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Infants With Bilirubin Levels of 30 mg/dL or More in a Large Managed Care Organization

Thomas B. Newman, MD, MPH*†§; Petra Liljestrand, PhD*§; and Gabriel J. Escobar, MD§¶

ABSTRACT. *Objective.* To describe the incidence, etiology, treatment, and outcome of newborns with total serum bilirubin (TSB) levels ≥ 30 mg/dL (513 $\mu\text{mol/L}$).

Design. Population-based case series.

Setting. Eleven Northern California Kaiser Permanente Medical Care Program hospitals and 1 affiliated hospital.

Patients. Eleven infants with TSB levels of ≥ 30 mg/dL in the first 30 days after birth, identified using computer databases from a cohort of 111 009 infants born 1995–1998.

Outcome Measures. Clinical data from the birth hospitalization, rehospitalization, and outpatient visits in all infants; psychometric testing at age 5 ($N = 3$), neurologic examinations by child neurologists at age 5 ($N = 3$), or primary care providers ($N = 7$; mean age: 2.2 years); Parent Evaluation of Developmental Status ($N = 8$; mean age: 4.2 years).

Results. Maximum TSB levels of the 11 infants ranged from 30.7 to 45.5 mg/dL (525 $\mu\text{mol/L}$ to 778 $\mu\text{mol/L}$; mean: 34.9 mg/dL [597 $\mu\text{mol/L}$]). Four were born at 35 to 36 weeks gestation, and 7 were exclusively breast-fed. Two had apparent isoimmunization; the etiology for the other 9 remained obscure, although only 4 were tested for glucose-6-phosphate dehydrogenase deficiency and 1 was bacteremic. None had acute neurologic symptoms. All received phototherapy and 5 received exchange transfusions. One infant died of sudden infant death syndrome; there was no kernicterus at autopsy. Two were lost to follow-up but were neurologically normal when last seen for checkups at 18 and 43 months. One child was receiving speech therapy at age 3. There were no significant parental concerns or abnormalities in the other children.

Conclusions. In this setting, TSB levels ≥ 30 mg/dL were rare and generally unaccompanied by acute symptoms. Although we did not observe serious neurodevelopmental sequelae in this small sample, additional studies are required to quantify the known, significant risk of kernicterus in infants with very high TSB levels. *Pediatrics* 2003;111:1303–1311; bilirubin, blood, jaundice, neonatal, kernicterus/prevention and control, cohort studies, health maintenance organizations, follow-up studies, neurologic examination.

ABBREVIATIONS. AAP, American Academy of Pediatrics; TSB, total serum bilirubin; KPMCP, Kaiser Permanente Medical Care Program; G6PD, glucose-6-phosphate dehydrogenase; JIFee, Jaundice and Infant Feeding Study; PEDS, Parent Evaluation of Developmental Status; DAT, direct antiglobulin test; Rh, rhesus; G, gravida; P, para.

Because of the risk of kernicterus, the American Academy of Pediatrics (AAP) recommends exchange transfusions for infants whose total serum bilirubin (TSB) levels remain above 30 mg/dL (513 $\mu\text{mol/L}$).¹ Such high bilirubin levels are fortunately very rare, occurring in only ~ 1 in 10 000 term infants in the Northern California Kaiser Permanente Medical Care Program (KPMCP),² the only setting for which recent population-based incidence data are available. Thus, most descriptions of infants with such extreme elevations of TSB have been anecdotal case reports, generally of infants that developed kernicterus,³ many of whom have had glucose-6-phosphate dehydrogenase (G6PD) deficiency,^{4–6} sepsis,⁷ or other identifiable causes of hyperbilirubinemia.

Recently, however, Harris et al⁸ reported 6 breast-fed infants without apparent hemolytic disease who had TSB levels above 25 mg/dL (428 $\mu\text{mol/L}$), of whom 5 had TSB levels over 30 mg/dL. Although 5 were described as having neurologic signs at the time of their marked hyperbilirubinemia, 4 were normal at follow-up. One had hearing loss (a common finding in children with kernicterus), whereas the other had cerebral palsy and mental retardation with magnetic resonance imaging findings not characteristic of kernicterus. The patient with hearing loss was the only one that had not received 1 or more exchange transfusions. The authors speculated that aggressive treatment with exchange transfusions had prevented more serious neurologic sequelae in the other infants. Limitations of that report are that the size and nature of the referral population from which these cases were identified are not known and the small sample size ($N = 1$) of infants not treated with exchange transfusion.

As part of a large follow-up study to assess neurodevelopmental outcome of term and near-term infants with TSB levels of 25 mg/dL or more, we have identified 11 infants born over a 4-year period in the KPMCP with peak TSB levels of 30 mg/dL or more. In this report, we present data on the possible etiology of the extreme hyperbilirubinemia in these infants, how they were evaluated and treated, and presently available information on their neurodevelopmental outcome.

