0021-7557/07/83-04/289
Jornal de Pediatria

Prevention of severe neonatal hyperbilirubinemia in healthy infants of 35 or more weeks of gestation: implementation of a systems-based approach

Vinod K. Bhutani,[1] Lois Johnson[2]

Newborns with jaundice or unrecognized hyperbilirubinemia are a vulnerable population which is likely to be deprived from preventive and/or therapeutic healthcare services in their transition from birthing hospital to their homes. Of the 4 million infants born each year in the United States, over 3.5 million are born at 35 or more weeks of gestation. Most have benign outcomes with little or no threat of neurological compromise from medical conditions during their first year of life. Over the past 4 decades, proven preventive health measures provided at well-baby nurseries and at delivery rooms have been effective in reducing infant mortality and morbidity. However, nearly all healthy infants have some degree of hyperbilirubinemia and over 60% develop jaundice during their first week of life. When unmonitored or untreated in a timely manner, hyperbilirubinemia can become excessive and may be unrecognized if the infant is not under medical supervision.[1] An adverse outcome could be a spectrum of bilirubin-induced neurologic dysfunction (BIND) and its severest manifestation: kernicterus, a lifelong athetoid cerebral palsy with sensorineural auditory impairment. Hyperbilirubinemia increases within hours after birth. Hour-specific total serum bilirubin (TSB) levels > 95th percentile (for healthy infants) is equivalent to > 17 mg/dL beyond the age of 72 hours. This cohort of "at-risk" infants could be vulnerable to BIND if the progression to excessive hyperbilirubinemia is unmonitored. Most of these "at-risk" infants have increased bilirubin production and/or impaired bilirubin elimination. Delay in the natural ability to eliminate bilirubin is evident in infants < 38 weeks of gestation, and in those with decreased milk intake or with intercurrent infection. Severe hyperbilirubinemia, either based on the risk for neurotoxicity[2] as defined by TSB threshold levels (20 mg/dL or more for a term healthy low-risk infant), or as a TSB increase > 0.20 mg/dL /hr,[3,4] has called forth the recommendation for intervention with intensive phototherapy. Clinicians have recognized that infants at risk for severe hyperbilirubinemia have more complex healthcare needs. These needs are often confounded by fractured healthcare services encountered by families during the first 2-3 weeks after birth.

See related article on page 313

The underlying root cause for the recent U.S. experience with kernicterus has been identified as a systems failure in neonatal services.[5] Primarily, health services are often provided by multiple providers at multiple sites. Secondly, the professional community of physicians, nurses, maternal child healthcare providers, child health advocates, lactation consultants, as well as the lay society, often has insufficient understanding and knowledge about the potential of bilirubin neurotoxicity. The resultant interacting root causes include a) early hospital discharge at age < 72 hours (before the extent of jaundice is known); b) lack of adequate concern for the risks of excessive jaundice in healthy term and near-term newborns; c) a laudable increase in breastfeeding, but without support and counseling to monitor adequacy of milk transfer and optimal lactogenesis; d) perceived medical cost

1. MD. Professor, Division of Neonatal and Developmental Medicine, Lucile Salter Packard Children's Hospital, Stanford University School of Medicine, Stanford, CA, USA.
2. MD. Research physician, Department of Pediatric Ophthalmology, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA.

Supported in part by grant number HRSA: U21MC03954-01-00.

Suggested citation: Bhutani VK, Johnson L. Prevention of severe neonatal hyperbilirubinemia in healthy infants of 35 or more weeks of gestation: implementation of a systems-based approach. J Pediatr (Rio J). 2007;83(4):289-293.

doi:10.2223/JPED.1673

constraints complicating reimbursement for follow-up at age 3 to 5 days; e) paucity of educational materials to enable and empower families to seek healthcare in a timely manner; and f) limitations within healthcare systems to provide pre-discharge screening, identification of families and infants at increased risk to ensure post-discharge follow-up. To address these root causes, we have proposed and implemented a model for a family-centered, systems-based approach that builds constructive parent/healthcare partnerships aimed at the prevention of BIND and related disabilities.[3,4]

