Risk of Sensorineural Hearing Loss and Bilirubin Exchange Transfusion Thresholds

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**abstract**

**BACKGROUND AND OBJECTIVES:** High bilirubin levels are associated with sensorineural hearing loss (SNHL). However, few large studies of relative and excess risk exist. We sought to quantify the risk of SNHL in newborns who had bilirubin levels at or above American Academy of Pediatrics exchange transfusion thresholds (ETT).

**METHODS:** Infants born at $\geq 35$ weeks gestation in 15 Kaiser Permanente Northern California hospitals from 1995-2011 were eligible ($N = 525,409$). We used a nested double cohort design. The exposed cohort included subjects with $\geq 1$ bilirubin level at or above ETT. The unexposed cohort was a 3.6% random sample of subjects with all bilirubin levels below ETT (10 unexposed per exposed). An audiologist, blinded to bilirubin levels, reviewed the charts of children in whom SNHL had been diagnosed before age 8 years to confirm the diagnosis. We calculated Cox proportional hazard ratios for time to diagnosis of SNHL.

**RESULTS:** SNHL was confirmed in 11 (0.60%) of the 1834 exposed subjects and in 43 (0.23%) of the 19,004 unexposed. Only bilirubin levels $\geq 10$ mg/dL above ETT were associated with a statistically significant increased risk of SNHL (hazard ratio: 36 [95% confidence interval (CI): 13 to 101]). Likewise, only bilirubin levels $\geq 35$ mg/dL were associated with a statistically significant increased risk of SNHL (hazard ratio: 91 [95% CI: 32 to 255]). For subjects with total serum bilirubin levels 0 to 4.9 mg/dL above ETT, the upper limit of the 95% CI for excess risk was 0.5%.

**CONCLUSIONS:** Only bilirubin levels well above ETT were associated with SNHL. At lower bilirubin levels, the excess risk of SNHL was low.

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**WHAT’S KNOWN ON THIS SUBJECT:** High bilirubin levels are associated with sensorineural hearing loss. Exchange transfusions are recommended when bilirubin levels reach certain thresholds. However, the relative and excess risks of hearing loss in infants with bilirubin levels at/above exchange transfusion thresholds are unknown.

**WHAT THIS STUDY ADDS:** In this Northern California population of term and late preterm infants, elevated bilirubin levels were not associated with an increased risk of sensorineural hearing loss unless the levels were at least 10 mg/dL above exchange transfusion thresholds.

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Dr Wickremasinghe assisted with study design, designed the data collection instrument, assisted with chart review, conducted the initial analyses, and drafted the initial manuscript; Mr Risley performed chart review and reviewed and revised the manuscript; Drs Kuzniewicz and Wu assisted with study design and reviewed and revised the manuscript; Ms Walsh coordinated the study, assisted with study design and chart review, and reviewed and revised the manuscript; Mr Wi constructed the study databases from electronic data sources and reviewed and revised the manuscript; Dr McCulloch provided statistical consultation and reviewed and revised the manuscript; Dr Newman conceptualized and designed the study, obtained funding, assisted with statistical analyses, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.


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Hearing loss and auditory dysfunction are well-recognized sequelae of hyperbilirubinemia.\(^1\)–\(^3\) The auditory system is particularly sensitive to the toxic effects of bilirubin.\(^2\) Bilirubin, at high levels, can damage retrocochlear structures such as the brainstem auditory nuclei, inferior colliculi, spiral ganglion neurons, and auditory nerve fibers.\(^4\) The effect of hyperbilirubinemia on auditory dysfunction is generally dose dependent, with greater dysfunction noted at higher total serum bilirubin (TSB) levels.

To prevent bilirubin-related sequelae, the American Academy of Pediatrics (AAP) recommends treatment (phototherapy and/or exchange transfusion) when TSB levels reach certain values.\(^5\) However, the degree of hyperbilirubinemia that confers an increased risk of hearing dysfunction is unknown. In addition, no studies have documented the risk of sensorineural hearing loss (SNHL) in infants whose TSB levels reach recommended exchange transfusion thresholds (ETT). In the present study, we evaluated the risk of SNHL among infants with TSB levels at or above AAP ETT.