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METHODS

Subjects

The cohort from which eligible cases were identified consists of 111 009 infants born alive at any of 11 Northern California KPMCP hospitals, or 1 affiliated hospital (Alta Bates Medical Center in Berkeley, to which KPMCP members were referred for obstetric care beginning in 1997). There were no program-wide protocols covering the care of jaundiced newborns during the study period. We obtained all bilirubin levels and the dates and times they were done on infants in this birth cohort from the Regional Integrated Laboratory Information System.² Subjects were eligible for inclusion if they had at least 1 TSB result of 30 mg/dL or more at <720 hours (30 days) of age. We excluded subjects if the elevated result was subsequently identified by the clinical laboratory as an error (1 infant with a TSB result of 60.0 mg/dL) or if the maximum conjugated bilirubin was >15% of the maximum TSB (1 infant with maximum TSB of 54 mg/dL and maximum conjugated bilirubin of 50.9 mg/dL).

Perinatal Clinical and Laboratory Data

Maximum TSB levels were measured using the Kodak Ektachem neonatal bilirubin assay (Kodak, Rochester, NY) on 10 infants or the DuPont Automated Chemical Analyzer neonatal bilirubin assay (DuPont Company, Wilmington, DE) on 1 infant. The TSB levels, reticulocyte counts, and G6PD activity levels were obtained directly from the regional laboratory information system. Other laboratory and perinatal data were abstracted from paper charts and electronic medical records. The readmission for jaundice for case 11 was at a non-KPMCP hospital, from which we had the discharge summary but not the entire medical record.

Modeling the Time From Maximum TSB to TSB of 20 mg/dL

The duration of hyperbilirubinemia may be relevant for prognosis, and the rapidity of the fall in TSB once therapy has begun is a measure of the success of therapy. One (admittedly arbitrary) way to summarize this duration is by estimating the time between the highest measured TSB level and the time when the TSB level was estimated to reach 20 mg/dL. This was simplified by the observation that no infant whose TSB level dropped below 20 mg/dL after their maximum TSB level had a repeat value above 20 mg/dL. We assumed a linear decline in TSB level between the last value above 20 mg/dL and the first value <20 mg/dL, and algebraically computed the infant's age when the TSB was projected to have declined to 20 mg/dL, assuming a linear decline between those 2 points. We estimated the time between the maximum TSB level and the first TSB level <20 mg/dL by subtracting the 2 ages.

Follow-Up and Outcome Data

The subjects and data elements collected for this report are a subset of those in a larger study (the Jaundice and Infant Feeding Study; JIFee) of 5-year neurodevelopmental outcome of neonatal jaundice and dehydration. The JIFee study was approved by the institutional review boards for the protection of human subjects of the University of California-San Francisco and the KPMCP.

Subjects for this study who enrolled in the JIFee study have had

($N = 3$) or are scheduled to have ($N = 3$) complete blinded neurodevelopmental evaluations at age 5. Blinding was accomplished by including a randomly selected control group and instructing parents not to tell examiners anything about the child's perinatal history. The evaluation includes the Wechsler Preschool and Primary Scale of Intelligence, Revised⁹ and the Beery-Buktenica test of Visual Motor Integration,¹⁰ both performed by a child psychologist, a neurologic examination by a child neurologist. In addition, research staff perform the Motor Performance Checklist,¹¹ a screening test designed to detect motor coordination problems in 5-year-olds, and parents complete the Child Behavior Checklist.¹² Finally, the Parent Evaluation of Developmental Status (PEDS) is administered annually to enrolled subjects by blinded study staff. The PEDS is a 10-item questionnaire that asks parents if they have any concerns about their child's development or behavior.¹³ For example, question number 5 asks, "Do you have any concerns about how your child uses his or her arms or legs?"

Parents declining to enroll in the full JIFee study are still asked to fill out the PEDS and Child Behavior Checklist. For families that could not be reached, we summarized available outcome data from KPMCP medical records. These were from well child visits, where standard age-specific forms have a box to check to indicate that the (presumably limited) neurologic examination was normal. Each such form also has ~6 specific age-related developmental tasks to check off. We considered the neurologic examination recorded by the primary care provider normal if the normal neurologic examination box and all age-specific developmental task boxes were checked.

RESULTS

Of the 111 009 infants born in the 4-year KPMCP birth cohort, 11 (0.01%) met inclusion criteria for the study. Brief case histories of all 11 subjects are provided in the appendix.

Demographic and Birth Hospitalization Data (Table 1)

Although the lowest birth weight of the study infants was 2900 g, 2 of the infants were born at 35 weeks gestation and 2 at 36 weeks. All 11 were born before 40 weeks. There were 6 boys and 5 girls. Race and ethnicity were diverse. Two of the infants had received phototherapy during the birth hospitalization; the other 9 were discharged on the second day after birth (age 24–44 hours) and received phototherapy later. Seven of the 11 infants were exclusively breastfed; the only exclusively formula-fed infant was the boy (no. 3) with rhesus (Rh) isoimmunization.

Bilirubin Levels and Treatment (Table 2)

The maximum TSB levels of the infants ranged from 30.7 mg/dL to 45.5 mg/dL; only 1 was over 40 mg/dL (mean \pm standard deviation = 34.9 \pm 4.4

TABLE 1. Demographic and Initial Birth Hospitalization Data

Case	Mother's Age	Race/Ethnicity of Mother	Gestational Age	Birth Weight (Grams)	Sex	Length of Stay (Hours)	Feeding at Initial Discharge
1	28	Asian	39	3550	F	27	Breast only
2	29	Asian	39	3500	F	24	Breast only
3	25	Black	36	3100	M	144	Formula only
4	35	White	38	4350	M	28	Breast only
5	34	Asian	39	3850	M	29	Breast + formula
6	39	Black	36	3250	M	95	Breast only
7	32	White	35	2900	M	36	Breast only
8	29	Hispanic	38	3700	F	32	Breast + formula
9	24	Hispanic	39	3600	F	25	Breast only
10	26	White	35	3100	M	44	Breast + formula
11	24	White	37	3350	F	33	Breast only

F indicates female; M, male.