Regardless of the cause of jaundice, the potential risk for unrecognized, unmonitored, untreated severe hyperbilirubinemia has raised concerns for patient safety. The focus of the 2004 AAP guidelines has shifted to a preventive approach.[2] Early and intermediate stages of acute bilirubin encephalopathy may be reversible with prompt and effective bilirubin reduction strategies. It is in this context that the AAP recommends universal application of the principles enunciated by the Institute of Medicine for patient centeredness, patient safety, and timeliness of care and use of effective interventions to prevent kernicterus.[2] A public health goal[6] for the contemporary society has been enunciated as: "One case of kernicterus is one too many; we can prevent them all". AAP has sought to monitor and facilitate the implementation of the guidelines and ascertain the barriers to the micro health environment unique to clinical practices, communities and healthcare infrastructure.[7] Practicing clinicians, at the front line of health delivery, often deal with realities of a non-existent seamless transfer of clinical information during the transition after birth and would benefit from strategies that provide continued vigilance. Fernando Perazzini Facchini et al.[8] report a systems approach implemented at Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil. This strategy includes universal pre-discharge bilirubin screening with an Ingram icterometer and/or transcutaneous bilirubin screening (TcB), selective TSB screening with a mandatory follow-up by a patient-friendly, nearly seamless follow-up of infants with pre-discharge bilirubin levels > 40th percentile and early identification of severe hyperbilirubinemia and its timely treatment. In a cohort of 11,259 neonates of 35 or more weeks of gestation managed through this approach, the frequency of excessive hyperbilirubinemia is shown and compared to several North American and European studies (Tables 1, 2, 3). None were identified with a TSB level ≥ 30 mg/dL. A commendable success!

Regional and practice variations that impact barriers to healthcare services, neonatal screening, and timely intervention have led 1 in 650 to 15,000 infants (35 or more weeks of gestation) to develop TSB values ≥ 427 µmol/L (≥ 25 mg /dL) and zero to 1 in every 10,000 infants to develop TSB levels ≥ 510 µmol, ≥ 30 mg/dL.[8-14] As shown in Tables 1 and 2, implementation of systems-based practices is associated with lower or minimal occurrences of excessive and dangerous hyperbilirubinemia. There are limited population-based studies of the incidence of either acute bilirubin encephalopathy and/or chronic bilirubin encephalopathy (kernicterus). In Denmark, Ebbesen reported eight cases of kernicterus for an incidence of 1.4/100,000 live births between 1994 and 2002, but no cases had been reported in the previous 20 years.[14] Between 2002 and 2005, with a more vigilant approach, no more cases were seen in Denmark, and the overall incidence dropped to 1.1/100,000 live births from1994 to 2005.[18] A UK surveillance study has reported an occurrence of kernicterus of 1 in 100,000 live-births.[11] The frequency of severe hyperbilirubinemia (serum bilirubin > 425 µmol/L) was 1 in 2,840 live births in Canada, of which 13 (2/100,000 live births) had abnormal neurologic outcomes at hospital discharge.[12] The frequency of extreme hyperbilirubinemia (serum bilirubin > 510 µmol/L) was 1 in 14,084 live births in the UK.[11] There is a societal expectation to provide a universally available safe birthing experience that includes a safe experience with neonatal jaundice. Thus, kernicterus (or a TSB level > 30 mg/dL, > 513 µmol/L)) is now considered a "never-event" by the public health community. A goal achieved by the Campinas program.

More importantly, 8,807 (78.2% of the Campinas cohort) were reassured and needed a less intensive follow-up.[8] Decision regret was limited to one infant who returned spontaneously with jaundice at a level requiring treatment. This failure was attributed to inadequate assessment at the time of discharge, since this patient was only observed clinically and was judged to be "mildly" jaundiced. The low frequency of infants with TSB levels > 15 mg/dL and occasional re-referral would also suggest an underestimation of TSB by noninvasive techniques, specifically by the Ingram icterometer. However, the perceived low-cost nature of this approach was suggested by the experience of a single post-discharge follow-up for 79.7% of the study infants. Only 11.4% needed two post-discharge visits, whereas 3.5% had three or more follow-up visits. These data are among the first to prospectively inform a post-discharge outpatient management strategy based on the percentile-based hour-specific nomogram. The Campinas study demonstrates an implementation strategy that may be applicable to similar clinical practices.

