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An Evidence-Based Review of Important Issues Concerning Neonatal Hyperbilirubinemia

ABSTRACT. This article is adapted from a published evidence report concerning neonatal hyperbilirubinemia with an added section on the risk of blood exchange transfusion (BET). Based on a summary of multiple case reports that spanned more than 30 years, we conclude that kernicterus, although infrequent, has at least 10% mortality and at least 70% long-term morbidity. It is evident that the preponderance of kernicterus cases occurred in infants with a bilirubin level higher than 20 mg/dL. Given the diversity of conclusions on the relationship between peak bilirubin levels and behavioral and neurodevelopmental outcomes, it is apparent that the use of a single total serum bilirubin level to predict long-term outcomes is inadequate and will lead to conflicting results. Evidence for efficacy of treatments for neonatal hyperbilirubinemia was limited. Overall, the 4 qualifying studies showed that phototherapy had an absolute risk-reduction rate of 10% to 17% for prevention of serum bilirubin levels higher than 20 mg/dL in healthy infants with jaundice. There is no evidence to suggest that phototherapy for neonatal hyperbilirubinemia has any long-term adverse neurodevelopmental effects. Transcutaneous measurements of bilirubin have a linear correlation to total serum bilirubin and may be useful as screening devices to detect clinically significant jaundice and decrease the need for serum bilirubin determinations. Based on our review of the risks associated with BETs from 15 studies consisting mainly of infants born before 1970, we conclude that the mortality within 6 hours of BET ranged from 3 per 1000 to 4 per 1000 exchanged infants who were term and without serious hemolytic diseases. Regardless of the definitions and rates of BET-associated morbidity and the various pre-exchange clinical states of the exchanged infants, in many cases the morbidity was minor (eg, postexchange anemia). Based on the results from the most recent study to report BET morbidity, the overall risk of permanent sequelae in 25 sick infants who survived BET was from 5% to 10%. *Pediatrics* 2004;114:e130–e153. URL: <http://www.pediatrics.org/cgi/content/full/114/1/e130>; *evidence-based review, hyperbilirubinemia, bilirubin, exchange transfusion, kernicterus, brainstem auditory evoked potential, brainstem auditory evoked response.*

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

This article is based on an evidence report produced by the Tufts-New England Medical Center's Evidence-Based Practice Center under contract to the Agency for Healthcare Research and Quality (contract 290-97-0019). PEDIATRICS (ISSN 0031 4005). Copyright © 2004 by the American Academy of Pediatrics.

ABBREVIATIONS. AAP, American Academy of Pediatrics; AHRQ, Agency for Healthcare Research and Quality; TcB, transcutaneous bilirubin; GA, gestational age; EGA, estimated gestational age; BET, blood exchange transfusion; Rh, rhesus; TSB, total serum bilirubin; NNT, number needed to treat; NICHD, National Institute of Child Health and Human Development; ROC, receiver operating characteristics; AUC, area under the curve; BAER, brainstem auditory evoked response; CPP, Collaborative Perinatal Project; BAEP, brainstem auditory evoked potential; CI, confidence interval; HPLC, high-performance liquid chromatography.

The American Academy of Pediatrics (AAP) requested an evidence report from the Agency for Healthcare Research and Quality (AHRQ) that would critically examine the available evidence regarding the effect of high levels of bilirubin on behavioral and neurodevelopmental outcomes, role of various comorbid effect modifiers (eg, sepsis and hemolysis) on neurodevelopment, efficacy of phototherapy, reliability of various strategies in predicting significant hyperbilirubinemia, and accuracy of transcutaneous bilirubin (TcB) measurements. The report was used by the AAP to update the 1994 AAP guidelines for the management of neonatal hyperbilirubinemia. This review focuses on otherwise healthy term or near-term (at least 34 weeks' estimated gestational age [EGA] or at least 2500 g birth weight) infants with hyperbilirubinemia. This article is adapted from that published report¹ with an added section on the risk of blood exchange transfusion (BET).

Neither hyperbilirubinemia nor kernicterus are reportable diseases, and there are no reliable sources of information providing national annual estimates. Since the advent of effective prevention of rhesus (Rh) incompatibility and treatment of elevated bilirubin levels with phototherapy, kernicterus has become uncommon. When laboratory records of a 1995–1996 birth cohort of more than 50 000 California infants were examined, Newman et al² reported that 2% had total serum bilirubin (TSB) levels higher than 20 mg/dL, 0.15% had levels higher than 25 mg/dL, and only 0.01% had levels higher than 30 mg/dL. (These data were from infants with clinically identified hyperbilirubinemia and, as such, represent a minimum estimate of the true incidence of extreme hyperbilirubinemia.) This is undoubtedly the result of successful prevention of hemolytic anemia and the

application of effective treatment of elevated serum bilirubin levels in accordance with currently accepted medical practice. Projecting the California estimates to the national birth rate of 4 million per year,³ one can predict 80 000, 6000, and 400 newborns per year with bilirubin levels of more than 20, 25, and 30 mg/dL, respectively.

Recently, concern has been expressed that the increase in early hospital discharges, coupled with a rise in breastfeeding rates, has led to a rise in the rate of preventable kernicterus resulting from "unattended to" hyperbilirubinemia.⁴ However, a report published in 2002, based on a national registry established since 1992, reported only 90 cases of kernicterus,⁵ although the efficiency of case ascertainment is not clear.⁶ Thus, there are no data to establish incidence trends reliably for either hyperbilirubinemia or kernicterus.

Despite these constraints, there has been substantial research on the neurodevelopmental outcomes of hyperbilirubinemia and its prediction and treatment. Subsequent sections of this review describe in more detail the precise study questions and the existing published work in this area.

METHODOLOGY

This evidence report is based on a systematic review of the medical literature. Our Evidence-Based Practice Center formed a review team consisting of pediatricians and Evidence-Based Practice Center methodologic staff to review the literature and perform data abstraction and analysis. For details regarding methodology, please see the original AHRQ report.¹

Key Questions

Question 1: What is the relationship between peak bilirubin levels and/or duration of hyperbilirubinemia and neurodevelopmental outcome?

Question 2: What is the evidence for effect modification of the results in question 1 by GA, hemolysis, serum albumin, and other factors?

Question 3: What are the quantitative estimates of efficacy of treatment for 1) reducing peak bilirubin levels (eg, number needed to treat [NNT] at 20 mg/dL to keep TSB from rising); 2) reducing the duration of hyperbilirubinemia (eg, average number of hours by which time TSB is higher than 20 mg/dL may be shortened by treatment); and 3) improving neurodevelopmental outcomes?

Question 4: What is the efficacy of various strategies for predicting hyperbilirubinemia, including hour-specific bilirubin percentiles?

Question 5: What is the accuracy of TcB measurements?

Search Strategies

We searched the Medline database on September 25, 2001, for publications from 1966 to the present using relevant medical subject heading terms ("hyperbilirubinemia"; "hyperbilirubinemia, hereditary"; "bilirubin"; "jaundice, neonatal"; and "kernicterus") and text words ("bilirubin," "hyperbilirubinemia," "jaundice," "kernicterus," and "neonatal"). The abstracts were limited to human subjects and English-language studies focusing on newborns between birth and 1 month of age. In addition, the same text words used for the Medline search were used to search the Pre-Medline database. The strategy yielded 4280 Medline and 45 Pre-Medline abstracts. We consulted domain experts and examined relevant review articles for additional studies. A supplemental search for case reports of kernicterus in reference lists of relevant articles and reviews was performed also.

Screening and Selection Process

In our preliminary screening of abstracts, we identified more than 600 potentially relevant articles in total for questions 1, 2, and 3. To handle this large number of articles, we devised the following scheme to address the key questions and ensure that the report

was completed within the time and resource constraints. We included only studies that measured neurodevelopmental or behavioral outcomes (except for question 3, part 1, for which we evaluated all studies addressing the efficacy of treatment). For the specific question of quantitative estimates of efficacy of treatment, all studies concerning therapies designed to prevent hyperbilirubinemia (generally bilirubin greater than or equal to 20 mg/dL) were included in the review.

Inclusion Criteria

The target population of this review was healthy, term infants. For the purpose of this review, we included articles concerning infants who were at least 34 weeks' EGA at the time of birth. From studies that reported birth weight rather than age, infants whose birth weight was greater than or equal to 2500 g were included. This cutoff was derived from findings of the National Institute of Child Health and Human Development (NICHD) hyperbilirubinemia study, in which none of the 1339 infants weighing greater than or equal to 2500 g were less than 34 weeks' EGA.⁷ Articles were selected for inclusion in the systematic review based on the following additional criteria:

Question 1 or 2 (Risk Association)

- Population: infants greater than or equal to 34 weeks' EGA or birth weight greater than or equal to 2500 g.
- Sample size: more than 5 subjects per arm
- Predictors: jaundice or hyperbilirubinemia
- Outcomes: at least 1 behavioral/neurodevelopmental outcome reported in the article
- Study design: prospective cohorts (more than 2 arms), prospective cross-sectional study, prospective longitudinal study, prospective single-arm study, or retrospective cohorts (more than 2 arms)

Case Reports of Kernicterus

- Population: kernicterus case
- Study design: case reports with kernicterus as a predictor or an outcome

Kernicterus, as defined by authors, included any of the following: acute phase of kernicterus (poor feeding, lethargy, high-pitched cry, increased tone, opisthotonos, or seizures), kernicterus sequelae (motor delay, sensorineural hearing loss, gaze palsy, dental dysplasia, cerebral palsy, or mental retardation), necropsy finding of yellow staining in the brain nuclei.

Question 3 (Efficacy of Treatment at Reducing Serum Bilirubin)

- Population: infants greater than or equal to 34 weeks' EGA or birth weight greater than or equal to 2500 g
- Sample size: more than 10 subjects per arm
- Treatments: any treatment for neonatal hyperbilirubinemia
- Outcomes: serum bilirubin level higher than or equal to 20 mg/dL or frequency of BET specifically for bilirubin level higher than or equal to 20 mg/dL
- Study design: randomized or nonrandomized, controlled trials

For All Other Issues

- Population: infants greater than or equal to 34 weeks' EGA or birth weight greater than or equal to 2500 g
- Sample size: more than 10 subjects per arm for phototherapy; any sample size for other treatments
- Treatments: any treatment for neonatal hyperbilirubinemia
- Outcomes: at least 1 neurodevelopmental outcome was reported in the article

Question 4 or 5 (Diagnosis)

- Population: infants greater than or equal to 34 weeks' EGA or birth weight greater than or equal to 2500 g
- Sample size: more than 10 subjects
- Reference standard: laboratory-based TSB

Exclusion Criteria

Case reports of kernicterus were excluded if they did not report serum bilirubin level or GA and birth weight.

Results of Screening of Titles and Abstracts

There were 158, 174, 99, 153, and 79 abstracts for questions 1, 2, 3, 4, and 5, respectively. Some articles were relevant to more than 1 question.

Results of Screening of Full-Text Articles

After full-text screening (according to the inclusion and exclusion criteria described previously), 138 retrieved articles were included in this report. There were 35 articles in the correlation section (questions 1 and 2), 28 articles of kernicterus case reports, 21 articles in the treatment section (question 3), and 54 articles in the diagnosis section (questions 4 and 5). There were inevitable overlaps, because treatment effects and assessment of neurodevelopmental outcomes were inherent in many study designs.

Reporting the Results

Articles that passed the full-text screening were grouped according to topic and analyzed in their entirety. Extracted data were synthesized into evidence tables.¹

Summarizing the Evidence of Individual Studies

Grading of the evidence can be useful for indicating the overall methodologic quality of a study. The evidence-grading scheme used here assesses 4 dimensions that are important for the proper interpretation of the evidence: study size, applicability, summary of results, and methodologic quality.¹

Definitions of Terminology

- Confounders (for question 1 only): 1) An ideal study design to answer question 1 would follow 2 groups, jaundiced and normal infants, without treating any infant for a current or consequent jaundice condition and observe their neurodevelopmental outcomes. Therefore, any treatment received by the subjects in the study was defined as a confounder. 2) If subjects had known risk factors for jaundice such as prematurity, breastfeeding, or low birth weight, the risk factors were defined as confounders. 3) Any disease condition other than jaundice was defined as a confounder. 4) Because bilirubin level is the essential predictor, if the study did not report or measure bilirubin levels for the subjects, lack of bilirubin measurements was defined as a confounder.
- Acute phase of kernicterus: poor feeding, lethargy, high-pitched cry, increased tone, opisthotonos, or seizures.
- Chronic kernicterus sequelae: motor delay, sensorineural hearing loss, gaze palsy, dental dysplasia, cerebral palsy, or mental retardation.

Statistical Analyses

In this report, 2 statistical analyses were performed in which there were sufficient data: the NNT and receiver operating characteristics (ROC) curve.