**METHODS**

**Study Design and Subjects**

We performed a nested double cohort study (Fig 1) due to the rarity of the primary exposure (TSB levels at or above AAP ETT) and the need for confirmation of hearing loss diagnoses by using a chart review. This study was part of the LIGHT (Late Impact of Getting Hyperbilirubinemia or photoTherapy) study, which was approved by the Kaiser Permanente Northern California (KPNC) institutional review board and by the University of California, San Francisco, Committee on Human Research.

The LIGHT cohort consisted of all 525 409 subjects born at \(\geq 35\) weeks’ gestation at any of 15 KPNC hospitals between January 1, 1995, and December 31, 2011. Because pediatric hearing loss can be caused by congenital disease, we excluded subjects who had any of the following diagnoses (based on *International Classification of Diseases, Ninth Revision*,\(^6\) diagnosis codes in KPNC electronic records) that could contribute to hearing loss: disorders of metabolism and immunity (270.0–271.1, 277–277.09, 277.3, 277.5–277.87, and 279.0–279.19), structural brain anomalies (740.0–740.2, 742.0, 741.00–741.03, 742.2, and 742.3), congenital anomalies (744.00–744.09, 744.23, 749.00–749.04, 749.20–749.25, and 759.5–759.83), renal agenesis (753.0), congenital ichthyosis (757.1), congenital ectodermal dysplasia (757.31), chromosomal anomalies (758.0–758.39 and 758.5–758.9), and prenatally acquired infections (771.0 and 771.1). In addition, we excluded subjects who had acquired hearing loss likely unrelated to hyperbilirubinemia: infectious meningitis and encephalitis after the first 30 days (036.0, 047.0–049.9, 054.3, 112.83, 320.0–323.81, and 323.9), acquired disorders of immunity (279.2–279.9), and acquired intracranial abnormalities (330.0 and 331.3–331.4). To be excluded for acquired hearing loss, subjects needed to have \(\geq 1\) inpatient diagnosis or \(\geq 2\) outpatient diagnoses of the acquired cause of hearing loss, and the exclusion diagnosis needed to precede the first hearing loss diagnosis. After these exclusions (\(n = 366\)), the remaining subjects comprised the LIGHT Hearing Loss Cohort (\(n = 525\) 043).

Within the LIGHT Hearing Loss Cohort we identified two separate cohorts. The “exposed” cohort included all subjects with any TSB levels at or above 2004 AAP ETT (\(n = 1834\)). The “unexposed” cohort included all subjects whose TSB levels were all below AAP ETT. We selected a 3.6% random sample from this cohort to obtain an approximate 10:1 ratio of unexposed:exposed subjects (\(n = 19\) 004).

**Predictor Variables**

The primary predictor variable was having a TSB level at or above AAP ETT. TSB levels (in milligrams per deciliter) were obtained from KPNC electronic laboratory data sources. The VITROS\(^7\) method (Ortho Clinical Diagnostics, Rochester, NY) was used to measure 96% of TSB levels. As in previous studies,\(^8\) because of limited electronic availability of data on neonatal illness, we approximated AAP risk groups as follows: (1) low risk, gestational age \(\geq 38\) weeks and no positive direct antiglobulin test (DAT) result; (2) medium risk, either gestational age \(< 38\) weeks or a positive DAT result but not both; and (3) high risk, gestational age \(< 38\) weeks and a positive DAT result. The risk groups were used to determine hour-specific potential need for exchange transfusion, per AAP guidelines.\(^5\) TSB levels \(\geq 5\) mg/dL with direct bilirubin levels \(\geq 50\%\) of the total were excluded from analysis, based on AAP recommendations. We defined glucose-6-phosphate dehydrogenase (G6PD) deficiency as a G6PD activity level \(< 8\) U/g of hemoglobin.\(^9\)

When evaluating the relationship between hyperbilirubinemia and SNHL, we initially used the dichotomous variable of having any TSB at or above AAP ETT (yes/no). We then evaluated TSB levels categorically in relation to ETT (ie, not measured or below ETT, 0–4.9 mg/dL above, 5–9.9 mg/dL above, \(\geq 10\) mg/dL above). To facilitate comparisons with previous studies,\(^4,10,11\) we also evaluated peak measured TSB in 5 mg/dL groupings (ie, not measured or \(< 20\) mg/dL, 20–24.9 mg/dL, 25–29.9 mg/dL,
30–34.9 mg/dL, \( \geq 35 \text{ mg/dL} \)). If a subject had multiple TSB levels measured, the highest measurement (in relation to ETT or as a raw value) was used for analysis.