Adoption of a variety of systems approaches to institutional, regional or national programs to prevent severe hyperbilirubinemia could reduce the burden of communities and possibly prevent BIND (Table 4). Fernando Perazzini Facchini et al. have demonstrated the first three steps at one clinical site.[8] The next two steps would require validation, review and consensus for a national strategy. Thus, as nationwide campaigns for prevention of severe neonatal hyperbilirubinemia are planned, an emphasis should focus on the education and

Table 1 - Frequency of total serum bilirubin ≥ 30 mg/dL

Regions	Health practice (type of review)	Study period	Frequency
Canada	National survey data[9]	2002-2004	NA
USA (CA)	HMO system data[10]	1995-1998	1 in 10,000
UK	National review data[11]	2003-2005	1 in 14,084
USA (HCA)	Health system data[12]	2003	1 in 14,651
USA (PA) prospective	Systems-based: universal bilirubin screening[3]	1990-2003	zero
Brazil (SP) prospective	Systems-based: universal bilirubin screening[8]	2001-2005	zero

The first four studies are retrospective: bilirubin screening and follow-up done at MD discretion.
CA = California; HCA = Hospital Corporation of America; HMO = Health Maintenance Organization; PA = Pennsylvania; SP = São Paulo.

Table 2 - Frequency of total serum bilirubin ≥ 25 mg/dL

Regions	Health practice (random review)	Study period	Frequency
USA (CA)	HMO system data[10]	1994-1998	1 in 700
USA (UT)	Health system data[13]	2002	1 in 1,522
USA (HCA)	Health system data[12]	2003	1 in 1,878
Canada	National survey data[9]	2002-2004	1 in 2,840
Denmark	National review: home follow-up[14]	1994-2002	1 in 4,320
Brazil (SP) prospective	Systems-based: universal bilirubin screening[8]	2001-2005	1 in 5,630
USA (PA) prospective	Systems-based: universal bilirubin screening[3]	1990-2003	1 in 15,000

The first four studies are retrospective: bilirubin screening and follow-up done at MD discretion.
CA = California; HCA = Hospital Corporation of America; HMO = Health Maintenance Organization; SP = São Paulo; PA = Pennsylvania; UT = Utah.

empowerment of both parents and clinical providers. Salient messages should rely on a) evidence-based and transparent public health messages and b) a coordinated outreach initiative that is consistent with the prevailing infrastructure of the healthcare system. On the other hand, alarmist public health messages for vulnerable communities of expectant mothers and new parents without adequate and concurrent attention to healthcare infrastructure may have unplanned consequences.

In summary, as we balance evidence-based medicine, patient safety and protective care for all newborns entrusted to the care of health professionals, partnership with parents should lead to implementation of a kinder, gentler and protective approach. An effective clinical and community health strategy would allow a clinician to more easily and effectively identify and worry about those few at risk-infants. Protective care of those at risk for severe neonatal hyperbilirubinemia would prevent virtually all cases of kernicterus.

Table 3 - Frequency of total serum bilirubin ≥ 15 or 17 mg/dL or 95th percentile

Study	Population	Frequency
Bhutani et al.[15] (1999; universal TSB screening)	230/2,840	8.1% (≥ 95th percentile)
Stevenson et al.[16] (2000; universal TSB screening)	125/1,625	8.8% (≥95th percentile)
Martinez et al.[17] (1999; universal TSB screening)	126/1,370	7.5% (TSB ≥17 mg/dL)
Newman et al.*[10] (2000; random TSB testing)	520/51,387	1.0% (TSB ≥15 mg/dL)
Facchini et al.[8] (2006; universal icterometer/TcB and selective TSB screening)	180/11,259	1.6% (TSB >15 mg/L)

* Retrospective study. All studies exclude infants who received phototherapy before discharge.
TcB = transcutaneous bilirubin screening; TSB = total serum bilirubin.

Table 4 - Five-step nationwide strategy to prevent severe neonatal hyperbilirubinemia

1	An institutional curriculum for the systems approach: universal prenatal, pre-discharge, and post-discharge risk assessment of severe neonatal hyperbilirubinemia.
2	Advocacy for on-site services that promote breastfeeding in the context of supervised and seamless healthcare delivery during the first month of life.
3	Effective parent-provider partnerships for safer management of neonatal jaundice.
4	Statewide (or regional) reporting of birthing institution outcome assessment for severe neonatal hyperbilirubinemia along with outcomes for neonatal screening for other inherited disorders.
5	Nationwide surveillance: reporting of severe neonatal hyperbilirubinemia.