NNT

The NNT can be a clinically meaningful metric to assess the benefits of clinical trials.⁸ It is calculated by taking the inverse of the absolute risk difference. The absolute risk difference is the difference between the event rates between the treatment and control groups. For example, if the event rate is 15% in the control group and 10% in the treatment group, the absolute risk difference is 5% (an absolute risk reduction of 5%). The NNT then would be 20 (1 divided by 0.05), meaning that 20 patients will need to be treated to see 1 fewer event. In the setting of neonatal hyperbilirubinemia, NNT might be interpreted as the number of newborns needed to be treated (with phototherapy) at 13 to 15 mg/dL to prevent 1 newborn from reaching 20 mg/dL.

ROC Curve

ROC curves were developed for individual studies in question 4 if multiple thresholds of a diagnostic technology were reported. The areas under the curves (AUCs) were calculated to provide an assessment of the overall accuracy of the tests.

Meta-analyses of Diagnostic Test Performance

Meta-analyses were performed to quantify the TcB measurements for which the data were sufficient. We used 3 complementary methods for assessing diagnostic test performance: summary ROC analysis, independently combined sensitivity and specificity values, and meta-analysis of correlation coefficients.

RESULTS

Question 1. What Is the Relationship Between Peak Bilirubin Levels and/or Duration of Hyperbilirubinemia and Neurodevelopmental Outcome?

The first part of the results for this question deals with kernicterus; the second part deals with otherwise healthy term or near-term infants who had hyperbilirubinemia.

Case Reports of Kernicterus

Our literature search identified 28 case-report articles^{9–35} of infants with kernicterus that reported sufficient data for analysis. (The largest case series of 90 healthy term and near-term infants with kernicterus was reported by Johnson et al in 2002,⁵ but no individual data were available and therefore were not included in this analysis. Those cases with available individual data previously reported were included in this analysis.) Most of the articles were identified in Medline and published since 1966. We retrieved additional articles published before 1966 based on review of references in articles published since 1966. Our report focuses on term and near-term infants (greater than or equal to 34 weeks' EGA). Only infants with measured peak bilirubin level and known GA or birth weight or with clinical or autopsy-diagnosed kernicterus were included in the analysis. It is important to note that some of these peak levels were obtained more than 7 days after birth and therefore may not have represented true peak levels. Similarly, some of the diagnoses of kernicterus were made only at autopsies, and the measured bilirubin levels were obtained more than 24 hours before the infants died, and therefore the reported bilirubin levels may not have reported the true peak levels. Because of the small number of subjects, none of the following comparisons are statistically significant. Furthermore, because case reports in this section represent highly selected cases, interpreting these data must be done cautiously.

Demographics of Kernicterus Cases

Articles identified through the search strategy span from 1955 to 2001 with a total of 123 cases of kernicterus. Twelve cases in 2 studies were reported before 1960; however, some studies reported cases that spanned almost 2 decades. Data on subjects' birth years were reported in only 55 cases. Feeding status, gender, racial background, and ethnicity were not noted in most of the reports. Of those that were reported, almost all the subjects were breastfed and most were males (see Tables 1 and 2).

Geographic Distribution of Reported Kernicterus Cases

The 28 case reports with a total of 123 cases are from 14 different countries. They are the United

TABLE 1. Feeding and Gender Status in Newborns Who Had Kernicterus

	Gender	Feeding			Total
		Breastfed	Formula	NI	
Newborns with idiopathic jaundice with KI	Male	7	1	6	14
	Female	2	0	4	6
	Unknown	11	0	4	15
Subtotal		20	1	14	35
Newborns with comorbid factors with KI	Male	8	0	17	25
	Female	1	1	19	21
	Unknown	6	0	36	42
Subtotal		15	1	72	88
Total		35	2	86	123

Cases were from refs. 9–35. KI indicates kernicterus; NI, no information.

TABLE 2. Race or Ethnicity Compositions in Newborns Who Had Kernicterus

	Race/Ethnicity							Total
	AA	AF	Chi	Mal	Whi/NE	Pal	NI	
Newborns with idiopathic jaundice with KI	0	0	6	2	9	1	17	35
Newborns with comorbid factors with KI	4	2	14	1	6		61	88
Total	4	2	23	3	15	1	78	123

Cases were from refs. 9–35. KI indicates kernicterus; AA, African American; AF, African; Chi, Chinese; Mal, Malay; Whi, white; NE, Northern European; Pal, Palestinian; NI, no information.

States, Singapore, Turkey, Greece, Taiwan, Denmark, Canada, Japan, United Kingdom, France, Jamaica, Norway, Scotland, and Germany (Fig 1). The number of kernicterus cases in each study ranged from 1 to 12.

Kernicterus has been defined by pathologic findings, acute clinical findings, and chronic sequelae (such as deafness or athetoid cerebral palsy). Because of the small number of subjects, all definitions of kernicterus have been included in the analysis. Exceptions will be noted in the following discussion.

Kernicterus Cases With Unknown Etiology

Among infants at greater than or equal to 34 weeks' GA or who weighed 2500 g or more at birth and had no known explanation for kernicterus, there were 35 infants with peak bilirubin ranging from 22.5 to 54 mg/dL. Fifteen had no information on gender, 14 were males, and 6 were females. Fourteen had no information on feeding, 20 were breastfed, and 1 was

formula-fed. More than 90% of the infants with kernicterus had bilirubin higher than 25 mg/dL: 25% of the kernicterus cases had peak TSB levels up to 29.9 mg/dL, and 50% had peak TSB levels up to 34.9 mg/dL (Fig 2). There was no association between bilirubin level and birth weight.

Four infants died.^{10–12} Four infants who had acute clinical kernicterus had normal follow-up at 3 to 6 years by telephone.¹⁶ One infant with a peak bilirubin level of 44 mg/dL had a flat brainstem auditory evoked response (BAER) initially but normalized at 2 months of age; this infant had normal neurologic and developmental examinations at 6 months of age.¹⁸ Ten infants had chronic sequelae of kernicterus when followed up between 6 months and 7 years of age. Seven infants were noted to have neurologic findings consistent with kernicterus; however, the age at diagnosis was not provided. Nine infants had a diagnosis of kernicterus with no follow-up information provided. To summarize, 11% of this group of infants died, 14% survived with no sequelae, and at least 46% had chronic sequelae (Table 3). The distribution of peak TSB levels was higher when only infants who died or had chronic sequelae were included (Fig 3).

Kernicterus Cases With Comorbid Factors

In the 88 term and near-term infants diagnosed with kernicterus and who had hemolysis, sepsis, and other neonatal complications, bilirubin levels ranged from 4.0 to 51.0 mg/dL (as previously mentioned, these may not represent true peak levels; the bilirubin level of 4 mg/dL was measured more than 24 hours before the infant died, the diagnosis of kernicterus was made by autopsy¹³). Forty-two cases provided no information on gender, 25 were males, and 21 were females. Seventy-two cases had no information on feeding, 15 were breastfed, and 1 was

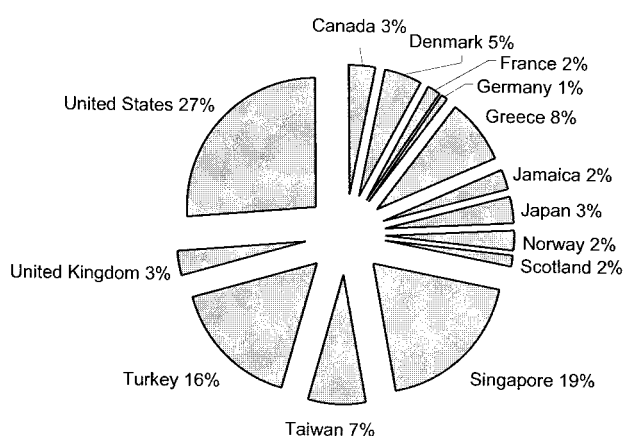


Fig 1. Geographic distribution of reported kernicterus cases. Cases were from refs 9–35.

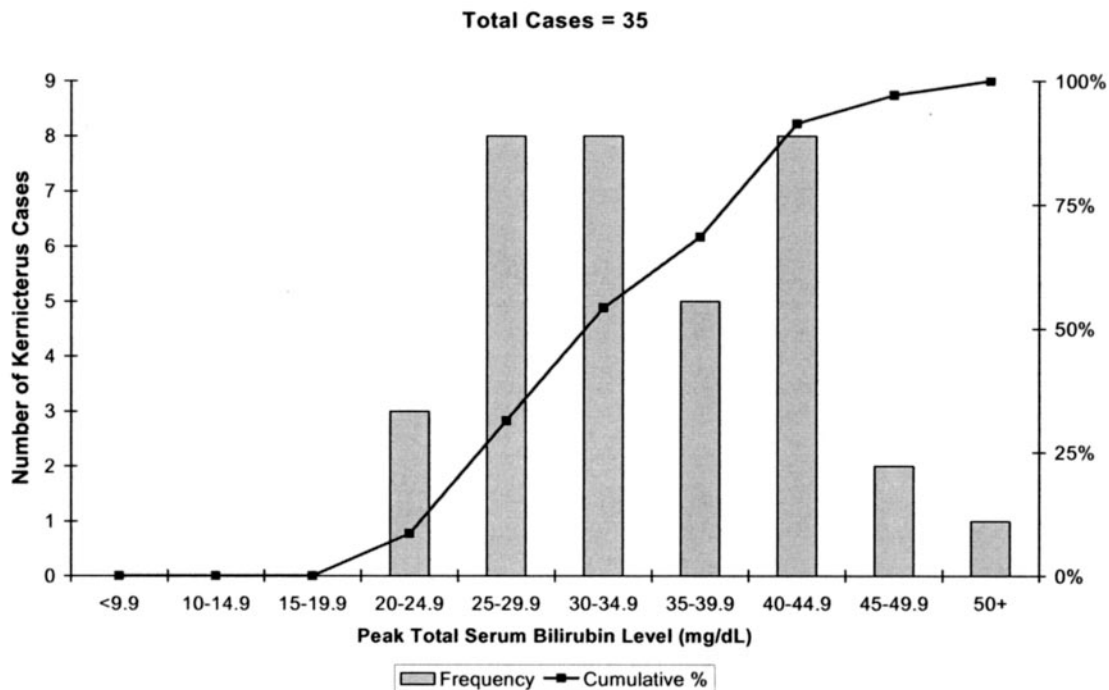


Fig 2. Distribution of peak TSB level in term and near-term (GA \geq 34 weeks) newborns with idiopathic jaundice who had kernicterus. Cases were from refs 9–12, 16, 18, 19, 21, 22, 28, 32, and 34.

TABLE 3. Summary of 35 Case Reports of Term and Near-Term (GA \geq 34 Weeks) Infants With Idiopathic Jaundice Who Had Kernicterus

Definitions of KI	N	Mean Peak TSB \pm SD (Range), mg/dL	Mean BW \pm SD* (Range), g	Gender
Acute phase of KI without long-term follow-up	9	33.4 \pm 11.4 (22.5–54.0)	3496 \pm 535 (2700–4500)	3 females, 2 males, 4 unknown
Acute phase of KI but normal, long-term follow-up	5	32.3 \pm 3.6 (27.0–36.0)	3088 \pm 575 (2400–3742)	5 unknown
Chronic KI sequelae	17	37.0 \pm 5.9 (29.5–49.7)	3271 \pm 442 (2700–4280)	1 female, 11 males, 6 unknown
Death	4†	36.9 \pm 11.0 (23.0–48.0)	2902 \pm 503 (2324–3357)	2 females, 1 male, 1 unknown
Total	35	35.4 \pm 8.0 (22.5–54.0)	3251 \pm 512 (2324–4500)	6 females, 14 males, 15 unknown

Cases were from refs 9–12, 16, 18, 19, 21, 22, 28, 28, 32, and 34. KI indicates kernicterus; BW, birth weight.

* Contain some missing data.

† One infant had acute phase of KI and chronic KI sequelae and then died at the age of 5 months. Necropsy was not done. One infant had acute phase of KI and died on the 5th day of life, necropsy found yellow staining in the brain nuclei.

formula-fed. Most infants with kernicterus had bilirubin levels higher than 20 mg/dL: 25% of the kernicterus cases had peak TSB levels up to 24.9 mg/dL, and 50% had peak TSB levels up to 29.9 mg/dL (Fig 4). In this group, there was no association between the bilirubin levels and birth weight.

Five infants without clinical signs of kernicterus were diagnosed with kernicterus by autopsy. Eight infants died of kernicterus. One infant was found to have a normal neurologic examination at 4 months of age.¹⁵ Another infant with galactosemia and a bilirubin level of 43.6 mg/dL who had acute kernicterus was normal at 5 months of age.¹² Forty-nine patients had chronic sequelae ranging from hearing loss to athetoid cerebral palsy; the follow-up age reported ranged from 4 months to 14 years. Twenty-one patients were diagnosed with kernicterus, with no follow-up information. Not including the autopsy-di-

agnosed kernicterus, 10% of these infants died (8/82), 2% were found to be normal at 4 to 5 months of age, and at least 60% had chronic sequelae (Table 4). The distribution of peak TSB levels was slightly higher when only infants who died or had chronic sequelae were included (Fig 5).

