Frequency of Neonatal Bilirubin Testing and Hyperbilirubinemia in a Large Health Maintenance Organization

Thomas B. Newman, MD, MPH*; Gabriel J. Escobar, MD†; Veronica M. Gonzales, BS‡; Mary Anne Armstrong, MA‡; Marla N. Gardner, BA‡; and Bruce F. Folck‡

Abstract. Objective. To determine the frequency and interhospital variation of bilirubin testing and identified hyperbilirubinemia in a large health maintenance organization.

Design. Retrospective cohort study.

Setting. Eleven Northern California Kaiser Permanente hospitals.


Main Outcome Measure. Bilirubin tests and maximum bilirubin levels recorded in the first month after birth.

Results. The proportion of infants receiving ≥1 bilirubin test varied across hospitals from 17% to 52%. The frequency of bilirubin levels ≥20 mg/dL (342 μmol/L) varied from .9% to 3.4% (mean: 2.0%), but was not associated with the frequency of bilirubin testing (R² = .02). Maximum bilirubin levels ≥25 mg/dL (428 μmol/L) were identified in .15% of infants and levels ≥30 mg/dL (513 μmol/L) in .01%.

Conclusions. Significant interhospital differences exist in bilirubin testing and frequency of identified hyperbilirubinemia. Bilirubin levels ≥20 mg/dL were commonly identified, but levels ≥25 mg/dL were not.

ABBREVIATIONS. AAP, American Academy of Pediatrics; TSB, total serum bilirubin; CPP, Collaborative Perinatal Project; KPMCP, Kaiser Permanente Medical Care Program; RILIS, Region-wide Integrated Laboratory Information System.

Although neonatal jaundice is generally benign, it can cause brain damage at very high levels.¹ The American Academy of Pediatrics (AAP) recommends phototherapy for term infants at total serum bilirubin (TSB) levels of 20 mg/dL or more (with lower thresholds for younger or sicker infants) and at least preparation for exchange transfusion at levels of 25 mg/dL or more.² How commonly are such high levels identified in the era of managed care and short hospital stays?

Several authors have expressed concern that extreme hyperbilirubinemia and its sequelae are becoming more common, as a result of shorter postpartum stays and/or less aggressive jaundice treatment.³–⁶ However, the frequency of very high TSB levels is difficult to estimate because they are rare and because most population-based data sources, such as discharge abstracts from hyperbilirubinemia hospitalizations, do not include data on the infant’s actual bilirubin level. Recently, Lee et al⁷ reported a study of Ontario hospital discharge abstracts complemented by medical record review at the Hospital for Sick Children in Toronto. Based on the number of births in catchment area hospitals, they estimated the proportion of infants with TSB ≥30 mg/dL (513 μmol/L) to be about .038% (1 in 2600) in 1992–1994, a sevenfold increase from the previous 5 years. No comparable studies from the United States have been done.

A prospective study large enough to provide estimates of the current frequency of TSB levels >20–25 mg/dL (342–428 μmol/L) would be difficult and expensive. The last such study done in the United States was the Collaborative Perinatal Project (CPP), which enrolled infants more than 30 years ago. Recently, the Kaiser Permanente Medical Care Program’s (KPMCP) Northern California medical centers developed and implemented a Region-wide Integrated Laboratory Information System (RILIS) that tracks all laboratory data using common electronic formats. Using RILIS we were able to obtain date, time, and results of all bilirubin tests on a cohort of >50 000 infants born in 11 hospitals. Because bilirubin levels were obtained at the discretion of clinicians, we first wished to investigate whether there was any association between frequency of bilirubin testing and the incidence of identified significant (≥20 mg/dL) hyperbilirubinemia. Such an association would suggest that significant numbers of hyperbilirubinemic infants might have been missed in hospitals doing less bilirubin testing. We then examined the predictors and incidence of various levels of hyperbilirubinemia in the 11 hospitals.
Data Sources

We scanned the RILIS database and extracted all inpatient and outpatient serum bilirubin tests for the 1995–1996 birth cohort. Data retrieved included: 1) a unique patient identifier, which was used to link to other KPMCP administrative and clinical databases, 2) the date and time of the test, 3) the test number, and 4) the test result. All TSB levels obtained at <720 hours of age (30 days) were included.

To ensure the accuracy of the extraction of bilirubin levels from RILIS, we double-checked all TSB results on 51 infants in whom we were particularly suspicious of missing or erroneous data, eg, infants with codes for phototherapy but no high TSB levels and vice versa. There was complete agreement between the TSB values downloaded from RILIS and those available in the clinical display system (felt by clinicians to be close to 100% reliable, and more reliable than the paper record) with one exception. The single discrepancy was a TSB of 60.0 mg/dL in RILIS, which was flagged as erroneous in the clinical display system, and corrected to 20.0 mg/dL. We found that computerized phototherapy data were less reliable, and hence not reported here.

