiker, & Hammerman, 2011). Kernicterus, which becomes a permanent state of neurotoxic debility if survived initially, involves degrees of mental retardation, deafness, abnormal movements, and cerebral palsy (Bhutani, Vilms, & Hamerman-Johnson, 2010; Maisels, 2006). Of a group of children with kernicterus (average age less than 8), 60% could not walk; 36% had severe or profound mental retardation; 12% required a feeding tube; and 56% had severe or profound hearing impairment (Kaplan et al., 2011).

Risk Factors for Developing Hyperbilirubinemia

Early Hospital Discharge

Discharge from the hospital at or before 48 hours postpartum increases risk of hyperbilirubinemia development because neonates are home, not under direct medical supervision at age 3 to 5 days when bilirubin levels are most likely to peak (Bhutani, Johnson, Schwoebel, & Gennaro, 2006; Goulet, Fall, D'Amour, & Pineault 2007; Maisels, 2010). Breastfeeding mothers and infants should be discharged only after the mother fully understands effective breastfeeding, and can restate teaching on infant monitoring for jaundice and how to reach support services (Academy of Breastfeeding Medicine, 2010). Nurses should be empowered to teach effective breastfeeding practices and symptoms for home discharge, as well as assessing infants for risk (ABM, 2010; Preer & Philipp, 2010).

Breastfeeding Difficulties

Some hyperbilirubinemia is associated with breastfeeding:

- "normal" breastfeeding jaundice (also called "human milk jaundice syndrome")
- "not enough" breastfeeding jaundice

Difficulties with breastfeeding can cause common and usually transient hyperbilirubinemia (Bhutani et al., 2010; Maisels, 2006; Preer & Philipp, 2010; Watchko, 2009; Watson, 2009). "Normal" breastfeeding jaundice, called "breastfeeding jaundice" or "human milk jaundice syndrome," occurs due to as-yet-unexplained metabolic changes involving factors in breast milk (Maisels, 2006; Preer & Philipp, 2010). These infants nurse appropriately, gain weight, and demonstrate adequate hydration and nutrition. The jaundice begins in the first or second week postpartum, can last up to 12 weeks, and usually resolves spontaneously (Preer & Philipp, 2010).

A more serious form of neonatal hyperbilirubinemia is due to lack of nutritional intake, caloric deprivation, weight loss, and dehydration (Preer and Philipp, 2010). Infants with "not enough breastfeeding jaundice," which manifests early (at 2–4 days old) often have poor latch or suck, lose weight, and become dehydrated, interfering with bilirubin excretion and leading to toxicity (Salas & Mazzi, 2008).

Increased Levels of Bilirubin in First 24 Hours of Life

Infant bilirubin that increases in the first 24 hours, refuses to drop, or has no obvious etiology should be suspected of pathology (Colletti et al., 2007) such as maternal–fetal ABO/Rh incompatibility (Maisels, 2006; Preer & Philipp,

2010; Watchko, 2009) and genetic conditions (Chang et al., 2011). Mutations at the UGT-1A1 gene can cause Gilbert syndrome and Crigler-Najjar syndrome types I and II. Glucose-6-phosphate dehydrogenase deficiency (G-6PD) is an important enzymopathic cause of severe neonatal hyperbilirubinemia found mostly in Mediterranean, Middle Eastern, African, and Asian populations as well as globally mixed throughout the population (Maisels, 2006; Preer & Philipp, 2010; Watchko, 2009).

Late Preterm Birth

Late preterm infants (born between 34 and 36 weeks gestation) are at increased risk due to extreme hepatic immaturity (Watchko, 2009) and feeding difficulties (Watchko, 2006). Late preterm infants are about 13 times more likely to be readmitted to the hospital for severe jaundice (Maisels, 2006), and neurotoxic effects tend to be more severe (Watchko, 2009).

Unconjugated bilirubin crosses the blood-brain barrier where it produces toxic effects on the central nervous system.

Assessment of Jaundice and Hyperbilirubinemia

Accurate assessment is paramount to appropriate treatment of hyperbilirubinemia. Visual assessment of jaundice may be difficult or inaccurate, especially in infants with pigmented skin, and those infants of less than 38 weeks gestation, although the guidelines do not recommend measuring a bilirubin level on all infants (AAP, 2004). Nurses can facilitate guidelines (AAP, 2004) that emphasize promoting and supporting breastfeeding, assessing infants for risk factors, assessing jaundice via total serum bilirubin (TSB) or transcutaneous bilirubin (TcB), educating, and promoting follow-up.

