Original Investigation

Risk for Cerebral Palsy in Infants With Total Serum Bilirubin Levels at or Above the Exchange Transfusion Threshold: A Population-Based Study

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IMPORTANT. Exchange transfusion is recommended for newborns with total serum bilirubin (TSB) levels thought to place them at risk for cerebral palsy (CP). However, the excess risk for CP among these infants is unknown.

OBJECTIVE. To quantify the risks for CP and CP consistent with kernicterus that are associated with high TSB levels based on the 2004 American Academy of Pediatrics exchange transfusion threshold (ETT) guidelines.

DESIGN, SETTING, AND PARTICIPANTS. We enrolled 2 cohorts from a population of 525,409 infants in the Late Impact of Getting Hyperbilirubinemia or Phototherapy (LIGHT) birth cohort. Eligible infants were born at a gestational age of at least 35 weeks at 15 hospitals within the Kaiser Permanente Northern California integrated medical care delivery system from January 1, 1995, through December 31, 2011.

EXPOSURES. The exposed cohort included all 1,833 infants with at least 1 TSB measurement at or above the ETT based on age at testing, gestational age, and results of direct antiglobulin testing. The unexposed cohort was a 20% random sample of 104,716 infants with TSB levels below the ETT.

MAIN OUTCOMES AND MEASURES. A pediatric neurologist blinded to the TSB levels reviewed medical records to determine the presence of CP, defined as a nonprogressive congenital motor dysfunction with hypertonia or dyskinesia. Cerebral palsy was judged to be consistent with kernicterus if magnetic resonance imaging of the brain revealed bilateral globus pallidus injury in the setting of dyskinetic CP.

RESULTS. We identified CP in 7 of 1,833 exposed (0.4%) vs 86 of 104,716 unexposed (0.1%) infants (relative risk, 4.7 [95% CI, 2.2-10.0]). Absolute risk differences were 0.2% (95% CI, 0.0%-0.5%) for a TSB level 0 to 4.9 mg/dL above the ETT (n = 1,705), 0.9% (95% CI, 0.1%-5.3%) for a TSB level 5.0 to 9.9 mg/dL above the ETT (n = 102), and 7.6% (95% CI, 2.1%-24.1%) for a TSB level 10 mg/dL or more above the ETT (n = 26). Cerebral palsy consistent with kernicterus occurred in 3 infants (incidence, 0.57 per 100,000 births); all 3 had TSB levels of more than 5.0 mg/dL above the ETT and at least 2 risk factors for neurotoxicity, such as prematurity, glucose-6-phosphate dehydrogenase deficiency, or hypoxia-ischemia.

CONCLUSIONS AND RELEVANCE. Cerebral palsy consistent with kernicterus occurred only in infants with 2 or more risk factors for neurotoxicity and TSB levels of more than 5 mg/dL above the ETT. Among infants with lower degrees of TSB level elevation, the excess risk for CP is minimal.
Neonatal jaundice is common and almost always benign. However, extremely high total serum bilirubin (TSB) levels can lead to kernicterus or chronic bilirubin encephalopathy. Kernicterus results from injury to the brain in areas that are susceptible to bilirubin staining, including the bilateral globus pallidus, subthalamic nuclei, brainstem, and cerebellum. This type of brain injury results in severe quadriplegic cerebral palsy (CP) with the classic extrapyramidal signs of choreoathetosis and/or dystonia. Kernicterus has been referred to as one of the few preventable causes of CP.

