Neonatal Jaundice and Kernicterus

ABBREVIATIONS. AAP, American Academy of Pediatrics; G-6-PD, glucose-6-phosphate dehydrogenase.

OBJECTIVE

The American Academy of Pediatrics (AAP) Subcommittee on Hyperbilirubinemia is currently revising the practice parameter (guidelines) on neonatal hyperbilirubinemia published in October 1994. Although this revision is in progress, the Subcommittee wishes to bring the issue of kernicterus to the attention of the pediatric community and provide additional information pending a more formal assessment of the literature and an analysis of the risks and benefits of new approaches to the jaundiced infant. The Joint Commission on Accreditation of Healthcare Organizations has already issued an alert on this subject.

BACKGROUND

Kernicterus, or bilirubin encephalopathy, is a condition caused by bilirubin toxicity to the basal ganglia and various brainstem nuclei. In the acute phase, severely jaundiced infants become lethargic, hypotonic and suck poorly. If the hyperbilirubinemia is not treated, the infant becomes hypotonic and may develop a fever and a high-pitched cry. The hypotonia is manifested by backward arching of the neck (retrocollis) and trunk (opisthotonus). Surviving infants usually develop a severe form of atelectasis cerebral palsy, hearing loss, dental dysplasia, paralysis of upward gaze and, less often, intellectual and other handicaps.

Kernicterus is a condition that is unfamiliar to most pediatricians practicing today. In the 1940s and 1950s, kernicterus was a common complication of hyperbilirubinemia associated with Rh erythroblastosis fetalis and, occasionally, ABO hemolytic disease. With the introduction of exchange transfusion, kernicterus became much less common. The use of Rh immunoglobulin all but eliminated erythroblastosis fetalis and phototherapy drastically reduced the need for exchange transfusion. In the last several years, however, there have been reports of kernicterus associated with extremely high serum bilirubin levels. Most of these infants did not have obvious hemolytic disease or another recognized cause of neonatal jaundice. Many appeared to be otherwise healthy, breastfed newborns although frequently they were not receiving adequate nutrition and hydration. A significant proportion were <38 weeks gestation (near-term infants).

From the American Academy of Pediatrics, Subcommittee on Neonatal Hyperbilirubinemia.

Revised for publication Jun 5, 2001; accepted Jun 5, 2001.

Reprint requests to (M.M.) Department of Pediatrics, William Beaumont Hospital, 3601 W Thirteen Mile Rd, Royal Oak, MI 48073-5706. E-mail: mmsveal@hb.wmbeaumont.edu.

PEDIATRICS (ISSN 0031-4005). Copyright © 2001 by the American Academy of Pediatrics.

TABLE 1. Common Clinical Risk Factors for Severe Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice in the first 24 h</td>
<td>Jaundice before discharge</td>
</tr>
<tr>
<td>Visible jaundice before discharge</td>
<td>Previous jaundiced sibling</td>
</tr>
<tr>
<td>Gestational age ≤35 wk</td>
<td>Exclusively breastfed</td>
</tr>
<tr>
<td>East Asian race</td>
<td>Male sex</td>
</tr>
<tr>
<td>Bruising, cephalhematoma</td>
<td>Maternal age ≥25 y</td>
</tr>
</tbody>
</table>

* The more risk factors present, the greater risk of severe hyperbilirubinemia.

RISK FACTORS FOR SEVERE HYPERBILIRUBINEMIA

A comprehensive list of risk factors for severe hyperbilirubinemia can be found in a recent review. The common clinical risk factors identified in epidemiologic studies are listed in Table 1 in approximate order of importance. Additional risk factors can be identified by laboratory or bedside measurement. They include Rh and ABO incompatibility, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and an elevated hour-specific serum or transcutaneous bilirubin level. Rh disease is now rare and the blood type and Rh sensitization status of the mother is usually known at the time of delivery, but many hospitals are no longer performing routine blood typing in infants of group O mothers so that the ABO status of the infant is often unknown. G-6-PD deficiency occurs in 1% to 13% of blacks and is more common among immigrants from the Mediterranean countries and Southeast Asia. It has been associated with cases of kernicterus in the United States. However, screening for G-6-PD deficiency is not performed routinely, in most hospitals the turnaround time for laboratory testing is 2 to 3 days, and appropriate evaluation for infants with abnormal levels is not well-defined.

ROOT CAUSES OF IDENTIFIED CASES OF KERNICTERUS

Individual members of the committee have undertaken detailed review of published and unpublished cases of kernicterus; these reviews have used the framework of root cause analysis to identify likely fundamental underlying contributors to these cases. This analysis has identified the following potentially correctable causes for kernicterus:

1. Early discharge (<48 hours) with no early follow-up (within 48 hours of discharge). This problem is particularly important in near-term infants (35–37 weeks’ gestation).
2. Failure to check the bilirubin level in an infant noted to be jaundiced in the first 24 hours.
3. Failure to recognize the presence of risk factors for hyperbilirubinemia.
4. Underestimating the severity of jaundice by clinical (i.e., visual) assessment.
5. Lack of concern regarding the presence of jaundice.
6. Delay in measuring serum bilirubin level despite marked jaundice or in initiating phototherapy in the presence of elevated bilirubin levels.

COMMENTARIES

765
7. Failure to respond to parental concern regarding jaundice, poor feeding, or lethargy.

