Prediction and Prevention of Extreme Neonatal Hyperbilirubinemia in a Mature Health Maintenance Organization

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Objective: To investigate biological and health services predictors of extreme neonatal hyperbilirubinemia in a health maintenance organization.

Design: Nested case-control study.

Setting: Eleven Northern California Kaiser Permanente hospitals.

Subjects: The cohort consisted of 51,387 newborns born at 36 weeks or later weighing 2000 g or more. Cases were newborns with peak total serum bilirubin levels greater than or equal to 428 µmol/L (≥25 mg/dL) (n = 73). Controls were a random sample of newborns from the cohort with peak bilirubin levels less than 428 µmol/L (<25 mg/dL) (n = 423).

Measurements: Review of medical records and telephone interviews.

Results: Early jaundice was most strongly associated with case status (odds ratio [OR]=7.3). After excluding subjects with early jaundice, the strongest predictors of hyperbilirubinemia were family history of jaundice in a newborn (OR=6.0), exclusive breastfeeding (OR=5.7), bruising (OR=4.0), Asian race (OR=3.5), cephalhematoma (OR=3.3), maternal age of 25 years or older (OR=3.1), and lower gestational age (OR=0.6/week). These variables identified 61% of newborns as very low risk (about 1/4200). However, the risk in the remaining 39% was still low (1/370). More cases (79%) than controls (59%) had newborn length-of-stay and follow-up consistent with the American Academy of Pediatrics guidelines, but phototherapy use within 8 hours of the time that the guidelines recommend was uncommon in both cases (26%) and controls (33%). There were no apparent cases of kernicterus.

Conclusions: Prevention of extreme hyperbilirubinemia may require closer follow-up than is currently recommended by the American Academy of Pediatrics and more use of phototherapy than was observed in this study. To prevent extreme hyperbilirubinemia (≥428 µmol/L [≥25 mg/dL]) in 1 newborn, many newborns would need to receive these interventions.

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Although most newborns develop some degree of jaundice, bilirubin levels high enough to put a newborn at risk of kernicterus or exchange transfusion are rare. In a previous study we found that extreme hyperbilirubinemia, defined here as a total serum bilirubin (TSB) level of greater than or equal to 428 µmol/L (≥25 mg/dL), occurs in about 1 in 700 term or near-term newborns in the Northern California Kaiser Permanente Medical Care Program (KPMP).

Why do some newborns develop this degree of hyperbilirubinemia? The answer depends upon the interplay of 2 types of predictor variables. First are biological variables—those that affect the rate of bilirubin production or excretion, such as hemolytic disease, gestational age, race, and breastfeeding. The second are health services variables—policies or decisions regarding timing of initial hospital discharge, follow-up appointments, and bilirubin-lowering interventions, that can lead to hyperbilirubinemia not being identified and treated at a level low enough to prevent it from reaching 428 µmol/L (25 mg/dL). The current study was undertaken to determine the importance of both types of variables as causes of extreme hyperbilirubinemia in a mature health maintenance organization. We specifically wished to estimate the proportion of newborns at high risk for subsequently developing extreme hyperbilirubinemia based on biological variables, and the proportion that

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METHODS

SUBJECTS

The cohort included all 51,387 infants horn alive at 11 KPMCP Northern California hospitals during the 1993 and 1996 calendar years whose birth weight was at least 2000 g and whose gestational age was at least 36 weeks. The cohort was identified entirely through KPMCP electronic databases as previously described.3,6

Cases were newborns whose maximum TSB levels within the first 30 days after birth were greater than or equal to 428 µmol/L (25 mg/dL). Data on TSB levels were obtained from the KPMCP integrated laboratory information system.2 Of 75 cases identified through computer databases, 2 were excluded because paper records revealed that their gestational ages or birth weights did not meet inclusion criteria, leaving 73 cases.

Controls were a random sample of the entire cohort. All had TSB levels less than 428 µmol/L (<25 mg/dL). Of 427 controls initially sampled, 1 infant’s initial birth hospitalization record could not be found, and 3 were ineligible due to birth weight or gestational age, leaving 423 controls. The high ratio of controls to cases occurred because the same control group was being used for a study of newborns readmitted for dehydration. For analyses examining use of phototherapy only, an additional random sample of 30 newborns with maximum TSB levels of 342 to 426 µmol/L (20–24.9 mg/dL) was added to the control group.

