AMERICAN ACADEMY OF PEDIATRICS

CLINICAL PRACTICE GUIDELINE

Subcommittee on Hyperbilirubinemia

Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation

ABSTRACT. Jaundice occurs in most newborn infants. Most jaundice is benign, but because of the potential toxicity of bilirubin, newborn infants must be monitored to identify those who might develop severe hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy or kernicterus. The focus of this guideline is to reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy while minimizing the risks of unintended harm such as maternal anxiety, decreased breastfeeding, and unnecessary costs or treatment. Although kernicterus should almost always be preventable, cases continue to occur. These guidelines provide a framework for the prevention and management of hyperbilirubinemia in newborn infants of 35 or more weeks of gestation. In every infant, we recommend that clinicians 1) promote and support successful breastfeeding; 2) perform a systematic assessment before discharge for the risk of severe hyperbilirubinemia; 3) provide early and focused follow-up based on the risk assessment; and 4) when indicated, treat newborns with phototherapy or exchange transfusion to prevent the development of severe hyperbilirubinemia and, possibly, bilirubin encephalopathy (kernicterus). *Pediatrics* 2004; 114:297–316; *hyperbilirubinemia, newborn, kernicterus, bilirubin encephalopathy, phototherapy.*

ABBREVIATIONS. AAP, American Academy of Pediatrics; TSB, total serum bilirubin; TcB, transcutaneous bilirubin; G6PD, glucose-6-phosphate dehydrogenase; $ETCO_c$, end-tidal carbon monoxide corrected for ambient carbon monoxide; B/A, bilirubin/albumin; UB, unbound bilirubin.

BACKGROUND

In October 1994, the Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia of the American Academy of Pediatrics (AAP) produced a practice parameter dealing with the management of hyperbilirubinemia in the healthy term newborn.[1] The current guideline represents a consensus of the committee charged by the AAP with reviewing and updating the existing guideline and is based on a careful review of the evidence, including a comprehensive literature review by the New England Medical Center Evidence-Based Practice Center.[2] (See "An Evidence-Based Review of Important Issues Concerning Neonatal Hyperbilirubinemia"[3] for a description of the methodology, questions addressed, and conclusions of this report.) This guideline is intended for use by hospitals and pediatricians, neonatologists, family physicians, physician assistants, and advanced practice nurses who treat newborn infants in the hospital and as outpatients. A list of frequently asked questions and answers for parents is available in English and Spanish at www.aap.org/family/jaundicefaq.htm.

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

DEFINITION OF RECOMMENDATIONS

The evidence-based approach to guideline development requires that the evidence in support of a policy be identified, appraised, and summarized and that an explicit link between evidence and recommendations be defined. Evidence-based recommendations are based on the quality of evidence and the balance of benefits and harms that is anticipated when the recommendation is followed. This guideline uses the definitions for quality of evidence and balance of benefits and harms established by the AAP Steering Committee on Quality Improvement Management.[4] See Appendix 1 for these definitions.

The draft practice guideline underwent extensive peer review by committees and sections within the AAP, outside organizations, and other individuals identified by the subcommittee as experts in the field. Liaison representatives to the subcommittee were invited to distribute the draft to other representatives and committees within their specialty organizations. The resulting comments were reviewed by the subcommittee and, when appropriate, incorporated into the guideline.

BILIRUBIN ENCEPHALOPATHY AND KERNICTERUS

Although originally a pathologic diagnosis characterized by bilirubin staining of the brainstem nuclei and cerebellum, the term "kernicterus" has come to be used interchangeably with both the acute and chronic findings of bilirubin encephalopathy. Bilirubin encephalopathy describes the clinical central nervous system findings caused by bilirubin toxicity to the basal ganglia and various brainstem nuclei. To avoid confusion and encourage greater consistency in the literature, the committee recommends that in infants the term "acute bilirubin encephalopathy" be used to describe the acute manifestations of bilirubin

toxicity seen in the first weeks after birth and that the term "kernicterus" be reserved for the chronic and permanent clinical sequelae of bilirubin toxicity.

See Appendix 1 for the clinical manifestations of acute bilirubin encephalopathy and kernicterus.

FOCUS OF GUIDELINE

The overall aim of this guideline is to promote an approach that will reduce the frequency of severe neonatal hyperbilirubinemia and bilirubin encephalopathy and minimize the risk of unintended harm such as increased anxiety, decreased breastfeeding, or unnecessary treatment for the general population and excessive cost and waste. Recent reports of kernicterus indicate that this condition, although rare, is still occurring.[2,5–10]

Analysis of these reported cases of kernicterus suggests that if health care personnel follow the recommendations listed in this guideline, kernicterus would be largely preventable.

These guidelines emphasize the importance of universal systematic assessment for the risk of severe hyperbilirubinemia, close follow-up, and prompt intervention when indicated. The recommendations apply to the care of infants at 35 or more weeks of gestation. These recommendations seek to further the aims defined by the Institute of Medicine as appropriate for health care:[11] safety, effectiveness, efficiency, timeliness, patient-centeredness, and equity. They specifically emphasize the principles of patient safety and the key role of timeliness of interventions to prevent adverse outcomes resulting from neonatal hyperbilirubinemia.

The following are the key elements of the recommendations provided by this guideline. Clinicians should:

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on infants jaundiced in the first 24 hours.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels according to the infant's age in hours.
6. Recognize that infants at less than 38 weeks' gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.
7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia.
8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

PRIMARY PREVENTION

In numerous policy statements, the AAP recommends breastfeeding for all healthy term and near-term newborns. This guideline strongly supports this general recommendation.

RECOMMENDATION 1.0: Clinicians should advise mothers to nurse their infants at least 8 to 12 times per day for the first several days[12] *(evidence quality C: benefits exceed harms).*

Poor caloric intake and/or dehydration associated with inadequate breastfeeding may contribute to the development of hyperbilirubinemia.[6,13,14] Increasing the frequency of nursing decreases the likelihood of subsequent significant hyperbilirubinemia in breastfed infants.[15–17] Providing appropriate support and advice to breastfeeding mothers increases the likelihood that breastfeeding will be successful.

Additional information on how to assess the adequacy of intake in a breastfed newborn is provided in Appendix 1.

RECOMMENDATION 1.1: The AAP recommends against routine supplementation of nondehydrated breastfed infants with water or dextrose water (evidence quality B and C: harms exceed benefits).

Supplementation with water or dextrose water will not prevent hyperbilirubinemia or decrease TSB levels.[18,19]

SECONDARY PREVENTION

RECOMMENDATION 2.0: Clinicians should perform ongoing systematic assessments during the neonatal period for the risk of an infant developing severe hyperbilirubinemia.

Blood Typing

RECOMMENDATION 2.1: All pregnant women should be tested for ABO and Rh (D) blood types and have a serum screen for unusual isoimmune antibodies (evidence quality B: benefits exceed harms).

RECOMMENDATION 2.1.1: If a mother has not had prenatal blood grouping or is Rh-negative, a direct antibody test (or Coombs' test), blood type, and an Rh (D) type on the infant's (cord) blood are strongly recommended (evidence quality B: benefits exceed harms).

RECOMMENDATION 2.1.2: If the maternal blood is group O, Rh-positive, it is an option to test the cord blood for the infant's blood type and direct antibody test, but it is not required provided that there is appropriate surveillance, risk assessment before discharge, and follow-up[20] *(evidence quality C: benefits exceed harms).*

Clinical Assessment

RECOMMENDATION 2.2: Clinicians should ensure that all infants are routinely monitored for the development of jaundice, and nurseries should have established protocols for the assessment of jaundice. Jaundice should be assessed whenever the infant's vital signs are measured but no less than every 8 to 12 hours (evidence quality D: benefits versus harms exceptional).

In newborn infants, jaundice can be detected by blanching the skin with digital pressure, revealing the underlying color of the skin and subcutaneous tissue. The assessment of jaundice must be per-