References

1. Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. J Pediatr. 2002;140:396-403.
2. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297-316.
3. Bhutani VK, Johnson LH, Keren R. Diagnosis and management of hyperbilirubinemia in the term neonate: for a safer first week. Pediatr Clin North Am. 2004;51:843-61,vii.
4. Bhutani VK, Johnson LH, Schwoebel A, Gennaro S. A systems approach for neonatal hyperbilirubinemia in term and near-term newborns. J Obstet Gynecol Neonatal Nurs. 2006;35:444-55.
5. Bhutani VK, Donn SM, Johnson LH. Risk management of severe neonatal hyperbilirubinemia to prevent kernicterus. Clin Perinatol. 2005;32:125-39.
6. Yeargin-Allsopp M. CDC Medical Officer Comment on "Prevent This" video for public education. http://www.cdc.gov/ncbddd/dd/kernicterus/kernicterusvideos/kervideotransc.htm.
7. Lannon C, Stark AR. Closing the gap between guidelines and practice: ensuring safe and healthy beginnings. Pediatrics. 2004;114:494-6.
8. Facchini FP, Mezzacappa MA, Rosa IR, Mezzacappa Fº F, Netto AA, Marba ST. Follow-up of neonatal jaundice in term and late premature newborns. J Pediatr (Rio J). 2007;83:313-8.
9. Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ. 2006;175:587-90.

10. Newman TB, Xiong B, Gonzales VM, Escobar GJ. Prediction and prevention of extreme neonatal hyperbilirubinemia in a mature health maintenance organization. Arch Pediatr Adolesc Med. 2000;154:1140-7.
11. Manning DJ, Maxwell MJ, Todd PJ, Platt MJ. Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the United Kingdom and Ireland. Arch Dis Child Fetal Neonatal Ed. 2006; [Epub ahead of print]. http://fn.bmj.com/cgi/rapidpdf/adc.2006.105361v1.
12. Bhutani VK, Rodriguez M; HCA Perinatal Safety Initiative Kernicterus Taskforce. Recent epidemiologic indices of severe hyperbilirubinemia and kernicterus for a diverse multi-state newborn population in USA [abstract]. Presented as an abstract at the Pediatric Academic Society Annual Meeting; 2005.
13. Eggert LD, Wiedmeier SE, Wilson J, Christensen RD. The effect of instituting a prehospital-discharge newborn bilirubin screening program in an 18-hospital health system. Pediatrics. 2006;117:e855-62.
14. Ebbesen F. Recurrence of kernicterus in term and near-term infants in Denmark. Acta Paediatr. 2000;89:1213-7.
15. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics.1999;103:6-14.
16. Stevenson DK, Fanaroff AA, Maisels MJ, Young BW, Wong RJ, Vreman HJ, et al. Prediction of hyperbilirubinemia in near term and term infants. Pediatrics. 2001;108:31-9.
17. Martinez JC, Garcia, HO, Otheguy LE, Drummond GS, Kappas A. Control of severe hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. Pediatrics. 1999;103:1-5.
18. Ebbesen F, Andersson C, Verder H, Grytter C, Pedersen-Bjergaard L, Petersen JR, et al. Extreme hyperbilirubinaemia in term and near-term infants in Denmark. Acta Paediatr. 2005;94:59-64.

Turn off the lights and the oxygen, when not needed: phototherapy and oxidative stress in the neonate

Augusto Sola *

In this issue of Jornal de Pediatria, Aycicek & Erel[1] publish an *illuminating* article on the potentially serious detrimental effects of "therapy with light" on neonatal defenses against oxidant stress. This is the first report showing an association between serum oxidant/antioxidant parameters in phototherapy-treated term infants. It is amazing, indeed, that little is known about the potential damage of phototherapy and its possible mechanisms and that so little attention has been paid to possible adverse effects of such a commonly used therapy. Who would have imagined that only 48 hours of exposure to phototherapy soon after birth in full term healthy neonates may lead to metabolic derangement of the already poorly functioning and underdeveloped neonatal defenses against oxidant stress? What the authors describe emphasizes my motto in relation to oxygenation and neonatal health hazards: "More important than what we see is what we do not see." Through the *illumination* of this manuscript, we must now wonder: What is the light doing that leaves us in the darkness? Based on these authors' findings, it seems that phototherapy oxidizes term babies. If this is so, what happens to preterm infants who are placed under the light 'just in case' and are also given oxygen in excess of what they need? What a potentially really bad combination: one therapy which decreases antioxidants and one which increases them! Sadly, most of the time healthcare providers give both these therapies to an infant, in combination or separately, without any proven need and to produce no known benefit. Making a newborn hyperoxic and

See related article on page 319

* Director of Neonatal Research and Academic Affairs, Atlantic Neonatal Research Institute, Goryeb Children's Center, Mid Atlantic Neonatology Associates, Morristown, New Jersey, USA.

Suggested citation: Sola A. Turn off the lights and the oxygen, when not needed: phototherapy and oxidative stress in the neonate. J Pediatr (Rio J). 2007;83(4):293-296.

doi:10.2223/JPED.1674