The study was approved by the KPMCP Institutional Review Board for the Protection of Human Subjects.

STUDY DESIGN

The study was a nested case-control study7 in which an identified cohort (in this case 51,387 live-born newborns) was chosen, all instances of the outcome were identified (in this case TSB ≥428 µmol/L [≥25 mg/dL]), and values of various predictors were compared between cases and a random sample of those in the cohort who did not develop the outcome (the controls).

DATA SOURCES AND VARIABLE DEFINITIONS

Record Reviews and Interviews

Medical record analysts abstracted records of cases and controls and their mothers. To obtain information not reliably present in medical records, we attempted telephone interviews of parents of all surviving cases and controls. Primary care physicians declined us permission to contact parents of 4 cases (5.5%) and 11 controls (2.6%). We sent parents of remaining newborns a letter describing the study, including a postcard to return if they did not wish to be contacted. Parents of 3 cases (4.5%) and 22 controls (5.2%) declined to be interviewed and 9 cases (12%) and 63 controls (77%) could not be located. One case and 2 controls had died. Interviews were successfully completed in 56 cases (77%) and 325 controls (77%). At the time of the interviews, most subjects were 2 to 3 years old. The interview primarily addressed issues related to breastfeeding, concerns of the parent in the first few weeks after the child’s birth, and any current health problems or special needs of the child.

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Phototherapy

We obtained the dates, times, and results of all total and conjugated bilirubin levels for each of the subjects from the KPMCP regional laboratory database.2 To investigate cholestasis as a cause of hyperbilirubinemia in the cases, we calculated the ratio of the maximum conjugated bilirubin level to the maximum TSB level.

Combining TSB results with the date and time of birth and the AAP’s age-specific phototherapy recommendations,4 we determined which newborns were documented to have exceeded the AAP thresholds for phototherapy, and the age at which this first occurred. The AAP recommendations do not specify thresholds for phototherapy within the first 24 hours after birth, but extrapolating from recommendations for 24 to 48 hours, we considered phototherapy to have been indicated if the TSB level was greater than or equal to 205 µmol/L (≥12 mg/dL) within the first 24 hours. Information on timing of phototherapy was obtained from review of medical records. If phototherapy was not begun within 8 hours of when the TSB level was first documented to exceed these treatment thresholds, we considered AAP guidelines for phototherapy not to have been followed.

For example, 1 case newborn first exceeded the AAP threshold for phototherapy at 68 hours of age, when his TSB level was 325 µmol/L (19 mg/dL), because the AAP recommends phototherapy at 48 to 72 hours of age if the TSB level is greater than 308 µmol/L (>18 mg/dL).4 Since he did not receive phototherapy until 123 hours of age, when his TSB level was 470 µmol/L (27.5 mg/dL), we considered AAP guidelines for phototherapy to have been followed for this newborn.

Length of Hospital Stay and Follow-up

We supplemented information from paper records with data from KPMCP outpatient registration, emergency department records, and telephone interviews of parents. Length of hospital stay was calculated as the number of day intervals from birth to the date of the first hospitalization record.

DESCRIPTIVE DATA

Most (85%) of the cases’ peak TSB levels were between 428 and 479 µmol/L (25-28 mg/dL); only 5 had levels greater than or equal to 513 µmol/L (≥30 mg/dL). The median age at which the TSB levels first were docu-
department, and home health databases to determine timing of outpatient and home health visits. We considered AAP guidelines for follow-up to have been met if the initial length of stay was at least 48 hours or if the initial length of stay was less than 48 hours and the newborn was seen either in the clinic or by a home health nurse within 72 hours of discharge. We obtained data from the KMCSC appointment system to distinguish between follow-up appointments that were and were not scheduled before the discharge from the birth hospitalization. The latter group included patients whose care-takers called for an appointment because they were instructed to do so during the birth hospitalization and patients whose care-takers either called for an appointment or dropped in because they were concerned about the newborn.