Management of hyperbilirubinemia involves interpretation of TSB or TcB measurements on a nomogram that plots neonatal age in hours against total serum bilirubin (Figure 1), along with consideration of the infant's additional risk factors (Maisels, 2010). A tailored management and follow-up plan can then be implemented. Age and bilirubin levels (Maisels, 2006) combined with medical factors (AAP, 2004; Bhutani, Maisels, Stark, & Buonocore, 2008; Maisels, 2010) are good predictors of subsequent bilirubin levels and risk (Maisels, DeRidder, Kring, & Balasubramaniam, 2009).

Measurement of Bilirubin

Visual assessment of bilirubin (VaB) uses the naked human eye to detect jaundice. Although it is possible to detect cutaneous jaundice at about 5 to 7 mg/dL (Watson, 2009), the difference between TSB values of 5 mg/dL and 8 mg/dL represent the 50th and 95th percentiles at 24 hours on the Nomogram (Figure 1) (Maisels, 2006); this is a very large difference that leaves infants at risk (Bhutani et al., 2006). Clinicians are therefore discouraged from reliance on VaB (Bhutani, Vilms, & Hamerman-Johnson, 2010; Lease & Whalen, 2010). However, AAP (2004) guidelines still recognize use of VaB in jaundice detection.

TcB is a quick, noninvasive test with confirmed accuracy (Mishra et al., 2009). Research has shown that use of TcB reduced the need for confirmatory TSB (and a needle stick) 34% over infants assessed visually; furthermore, TcB readings correlated significantly with TSB levels (Kuzniewicz, Escobar, & Newman, 2009; Mishra et al., 2009). Total cutaneous bilirubin is used as a screening test; infants with at-risk TcB levels have TSB drawn as confirmation prior to determining treatment (AAP, 2004; Burgos, Flaherman, & Newman, 2011). Serial TcB values have been shown to increase accuracy of risk prediction (Maisels et al., 2009). Nomogram-plotted TcB values have been found to be good predictors of hyperbilirubinemia risk (Maisels et al., 2009), decreasing need for needles.

Universal Bilirubin Screening

Universal bilirubin screening is a powerful tool for efficiently finding cases and preventing adverse effects of hyperbilirubinemia (Kuzniewicz et al., 2009). Accurate prediction and timely discovery lead to prompt treatment, which is critically important. Even seriously jaundiced infants (25 mg/dL and above) may thus recover to become neurologically and cognitively equal to their peers by age 2 (Newman et al., 2006).

Universal bilirubin screening in neonates is increasingly valued, with accurate, noninvasive TcB an effective tool (Dijk & Hulzebos, 2012). Denmark (Bjerre, Petersen, & Ebbesen, 2008) and major U.S. hospital systems (Bhutani et al., 2010; Maisels et al., 2009) have instituted universal TcB screening for infants. The Hospital Corporation of America, handling about 5% of all U.S. births, instituted a nationwide all-neonate screening policy that led to a 38% drop in the incidence of bilirubins in the 25 to 29.9 mg/dL range and a 65% drop in bilirubins 30 mg/dL and over, major successes of their program (Mah et al., 2010). Other studies have found similar results, in the range of 40% to 70% decreases in TSB levels at or over 25 mg/dL (Burgos et al., 2011). Kaiser Permanente found that increased detection of bilirubin levels at 15 to 19.9 mg/dL was associated with a decline in higher and more dangerous TSB levels (Burgos et al., 2011). Universal hospital bilirubin screening programs result in net savings based on the cost per test of TcB versus risk and costs of treating children with the lifelong sequelae of kernicterus (Bhutani et al., 2010). Considering such data, universal bilirubin screening has been supported by many experts in the field (Burgos et al., 2011; National Association of Neonatal Nurses, 2010; Slusher, Zipursky, & Bhutani, 2011), and should be considered for comprehensive, widespread implementation.

Treatment Modalities

Phototherapy

Phototherapy is highly effective for the treatment of high and severely high levels of bilirubin (Bhutani & the Committee on Fetus and Newborn, 2011; Bhutani et al., 2008; DeLuca, 2010; Schwartz, Haberman, & Ruddy, 2011; Stevenson & Wong, 2010). Four decades of use have indicated its safety, efficacy, and lack of serious adverse effects in populations of newborns ≥35 weeks gestation (Bhutani & the Committee on Fetus and Newborn, 2011), making it the "cornerstone" of hyperbilirubinemia therapy (Kijk & Hulzebos, 2012). Phototherapy involves the use of light in a specific spectrum that, when delivered via lamp, pad, blanket, or cover-body devices (Bhutani & the Committee on Fetus and Newborn, 2011; Watson, 2009), converts bilirubin cutaneously from unconjugated to conjugated form, rendering it able to bypass the liver and progress directly to excretion in bile or urine (Maisels, 2006; Watson 2009). The type of device used, duration of therapy, strength of light treatment, and venue (hospital or home) depend on the severity of hyperbilirubinemia (Bhutani & the Committee on Fetus and Newborn, 2011; Schwartz et al., 2011; Watson, 2009).