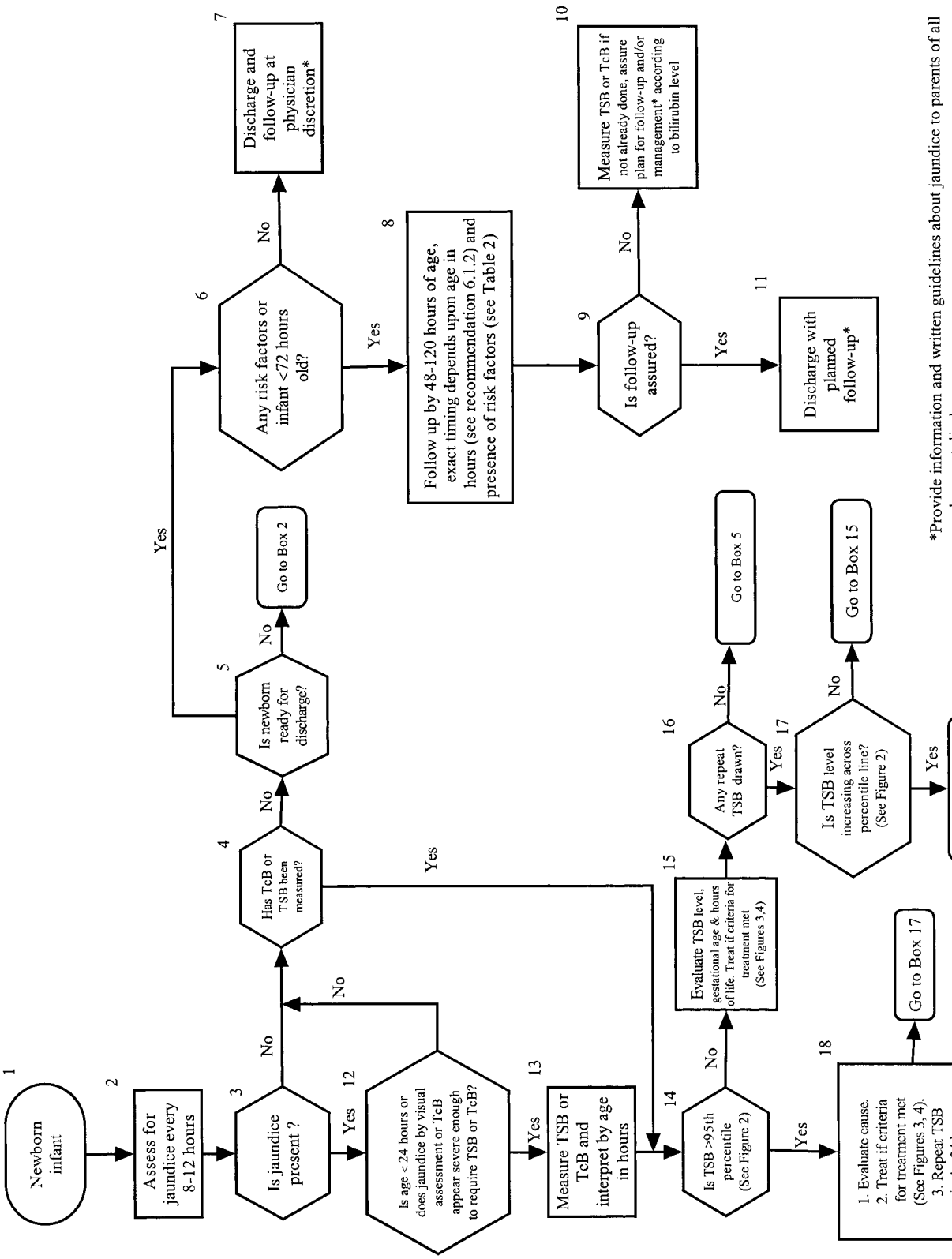


Fig 1. Algorithm for the management of jaundice in the newborn nursery.

formed in a well-lit room or, preferably, in daylight at a window. Jaundice is usually seen first in the face and progresses caudally to the trunk and extremities,[21] but visual estimation of bilirubin levels from the degree of jaundice can lead to errors.[22–24] In most infants with TSB levels of less than 15 mg/dL (257 μmol/L), noninvasive TcB-measurement devices can provide a valid estimate of the TSB level.[2,25–29] See Appendix 1 for additional information on the clinical evaluation of jaundice and the use of TcB measurements.

RECOMMENDATION 2.2.1: Protocols for the assessment of jaundice should include the circumstances in which nursing staff can obtain a TcB level or order a TSB measurement (evidence quality D: benefits versus harms exceptional).

Laboratory Evaluation

RECOMMENDATION 3.0: A TcB and/or TSB measurement should be performed on every infant who is jaundiced in the first 24 hours after birth (Fig 1 and Table 1)[30] (evidence quality C: benefits exceed harms). The need for and timing of a repeat TcB or TSB measurement will depend on the zone in which the TSB falls (Fig 2),[25,31] the age of the infant, and the evolution of the hyperbilirubinemia. Recommendations for TSB measurements after the age of 24 hours are provided in Fig 1 and Table 1.

See Appendix 1 for capillary versus venous bilirubin levels.

RECOMMENDATION 3.1: A TcB and/or TSB measurement should be performed if the jaundice appears excessive for the infant's age (evidence quality D: benefits versus harms exceptional). If there is any doubt about the degree of jaundice, the TSB or TcB should be measured. Visual estimation of bilirubin levels from the degree of jaundice can lead to errors, particularly in darkly pigmented infants (evidence quality C: benefits exceed harms).

RECOMMENDATION 3.2: All bilirubin levels should be interpreted according to the infant's age in hours (Fig 2) (evidence quality C: benefits exceed harms).

Cause of Jaundice

RECOMMENDATION 4.1: The possible cause of jaundice should be sought in an infant receiving phototherapy or whose TSB level is rising rapidly (ie, crossing percentiles [Fig 2]) and is not explained by the history and physical examination (evidence quality D: benefits versus harms exceptional).

RECOMMENDATION 4.1.1: Infants who have an elevation of direct-reacting or conjugated bilirubin should have a urinalysis and urine culture.[32] Additional laboratory evaluation for sepsis should be performed if indicated by history and physical examination (evidence quality C: benefits exceed harms).

See Appendix 1 for definitions of abnormal levels of direct-reacting and conjugated bilirubin.

RECOMMENDATION 4.1.2: Sick infants and those who are jaundiced at or beyond 3 weeks should have a measurement of total and direct or conjugated bilirubin to identify cholestasis (Table 1) (evidence quality D: benefit versus harms exceptional). The results of the newborn thyroid and galactosemia screen should also be checked in these infants (evidence quality D: benefits versus harms exceptional).

RECOMMENDATION 4.1.3: If the direct-reacting or conjugated bilirubin level is elevated, additional evaluation for the causes of cholestasis is recommended (evidence quality C: benefits exceed harms).

RECOMMENDATION 4.1.4: Measurement of the glucose-6-phosphate dehydrogenase (G6PD) level is recommended for a jaundiced infant who is receiving phototherapy and whose family history or ethnic or geographic origin suggest the likelihood of G6PD deficiency or for an infant in whom the response to phototherapy is poor (Fig 3) (evidence quality C: benefits exceed harms).

G6PD deficiency is widespread and frequently unrecognized, and although it is more common in the populations around the Mediterranean and in the Middle East, Arabian peninsula, Southeast Asia, and Africa, immigration and intermarriage have transformed G6PD deficiency into a global problem.[33,34]

TABLE 1. Laboratory Evaluation of the Jaundiced Infant of 35 or More Weeks' Gestation

Indications	Assessments
Jaundice in first 24 h	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (ie, crossing percentiles [Fig 2]) and unexplained by history and physical examination	Blood type and Coombs' test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin It is an option to perform reticulocyte count, G6PD, and $ETCO_c$, if available Repeat TSB in 4–24 h depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, $ETCO_c$, if available
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture. Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism

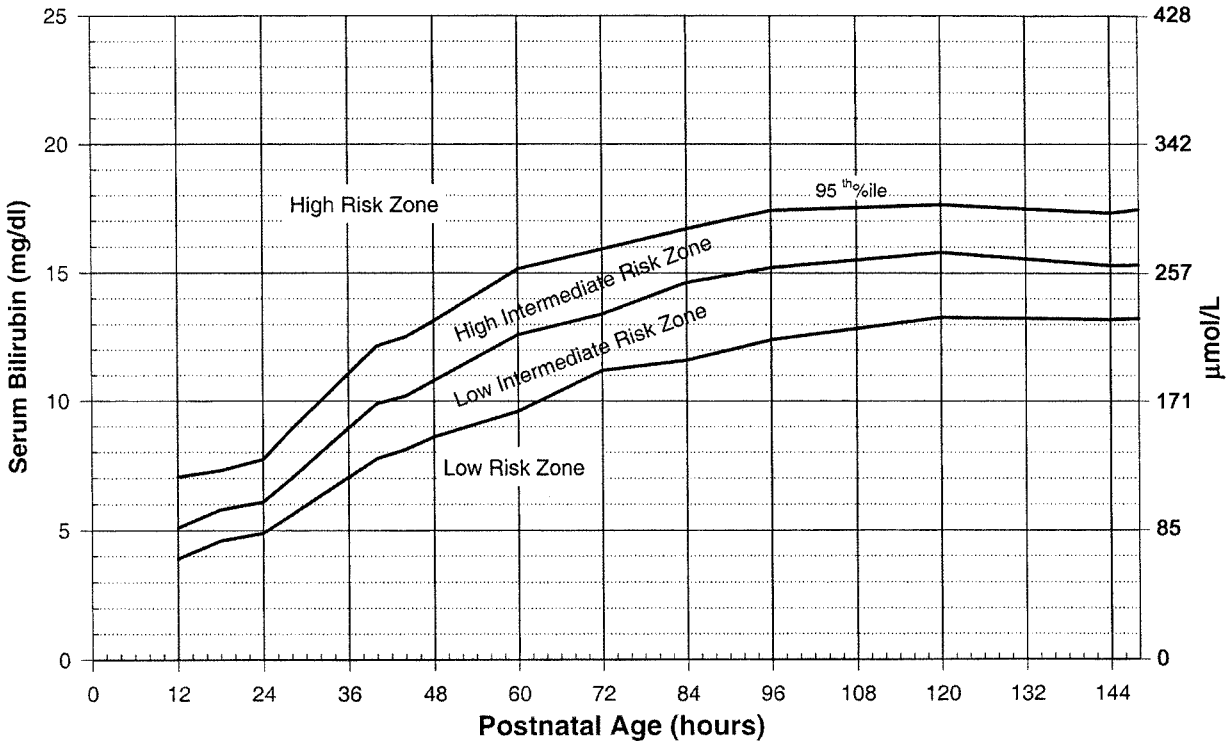


Fig 2. Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone) as shown in Appendix 1, Table 4. Used with permission from Bhutani et al.[31] See Appendix 1 for additional information about this nomogram, which should not be used to represent the natural history of neonatal hyperbilirubinemia.