**Outcome Variable**

The outcome variable was confirmed SNHL. All subjects with potential SNHL, which we defined as \( \geq 2 \) diagnoses of sensorineural or mixed hearing loss, were identified from KPNC electronic data sources by using inpatient and outpatient *International Classification of Diseases, Ninth Revision*, diagnosis codes (V53.2 and 389.1–389.9) and procedure codes (20.95–20.98 and 95.48). A single audiologist (R.J.R.), blinded to TSB levels, reviewed the medical records of all subjects with potential SNHL in both cohorts to confirm that SNHL was present and could not clearly be attributed to a nonbilirubin-related cause (eg, trauma, connexin mutation, stroke). We included only those subjects with hearing loss diagnosed before age 8 years; we reasoned that SNHL loss due to hyperbilirubinemia would be diagnosed by that age and that SNHL first diagnosed after age 8 years would be much more likely to have a postneonatal cause.

We ascertained hearing loss characteristics from chart review, including type of SNHL (pure SNHL or mixed hearing loss), laterality (left, right, or bilateral), and severity (normal, \(< 15 \) dB hearing level [HL]; slight, 20 dB HL; mild, 25–35 dB HL; moderate, 40–50 dB HL; moderately severe, 55–65 dB HL; severe, 70–85 dB HL; and profound, \( \geq 90 \) dB HL). The overall severity of each subject’s hearing loss was determined by using the highest amplitude of hearing loss (in decibels HL) at any frequency. We organized de-identified chart review data by using Research Electronic Data Capture\textsuperscript{12} tools hosted at the University of California, San Francisco.

**Statistical Analyses**

We performed bivariate analyses by comparing: (1) exposed and unexposed subjects; and (2) those with and without SNHL in the exposed group. We used \( \chi^2 \) tests and Fisher’s exact tests for categorical variables and \( t \) tests and Mann–Whitney tests for continuous variables. We used Cox proportional hazards models for time to first diagnosis of hearing loss.
SNHL for the primary analyses. Time-to-event analyses were performed because follow-up time differed between those who did and did not have TSB levels that exceeded ETT (as noted in the Results). Follow-up time differed between exposed and unexposed infants because jaundice was monitored and treated more aggressively in later years of the study in this population; therefore, fewer subjects reached exchange levels, and follow-up time was shorter for subjects born later. For the purposes of the proportional hazards models, follow-up time ended with the date of first diagnosis of SNHL, death (for subjects who died before 8 years of age), last membership in the health plan (if before 8 years of age), or the day before the subject’s eighth birthday. No subjects with maximum TSB levels in the range of 30 to 34.9 mg/dL had SNHL; we therefore used a likelihood ratio-based confidence interval (CI) for that hazard ratio (HR). To estimate the maximum excess risk of SNHL consistent with our data, crude risk differences and 95% CIs of the risk differences were calculated by using the Agresti-Caffo method.13

Potential confounding or effect-modifying variables included gender, gestational age 35 to 37 501/7 weeks, birth weight <2500 g, small for gestational age (SGA) status (birth weight <10th percentile according to the Fenton growth curve14), and 5-minute Apgar scores <7. We tested for confounding by determining whether these variables were associated with SNHL in Cox models including bilirubin exposure variables. We tested for effect modification by including interaction terms with these variables in Cox models. Subgroup analyses are presented for variables exhibiting effect modification.

To determine whether the peak difference between TSB level and ETT or peak TSB level itself better predicts SNHL, we compared areas under receiver operating characteristic curves for prediction of SNHL, treating both as continuous variables.

We performed all analyses by using Stata version 13 (Stata Corp, College Station, TX).

**RESULTS**

Subjects in the exposed cohort were more likely to be born in the early years of the study and to have longer follow-up (Table 1). As expected, exposed subjects were more likely to have risk factors for hyperbilirubinemia, including male gender, lower gestational age, Asian race, and older maternal age.5 Subjects in the exposed cohort were more likely to undergo DAT and to be DAT-positive. Exposed subjects were also more likely to undergo G6PD testing but not to be G6PD-deficient. Most subjects in the exposed cohort had neurotoxicity risk factors, as evidenced by 75% of them being in the medium and high AAP risk groups and 72% having maximum TSB levels <25 mg/dL.