STATISTICAL ANALYSIS

Early Jaundice

Because we wished to predict hyperbilirubinemia after initial hospital discharge, we identified a subset of newborns that already had significant jaundice during their birth hospitalization. We excluded these infants with early jaundice from some of the multivariate prediction models. A newborn was considered to have early jaundice if (1) bilirubin level during the birth hospitalization was documented to exceed the recommended phototherapy threshold for age or to exceed half the newborn's age in hours; (2) phototherapy was administered during the birth hospitalization; or (3) jaundice was noted at less than 20 hours of age and a bilirubin level was not measured within 6 hours of that time.

Data Extraction and Bivariate and Multivariate Analyses

We extracted initial data from KMCSC databases using SAS (Statistical Analysis Software, Cary, NC) and did subsequent analyses using Stata 5.0 or 6.0 for Windows (Statacorp, College Station, Tex) or Excel 5.0 (Microsoft, Redmond, Wash). We began with simple bivariate analyses, calculating the odds ratios (ORs) for clinical and demographic predictors of case/control status. For nominal and ordinal categorical variables we generally dichotomized or created appropriate indicator variables, using the most prevalent category as the comparison group. We collapsed gestational age into 4 categories based on apparent homogeneity of risk within categories. P values for these bivariate comparisons were calculated using χ² or Fisher exact tests as appropriate.

We entered variables associated with hyperbilirubinemia in previous studies or in bivariate analyses into backward stepwise multiple logistic regression analyses to identify significant (P<0.05) independent predictors of hyperbilirubinemia. We did these analyses both including and excluding early jaundice cases. We quantified discrimination of logistic models using the c statistic, equal to the area under the receiver operating characteristic curve, and used the Hosmer-Lemeshow goodness-of-fit-test with 10 groups.

Risk Group Analysis

Using a method described by Scholer et al, we created a risk index by assigning points approximately equal to the OR for risk factors that were significant in the logistic model with early jaundice cases excluded. For example, exclusive breastfeeding and a family history of jaundice in a newborn each were worth 6 points because each had an OR of about 6, whereas maternal age of 25 years or older and presence of a cephalhematoma each were worth 3 points because each had an OR of about 3. The OR for gestational age of 0.6 per week indicated that greater gestational age was associated with lower risk. Thus a 42-week infant was at lower than average risk and had points subtracted, while a 37-week infant was at higher than average risk and had points added. We assigned points for gestational age by subtracting the subject's gestational age from 40 and multiplying by 2. When early jaundice cases were excluded there were no black newborns in the case group (OR=0). In this study and in our previous studies the OR for black race was about 0.5, therefore we chose to subtract 2 for black race. Although male sex was not statistically significant in this study, in our larger study male sex was a significant predictor (OR=1.95; P=.007), so we included an additional point for male sex.

The risk index was then categorized to facilitate calculation of likelihood ratios and posterior probability. The prior probability was estimated as the number of late cases with TSB levels at or exceeding 428 µmol/L (≥25 mg/dL) (n=59) divided by the population at risk. The population at risk was estimated to be the entire cohort (51387) times the proportion in the control group that did not have early jaundice (402/423). Thus, the prior probability was about 0.59/48836=1.2/1000. Because both prior and posterior probabilities of TSB levels greater than or equal to 428 µmol/L (≥25 mg/dL) were very low in this study, they did not need to be converted to prior odds, and the posterior probability could be estimated simply by multiplying the prior probability (1.2/1000) times the likelihood ratio.

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BIOLOGICAL PREDICTORS OF EXTREME HYPERBILIRUBINEMIA

Bivariate Analyses

Distributions of biological predictors of hyperbilirubinemia in cases and controls are shown in Table 1. There were 14 cases and 21 controls with early jaundice. Except as noted below, results were similar among the entire group as well as among the subset in which we excluded cases and controls with early jaundice.

Maternal and prenatal factors associated with TSB levels greater than or equal to 428 µmol/L (≥25 mg/dL) in bivariate analyses included race, maternal age, a family history of jaundice in a newborn, and a history of bruising or cephalhematoma. After exclusion of early jaundice, there was no evidence of association with any of these factors. There was a weak association with oxytocin use and no evidence of an association with maternal diabetes. A trend toward a protective effect of maternal tobacco use was not significant, but the numbers of exposed newborns were small.