Evidence Associating Bilirubin Exposures With Neurodevelopmental Outcomes in Healthy Term or Near-Term Infants

This section examines the evidence associating bilirubin exposures with neurodevelopmental outcomes primarily in subjects without kernicterus. Studies that were designed specifically to address the behavioral and neurodevelopmental outcomes in healthy infants at more than or equal to 34 weeks' GA will be discussed first. With the exception of the results from the Collaborative Perinatal Project (CPP)

Fig 3. Cumulative percentage of peak TSB levels in term and near-term (GA \geq 34 weeks) newborns with idiopathic jaundice who had kernicterus. Cases were from refs 9–12, 16, 18, 19, 21, 22, 28, 32, and 34.

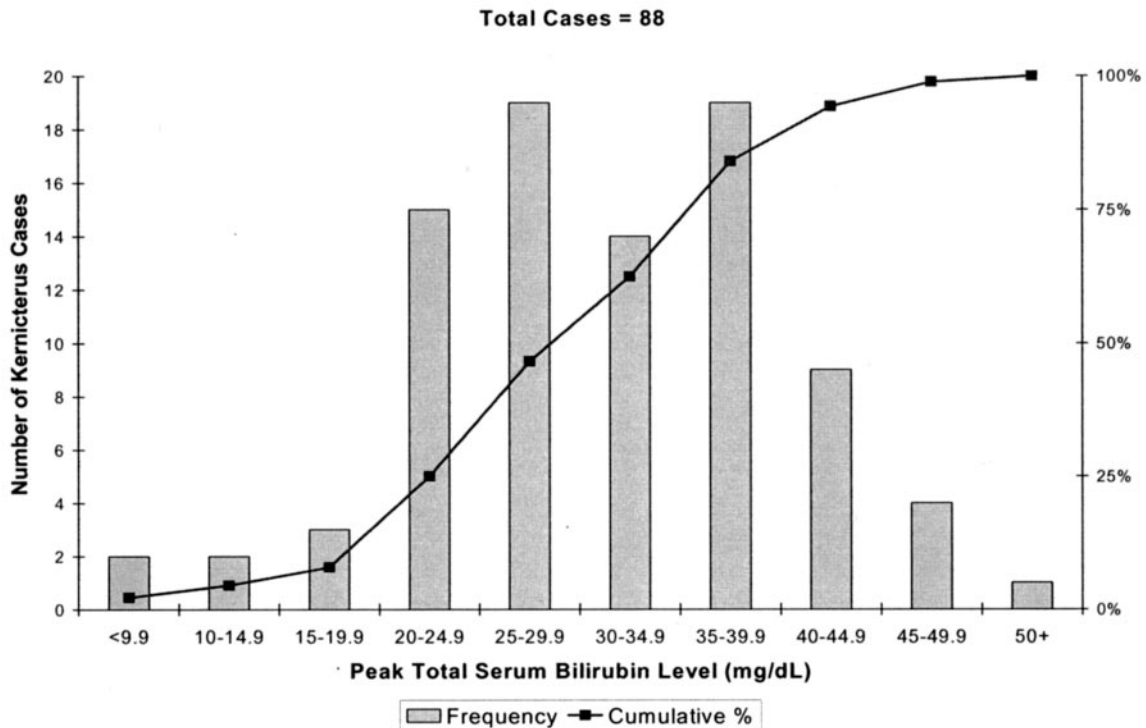
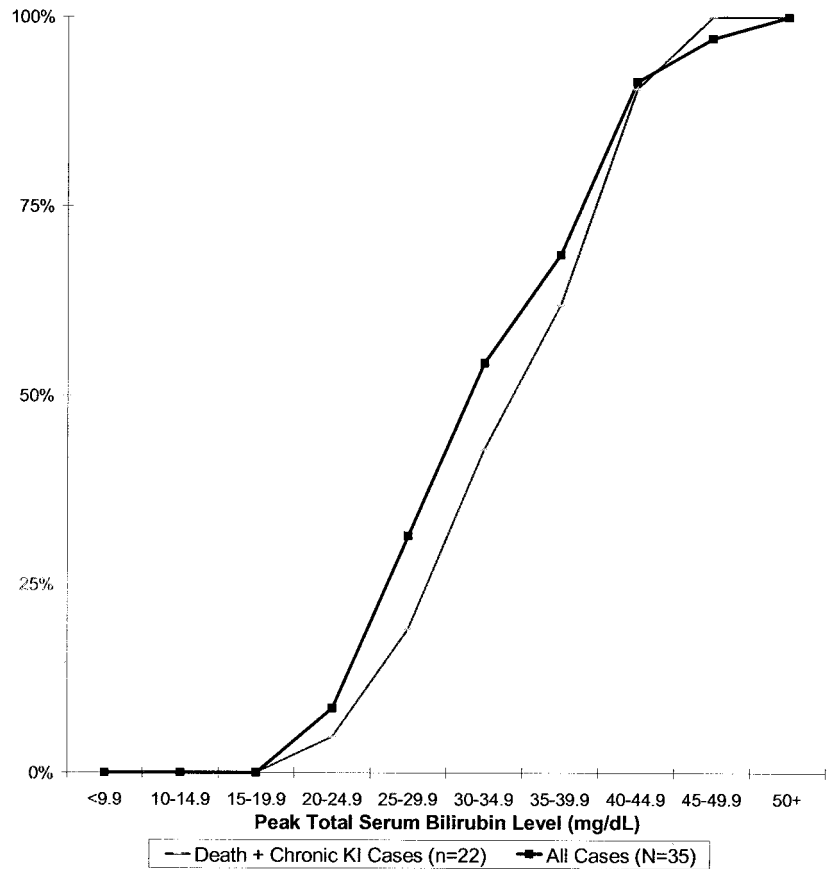


Fig 4. Distribution of peak TSB level in term and near-term (GA \geq 34 weeks) newborns with comorbid factors who had kernicterus. Cases were from refs 9–35.

(CPP, with 54 795 subjects, has generated many follow-up studies with a smaller number of subjects, and those studies were discussed together in a separate section in the AHRQ summary report¹), the

remainder of the studies that include mixed subjects (preterm and term, diseased and nondiseased) were categorized and discussed by outcome measures. These measures include behavioral and neurologic

TABLE 4. Summary of 88 Case Reports of Term and Near-Term (GA \geq 34 Weeks) Infants With Comorbid Factors Who Had Kernicterus

Comorbidity	Diagnosis of KI			Total (N)	Mean Peak TSB \pm SD (Range), mg/dL	Mean BW \pm SD* (Range), g	Gender
	Clinical		Autopsy				
	Acute Phase Without Follow-up	Acute Phase but Normal Follow-up					
ABO incompatibility	6	0	12	19	31.6 \pm 8.2 (19.0–51.0)	3118 \pm 680 (2270–4313)	6 females, 11 males, 2 unknown
Rh incompatibility	3	2	27	33	32.1 \pm 7.1 (17.7–46.0)	3063 \pm 387 (2300–3969)	5 females, 4 males, 24 unknown
G6PD deficiency	10	0	1	13	31.8 \pm 8.5 (23.0–50.0)	3353 \pm 437 (2700–4100)	2 males, 11 unknown
Sepsis or infections	3	1	4	13	31.8 \pm 9.9 (14.5–47.8)	3368 \pm 586 (2580–4360)	7 females, 4 males, 2 unknown
Multiple conditions	3	0	4	10	29.1 \pm 16.1 (4.0–49.2)	2913 \pm 750 (1780–3686)	3 females, 4 males, 3 unknown
Total	25	3	48	88	31.6 \pm 9.0 (4.0–51.0)	3155 \pm 534 (1780–4360)	20 females, 25 males, 42 unknown

Cases were from refs. 9–35. KI indicates kernicterus; BW, birth weight; G6PD, glucose-6-phosphate dehydrogenase.

* Contain some missing data.

† This infant had acute phase of KI and chronic KI sequelae and then died at the age of 19 months.

outcomes; hearing impairment, including sensorineural hearing loss; and intelligence measurements.

The CPP, with 54 795 live births between 1959 and 1966 from 12 centers in the United States, produced the largest database for the study of hyperbilirubinemia. Newman and Klebanoff,³⁶ focusing only on black and white infants weighing 2500 g or more at birth, did a comprehensive analysis of 7-year outcome in 33 272 subjects. All causes of jaundice were included in the analysis. The study found no consistent association between peak bilirubin level and intelligence quotient (IQ). Sensorineural hearing loss was not related to bilirubin level. Only the frequency of abnormal or suspicious neurologic examinations was associated with bilirubin level. The specific neurologic examination items most associated with bilirubin levels were mild and nonspecific motor abnormalities.

In other studies stemming from the CPP population, there was no consistent evidence to suggest neurologic abnormalities in children with neonatal bilirubin higher than 20 mg/dL when followed up to 7 years of age.^{37–40}

A question that has concerned pediatricians for many years is whether moderate hyperbilirubinemia is associated with abnormalities in neurodevelopmental outcome in term healthy infants without perinatal or neonatal problems. Only 4 prospective studies and 1 retrospective study have the requisite subject characteristics to address this issue.^{41–45} Although there were some short-term (less than 12 months) abnormal neurologic or behavioral characteristics noted in infants with high bilirubin, the studies had methodologic problems and did not show consistent results.

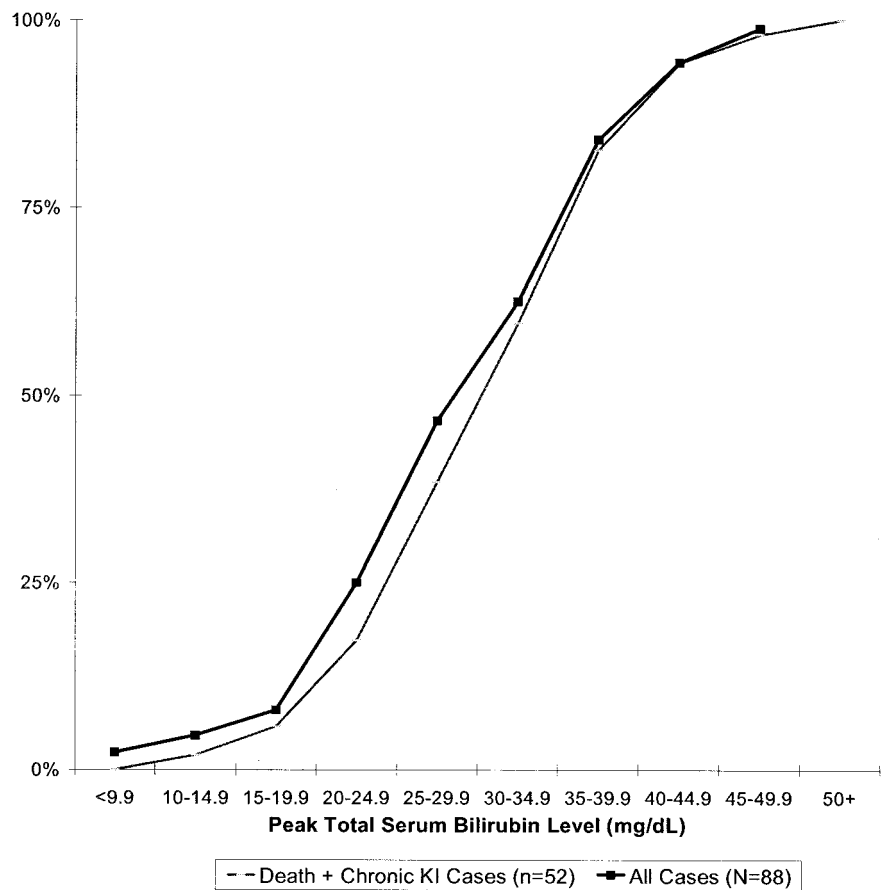
Evidence Associating Bilirubin Exposures With Neurodevelopmental Outcomes in All Infants

These studies consist of subjects who, in addition to healthy term newborns, might include newborns less than 34 weeks' GA and neonatal complications such as sepsis, respiratory distress, hemolytic disorders, and other factors. Nevertheless, some of the conclusions drawn might be applicable to a healthy term population. In these studies, greater emphasis will be placed on the reported results for the group of infants who were at greater than or equal to 34 weeks' EGA or weighed 2500 g or more at birth.

