abstract

BACKGROUND AND OBJECTIVES: Total serum bilirubin (TSB) levels ≥30 mg/dL are rare but potentially hazardous. A better understanding of their incidence, causes, and outcomes could help inform preventive efforts.

METHODS: We identified infants born ≥35 weeks’ gestational age from 1995–2011 in Kaiser Permanente Northern California (n = 525,409) and examined the medical records of infants with a TSB ≥30 mg/dL to determine etiology and the occurrence of acute bilirubin encephalopathy. We reviewed inpatient and outpatient encounters through 2013 for evidence of sensorineural hearing loss (SNHL) or cerebral palsy (CP).

RESULTS: We identified 47 infants with TSB ≥30 mg/dL (8.6 per 100,000 births). In 44 infants (94%), the hyperbilirubinemia occurred after the initial birth hospitalization. The etiology was not identified in 33 (70%). Glucose-6-phosphate dehydrogenase (G6PD) activity was measured in only 25 (53%) of whom 10 (40%) were deficient. Four children had acute bilirubin encephalopathy of whom 2 developed both CP and SNHL, and 1 developed isolated SNHL. These 3 infants all had G6PD deficiency and TSB >40 mg/dL. One additional 35-week infant with TSB 38.2 mg/dL had SNHL.

CONCLUSIONS: Hazardous (≥30 mg/dL) hyperbilirubinemia is a rare event. No etiology could be identified from the clinical record in most cases. G6PD deficiency was the leading cause of hazardous hyperbilirubinemia when an etiology was identified, but many were not tested. Chronic, bilirubin-induced neurotoxicity was uncommon and occurred only in the setting of additional risk factors and TSB values well over (>15 mg/dL) the American Academy of Pediatrics exchange transfusion thresholds. Pediatrics 2014;134:504–509

WHAT’S KNOWN ON THIS SUBJECT: Total serum bilirubin levels ≥30 mg/dL have been labeled as “hazardous.” Levels this high are rare, occurring in 3 to 10 per 100,000 births. Few studies have examined etiologies and long-term outcomes in these infants.

WHAT THIS STUDY ADDS: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a major identifiable cause, but is under-assessed. Chronic, bilirubin-induced neurotoxicity is rare and only occurred in the setting of additional risk factors (prematurity, G6PD deficiency, sepsis) and at levels far above recommended exchange transfusion thresholds.

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KEY WORDS
hyperbilirubinemia, kernicterus, neonate, neurotoxicity

ABBREVIATIONS
AAP—American Academy of Pediatrics
GBE—chronic bilirubin encephalopathy
CP—cerebral palsy
DAT—direct antiglobulin test
G6PD—glucose-6-phosphate dehydrogenase
Hb—hemoglobin
KPNC—Kaiser Permanente Northern California
SNHL—sensorineural hearing loss
TSB—total serum bilirubin

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

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The possibility that newborns will develop total serum bilirubin (TSB) levels that put them at risk for neurotoxicity drives recommendations for testing, follow-up, and treatment.1–4 Although there is no single threshold at which bilirubin becomes neurotoxic,5 a 2003 Eunice Kennedy Shriver National Institute of Child Health and Human Development sponsored conference proposed that TSB levels ≥30 mg/dL be defined as “hazardous” hyperbilirubinemia because of the perceived higher risk of neurologic injury.6

The incidence of hazardous hyperbilirubinemia in populations in Western Europe7–12 and the United States13–17 ranges from 2 to 12/100 000, with the lowest rates in Switzerland (where the mean postpartum stay after a vaginal delivery was 5.6 days)11 and in US hospital systems after implementation of universal bilirubin screening.14,15,17

The distribution of causes of hazardous hyperbilirubinemia varies in different populations, with isoimmunization more common in Europe9,10,12 and glucose-6-phosphate dehydrogenase (G6PD) deficiency predominating in the United States and Canada.16,18