TABLE 2. Bilirubin Levels of Study Infants and Response to Treatment

Case	First TSB (mg/dL)	Age at First TSB (Hours)	Maximum TSB (mg/dL)	Age at Maximum TSB (Hours)	Maximum Conjugated Bilirubin (mg/dL)	Exchange Transfusion	Intravenous Fluids?	Estimated Time to TSB <20 mg/dL (See Text)
1	38.5	148	38.5	148	1.7	No	Yes	32
2	28.1	122	32.4	128	1.1	No	Yes	22
3	14.3	23	34.2	61	2.2	Double volume × 1	Yes	15
4	>30	203	45.5	204	2.4	Double volume × 1	Yes	26
5	30.6	102	35.3	108	2.1	Double volume × 1	Yes	6
6	16.5	41	31.1	142	0.5	No	No	6
7	14.6	33	38.2	83	3.2	No	No	13
8	32.6	81	32.6	81	2.5	Double volume × 1	Yes	7
9	32.1	92	32.1	92	3.6	Near double volume × 1	Yes	4
10	33.8	111	33.8	111	2.3	No	No	37
11	30.7	106	30.7	106	0.7	No	No	Not available

mg/dL). In 3 infants (cases 3, 6, and 7) a TSB level had been obtained >24 hours before the peak TSB. All 3 TSB had levels well above the reported 95th percentile for the infants' age.¹⁴ Five of the infants were treated with a single double-volume exchange transfusion; 7 received intravenous fluids, and all were treated with phototherapy with at least 2 lights. The overall average time until the TSB declined to 20 mg/dL was 17 hours, with an average of 12 hours in those who received exchange transfusions and 22 hours in those treated only with phototherapy (*P* by 2-tailed *t* test = .17).

Additional Diagnostic Evaluation (Table 3)

Two infants had apparent isoimmunization: infant 3, whose mother was known to be Rh-sensitized and infant 8, who had an O/A incompatibility and a weakly positive direct antiglobulin (Coombs) test. Infant 1 also had an O/A incompatibility and a progress note in her chart indicating a positive direct antiglobulin test (DAT); however, no confirmation of this result could be found in other paper or electronic records. Hemoglobin levels or hematocrit values close to the time of the maximum TSB were generally normal, although 3 infants (numbers 4, 5, and 11) had hemoglobin levels over 18 g/dL. Infant 6, who had an O/B incompatibility but negative DAT, had the lowest hemoglobin level and highest reticulocyte count. His G6PD screen was normal and no other evaluation for hemolysis was done. Three other infants had G6PD screens that were considered normal, although the normal range provided by the clinical laboratory for this test (4.2–10.1 U/g hemoglobin) is low for newborns. Of 471 G6PD screens done on this birth cohort in 1995–1998, the mean was 12.2 U/g hemoglobin with a standard deviation of 5.3 U/g hemoglobin. Blood smears were done in all infants, but apart from polychromasia, results were generally not helpful.

Acute Symptoms, Follow-Up, and Outcome (Table 4)

With the possible exception of infant 5, who had a brief cyanotic episode, none of the infants showed any signs of acute bilirubin encephalopathy. Of the

10 infants whose maximum bilirubin occurred after the birth hospitalization, 6 had hyperbilirubinemia noted at a regularly scheduled follow-up visit, rather than as a result of parent-initiated visit attributed to concern about the infant's jaundice or behavior. In 4 of these 6 infants, the providers seeing the infants (1 lactation consultant and 3 pediatricians) sent the infant home while the TSB result was still pending.

Infant 3 died of apparent sudden infant death syndrome; there was no evidence of kernicterus at autopsy (Appendix). Of the remaining 10 infants, we have been able to reach 8, of whom 6 are enrolled in the JIFee study, and 2 (of whom 1 lives out of state) declined to be in the full study, but provided us with the PEDS. The 2 infants lost to follow-up had had regular well child visits in the KPMCP, with normal examinations at their last recorded visits at 18 months and 3.8 years. The neurologic outcomes of the subjects reached for follow-up also appear to be good. The neurologist's rating of "normal-questionable" for subject 4, who had a TSB of 45.5 mg/dL at 8 days, was attributed to slight dysarthria when he was asked to repeat the sound "la, la, la," and to some hyperreflexia. To date, 26 of the 87 infants in the control group (30%) have had "normal/questionable" or worse as their overall neurologic examination rating, reflecting the instruction to the study neurologists to use the "normal/questionable" category for findings that, while noticeable, do not cause disability and may not even be abnormal.