Furthermore, G6PD deficiency occurs in 11% to 13% of African Americans, and kernicterus has occurred in some of these infants.[5,33] In a recent report, G6PD deficiency was considered to be the cause of hyperbilirubinemia in 19 of 61 (31.5%) infants who developed kernicterus.[5] (See Appendix 1 for additional information on G6PD deficiency.)

Risk Assessment Before Discharge

RECOMMENDATION 5.1: Before discharge, every newborn should be assessed for the risk of developing severe hyperbilirubinemia, and all nurseries should establish protocols for assessing this risk. Such assessment is particularly important in infants who are discharged before the age of 72 hours (evidence quality C: benefits exceed harms).

RECOMMENDATION 5.1.1: The AAP recommends 2 clinical options used individually or in combination for the systematic assessment of risk: predischarge measurement of the bilirubin level using TSB or TcB and/or assessment of clinical risk factors. Whether either or both options are used, appropriate follow-up after discharge is essential (evidence quality C: benefits exceed harms).

The best documented method for assessing the risk of subsequent hyperbilirubinemia is to measure the TSB or TcB level[25,31,35–38] and plot the results on a nomogram (Fig 2). A TSB level can be obtained at the time of the routine metabolic screen, thus obviating the need for an additional blood sample. Some authors have suggested that a TSB measurement should be part of the routine screening of all newborns.[5,31] An infant whose predischarge TSB is in the low-risk zone (Fig 2) is at very low risk of developing severe hyperbilirubinemia.[5,38]

Table 2 lists those factors that are clinically signif-

TABLE 2. Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation (in Approximate Order of Importance)

Major risk factors
Predischarge TSB or TcB level in the high-risk zone (Fig 2)[25,31]
Jaundice observed in the first 24 h[30]
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated $ETCO_c$
Gestational age 35–36 wk[39,40]
Previous sibling received phototherapy[40,41]
Cephalohematoma or significant bruising[39]
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive[39,40]
East Asian race[39]*
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone[25,31]
Gestational age 37–38 wk[39,40]
Jaundice observed before discharge[40]
Previous sibling with jaundice[40,41]
Macrosomic infant of a diabetic mother[42,43]
Maternal age ≥25 y[39]
Male gender[39,40]
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone (Fig 2)[25,31]
Gestational age ≥41 wk[39]
Exclusive bottle feeding[39,40]
Black race[38]*
Discharge from hospital after 72 h[40,44]

* Race as defined by mother's description.

icant and most frequently associated with an increase in the risk of severe hyperbilirubinemia. But, because these risk factors are common and the risk of hyperbilirubinemia is small, individually the factors are of limited use as predictors of significant hyperbilirubinemia.[39] Nevertheless, if no risk factors are present, the risk of severe hyperbilirubinemia is extremely low, and the more risk factors present, the greater the risk of severe hyperbilirubinemia.[39] The important risk factors most frequently associated with severe hyperbilirubinemia are breastfeeding, gestation below 38 weeks, significant jaundice in a previous sibling, and jaundice noted before discharge.[39,40] A formula-fed infant of 40 or more weeks' gestation is at very low risk of developing severe hyperbilirubinemia.[39]

Hospital Policies and Procedures

RECOMMENDATION 6.1: All hospitals should provide written and verbal information for parents at the time of discharge, which should include an explanation of jaundice, the need to monitor infants for jaundice, and advice on how monitoring should be done (evidence quality D: benefits versus harms exceptional).

An example of a parent-information handout is available in English and Spanish at www.aap.org/family/jaundicefaq.htm.

Follow-up

RECOMMENDATION 6.1.1: All infants should be examined by a qualified health care professional in the first few days after discharge to assess infant well-being and the presence or absence of jaundice. The timing and location of this assessment will be determined by the length of stay in the nursery, presence or absence of risk factors for hyperbilirubinemia (Table 2 and Fig 2), and risk of other neonatal problems (evidence quality C: benefits exceed harms).

Timing of Follow-up

RECOMMENDATION 6.1.2: Follow-up should be provided as follows:

Infant Discharged	Should Be Seen by Age
Before age 24 h	72 h
Between 24 and 47.9 h	96 h
Between 48 and 72 h	120 h

For some newborns discharged before 48 hours, 2 follow-up visits may be required, the first visit between 24 and 72 hours and the second between 72 and 120 hours. Clinical judgment should be used in determining follow-up. Earlier or more frequent follow-up should be provided for those who have risk factors for hyperbilirubinemia (Table 2), whereas those discharged with few or no risk factors can be seen after longer intervals (evidence quality C: benefits exceed harms).

RECOMMENDATION 6.1.3: If appropriate follow-up cannot be ensured in the presence of elevated risk for developing severe hyperbilirubinemia, it may be necessary to delay discharge either until appropriate follow-up can be ensured or the period of greatest risk has passed (72-96 hours) (evidence quality D: benefits versus harms exceptional).

Follow-up Assessment

RECOMMENDATION 6.1.4: The follow-up assessment should include the infant's weight and percent change from birth weight, adequacy of intake, the pattern of voiding and stooling, and the presence or absence of jaundice (evidence quality C: benefits exceed harms). Clinical judgment should be used to determine the need for a bilirubin measurement. If there is any doubt about the degree of jaundice, the TSB or TcB level should be measured. Visual estimation of bilirubin levels can lead to errors, particularly in darkly pigmented infants (evidence quality C: benefits exceed harms).

See Appendix 1 for assessment of the adequacy of intake in breastfeeding infants.

TREATMENT

Phototherapy and Exchange Transfusion

RECOMMENDATION 7.1: Recommendations for treatment are given in Table 3 and Figs 3 and 4 (evidence quality C: benefits exceed harms). If the TSB does not fall or continues to rise despite intensive phototherapy, it is very likely that hemolysis is occurring. The committee's recommendations for discontinuing phototherapy can be found in Appendix 2.

RECOMMENDATION 7.1.1: In using the guidelines for phototherapy and exchange transfusion (Figs 3 and 4), the direct-reacting (or conjugated) bilirubin level should not be subtracted from the total (evidence quality D: benefits versus harms exceptional).

In unusual situations in which the direct bilirubin level is 50% or more of the total bilirubin, there are no good data to provide guidance for therapy, and consultation with an expert in the field is recommended.

RECOMMENDATION 7.1.2: If the TSB is at a level at which exchange transfusion is recommended (Fig 4) or if the TSB level is 25 mg/dL (428 μmol/L) or higher at any time, it is a medical emergency and the infant should be admitted immediately and directly to a hospital pediatric service for intensive phototherapy. These infants should not be referred to the emergency department, because it delays the initiation of treatment[54] (evidence quality C: benefits exceed harms).

RECOMMENDATION 7.1.3: Exchange transfusions should be performed only by trained personnel in a neonatal intensive care unit with full monitoring and resuscitation capabilities (evidence quality D: benefits versus harms exceptional).

RECOMMENDATION 7.1.4: In isoimmune hemolytic disease, administration of intravenous γ-globulin (0.5-1 g/kg over 2 hours) is recommended if the TSB is rising despite intensive phototherapy or the TSB level is within 2 to 3 mg/dL (34-51 μmol/L) of the exchange level (Fig 4).[55] If necessary, this dose can be repeated in 12 hours (evidence quality B: benefits exceed harms).

Intravenous γ-globulin has been shown to reduce the need for exchange transfusions in Rh and ABO hemolytic disease.[55–58] Although data are limited, it is reasonable to assume that intravenous γ-globulin will also be helpful in the other types of Rh hemolytic disease such as anti-C and anti-E.

TABLE 3. Example of a Clinical Pathway for Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion

Treatment
Use intensive phototherapy and/or exchange transfusion as indicated in Figs 3 and 4 (see Appendix 2 for details of phototherapy use)
Laboratory tests
TSB and direct bilirubin levels
Blood type (ABO, Rh)
Direct antibody test (Coombs')
Serum albumin
Complete blood cell count with differential and smear for red cell morphology
Reticulocyte count
$ETCO_c$ (if available)
G6PD if suggested by ethnic or geographic origin or if poor response to phototherapy
Urine for reducing substances
If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture
Interventions
If TSB ≥25 mg/dL (428 μmol/L) or ≥20 mg/dL (342 μmol/L) in a sick infant or infant <38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary
In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2–3 mg/dL (34–51 μmol/L) of exchange level (Fig 4), administer intravenous immunoglobulin 0.5–1 g/kg over 2 h and repeat in 12 h if necessary
If infant's weight loss from birth is >12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids.
For infants receiving intensive phototherapy
Breastfeed or bottle-feed (formula or expressed breast milk) every 2–3 h
If TSB ≥25 mg/dL (428 μmol/L), repeat TSB within 2–3 h
If TSB 20–25 mg/dL (342–428 μmol/L), repeat within 3–4 h. If TSB <20 mg/dL (342 μmol/L), repeat in 4–6 h. If TSB continues to fall, repeat in 8–12 h
If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Fig 4, consider exchange transfusion (see Fig 4 for exchange transfusion recommendations)
When TSB is <13–14 mg/dL (239 μmol/L), discontinue phototherapy
Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 h after discharge to check for rebound

Serum Albumin Levels and the Bilirubin/Albumin Ratio

RECOMMENDATION 7.1.5: It is an option to measure the serum albumin level and consider an albumin level of less than 3.0 g/dL as one risk factor for lowering the threshold for phototherapy use (see Fig 3) (evidence quality D: benefits versus risks exceptional.).