Studies Measuring Behavioral and Neurologic Outcomes in Infants With Hyperbilirubinemia

A total of 9 studies in 11 publications^{46–56} examined primarily behavioral and neurologic outcomes in patients with hyperbilirubinemia (Table 5). Of these 9 studies, 3 were of high methodologic quality. One short-term study showed a correlation between bilirubin level and decreased scores on newborn behavioral measurements.^{52,53} One study found no difference in prevalence of central nervous system abnormalities at 4 years old if bilirubin levels were less than 20 mg/dL, but infants with bilirubin levels higher than 20 mg/dL had a higher prevalence of central nervous system abnormalities.⁵⁰ Another study that followed infants with bilirubin levels

Fig 5. Cumulative percentage of peak TSB levels in term and near-term (GA \geq 34 weeks) newborns with comorbid factors who had kernicterus. Cases were from refs 9–35.



higher than 16 mg/dL found no relationship between bilirubin and neurovisuomotor testing at 61 to 82 months of age.⁵¹ Although data reported in the remainder of the studies are of lower methodologic quality, there is a suggestion of abnormalities in neurodevelopmental screening tests in infants with bilirubin levels higher than 20 mg/dL, at least by the Denver Developmental Screening Test, when infants were followed up at 1 year of age. It seems that bilirubin levels higher than 20 mg/dL may have short-term (up to 1 year of age) adverse effects at least by the Denver Developmental Screening Test, but there is no strong evidence to suggest neurologic abnormalities in children with neonatal bilirubin levels higher than 20 mg/dL when followed up to 7 years of age.

Effect of Bilirubin on Brainstem Auditory Evoked Potential (BAEP)

The following group of studies, in 14 publications,^{19,50,52,53,57–64} primarily examined the effect of bilirubin on BAEP or hearing impairment. Eight high-quality studies showed a significant relationship between abnormalities in BAEP and high bilirubin levels. Most reported resolution of abnormalities with treatment. Three studies reported hearing impairment associated with elevated bilirubin (higher than 16–20 mg/dL).^{19,50,51}

Effect of Bilirubin on Intelligence Outcomes

Eight studies looked primarily at the effect of bilirubin on intelligence outcomes.^{19,50,61,65–69} Four

high-quality studies with follow-up ranging from 6.5 to 17 years reported no association between IQ and bilirubin level (Tables 6 and 7).

Question 2. What Is the Evidence for Effect Modification of the Results in Question 1 by GA, Hemolysis, Serum Albumin, and Other Factors?

There is only 1 article that directly addressed this question. Naeye,³⁸ using the CPP population, found that at 4 years old the frequency of low IQ with increasing bilirubin levels increased more rapidly in infants with infected amniotic fluid. At 7 years old, neurologic abnormalities also were more prevalent in that subgroup of infants.

When comparing the group of term and near-term infants with comorbid factors who had kernicterus to the group of infants with idiopathic hyperbilirubinemia and kernicterus, the overall mean bilirubin was 31.6 ± 9 mg/dL in the former, versus 35.4 ± 8 mg/dL in the latter (difference not significant). Infants with glucose-6-phosphate dehydrogenase deficiency, sepsis, ABO incompatibility, or Rh incompatibility had similar mean bilirubin levels. Infants with more than 1 comorbid factor had a slightly lower mean bilirubin level of 29.1 ± 16.1 mg/dL.

Eighteen of 23 (78%) term infants with idiopathic hyperbilirubinemia and who developed acute kernicterus survived the neonatal period with chronic sequelae. Thirty-nine of 41 (95%) term infants with kernicterus and ABO or Rh incompatibility had chronic sequelae. Four of 5 (80%) infants with sepsis

TABLE 5. Effect of Serum Bilirubin Levels on Neurologic or Behavioral Outcomes in All Infants

Author, Year	Subjects, N (Control)	Peak Bilirubin Level (Range), mg/dL	Outcomes	Confounders or Biases	Quality
Vohr et al ⁵³ (1989)	23* (27)	14.3 ± 2.8 (10–20)	On day 1 to 2: BNBAS. Jaundiced infants had significantly lower BNBAS scores in every behavioral item except autonomic stability. Significant correlations were found in increased levels of TSB with decreased scores on the individual BNBAS items. After controlling for PhotoRx by partial correlations, most correlations remained significant except for state regulation and autonomic stability.	PhotoRx	A
Vohr et al ⁵² (1990)					
Hyman et al ⁵⁰ (1969)	405†	≥15	At 4 years of age: CNS abnormalities. No significant difference in incidence of CNS abnormalities among infants exposed to different levels of bilirubin <20 mg/dL. However, with TSB >20 mg/dL, the incidence of CNS abnormalities increased sharply.	BET; streptomycin Rx; BW; selection bias	B
Valaes et al ⁵¹ (1980)	44‡ (445)	47% (16–20) 29% (20–25) 24% (>25)	At 61–81 months of age: visual-motor integration test. Degree of jaundice was found not to be associated with neurologic scores.	Prematurity; BET; phenobarbital	B
Yilmaz et al ⁵⁶ (2001)	87§	11% (23–20) 49% (20–23.9) 39% (≥24)	At 10–72 months: neurologic examination. Subjects with maximum TSB <20 mg/dL did not show any neurologic abnormalities, whereas 9.3% of the subjects with TSB 20–23.9 mg/dL (N = 43) had only disconjugate gaze and 17.6% of the subjects with TSB ≥24 mg/dL had neurologic manifestations.	PhotoRx; BET; duration of jaundice	C
Agrawal et al ⁴⁶ (1998)	30 (25)	22.4 ± 2.7	At 1 year of age: DDST. Neurologic development was normal in all infants with TSB levels of 15–20 mg/dL, in 89% of infants with TSB levels of 21–25 mg/dL, and in 67% infants with TSB >25 mg/dL.	PhotoRx; BET; lost to follow-up	C
Wolf et al ⁵⁵ (1997)	45¶ at 4 months	28.5 ± 6.3	At 4 months of age: infant motor screening (IMS). Linear correlation showed an association of maximum TSB and test rating at 4 months ($r = .32, P < .05$) and test scores at 4 months ($r = .44, P < .03$). The mean TSB level in the normal IMS group was 27.3 ± 5.3 mg/dL; in the suspect and abnormal IMS group, the mean TSB levels were 28 ± 4 and 33.7 ± 10.3 mg/dL, respectively. These differences were not significant ($P = .06$).	PhotoRx; BET; prematurity; illness	C
Wolf et al ⁵⁴ (1999)	35 at 1 year		At 1 year of age: Bayley (BSID-PDI). Eight (23%) term infants, with a mean TSB level of 33.4 mg/dL, had abnormal and suspect BSID and clinical diagnosis. Twenty-seven (77%) term infants, with a mean TSB level of 26.5 mg/dL, scored normal on the BSID. "The correlation between the Bayley raw scores at 10 months and TSB concentration was 0.59 ($P < .001$)"	PhotoRx; BET	C
Chen et al ⁴⁷ (1995)	72 (22)	39% (10–15) 32% (15–20) 29% (>20)	At 1 year of age: DDST and neurologic examination. None (0%) of the infants with TSB levels of 10–20 mg/dL showed any abnormality in the DDST and neurologic examination. Among infants with TSB >20 mg/dL, 4 (22%) were abnormal in gross motor and fine motor skills on DDST.		
Grunebaum et al ⁴⁸ (1991)	46	12.06 ± 2.6	At age 31.1 ± 16.6 months: growth, neurologic examination, and DDST. Growth and neurologic examinations were normal in all infants. Two (4%) had abnormal DDST, but all had normal DDST repeated 1 month later.	PhotoRx; lost to follow-up	C
Holmes et al ⁴⁹ (1968)	63 (17)#	6.4–24 (46% 6.4–12.5; 54% 15–24)	At 4 years, 7 months to 7 years, 8 months: neurologic examination, motor development (Oseretsky test), and audiometric examinations. In normal term babies, mild-to-moderate hyperbilirubinemia is not associated with findings on the Oseretsky motor development test. All had normal hearing, including a subset with streptomycin Rx.	Age; BET; streptomycin Rx	C

BNBAS indicates Brazelton Neonatal Behavioral Assessment Scale; PhotoRx, phototherapy; CNS, central nervous system; DDST, Denver Developmental Screening Test; BSID, Bayley's Scales of Infant Development; PDI, Psychomotor Development Index; Rx, prescription.

* Sixty percent ABO incompatibility (56% of controls had ABO incompatibility as well).

† Including 10% preterm infants and some hemolytic diseases.

‡ Twenty-nine percent ABO incompatibility, 2% glucose-6-phosphate dehydrogenase deficiency, and 69% unknown cause of jaundice.

§ Forty-four percent ABO incompatibility, 16% Rh incompatibility, and 40% nonhemolytic jaundice.

|| Approximately one fourth (26.7%) had ABO incompatibility, and 63.3% had idiopathic hyperbilirubinemia.

¶ Forty-three percent term + 57% preterm (mean GA 36.6 ± 3.5 weeks). Forty-four percent low birth weight, 16% ABO incompatibility, 16% sepsis, and 6% congenital syphilis.

All causes of jaundice were included in the study.

TABLE 6. Effect of Serum Bilirubin Level on Intelligence Outcome in All Infants (GA \geq 34 Weeks)

Study, Year	Subjects, N (Control)	Bilirubin Level (Range), mg/dL	Outcomes	Confounders	Quality
Bengtsson and Verneholt ⁶⁵ (1974)	111* (115)	20.0–51.0	At 6.5–13 years old: IQ; sensorineural hearing loss. No statistically significant correlation was found between IQ and maximal bilirubin values. Three (7%) children with ABO-incompatible hyperbilirubinemia had neurogenic hearing loss, whereas none were found in control ($P > .05$).	BET	B
Rosta et al ⁶¹ (1971)	84†	\geq 15	At 8 years of age: IQ. Distribution of IQ was the same as in the normal population. Four (5%) children had an IQ $<$ 0.70, and 11 (13%) had an IQ between 0.70 and 0.80.	BET, streptomycin Rx	C
Hyman et al ⁵⁰ (1969)	29‡	\geq 15	At 4 years of age: IQ; auditory rote memory difficulties. No association was found between high bilirubin exposure and low IQ ($N = 38$). No significant difference in the prevalence of auditory rote memory difficulties between infants with TSB \geq 20 mg/dL ($N = 17$) and infants with TSB $<$ 20 mg/dL ($N = 21$).	BET; streptomycin Rx; BW; selection bias	C

Rx indicates treatment.

* All had negative Coombs' tests.

† "Nearly equal distribution of Rh and ABO immune-hemolysis, and hyperbilirubinemia of unknown origin."

‡ From original 405 subjects, including 10% preterm infants and some hemolytic diseases.

TABLE 7. Mean IQ of Children With a History of Hyperbilirubinemia

Author, Year	Sample, N (Controls)	Bilirubin Level (Range), mg/dL	Mean IQ			Confounders	Quality
			Full	Verbal	Performance		
Bengtsson and Verneholt ⁶⁵ (1974)	66	20–35	107	—	—	BET	B
Seidman et al ⁶⁹ (1991)	45*	20–51	106	—	—	PhotoRx, BET	B
	308† (1496)	Var1‡	103	—	—		
Culley et al ⁶⁶ (1970)	144§ (1496)	Var2	103	—	—	Estimated TSB levels	B
	73¶ (48)	12–16	106	—	—		
Ozmert et al ⁶⁸ (1996)	13 (27)	$>$ 16	107	—	—	Possible selection bias (unknown Rx effect)	C
	26 (27)	17–20	102	102	102		
	27 (27)	20–22	103	106	101		
	19 (27)	22–25	99	101	95		
	17# (27)	$>$ 25	102	103	101		
Odell et al ⁶⁷ (1970)	17# (27)	$>$ 20	87	95	93	BET	C
	8 (6)**	$>$ 19	94	—	—		
Johnston et al ¹⁹ (1967)	129‡‡ (82)	$>$ 20	105	—	—	BET, prematurity	C

PhotoRx indicates phototherapy.

* 100% ABO incompatibility.

† Including some infants with Coombs' positive tests.

‡ Var1 = 5–8 mg/dL on first day of life, 10–15 mg/dL on the second day of life, and 13–20 mg/dL thereafter.

§ Including infants with hemolytic disease (2% of the subjects had Coombs' positive tests).

|| Var2 = $>$ 8 mg/dL on the first day of life, $>$ 15 mg/dL on the second day of life, and $>$ 20 mg/dL thereafter.

¶ Healthy infants (no hemolytic disease, congenital malformations, perinatal asphyxia, neonatal illness, or infections).

Sixty-five percent Rh and 35% ABO incompatibility.

** Forty-three percent Rh incompatibility, 14% ABO incompatibility, 14% other blood incompatibility, and 21% unknown cause of jaundice.

‡‡ 71% isoimmunization, 20% ABO incompatibility.

and kernicterus had chronic sequelae. All 4 infants with multiple comorbid factors had sequelae.

No firm conclusions can be drawn regarding comorbid factors and kernicterus, because this is a small number of patients from a variety of case reports.

There was no direct study concerning serum albumin level as an effect modifier of neurodevelopmental outcome in infants with hyperbilirubinemia. One

report found a significant association between reserve albumin concentration and latency to wave V in BAEP studies.⁵⁸

In addition, Ozmert et al⁶⁸ noted that exchange transfusion and the duration that the infant's serum indirect bilirubin level remained higher than 20 mg/dL were important risk factors for prominent neurologic abnormalities.

