Practice Parameter: Management of Hyperbilirubinemia in the Healthy Term Newborn

Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia

Each year approximately 60% of the 4 million newborns in the United States become clinically jaundiced. Many receive various forms of evaluation and treatment. Few issues in neonatal medicine have generated such long-standing controversy as the possible adverse consequences of neonatal jaundice and when to begin treatment. Questions regarding potentially detrimental neurologic effects from elevated serum bilirubin levels prompt continuing concern and debate, particularly with regard to the management of the otherwise healthy term newborn without risk factors for hemolysis.1-6 Although most data are based on infants with birth weights ≥2500 g, “term” is hereafter defined as 37 completed weeks of gestation.

Under certain circumstances, bilirubin may be toxic to the central nervous system and may cause neurologic impairment even in healthy term newborns. Most studies, however, have failed to substantiate significant associations between a specific level of total serum bilirubin (TSB) during nonhemolytic hyperbilirubinemia in term newborns and subsequent IQ or serious neurologic abnormality (including hearing impairment).3-5 Other studies have detected subtle differences in outcomes associated with TSB levels, particularly when used in conjunction with albumin binding tests and/or duration of exposure.5,13,17,18 In almost all published studies, the TSB concentration has been used as a predictor variable for outcome determinations.

Factors influencing bilirubin toxicity to the brain cells of newborn infants are complex and incompletely understood; they include those that affect the serum albumin concentration and those that affect the binding of bilirubin to albumin, the penetration of bilirubin into the brain, and the vulnerability of brain cells to the toxic effects of bilirubin. It is not known at what bilirubin concentration or under what circumstances significant risk of brain damage occurs or when the risk of damage exceeds the risk of treatment. Concentrations considered harmful may vary in different ethnic groups or geographic locations and may be lower outside North America or northern Europe. Reasons for apparent geographic differences in risk for kernicterus are not clear; the following practice parameter may not apply worldwide.

There are no simple solutions to the management of jaundiced neonates. Continuing uncertainties about the relationship between serum bilirubin levels and brain damage as well as differences in patient populations and practice settings contribute to variations in the management of hyperbilirubinemia. Early postpartum discharge from the hospital further complicates the management of jaundiced newborns, because it places additional responsibilities on parents or guardians to recognize and respond to developing jaundice or clinical symptoms. Some conditions significantly increase the risk of hyperbilirubinemia, including history of a previous sibling with hyperbilirubinemia, decreasing gestational age, breast-feeding, and large weight loss after birth. Although newborns of 37 weeks’ gestation and above are considered “term,” infants 37 to 38 weeks of gestation may not nurse as well as more mature infants, and there is a strong correlation between decreasing gestational age and risk for hyperbilirubinemia. Infants born at 37 weeks’ gestation are much more likely to develop a serum bilirubin level of 13 mg/dL or higher than are those born at 40 weeks’ gestation.19-22

METHODOLOGY

The Task Force on Quality Assurance (now designated the Provisional Committee on Quality Improvement) selected the management of hyperbilirubinemia as a topic for practice parameter development and appointed a subcommittee that performed a comprehensive literature review. Two independent MEDLINE searches identified primarily retrospective epidemiologic data derived almost exclusively from North American and European literature. The subcommittee also relied heavily on
both the data and analyses contained in a 1990 report by Newman and Maisels. Moreover, the total experience analyzed involved a relatively limited number of healthy term infants with bilirubin levels in excess of 25 mg/dL (428 μmol/L) making it difficult to draw firm conclusions from the published data. The recommendations that follow stem from careful consideration of currently available information, as analyzed and interpreted by subcommittee members and consultants, and are based on evidence when appropriate data exist and derived from consensus when data are lacking. The subcommittee’s recommendations are supported by a technical report containing a world literature search and analysis, and updated literature review. The technical report is available from the Publications Department of the American Academy of Pediatrics (AAP).

RECOMMENDATIONS

The following recommendations were developed by the AAP to aid in the evaluation and treatment of the healthy term infant with hyperbilirubinemia. Important in the development of these guidelines is the general belief that therapeutic interventions for hyperbilirubinemia in the healthy term infant may carry significant risk relative to the uncertain risk of hyperbilirubinemia in this population. In these guidelines, the AAP has attempted to describe a range of acceptable practices, recognizing that adequate data are not available from the scientific literature to provide more precise recommendations.

Evaluation

1. Maternal prenatal testing should include ABO and Rh(D) typing and a serum screen for unusual isoimmune antibodies.

2. A direct Coombs’ test, a blood type, and an Rh(D) type on the infant’s (cord) blood are recommended when the mother has not had prenatal blood grouping or is Rh-negative.

3. Institutions are encouraged to save cord blood for future testing, particularly when the mother’s blood type is group O. Appropriate testing may then be performed as needed.