Only 3 subjects have had formal intelligence testing. All 3 had both verbal and performance intelligence quotients in the normal range or above, although in all 3 cases the "verbal" intelligence quotient on the Wechsler Preschool and Primary Scale of Intelligence, Revised was less than the "performance" intelligence quotient (which tests nonverbal skills) by at least 12 points. The gap between verbal and performance scores for case 2 is probably because the primary language spoken in her household is Cantonese. The other outcomes also appear to be good in these children. With the exception of speech therapy mentioned for case 8, none of the

TABLE 3. Weight Loss and Laboratory Evaluation of Study Infants

Case	Weight Change From BW at Readmission	Mother/Infant Blood Type, DAT	Hemoglobin Closest to When TSB Maximum (g/dL); Age Done	Reticulocyte Count (%) Closest to TSB Maximum; Age Done	Blood Smear	G6PD (U/g Hb; Normal Range: 4.2–10.1)	Albumin (g/dL); Age Done
1	-4.8%	O ⁺ /A ⁺ DAT ? (see text)	14.7; 148 h	2.6%; 287 h (6 days after max TSB)	Normal	ND	2.6; 152 h
2	-5.0%	A ⁺ /O ⁺ , DAT ⁻	17.3; 128 h	ND	Normal	6.9	ND
3	N/A	A ⁻ /O ⁺ DAT ⁺	Spun hematocrit = 50; 61 h	ND	3+ polychromasia, 2 n RBC/100 WBC	17.3	3.6; 67 h
4	-2.0%	O ⁺ /O ⁺ , DAT ⁻	18.8; 204 h	ND	2+ polychromasia, 2+ aniso	ND	ND
5	-7.0%	B ⁺ /O ⁺ DAT ⁻	21.8; 108 h	3.8%; 106 h	1+ polychromasia, 2+ aniso	10.8	ND
6	-7.9%	O ⁺ /B ⁺ DAT ⁻	13.5; 47 h; 13.4; 142 h; 11.1; 181 h	8.3%; 48 h	Normal	12.8	ND
7	-12.0%	O ⁺ /O ⁺ DAT ⁻	16.5; 83 h	4.7%; 83 h	2+ poly, 2+ aniso, 2+ poikilo, 3 nRBC/100 WBC	ND	ND
8	-9.0%	O ⁺ /A ⁺ DAT ^{weak+}	14.5; 81 h	6.4%; 83 h	2+ microcytes, 1+ poikilo	ND	ND
9	4.0%	O ⁺ /A ⁺ DAT ⁻	15.2; 92 h	6.2%; 92 h	1+ polychromasia, 2+ aniso; 2+ poikilo	ND	3.0; 96 h (post ET; pre ET Calcium was 6.9 mg/dl)
10	-10.4%	A ⁺ /A ⁺ DAT ⁻	15.5; 111 h	1.1%; 152 h	Normal	ND	ND
11	-16.9%	A ⁺ /O ⁺ DAT ⁻	18.1 at time of readmission				

BW indicates birth weight; HB, hemoglobin; ND, not done; nRBC, nucleated red blood cells; WBC, white blood cells; aniso, anisocytosis; poikilo, poikilocytosis; ET, exchange transfusion.

parents had concerns about their children's growth or development.

DISCUSSION

We found that over a 4-year period, ~1 in 10 000 newborn infants in the Northern California KPMCP developed a documented peak TSB of 30 mg/dL or more. This is the same as the incidence we previously reported for infants born in 1995 and 1996.² Unlike studies where case identification has been based on either anecdotal reports or physician-assigned diagnoses, our cases were ascertained from a defined population using objective laboratory data.

To our knowledge, there are no other population-based data on the frequency of this degree of hyperbilirubinemia. The incidence in the current study may be lower than is typical in the United States, because the infants in this cohort were born into an integrated health system and had no financial barriers to access care. In contrast, treatment of hyperbilirubinemia in the KPMCP at this time included significantly less use of phototherapy than recommended by the AAP.¹⁵ We have previously shown that although adherence to guidelines for follow-up after early discharge is also inconsistent in this population, such adherence was actually more common among infants whose TSB exceeded 25 mg/dL than among other infants.¹⁶

Although 2 of the infants had apparent isoimmunization, for the other 9 no biological cause for their extreme hyperbilirubinemia other than breastfeeding and immaturity was determined. In at least 2 patients (cases 3 and 6), the possibility of a laboratory error is suggested by much lower TSB levels before and soon after the level over 30 mg/dL. Red cell morphology was reported on 10 of the 11 infants, but interpretation of that test is hampered by lack of standardization across laboratories and absence of a well-defined normal range.¹⁷ This is also true of reticulocyte counts, which were done on 7 infants, and were perhaps mildly elevated in 2. Only 4 of the infants had G6PD screens done. Thus, lack of an identified etiology of the extreme hyperbilirubinemia in these infants may be partly attributed to difficulty interpreting nonspecific tests and lack of diagnostic evaluation. Nonetheless, the results are consistent with other series of infants with extreme elevations of TSB, in which specific causes other than isoimmunization were seldom identified.^{8,18}

Extremely elevated TSB levels occur as a result not only of biological causes, but also as a result of jaundice not being recognized and treated at lower levels.¹⁶ In 5 of the cases reported here (cases 2, 5, 6, 8, and 11), treatment and follow-up were in accordance with AAP guidelines,^{1,19} and it is hard, even in retrospect, to say that the elevated TSB was attributable to health services causes. Case 2, for example, was jaundiced to the chest 52 hours of age. Although a TSB level at this time would have been reasonable, it was not obviously required; jaundice to the chest suggests a TSB level of ~7 mg/dL (range: 5–12 mg/dL),²⁰ which is normal at 52 hours. In case 5, a cephalhematoma may have been initially missed, but because follow-up was scheduled at 4 days of age