Newborn factors associated with TSB levels greater than or equal to 428 µmol/L (≥25 mg/dL) in bivariate analyses included male sex, lower gestational age, early jaundice, cephalhematoma, bruising, and breastfeeding at the time of discharge from the birth hospitalization. The latter showed a gradient of risk (compared with exclusive bottle-feeding), with an OR of 2.7 for breastfeeding plus bottle-feeding and an OR of 7.8 for exclusive breastfeeding.

When cases and controls with early jaundice were excluded (data not shown), the main differences in bivariate results were that the OR for exclusive breastfeeding became statistically significant (OR=2.1, P=.03).

Multivariate Models

Significant biological predictors of hyperbilirubinemia in backward stepwise multiple logistic regression models included gestational age, exclusive breastfeeding, Asian race, presence of bruising or cephalhematomas, and maternal age of 25 years or older (Table 2). Results for all cases and the subset that excluded cases with early jaundice were similar, except that a family
developing a TSB level greater than or equal to 428 µmol/L (25 mg/dL) with a risk of about 1/4200. Among the 39% of newborns at low risk, 61% of newborns would be in the low-risk group, about 2% in the 1% of newborns with index scores greater than or equal to 428 µmol/L (25 mg/dL) (ie, positive predictive value) was only about 1 in 370 (0.27%).

**Risk Index**

A simple risk index that combines values for the biological predictors of TSB levels greater than or equal to 428 µmol/L (≥ 25 mg/dL) (Table 3) predicted the outcome (c=0.85) as well as the complete logistic model (c=0.85). The 32% of newborns whose risk index was 7 or less had a risk of developing a TSB level greater than or equal to 428 µmol/L (≥ 25 mg/dL) of about 1 in 16000, compared with a risk of about 2% in the 1% of newborns with index scores greater than 20 (Table 4)—a 330-fold difference in risk. If a score of 10 or less is used as the cutoff for low risk, 61% of newborns would be in the low-risk group, with a risk of about 1/4200. Among the 39% of newborns that would be classified as high risk, the risk of developing a TSB level greater than or equal to 428 µmol/L (≥ 25 mg/dL) (ie, positive predictive value) was only about 1 in 370 (0.27%).

**Health Services Predictors**

With adjustment for biological predictors, newborns born at hospital 4 were at 2 to 3 times the risk of developing TSB levels greater than or equal to 428 µmol/L (≥ 25 mg/dL) (Table 2; P=.02).

Use of phototherapy in relation to the age the newborns’ TSB levels exceeded the AAP’s phototherapy treatment thresholds is shown for cases and controls in Table 5. Twenty-three cases exceeded the AAP phototherapy threshold before their TSB levels reached 428 µmol/L (25 mg/dL). Of these, only 6 (26%) received phototherapy within 8 hours of exceeding the threshold. The use of phototherapy within 8 hours of the AAP guidelines in the control group and in the additional group of 30 randomly selected newborns whose maximum TSB levels were 342 to 426 µmol/L (20-24.9 mg/dL), was only 33%, a proportion not significantly different from that observed in the cases (P=.8).

If adherence to AAP length-of-stay and follow-up guidelines were protective against TSB levels greater than or equal to 428 µmol/L (≥ 25 mg/dL), we would have expected to see greater adherence to the guidelines in the controls than in the cases. This was not observed (Table 6). Initial length of stay did not differ between cases and controls whether or not early jaundice cases were included (median length of stay was 33.4 hours for cases, 32.4 hours for cases excluding early jaundice, and 30.1 hours for controls; P=.3 by Kruskal-Wallis for both comparisons with controls). Cases were more likely to have received follow-up adherent to AAP guidelines (79%) than were controls (59%). This is primarily because of an almost 20% greater unscheduled outpatient visit rate in the 72 hours following an initial stay of less than 48 hours.