Demographic and other data related to the birth hospitalizations of these infants were obtained from the KPMCP hospitalization database, which includes admission and discharge data, birth weight, gestational age, and 7 self-reported maternal race categories. A chart review of a random sample of 347 births from this cohort showed that 99% of the birth weights from the KPMPC database were within 100 g of those recorded in the chart and 96% of the gestational age estimates from the 2 data sources were within 1 week of each other. There were no significant interhospital differences in discrepancies between electronic and chart review data. Because of small numbers, we combined the Native American, Other, and Unknown race categories.

RESULTS

Descriptive and Ecological Analyses

Demographic characteristics and their variability by hospital of birth are shown for the 51 387 study infants in Table 1. The median length of stay for these term or near-term infants in the 11 hospitals ranged from 17.6 to 34.0 hours. The racial mix of the hospitals varied as well. Overall, 9% of the cohort was black, 16% Asian, 19% Latino, and 53% white. There were smaller (although highly statistically significant) interhospital differences in mean birth weight, gestational age, and maternal age.

The proportion of infants at each birth hospital receiving at least 1 TSB test varied threefold, from 17% to 52% (Table 2). However, there was little correlation between the proportion of infants in each hospital having at least 1 TSB test and the proportion identified as having maximum TSB ≥15 mg/dL (257 μmol/L; $P^2 = .006$; $P = .8$) or maximum TSB ≥20 mg/dL (342 μmol/L; $P^2 = .02$; $P = .7$). On the other hand, there was a strong correlation across hospitals between the proportion of infants receiving at least 1 TSB test and the proportion whose maximum TSB level was measured and <10 mg/dL (171 μmol/L; $P^2 = .90$; $P < .0001$). This suggests that the main effect of more frequent TSB testing was the identification of more infants with low TSB levels.

Maximum TSB levels ≥20 mg/dL were identified in about 2.0% of births and levels ≥25 mg/dL in .15% of births (Table 2). Although there was significant interhospital variation, the frequency of these
elevated TSB levels was not associated with the frequency of TSB testing. The 95th and 99th percentiles for maximum TSB level were similar across hospitals. Only 5 infants (about .01%, or 1 in 10 000) had recorded maximum TSB values of $30 \text{ mg/dL}$ (513 $\text{mmol/L}$).

### Multivariate Analyses

To assess independent effects of these predictor variables on risk of maximum observed TSB levels $\geq 20 \text{ mg/dL}$ (342 $\text{mmol/L}$) and $\geq 25 \text{ mg/dL}$ (428 $\text{mmol/L}$), we did stepwise multiple logistic regression (Table 4). Birth hospital, gestational age 36 to 37 or 38 weeks, male sex, Asian race, and older maternal age were positively associated, and black race and gestational age $\geq 41$ weeks were negatively associated with maximum TSB levels $\geq 20 \text{ mg/dL}$.

### Bivariate Analyses

Besides the association with hospital of birth, hyperbilirubinemia was strongly associated with gestational age, race, sex, and maternal age in bivariate analyses (Table 3). The effect of gestational age was particularly noteworthy. For example, 20 of 4525 infants (.4%) born at <38 weeks’ gestation developed TSB $\geq 25 \text{ mg/dL}$, compared with only 1 of 9810 infants (.01%) born at 41 weeks or more, a 40-fold difference. Compared with whites, rates of identified hyperbilirubinemia were about twice as high in Asians, half as high in blacks, and the same in Latinos. The effect of gestational age on both TSB $\geq 20 \text{ mg/dL}$ and TSB $\geq 25 \text{ mg/dL}$ appeared similar in all races and in both boys and girls.

### Table 1.

<table>
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<tr>
<th>Hospital No.</th>
<th>Number of Infants in Study</th>
<th>Mean Maternal Age (Years)</th>
<th>Mean Gest. Age (Weeks)</th>
<th>Mean Birth Weight (g)</th>
<th>% Black</th>
<th>% Asian</th>
<th>% Latino</th>
<th>Median Length of Stay (Hours)</th>
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<td>SD of average across hospitals</td>
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</tbody>
</table>