In 2004, the American Academy of Pediatrics (AAP) published a guideline for the management of hyperbilirubinemia in infants born at a gestational age of at least 35 weeks. The guideline recommends exchange transfusion in infants with TSB levels that remain above the exchange transfusion threshold (ETT), despite intensive phototherapy. The ETT takes into account gestational age, risk factors for neurotoxicity, the TSB level, and the age of the infant. The guidelines are based on studies addressing the excess risk for neurodevelopmental abnormalities in infants exposed to various levels of TSB. However, most of these studies are limited by a short duration of follow-up, excessive loss to follow-up, and/or small numbers of study participants at the highest levels of exposure. Furthermore, previous studies examined neurologic outcomes in relation to hyperbilirubinemia defined by a fixed TSB cutoff (eg, 225 mg/dL [to convert to micromoles per liter, multiply by 17.104]). In contrast, the AAP ETTS are dynamic and can vary widely depending on the infant’s age (in hours) and gestational age and the presence of risk factors for neurotoxicity.

We sought to quantify the excess risk for CP in newborns with TSB levels at or above the ETT levels based on age, gestational age, and risk group. We took advantage of electronic medical records that included all TSB levels and subsequent diagnoses in a birth cohort of term and late preterm infants born in a large health care organization.

Methods

These analyses were planned as part of the Late Impact of Getting Hyperbilirubinemia or Phototherapy (LIGHT) study, which was approved by the California Committee for Human Subjects and the institutional review boards at Kaiser Permanente Northern California (KPNC) and the University of California, San Francisco. Informed consent was waived for this study. This double-cohort study was nested within the population of all 525,409 infants born at a gestational age of at least 35 weeks at 15 KPNC hospitals from January 1, 1995, through December 31, 2011. Kaiser Permanente Northern California is an integrated community medical care delivery system that serves 3.4 million members, constituting nearly half of the insured population of Northern California.

Bilirubin Exposure

We obtained all TSB levels for the entire birth cohort. We compared TSB levels with the 2004 AAP ETTS, which we assigned to each TSB level based on the infant’s age (in hours), gestational age, and result of direct antiglobulin testing, as previously described. We categorized the peak TSB level in relation to the ETT in the following groupings: below the ETT or 0 to 4.9, 5.0 to 9.9, or 10.0 mg/dL or more above the ETT. We similarly classified the highest single TSB value for each infant as less than 20.0, 20.0 to 24.9, 25.0 to 29.9, 30.0 to 34.9, or at least 35.0 mg/dL so that cutoffs would match those used in previous studies.

We excluded TSB levels in which the direct or conjugated bilirubin measurement constituted more than 50% of the total because such levels were excluded from the AAP guidelines. We assumed that the 49% of infants who did not undergo any TSB measurements did not have significant jaundice and grouped them with infants with TSB levels of less than 20 mg/dL and TSB levels below the ETT. We collected all available results of testing for glucose-6-phosphate dehydrogenase (G6PD) activity and the direct antiglobulin test. The G6PD activity level was considered low at less than 8 U/g of hemoglobin (to convert to nanokatals per gram of hemoglobin, multiply by 0.0167). We did not use G6PD results to classify the infants’ risk when determining their ETT because the G6PD results were generally not available at the time that the clinical decision was made. We excluded a priori infants with 2 or more physician diagnoses of a major congenital anomaly (n = 350) and those diagnosed as having meningitis or encephalitis before the first patient encounter in which CP was diagnosed (n = 21). From the remaining births, we selected 2 study cohorts based on bilirubin exposure (Figure). The exposed cohort included all 1833 infants who had at least 1 TSB level that met or exceeded the ETT. The unexposed cohort consisted of a 20% random sample of infants whose TSB levels were below the ETT (n = 104,716).