**Table 3. Risk Index for Predicting TSB ≥428 µmol/L (25 mg/dL) in Newborns Who Do Not Have Early Jaundice**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusive breastfeeding</td>
<td>6</td>
</tr>
<tr>
<td>Family history of jaundice in a newborn</td>
<td>6</td>
</tr>
<tr>
<td>Bruising noted</td>
<td>4</td>
</tr>
<tr>
<td>Asian race</td>
<td>4</td>
</tr>
<tr>
<td>Cephalhematoma noted</td>
<td>3</td>
</tr>
<tr>
<td>Maternal age ≥25 y</td>
<td>3</td>
</tr>
<tr>
<td>Male sex</td>
<td>1</td>
</tr>
<tr>
<td>Black race</td>
<td>2</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>2</td>
</tr>
</tbody>
</table>

*Risk index score is calculated as the sum of all characteristics that apply to the patient, except that points for gestational age (GA) are assigned based on twice the difference of GA from 40 weeks. For example, a 37-week bottle-fed Asian male newborn whose mother was 30 years old would receive a score of 14: 6 (2 × [40-37]) + 4 (Asian) + 1 (male) + 3 (mother > 25 y). TSB indicates total serum bilirubin.

In this nested case-control study, we found that several biological variables, particularly early jaundice, a family history of jaundice in a newborn, breastfeeding, race, gestational age, maternal age, bruising, and cephalhematomas, strongly predict a newborn’s risk of developing a TSB level greater than or equal to 428 µmol/L (≥ 25 mg/dL). Not surprisingly, predictors of this level of extreme hyperbilirubinemia previously have been found to predict milder levels of hyperbilirubinemia10-13 and to predict readmission to the hospital for jaundice14 with ORs similar to those reported here.

Because this was a retrospective observational study, we were only able to study predictors available in all or almost of all of the study cohort. We thus could not examine results of direct Coombs tests or blood cell counts because these tests were much more likely to be ordered for the cases with jaundice than for the controls. We considered the 14 cases and 21 controls with jaundice at younger than 20 hours or with a TSB level exceeding AAP phototherapy thresholds during the birth hospitalization to have had early jaundice. We excluded these newborns from the multivariate prediction models and risk index because indications for treating them were already present during the birth hospitalization.

Combining the other clinical predictors of hyperbilirubinemia available at the time of hospital discharge, we created a bilirubin risk index that showed a 330-fold gradient in risk between those at lowest and highest risk for subsequent TSB levels greater than or equal to 428 µmol/L (≥ 25 mg/dL). Nonetheless, because of the rarity of the outcome and the high prevalence of the strongest risk factors (especially exclusive breastfeeding), clinical variables were better at predicting newborns at low risk than at high risk. This result is similar to that of Bhutani et al,13 who used TSB levels drawn at the time of neonatal screening to identify
40% of newborns at very low risk of subsequent hyperbilirubinemia.

Using a risk index cutoff sufficiently sensitive to label 88% of cases as high risk leads to a positive predictive value of only about 0.27%. This means that if a preventive intervention were 100% effective, about 370 (ie, 1/0.27%) “high-risk” newborns would need to be treated to prevent 1 infant’s TSB level from reaching 428 µmol/L (25 mg/dL). Even if only those in the top 1% of risk were targeted (ie, those with risk index scores greater than 20), the number needed to treat would be about 50, and 86% of cases would be missed.

A few cautions about application of the risk index in other settings are needed. First, since performance of the risk index was evaluated based on the data set from which it was derived, its predictive ability at other times and places will probably be lower. Second, as mentioned previously, it is derived from the group in which early jaundice cases were excluded. Newborns with early jaundice should be considered at high risk, regardless of their risk score, especially if they have Rh disease or another known cause of hemolysis. Finally, although the factors included in the risk index are likely to be predictors of significant jaundice elsewhere, the absolute level of risk is likely to vary in different settings, as it did across hospitals in our study.