Question 3. What Are the Quantitative Estimates of Efficacy of Treatment at 1) Reducing Peak Bilirubin Levels (eg, NNT at 20 mg/dL to Keep TSB From Rising); 2) Reducing the Duration of Hyperbilirubinemia (eg, Average Number of Hours by Which Time TSB Levels Higher Than 20 mg/dL May Be Shortened by Treatment); and 3) Improving Neurodevelopmental Outcomes?

Studies on phototherapy efficacy in terms of preventing TSB rising to the level that would require BET (and therefore would be considered "failure of phototherapy") were reviewed for the quantitative estimates of efficacy of phototherapy. Because trials evaluating the efficacy of phototherapy at improving neurodevelopmental outcomes by comparing 1 group of infants with treatment to an untreated group do not exist, the effects of treatment on neurodevelopmental outcomes could only be reviewed descriptively. Furthermore, all the reports primarily examined the efficacy of treatment at 15 mg/dL to prevent TSB from exceeding 20 mg/dL. There is no study to examine the efficacy of treatment at 20 mg/dL to prevent the TSB from rising.

Efficacy of Phototherapy for Prevention of TSB Levels Higher Than 20 mg/dL

Four publications examined the clinical efficacy of phototherapy for prevention of TSB levels higher than 20 mg/dL.⁷⁰⁻⁷³

Two studies evaluated the same sample of infants. Both reports were derived from a randomized, controlled trial of phototherapy for neonatal hyperbilirubinemia commissioned by the NICHD between 1974 and 1976.^{70,73}

Because the phototherapy protocols differed significantly in the remaining studies, their results could not be statistically combined and are reported here separately. A total of 893 term or near-term jaundiced infants (325 in the treatment group and 568 in the control group) were evaluated in the current review.

The development, design, and sample composition of NICHD phototherapy trial were reported in detail elsewhere.⁷ The NICHD controlled trial of phototherapy for neonatal hyperbilirubinemia consisted of 672 infants who received phototherapy and 667 control infants. Brown et al⁷⁰ evaluated the efficacy of phototherapy for prevention of the need for BET in the NICHD study population. For the purpose of current review, only the subgroup of 140 infants in the treatment groups and 136 in the control groups with birth weights 2500 g or more and greater than or equal to 34 weeks' GA were evaluated. The serum bilirubin level as criterion for BET in infants with birth weights of 2500 g or more was 20 mg/dL at standard risk and 18 mg/dL at high risk. It was found that infants with hyperbilirubinemia secondary to nonhemolytic causes who received phototherapy had a 14.3% risk reduction of BET than infants in no treatment group. NNT for prevention of the need for BET or for TSB levels higher than 20 mg/dL was 7 (95% confidence interval [CI]: 6-8). However, phototherapy did not reduce the need for BET for infants

with hemolytic diseases or in the high-risk group. No therapeutic effect on reducing the BET rate in infants at greater than or equal to 34 weeks' GA with hemolytic disease was observed.

The same group of infants, 140 subjects in the treatment group and 136 controls with birth weights 2500 g or more and greater than or equal to 34 weeks' GA, were evaluated for the effect of phototherapy on the hyperbilirubinemia of Coombs' positive hemolytic disease in the study of Maurer et al.⁷³ Of the 276 infants whose birth weights were 2500 g or more, 64 (23%) had positive Coombs' tests: 58 secondary to ABO incompatibility and 6 secondary to Rh incompatibility. Thirty-four of 64 in this group received phototherapy. The other 30 were placed in the control group. Of the 212 subjects who had negative Coombs' tests, 106 were in the treatment group and the same number was in the control group. No therapeutic effect on reducing the BET rate was observed in infants with Coombs' positive hemolytic disease, but there was a 9.4% absolute risk reduction in infants who had negative Coombs' tests. In this group of infants, the NNT for prevention of the need for BET, or a TSB higher than 20 mg/dL, was 11 (95% CI: 10-12).

A more recent randomized, controlled trial compared the effect of 4 different interventions on hyperbilirubinemia (serum bilirubin concentration greater than or equal to 291 $\mu\text{mol/L}$ or 17 mg/dL) in 125 term breastfed infants. Infants with any congenital anomalies, neonatal complications, hematocrit more than 65%, significant bruising or large cephalohematomas, or hemolytic disease were excluded. The 4 interventions in the study were 1) continue breastfeeding and observe ($N = 25$); 2) discontinue breastfeeding and substitute formula ($N = 26$); 3) discontinue breastfeeding, substitute formula, and administer phototherapy ($N = 38$); and 4) continue breastfeeding and administer phototherapy ($N = 36$). The interventions were considered failures if serum bilirubin levels reached 324 $\mu\text{mol/L}$ or 20 mg/dL.⁷² For the purpose of the current review, we regrouped the subjects into treatment group or phototherapy group and control group or no-phototherapy group. Therefore, the original groups 4 and 3 became the treatment groups I and II, and the original groups 1 and 2 were the corresponding control groups I and II. It was found that treatment I, phototherapy with continuation of breastfeeding, had a 10% absolute risk-reduction rate, and the NNT for prevention of a serum bilirubin level higher than 20 mg/dL was 10 (95% CI: 9-12). Compared with treatment I, treatment II (phototherapy with discontinuation of breastfeeding) was significantly more efficacious. The absolute risk-reduction rate was 17%, and the NNT for prevention of a serum bilirubin level exceeding 20 mg/dL was 6 (95% CI: 5-7).

John⁷¹ reported the effect of phototherapy in 492 term neonates born during 1971 and 1972 who developed unexplained jaundice with bilirubin levels higher than 15 mg/dL. One hundred eleven infants received phototherapy, and 381 did not. The author stated: "The choice of therapy was, in effect, random since two pediatricians approved of the treatment

and two did not.” The results showed that phototherapy had an 11% risk reduction of BET, performed in treatment and control groups when serum bilirubin levels exceeded 20 mg/dL. Therefore, the NNT for prevention of a serum bilirubin level higher than 20 mg/dL was 9 (95% CI: 8–10).

Regardless of different protocols for phototherapy, the NNT for prevention of serum bilirubin levels higher than 20 mg/dL ranged from 6 to 10 in healthy term or near-term infants. Evidence for the efficacy of treatments for neonatal hyperbilirubinemia was limited. Overall, the 4 qualifying studies showed that phototherapy had an absolute risk-reduction rate of 10% to 17% for prevention of serum bilirubin exceeding 20 mg/dL in healthy and jaundiced infants (TSB levels higher than or equal to 13 mg/dL) born at greater than or equal to 34 weeks’ GA. Phototherapy combined with cessation of breastfeeding and substitution with formula was found to be the most efficient treatment protocol for healthy term or near-term infants with jaundice (Tables 8 and 9).

Effectiveness of Reduction in Bilirubin Level on BAER in Jaundiced Infants With Greater Than or Equal to 34 Weeks’ EGA

Eight studies that compared BAER before and after treatments for neonatal hyperbilirubinemia are discussed in this section. Of the 8 studies, 3 studies treated jaundiced infants by administering phototherapy followed by BET according to different guidelines,^{46,62,74} 4 studies treated jaundiced infants with BET only,^{75–78} and 1 study did not specify what treatments jaundiced infants received.⁷⁹ All the studies consistently showed that treatments for neonatal hyperbilirubinemia significantly improved abnormal BAERs in healthy jaundiced infants and jaundiced infants with hemolytic disease.

Effect of Phototherapy on Behavioral and Neurologic Outcomes and IQ

Five studies looked at the effect of hyperbilirubinemia and phototherapy on behavior.^{80–84} Of the 5 studies, 4 used the Brazelton Neonatal Behavioral Assessment Scale and 1 used the Vineland Social Maturity Scale. Three studies reported lower scores in the orientation cluster of the Brazelton Neonatal Behavioral Assessment Scale in the infants treated with phototherapy. The other 2 studies did not find behavioral changes in the phototherapy group. One study evaluated IQ at the age of 17 years. In 42 term infants with severe hyperbilirubinemia who were treated with phototherapy, 31 were also treated with BET. Forty-two infants who did not receive phototherapy were selected as controls. No significant difference in IQ between the 2 groups was found.⁶⁹

Effect of Phototherapy on Visual Outcomes

Three studies were identified that studied the effect of serum bilirubin and treatment on visual outcomes.^{84–86} All showed no short- or long-term (up to 36 months) effect on vision as a result of phototherapy when infants’ eyes are protected properly during treatment.

Question 4. What Is the Accuracy of Various Strategies for Predicting Hyperbilirubinemia, Including Hour-Specific Bilirubin Percentiles?

Ten qualifying studies published from 1977 to 2001 examining 5 prediction methods of neonatal hyperbilirubinemia were included. A total of 8167 neonates, most healthy near-term or term infants, were subjects. These studies were conducted among multiple racial groups in multiple countries including China, Denmark, India, Israel, Japan, Spain, and the United States. Some studies included subjects with

TABLE 8. Summary of Individual Studies of Efficacy of Phototherapy for Prevention of TSB Levels >20 mg/dL in Healthy* Term or Near-Term (GA ≥34 Weeks) Infants

Study, Year	Country	Subject Details	Phototherapy Protocol	Outcome	Study Design	Quality
Brown et al ⁷⁰ (1985) Maurer et al ⁷³ (1985)	US	Racially diverse jaundiced infants with BW >2500 g and TSB >13 mg/dL	Continuous PhotoRx began at the time the TSB level reached 13 mg/dL in the first 96 h. Duration of PhotoRx was 96 h. Infants’ eyes were covered.	BET: carried out when TSB levels were >20 mg/dL in both groups	RCT	A
Martinez ⁷² (1993)	US	Full-time breastfed infants with TSB ≥17 mg/dL	(I) Continue breastfeeding, administer PhotoRx. (II) Discontinue breastfeeding, substitute formula, and administer PhotoRx. The infants’ eyes were covered.	TSB ≥20 mg/dL	RCT	A
John ⁷¹ (1975)	Australia	Mature infants who developed unexplained jaundice with TSB >15 mg/dL	Each course consisted of continuous PhotoRx for 18 h, followed by a 6-h break. Three or 4 courses were given. The infants’ eyes were covered.	BET: carried out when TSB >20 mg/dL in both groups	Non-RCT	C

BW indicates birth weight; RCT, randomized, controlled trial.

* Healthy indicates no hemolytic disease, congenital malformations, perinatal asphyxia, neonatal illness, or infections.

TABLE 9. NNT to Keep TSB From Exceeding 20 mg/dL by Phototherapy in Jaundiced Term or Near-Term (GA ≥34 Weeks) Infants

Study, Year	Groups	Infants With TSB >20 mg/dL, N (%)	Total Infants, No.	Mean TSB Level at Entry (Range), mg/dL	Follow-Up, h	ARR	NNT, 95% CI
Brown et al ⁷⁰ (1985)*	Control group I†	10 (17)	60	≥13	144	+0.5%	—
	Rx group I†	12 (17)	70				
	Control group II	13 (17)	76	≥13	144	14.3%	7 (6–8)
Maurer et al ⁷³ (1985)*	Rx group II	2 (3)	70				
	Control group I‡	6 (20)	30	15.8 (13–23)	144	+0.6%	—
	Rx group I‡	7 (21)	34	16.5 (10–23)			
Martinez et al ⁷² (1993)	Control group II§	17 (16)	106	15.6 (10–24)	144	9.4%	11 (10–12)
	Rx group II§	7 (7)	106	15.5 (10–22)			
	Control group I	6 (24)	25	17.8	48	10.1%	10 (8–11)
John ⁷¹ (1975)	Rx group I	5 (14)	36	18.0			
	Control group II	5 (19)	26	17.8	48	16.6%	6 (5–7)
	Rx group II	1 (3)	38	17.9			
John ⁷¹ (1975)	Control group	70 (18)	381	15–18	Nodata	11.2%	9 (8–10)
	Rx group	8 (7)	111				

ARR indicates absolute risk reduction rate; Rx, treatment.

* Sample from NICHD study.

† Hemolytic disease group (infants with hemolysis, high-risk group). BETs were carried when infants' TSB levels were >18 mg/dL in the high-risk group.

‡ Coombs' test positive (91% ABO incompatibility; 9% Rh incompatibility).

§ Including some infants in the high-risk group. BETs were performed when infants' TSB levels were >18 mg/dL in the high-risk group.

ABO incompatibility, and some did not. Four studies examined the accuracy of cord bilirubin level as a test for predicting the development of clinically significant neonatal jaundice.^{87–90} Four studies investigated the test performance of serum bilirubin levels before 48 hours of life to predict hyperbilirubinemia.^{87,90–92} Two studies^{88,91} further compared the test performances of cord bilirubin with that of early serum bilirubin levels. The accuracy of end-tidal carbon monoxide concentration as a predictor of the development of hyperbilirubinemia was examined in Okuyama et al⁹³ and Stevenson et al.⁹⁴ The study by Stevenson et al also examined the test performance of a combined strategy of end-tidal carbon monoxide concentration and early serum bilirubin levels. Finally, 2 studies tested the efficacy of predischarge risk assessment, determined by a risk index model and hour-specific bilirubin percentile, respectively, for predicting neonatal hyperbilirubinemia.^{95,96}

ROC curves were developed for 3 of the predictive strategies. The AUCs were calculated to provide an assessment of the overall accuracy of the tests. Hour-specific bilirubin percentiles had an AUC of 0.93,⁹⁵ cord bilirubin levels had an AUC of 0.74⁸⁸, and predischarge risk index had an AUC of 0.80⁹⁶. These numbers should not be compared directly with each other, because the studies had different population characteristics and different defining parameters for hyperbilirubinemia.