RECOMMENDATION 7.1.6: If an exchange transfusion is being considered, the serum albumin level should be measured and the bilirubin/albumin (B/A) ratio used in conjunction with the TSB level and other factors in determining the need for exchange transfusion (see Fig 4) (evidence quality D: benefits versus harms exceptional).

The recommendations shown above for treating hyperbilirubinemia are based primarily on TSB levels and other factors that affect the risk of bilirubin encephalopathy. This risk might be increased by a prolonged (rather than a brief) exposure to a certain TSB level.[59,60] Because the published data that address this issue are limited, however, it is not possible to provide specific recommendations for intervention based on the duration of hyperbilirubinemia.

See Appendix 1 for the basis for recommendations 7.1 through 7.1.6 and for the recommendations provided in Figs 3 and 4. Appendix 1 also contains a discussion of the risks of exchange transfusion and the use of B/A binding.

Acute Bilirubin Encephalopathy

RECOMMENDATION 7.1.7: Immediate exchange transfusion is recommended in any infant who is jaundiced and manifests the signs of the intermediate to advanced stages of acute bilirubin encephalopathy[61,62] (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) even if the TSB is falling (evidence quality D: benefits versus risks exceptional).

Phototherapy

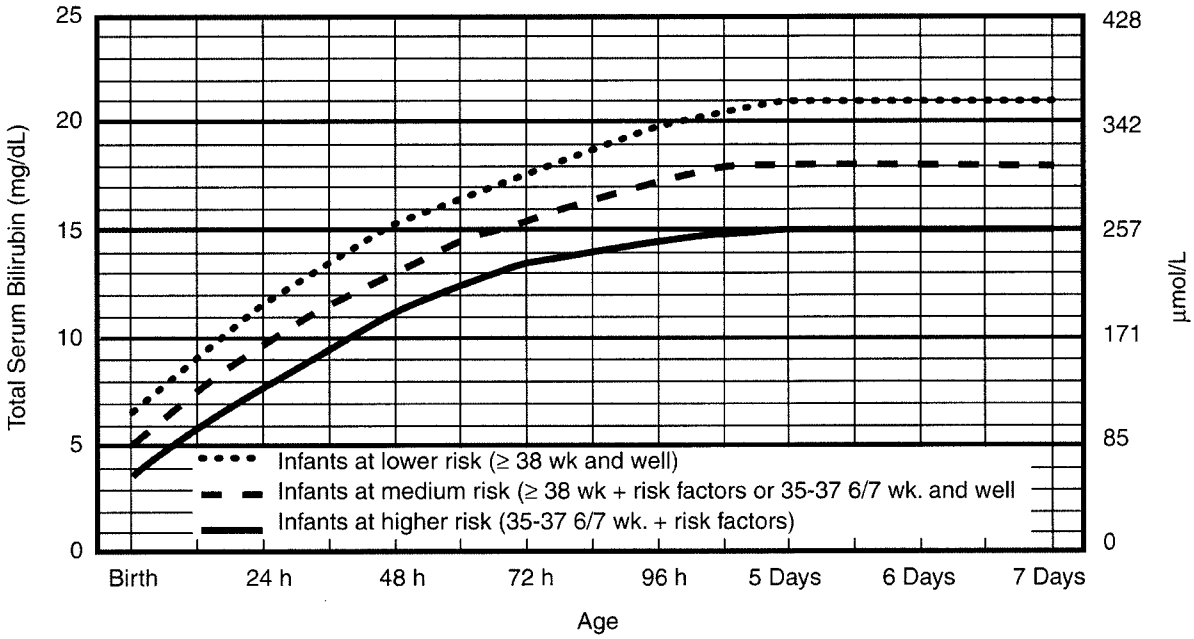
RECOMMENDATION 7.2: All nurseries and services treating infants should have the necessary equipment to provide intensive phototherapy (see Appendix 2) (evidence quality D: benefits exceed risks).

Outpatient Management of the Jaundiced Breastfed Infant

RECOMMENDATION 7.3: In breastfed infants who require phototherapy (Fig 3), the AAP recommends that, if possible, breastfeeding should be continued (evidence quality C: benefits exceed harms). It is also an option to interrupt temporarily breastfeeding and substitute formula. This can reduce bilirubin levels and/or enhance the efficacy of phototherapy[63–65] (evidence quality B: benefits exceed harms). In breastfed infants receiving phototherapy, supplementation with expressed breast milk or formula is appropriate if the infant's intake seems inadequate, weight loss is excessive, or the infant seems dehydrated.

IMPLEMENTATION STRATEGIES

The Institute of Medicine[11] recommends a dramatic change in the way the US health care system



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Fig 3. Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.

Note: These guidelines are based on limited evidence and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy which should be used when the TSB exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin,[45–47] the blood-brain barrier,[48] and the susceptibility of the brain cells to damage by bilirubin.[48]

"Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 $\mu W/cm^2$ per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system.

See Appendix 2 for additional information on measuring the dose of phototherapy, a description of intensive phototherapy, and of light sources used. If total serum bilirubin levels approach or exceed the exchange transfusion line (Fig 4), the sides of the bassinet, incubator, or warmer should be lined with aluminum foil or white material.[50] This will increase the surface area of the infant exposed and increase the efficacy of phototherapy.[51]

If the total serum bilirubin does not decrease or continues to rise in an infant who is receiving intensive phototherapy, this strongly suggests the presence of hemolysis.

Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice) may develop the bronze-baby syndrome. See Appendix 2 for the use of phototherapy in these infants.

ensures the safety of patients. The perspective of safety as a purely individual responsibility must be replaced by the concept of safety as a property of systems. Safe systems are characterized by a shared knowledge of the goal, a culture emphasizing safety, the ability of each person within the system to act in a manner that promotes safety, minimizing the use of memory, and emphasizing the use of standard procedures (such as checklists), and the involvement of patients/families as partners in the process of care.

These principles can be applied to the challenge of preventing severe hyperbilirubinemia and kernicterus. A systematic approach to the implementation of these guidelines should result in greater safety. Such approaches might include

- The establishment of standing protocols for nursing assessment of jaundice, including testing TcB and TSB levels, without requiring physician orders.
- Checklists or reminders associated with risk factors, age at discharge, and laboratory test results that provide guidance for appropriate follow-up.
- Explicit educational materials for parents (a key component of all AAP guidelines) concerning the identification of newborns with jaundice.

FUTURE RESEARCH

Epidemiology of Bilirubin-Induced Central Nervous System Damage

There is a need for appropriate epidemiologic data to document the incidence of kernicterus in the newborn population, the incidence of other adverse effects attributable to hyperbilirubinemia and its management, and the number of infants whose TSB levels exceed 25 or 30 mg/dL (428-513 μmol/L). Organizations such as the Centers for Disease Control and Prevention should implement strategies for appropriate data gathering to identify the number of

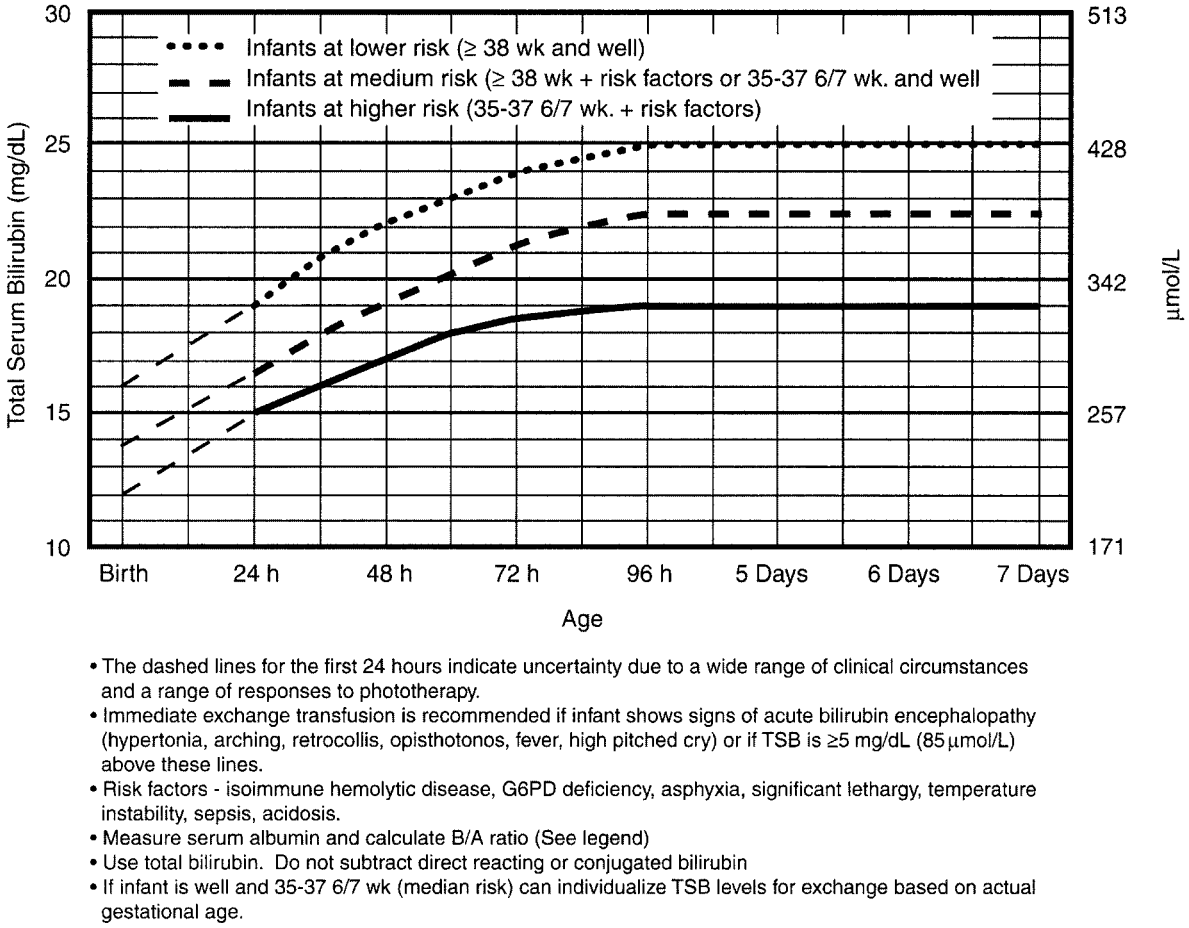


Fig 4. Guidelines for exchange transfusion in infants 35 or more weeks' gestation.

Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. See ref. 3 for risks and complications of exchange transfusion. During birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours.

The following B/A ratios can be used together with but in not in lieu of the TSB level as an additional factor in determining the need for exchange transfusion[52]:

Risk Category	B/A Ratio at Which Exchange Transfusion Should be Considered	
	TSB mg/dL/Alb, g/dL	TSB µmol/L/Alb, µmol/L
Infants ≥38 0/7 wk	8.0	0.94
Infants 35 0/7–36 6/7 wk and well or ≥38 0/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	7.2	0.84
Infants 35 0/7–37 6/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.80

If the TSB is at or approaching the exchange level, send blood for immediate type and crossmatch. Blood for exchange transfusion is modified whole blood (red cells and plasma) crossmatched against the mother and compatible with the infant.[53]

infants who develop serum bilirubin levels above 25 or 30 mg/dL (428-513 µmol/L) and those who develop acute and chronic bilirubin encephalopathy. This information will help to identify the magnitude of the problem; the number of infants who need to be screened and treated to prevent 1 case of kernicterus; and the risks, costs, and benefits of different strategies for prevention and treatment of hyperbilirubinemia. In the absence of these data, recommendations for intervention cannot be considered definitive.

Effect of Bilirubin on the Central Nervous System

The serum bilirubin level by itself, except when it is extremely high and associated with bilirubin encephalopathy, is an imprecise indicator of long-term neurodevelopmental outcome.[2] Additional studies are needed on the relationship between central nervous system damage and the duration of hyperbilirubinemia, the binding of bilirubin to albumin, and changes seen in the brainstem auditory evoked response. These studies could help to better identify

risk, clarify the effect of bilirubin on the central nervous system, and guide intervention.

Identification of Hemolysis

Because of their poor specificity and sensitivity, the standard laboratory tests for hemolysis (Table 1) are frequently unhelpful.[66,67] However, end-tidal carbon monoxide, corrected for ambient carbon monoxide ($ETCO_c$), levels can confirm the presence or absence of hemolysis, and measurement of $ETCO_c$ is the only clinical test that provides a direct measurement of the rate of heme catabolism and the rate of bilirubin production.[68,69] Thus, $ETCO_c$ may be helpful in determining the degree of surveillance needed and the timing of intervention. It is not yet known, however, how $ETCO_c$ measurements will affect management.

Nomograms and the Measurement of Serum and TcB

It would be useful to develop an age-specific (by hour) nomogram for TSB in populations of newborns that differ with regard to risk factors for hyperbilirubinemia. There is also an urgent need to improve the precision and accuracy of the measurement of TSB in the clinical laboratory.[70,71] Additional studies are also needed to develop and validate noninvasive (transcutaneous) measurements of serum bilirubin and to understand the factors that affect these measurements. These studies should also assess the cost-effectiveness and reproducibility of TcB measurements in clinical practice.[2]

Pharmacologic Therapy

There is now evidence that hyperbilirubinemia can be effectively prevented or treated with tin-mesoporphyrin,[72–75] a drug that inhibits the production of heme oxygenase. Tin-mesoporphyrin is not approved by the US Food and Drug Administration. If approved, tin-mesoporphyrin could find immediate application in preventing the need for exchange transfusion in infants who are not responding to phototherapy.[75]

Dissemination and Monitoring

Research should be directed toward methods for disseminating the information contained in this guideline to increase awareness on the part of physicians, residents, nurses, and parents concerning the issues of neonatal hyperbilirubinemia and strategies for its management. In addition, monitoring systems should be established to identify the impact of these guidelines on the incidence of acute bilirubin encephalopathy and kernicterus and the use of phototherapy and exchange transfusions.

CONCLUSIONS

Kernicterus is still occurring but should be largely preventable if health care personnel follow the recommendations listed in this guideline. These recommendations emphasize the importance of universal, systematic assessment for the risk of severe hyperbilirubinemia, close follow-up, and prompt intervention, when necessary.

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APPENDIX 1: Additional Notes

Definitions of Quality of Evidence and Balance of Benefits and Harms

The Steering Committee on Quality Improvement and Management categorizes evidence quality in 4 levels:

1. Well-designed, randomized, controlled trials or diagnostic studies on relevant populations
2. Randomized, controlled trials or diagnostic studies with minor limitations; overwhelming, consistent evidence from observational studies
3. Observational studies (case-control and cohort design)
4. Expert opinion, case reports, reasoning from first principles

The AAP defines evidence-based recommendations as follows:[1]

- Strong recommendation: the committee believes that the benefits of the recommended approach clearly exceed the harms of that approach and that the quality of the supporting evidence is either excellent or impossible to obtain. Clinicians should follow these recommendations unless a clear and compelling rationale for an alternative approach is present.
- Recommendation: the committee believes that the benefits exceed the harms, but the quality of evidence on which this recommendation is based is not as strong. Clinicians should also generally follow these recommendations but should be alert to new information and sensitive to patient preferences. In this guideline, the term "should" implies a recommendation by the committee.
- Option: either the quality of the evidence that exists is suspect or well-performed studies have shown little clear advantage to one approach over another. Patient preference should have a substantial role in influencing clinical decision-making when a policy is described as an option.
- No recommendation: there is a lack of pertinent evidence and the anticipated balance of benefits and harms is unclear.

Anticipated Balance Between Benefits and Harms

The presence of clear benefits or harms supports stronger statements for or against a course of action. In some cases, however, recommendations are made when analysis of the balance of benefits and harms provides an exceptional dysequilibrium and it would be unethical or impossible to perform clinical trials to "prove" the point. In these cases the balance of benefit and harm is termed "exceptional."

Clinical Manifestations of Acute Bilirubin Encephalopathy and Kernicterus

Acute Bilirubin Encephalopathy

In the early phase of acute bilirubin encephalopathy, severely jaundiced infants become lethargic and hypotonic and suck poorly.[2,3] The intermediate phase is characterized by moderate stupor, irritability, and hypertonia. The infant may develop a fever and high-pitched cry, which may alternate with drowsiness and hypotonia. The hypertonia is manifested by backward arching of the neck (retrocollis) and trunk (opisthotonos). There is anecdotal evidence that an emergent exchange transfusion at this stage, in some cases, might reverse the central nervous system changes.[4] The advanced phase, in which central nervous system damage is probably irreversible, is characterized by pronounced retrocollis-opisthotonos, shrill cry, no feeding, apnea, fever, deep stupor to coma, sometimes seizures, and death.[2,3,5]

Kernicterus

In the chronic form of bilirubin encephalopathy, surviving infants may develop a severe form of athetoid cerebral palsy, auditory dysfunction, dental-enamel dysplasia, paralysis of upward gaze, and, less often, intellectual and other handicaps. Most infants who develop kernicterus have manifested some or all of the signs listed above in the acute phase of bilirubin encephalopathy. However, occasionally there are infants who have developed very high bilirubin levels and, subsequently, the signs of kernicterus but have exhibited few, if any, antecedent clinical signs of acute bilirubin encephalopathy.[3,5,6]

Clinical Evaluation of Jaundice and TcB Measurements

Jaundice is usually seen in the face first and progresses caudally to the trunk and extremities,[7] but because visual estimation of bilirubin levels from the degree of jaundice can lead to errors,[8–10] a low threshold should be used for measuring the TSB.

Devices that provide a noninvasive TcB measurement have proven very useful as screening tools,[11] and newer instruments give measurements that provide a valid estimate of the TSB level.[12–17] Studies using the new TcB-measurement instruments are limited, but the data published thus far suggest that in most newborn populations, these instruments generally provide measurements within 2 to 3 mg/dL (34–51 μmol/L) of the TSB and can replace a measurement of serum bilirubin in many circumstances, particularly for TSB levels less than 15 mg/dL (257 μmol/L).[12–17] Because phototherapy "bleaches" the skin, both visual assessment of jaundice and TcB measurements in infants undergoing phototherapy are not reliable. In addition, the ability of transcutaneous instruments to provide accurate measurements in different racial groups requires additional study.[18,19] The limitations of the accuracy and reproducibility of TSB measurements in the clinical laboratory[20–22] must also be recognized and are discussed in the technical report.[23]

Capillary Versus Venous Serum Bilirubin Measurement

Almost all published data regarding the relationship of TSB levels to kernicterus or developmental outcome are based on capillary blood TSB levels. Data regarding the differences between capillary and venous TSB levels are conflicting.[24,25] In 1 study the capillary TSB levels were higher, but in another they were lower than venous TSB levels.[24,25] Thus, obtaining a venous sample to "confirm" an elevated capillary TSB level is not recommended, because it will delay the initiation of treatment.