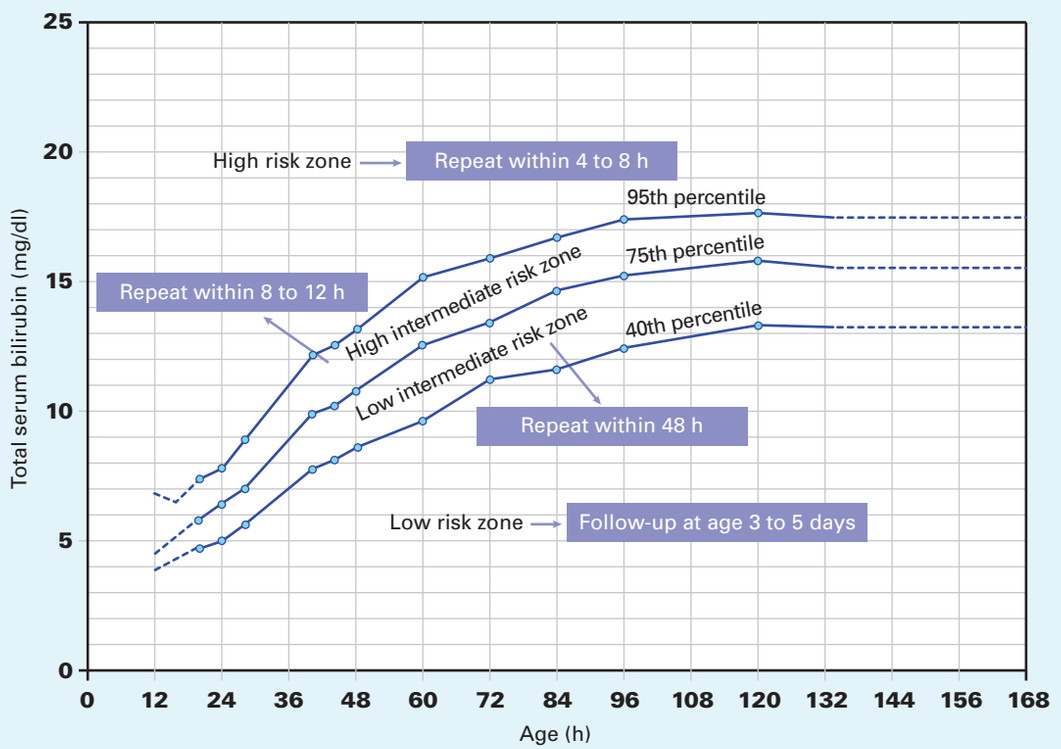
Phototherapy can be safely interrupted for up to 30 minutes at a time to facilitate breastfeeding and other necessities (ABM, 2010). Bilirubin usually decreases within 2 hours of onset of phototherapy, at which point it is considered medically permissible to allow interruption for feeding and bonding (Bhutani & the Committee on Fetus and Newborn, 2011). Risk of dehydration due to insensible water loss may be a concern for exclusively breastfed babies and should be monitored (ABM, 2010; NCC, 2010).

Nursing considerations include ensuring eye protection for the infant and minimizing diaper covers and monitoring patches to increase skin surface area treated. Plastic covers or optical filters are used over lights to filter out ultraviolet light and prevent skin damage (Bhutani & the Committee on Fetus and Newborn, 2011). Nurses monitor the infant's insensible water loss, temperature control, maintenance of the parent/infant bond, and ensure continuity of the infant's feeding, caring, and medical needs in treatment (Watson, 2009). Rare adverse effects of phototherapy include photosensitivity and blistering, purpura, bullae, and the development of bronze baby syndrome, which although poorly understood, involves a grayish-brown darkening of skin, serum, and urine (Watson, 2009).

Exchange Transfusion

Aggressive use of phototherapy has decreased the use of the invasive exchange transfusion (ET) method (Bhutani &

Figure 1. Nomogram of Neonatal Age in Hours Versus Total Serum Bilirubin. Graphic representation of guidelines for predischarge TSB or TcB levels in neonates.