Cerebral Palsy

We identified KPNC inpatient and outpatient physician diagnoses of CP (codes 343.0-343.9 and 333.71 from the International Classification of Diseases, Ninth Revision, Clinical Modification) or paresis (codes 342.1, 342.8, 342.9, 344.0, 344.1, 344.30-344.32, and 344.5) by reviewing electronically available diagnoses from all patient encounters through July 31, 2013, or until the child left the KPNC network, whichever came first. Almost 90% of infants in the birth cohort were followed up to 15 months or older. To capture additional CP cases that might have been lost to follow-up in the KPNC network, we linked all infants born from 2005 through 2010 to California Department of Developmental Services records of infants who qualified for state services owing to CP through May 31, 2013. Because this process did not identify any previously missed cases of CP, we did not link additional birth years. A single child neurologist (Y.W.W.) blinded to TSB levels reviewed the medical records of infants who had 2 or more separate inpatient or outpatient encounters with diagnoses of CP or paresis to determine which infants met study criteria for CP, defined as a nonprogressive congenital motor dysfunction with examination findings of hypertonicity (spasticity or rigidity) or dyskinesia (dystonia or choreoathetosis). The CP diagnosis was confirmed only if patients were followed up within the KPNC network for 15 months or longer. We excluded participants from the exposed and unexposed cohorts who did not meet study criteria for CP for the following reasons: hypotonia (n = 22) or...
ataxia (n = 7) with no signs of hypertonicity or dyskinesia; resolution of CP at older than 3 years (n = 20); genetic abnormality (n = 15); postneonatal brain injury (n = 13); acute or progressive neurologic disorder (n = 10); congenital viral infection (n = 3); loss to follow-up before 15 months (n = 2); or the absence of any neurologic condition suggesting CP (n = 28) (Figure).

For all participants with confirmed CP, we determined distribution of limb involvement, ie, quadriplegia, hemiplegia/monoplegia, or diplegia; reviewed reports of magnetic resonance imaging (MRI) of the brain; and collected covariate data from KPNC electronic data sources regarding maternal race or ethnicity, gestational age, infant sex, mode of delivery, 5-minute Apgar scores, and birth year. We identified patients who received an exchange transfusion by searching electronically for ICD-9-CM procedure code 99.01 and confirmed the use of this therapy via medical record review.

Cerebral palsy is a heterogeneous condition. Hyperbilirubinemia accounts for a very small percentage of CP in the United States. The mere presence of a high TSB level is not sufficient to attribute CP to hyperbilirubinemia. Neuroimaging plays an important role in diagnosing kernicterus. For instance, if a high-quality MRI of the brain performed beyond early infancy shows normal findings or an alternative abnormality, such as a brain malformation, the cause of the CP is unlikely to be kernicterus, even in the setting of a high neonatal TSB level. We considered CP to be consistent with classic kernicterus when CP was accompanied by documented dyskinesias (ie, dystonia or choreoathetosis) in a child with T2-weighted hyperintensities of bilateral globus pallidus on MRI of the brain given the specificity of these findings for the neurotoxic effects of bilirubin. An audiologist blinded to the CP levels confirmed diagnoses of sensorineural hearing loss; details of hearing loss in this population will be reported separately.
Statistical Analysis

We compared clinical characteristics of infants in both study cohorts using unpaired 2-tailed χ² and t tests, and Fisher exact tests as appropriate and calculated relative risks and absolute risk differences with exact 95% CIs for CP in each category of elevated TSB level. We compared discrimination of the degree of TSB level elevation above the ETT with that of the peak TSB level by comparing the area under the receiver operating characteristic curve. Because patients with no measurement of TSB levels or with a TSB level of less than 15 mg/dL are unlikely to contribute diagnostic value, we excluded them from the receiver operating characteristic curve analyses. In a sensitivity analysis, we evaluated the association between TSB levels above the ETT and all types of CP (ie, hypertonic, dystonic, hypotonic, and ataxic). We used commercially available software (Stata, version 12; StataCorp) for all analyses. We managed study data using REDCap (research electronic data capture) tools hosted at the University of California, San Francisco.24

Results

We identified 1833 infants (0.3%) who were exposed to at least 1 TSB level at or above the ETT and 523 205 unexposed infants (99.7%) (Figure). Exposed infants were more likely to be male, Asian, and preterm (Table 1). Length of follow-up was longer in the exposed than in the unexposed groups (7.6 vs 6.2 years; P < .001) because exposed infants were more likely to be born in the earlier years of the study (Table 1). This difference was expected because the adoption of universal bilirubin screening within the KPNC network from 2004 through 2007 was associated with a lower rate of hyperbilirubinemia during the later years of the study.25 An exchange transfusion was performed in the following proportion of infants: 0.02% if the TSB level was below the ETT, 0.9% if the TSB level was 0 to 4.9 mg/dL above the ETT, 14.7% if the TSB level was 5.0 to 9.9 mg/dL above the ETT, and 46.2% if the TSB level was at least 10 mg/dL above the ETT.

