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Screening for Neonatal Hyperbilirubinemia—First Do No Harm?

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Screening of newborn infants for hyperbilirubinemia (NHB) is a common clinical practice in the United States. Since 2004, the American Academy of Pediatrics has endorsed either universal or risk-based predischarge screening of bilirubin levels in newborns of 35 weeks' gestational age or older to evaluate the risk for NHB using a nomogram standardized to age in hours and follow-up management using consensus-based treatment guidelines.[1] The anticipated benefits of screening for NHB, followed by phototherapy and/or exchange transfusion when indicated, are to prevent acute bilirubin encephalopathy, which has a direct burden of morbidity and can also progress to chronic bilirubin encephalopathy (CBE) with devastating neurodevelopmental consequences (also known as *kernicterus*). However, it is important to consider the balance of benefits and harms of screening and treatment; newly published evidence[2] that treatment of NHB is associated with elevated risks of epilepsy might lead hospitals to reevaluate the balance of benefits and risks of referring newborns for phototherapy on the basis of screening for NHB.

Although phototherapy is known to be effective in reducing serum bilirubin levels, the efficacy of phototherapy in reducing the incidence of kernicterus remains unquantified. Further, phototherapy is associated with harms. Two US organizations have concluded that there was insufficient evidence to warrant universal screening of term or near-term infants for NHB as a clinical practice guideline: the US Preventive Services Task Force in 2009[3] and the American Academy of Family Physicians (AAFP) in 2014.[4] The AAFP cited unsupported reports of associations of neonatal jaundice with asthma and type 1 diabetes as

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evidence of potential long-term risks of phototherapy. The AAFP also cited evidence that universal screening for NHB is associated with frequent inappropriate use of phototherapy for infants who do not meet clinical guidelines for treatment.

In addition, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) in 2012 considered whether to recommend that NHB be added to the US Department of Health and Human Services Recommended Uniform Screening Panel for mandated public health newborn screening.[5] The ACHDNC follows a decision matrix that includes consideration of evidence of both benefits and harms of screening and treatment. The ACHDNC decided not to recommend that screening for NHB be added to the Recommended Uniform Screening Panel, based on the lack of direct evidence that screening reduces the occurrence of CBE. The evidence review[6] conducted for the ACHDNC acknowledged evidence of minor (temporary) harms associated with phototherapy but identified no evidence of long-term harms. The review noted that a 6-year follow-up of a randomized clinicaltrial[7] of phototherapy for NHB by the National Institutes for Child Health and Development found no differences in developmental outcomes. However, since only 335 children who received phototherapy were examined at 6 years, the study was not powered to evaluate risks of uncommon neurological sequelae.

Although cohort studies conducted at Kaiser Permanente of Northern California (KPNC) found no associations of phototherapy with the long-term harms of either type 1 diabetes or asthma, KPNC research[2] did confirm a previous finding from Denmark[8] that phototherapy for NHB was associated with significantly increased risk of epilepsy in boys, although not girls. The KPNC study[2] of prospectively gathered data for a cohort of a half million children born at term or near term, of whom 37 683 received phototherapy, found a crude epilepsy hazard ratio of 1.55 (95% CI, 0.83–2.66), similar to that reported in the Danish study. After adjusting for serum bilirubin levels and other potential confounders (eg, race/ ethnicity, gestational age, birth weight, other diagnoses), the adjusted hazard ratio for a diagnosis of a seizure disorder plus receipt of antiepileptic medication was reduced to 1.22 (95% CI, 1.05–1.42) for all children; among boys alone, it was 1.33 (95% CI, 1.10–1.61). The authors[2] noted that the findings were consistent with sex differences in susceptibility to perinatal injury, as well as induced epilepsy in laboratory animals. However, they noted that they could not exclude the possibility of confounding by unobserved factors that might be associated with both phototherapy in early childhood and later seizures.

A relevant question for screening policy and practice is the balance of benefits and harms associated with treatments after screening. Newman and colleagues[2] reported a “small increased risk of childhood seizures,”[2] with an absolute excess 10-year risk of epilepsy of 2.4 per 1000 children treated with phototherapy, with epilepsy assessed as the presence of 1 or more encounter for nonfebrile seizures together with 1 or more filled prescription for an antiepileptic medication. Although the absolute risk of epilepsy is small, it is large relative to the number of potentially preventable cases of kernicterus. The findings imply that in a hypothetical cohort of 1 000 000 infants, of whom 76 000 receive phototherapy, 182 children will develop epilepsy as a result of treatment. The risk of kernicterus was estimated in the ACHDNC evidence review to be 0.47 to 1.30 per 100 000 newborns without screening, and the incidence of kernicterus with screening is estimated by KPNC researchers to be 0.57 per

100 000 newborns.[9] That implies screening 1 000 000 infants for NHB and treatment could prevent up to 7 cases of kernicterus. Since many infants receive phototherapy for jaundice in the absence of screening, only a subset of the 182 cases of epilepsy could be attributed to the indirect effect of screening for NHB. Although CBE is more devastating than epilepsy and the association of phototherapy with epilepsy requires further study, the balance of benefit to risk is not clearly favorable to phototherapy for all infants diagnosed with NHB through screening.

One implication is that changes in treatment and bilirubin testing protocols that reduce the number of children who receive phototherapy could reduce the risk of harm without necessarily reducing the number of children who benefit clinically. Consistent with this approach, Newman et al[2] suggest that restricting the number of children who receive phototherapy based on elevated bilirubin levels could greatly reduce the risk of harm. In particular, the KPNC data[9] suggest that the risk of kernicterus may be limited to infants whose bilirubin levels are substantially higher than currently recommended thresholds and who also have other risk factors for neurotoxicity. Another way to reduce the overall number of children who receive phototherapy without excluding those who would be more likely to benefit could be to limit bilirubin testing to infants with clinical signs, chiefly jaundice. Infants born in KPNC hospitals after universal bilirubin testing was introduced were more likely to receive phototherapy than infants born in those hospitals previously and were less likely to be referred for exchange transfusion.[10]

The National Institutes for Child Health and Development phototherapy follow-up study was not powered to evaluate rare adverse outcomes, such as epilepsy. That is a cautionary lesson for policy makers: absence of evidence of harm is not evidence of absence of harm. Large-scale, long-term follow-up studies of outcomes of screening and treatment are important to ensure that the anticipated positive balance of benefits and harms of newborn screening is realized in practice.

In conclusion, the stances of the AAFP, ACHDNC, and the US Preventive Services Task Force, which do not endorse universal screening for NBH, are reinforced by emerging data on the apparent risk of long-term harm of phototherapy associated with hyperbilirubinemia. These views are also reinforced by the persistent lack of clarity regarding which infants are at risk of developing CBE and the lack of direct evidence that screening reduces the risk of CBE.

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