4. When family history, ethnic or geographic origin, or the timing of the appearance of jaundice suggests the possibility of glucose-6-phosphate dehydrogenase deficiency or some other cause of hemolytic disease, appropriate laboratory assessment of the infant should be performed.

5. A TSB level needs to be determined in infants noted to be jaundiced in the first 24 hours of life.

6. 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 clinical assessment of jaundice must be done in a well-lighted room. Dermal icterus is seen first in the face and progresses caudally to the trunk and extremities. As the TSB level rises, the extent of cephalocaudad progression may be helpful in quantifying the degree of jaundice; use of an icterometer or transcutaneous jaundice meter may also be helpful.

7. Evaluation of newborn infants who develop abnormal signs such as feeding difficulty, behavior changes, apnea, or temperature instability is recommended—regardless of whether jaundice has been detected—to rule out underlying illness (Table 1).

8. Follow-up should be provided to all neonates discharged less than 48 hours after birth by a health care professional in an office, clinic, or at home within 2 to 3 days of discharge.

9. Approximately one third of healthy breast-fed infants have persistent jaundice after 2 weeks of age. A report of dark urine or light stools should prompt a measurement of direct serum bilirubin. If the history (particularly the appearance of the urine and stool) and physical examination results are normal, continued observation is appropriate. If jaundice persists beyond 3 weeks, a urine sample should be tested for bilirubin, and a measurement of total and direct serum bilirubin obtained.

Treatment

Decisions about therapeutic intervention are tempered by clinical judgment based on the infant’s history, course, and physical findings and are balanced by comparing the potential benefits with the risks. As appropriate, physicians are encouraged to discuss management options and their recommendations with parents or other guardians. The guidelines in Table 2 are recommended for infants initially seen with elevated TSB levels, as well as for infants who have been followed up for clinical jaundice. Similar guidelines have been used in Great Britain. Direct bilirubin measurements vary substantially as a function of individual laboratories and their instrumentation. For the purposes of the otherwise

Table 1. Factors To Be Considered When Assessing a Jaundiced Infant

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Onset of jaundice before 48 h</td>
<td>A rise in serum bilirubin levels of more than 0.5 mg/dL/h is an important sign.</td>
</tr>
<tr>
<td>Pallor, hepatosplenomegaly</td>
<td>Rapid increase in the TSB level after 24-48 h (consider G6PD deficiency)</td>
</tr>
<tr>
<td>Persistent jaundice for &gt;3 wk</td>
<td>Failure of phototherapy to lower the TSB level</td>
</tr>
<tr>
<td>Sepsis or galactosemia in which jaundice may be one manifestation of the disease</td>
<td>Clinical signs suggesting the possibility of other diseases such as sepsis or galactosemia in which jaundice may be one manifestation of the disease</td>
</tr>
</tbody>
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<td>Fever</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>Poor feeding</td>
</tr>
<tr>
<td>Excessive weight loss</td>
<td>Hepatosplenomegaly</td>
</tr>
<tr>
<td>Apnea</td>
<td>Excessive weight loss</td>
</tr>
<tr>
<td>Temperature instability</td>
<td>Apnea</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Temperature instability</td>
</tr>
<tr>
<td>Signs of cholestasis suggesting the need to rule out biliary atresia or other causes of cholestasis</td>
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</tr>
<tr>
<td>Dark urine or urine positive for bilirubin</td>
<td>Dark urine or urine positive for bilirubin</td>
</tr>
<tr>
<td>Light-colored stools</td>
<td>Light-colored stools</td>
</tr>
<tr>
<td>Persistent jaundice for &gt;3 wk</td>
<td>Persistent jaundice for &gt;3 wk</td>
</tr>
</tbody>
</table>

* TSB indicates total serum bilirubin; G6PD, glucose-6-phosphate dehydrogenase.
Healthy appearing jaundiced newborn, it is recommended that the direct bilirubin measurement not be subtracted from the TSB level and that the TSB level be relied on as the relevant criterion.

Determination of the rate of rise of TSB and the infant’s age may help determine how often to monitor bilirubin levels and whether to begin phototherapy. Continued observation may be an appropriate alternative to repeated TSB testing and phototherapy.

There is continuing uncertainty about what specific TSB levels warrant exchange transfusion. Intensive phototherapy (Appendix) is recommended in infants initially seen with a TSB concentration in the exchange transfusion range (Table 2) while preparations are being made for exchange transfusion. Intensive phototherapy should produce a decline in the TSB level of 1 to 2 mg/dL within 4 to 6 hours and the TSB level should continue to fall and remain below the threshold level for exchange transfusion. If this does not occur, it is considered a failure of phototherapy.

These guidelines apply to infants without signs of illness or apparent hemolytic disease. It may be difficult to rule out ABO hemolytic disease as well as rarer causes of hemolysis.