Among the exposed and unexposed cohorts, we identified 217 patients with at least 2 KPNC physician diagnoses of CP (Figure). Medical record review confirmed the presence of CP in 7 of 1833 infants (0.4%) exposed to a TSB level above the ETT compared with 86 of 104 716 unexposed infants (0.1%) (relative risk, 4.7 [95% CI, 2.2-10.0]; P < .001). Of the 7 exposed infants with CP, 5 were male, and the maternal race was white in 3, Asian in 3, and African American in 1. Exchange transfusion was performed in 2 of the 7 infants who later developed CP (28.6%) and in 40 of the 1826 infants who did not develop CP (2.2%).

Greater risks for hypertonic/dystonic CP occurred in groups with more severe elevations of TSB levels (Table 2). Absolute risk differences were 0.2% (95% CI, 0%-0.5%) for a TSB level 0 to 4.9 mg/dL above the ETT (n = 1705); 0.9% (95% CI, 0.1%-5.3%) for a TSB level 5.0 to 9.9 mg/dL above the ETT (n = 102); and 7.6% (95% CI, 2.1%-24.1%) for a TSB level at least 10.0 mg/dL above the ETT (n = 26). The absolute risk for hypertonic/dystonic CP was 2 of 26 patients (7.7%) with a TSB level at least

### Table 1. Characteristics of Infants With and Without a TSB Level Above the ETT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed (n = 1833)</th>
<th>Unexposed (n = 104 716)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>57.0</td>
<td>51.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>42.4</td>
<td>51.1</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>29.8</td>
<td>20.3</td>
<td>.001</td>
</tr>
<tr>
<td>African American</td>
<td>7.7</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.4</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>17.7</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>Birth at term (GA ≥37 wk)</td>
<td>78.3</td>
<td>94.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g)</td>
<td>5.0</td>
<td>3.5</td>
<td>.001</td>
</tr>
<tr>
<td>Birth years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995-1999</td>
<td>38.3</td>
<td>27.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2000-2003</td>
<td>33.0</td>
<td>23.3</td>
<td></td>
</tr>
<tr>
<td>2004-2007</td>
<td>16.7</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>2008-2011</td>
<td>12.1</td>
<td>25.2</td>
<td></td>
</tr>
<tr>
<td>Follow-up ≥15 mo³</td>
<td>89.4</td>
<td>86.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean length of follow-up, y</td>
<td>7.6</td>
<td>6.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Delivery mode</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Normal spontaneous vaginal</td>
<td>72.1</td>
<td>69.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Assisted vaginal</td>
<td>15.9</td>
<td>7.4</td>
<td></td>
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<tr>
<td>Cesarean section</td>
<td>10.8</td>
<td>22.4</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>1.3</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>5-min Apgar score &lt;7</td>
<td>1.1</td>
<td>1.0</td>
<td>.69</td>
</tr>
</tbody>
</table>

Abbreviations: ETT, exchange transfusion threshold; GA, gestational age; TSB, total serum bilirubin.

*Unless otherwise indicated, data are expressed as percentage of infants. Percentages have been rounded and may not total 100.

Indicates exposure to a TSB level above the American Academy of Pediatrics ETT.

Indicates last visit within the Kaiser Permanente Northern California network was at 15 months or older.
10.0 mg/dL above the ETT and similarly high in the 2 of 15 infants (13.3%) with a TSB level of at least 35.0 mg/dL. We found no difference between the degree of elevation in TSB levels above the ETT and the peak TSB levels in ability to predict hypertonic/dystonic CP (areas under the receiver operating characteristic curve, 0.71 vs 0.70; \( P = .79 \)).