TABLE 4. Treatment, Follow-Up, and Outcomes of Study Infants

Case	Acute Symptoms	Follow-Up and Comments	Neurologic Examination	PEDS, Age	CBC-L	MPC Score†	IQ at Age 5	VMI (Standard Score)
1	None	Declined full participation in JIFee ("No time") but completed questionnaires	Normal by primary pediatrician at 4.5 years	No concerns, age 5	Normal	Not done	Not done	Not done
2	None	Completed JIFee evaluation. Comment by psychologist: "Excelled in tasks of manipulating visual information, such as copying geometric figures, and also excelled in arithmetic. Motorically quite active."	Normal by child neurologist	No concerns, age 5	Normal	5	Performance IQ = 129; Verbal IQ = 105	Visual = 113; Motor = 130
3	None	Died of apparent SIDS; see text. No kernicterus at autopsy.	Not done	Not done	Not done	Not done	Not done	Not done
4	None	Completed JIFee evaluation. Comment by psychologist: "Bright. Better nonverbal than verbal. Articulation problems but overall could be understood and talkative."	Normal/questionable by child neurologist-hyperreflexia and "mildly ataxic at saying 'lala'"	No concerns, age 5	Normal	4	Performance IQ = 124; Verbal IQ = 111	Visual = 130; Motor = 97
5	Brief cyanotic spell after admission	Completed JIFee evaluation. Comment by psychologist: "Did visual-motor tasks carefully, slowly. Moderately talkative. Not antsy."	Normal by child neurologist	No concerns, age 5	Normal	4	Performance IQ = 105; Verbal IQ = 93	Visual = 130; Motor = 124
6	None	Family has moved to Europe. At a well child visit at 3 years 10 months, neurologic examination and developmental milestones were normal and the child was noted to be "very articulate."	Normal by primary pediatrician at 3.8 years	Not done	Not done	Not done	Not done	Not done
7	None	JIFee evaluation pending. Multiple episodes of otitis media, intermittent conductive but no sensorineural hearing loss.	Normal by primary pediatrician age 3.5 years	No concerns, age 4	Not done	Not done	Not done	Not done
8	None	Still trying to reach for JIFee. Regular well baby visits through 18 months, all normal. At 18 months, "healthy, thriving," normal development, 10+ words.	Normal by primary pediatrician at 18 months	Not done	Not done	Not done	Not done	Not done
9	None	Enrolled in JIFee, full evaluation pending.	Normal by primary pediatrician at 6 months	No concerns, age 4	Not done	Not done	Not done	Not done
10	None	Family moved out of state, but finally reached by telephone by T.B.N. at age 3.7 years, hence PEDS not blinded.	Normal by primary pediatrician at 15 days	Speech therapy since age 3.3; no other concerns, age 3.7	Not done	Not done	Not done	Not done
11	None	Enrolled in JIFee; full evaluation pending.	Normal by primary pediatrician at 22 months	No concerns except "pigeon toed" and "has temper," age 3	Not done	Not done	Not done	Not done

CBC-L indicates Child Behavior Checklist; VMI, visual-motor integration; MPC, Motor Performance Checklist; IQ, intelligence quotient; SIDS, Sudden infant death syndrome. † Scored 1 point for each item failed. To date in the JIFee control group (N = 84); 32% have scores ≥4.

anyway, it is hard to argue that the management would have been altered if it had been found. Case 6's phototherapy was discontinued at 4 days when the TSB was 13.9 mg/dL. Not checking a "rebound" TSB is certainly consistent with AAP guidelines¹ and the literature,²¹⁻²³ especially given a scheduled follow-up visit 2 days later. In case 8, a possible A/O incompatibility was missed, and although jaundice was noted at 28 hours of age, no TSB requested. But jaundice at 28 hours is not abnormal,^{14,24,25} and follow-up at only 3 days of age was appropriate.

For 3 of the cases there was a clear departure from AAP guidelines. The guidelines call for a follow-up visit within 48 to 72 hours after discharge for infants discharged at <48 hours of age. Cases 1 and 4 were discharged at 26 and 27 hours with follow-up scheduled in 2 weeks, despite strong risk factors for jaundice. The guidelines also state that the TSB should be measured in infants noted to be jaundiced at <24 hours of age. Case 10 was noted to be jaundiced at 18 hours, and no TSB was done. A transcutaneous bilirubin measurement was done, and was high for the infant's age.

The final 3 cases, at least in retrospect, also could probably have been prevented with different follow-up or treatment decisions, but they occurred in infants not covered by the AAP jaundice guideline. Case 3 was not covered by the guideline because jaundice was attributable to known Rh disease. In this infant it would have been prudent to have begun phototherapy and rechecked the TSB sooner after the TSB of 14.3 mg/dL at 22 hours, but given that the TSB increased only 3.7 mg/dL off phototherapy between 22 and 45 hours, the increase from 18 mg/dL to 34.2 mg/dL over the following 20 hours while on phototherapy was unexpected. Cases 7 and 10 were not covered by the guideline because their gestational age was only 35 weeks. Case 7's TSB of 14.6 mg/dL at 33 hours of age would have put him in the "consider phototherapy" category if he had been born at term.