The crude risk of confirmed SNHL (without a known nonbilirubin cause) was 11 of 1834 (6.0 per 1000) in the exposed cohort and 43 of 19 004 (2.3 per 1000) in the unexposed cohort (risk ratio: 2.65; exact P = .007).

In unadjusted Cox proportional hazards models, subjects with TSB levels at or above AAP ETT (as a dichotomous variable) did not have a statistically significant increased risk of having SNHL (HR: 1.6 [95% CI: 0.8 to 3.1]; P = .18). In models that included TSB categories, there was no evidence of an association between SNHL and gender, gestational age, birth weight, or Apgar score. There was possible effect modification according to SGA status, with a higher

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**Table 1** Comparison of Subjects in Exposed and Unexposed Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed Cohort (n = 1834)</th>
<th>Unexposed Cohort (n = 19 004)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of birth before 2004</td>
<td>1306 (71.2)</td>
<td>9607 (50.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3280 ± 503</td>
<td>3432 ± 511</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>37.7 ± (1.5)</td>
<td>39.1 ± (1.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age 35–37 501/7 wk</td>
<td>1040 (56.7)</td>
<td>2269 (11.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1046 (57.0)</td>
<td>9717 (51.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>608 (33.2)</td>
<td>8042 (42.3)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>529 (28.8)</td>
<td>3767 (19.8)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>136 (7.4)</td>
<td>1470 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>421 (23.0)</td>
<td>4702 (24.7)</td>
<td></td>
</tr>
<tr>
<td>Other or unknown</td>
<td>140 (7.5)</td>
<td>1023 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Maternal age, y</td>
<td>30.1 ± 5.9</td>
<td>29.3 ± 6.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td>19 /1723 (1.1)</td>
<td>183/17 614 (1.0)</td>
<td>.80</td>
</tr>
<tr>
<td>Maximum TSB, mg/dL</td>
<td>&lt;20 or not done</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>225 (12.3)</td>
<td>18 713 (88.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20–24.9</td>
<td>1104 (60.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>505 (27.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DAT-positive</td>
<td>512/1633 (31.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>408/7088 (5.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G6PD, % deficient (&lt;8 U/g of Hb)</td>
<td>25/216 (11.6)</td>
<td>7/86 (8.1)</td>
<td>.38</td>
</tr>
<tr>
<td>Approximated AAP risk groupb</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Low</td>
<td>451 (24.6)</td>
<td>16 563 (86.1)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>1226 (66.9)</td>
<td>2614 (13.8)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>157 (8.6)</td>
<td>27 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Phototherapy (ever)</td>
<td>1599 (87.3)</td>
<td>1237 (6.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Exchange transfusion (ever)</td>
<td>42 (2.3)</td>
<td>1 (0.01)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>3.0 ± 4.3</td>
<td>2.2 ± 3.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of follow-up, y</td>
<td>8.3 ± 5.2</td>
<td>6.7 ± 5.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are presented as n (%) or mean ± SD. Hb, hemoglobin.

a Denominators provided when data were not available on all subjects.

b Approximated AAP risk group: (1) low risk, gestational age ≥38 weeks and no positive DAT result; (2) medium risk, either a gestational age <38 weeks or a positive DAT result but not both; and (3) high risk, gestational age <38 weeks and a positive DAT result.
HR for exposure to TSB at or above ETT and SNHL in SGA subjects than in non-SGA subjects (SGA HR: 8.4 [95% CI: 1.1 to 63.2]; non-SGA HR: 1.4 [95% CI: 0.6 to 2.8]). P value for interaction term, .05.

When we analyzed TSB levels according to the amount by which they exceeded AAP ETT (as a categorical variable), only levels ≥10 mg/dL above ETT exhibited a statistically significant increase in risk of SNHL (Table 2). Furthermore, at TSB levels up to 5 mg/dL above ETT, the upper limit of the 95% CI for the excess risk was only 0.5%. Likewise, when we analyzed peak TSB levels in 5 mg/dL groupings, only TSB levels ≥35 mg/dL conferred a statistically significant increased risk of SNHL. In the exposed cohort, 15 subjects had TSB levels ≥35 mg/dL (range: 35.3 to 49.1 mg/dL); those who developed SNHL had TSB levels between 38.2 and 49.1 mg/dL. TSB predicted SNHL with the same area under the receiver operating characteristic curve (0.59) whether expressed in maximum TSB categories or as the degree to which the TSB exceeded AAP ETT.