Although some previous studies have revealed the frequency of acute bilirubin encephalopathy in the children with hazardous hyperbilirubinemia,8,10 few have had the necessary long-term follow-up to estimate the risk of chronic sequelae. Most estimates of the incidence of chronic bilirubin encephalopathy (CBE) have been in the range of 1/100 000,10,19 but a recent study from Canada revealed a higher incidence of 2.3/100 000.18 In our previous reports from Kaiser Permanente Northern California (KPNC), we identified 11 infants with TSB levels ≥30 mg/dL from a cohort of 111 009 born during 1995–1998, none of whom had long-term sequelae.15,20

The objective of this study was to update the cohort to include an additional 13 years of births, to report on the incidence, etiologies, and outcomes of infants with TSB levels ≥30 mg/dL managed and followed in a large, integrated health care delivery system.

METHODS

**Subject and Settings**

We identified all infants born ≥35 weeks’ gestational age from 1995 through 2011 in KPNC (n = 525 409). KPNC serves a population of 3.4 million members, which constitutes nearly half of the insured population in Northern California. Fifteen facilities were included in the study. KPNC facilities share the same common medical record numbers and database systems, which permits linkage of maternal and neonatal records to each other and to multiple information systems (eg, laboratory and hospitalization data).21 Currently all KPNC facilities employ either serum or transcutaneous universal bilirubin screening. Universal bilirubin screening began in some facilities in September 2004 and was fully implemented in all facilities by February 2007.14

**Measurements**

From existing KPNC databases, we obtained all TSB values from an infant’s first month after birth, by using previously described methods.14,22 We excluded any TSB measurements for which a corresponding conjugated or direct bilirubin measurement constituted ≥50% of the TSB level. We identified infants with a maximum TSB ≥30 mg/dL. Additional laboratory values obtained from the data sources were the direct antiglobulin test (DAT) and G6PD activity, if performed. Testing for G6PD deficiency was done at the discretion of the treating physician; no screening protocol was in place. We considered G6PD activity low if activity was <8 U/g hemoglobin (Hb).23 To allow comparison with American Academy of Pediatrics (AAP) treatment guidelines, which define 3 risk groups for bilirubin-induced neurotoxicity,1 we assigned risk groups to the infants in our cohort as previously described.24

**Medical Record Review**

The birth hospitalization and any subsequent readmissions in the first 30 days were reviewed in infants with a TSB ≥30 mg/dL to determine the presence of acute bilirubin encephalopathy (eg, posturing, seizures), the presence of concomitant infection, metabolic disease, feeding difficulties present at discharge from the birth hospitalization, phototherapy, and exchange transfusion. Because criteria do not exist to determine whether neurologic deficits or developmental problems later in life are secondary to hyperbilirubinemia,25 we defined CBE as sensorineural hearing loss (SNHL), dystonic or choreathetotic cerebral palsy (CP), or both. All inpatient and outpatient encounters of these children were reviewed for evidence of SNHL or CP through December 2013 or until the child left the health system. An audiologist blinded to TSB levels reviewed the medical records and audiology to confirm SNHL, and a child neurologist blinded to TSB levels reviewed medical records to confirm the diagnostic features of CP.

**Data Management**

Deidentified study data were collected and managed by using REDCap (Research Electronic Data Capture) tools hosted at the University of California, San Francisco.26

**Statistical Methods**

We used χ² tests to compare patient characteristics between those infants who developed hazardous hyperbilirubinemia and those who did not, as well as to compare the incidence of hazardous hyperbilirubinemia in before
and after implementation of universal screening.

This study is part of the larger Late Impact of Getting Hyperbilirubinemia or Phototherapy study. The KPNC Institutional Review Board and the University of California San Francisco Committee on Human Research approved this study.

RESULTS

Incidence and Patient Characteristics

The incidence of TSB ≥30 mg/dL during this 17-year period was 8.6 per 100,000 live births (47 cases). There was a higher incidence before universal bilirubin screening (11.5 per 100,000 live births) versus after universal bilirubin screening (4.3 per 100,000 live birth), $P = .009$.