Direct-Reacting and Conjugated Bilirubin

Although commonly used interchangeably, direct-reacting bilirubin is not the same as conjugated bilirubin. Direct-reacting bilirubin is the bilirubin that reacts directly (without the addition of an accelerating agent) with diazotized sulfanilic acid. Conjugated bilirubin is bilirubin made water soluble by binding with glucuronic acid in the liver. Depending on the technique used, the clinical laboratory will report total and direct-reacting or unconjugated and conjugated bilirubin levels. In this guideline and for clinical purposes, the terms may be used interchangeably.

Abnormal Direct and Conjugated Bilirubin Levels

Laboratory measurement of direct bilirubin is not precise,[26] and values between laboratories can vary widely. If the TSB is at or below 5 mg/dL (85 μmol/L), a direct or conjugated bilirubin of more than 1.0 mg/dL (17.1 μmol/L) is generally considered abnormal. For TSB values higher than 5 mg/dL (85 μmol/L), a direct bilirubin of more than 20% of the TSB is considered abnormal. If the hospital laboratory measures conjugated bilirubin using the Vitros (formerly Ektachem) system (Ortho-Clinical Diagnostics, Raritan, NJ), any value higher than 1 mg/dL is considered abnormal.

Assessment of Adequacy of Intake in Breastfeeding Infants

The data from a number of studies[27–34] indicate that unsupplemented, breastfed infants experience their maximum weight loss by day 3 and, on average, lose 6.1% ± 2.5% (SD) of their birth weight. Thus, ~5% to 10% of fully breastfed infants lose 10% or more of their birth weight by day 3, suggesting that adequacy of intake should be evaluated and the infant monitored if weight loss is more than 10%.[35] Evidence of adequate intake in breastfed infants also includes 4 to 6 thoroughly wet diapers in 24 hours and the passage of 3 to 4 stools per day by the fourth day. By the third to fourth day, the stools in adequately breastfed infants should have changed from meconium to a mustard yellow, mushy stool.[36] The above assessment will also help to identify breastfed infants who are at risk for dehydration because of inadequate intake.

Nomogram for Designation of Risk

Note that this nomogram (Fig 2) does not describe the natural history of neonatal hyperbilirubinemia, particularly after 48 to 72 hours, for which, because of sampling bias, the lower zones are spuriously elevated.[37] This bias, however, will have much less effect on the high-risk zone (95th percentile in the study).[38]

G6PD Dehydrogenase Deficiency

It is important to look for G6PD deficiency in infants with significant hyperbilirubinemia, because some may develop a sudden increase in the TSB. In addition, G6PD-deficient infants require intervention at lower TSB levels (Figs 3 and 4). It should be noted also that in the presence of hemolysis, G6PD levels can be elevated, which may obscure the diagnosis in the newborn period so that a normal level in a hemolyzing neonate does not rule out G6PD deficiency.[39] If G6PD deficiency is strongly suspected, a repeat level should be measured when the infant is 3 months old. It is also recognized that immediate laboratory determination of G6PD is generally not available in most US hospitals, and thus translating the above information into clinical practice is cur-

TABLE 4. Risk Zone as a Predictor of Hyperbilirubinemia[39]

TSB Before Discharge	Newborns (Total = 2840), *n* (%)	Newborns Who Subsequently Developed a TSB Level >95th Percentile, *n* (%)
High-risk zone (>95th percentile)	172 (6.0)	68 (39.5)
High intermediate-risk zone	356 (12.5)	46 (12.9)
Low intermediate-risk zone	556 (19.6)	12 (2.26)
Low-risk zone	1756 (61.8)	0

rently difficult. Nevertheless, practitioners are reminded to consider the diagnosis of G6PD deficiency in infants with severe hyperbilirubinemia, particularly if they belong to the population groups in which this condition is prevalent. This is important in the African American population, because these infants, as a group, have much lower TSB levels than white or Asian infants.[40,41] Thus, severe hyperbilirubinemia in an African American infant should always raise the possibility of G6PD deficiency.

Basis for the Recommendations 7.1.1 Through 7.1.6 and Provided in Figs 3 and 4

Ideally, recommendations for when to implement phototherapy and exchange transfusions should be based on estimates of when the benefits of these interventions exceed their risks and cost. The evidence for these estimates should come from randomized trials or systematic observational studies. Unfortunately, there is little such evidence on which to base these recommendations. As a result, treatment guidelines must necessarily rely on more uncertain estimates and extrapolations. For a detailed discussion of this question, please see "An Evidence-Based Review of Important Issues Concerning Neonatal Hyperbilirubinemia."[23]

The recommendations for phototherapy and exchange transfusion are based on the following principles:

- The main demonstrated value of phototherapy is that it reduces the risk that TSB levels will reach a level at which exchange transfusion is recommended.[42–44] Approximately 5 to 10 infants with TSB levels between 15 and 20 mg/dL (257–342 μmol/L) will receive phototherapy to prevent the TSB in 1 infant from reaching 20 mg/dL (the number needed to treat).[12] Thus, 8 to 9 of every 10 infants with these TSB levels will not reach 20 mg/dL (342 μmol/L) even if they are not treated. Phototherapy has proven to be a generally safe procedure, although rare complications can occur (see Appendix 2).
- Recommended TSB levels for exchange transfusion (Fig 4) are based largely on the goal of keeping TSB levels below those at which kernicterus has been reported.[12,45–48] In almost all cases, exchange transfusion is recommended only after phototherapy has failed to keep the TSB level below the exchange transfusion level (Fig 4).
- The recommendations to use phototherapy and exchange transfusion at lower TSB levels for infants of lower gestation and those who are sick are based on limited observations suggesting that sick infants (particularly those with the risk factors listed in Figs 3 and 4)[49–51] and those of lower gestation[51–54] are at greater risk for developing kernicterus at lower bilirubin levels than are well infants of more than 38 6/7 weeks' gestation. Nevertheless, other studies have not confirmed all of these associations.[52,55,56] There is no doubt, however, that infants at 35 to 37 6/7 weeks' gestation are at a much greater risk of developing very high TSB levels.[57,58] Intervention for these infants is based on this risk as well as extrapolations from more premature, lower birth-weight infants who do have a higher risk of bilirubin toxicity.[52,53]
- For all newborns, treatment is recommended at lower TSB levels at younger ages because one of the primary goals of treatment is to prevent additional increases in the TSB level.

Subtle Neurologic Abnormalities Associated With Hyperbilirubinemia

There are several studies demonstrating measurable transient changes in brainstem-evoked potentials, behavioral patterns, and the infant's cry[59–63] associated with TSB levels of 15 to 25 mg/dL (257–428 μmol/L). In these studies, the abnormalities identified were transient and disappeared when the serum bilirubin levels returned to normal with or without treatment.[59,60,62,63]

A few cohort studies have found an association between hyperbilirubinemia and long-term adverse neurodevelopmental effects that are more subtle than kernicterus.[64–67] Current studies, however, suggest that although phototherapy lowers the TSB levels, it has no effect on these long-term neurodevelopmental outcomes.[68–70]

Risks of Exchange Transfusion

Because exchange transfusions are now rarely performed, the risks of morbidity and mortality associated with the procedure are difficult to quantify. In addition, the complication rates listed below may not be generalizable to the current era if, like most procedures, frequency of performance is an important determinant of risk. Death associated with exchange transfusion has been reported in approximately 3 in 1000 procedures,[71,72] although in otherwise well infants of 35 or more weeks' gestation, the risk is probably much lower.[71–73] Significant morbidity (apnea, bradycardia, cyanosis, vasospasm, thrombosis, necrotizing enterocolitis) occurs in as many as 5% of exchange transfusions,[71] and the risks associated with the use of blood products must always be considered.[74] Hypoxic-ischemic encephalopathy and acquired immunodeficiency syndrome have occurred in otherwise healthy infants receiving exchange transfusions.[73,75]

Serum Albumin Levels and the B/A Ratio

The legends to Figs 3 and 4 and recommendations 7.1.5 and 7.1.6 contain references to the serum albumin level and the B/A ratio as factors that can be considered in the decision to initiate phototherapy (Fig 3) or perform an exchange transfusion (Fig 4). Bilirubin is transported in the plasma tightly bound to albumin, and the portion that is unbound or loosely bound can more readily leave the intravascular space and cross the intact blood-brain barrier.[76] Elevations of unbound bilirubin (UB) have been associated with kernicterus in sick preterm newborns.[77,78] In addition, elevated UB concentrations are more closely associated than TSB levels with transient abnormalities in the audiometric brainstem response in term[79] and preterm[80] infants. Long-term

studies relating B/A binding in infants to developmental outcome are limited and conflicting.[69,81,82] In addition, clinical laboratory measurement of UB is not currently available in the United States.