In the exposed cohort, subjects with SNHL (n = 11) were similar to those without SNHL (n = 1819 [1814 with <2 diagnoses of SNHL and 5 with no SNHL after chart review]) in terms of birth weight, gestational age, gender, race/ethnicity, Apgar scores, and DAT-positive results. Exposed subjects who developed SNHL had higher peak TSB levels (mean ± SD: 30.1 ± 11.7 vs 23.4 ± 3.1; P < .001), and a greater proportion underwent exchange transfusion (18.2% vs 2.2%; P = .03). In addition, G6PD deficiency was more prevalent in exposed subjects who developed SNHL (60% vs 10.4% of those tested; P = .01). However, in the exposed cohort, G6PD testing was only performed on 45.5% of those with SNHL and 11.6% of those without.

Table 3 depicts the clinical characteristics of the 11 subjects in the exposed cohort who had SNHL; data on hearing loss characteristics were available for 10 of the 11 subjects. Of these, 8 (80%) had bilateral hearing loss and 6 (60%) had at least moderate hearing loss (≥40 dB HL). There was no consistent pattern of SNHL severity in the exposed cohort according to frequency, other than hearing at 250 Hz was less affected in both exposed and unexposed subjects. Among those with hearing loss, there was no difference in the proportion with severe/profound SNHL (≥70 dB HL) between exposed and unexposed subjects (30% vs 37%; P = .67). Of subjects with severe/profound SNHL, exposed subjects had higher TSB values (median: 20.9 mg/dL; range: 18.3–49.1 mg/dL; n = 3) than unexposed subjects (median: 7.4 mg/dL; range: 1.4–18.5 mg/dL; n = 6 [TSB not measured in 10 of 16]).

Two of 3 exposed subjects with severe/profound SNHL reached their peak measured TSB value within 30 hours of birth. Four subjects had SNHL and TSB ≥10 mg/dL above ETT; 2 of these subjects were diagnosed with cerebral palsy.15

**DISCUSSION**

In the present study, we found that only extremely high TSB levels (≥10 mg/dL above AAP ETT or ≥35 mg/dL) were associated with an increased risk of SNHL. Bilirubin levels typically considered concerning (ie, TSB levels just above AAP ETT and levels of 20–34.9 mg/dL) were not associated with a statistically significant increased risk of SNHL in this population.

SNHL is a manifestation of bilirubin neurotoxicity.16 A recent systematic review of 19 studies4 reported a 13% to 83% incidence of hearing loss at initial testing among infants with varying definitions of increased TSB levels, decreasing to 7% to 14% at 3 months of follow-up. However, the included studies were not population based, and hearing loss was determined on the basis of auditory brainstem responses, which frequently normalize when TSB levels decline.11,17,18 In addition, it is difficult to compare studies that evaluated hearing loss in infants versus studies like ours, which evaluated hearing loss in childhood.

Population-based studies with longer follow-up and audiologic evaluations have yielded much lower rates of hearing loss.19,20 In the US Collaborative Perinatal Project, 16 886 subjects born between 1959 and 1966 had neonatal TSB levels and follow-up pure-tone audiometry assessed at 8 years of age.19 In that cohort, 3 (2.2%) of 137 subjects with TSB levels ≥20 mg/dL had SNHL, the same rate as was observed in those with lower TSB levels (relative risk: 10.6; 95% CI: 0.6 to 2.8).