Three infants with CP demonstrated MRI findings of T2-weighted hyperintense lesions in the bilateral globus pallidus at ages 7, 13, and 19 months (Table 3). Two of the 3 infants with these classic neuroimaging findings of kernicterus also had sensorineural hearing loss (Table 3). The population incidence of CP consistent with kernicterus was 0.57 per 100 000 births. The risk for CP consistent with kernicterus was significantly higher in exposed than in unexposed infants (3 of 1833 vs 0 of 104 716; \( P < .001 \)). Brain injury in the bilateral globus pallidus was similarly more common in exposed than in unexposed infants with CP (3 of 7 vs 0 of 86; \( P < .001 \)). Choreoathetosis was more common in exposed than unexposed infants with CP (3 of 7 vs 4 of 86; \( P = .008 \)), whereas the difference in the presence of dystonia was not statistically significant between the 2 groups (1 of 7 vs 6 of 86; \( P = .43 \)).

The 3 infants with CP and kernicterus had TSB levels of 49.1 mg/dL (27 mg/dL > ETT), 48.5 mg/dL (26 mg/dL > ETT), and 28.4 mg/dL (5.5 mg/dL > ETT). Each of the 3 affected infants also had at least 2 of the following risk factors for neurotoxicity (Table 3): prematurity (\( n = 2 \)), G6PD deficiency (\( n = 2 \)), hypoaalbuminemia (\( n = 2 \)), hypoxia-ischemia (\( n = 1 \)), and/or sepsis (\( n = 1 \)).
nicterus and a peak TSB level of 28.4 mg/dL had congenital volvulus and hypotension; the MRI revealed watershed distribution of white matter injury related to hypoxia-ischemia as well as bilateral globus pallidus injury.

Of the 4 exposed infants with hypertonic/dystonic CP but without classic kernicterus on MRI, all had TSB levels less than 5 mg/dL above the ETT. Three of these 4 patients had MRI findings considered unrelated to bilirubin (Table 3), including global hypoxic-ischemic brain injury caused by massive subgaleal hemorrhage, polymicrogyria, and in utero periventricular hemorrhagic infarction. The infant with the massive subgaleal hemorrhage developed hyperbilirubinemia as a result of disseminated intravascular coagulation requiring multiple transfusions of red blood cells; thus, the brain injury and the hyperbilirubinemia were caused by the same underlying condition.

All infants who were diagnosed with hypotonic (n = 22) or ataxic (n = 7) CP were in the unexposed cohort. Total serum bilirubin levels above the ETT remained associated with CP when hypotonic and ataxic subtypes were included (odds ratio, 4.1 [95% CI, 2.0-8.4]). When the 3 cases of CP consistent with kernicterus were removed from the analysis, the association between TSB levels above the ETT and CP was attenuated and no longer statistically significant (odds ratio, 2.7 [95% CI, 1.0-7.3]).

### Discussion

In 2004, the AAP published ETT guidelines based on hour-specific TSB levels and the presence of risk factors for neurotoxicity in an effort to prevent kernicterus. We found that these ETT guidelines effectively identified all cases of CP consistent with kernicterus in a large population. All 3 patients with CP consistent with kernicterus had peak TSB levels that were 5 mg/dL or more above the ETT and 2 or more risk factors for neurotoxicity that increased susceptibility to bilirubin-induced brain injury.

The exact incidence of kernicterus in the United States is unknown. The incidence of CP attributed to kernicterus in our population (0.57 per 100,000 births) falls within the lower end of the spectrum of reported population-based estimates in Europe and North America (0.4 to 2.7 per 100,000 births). Initial concerns about a possible resurgence of kernicterus after the “kinder, gentler” treatment guidelines for hyperbilirubinemia have been difficult to substantiate.