The evaluation and treatment of hyperbilirubinemia in the healthy term infant is presented in the clinical algorithm.

Management of Hyperbilirubinemia in the Healthy Term Newborn by Age (in Hours)

1. Infants ≤24 hours old are excluded from Table 2, because jaundice occurring before age 24 hours is generally considered “pathologic” and requires further evaluation. Although some healthy infants appear slightly jaundiced by 24 hours, the presence of jaundice before 24 hours requires (at least) a serum bilirubin measurement and, if indicated, further evaluation for possible hemolytic disease or other diagnoses. Phototherapy and/or exchange transfusion may be indicated for rapidly rising TSB levels in the first 24 hours of life.

2. For the treatment of the 25- to 48-hour-old infant, phototherapy may be considered (see Table 2 for definition) when the TSB level is ≥12 mg/dL (170 μmol/L). Phototherapy should be implemented when the TSB level is ≥15 mg/dL (260 μmol/L). If intensive phototherapy fails to lower a TSB level of ≥20 mg/dL (340 μmol/L), exchange transfusion is recommended. If the TSB level is ≥25 mg/dL (430 μmol/L) when the infant is first seen, intensive phototherapy is recommended while preparations are made for an exchange transfusion. If intensive phototherapy fails to lower the TSB level, exchange transfusion is recommended. The higher TSB levels in a 25- to 48-hour-old infant suggest that the infant may not be healthy and indicate the need for investigation into the cause of hyperbilirubinemia, such as hemolytic disease.

3. Phototherapy may be considered for the 49- to 72-hour-old jaundiced infant when the TSB level is ≥15 mg/dL (260 μmol/L). Phototherapy is recommended when the TSB level reaches 18 mg/dL (310 μmol/L). If intensive phototherapy fails to lower the TSB level when it reaches or is predicted to reach 25 mg/dL (430 μmol/L), an exchange transfusion is recommended. If the TSB level is ≥30 mg/dL (510 μmol/L) when the infant is first seen, intensive phototherapy is recommended while preparations are made for exchange transfusion. If intensive phototherapy fails to lower the TSB level, an exchange transfusion is recommended.

4. For the infant >72 hours old, phototherapy may be considered if the TSB level reaches 17 mg/dL (290 μmol/L). Phototherapy needs to be implemented at a TSB level of ≥20 mg/dL (340 μmol/L). If intensive phototherapy fails to lower a TSB level of ≥25 mg/dL (430 μmol/L), exchange transfusion is recommended. If the TSB level is ≥30 mg/dL (510 μmol/L) when the infant is first seen, intensive phototherapy is recommended while preparations are made for an exchange transfusion. If intensive phototherapy fails to lower the TSB level, an exchange transfusion is recommended.

In all of the above situations, intensive phototherapy (Appendix) should be used if the TSB level does not decline under conventional phototherapy. Intensive phototherapy should produce a steady decline in the concentration of TSB. If this does not occur, the presence of hemolytic disease or some other pathologic process is suggested and warrants further investigation.

<table>
<thead>
<tr>
<th>Age, hours</th>
<th>Consider Phototherapy</th>
<th>Phototherapy</th>
<th>Exchange Transfusion if Intensive</th>
<th>Exchange Transfusion Phototherapy Phototherapy Fails</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24</td>
<td></td>
<td></td>
<td></td>
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<td>25-48</td>
<td>≥12 (170)</td>
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<td>49-72</td>
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<td>≥25 (430)</td>
<td>≥30 (510)</td>
</tr>
<tr>
<td>&gt;72</td>
<td>≥17 (290)</td>
<td>≥20 (340)</td>
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<td>≥30 (510)</td>
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* TSB indicates total serum bilirubin.
† Phototherapy at these TSB levels is a clinical option, meaning that the intervention is available and may be used on the basis of individual clinical judgment. For a more detailed description of phototherapy, see the Appendix.
‡ Intensive phototherapy (Appendix) should produce a decline of TSB of 1 to 2 mg/dL within 4 to 6 hours and the TSB level should continue to fall and remain below the threshold level for exchange transfusion. If this does not occur, it is considered a failure of phototherapy.
§ Term infants who are clinically jaundiced at ≤24 hours old are not considered healthy and require further evaluation (see text).
Table 3. Treatment Options for Jaundiced Breast-fed Infants

<table>
<thead>
<tr>
<th>Option</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observe</td>
<td>Continue breast-feeding; administer phototherapy</td>
</tr>
<tr>
<td>Continue breast-feeding with formula with or without phototherapy</td>
<td></td>
</tr>
<tr>
<td>Interrupt breast-feeding; substitute formula</td>
<td></td>
</tr>
<tr>
<td>Interrupt breast-feeding; substitute formula; administer phototherapy</td>
<td></td>
</tr>
</tbody>
</table>

Treatment of Jaundice Associated With Breast-feeding in the Healthy Term Newborn

The AAP discourages the interruption of breast-feeding in healthy term newborns and encourages continued and frequent breast-feeding (at least eight to ten times every 24 hours). Supplementing nursing with water or dextrose water does not lower the frequent breast-feeding (at least eight continued and interruption of breast-feeding and substitution with formula, either of which can be accompanied by phototherapy.