The ratio of bilirubin (mg/dL) to albumin (g/dL) does correlate with measured UB in newborns[83] and can be used as an approximate surrogate for the measurement of UB. It must be recognized, however, that both albumin levels and the ability of albumin to bind bilirubin vary significantly between newborns.[83,84] Albumin binding of bilirubin is impaired in sick infants,[84–86] and some studies show an increase in binding with increasing gestational[86,87] and postnatal[87,88] age, but others have not found a significant effect of gestational age on binding.[89] Furthermore, the risk of bilirubin encephalopathy is unlikely to be a simple function of the TSB level or the concentration of UB but is more likely a combination of both (ie, the total amount of bilirubin available [the miscible pool of bilirubin] as well as the tendency of bilirubin to enter the tissues [the UB concentration]).[83] An additional factor is the possible susceptibility of the cells of the central nervous system to damage by bilirubin.[90] It is therefore a clinical option to use the B/A ratio together with, but not in lieu of, the TSB level as an additional factor in determining the need for exchange transfusion[83] (Fig 4).

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APPENDIX 2: Phototherapy

There is no standardized method for delivering phototherapy. Phototherapy units vary widely, as do the types of lamps used in the units. The efficacy of phototherapy depends on the dose of phototherapy administered as well as a number of clinical factors (Table 5).[1]

Measuring the Dose of Phototherapy

Table 5 shows the radiometric quantities used in measuring the phototherapy dose. The quantity most commonly reported in the literature is the spectral irradiance. In the nursery, spectral irradiance can be measured by using commercially available radiometers. These instruments take a single measurement across a band of wavelengths, typically 425 to 475 or 400 to 480 nm. Unfortunately, there is no standardized method for reporting phototherapy dosages in the clinical literature, so it is difficult to compare published studies on the efficacy of phototherapy and manufacturers' data for the irradiance produced by different systems.[2] Measurements of irradiance from the same system, using different radiometers,

TABLE 5. Factors That Affect the Dose and Efficacy of Phototherapy

Factor	Mechanism/Clinical Relevance	Implementation and Rationale	Clinical Application
Spectrum of light emitted	Blue-green spectrum is most effective. At these wavelengths, light penetrates skin well and is absorbed maximally by bilirubin.	Special blue fluorescent tubes or other light sources that have most output in the blue-green spectrum and are most effective in lowering TSB.	Use special blue tubes or LED light source with output in blue-green spectrum for intensive PT.
Spectral irradiance (irradiance in certain wavelength band) delivered to surface of infant	↑ irradiance → ↑ rate of decline in TSB	Irradiance is measured with a radiometer as $\mu W/cm^2$ per nm. Standard PT units deliver 8–10 $\mu W/cm^2$ per nm (Fig 6). Intensive PT requires >30 $\mu W/cm^2$ per nm.	If special blue fluorescent tubes are used, bring tubes as close to infant as possible to increase irradiance (Fig 6). Note: This cannot be done with halogen lamps because of the danger of burn. Special blue tubes 10–15 cm above the infant will produce an irradiance of at least 35 $\mu W/cm^2$ per nm.
Spectral power (average spectral irradiance across surface area)	↑ surface area exposed → ↑ rate of decline in TSB	For intensive PT, expose maximum surface area of infant to PT.	Place lights above and fiber-optic pad or special blue fluorescent tubes* below the infant. For maximum exposure, line sides of bassinet, warmer bed, or incubator with aluminum foil.
Cause of jaundice	PT is likely to be less effective if jaundice is due to hemolysis or if cholestasis is present. (↑ direct bilirubin)		When hemolysis is present, start PT at lower TSB levels. Use intensive PT. Failure of PT suggests that hemolysis is the cause of jaundice. If ↑ direct bilirubin, watch for bronze baby syndrome or blistering.
TSB level at start of PT	The higher the TSB, the more rapid the decline in TSB with PT.		Use intensive PT for higher TSB levels. Anticipate a more rapid decrease in TSB when TSB >20 mg/dL (342 μmol/L).

PT indicates phototherapy; LED, light-emitting diode.
* Available in the Olympic BiliBassinet (Olympic Medical, Seattle, WA).

can also produce significantly different results. The width of the phototherapy lamp's emissions spectrum (narrow versus broad) will affect the measured irradiance. Measurements under lights with a very focused emission spectrum (eg, blue light-emitting diode) will vary significantly from one radiometer to another, because the response spectra of the radiometers vary from manufacturer to manufacturer. Broader-spectrum lights (fluorescent and halogen) have fewer variations among radiometers. Manufacturers of phototherapy systems generally recommend the specific radiometer to be used in measuring the dose of phototherapy when their system is used.

It is important also to recognize that the measured irradiance will vary widely depending on where the measurement is taken. Irradiance measured below the center of the light source can be more than double that measured at the periphery, and this dropoff at the periphery will vary with different phototherapy units. Ideally, irradiance should be measured at multiple sites under the area illuminated by the unit and the measurements averaged. The International Electrotechnical Commission[3] defines the "effective surface area" as the intended treatment surface that is illuminated by the phototherapy light. The commission uses 60 × 30 cm as the standard-sized surface.

Is It Necessary to Measure Phototherapy Doses Routinely?

Although it is not necessary to measure spectral irradiance before each use of phototherapy, it is important to perform periodic checks of phototherapy units to make sure that an adequate irradiance is being delivered.

The Dose-Response Relationship of Phototherapy

Figure 5 shows that there is a direct relationship between the irradiance used and the rate at which the serum bilirubin declines under phototherapy.[4] The data in Fig 5 suggest that there is a saturation point beyond which an increase in the irradiance produces no added efficacy. We do not know, however, that a saturation point exists. Because the conversion of bilirubin to excretable photoproducts is partly irreversible and follows first-order kinetics, there may not be a saturation point, so we do not know the maximum effective dose of phototherapy.

Effect on Irradiance of the Light Spectrum and the Distance Between the Infant and the Light Source

Figure 6 shows that as the distance between the light source and the infant decreases, there is a corresponding increase in the spectral irradiance.[5] Fig 6 also demonstrates the dramatic difference in irradi-

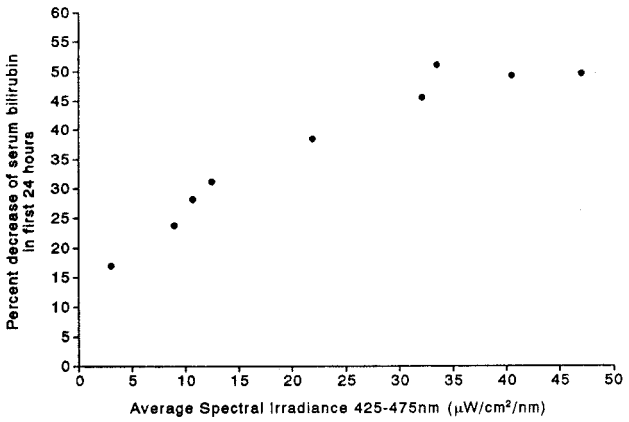

Fig 5. Relationship between average spectral irradiance and decrease in serum bilirubin concentration. Term infants with nonhemolytic hyperbilirubinemia were exposed to special blue lights (Phillips TL 52/20W) of different intensities. Spectral irradiance was measured as the average of readings at the head, trunk, and knees. Drawn from the data of Tan.[4] Source: *Pediatrics*. 1996;98: 283-287.

ance produced within the important 425- to 475-nm band by different types of fluorescent tubes.

What is Intensive Phototherapy?

Intensive phototherapy implies the use of high levels of irradiance in the 430- to 490-nm band (usually 30 $\mu W/cm^2$ per nm or higher) delivered to as much of the infant's surface area as possible. How this can be achieved is described below.

Using Phototherapy Effectively

Light Source

The spectrum of light delivered by a phototherapy unit is determined by the type of light source and any filters used. Commonly used phototherapy units contain daylight, cool white, blue, or "special blue" fluorescent tubes. Other units use tungsten-halogen lamps in different configurations, either free-standing or as part of a radiant warming device. Recently, a system using high-intensity gallium nitride light-emitting diodes has been introduced.[6] Fiber-optic systems deliver light from a high-intensity lamp to a fiber-optic blanket. Most of these devices deliver enough output in the blue-green region of the visible spectrum to be effective for standard phototherapy use. However, when bilirubin levels approach the range at which intensive phototherapy is recommended, maximal efficiency must be sought. The most effective light sources currently commercially available for phototherapy are those that use special blue fluorescent tubes[7] or a specially designed light-emitting diode light (Natus Inc, San Carlos, CA).[6] The special blue fluorescent tubes are labeled F20T12/BB (General Electric, Westinghouse, Sylvania) or TL52/20W (Phillips, Eindhoven, The Netherlands). It is important to note that special blue tubes provide much greater irradiance than regular blue tubes (labeled F20T12/B) (Fig 6). Special blue tubes are most effective because they provide light predominantly in the blue-green spectrum. At these wavelengths, light penetrates skin well and is absorbed maximally by bilirubin.[7]

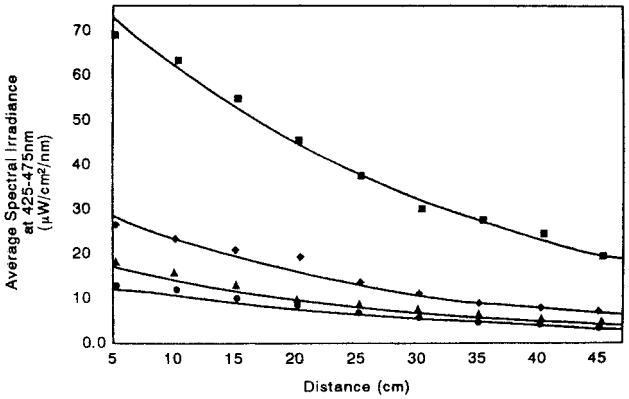

Fig 6. Effect of light source and distance from the light source to the infant on average spectral irradiance. Measurements were made across the 425- to 475-nm band by using a commercial radiometer (Olympic Bilimeter Mark II) and are the average of measurements taken at different locations at each distance (irradiance at the center of the light is much higher than at the periphery). The phototherapy unit was fitted with eight 24-in fluorescent tubes. ■ indicates special blue, General Electric 20-W F20T12/BB tube; ◆, blue, General Electric 20-W F20T12/B tube; ▲, daylight blue, 4 General Electric 20-W F20T12/B blue tubes and 4 Sylvania 20-W F20T12/D daylight tubes; •, daylight, Sylvania 20-W F20T12/D daylight tube. Curves were plotted by using linear curve fitting (True Epistat, Epistat Services, Richardson, TX). The best fit is described by the equation $y = Ae^{Bx}$. Source: *Pediatrics*. 1996;98:283-287.