Question 5. What Is the Accuracy of TcB Measurements?

A total of 47 qualifying studies in 50 publications examining the test performance of TcB measurements and/or the correlation of TcB measurements to serum bilirubin levels was reviewed in this section. Of the 47 studies, the Minolta Air-Shields jaundice meter (Air-Shields, Hatboro, PA) was used in 41 studies,^{87–89,97–136} the BiliCheck (SpectRx Inc, Norcross, GA) was used in 3 studies,^{137–139} the In-

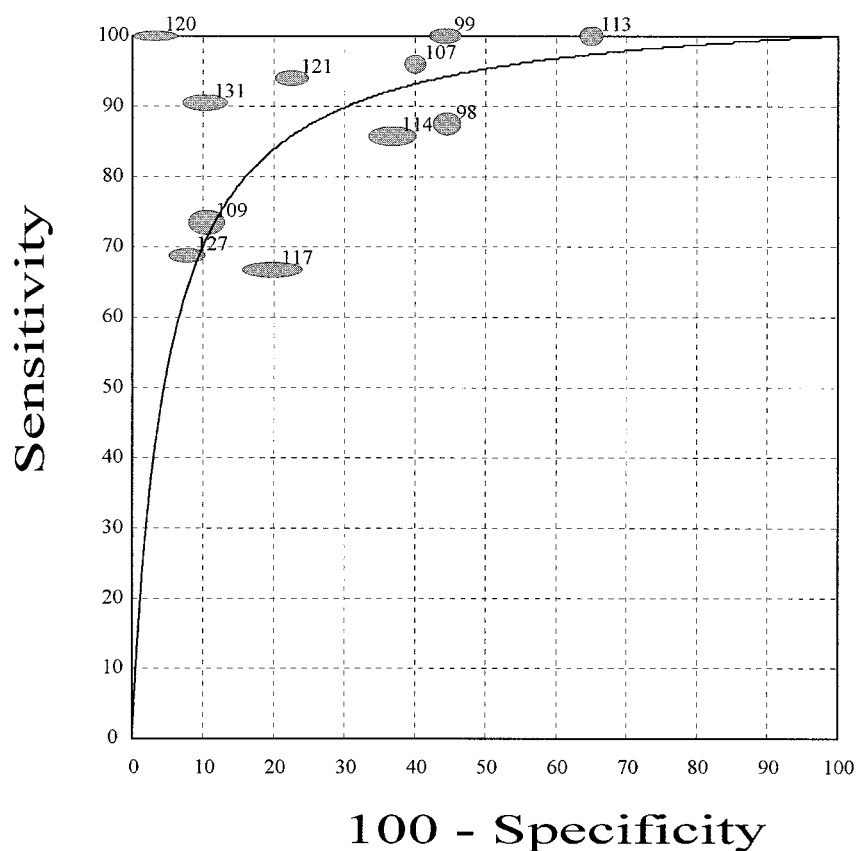
gram icterometer (Thomas A. Ingram and Co, Birmingham, England; distributed in the United States by Cascade Health Care Products, Salem, OR) was used in 4 studies,^{99,121,140,141} and the ColorMate III (Chromatics Color Sciences International Inc, New York, NY) was used in 1 study.¹⁴²

Based on the evidence from the systematic review, TcB measurements by each of the 4 devices described in the literature (the Minolta Air-Shields jaundice meter, Ingram icterometer, BiliCheck, and Chromatics ColorMate III) have a linear correlation to TSB and may be useful as screening devices to detect clinically significant jaundice and decrease the need for serum bilirubin determinations.

Minolta Air-Shields Jaundice Meter

Generally, TcB readings from the forehead or sternum have correlated well with TSB but with a wide range of correlation coefficients, from a low of 0.52 for subgroup of infants less than 37 weeks' GA to as high as 0.96.^{97,118} Comparison of correlations across studies is difficult because of differences in study design and selection procedures. TcB indices that correspond to various TSB levels vary from institution to institution but seem to be internally consistent. Different TSB threshold levels were used across studies; therefore, there is limited ability to combine data across the studies. Most of the studies used TcB measurements taken at the forehead, several studies used multiple sites and combined results, 1 study used only the midsternum site, and 3 studies took the TcB measurement at multiple sites.

The Minolta Air-Shields jaundice meter seems to perform less well in black infants, compared with white infants, performs best when measurements are made at the sternum, and performs less well when infants have been exposed to phototherapy. This instrument requires daily calibration, and each institution must develop its own correlation curves of TcB to TSB. Eleven studies of the test performance of the



Study, Year	Threshold	TP/FN	FP/TN	Sens	95% CI	Spec	95% CI
Lin et al ¹¹⁷ (1993)	Multiple*	12/6	57/230	0.67	0.41–0.86	0.80	0.75–0.84
Knudsen ¹¹⁴ (1990)	17	24/4	66/113	0.86	0.67–0.95	0.63	0.56–0.70
Tsai and Lu ¹³¹ (1988)	16	19/2	16/141	0.90	0.68–0.98	0.90	0.84–0.94
Maisels and Conrad ¹²⁰ (1982)	24	7/0	5/145	1.00	0.59–1.00	0.97	0.92–0.99
Karrar et al ¹⁰⁹ (1989)	21	36/13	11/95	0.73	0.59–0.85	0.90	0.82–0.94
Taha et al ¹²⁷ (1984)	22.5	11/15	8/96	0.69	0.42–0.88	0.92	0.85–0.96
Schumacher et al ¹²¹ (1985)	20	16/1	20/69	0.94	0.69–1.00	0.78	0.67–0.85
Bhutta and Yusuf ⁹⁸ (1991)	17	35/5	28/35	0.88	0.72–0.95	0.56	0.43–0.68
Bilgen et al ⁹⁹ (1998)	13	17/0	35/44	1.00	0.80–1.00	0.56	0.44–0.67
Knudsen et al ¹¹³ (1993)	15	30/0	28/15	1.00	0.88–1.00	0.35	0.21–0.51
Harish and Sharma ¹⁰⁷ (1998)	18	24/1	14/21	0.96	0.78–1.00	0.60	0.42–0.76
Total (Range)		268	1,292		0.67–1.00		0.35–0.97
		REM Pooled		0.85	0.77–0.91	0.77	0.66–0.85

Fig 6. Summary ROC curve of the Minolta Air-Shields jaundice meter measuring at forehead as a screening tool for serum bilirubin level at or higher than 13 mg/dL in healthy infants with GA greater than or equal to 34 weeks not on phototherapy or exchange transfusion. The asterisk indicates multiple thresholds at TcB level of 11, 16, or 20 on the first, second, and following days of life. TP indicates true positive; FN, false negative; FP, false positive; TN, true negative; Sens, sensitivity; Spec, specificity; CI, confidence interval.

Minolta Air-Shields jaundice meter measuring at forehead to predict a serum bilirubin threshold of higher than or equal to 13 mg/dL were included in the following analysis (Fig 6). A total of 1560 paired TcB and serum bilirubin measurements were evaluated. The cutoff points of Minolta Air-Shields TcB measurements (TcB index) ranged from 13 to 24 for predicting a serum bilirubin level higher than or equal to 13 mg/dL. As a screening test, it does not perform consistently across studies, as evidenced by the heterogeneity in the summary ROC curves not explained by threshold effect. The overall unweighted pooled estimates of sensitivity and specificity were 0.85 (0.77–0.91) and 0.77 (0.66–0.85).

Ingram Ictrometer

The Ingram icterometer consists of a strip of transparent Plexiglas on which 5 yellow transverse stripes of precise and graded hue are painted. The correlation coefficients (r) in the 4 studies ranged from 0.63 to 0.97. The icterometer has the added limitation of lacking the objectivity of the other methods, because it depends on observer visualization of depth of yellow color of the skin.

BiliCheck

The recently introduced BiliCheck device, which uses reflectance data from multiple wavelengths,

seems to be a significant improvement over the older devices (the Ingram icterometer and the Minolta Air-Shields jaundice meter) because of its ability to determine correction factors for the effect of melanin and hemoglobin. Three studies examined the accuracy of the BiliCheck TcB measurements to predict TSB (“gold standard”). All studies were rated as high quality. The correlation coefficient ranged from 0.83 to 0.91. In 1 study, the BiliCheck was shown to be as accurate as the laboratory measurement of TSB when compared with the reference gold-standard high-performance liquid chromatography (HPLC) measurement of TSB. Analysis of covariance found no differences in test performance by postnatal age, GA, birth weight, or race; however, 66.7% were white and only 4.3% were black.¹³⁹

Chromatics ColorMate III

One study that evaluated the performance of the ColorMate III transcutaneous bilirubinometer was reviewed. The correlation coefficient for the whole study group was 0.9563, and accuracy was not affected by race, weight, or phototherapy. The accuracy of the device is increased by the determination of an infant’s underlying skin type before the onset of visual jaundice; thus, a drawback to the method when used as a screening device is that all infants would require an initial baseline measurement.¹⁴²

CONCLUSIONS AND DISCUSSION

Summarizing case reports of kernicterus from different investigators in different countries from different periods is problematic. First, definitions of kernicterus used in these reports varied greatly. They included gross yellow staining of the brain, microscopic neuronal degeneration, acute clinical neuromotor impairment, neuroauditory impairment, and chronic neuromotor impairment. In some cases, the diagnoses were not established until months or years after birth. Second, case reports without controls makes interpretation difficult, especially in infants with comorbid factors, and could very well lead to misinterpretation of the role of bilirubin in neurodevelopmental outcomes. Third, different reports used different outcome measures. “Normal at follow-up” may be based on parental reporting, physician assessment, or formal neuropsychologic testing. Fourth, time of reported follow-up ranged from days to years. Fifth, cases were reported from different countries at different periods and with different standards of practice managing hyperbilirubinemia. Some countries have a high prevalence of glucose-6-phosphate dehydrogenase deficiency. Some have cultural practices that predispose their infants to agents that cause hyperbilirubinemia (such as clothing stored in dressers with naphthalene moth balls). The effect of the differences on outcomes cannot be known for certain. Finally, it is difficult to infer from case reports the true incidence of this uncommon disorder.

To recap our findings, based on a summary of multiple case reports that spanned more than 30 years, we conclude that kernicterus, although infrequent, has significant mortality (at least 10%) and

long-term morbidity (at least 70%). It is evident that the preponderance of kernicterus cases occurred in infants with high bilirubin (more than 20 mg/dL).

Of 26 (19%) term or near-term infants with acute manifestations of kernicterus and reported follow-up data, 5 survived without sequelae, whereas only 3 of 63 (5%) infants with acute kernicterus and comorbid factors were reported to be normal at follow-up. This result suggests the importance of comorbid factors in determining long-term outcome in infants initially diagnosed with kernicterus.

For future research, reaching a national consensus in defining this entity, as in the model suggested by Johnson et al,⁵ will help in formulating a valid comparison of different databases. It is also apparent that, without good prevalence and incidence data on hyperbilirubinemia and kernicterus, one would not be able to estimate the risk of kernicterus at a given bilirubin level. Making severe hyperbilirubinemia (eg, greater than or equal to 25 mg/dL) and kernicterus reportable conditions would be a first step in that direction. Also, because kernicterus is infrequent, doing a multicenter case-control study with kernicterus may help to delineate the role of bilirubin in the development of kernicterus.

Hyperbilirubinemia, in most cases, is a necessary but not sufficient condition to explain kernicterus. Factors acting in concert with bilirubin must be studied to seek a satisfactory explanation. Information from duration of exposure to bilirubin and albumin binding of bilirubin may yield a more useful profile of the risk of kernicterus.

Only a few prospective controlled studies looked specifically at behavioral and neurodevelopmental outcomes in healthy term infants with hyperbilirubinemia. Most of these studies have a small number of subjects. Two short-term studies with well-defined measurement of newborn behavioral organization and physiologic measurement of cry are of high methodologic quality^{41,44}; however, the significance of long-term abnormalities in newborn behavior scales and variations in cry formant frequencies are unknown. There remains little information on the long-term effects of hyperbilirubinemia in healthy term infants.