Case 7 and the other 3 cases with gestational ages of 35 to 36 weeks are concerning because less mature infants are thought to be at greater risk of bilirubin toxicity than term infants, and hence to require more aggressive treatment and follow-up.²⁶ It is noteworthy that all 4 infants 35 to 36 weeks had birth weights of >2900 g, suggesting they may have been treated as more mature than their gestational age because of their birth weights. A growing literature reports that infants who are moderately premature experience significant mortality²⁷ as well as morbidity,²⁸⁻³⁴ particularly in the immediate neonatal period.^{35,36} Educational efforts aimed at clinicians must emphasize the need to base risk assessment on infants' gestational age rather than only on their birth weight.

Similar to the outcomes recently reported by Harris et al,⁸ the outcomes of the infants in this study were generally good. However, 2 differences are striking. First, unlike the infants reported by Harris et al,⁸ the infants in the current series generally did not appear ill. In fact, 4 of them were sent home while awaiting the TSB results that turned out to be very high. Second, only 5 of 11 infants in the current

series received exchange transfusions, compared with 5 of 6 in the Harris study. This suggests that there may be many infants with very high bilirubin levels who do not receive exchange transfusions and do well, as reported by Hansen.³⁷ Whether the benefits of exchange transfusion exceed the risks in these infants is not known.

Although there are many case reports of infants with TSB ≥ 30 mg/dL who developed kernicterus, previous studies of infants with markedly elevated TSB levels have generally found good outcomes in those without isoimmunization. However, few have separated out the infants with TSB ≥ 30 mg/dL. Mores et al³⁸ reported 7 infants with TSB ≥ 30 mg/dL, but only 2 were ≥ 2000 g; these 2 infants had normal development at age 3. Our results are also consistent with a report of medical-legal cases,³⁹ in which all 6 term infants who developed apparent kernicterus in the absence of isoimmunization or other illnesses had TSB levels ≥ 39 mg/dL, a level reached by only 1 of the infants reported here and none of the infants reported by Harris et al.⁸

Our findings should not be interpreted as indicating TSB levels above 30 mg/dL as safe. Kernicterus is devastating and continues to occur⁴⁰ and available data with denominators are not nearly large enough to rule out a clinically significant risk. Although most reported cases of kernicterus in otherwise well infants have occurred at TSB levels above the mid-thirties, an infant with a TSB level in that range could easily be or become a sick infant (eg, from infection or G6PD deficiency). Thus, aggressive lowering of TSB levels with phototherapy and formula³⁷ and preparations for exchange transfusion are indicated in these infants.

Our study can also serve as an example of how health services research can complement quality and patient safety improvement efforts. Our findings are consistent with other research, such as that of Clasen et al,⁴¹ which has shown that electronic surveillance is superior to traditional incident reporting. In the course of our research, we have presented these and other findings to all of the KPMCP Chiefs of Pediatrics and Nursery Directors. The large covered population and integrated information systems enable us not only to do this study, but to provide clinicians and managers with a low-cost, reliable electronic quality indicator (frequency of extremely elevated bilirubin levels) that can be used to facilitate ongoing quality improvement. It is unlikely that the high bilirubin cases reported here would have been available for review by individual quality departments, because these patients did not have problematic outcomes.

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APPENDIX

Case 1

A 3550-g, 39-week girl was born in 1995 to a 28-year-old O⁺ Ab⁻ gravida (G) 3 para (P) 2 Asian mother by spontaneous vaginal delivery with oxytocin augmentation. She was exclusively breastfed. There were notations of pallor at 18 hours of age and jaundice at 23 hours. She was discharged at 26 hours and told to follow-up at 2 weeks. She was seen again at 6 days of age for jaundice. The weight was 5% below birth weight. The TSB was 38.5 mg/dL; the conjugated bilirubin was 1.7 mg/dL. A clinic note indicates that the blood type was A⁺ with a positive DAT; however, we could not confirm or refute this elsewhere in the chart or in the electronic medical record. Her initial hemoglobin was 14.7 g/dL. She was treated with phototherapy and recovered uneventfully.

Case 2

A 3500-g 39-week girl was born in 1996 to a 28-year-old A⁺ Ab⁻ gravida 2 para 1 Asian mother by vacuum-assisted delivery with oxytocin augmentation. She was exclusively breastfed. She was discharged at 24 hours of age with no jaundice or cephalhematoma noted. When seen by a home health nurse at 52 hours of age, her weight was down 7%, and she was described as jaundiced to the chest. The nurse instructed the mother about breastfeeding and told her to return if the jaundice got worse. She returned at 5 days for worsening jaundice. At that time she was breastfeeding 10 minutes on each side every 2 to 3 hours, was having 3 to 4 yellow stools per day, and was voiding 4 to 6 times per day. On physical examination she was awake and alert. Her weight was down 5% from the birth weight, but increased by 2% from 3 days before. She was jaundiced to her thighs with a TSB of 28.1 mg/dL (conjugated bilirubin 1.0 mg/dL), so she was admitted. On repeat, the TSB was 32.4 mg/dL. She was admitted to the intensive care nursery and treated with intravenous fluids and triple phototherapy. The TSB dropped to 25.1 mg/dL pre-exchange, so no exchange transfusion was done. She recovered uneventfully.