There is a common misconception that ultraviolet light is used for phototherapy. The light systems used do not emit significant ultraviolet radiation, and the small amount of ultraviolet light that is emitted by fluorescent tubes and halogen bulbs is in longer wavelengths than those that cause erythema. In addition, almost all ultraviolet light is absorbed by the glass wall of the fluorescent tube and the Plexiglas cover of the phototherapy unit.

Distance From the Light

As can be seen in Fig 6, the distance of the light source from the infant has a dramatic effect on the spectral irradiance, and this effect is most significant when special blue tubes are used. To take advantage of this effect, the fluorescent tubes should be placed as close to the infant as possible. To do this, the infant should be in a bassinet, not an incubator, because the top of the incubator prevents the light from being brought sufficiently close to the infant. In a bassinet, it is possible to bring the fluorescent tubes within approximately 10 cm of the infant. Naked term infants do not become overheated under these lights. It is important to note, however, that the halogen spot phototherapy lamps cannot be positioned closer to the infant than recommended by the manufacturers without incurring the risk of a burn. When halogen lamps are used, manufacturers recommendations should be followed. The reflectors, light source, and transparent light filters (if any) should be kept clean.

Surface Area

A number of systems have been developed to provide phototherapy above and below the infant.[8,9] One commercially available system that does this is the BiliBassinet (Olympic Medical, Seattle, WA). This

unit provides special blue fluorescent tubes above and below the infant. An alternative is to place fiber-optic pads below an infant with phototherapy lamps above. One disadvantage of fiber-optic pads is that they cover a relatively small surface area so that 2 or 3 pads may be needed.[5] When bilirubin levels are extremely high and must be lowered as rapidly as possible, it is essential to expose as much of the infant's surface area to phototherapy as possible. In these situations, additional surface-area exposure can be achieved by lining the sides of the bassinet with aluminum foil or a white cloth.[10]

In most circumstances, it is not necessary to remove the infant's diaper, but when bilirubin levels approach the exchange transfusion range, the diaper should be removed until there is clear evidence of a significant decline in the bilirubin level.

What Decline in the Serum Bilirubin Can You Expect?

The rate at which the bilirubin declines depends on the factors listed in Table 5, and different responses can be expected depending on the clinical circumstances. When bilirubin levels are extremely high (more than 30 mg/dL [513 μmol/L]), and intensive phototherapy is used, a decline of as much as 10 mg/dL (171 μmol/L) can occur within a few hours,[11] and a decrease of at least 0.5 to 1 mg/dL per hour can be expected in the first 4 to 8 hours.[12] On average, for infants of more than 35 weeks' gestation readmitted for phototherapy, intensive phototherapy can produce a decrement of 30% to 40% in the initial bilirubin level by 24 hours after initiation of phototherapy.[13] The most significant decline will occur in the first 4 to 6 hours. With standard phototherapy systems, a decrease of 6% to 20% of the initial bilirubin level can be expected in the first 24 hours.[8,14]

Intermittent Versus Continuous Phototherapy

Clinical studies comparing intermittent with continuous phototherapy have produced conflicting results.[15–17] Because all light exposure increases bilirubin excretion (compared with darkness), no plausible scientific rationale exists for using intermittent phototherapy. In most circumstances, however, phototherapy does not need to be continuous. Phototherapy may be interrupted during feeding or brief parental visits. Individual judgment should be exercised. If the infant's bilirubin level is approaching the exchange transfusion zone (Fig 4), phototherapy should be administered continuously until a satisfactory decline in the serum bilirubin level occurs or exchange transfusion is initiated.

Hydration

There is no evidence that excessive fluid administration affects the serum bilirubin concentration. Some infants who are admitted with high bilirubin levels are also mildly dehydrated and may need supplemental fluid intake to correct their dehydration. Because these infants are almost always breastfed, the best fluid to use in these circumstances is a milk-based formula, because it inhibits the enterohepatic circulation of bilirubin and should help to lower the serum bilirubin level. Because the photoproducts responsible for the decline in serum bilirubin are excreted in urine and bile,[18] maintaining adequate hydration and good urine output should help to improve the efficacy of phototherapy. Unless there is evidence of dehydration, however, routine intravenous fluid or other supplementation (eg, with dextrose water) of term and near-term infants receiving phototherapy is not necessary.

When Should Phototherapy Be Stopped?

There is no standard for discontinuing phototherapy. The TSB level for discontinuing phototherapy depends on the age at which phototherapy is initiated and the cause of the hyperbilirubinemia.[13] For infants who are readmitted after their birth hospitalization (usually for TSB levels of 18 mg/dL [308 μmol/L] or higher), phototherapy may be discontinued when the serum bilirubin level falls below 13 to 14 mg/dL (239-239 μmol/L). Discharge from the hospital need not be delayed to observe the infant for rebound.[13,19,20] If phototherapy is used for infants with hemolytic diseases or is initiated early and discontinued before the infant is 3 to 4 days old, a follow-up bilirubin measurement within 24 hours after discharge is recommended.[13] For infants who are readmitted with hyperbilirubinemia and then discharged, significant rebound is rare, but a repeat TSB measurement or clinical follow-up 24 hours after discharge is a clinical option.[13]

Home Phototherapy

Because the devices available for home phototherapy may not provide the same degree of irradiance or surface-area exposure as those available in the hospital, home phototherapy should be used only in infants whose bilirubin levels are in the "optional phototherapy" range (Fig 3); it is not appropriate for infants with higher bilirubin concentrations. As with hospitalized infants, it is essential that serum bilirubin levels be monitored regularly.

Sunlight Exposure

In their original description of phototherapy, Cremer et al[21] demonstrated that exposure of newborns to sunlight would lower the serum bilirubin level. Although sunlight provides sufficient irradiance in the 425- to 475-nm band to provide phototherapy, the practical difficulties involved in safely exposing a naked newborn to the sun either inside or outside (and avoiding sunburn) preclude the use of sunlight as a reliable therapeutic tool, and it therefore is not recommended.

Complications

Phototherapy has been used in millions of infants for more than 30 years, and reports of significant toxicity are exceptionally rare. Nevertheless, phototherapy in hospital separates mother and infant, and eye patching is disturbing to parents. The most important, but uncommon, clinical complication occurs in infants with cholestatic jaundice. When these infants are exposed to phototherapy, they may develop a dark, grayish-brown discoloration of the skin, serum, and urine (the bronze infant syndrome).[22] The

pathogenesis of this syndrome is unknown, but it may be related to an accumulation of porphyrins and other metabolites in the plasma of infants who develop cholestasis.[22,23] Although it occurs exclusively in infants with cholestasis, not all infants with cholestatic jaundice develop the syndrome.

This syndrome generally has had few deleterious consequences, and if there is a need for phototherapy, the presence of direct hyperbilirubinemia should not be considered a contraindication to its use. This is particularly important in sick neonates. Because the products of phototherapy are excreted in the bile, the presence of cholestasis will decrease the efficacy of phototherapy. Nevertheless, infants with direct hyperbilirubinemia often show some response to phototherapy. In infants receiving phototherapy who develop the bronze infant syndrome, exchange transfusion should be considered if the TSB is in the intensive phototherapy range and phototherapy does not promptly lower the TSB. Because of the paucity of data, firm recommendations cannot be made. Note, however, that the direct serum bilirubin should not be subtracted from the TSB concentration in making decisions about exchange transfusions (see Fig 4).

Rarely, purpura and bullous eruptions have been described in infants with severe cholestatic jaundice receiving phototherapy,[24,25] and severe blistering and photosensitivity during phototherapy have occurred in infants with congenital erythropoietic porphyria.[26,27] Congenital porphyria or a family history of porphyria is an absolute contraindication to the use of phototherapy, as is the concomitant use of drugs or agents that are photosensitizers.[28]

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All clinical practice guidelines from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation

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ERRATUM

Two errors appeared in the American Academy of Pediatrics clinical practice guideline, titled "Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation," that was published in the July 2004 issue of *Pediatrics* (2004;114:297–316). On page 297, Background section, first paragraph, the second sentence should read: "The current guideline represents a consensus of the committee charged by the AAP with reviewing and updating the existing guideline and is based on a careful review of the evidence, including a comprehensive literature review by the Agency for Healthcare Research and Quality and the New England Medical Center Evidence-Based Practice Center.[2]" On page 308, Appendix 1, first paragraph, the 4 levels of evidence quality should have been labeled A, B, C, and D rather than 1, 2, 3, and 4, respectively. The American Academy of Pediatrics regrets these errors.

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