Among the mixed studies (combined term and preterm, nonhemolytic and hemolytic, nondiseased and diseased), the following observations can be made:

- Nine of 15 studies (excluding the CPP) addressing neuroauditory development and bilirubin level were of high quality. Six of them showed BAER abnormalities correlated with high bilirubin levels. Most reported resolution with treatment. Three studies reported hearing impairment associated with elevated bilirubin (more than 16 to more than 20 mg/dL). We conclude that a high bilirubin level does have an adverse effect on neuroauditory function, but the adverse effect on BAER is reversible.
- Of the 8 studies reporting intelligence outcomes in subjects with hyperbilirubinemia, 4 studies were considered high quality. These 4 studies reported

no association between IQ and bilirubin level, with follow-up ranging from 6.5 to 17 years. We conclude that there is no evidence to suggest a linear association of bilirubin level and IQ.

- The analysis of the CPP population found no consistent association between peak bilirubin level and IQ. Sensorineural hearing loss was not related to bilirubin level. Only the frequency of abnormal or suspicious neurologic examinations was associated with bilirubin level. In the rest of the studies from the CPP population, there was no consistent evidence to suggest neurologic abnormalities in children with neonatal bilirubin levels more than 20 mg/dL when followed up to 7 years of age.

A large prospective study comprising healthy infants greater than or equal to 34 weeks' GA with hyperbilirubinemia, specifically looking at long-term neurodevelopmental outcomes, has yet to be done. The report of Newman and Klebanoff³⁶ came closest to that ideal because of the large number of subjects and the study's analytic approach. However, a population born from 1959 to 1966 is no longer representative of present-day newborns: 1) there is now increased ethnic diversity in our newborn population; 2) breast milk jaundice has become more common than hemolytic jaundice; 3) phototherapy for hyperbilirubinemia has become standard therapy; and 4) hospital stays are shorter. These changes in biologic, cultural, and health care characteristics make it difficult to apply the conclusions from the CPP population to present-day newborns.

Although short-term studies, in general, have good methodologic quality, they use tools that have unknown long-term predictive abilities. Long-term studies suffer from high attrition rates of the study population and a nonuniform approach to defining "normal neurodevelopmental outcomes." The total bilirubin levels reported in all the studies mentioned were measured anywhere from the first day of life to more than 2 weeks of life. Definitions of significant hyperbilirubinemia ranged from greater than or equal to 12 mg/dL to greater than or equal to 20 mg/dL.

Given the diversity of conclusions reported, except in cases of kernicterus with sequelae, it is evident that the use of a single TSB level (within the range described in this review) to predict long-term behavioral or neurodevelopmental outcomes is inadequate and will lead to conflicting results.

Evidence for the efficacy of treatments for neonatal hyperbilirubinemia was limited. Overall, the 4 qualifying studies showed that phototherapy had an absolute risk-reduction rate of 10% to 17% for prevention of serum bilirubin exceeding 20 mg/dL in healthy jaundiced infants (TSB higher than or equal to 13 mg/dL) of greater than or equal to 34 weeks' GA. Phototherapy combined with cessation of breastfeeding and substitution with formula was found to be the most efficient treatment protocol for healthy term or near-term infants with jaundice. There is no evidence to suggest that phototherapy for neonatal hyperbilirubinemia has any long-term adverse neurodevelopmental effects in either healthy

jaundiced infants or infants with hemolytic disease. It is also noted that in all the studies listed, none of the infants received what is currently known as "intensive phototherapy."¹⁴³ Although phototherapy did not reduce the need for BET in infants with hemolytic disease in the NICHD phototherapy trial, it could be attributable to the low dose of phototherapy used. Proper application of "intensive phototherapy" should decrease the need for BET further.

It is difficult to draw conclusions regarding the accuracy of various strategies for prediction of neonatal hyperbilirubinemia. The first challenge is the lack of consistency in defining clinically significant neonatal hyperbilirubinemia. Not only did multiple studies use different levels of TSB to define neonatal hyperbilirubinemia, but the levels of TSB defined as significant also varied by age, but age at TSB determination varied by study as well. For example, significant levels of TSB were defined as more than 11.7,⁸⁸ more than or equal to 15,⁹³ more than 15,⁹¹ more than 16,⁹⁰ more than 17,⁸⁷ and more than or equal to 25 mg/dL.⁹⁶

A second challenge is the heterogeneity of the study populations. The studies were conducted in many racial groups in different countries including China, Denmark, India, Israel, Japan, Spain, and the United States. Although infants were defined as healthy term and near-term newborns, these studies included neonates with potential for hemolysis from ABO-incompatible pregnancies⁹⁰ as well as breastfed and bottle-fed infants (often not specified). Therefore, it is not possible to directly compare the different predicting strategies. However, all the strategies provided strong evidence that early jaundice predicts late jaundice.

Hour-specific bilirubin percentiles had an AUC of 0.93, implying great accuracy of this strategy. In that study,⁹⁵ 2976 of 13 003 eligible infants had a postdischarge TSB measurement, as discussed by Maisels and Newman.¹⁴⁴ Because of the large number of infants who did not have a postdischarge TSB, the actual study sample would be deficient in study participants with low pre-discharge bilirubin levels, leading to false high-sensitivity estimates and false low-specificity estimates. Moreover, the population in the study is not representative of the entire US population. The strategy of using early hour-specific bilirubin percentiles to predict late jaundice looks promising, but a large multicenter study (with evaluation of potential differences by race and ethnicity as well as prenatal, natal, and postnatal factors) may need to be undertaken to produce more applicable data.

TcB measurements by each of the 3 devices described in the literature, the Minolta Air-Shields jaundice meter, the Ingram icterometer, and the Bili-Check, have a linear correlation to TSB and may be useful as screening devices to detect clinically significant jaundice and decrease the need for serum bilirubin determinations.

The recently introduced BiliCheck device, which uses reflectance data from multiple wavelengths, seems to be a significant improvement over the older devices (the Ingram icterometer and the Minolta Air-

TABLE 10. Summary Table for the Risk of BET

Study, year	Birth Year (Country)	BET Infants, No (BETs, No)	Pre-BET Condition or Etiology of Jaundice	Bilirubin Level When BET Performed	BET-Associated Mortality*	BET-Associated Morbidity†	Subjects' Category
Boggs and Westphal ¹⁴⁸ (1960)	1952–1958 (US)	519 (875)	83% vigorous pre-BET (Rh, ABO, KI, moribund)	No data	6-hour mortality = 3.3% Overall = 7.3%	No data	I
Boggs and Westphal ¹⁴⁸ (1960)	1952–1959 (US)	645‡ (1123)	Rh, ABO, KI, prematurity, moribund	No data	6-hour mortality = 3.3%	No data	I
Ellis et al ¹⁵⁰ (1979)	1951–1977 (UK)	2440 (1.01–1.49 BETs per infant)	100% Rh	No data	1951–1965 = 1.2%	"Incidence of circulatory arrest has remained virtually constant at 1.5 per 100 BETs."	III
Jablonski ¹⁵³ (1962)	1956–1960 (US)	No data (263)	Nonhemolytic jaundice	No data	1966–1980 = 0% Overall (1951–1980) = 0.7% 1.5%§	Unspecified % of recovery or leading to deaths No data	I
Weldon and Odell ¹⁶¹ (1968)	1957–1963 (US)	232 (351)	64% vigorous pre-BET Others: LBW, KI, moribund	No data	6-hour mortality = 0.9% Overall = 4.7%	No data	I
Panagopoulos et al ¹⁵⁸ (1969)	1962–1966 (Greece)	502 (606)	46% idiopathic jaundice	TSB near or above 25 mg/dL, unless other indication for BET	6-hour mortality = 0.79%	2.5%§	II
Singh and Mittal ¹⁵⁹ (1969)	1967–1968 (India)	14 (28)	Others: LBW, ABO, Rh Rh, ABO, sepsis, Crigler-Najjar	Cord bilirubin >4 mg/dL, TSB >10 mg/dL at 12 hours or >20 mg/dL at any time, or hourly increase in TSB >0.5 mg/dL	6-hour mortality = 21.4%	BET-induced malaria <3 weeks later = 7.1%	III
Tan et al ¹⁶⁰ (1976)	ND (Singapore)	122 (140)	67% vigorous and idiopathic jaundice	TSB ≥ 20 mg/dL, or >15 mg/dL in the first or second days of life.	0.8%	BET terminated due to deteriorated conditions: 6.6%	I
Hovi and Siimes ¹⁵² (1985)	1968, 1971, 1974, 1977, and 1981 (Finland)	1069 (1472)	Others: ABO, LBW, VLBW, G6PD, KI 22% idiopathic jaundice	No data	0.4%	1.3%¶	II
Palmer and Drew ¹⁵⁷ (1983)	1970–1980 (Australia)	132# (181)	Others: Rh, ABO, hemolysis, prematurity	4% nonjaundiced infants	1.5%	1.5%**	III
Guaran et al ¹⁵¹ (1992)	1971–1989 (Australia)	248†† (353)	Rh, ABO, prematurity, multiple conditions 8% idiopathic jaundice	No data	1.2%	Some description of morbidity but no number of cases	III
Keenan et al ¹⁵⁵ (1985)	1974–1976 (US)	190 (331)	Others: Rh, ABO, sepsis, prematurity, G6PD, sepsis About 22% normal BW and vigorous	All infants had a TSB >9 mg/dL before treatments. TSB ≥ 20 mg/dL.	6-hour mortality = 0.5%	6.7%§ defined in Table 6 of the original article	II
Dikshit and Gupta ¹⁴⁹ (1989)	1978–1988 (India)	335 (433)	Others: LBW, unstable, moribund 6% idiopathic jaundice	For premature or sick infants, TSB ≥ 18 mg/dL. No data	1.2%	Full term: 20.4% Premature: 41.8% (These rates included deaths.)	III
Jackson ¹⁵⁴ (1997)	1981–1995 (US)	106 (140)	G6PD, multiple conditions, prematurity/LBW 76% asymptomatic jaundice (Rh, ABO, prematurity)	No data	2%	Moderate to Serious: 24.5%‡‡	II
Narang et al ¹⁵⁶ (1997)	1994–1995 (India)	141 (162)	35% idiopathic jaundice Others: sepsis, G6PD, Rh, ABO, other conditions	39 (27%) had a TSB <15 mg/dL; 102 (73%) had a TSB ≥ 15 mg/dL	6-hour mortality = 0% Overall = 2.8%	No data	II

TABLE 10. Continued

BET indicates blood exchange transfusion; Rh, rhesus incompatibility; ABO, ABO incompatibility; KI, kernicterus; LBW, low birth weight; TSB, total serum bilirubin; VLBW, very low birth weight; G6PD, glucose-6-phosphate dehydrogenase deficiency; BW, birth weight.

* Definitions of BET-associated mortality varied between studies. No explicit definition could be found in the original article if no definition was provided in the table. The denominator of the calculated mortality rate is total number of infants (within specific group, if available), unless noted.

† Definition of BET-associated morbidity varied between studies. No explicit definition could be found in the original article, unless noted. The denominator of the calculated mortality rate is total number of infants (within specific group, if available) and deaths were not counted for morbidity, unless noted.

‡ Including all infants from 1952 to 1958 plus an additional 137 infants in 1959.

§ Rate is based on the number of exchange transfusion as the denominator.

¶ Fifty percent of these infants had good or relatively good condition before BET; the authors stated that the complications of the other half could be considered to have resulted at least in part from their diseases.

Infants may overlap with Guaran et al, 1992.

** Nonfatal complication included apneic episodes. One requiring assisted ventilation and isolated cases of transient hypocalcemia and hypoglycemia, asymptomatic bacteremia, perforated bowel, nonfatal necrotizing enterocolitis, inspissated bile syndrome, and disseminated intravascular coagulopathy.

†† Infants may overlap with Palmer and Drew, 1983.

‡‡ Severe indicates permanent serious sequelae; serious indicates serious, prolonged complications; moderate indicates serious, transient complications; treated indicates asymptomatic, treated complications; lab indicates asymptomatic lab abnormalities. The denominator of the calculated mortality rate is total number of infants (within specific group, if available), unless noted. The BET-related morbidity does not include death. See original Jackson (1997) paper for more detailed descriptions.

Shields jaundice meter) because of its ability to determine correction factors for the effect of melanin and hemoglobin. In 1 study, the BiliCheck was shown to be as accurate as laboratory measures of TSB when compared with the reference gold-standard HPLC measurement of TSB.¹³⁹

Future research should confirm these findings in larger samples of diverse populations and address issues that might affect performance, such as race, GA, age at measurement, phototherapy, sunlight exposure, feeding and accuracy as screening instruments, performance at higher levels of bilirubin, and ongoing monitoring of jaundice. Additionally, studies should address cost-effectiveness and reproducibility in actual clinical practice. Given the interlaboratory variability of measurements of TSB,¹⁴⁵⁻¹⁴⁷ future studies of noninvasive measures of bilirubin should use HPLC and routine laboratory methods of TSB as reference standards, because the transcutaneous measures may prove to be as accurate as the laboratory measurement when compared with HPLC as the gold standard.