Factors that increase an infant’s susceptibility to kernicterus include prematurity, G6PD deficiency, hypoxia-ischemia, sepsis, hemolytic anemia, acidosis, and hypoalbuminemia. Each of our 3 patients with kernicterus had at least 2 of these risk factors for neurotoxicity. We found G6PD deficiency in 2 premature infants who developed kernicterus. This finding is consistent with other recent studies that have found that most cases of kernicterus occur in patients with hemolysis or sepsis. Another patient had clinical and neuroimaging evidence of coexisting kernicterus and hypoxic-ischemic brain injury. Hypoxia-ischemia increases the susceptibility to kernicterus, possibly because of the increased permeability of the blood-brain barrier and/or reduced albumin-binding capacity.

Kernicterus has been referred to as a never event, that is, an illness that should never occur in the setting of adequate health care delivery. However, other investigators have contested this assertion because certain situations may not always be amenable to current treatment measures. Acute severe hyperbilirubinemia due to G6PD deficiency often produces a rapid rise of bilirubin levels that may produce brain damage despite appropriate intervention. In select populations at high risk for G6PD deficiency, routine screening for G6PD deficiency has been proposed to prevent all cases of kernicterus. Although a G6PD screening program in Singapore eliminated kernicterus among G6PD-deficient infants, this result was achieved at the cost of keeping all G6PD-deficient newborns in the hospital for 14 days after birth. Although the present study suggests that maximum TSB levels to 5 mg/dL above the ETT were almost always benign, infants with such levels should not be excluded from treatment. An inherent limitation of using maximum TSB levels as a predictor variable is that the maximum level is not known at the time an infant is being treated. Infants with maximum TSB levels up to 5 mg/dL above the ETT may have good outcomes precisely because they were treated and their TSB levels were prevented from increasing. On the other hand, to the extent that current phototherapy thresholds are meant to minimize the possibility of the infant’s TSB level crossing the ETT, our finding that exceeding the ETT by up to 5 mg/dL is a benign occurrence is important.

Our study has several additional limitations. The measured maximum TSB levels are only estimates of the true peak exposure levels. We lack good data on the rate of bilirubin rise, duration of exposure, and unbound circulating bilirubin levels, although extremely high TSB levels strongly predicted the presence of CP consistent with kernicterus, even without this additional information. Our CP diagnoses relied on clinical records because we did not personally examine the children. Calculations of the absolute risk differences for extreme levels of hyperbilirubinemia were based on small numbers of exposed infants and a relatively rare outcome, thus generating wide CIs. The MRI studies of the brain were performed at different ages without a standard protocol and were interpreted by neuroradiologists who were not all certified in pediatric neuroimaging. Whether hyperbilirubinemia increases the risk for poor coordination, lower IQ, developmental delays, attention-deficit disorder, or autism is beyond the scope of this study.

Advantages of our study include the large population spanning 17 birth years, the comprehensive laboratory data that allowed us to categorize peak TSB levels in relation to 2004 AAP ETT values, a robust long-term follow-up, and the categorization of CP, a vastly heterogeneous condition, into subgroups based on tone abnormalities and brain MRI findings. Unlike studies that are based on case series or kernicterus registries, our study includes exposed infants who did not develop kernicterus, allowing us to estimate the degree of increased risk associated with varying degrees of hyperbilirubinemia.
Conclusions

We found that CP consistent with kernicterus was rare in this modern cohort of term and late preterm infants and did not occur in a single infant with hyperbilirubinemia who was otherwise healthy with no risk factors for neurotoxicity present, regardless of the severity of elevation of the TSB level. Together our findings support the suggestion that infants with hyperbilirubinemia without risk factors for neurotoxicity may have a higher tolerance than recognized in current management guidelines.16,20,43 These data, along with estimates of risks and costs of treatment, should be considered when developing future updated guidelines for the management of jaundice in term and late preterm newborns.

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30. American Academy of Pediatrics; Provisional Committee for Quality Improvement and