Only a few studies have examined health services variables as predictors of extreme hyperbilirubinemia. Of those studies, most attention has been focused on the initial lengths of stay as a predictors of subsequent newborn readmissions, most of which were for jaundice. Results have been mixed: some studies have found small associations between early postpartum discharge and readmission for hyperbilirubinemia,16,17 while others have found no association18-20 or an association only with discharge before 72 hours (as opposed to discharge before <24-48 hours).14,21

### Table 4. Performance of a Hyperbilirubinemia Risk Index*

<table>
<thead>
<tr>
<th>Score</th>
<th>Cases Excluding Early Jaundice (n = 59)</th>
<th>Controls Excluding Early Jaundice (n = 402)</th>
<th>Likelihood Ratio</th>
<th>Posterior Probability (Positive Predictive Value)</th>
<th>Posterior Probability as Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7</td>
<td>1 (2)</td>
<td>129 (32)</td>
<td>0.053</td>
<td>0.00006</td>
<td>1/15653</td>
</tr>
<tr>
<td>8-10</td>
<td>6 (10)</td>
<td>115 (29)</td>
<td>0.36</td>
<td>0.0043</td>
<td>1/2327</td>
</tr>
<tr>
<td>11-15</td>
<td>27 (46)</td>
<td>120 (30)</td>
<td>3.3</td>
<td>0.0040</td>
<td>1/251</td>
</tr>
<tr>
<td>16-20</td>
<td>17 (29)</td>
<td>35 (9)</td>
<td>3.3</td>
<td>0.0040</td>
<td>1/251</td>
</tr>
<tr>
<td>&gt;20</td>
<td>8 (14)</td>
<td>3 (1)</td>
<td>18.2</td>
<td>0.022</td>
<td>1/47</td>
</tr>
<tr>
<td>≤10</td>
<td>7 (12)</td>
<td>244 (61)</td>
<td>0.20</td>
<td>0.0024</td>
<td>1/4230</td>
</tr>
<tr>
<td>&gt;10</td>
<td>52 (88)</td>
<td>158 (39)</td>
<td>2.2</td>
<td>0.0027</td>
<td>1/370</td>
</tr>
</tbody>
</table>

* The risk index is defined in Table 3.

### Table 5. Adherence to AAP Phototherapy Guidelines Among Cases and Controls†

<table>
<thead>
<tr>
<th>Age Phototherapy Threshold Exceeded Before TSB ≥ 428 µmol/L (≥ 25 mg/dL)</th>
<th>&lt;24</th>
<th>24-47.9</th>
<th>48-71.9</th>
<th>≥72</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. that qualified for PT</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>No. that received PT within 8 h of qualifying</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>% Adhering to PT guidelines</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td><strong>Controls‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. that qualified for PT</td>
<td>0</td>
<td>2 (1)</td>
<td>11 (3)</td>
<td>26 (5)</td>
<td>39 (9)</td>
</tr>
<tr>
<td>No. that received PT within 8 h of qualifying</td>
<td>0</td>
<td>1 (0)</td>
<td>3 (0)</td>
<td>9 (2)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>% Adhering to PT guidelines</td>
<td>0</td>
<td>50</td>
<td>27</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

* AAP indicates American Academy of Pediatrics; TSB, total serum bilirubin; and PT, phototherapy.
† Control data include 30 additional randomly selected infants with TSB 342-427 µmol/L (20-24.9 mg/dL). Data from only the original control group are in parentheses.

### Table 6. Health Services Predictors of Hyperbilirubinemia*

<table>
<thead>
<tr>
<th>LOS, h</th>
<th>Cases (n = 73)</th>
<th>Controls (n = 423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24</td>
<td>16 (22)</td>
<td>125 (30)</td>
</tr>
<tr>
<td>24-47.9</td>
<td>41 (56)</td>
<td>200 (47)</td>
</tr>
<tr>
<td>48-71.9</td>
<td>9 (12)</td>
<td>66 (16)</td>
</tr>
<tr>
<td>≥72</td>
<td>7 (10)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Adherence to follow-up guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial LOS ≥ 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial LOS &lt; 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appointment made and kept</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AAP follow-up guidelines met</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appointment made but not kept</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No appointment made</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AAP follow-up guidelines not met</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* LOS indicates length of stay; AAP, American Academy of Pediatrics.
current study differs from these previous studies in that the cases all had TSB levels greater than or equal to 428 µmol/L (≥25 mg/dL) and that timing of outpatient visits and phototherapy use were considered as possible health services predictors in addition to the initial length of stay.