Using correlation coefficients to determine the accuracy of TcB measurements should be interpreted carefully because of several limitations:

- The correlation coefficient does not provide any information about the clinical utility of the diagnostic test.
- Although correlation coefficients measure the association between TcB and "standard" serum bilirubin measurements, the correlation coefficient is highly dependent on the distribution of serum bilirubin in the study population selected.
- Correlation measures ignore bias and measure relative rather than absolute agreement.

ADDENDUM: THE RISK OF BET

At the suggestion of AAP technical experts, a review of the risks associated with BET was also undertaken after the original AHRQ report was published. Articles were obtained from an informal survey of studies published since 1960 dealing with large populations that permitted calculations of the

risks of morbidity and mortality. Of 15 studies, 8 consisted of subjects born before 1970. One article published in 1997 consisted of subjects born in 1994 and 1995.

Fifteen studies¹⁴⁸⁻¹⁶¹ that reported data on BET-related mortality and/or morbidity were included in this review. Three categories were created to describe the percentage of subjects who met the criteria of the target population of our evidence report (ie, term idiopathic jaundice infants). Category I indicates that more than 50% of the study subjects were term infants whose pre-exchange clinical state was vigorous or stable and without disease conditions other than jaundice. Category II indicates that between 10% and 50% of the study subjects had category I characteristics. Category III indicates that more than 90% of the study subjects were preterm infants and/or term infants whose pre-exchange clinical state was not stable or was critically ill and with other disease conditions. The study subjects' characteristics, their bilirubin levels when BETs were performed, and BET-related mortality and/or morbidity are summarized in Table 10. Because of inconsistent definitions of a BET-related death, case reports of mortality due to BET are described in Table 11.

BET Subject and Study Characteristics

Because BET is no longer the mainstay of treatment for hyperbilirubinemia, most infants who underwent BETs were born in the 1950s to 1970s (Table 11). Two recent studies^{154,156} reported BET-related mortality and morbidity for infants born from 1981 to 1995. After 1970, there were more infants who were premature, low birth weight or very low birth weight, and/or had a clinical condition(s) other than jaundice who received BETs than those born in earlier years. Not all infants in this review received BETs for hyperbilirubinemia. Because of limited data on subjects' bilirubin levels when the BETs were performed, we could not exclude those nonjaundiced infants.

TABLE 11. Deaths From BET: Case Reports

Study, Year	Birth Year (Country)	BET Infants, N (BETs, N)	Case Reports of Deaths Due to BET
Boggs and Westphal ¹⁴⁸ (1960)	1952–1958 (US)	519 (875)	Seventeen (3.3%) infants died from BET, defined as death within 6 h after BET. Of the total 17 infants who died from BET, 1 infant was vigorous with ABO incompatibility before BET, 10 Rh-incompatible infants were weak or kernicteric before BET, and 6 Rh-incompatible infants were hydropic or moribund before BET. There were an additional 21 infants dying >6 h after their last BET. Thus, the overall mortality rate for the total of 519 infants was 7.3%.
Boggs and Westphal ¹⁴⁸ (1960)	1952–1959 (US)	645* (1123)	Cases above were included here, plus additional 137 infants born in 1959. Twenty-one (3.3%) infants died from BET, defined as death within 6 h after BET. Of the total 21 infants who died from BET, 2 infants were term with ABO incompatibility, 10 infants were term with Rh incompatibility, and 9 infants were premature with Rh incompatibility. Counting only those 2 term infants with ABO incompatibility, the 6-h mortality rate is 3 per 1000.
Ellis et al ¹⁵⁰ (1979)	1951–1977 (UK)	2440 (ND)	From 1951–1965, 17 (1.2%) infants with Rh incompatibility in whom no cause for the sudden and unexpected death during or shortly after BET could be found, although one infant probably died from air embolus. No infant (0%) with Rh incompatibility died from 1966–1980.
Jablonski ¹⁵³ (1962)	1956–1960 (US)	263 (263)	All infants had nonhemolytic jaundice before BET. The 4 BET-related deaths included 2 small preterm infants weighing 1049 g and 1757 g. Another preterm infant weighing 2381 g, who tolerated the BET poorly and died afterward, and an infant with hyaline-membrane disease and kernicterus went into heart failure during BET and died several h later.
Weldon and Odell ¹⁶¹ (1968)	1957–1963 (US)	232 (351)	Two (0.9%) infants died within 6 h of BETs: A term black female infant with blood incompatibility with her mother developed hyperbilirubinemia before BET. TSB rose > 20 mg/dL after the first BET. During the second BET ~10 mL of air entered the umbilical catheter consequently resulted in apnea and died at 29 h later. Postmortem examination showed kernicterus, cardiac dilatation, hydropericardium, bilateral hydrothoraces, pulmonary edema, and congestion. A black male infant had a birth weight of 3100 g and TSB 62.5 mg/dL at day 5, underwent 2 BETs. He died at 48 h after the 2nd BET. The autopsy found acute omphalitis with erosion of the umbilical vessels as well as kernicterus. The authors stated that the infection of the umbilical cord and kernicterus are “equally probable” causes of his death. Counting only the first case, the 6-h mortality would be 4 per 1000 infants. There are 9 deaths occurred beyond the 6-h period. The authors state, “none could definitely be attributed directly to the procedure.” Only 1 out of the 9 infants was vigorous before BET(s). Including these cases, the overall mortality for all 232 infants was 4.7%.
Panagopoulos et al ¹⁵⁸ (1969)	1962–1966 (Greece)	502 (606)	Four (0.79%) infants died within 6 h after BET, only one was critically ill before BET and another only had LBW (1900 g). Excluding these 2 infants, the 6-h mortality would be 4 per 1000 infants.
Singh and Mittal ¹⁵⁹ (1969)	1967–1968 (India)	14 (28)	Three (21.4%) infants died during BET(s). One male infant, who had a BW of 2400 g and Rh incompatibility, developed pulmonary edema during second exchange and died. The other 2 female infants had very poor general condition before BETs. One female infant, who had a BW of 2420 g, Rh incompatibility at birth, and TSB 26.7 mg/dL at 55 h of age, had one BET and died 1 month later due to staphylococcal septicemia. Counting all of these 4 cases, the overall mortality rate was 28.6%.

TABLE 11. Continued

Study, Year	Birth Year (Country)	BET Infants, N (BETs, N)	Case Reports of Deaths Due to BET
Hovi and Siimes ¹⁵² (1985)	1968, 1971, 1974, 1977, & 1981 (Finland)	1069 (1472)	Four (0.4%) infants died from BET: The first infant was severely affected after Rh immunization, 6 BETs and died of necrotizing enterocolitis at 5 days. The second infant was also severely affected after Rh immunization and died of Pseudomonas septicemia after 5 BETs at the age of 5 days. The third infant had hyperbilirubinemia and signs of sepsis prior to BET, and died of necrotizing enterocolitis at 3 weeks. The fourth infant was a term baby with clinical signs of trisomy 21 and bacterial septicemia prior to BET, and died of necrotizing enterocolitis at the age of 2 days.
Tan et al ¹⁶⁰ (1976)	ND (Singapore)	122 (140)	One (0.8%) BET-related death was found. The authors stated that this death was "partly" contributed by exchange transfusion procedure, because the infant was kernicteric before BET and necrotizing enterocolitis was present in addition to the kernicterus after BET.
Palmer and Drew ¹⁵⁷ (1983)	1970–1980 (Australia)	132† (181)	Two (1.5%) BET-related deaths were found. Both deaths were due to necrotizing enterocolitis.
Guaran et al ¹⁵¹ (1992)	1971–1989 (Australia)	248‡ (353)	Three (1.2%) BET-related deaths were found. No further information was available.
Keenan et al (1985 ¹⁵⁵)	1974–1976 (US)	190 (331)	One (0.5%) infant died within 6 h after BET. This is a white male infant with a birth weight of 850 g in the phototherapy group, had severe respiratory distress syndrome, hypocalcemia, and thrombocytopenia before BET. Toward the end of BET, he was noted to be cyanotic and hypotensive, and he died 3.5 h later.
Dikshit and Gupta ¹⁴⁹ (1989)	1978–1988 (India)	335 (433)	Four (1.2%) BET-related deaths were found. All deaths were due to sudden cardiorespiratory arrest during BETs.
Jackson ¹⁵⁴ (1997)	1981–1995 (US)	106 (140)	Two probable BET-related deaths were found. These 2 infants were sick before BET: One infant suffered cardiac arrest associated with severe hypocalcemia during BET, and died several days later due to intraventricular hemorrhage and intractable seizures. The other infant suffered respiratory deterioration necessitating discontinuation of the BET. Necrosis of the cardiac conduction system possibly related to emboli from the BET was observed from the infant's autopsy.
Narang et al ¹⁵⁶ (1997)	1994–1995 (India)	141 (162)	No death (0%) within 6 h after BET. There were 2 deaths (2 premature infants) presumably due to infection and/or bleeding occurred within 48 h of BET. Thus, the overall mortality for the total of 141 infants was 2.8%.

LBW indicates low birth weight; BW, birth weight.

* Including all infants from 1952 to 1958, plus an additional 137 infants in 1959.

† Infants may overlap with Guaran et al.¹⁵⁶

‡ Infants may overlap with Palmer and Drew.¹⁵⁵

BET-Associated Mortality

For all infants, the reported BET-related mortality ranged from 0% to 7%. There were no consistent definitions for BET-related mortality in the studies. An infant who died within 6 hours after the BET was the first used to define a BET-related death by Boggs and Westphal¹⁴⁸ in 1960. Including the study from Boggs and Westphal, there were 3 studies^{155,156,158} reporting the 6-hour mortality, and they ranged from 0% to 1.9%. As shown in Table 11, it is difficult to isolate BET as the sole factor in explaining mortality, because most of the subjects have significant associated pre-exchange disease morbidities. Most of the infants who died from BET had blood incompatibility and sepsis or were premature, had kernicterus, and/or were critically ill before undergoing BET. When only term infants were counted, the 6-hour

mortality ranged from 3 to 19 per 1000 exchanged.^{148,158,161} When those term infants with serious hemolytic diseases (such as Rh incompatibility) were excluded, the 6-hour mortality ranged from 3 to 4 per 1000 exchanged infants.^{148,158,161} All these infants were born before 1970, and their jaundice was primarily due to ABO incompatibility.

BET-Associated Morbidity

There is an extensive list of complications that have been associated with BETs.^{162,163} Complications include those related to the use of blood products (infection, hemolysis of transfused blood, thromboembolization, graft versus host reactions), metabolic derangements (acidosis and perturbation of the serum concentrations of potassium, sodium, glucose, and calcium), cardiorespiratory reactions (including

arrhythmias, apnea, and cardiac arrest), complications related to umbilical venous and arterial catheterization, and other miscellaneous complications. As noted previously and in Table 10, the pre-exchange clinical state of the infants studied varied widely, as did the definitions and rates of BET-associated morbidity. In many cases, however, the morbidity was minor (eg, postexchange anemia).

In the NICHD cooperative phototherapy study,¹⁵⁵ morbidity (apnea, bradycardia, cyanosis, vasospasm, thrombosis) was observed in 22 of 328 (6.7%) patients in whom BETs were performed (no data available in 3 BETs). Of the 22 adverse events, 6 were mild episodes of bradycardia associated with calcium infusion. If those infants are excluded, as well as 2 who experienced transient arterial spasm, the incidence of "serious morbidity" associated with the procedure itself was 5.22%.

The most recent study to report BET morbidity in the era of contemporary neonatal care provides data on infants cared for from 1980 to 1995 at the Children's Hospital and University of Washington Medical Center in Seattle.¹⁵⁴ Of 106 infants receiving BET, 81 were healthy and there were no deaths; however, 1 healthy infant developed severe necrotizing enterocolitis requiring surgery. Of 25 sick infants (12 required mechanical ventilation), there were 5 deaths, and 3 developed permanent sequelae, including chronic aortic obstruction from BET via the umbilical artery, intraventricular hemorrhage with subsequent developmental delay, and sudden respiratory deterioration from a pulmonary hemorrhage and subsequent global developmental delay. The author classified the deaths as "possibly" ($n = 3$) or "probably" ($n = 2$) and the complications as "possibly" ($n = 2$) or "probably" ($n = 1$) resulting from the BET. Thus in 25 sick infants, the overall risk of death or permanent sequelae ranged from 3 of 25 to 8 of 25 (12%–32%) and of permanent sequelae in survivors from 1 of 20 to 2 of 20 (5%–10%).

Most of the mortality and morbidity rates reported in Table 10 date from a time at which BET was a common procedure in nurseries. This is no longer the case, and newer phototherapy techniques are likely to reduce the need for BETs even further.¹⁴³ Because the frequency of performance of any procedure is an important determinant of risk, the fact that BET is so rarely performed today could result in higher mortality and morbidity rates. However, none of the reports before 1986 included contemporary monitoring capabilities such as pulse oximetry, which should provide earlier identification of potential problems and might decrease morbidity and mortality. In addition, current standards for the monitoring of transfused blood products has significantly reduced the risk of transfusion-transmitted viral infections.¹⁶⁴

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