Infants with a TSB ≥30 mg/dL were more likely to be boys, nonwhite, large for gestational age, and of lower gestational age (Table 1). Among the infants with a TSB ≥30 mg/dL, 40% were <38 weeks' gestational age. Most were in the AAP low risk group (54%), 44% were medium risk, and only 2% were high risk. All of the infants with a TSB ≥30 mg/dL received treatment with phototherapy and 17 (36%) underwent at least 1 exchange transfusion.

Etiology

Only 3 of the 47 infants with TSB ≥30 mg/dL had their peak TSB occur during the birth hospitalization; the other 44 were readmitted for high TSB levels identified as outpatients. Those readmitted had been discharged from their birth hospitalization at a median age of 36 hours (interquartile range: 28.8–44.4). TSB levels peaked between 3 and 7 days in 72% of the infants (Fig 1). Only 13 of 47 infants had a TSB sent during the birth hospitalization; 3 additional infants had a transcutaneous bilirubin measurement done during the birth hospitalization.

Two patients had their maximum TSB measured after 10 days of age. The first was noted to be jaundiced at a well-infant visit at 15 days of age. The parents reported the infant to be yellow for several days before the visit and described abnormal posturing; the infant had electrographic seizures on admission. A transcutaneous bilirubin had been 8.7 mg/dL at 57 hours of age. DAT testing was negative, and the infant had normal G6PD activity. The second infant who presented late had a sibling with a history of prolonged hyperbilirubinemia (lasting 3–4 weeks) and was followed with serial TSB levels. The infant's previous maximum TSB level had been 16.9 mg/dL at 8 days of age, before being brought in by the parents at 19 days because of increased sleepiness and jaundice. The infant had a negative DAT, but evidence of hemolysis and required blood transfusion. Testing for hereditary spherocytosis by osmotic gradient ectacytometry was inconclusive.

The most likely causes of the hyperbilirubinemia are shown in Table 2. In most cases, a cause was not identified. Although 21% of the cases could be attributed to decreased G6PD activity, G6PD testing was only performed on 53% of the infants with a TSB ≥30 mg/dL. Three infants had positive blood cultures: *Escherichia coli*, *Enterococcus*, and *Staphylococcus aureus*. The blood type was O in 42% of the infants, although only 4 infants had a positive DAT. Exclusive breastfeeding at discharge had been noted in 78% of the infants.

Outcomes

Median follow-up time was 7.9 years (interquartile range: 2.2–11.7 years); 85% were followed ≥18 months. As previously reported,13 1 child died of sudden infant death syndrome 1 week after discharge; an autopsy revealed no evidence of kernicterus. Four children (8.5%) exhibited acute bilirubin encephalopathy as evidenced by opisthotonic posturing and/or seizures at the time of hospitalization (Fig 1). Three of these children later exhibited signs of CBE. The child without any apparent chronic manifestations has currently been followed for 33 months, and has received evaluations by neurology and audiology.

In total, 4 of 47 (8.5%) children have CBE in follow-up (Table 3). Two of these children have isolated SNHL, and the other 2 have both CP and SNHL. No cases of CBE were identified in infants with peak TSB levels 30 to 35 mg/dL. All infants with SNHL had a peak TSB ≥35 mg/dL, and both children with CP had a peak TSB ≥45 mg/dL. There was 1 additional infant with a maximum TSB ≥45 mg/dL who had a complete neurodevelopmental evaluation as part of the JFEE study20 and was normal except for mild difficulty with speech articulation.