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>SNHL</th>
<th>SNHL/1000</th>
<th>HR</th>
<th>95% CI of HR</th>
<th>RD, %</th>
<th>95% CI of RD, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum TSB–ETT, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No TSB or &lt;0</td>
<td>19 004</td>
<td>43</td>
<td>2.3</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>0–4.9</td>
<td>1706</td>
<td>6</td>
<td>3.5</td>
<td>0.97</td>
<td>0.41 to 2.3</td>
<td>0.13</td>
<td>−0.1 to 0.5</td>
</tr>
<tr>
<td>5–9.9</td>
<td>102</td>
<td>1</td>
<td>9.8</td>
<td>1.8</td>
<td>0.24 to 13</td>
<td>0.75</td>
<td>−0.9 to 4.3</td>
</tr>
<tr>
<td>≥10</td>
<td>26</td>
<td>4</td>
<td>154</td>
<td>36</td>
<td>13 to 101</td>
<td>15</td>
<td>−3.4 to 32</td>
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<tr>
<td>Maximum TSB, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No TSB or TSB &lt;20</td>
<td>18 938</td>
<td>44</td>
<td>2.3</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>20–24.9</td>
<td>1395</td>
<td>4</td>
<td>2.9</td>
<td>0.87</td>
<td>0.31 to 2.4</td>
<td>0.05</td>
<td>−0.2 to 0.4</td>
</tr>
<tr>
<td>25–29.9</td>
<td>458</td>
<td>2</td>
<td>4.4</td>
<td>1.9</td>
<td>0.46 to 7.9</td>
<td>0.2</td>
<td>−0.3 to 1.2</td>
</tr>
<tr>
<td>30–34.9</td>
<td>32</td>
<td>0</td>
<td>0</td>
<td>&lt;0.01</td>
<td>0 to 3.3</td>
<td>−0.23</td>
<td>−3 to 8.4</td>
</tr>
<tr>
<td>≥35</td>
<td>15</td>
<td>4</td>
<td>267</td>
<td>91</td>
<td>32 to 255</td>
<td>26</td>
<td>7.5 to 51</td>
</tr>
</tbody>
</table>

RD, risk difference.
TABLE 3 Clinical Characteristics of Subjects With SNHL in the Exposed Cohort

<table>
<thead>
<tr>
<th>Subject</th>
<th>TSB Data</th>
<th>Demographics</th>
<th>Risk Factors</th>
<th>SNHL Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSB – ETT Category, mg/dL</td>
<td>TSB Maximum Category, mg/dL</td>
<td>Age at TSB, Maximum, h</td>
<td>Approximated AAP Risk Groupa</td>
<td>Gender</td>
</tr>
<tr>
<td>1 0–5</td>
<td>&lt;20</td>
<td>24–47</td>
<td>Medium</td>
<td>Male</td>
</tr>
<tr>
<td>2 0–5</td>
<td>20–24.9</td>
<td>24–47</td>
<td>Medium</td>
<td>Female</td>
</tr>
<tr>
<td>3 0–5</td>
<td>20–24.9</td>
<td>48–71</td>
<td>Medium</td>
<td>Male</td>
</tr>
<tr>
<td>4 0–5</td>
<td>20–24.9</td>
<td>48–71</td>
<td>Medium</td>
<td>Male</td>
</tr>
<tr>
<td>5 0–5</td>
<td>25–29.9</td>
<td>48–71</td>
<td>Low</td>
<td>Male</td>
</tr>
<tr>
<td>6 0–5</td>
<td>25–29.9</td>
<td>72–95</td>
<td>Low</td>
<td>Male</td>
</tr>
<tr>
<td>7 5–9.9</td>
<td>20–24.9</td>
<td>24–47</td>
<td>High</td>
<td>Male</td>
</tr>
<tr>
<td>8 ≥10</td>
<td>≥35</td>
<td>72–96</td>
<td>Medium</td>
<td>Male</td>
</tr>
<tr>
<td>9 ≥10</td>
<td>≥35</td>
<td>72–96</td>
<td>Medium</td>
<td>Female</td>
</tr>
<tr>
<td>10 ≥10</td>
<td>≥35</td>
<td>&gt;96</td>
<td>Low</td>
<td>Male</td>
</tr>
<tr>
<td>11 ≥10</td>
<td>≥35</td>
<td>&gt;96</td>
<td>Medium</td>
<td>Male</td>
</tr>
</tbody>
</table>

Dx, diagnosis; Hb, hemoglobin; NA, not available; ND, not done.

a Approximated AAP risk group: (1) low risk, gestational age ≥38 weeks and no positive DAT result; (2) medium risk, either gestational age <38 weeks or a positive DAT result but not both; and (3) high risk, gestational age <38 weeks and a positive DAT result.

1 [95% CI: 0.3 to 3)]. In a cohort of subjects born in Nova Scotia between 1994 and 2000 (N = 61,238), TSB levels ≥19 mg/dL were not associated with a statistically significant increased risk of deafness (based on linked diagnoses) (relative risk: 1.3 [95% CI: 0.8 to 2.1]).20 Our results were similar to these population-based studies, demonstrating that TSB levels up to 35 mg/dL were not associated with a statistically significant increased risk of SNHL.