We were surprised by some of the results. We thought that most cases would be newborns whose follow-up did not meet AAP guidelines. In fact, AAP guidelines for follow-up were met in 79% of the cases—substantially more than in the control group. The difference in adherence to guidelines between cases and controls was because there were a greater number of drop-in visits and/or appointments made after discharge by the parents of the cases—presumably for jaundice. Length of initial stay and outpatient appointments scheduled before discharge did not differ between cases and controls. This suggests that if policies are to be changed to decrease the frequency of TSB at or exceeding 428 µmol/L (≥25 mg/dL), it will not be sufficient to assure adherence to AAP length-of-stay and follow-up guidelines—follow-up within 24 to 48 hours after hospital discharge (as opposed to 72 hours as recommended by the AAP) might be necessary.

Of course, closely monitoring newborns is likely to reduce the frequency of excessively high TSB levels only if accompanied by interventions to prevent the bilirubin level from rising further. We found that 23 of our cases (32%) had documented TSB levels exceeding AAP treatment thresholds before their bilirubin exceeded 428 µmol/L (25 mg/dL), but that only 6 of them (26%) had been treated with phototherapy within 8 hours. Thus, interventions to promote adherence to guidelines as a way of reducing the frequency of extreme hyperbilirubinemia should target treatment of identified high bilirubin levels at least as aggressively as they target the scheduling of follow-up visits.

Lack of adherence to AAP phototherapy guidelines was frequent in the treatment of both cases and controls. Phototherapy was provided within 8 hours to only 13 (33%) of 39 control newborns whose bilirubin levels exceeded AAP treatment thresholds. This lack of adherence to AAP guidelines may be partly because some clinicians were unaware of them. The AAP guidelines were first published in 1994 and newborns in this study were born in 1995 and 1996. Chrestakis and Rivara,22 in a 1996 survey, found that 34% of responding practicing pediatricians were unaware of the AAP's jaundice guideline. However, since the AAP guideline has higher treatment thresholds than had been previously recommended, lack of awareness would be more likely to result in overtreatment than undertreatment. It seems more likely that some clinicians believe the AAP guidelines are too conservative,23,24 since their own experience is likely to be that newborns appear to do well whether or not their jaundice is treated at the thresholds recommended by the AAP. This may have been the case at hospital 4, where the adjusted rate of TSB levels greater than or equal to 428 µmol/L (≥25 mg/dL) was highest (OR=2.6) and the frequency of bilirubin testing was lowest (0.4 TSB tests per newborn, compared with the average of 0.7).2

Despite the frequency with which phototherapy was deferred, a TSB level greater than or equal to 428 µmol/L (≥25 mg/dL) was uncommon, occurring in only about 7.5% of those whose TSB levels were greater than or equal to 342 µmol/L (≥20 mg/dL). In fact, most newborns in whom phototherapy guidelines were not followed did not become cases. Hence, as was suggested by the analysis of the bilirubin risk index, data on timing and use of phototherapy in cases and controls suggest that phototherapy would have to be done on a large number of newborns to prevent the TSB level in 1 newborn from exceeding 428 µmol/L (25 mg/dL).

To determine the circumstances under which the health benefits justify the cost and effort of treating the large numbers of newborns at risk, further studies examining data on the long-term outcome of newborns with extreme hyperbilirubinemia are called for. Few such data exist, and data from the current study, while reassuring, must be considered preliminary. Although there has been an increase in reports of kernicterus in the last 5 years,25-28 there are no denominators for these cases, making calculation of rates impossible.29 Only a few studies have looked systematically at outcomes in children with bilirubin levels greater than or equal to 428 µmol/L (≥25 mg/dL).30,31 Although these studies have not found adverse effects, sample sizes have been small. Similarly, although no apparent kernicterus was observed in our study, follow-up of these newborns was not complete and the upper limit of the 95% confidence interval for the observed 0% rate was 4%—a rate of a disastrous outcome that would justify a great deal of preventive effort. Thus, additional studies of large, defined populations with careful ascertainment of neurologic outcomes are needed to develop more evidence-based neonatal jaundice treatment guidelines. Such evidence may be needed to convince clinicians to follow them.29

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REFERENCES

4. American Academy of Pediatrics Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia. Practice parameter: manage-


Books for Review


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