Three of the 4 infants with CBE were tested for G6PD activity; all had decreased activity. The 2 boys had G6PD activity of 0.8 U/g Hb and 6.6 U/g Hb, and

<table>
<thead>
<tr>
<th>Race/ethnicity, %</th>
<th>TSB max &lt;30 mg/dL (n = 525 362)</th>
<th>TSB max ≥30 mg/dL (n = 47)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boy, %</td>
<td>51.1</td>
<td>61.7</td>
<td>.15</td>
</tr>
<tr>
<td>Hispanic</td>
<td>24.6</td>
<td>39.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>7.1</td>
<td>7.1</td>
<td>---</td>
</tr>
<tr>
<td>Birth weight, g, mean ± SD</td>
<td>3435 ± 510</td>
<td>3436 ± 440</td>
<td>.99</td>
</tr>
<tr>
<td>Gestational age, wk mean ± SD</td>
<td>39.1 ± 1.4</td>
<td>37.9 ± 1.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Small for gestational age, &lt;5th, %</td>
<td>2.0</td>
<td>0%</td>
<td>.3</td>
</tr>
<tr>
<td>Large for gestational age, &gt;95th, %</td>
<td>4.4</td>
<td>14.9%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
the girl had G6PD activity of 7.6 U/g Hb. Both infants with borderline G6PD activity had acute hemolysis at the time of the testing, which can lead to falsely high G6PD activity.27 One of these children also had culture-positive sepsis.

Three cases of CBE occurred at facilities before universal bilirubin screening (0.88 per 100 000 infants), and 1 case occurred after universal bilirubin screening (0.54 per 100 000 infants), \( P = .70 \). None of the 4 infants with CBE received phototherapy during their birth hospitalization. Three of the 4 were born at <37 weeks. Three received an exchange transfusion; the other had a rapid fall in TSB with phototherapy alone.

**DISCUSSION**

Hazardous hyperbilirubinemia (TSB \( \geq 30 \) mg/dL) is a rare event whose incidence has been further reduced by universal bilirubin screening. Even among infants who have had a peak TSB \( \geq 30 \) mg/dL, chronic, bilirubin-induced neurotoxicity is uncommon, occurring in 8.5% of these infants. The incidence of CBE with peak TSB \( \geq 30 \) mg/dL in our population was 0.8 per 100 000 births. The incidence of CBE was <37 weeks, which may have contributed to their vulnerability. No evidence of CBE was seen in infants \( n = 31 \) with peak TSB levels 30 to 35 mg/dL. Both children with CP had peak TSB levels \( \geq 45 \) mg/dL. All infants with CBE had an additional factor (prematurity, decreased G6PD activity, sepsis) and a TSB level \( \geq 15 \) mg/dL above AAP exchange levels. The incidence of TSB \( \geq 30 \) mg/dL in our study (8.6 per 100 000) was similar to what was observed in other large populations, including Hospital Corporation of America 9 per 100 000 (preuniversal bilirubin screening), and the Intermountain Healthcare system 10.6 per 100 000.16,17 Similar to these studies, we also observed a statistically significant reduction in the incidence of TSB \( \geq 30 \) mg/dL after universal bilirubin screening.

A Danish population-based study revealed acute bilirubin encephalopathy in 27% of infants with a TSB \( \geq 35 \) mg/dL and no cases in infants with a TSB \(<35 \) mg/dL.8 Similarly, we observed no cases of acute bilirubin encephalopathy in infants with a peak TSB 30 to 34.9 mg/dL. A UK/Irish study revealed the incidence of bilirubin encephalopathy to be 0.9 per 100 000 births similar to our population incidence of 0.8 per 100 000 births.10 Brooks et al19 reported a rate of 0.44 per 100 000 among California children, but acknowledged the likelihood of incomplete ascertainment in the data set from the Department of Developmental Services. In contrast, the 2.7 per 100 000 incidence reported by Burke et al28 is probably an overestimate because of lack of specificity of International Classification of Diseases, Ninth Revision discharge diagnosis codes for kernicterus.29 Sgro et al18 examined the incidence of CBE with data collected through the Canadian Pediatric Surveillance Program.18 Their case definition included a history of peak TSB \( >24.8 \) mg/dL and a combination of clinical findings or an
abnormal MRI with bilateral lesions of the basal ganglia/midbrain. Over a 2-year period (with a birth rate ~370,000/year), 20 cases of CBE were identified, of whom 3 were normal at follow-up. The authors’ estimate an incidence of 2.3 per 100,000, assuming all 6 lost to follow-up had CBE. In contrast, our rate was lower, but we only included infants with a TSB ≥30 mg/dL and did not identify infants by abnormal MRI. The Danish study revealed a CBE rate similar to our study with an incidence of 0.6 per 100,000 births. All 3 Danish cases had a maximum TSB ≥38 mg/dL.