The aforementioned population-based studies had few subjects with very high TSB levels, which may be why an association between TSB and SNHL was not seen. A study in the United Kingdom of subjects born between 2003 and 2005 included 108 with TSB levels ≥29.8 mg/dL, 14 of whom had bilirubin encephalopathy.21 Of the 12 subjects with bilirubin encephalopathy for whom follow-up information was available, 3 had hearing loss. The subjects with hearing loss were all born at <38 weeks' gestation, were at risk for hemolysis (G6PD deficiency, ABO incompatibility, or unspecified hemolysis), and had TSB levels ranging from 32 to 38.8 mg/dL.

The AAP recommends treatment of infants with high bilirubin levels to prevent bilirubin-related encephalopathy. We found that at TSB values up to 5 mg/dL above ETT, the upper limit of the 95% CI for excess risk of SNHL was only 0.5%. Although recent data are lacking, it is estimated that exchange transfusions carry morbidity risks of 5% and mortality risks of 0.3% to 1.9%.11 At TSB values up to 5 mg/dL above AAP ETT, the risk of complications from exchange transfusions likely exceeds the risk of SNHL, although at the time the exchange transfusion is ordered, the maximum TSB is not yet known and one must consider the risks of other morbidities associated with hyperbilirubinemia (ie, cerebral palsy).

Hyperbilirubinemia is not only associated with SNHL but also with a specific type of hearing dysfunction called auditory dysynchrony or auditory neuropathy spectrum disorder (ANSD).3 Individuals with ANSD may or may not be deaf.22 They have abnormal auditory nerve function but normal cochlear function; therefore, they have abnormal results on audiometry brainstem response testing but normal results on otoacoustic emission testing.3 Children with ANSD may be at increased risk of having language and speech impairments.22 Notably, several studies have shown that hyperbilirubinemia-associated abnormalities in brainstem auditory evoked responses may be reversible with treatment of hyperbilirubinemia.11,22–24 We were unable to assess for ANSD in the present study because only a small number of participants had auditory nerve testing performed (most were tested with audiograms at their audiology visits).

We found that follow-up time was longer in exposed versus unexposed subjects because exposed subjects were more likely to be born in the early years of the study (and thus have longer follow-up). The decrease in severe hyperbilirubinemia in the later years was associated with universal screening for hyperbilirubinemia, which was adopted within KPNC between 2004 and 2007.25
neurotoxicity. However, because no widely available method of obtaining unbound bilirubin levels currently exists, TSB measurements continue to be used to guide bilirubin management decisions. Third, as mentioned earlier, auditory brainstem response testing data (from birth and/or follow-up) were not consistently available and therefore could not be analyzed. Fourth, the present article focused on SNHL; other bilirubin-related neurologic morbidities were not evaluated. In addition, although kernicterus is rare in the United States, it is more common in developing countries, perhaps due to increased sepsis\(^2,27,28\) Rh isoimmunization,\(^27\) and G6PD deficiency.\(^28\) Our results may thus be less generalizable to subjects in resource-poor settings. Advantages of our study include the large size of the cohort (>500,000 subjects) from which our double cohort was derived, the larger number of cases of SNHL compared with previous population-based studies, and the ability to stratify risk according to higher bilirubin levels than those studied in the past.

CONCLUSIONS

We found that subjects with extremely elevated TSB levels (>10 mg/dL above AAP ETT or ≥35 mg/dL) were more likely to have SNHL than those with lower TSB levels. At TSB levels just above ETT, exchange transfusions may not be needed to prevent SNHL and may result in additional risk with no clear benefit in terms of hearing loss. As we accumulate more evidence on the actual risks of SNHL and other bilirubin-induced neurologic morbidities, we may need to reexamine current recommendations for the treatment of hyperbilirubinemia.

ABBREVIATIONS

AAP: American Academy of Pediatrics
ANSD: auditory neuropathy spectrum disorder
CI: confidence interval
DAT: direct antiglobulin test
ETT: exchange transfusion thresholds
G6PD: glucose-6-phosphate dehydrogenase
HL: hearing level
HR: hazard ratio
KPN: Kaiser Permanente Northern California
SGA: small for gestational age
SNHL: sensorineural hearing loss
TSB: total serum bilirubin

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