Case 3

A 3100-g 36-week boy was born in 1996 to a 24-year-old O⁻, Rh-sensitized gravida 7 para 4 black mother by vaginal delivery. His cord blood was O⁺, with a positive DAT. He was noted to be jaundiced at 18.5 hours of age. His first TSB at 22.5 hours was 14.3 mg/dL. After a TSB of 18.0 mg/dL at 40.5 hours, phototherapy was begun at 45.5 hours. The next TSB, at 61 hours, was 34.2 mg/dL; it was 26.5 mg/dL on repeat 2 hours later. When the next TSB 4 hours later was 28.4 mg/dL, a double-volume exchange transfusion was done, with a decline in TSB to 17.0 mg/dL, and a further uneventful decline with phototherapy. The infant had no neurologic symptoms and was discharged apparently well at 6 days of age. One week later he died of apparent sudden infant death syndrome. The coroner's report indicated that he had been lying face down between his father's thighs when his father fell asleep and was dead when his father woke up. There was no sign of kernicterus at autopsy, which included sections through the cortex, ventricles, basal ganglia, hippocampi, midbrain, pons, and medulla.

Case 4

A 4350-g 38-week boy was born in 1996 to a 34-year-old O⁺ Ab⁻ gravida 8 para 7 white mother after a normal pregnancy, labor, and delivery. There was no maternal diabetes. There was a history of jaundice in all 6 siblings but only 1 had required phototherapy. Some bruising was noted on initial examination. The infant was exclusively breastfed, discharged at 27 hours, and advised to provide frequent feedings and to expose the infant to sunlight, although no jaundice was noted in the medical record before discharge. He was readmitted at 8 days of age after 1 day of poor feeding, and a few days' history of increasing jaundice and maternal mastitis. His TSB was then 45.5 mg/dL. On physical examination he was awake, alert, responded vigorously to blood

drawing, and had good tone. His weight was down 2% from the birth weight, and the blood and urine cultures were negative. He was treated with intravenous fluids, antibiotics, and double-volume exchange transfusion and phototherapy and recovered uneventfully, never demonstrating any neurologic symptoms.

Case 5

A 3850-g 39-week boy was born in 1996 to a 34-year-old B⁺ Ab⁻ gravida 2 para 2 Asian mother with gestational diabetes controlled by diet, and asthma treated with albuterol and prednisone, but otherwise normal pregnancy, labor, and delivery. The initial examination of the infant was normal except for bruising of the arm. A caput, but no cephalhematoma was noted. He had some mild hypoglycemia (30–35 mg/dL) and was treated with supplemental feedings. He was discharged at 29 hours. When he returned at 4 days for a scheduled follow-up visit, the parents had noted that he was yellow. He was then voiding 4 to 5 times per day, stooling 2 to 3 times per day, and his weight down 7% from birth weight. A TSB was drawn and the infant was sent home. When the TSB result of 30.6 mg/dL became available, the parents were called to return for admission of the infant, which was delayed because of the mother needing to pick up a sibling from school. On readmission, a cephalhematoma was noted, and the TSB had risen to 35.3 mg/dL, 6 hours after the first TSB. There was a brief cyanotic spell shortly after admission. The infant was treated with albumin, a double-volume exchange transfusion, and triple phototherapy for 4 days. A blood culture on admission positive for *Staphylococcus epidermidis*, which was believed to be a contaminant. An electroencephalogram and a head ultrasound during this admission were normal, and the admission and recovery were otherwise uneventful.

Case 6

A 3250-g 36-week boy was born in 1997 to a 39-year-old O⁺ Ab⁻ gravida 2 para 2 black mother after a normal pregnancy, labor, and delivery except for a slight preterm labor. He was exclusively breastfed. The infant was noted to be jaundiced at 38 hours and had a TSB of 16.5 mg/dL at 40 hours; a DAT was negative. A G6PD screen was sent and subsequently found to be normal, although this result was not available until after the readmission. The infant was treated with phototherapy for 2 days, then discharged at 4 days of age after the TSB had fallen to 13.9 mg/dL. When he returned for a scheduled follow-up visit at 6 days to check TSB, he was very jaundiced. He was then breast-feeding every 2 hours and voiding. His weight was down 8% from the birth weight. He was sent home, but called back for immediate readmission when a TSB of 23.2 mg/dL was reported. The next bilirubin level, 6.7 hours later (1 hour after triple phototherapy was started), was 31.1 mg/dL. After only 4 hours, the TSB was down to 20.8 mg/dL and the treating physicians questioned whether the 31.1 value had been spurious. Further recovery was uneventful. At a well child visit at 3 years and 10 months of age, neurologic examination and developmental milestones were normal, and the child was noted to be "very articulate." This note indicated that the family was planning to move abroad shortly thereafter.

Case 7

A 2900-g 35-week boy was born in 1997 to a 32-year-old O⁺ Ab⁻ gravida 1 para 1 mother after a normal pregnancy, and vacuum delivery with oxytocin augmentation. The infant was O⁺, DAT negative. He was noted to be jaundiced at 21 hours of age, and had a TSB of 14.6 mg/dL at 33 hours of age. He was seen for follow-up by a lactation consultant at 80 hours of age for latching problems attributable to engorgement. His weight was then down 12% to 2557 g, and he was "slightly yellow." A TSB level was drawn, lactation support was given, and the infant was sent home. When the TSB came back 37.2 mg/dL, the family was called and the infant admitted to the Intensive Care Nursery for an exchange transfusion. A repeat TSB on admission was 38.2 (conjugated bilirubin, 3.1 mg/dL). The infant did not look ill in any way. Attempts to place an umbilical catheter were unsuccessful, but the TSB dropped very rapidly with triple phototherapy—down to 23 mg/dL 7 hours after admission, and to 15 mg/dL 18 hours after admission—so no exchange transfusion was done. He was followed in a special clinic for infants at high developmental risk for

17 months, and was at that age noted to have excellent development.