Our finding that CBE occurred mainly with additional neurotoxicity risk factors (prematurity, decreased G6PD activity, sepsis) is consistent with previous studies. Gamaleldin et al from Cairo observed that infants without risk factors for neurotoxicity have a higher tolerance for hyperbilirubinemia than recognized in management guidelines. They found no cases of acute bilirubin encephalopathy in infants with TSB ≤31.8 mg/dL and absence of additional neurotoxicity risk factors. Variation in susceptibility of infants to a given TSB level may be secondary to a more rapid rise in TSB. During acute hemolytic events in infants with G6PD deficiency, intolerance to a rapid bilirubin load has been described.

In this study, the etiology of hazardous hyperbilirubinemia could not be identified from the clinical record in 70% of infants. Christensen et al similarly did not identify a cause of TSB ≥30 mg/dL in 75.9% of their 112 cases. However, we did find 21% of the cases had decreased G6PD activity, despite only 54% being tested. Decreased G6PD activity was identified in 40% of those tested, suggesting testing for G6PD deficiency is underused. We propose that the workup for hazardous hyperbilirubinemia include G6PD activity given the high prevalence of deficiency among these infants. However, during an acute hemolytic event, it can be difficult to detect G6PD enzyme deficiency by quantitative or qualitative assays as older G6PD-deficient red blood cells are broken down, leaving younger, G6PD-sufficient cells, resulting in falsely normal G6PD activity levels.

Although some have asserted that all cases of kernicterus are preventable, this may be hard to actualize when the hyperbilirubinemia is caused by sepsis or acute hemolysis. Although universal bilirubin screening can help prevent system failures and will identify infants with known risk factors, it may not prevent hyperbilirubinemia secondary to G6PD deficiency, which may present as an acute neonatal hemolytic event precipitated by oxidative stress.

Whether newborns should be screened for G6PD deficiency is unknown. It remains to be determined whether diagnosing G6PD-deficiency during the birth hospitalization could reduce the incidence of hazardous hyperbilirubinemia and bilirubin-induced neurotoxicity.

Although identification may lead to increased surveillance postdischarge, parents would ultimately be responsible for identifying rapidly rising bilirubin levels and seeking prompt medical attention. Our study had some limitations. Our correlations of bilirubin levels with outcomes only report on measured bilirubin levels. Because most of the hazardous bilirubin levels occur after discharge from the birth hospital, levels may have peaked before the infant received testing and the measured values may be an underestimation of the infant’s true maximum bilirubin exposure. In this analysis, we only addressed outcomes in infants with a TSB ≥30 mg/dL. We are currently systematically investigating CP and SNHL at lower TSB levels in this cohort; however, previous work has shown a low incidence of adverse outcome in infants with TSB 25 to 29.9 mg/dL. Lastly, we did not have follow-up after the infants left the health system, although we had >1.5 years of follow-up in 40 of 47 infants with a TSB ≥30 mg/dL.

CONCLUSIONS

Hazardous hyperbilirubinemia (TSB ≥30 mg/dL) is a rare event, occurring in <5 per 100,000 live births after universal bilirubin screening. In most cases, an etiology from the clinical records could not be identified. G6PD deficiency was the leading cause of hazardous hyperbilirubinemia when an etiology was identified; however, testing for G6PD activity is often underused. Even among children with a maximum TSB ≥30 mg/dL, chronic bilirubin-induced neurotoxicity was uncommon (8.5%, 4 of 47) and occurred in the setting of additional risk factors (prematurity, decreased G6PD activity) and TSB values well over (>15 mg/dL) the AAP exchange transfusion thresholds.

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Incidence, Etiology, and Outcomes of Hazardous Hyperbilirubinemia in Newborns

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