### Table 2.

<table>
<thead>
<tr>
<th>Hospital No.</th>
<th>% With at Least 1 TSB Test</th>
<th>Mean TSB &lt;10 mg/dL per Infant</th>
<th>TSB 95th Percentile (mg/dL)</th>
<th>TSB 99th Percentile (mg/dL)</th>
<th>Proportion With Measured TSB $\geq 15 \text{ mg/dL}$</th>
<th>Proportion With Measured TSB $\geq 20 \text{ mg/dL}$</th>
<th>Proportion With Measured TSB $\geq 25 \text{ mg/dL}$</th>
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</thead>
<tbody>
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<td>25%</td>
<td>.6</td>
<td>1.4</td>
<td>18.5</td>
<td>22.3</td>
<td>12.7%</td>
<td>2.8%</td>
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<td>2</td>
<td>52%</td>
<td>1.2</td>
<td>2.8</td>
<td>16.9</td>
<td>21.0</td>
<td>8.4%</td>
<td>1.7%</td>
</tr>
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<td>22%</td>
<td>.5</td>
<td>1.1</td>
<td>17.0</td>
<td>21.1</td>
<td>8.2%</td>
<td>1.6%</td>
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<tr>
<td>4</td>
<td>17%</td>
<td>.4</td>
<td>1.9</td>
<td>17.0</td>
<td>21.9</td>
<td>7.5%</td>
<td>2.0%</td>
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<tr>
<td>5</td>
<td>20%</td>
<td>.5</td>
<td>1.1</td>
<td>17.0</td>
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<td>8.2%</td>
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<tr>
<td>6</td>
<td>19%</td>
<td>.4</td>
<td>1.1</td>
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</tr>
<tr>
<td>7</td>
<td>22%</td>
<td>.6</td>
<td>1.4</td>
<td>17.0</td>
<td>20.4</td>
<td>9.1%</td>
<td>1.2%</td>
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<tr>
<td>8</td>
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<tr>
<td>10</td>
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<td>1.0</td>
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<td>19.9</td>
<td>8.6%</td>
<td>.9%</td>
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<tr>
<td>11</td>
<td>18%</td>
<td>.5</td>
<td>1.2</td>
<td>16.2</td>
<td>20.6</td>
<td>6.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Average</td>
<td>27%</td>
<td>.7</td>
<td>1.4</td>
<td>17.5</td>
<td>21.3</td>
<td>10%</td>
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<tr>
<td>SD of average across hospitals</td>
<td>10%</td>
<td>.2</td>
<td>.5</td>
<td>.9</td>
<td>.8</td>
<td>2%</td>
<td>.8%</td>
</tr>
</tbody>
</table>
Strong effects of gestational age, sex, and Asian race remained and effects of birth at 3 particular hospitals appeared to become greater. The fit of the logistic model was excellent (Hosmer–Lemeshow with 10 groups; $P = .98$). Overall ability to predict TSB $\geq 20$ mg/dL was a little better than the ability to predict TSB $\geq 25$ mg/dL ($c = .79$).

**DISCUSSION**

In this retrospective cohort study we found that significant hyperbilirubinemia was common. Maximum TSB of $\geq 15$ mg/dL (257 μmol/L) was identified in 9.3% of all births and levels of 20 mg/dL (342 μmol/L) or more in 2%. More extreme hyperbilirubinemia, on the other hand, was relatively rarely identified: only about 1 in 650 infants had maximum TSB of 25 mg/dL (428 μmol/L) or more, and only 5 of the $>50,000$ infants in the birth cohort had maximum levels $\geq 30$ mg/dL (513 μmol/L). Gestational age, race, sex and maternal age were predictors of hyperbilirubinemia; the effects of gestational age and race were particularly strong. However, large interhospital differences in risk of identified hyperbilirubinemia persisted after adjusting for these predictors. The ecological analyses suggest that these differences are not attributable to differences in bilirubin testing practices.

**Important Features of the Study Population and Study Design**

Several features of the study design should be kept in mind when interpreting the results. First,
the study was done entirely in a mature health maintenance organization. It is likely that in other settings bilirubin testing and the incidence of hyperbilirubinemia might differ. Treatment might be more aggressive in settings where reimbursement is fee-for-service, rather than capitated, leading to higher rates of testing and lower rates of extreme hyperbilirubinemia in these settings. In contrast, testing and (early) treatment might be less common where there are greater financial or other barriers to medical care than are present for the insured and predominantly employed KPMCP enrollees. Nonetheless, the finding of considerable interhospital variation in bilirubin testing and in the frequency of hyperbilirubinemia is more striking given that all hospitals were part of the same managed care organization. If a more diverse group of health care systems had been studied, the interhospital variability we observed might have been even greater.