Case 8

A 3700-g 38-week girl was born in 1997 to a 28-year-old O⁺ Ab⁻ gravida 3 para 3 Hispanic mother after a pregnancy complicated by gestational diabetes treated with diet, but otherwise normal pregnancy, labor, and delivery. He was breast- and bottle-fed. An older sibling had required phototherapy for jaundice. Jaundice was noted at 28 hours, but no TSB was sent. At a routine follow-up at 3 days of age, he was breastfeeding every 2 to 3 hours, voiding 3 to 5 times per day, and stooling once per day. Jaundice to the legs was noted, and the weight was down 9% to 3374 g. The TSB was then 32.6 mg/dL. He was admitted, treated with a single double-volume exchange transfusion, triple phototherapy, and intravenous fluids and recovered uneventfully.

Case 9

A 3600-g 39-week girl was born in 1997 to a 24-year-old O⁺ Ab⁻ gravida 2 para 2 Hispanic mother after an uncomplicated pregnancy, labor, and delivery. She was exclusively breastfed. She was noted to be jaundiced at 18 hours of age. The chart indicates that "jaundice meter readings" (generally done in pairs) at that time were 14 and 14. According to staff at the birth hospital, the TSB level in mg/dL was generally 5 to 8 less than the jaundice meter reading. The infant was found to be O⁺ with a negative DAT. She was discharged at 20 hours of age, to follow-up in 2 days. She was not seen until 3 days, when she was breastfeeding every 2 hours, 10 minutes each side, with "5 wet diapers." Her weight was down 4% from the birth weight, a urine-specific gravity was 1.005, and she was "very jaundiced." The TSB level was 32.1 mg/dL and she was immediately readmitted. A repeat TSB after 3.5 hours of phototherapy was 26.7 mg/dL. A near double-volume exchange transfusion was done and she was treated with double phototherapy. Although the infant was not febrile or ill-appearing, a blood culture was drawn through the umbilical vein at the time of the exchange transfusion and was positive for *S aureus*. A lumbar puncture was negative. Pustules appeared in the groin area on the second hospital day. She was further treated with antibiotics and phototherapy and recovered uneventfully.

Case 10

A 3100-g 35-week boy was born in 1998 to a 26-year-old A⁺ Ab⁻ gravida 4 para 2 white mother after premature rupture of membranes and oxytocin induction, but otherwise uncomplicated pregnancy, labor, and delivery. Bruising and pallor were noted on the initial examination. "Minimal" jaundice was noted at 33.5 hours of age. He was discharged at 43 hours of age (a Friday) on breast milk, with a scheduled follow-up visit Monday, or earlier if needed. He was noted to be jaundiced when he returned for the scheduled follow-up on Monday. He was then 4.5 days old, and his weight was down 10%. A TSB was drawn, and the infant was sent home, but he was called back when the TSB came back 33.8. He was admitted and treated with formula and double phototherapy. After 12 hours, the TSB had dropped to 26.7 mg/dL; the TSB then hovered in the low 20s an additional 25 hours on double phototherapy. His neurologic examination was normal throughout the hospitalization. The family moved out of state and was hard to reach, but finally responded to telephone calls by one of the investigators (T.B.N.). Hence, the PEDS was not blinded on this infant. The only parental concern at age 3.7 years was that his speech is difficult to understand, for which he is receiving speech therapy.

Case 11

This 3350-g 37-week girl was born in 1998 to a 24-year-old A⁺ Ab⁻ gravida 2 para 2 white mother after a pregnancy complicated by preterm labor, treated with terbutaline for 5 weeks. Delivery was vaginal without instruments. A scalp bruise but no cephalohematoma was noted at birth. She was discharged at 33 hours of age, exclusively breastfeeding. When seen for routine follow-up at 2 days of age, her weight was down 13%, she was mildly jaundiced, and not breastfeeding well, which was attributed to the mother's flat nipples. She was told to continue breastfeeding but to supplement with either expressed breast milk or formula, and to come for weight check in 2 days. At the time of the follow-up

visit (age 4 days), breastfeeding was going poorly. The infant had breastfed only once the previous night and her mother was pumping milk and feeding her with a dropper. The infant had urinated twice that day. Her weight was down 17% from birth weight. The TSB was 30.7 mg/dL. She was treated with oral formula and expressed breast milk, and admitted to an outside hospital. On admission, the TSB was 26.1 mg/dL, which then decreased to 16.9 mg/dL the next morning with just phototherapy. At a well child visit at 13 months of age there were no maternal concerns and neurologic examination and developmental milestones were normal.

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Johnson G. *New York Times.* November 17, 2002

Noted by James W. Kendig, MD

Infants With Bilirubin Levels of 30 mg/dL or More in a Large Managed Care Organization

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