CHANGES IN NEWBORN CARE

Over the past decade, the most striking change in newborn practice has been the shortening of hospital stays. Shortened length of stay can affect the risk of severe jaundice in 2 ways. First, discharge at 48 hours or less means that in breastfeeding mothers the milk has not yet come in. These infants are therefore at risk for receiving inadequate fluid and nutrition, particularly if they are <38 weeks' gestation. Inadequate intake and hepatic immaturity together also place these infants at much greater risk for developing hyperbilirubinemia. In addition, short hospital stays mean that in almost all infants the peak bilirubin level will not occur until after discharge. Taken together, these changes mean that the management of neonatal jaundice is primarily an outpatient problem and that particular attention must be paid to breastfeeding infants and to infants who are <38 weeks' gestation.

CURRENT AAP GUIDELINES

The current AAP practice guidelines outline an approach to the management of the jaundiced newborn. All pediatricians should be familiar with the existing guidelines of the AAP, also available on the AAP's Web site at www.aap.org/policy/hyperb.htm. Although these guidelines cannot be applied to all cases, clinicians should document their management strategies including any significant deviation from the guidelines and the rationale for the course of action taken.

The current guidelines address only healthy infants ≥37 weeks' gestation who do not have hemolytic disease. Preterm and sick infants and infants with hemolysis require much closer follow-up and more aggressive therapy. In otherwise healthy full-term and near-term newborn infants, kernicterus occurs only in the presence of severe hyperbilirubinemia. Thus, appropriate surveillance of newborns should identify those in need of phototherapy and, if necessary, exchange transfusion. If the current AAP guidelines for surveillance and treatment are followed, most cases of kernicterus should be prevented. This surveillance requires assessment in the nursery, early follow-up, and outpatient monitoring.

RECOMMENDATIONS

Current AAP Guidelines

Recommendations from the current guidelines that deserve emphasis include the following:

1. Any infant who is jaundiced before 24 hours requires a measurement of the serum bilirubin level and, if it is elevated, the infant should be evaluated for possible hemolytic disease.

2. Follow-up should be provided within 2 to 3 days of discharge to all neonates discharged at <48 hours after birth. Early follow-up is particularly important for infants <38 weeks' gestation. The timing of follow-up depends on the age of discharge and the presence of risk factors. In some cases, follow-up within 24 hours is necessary.

Risk Assessment

If early follow-up as currently recommended is uncertain or impossible, a decision regarding the timing of discharge or other follow-up should be based on risk assessment. There are now well-documented clinical and laboratory strategies for identifying newborns at risk for developing severe hyperbilirubinemia. They include the use of common clinical risk factors (Table 1) and the calculation of a risk index for predicting hyperbilirubinemia. An alternative strategy involves measurement of a serum or transcutaneous bilirubin level before discharge, which places an infant in a low, intermediate, or high-risk category for the subsequent development of hyperbilirubinemia. The timing of follow-up and the need for additional bilirubin levels will depend on the infant's age and the assessed risk.

Breastfeeding Support

Active support and advice to breastfeeding mothers should be provided both in the hospital and after discharge to ensure adequacy of intake for breastfed newborns.

Information for Parents

Pediatricians should convey a balanced approach when communicating with parents about jaundice. Most infants will become jaundiced and in the overwhelming majority of these infants, jaundice is entirely benign. A small fraction of these infants is at risk for developing extreme hyperbilirubinemia and kernicterus. As with other conditions in pediatrics (such as fever in the young infant), monitoring and surveillance of many infants are necessary to prevent a few infants from coming to harm. As with febrile infants, risk assessment strategies are needed to reliably identify almost all infants who are at serious risk of harm, while minimizing the burden and potential labeling of infants who are well.

AREAS REQUIRING ADDITIONAL RESEARCH

Incidence of Kernicterus and Outcomes

Neonatal jaundice is very common but kernicterus is rare. Thus it is regrettable that no data exist on the incidence and prevalence of kernicterus in the US population. Such data are necessary to quantify the risks, benefits, and costs of various strategies aimed at preventing kernicterus. Additional research is also needed on the relationship of known risk factors to the development of kernicterus as well as on the role of other developmental sequelae that have been associated with hyperbilirubinemia. These risk factors include the serum bilirubin level, duration of hyperbilirubinemia, the binding of bilirubin to albumin, gestational age, hemolysis, sepsis, acidosis, and other factors affecting the entry of bilirubin into the brain as well as the susceptibility of the neurons themselves to bilirubin.
toxicity. Evaluation of the effect of treatment on these risk factors and outcomes is also needed.

**Predicting Hyperbilirubinemia**

Measurement of a serum or transcutaneous bilirubin level on every infant before discharge has been recommended as a standard screening procedure to identify the level of risk for severe hyperbilirubinemia and the need for follow-up bilirubin levels. Measurement of end-tidal carbon monoxide levels, an index of bilirubin production, can provide information about the presence or absence of hemolysis. Additional research is needed to quantify the risks, benefits, and costs of these and other strategies to prevent kernicterus. Until such information is available, the 1994 practice guidelines represent a good approach for most infants.

**CONCLUSION**

Recent reports of kernicterus indicate that this condition, although rare, is still occurring, and most cases are preventable. This commentary emphasizes the importance of universal and close follow-up, responsiveness to parental concerns, and awareness of the real risk of extreme hyperbilirubinemia and kernicterus. In addition, particular attention should be paid to breastfeeding infants and to near-term infants who are at significant risk for severe hyperbilirubinemia.

**AAP Subcommittee on Neonatal Hyperbilirubinemia**

M. Jeffrey Maisels, MB, BCH, Chairperson
Richard D. Baltz, MD
Vino K. Bhutani, MD
Thomas B. Newman, MD, MPH
Warren Rosenfeld, MD
David K. Stevenson, MD
Howard B. Weinblatt, MD

**Consultant**

Charles J. Homer, MD, MPH
Chairperson, AAP

**Committee on Quality Improvement**

**STAFF**

Carla Herreras

**REFERENCES**