A strength of the study is the large sample size, which allowed us to estimate the frequency of uncommonly high TSB levels with good precision. However, this study of 51387 infants was feasible only because it relied entirely on data already available in KPMCP databases. Information on other predictors of hyperbilirubinemia, particularly breastfeeding and the timing and nature of bilirubin-lowering interventions that were not reliably available in electronic form are clearly essential for investigating predictors of hyperbilirubinemia. A nested case-control study of extreme hyperbilirubinemia and dehydration, in which we are obtaining these data from chart reviews and parent interviews on subsets of the cohort, is currently in progress.

Finally, because bilirubin levels were not checked in all infants, this was a study of identified hyperbilirubinemia. As such, it represents a minimum estimate of the true incidence of extreme hyperbilirubinemia. Some infants with TSB levels ≥20 mg/dL (342 μmol/L), or even ≥25 mg/dL (513 μmol/L), may have had resolution of their hyperbilirubinemia without it having been identified. However, we found no association across hospitals between frequency of bilirubin testing and identification of elevated bilirubin levels, suggesting that underestimation of the frequency of hyperbilirubinemia as a result of selective ordering of bilirubin levels is not severe.

A comparison with results of the CPP, the only previous study of this magnitude, suggests that our ascertainment is reasonably complete. In the CPP, in which TSB levels were checked in all infants and no phototherapy was done, rates of maximum TSB ≥20 mg/dL in infants ≥2500 g were 1% in whites and 0.6% in blacks, compared with 1.7% in whites and 1.0% in blacks in the current study. The higher rate in 1995–1996 than 1959–1966 presumably reflects increased breastfeeding. Because hyperbilirubinemia rates are higher in the current study than in a previous study that was likely to have had more complete ascertainment, we believe the extent of underascertainment is probably low. Nonetheless, it should be emphasized that the estimates of the frequency of identified hyperbilirubinemia at each level are minimum estimates of the frequency of hyperbilirubinemia.

Clinical and Policy Implications

The findings reported here have several clinical and policy implications. First, hospitals that did more TSB tests had more TSB results <10 mg/dL, but not more identified hyperbilirubinemia. This suggests that more selective TSB test-ordering policies in these high-testing hospitals could save on venipunctures and their associated costs and discomfort, with little increased risk of missing extreme hyperbilirubinemia, provided that the infants still receive appropriate follow-up.11

Second, the high (>5%) rate of TSB ≥20 mg/dL that we observed in the 36- to 37-week-old infants suggests that (in 1995–1996) KPMCP clinicians, lacking any other specific guidelines for managing hyperbilirubinemia in these infants, may have been extending recent less aggressive jaundice treatment recommendations for full-term infants2,12 to 36-week-old infants as well. Seidman et al13 presented similar findings in a study from Israel: rates of exchange transfusion for hyperbilirubinemia declined similarly in term and preterm infants following publication of the AAP’s hyperbilirubinemia practice parameter, even although the parameter was explicitly directed at term infants. This is not necessarily wrong, but it does illustrate the need for better data on which to base explicit guidelines for management of hyperbilirubinemia in these near- and early term infants. The strong association with gestational age also emphasizes the need for particularly close follow-up of these less mature infants, and also the very low risk of postterm (41+ weeks) infants.

Third, the incidence of TSB ≥20 mg/dL and TSB ≥25 mg/dL varied significantly across hospitals, even after controlling for race and gestational age differences. This residual variation may be partly attributable to differences in known biologic predictors that were not available electronically for this study, such as breastfeeding, blood group incompatibility, or glucose 6-phosphate dehydrogenase deficiency. However, given the magnitude of the differences, it is likely that variations in practice also contribute to the interhospital differences in hyperbilirubinemia. This would hardly be surprising, given the continued variation in published recommendations. For example, some authorities still recommend exchange transfusion in well, term infants with TSB 20–25 mg/dL, whereas exchange transfusion is not recommended in the AAP practice parameter unless the TSB is >25 mg/dL and fails to respond to phototherapy.2 Again, the need for better evidence on which to base treatment guidelines is apparent.

Finally, the rarity of TSB ≥30 mg/dL (513 μmol/L) is somewhat reassuring. Lee et al7 attributed the high (1/2600) rate of TSB ≥30 mg/dL, they observed in Ontario in 1992–1994 in part to shortened postpartum stays, which declined from a median of 4.5 to 2.7 days over the time period of their
The current study, with only 5 such infants in 51,387 births (1/10,000), provides an estimate only about one fourth as high, despite a median length of stay of only 1.2 days. We plan future studies, including examining the outcomes in these infants, to determine if the low rate of TSB levels \( \geq 25-30 \text{ mg/dL} \) observed in the current study can and should be further reduced.

**ACKNOWLEDGMENTS**

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**REFERENCES**

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