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the Committee on Fetus and Newborn, 2011), relegating ET to only severely emergent cases (Bhutani & the Committee on Fetus and Newborn, 2011; Bhutani et al., 2008; DeLuca, 2010; Schwartz et al., 2011; Stevenson & Wong, 2010). Lack of adequate phototherapy and facilities, severity of hyperbilirubinemia complicated by genetic factors, and systems deficits make ET a more common treatment in developing countries (Dijk & Hulzebos, 2012; Slusher et al., 2011). ET involves removing high-bilirubin aliquots of the infant's own blood and then systematically replacing it with "clean" donor blood to effect a rapid bilirubin decrease (Maisels, 2006; Watson, 2009). ET takes place through one to two central or peripheral catheters, usually umbilical access (Chen, Lee, & Tsao, 2008; Patra, Storfer-Isser, Siner, Moore, & Hack, 2004). Infusion of blood products involves metabolic risks and blood-products risks, though most are transient and treatable findings (Behjati, Sagheb, Aryasepehr, & Yaghmai, 2009; Steiner, Bizarro, Ehrenkranz, & Gallagher, 2007). Adverse effects may also include apnea (Behjati et al., 2009), necrotizing enterocolitis, renal failure, seizure, and progression to kernicterus (Salas & Mazzi, 2008). Death has been reported, but it is often difficult to separate out preexisting comorbidities in finding cause (Patra et al., 2004).

Immunoglobulin and Metalloporphyrins

Intravenous infusion of immunoglobulin is most often used as a primary treatment for hyperbilirubinemia in infants with immunological disorders (Bratlid, Nakstad, & Hansen, 2011), although it may also be used as adjunctive therapy to phototherapy, decreasing duration of phototherapy and hospital stay (Schwartz et al., 2011). Infants with isoimmune hemolytic jaundice have particularly benefitted from the use of immunoglobulins, decreasing the need for ET (Schwartz et al., 2011). Intravenous immunoglobulin infusion is generally well tolerated and safe; rare complications include risk of hemolysis, sepsis, and renal failure (Schwartz et al., 2011).

Metalloporphyrins function by targeting the enzyme heme oxygenase to limit production of bilirubin (Schwartz et al., 2011; Stevenson & Wong, 2010) to treat hyperbilirubinemia (Dennery, 2005). Unlike other methods, metalloporphyrins may also be used as a prevention strategy in infant populations known to be highly vulnerable to hyperbilirubinemia (Stevenson & Wong, 2010), such as extremely low birthweight infants and those with genetic risk factors such as Gilbert's syndrome, glucose-6-phosphate dehydrogenase, and UGT-1A1 mutations (Stevenson & Wong, 2010). However, they are still considered to be experimental (Dennery, 2005), have not been proven unequivocally safe in humans (Shulz, Wong, Vreman, & Stevenson, 2012), are not approved by the FDA, and are specifically labeled "not recommended" as therapy by some guidelines (National Collaborating Centre for Women and Children's Health, 2010).

Conclusion

Kernicterus is a "never event," preventable with appropriate interventions. Universal screening is more than promising; it is working in a variety of settings. Transcutaneous bilirubin screening is noninvasive, practical, and effective; when followed by appropriate treatment, it saves lives and prevents permanent neurological debility. Nurses are powerful advocates, treating and teaching at the bedside as well as initiating risk assessment for infants and promoting correct follow-up postdischarge. Appropriate assessment and teaching regarding breastfeeding, and ensuring mother/baby competence in feeding prior to discharge is essential for prevention of kernicterus. Using an evidence-based approach, we can hope for acute bilirubin encephalopathy and kernicterus to become historical reminders of the power of persistent commitment to prevention in achieving child health. ✣

Nursing Implications

- Nurses who work with mothers and infants at the bedside are often first to identify risks and needs.
- Nurses should be diligent in teaching effective breastfeeding practices that prevent infant dehydration, malnutrition, and jaundice.
- Continuing assessment of whether clinicians are complying with protocols to recognize hyperbilirubinemia is essential.
- Prior to discharge, nurses should be sure to teach caregivers to recognize jaundice and to follow up appropriately with clinicians.
- Nurses should consider advocating for universal bilirubin screening of all infants prior to discharge to assess risk and prevent adverse events.

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www.pickonline.org

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www.ncbi.nlm.nih.gov

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www.emedicine.medscape.com/article/975276-overview
www.guidelines.gov/content/aspx?id=23806&search=hyperbilirubinemia

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