DOCUMENTATION

This practice parameter is designed to assist the pediatrician and other health care providers by providing a framework for the management of hyperbilirubinemia in the healthy term newborn. It is not intended to replace the physician’s clinical judgment or to establish a single protocol applicable to all such newborns with hyperbilirubinemia. It is understood that some clinical problems may not be adequately addressed by the practice parameter, which cannot be considered to represent an exclusive standard of care. Physicians are urged to document their management strategies, including any significant deviation from these or other guidelines and the rationale for the course of action taken.

Finally, all physicians and other health care providers caring for jaundiced newborns are encouraged to continue appraising and incorporating into their practices new scientific and technical advances as clinical evidence of their effectiveness becomes established.

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REFERENCES

25. Ebbesen F. The relationship between the cephalopedal progress of clinical icterus and the serum bilirubin concentration in newborn in-
The third way to improve phototherapy efficiency is to increase the surface area of the infant exposed to the lights. This can be done by using a standard phototherapy system that delivers enough output to be effective for standard phototherapy use. When bilirubin levels approach the range at which exchange transfusion might be indicated, maximal efficacy should be sought. This can be achieved in the following manner.

Commonly used phototherapy units contain a number of 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. Most recently, fiberoptic systems have been developed that deliver light from a high-intensity lamp to a fiberoptic blanket. Most of these devices deliver enough output in the blue-green region of the visible spectrum to be effective for standard phototherapy use. When bilirubin levels approach the range at which exchange transfusion might be indicated, maximal efficacy should be sought. This can be achieved in the following manner.

When Should Phototherapy Be Stopped?

A recent study found that, in infants who do not have hemolytic disease, the average bilirubin rebound after phototherapy is less than 1 mg/dL (17 μmol/L). Phototherapy may be discontinued when the serum bilirubin level falls below 14 to 15 mg/dL. Discharge from the hospital need not be delayed in order to observe the infant for rebound and, in most cases, no further measurement of bilirubin is necessary. If phototherapy is initiated early and discontinued before the infant is 3 to 4 days old, additional outpatient follow-up may be necessary.

APPENDIX REFERENCES

Algorithm
Management of Hyperbilirubinemia in the Healthy Term Infant

1. Pediatric clinician evaluates term newborn with jaundice

2. Does the infant have signs of underlying serious illness (lethargy, apnea, tachypnea, temperature instability, behavior changes, hepatosplenomegaly, persistent vomiting, or persistent feeding difficulty)?

3. Exit this algorithm to individualized clinical evaluation, including assessment of jaundice and underlying disease

4. Is the infant <37 weeks, gestational age?

5. Exit this algorithm to individualized clinical evaluation, including assessment of jaundice in light of prematurity

6. Is the mother's ABO and Rh blood typing and isoimmune antibody screen status known?

7. Is the mother's blood Rh positive?

8. Does the mother's blood have any immune antibodies?

9. Consider holding the infant's cord blood in a blood bank in case future testing is necessary

10. Perform blood typing (ABO and Rh) and direct Coombs' testing on the infant's cord (preferably) or venous blood

11. Is the infant's blood direct Coombs' positive?

12. Exit this algorithm to individualized clinical evaluation, including assessment of jaundice and isoimmune hemolytic disease

13. Go to Box 13
Perform appropriate laboratory assessment of infant including (but not limited to consideration of):

- Complete blood count, differential, smear, reticulocyte count;
- G6PD screen;
- Hemoglobin electrophoresis.

Does the evaluation suggest hemolytic disease?

Is the infant jaundiced and ≤24 hours of age?

Is jaundice "clinically significant" by medical judgment?

Healthy term infant with jaundice not clinically significant by medical judgment

Follow infant in routine clinical supervision

Go to Box 22

Exit this algorithm to individualized clinical evaluation, including assessment of jaundice and non-immune hemolytic disease.
Algorithm
Management of Hyperbilirubinemia in the Healthy Term Infant
Part 3

TABLE 2. Management of Hyperbilirubinemia in the Healthy Term Newborn

<table>
<thead>
<tr>
<th>TSB Level (mg/dL) (μmol/L)</th>
<th>Consider phototherapy†</th>
<th>Phototherapy</th>
<th>Exchange Transfusion if Intensive Phototherapy Fails‡</th>
<th>Exchange Transfusion and Intensive Phototherapy</th>
</tr>
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<tbody>
<tr>
<td>TSB LEVEL (mg/dL)‡</td>
<td></td>
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<td></td>
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