MEMORANDUM

DATE: May 14, 2003

TO: Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee

FROM: Division of Pediatric Drug Development

SUBJECT: Briefing Document for June 11 Open Session of the Pediatric Advisory Committee on Hyperbilirubinemia and Drug Development in the Term and Near – Term Newborn Infant

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Introduction

Jaundice occurs in about 60% of all newborns. The management of hyperbilirubinemia in the healthy term and near-term newborn has long been controversial. Central to the controversy is the need to find a balance between the risk of the rare but devastating occurrence of kernicterus and the potential adverse consequences of therapeutic interventions to prevent it. Eleven years ago, Newman and Maisels highlighted this controversy proposing that jaundiced infants without an underlying illness were at low-risk for bilirubin toxicity and that "the risks and costs of identifying and treating high bilirubin levels may exceed the benefits"(1). In 1994, the American Academy of Pediatrics (AAP) issued its first practice parameter on the management of hyperbilirubinemia in healthy newborns. It was defined as otherwise healthy, non-isoimmunized newborns of at least 37 weeks of gestation who did not exhibit jaundice in the first 24 hours of life (2).

Subsequent reports have suggested an increase in the frequency of kernicterus in this population, thus raising concerns that the treatment pendulum has swung too far with serious hyperbilirubinemia in healthy newborns going untreated and significant neurotoxicity in the form of kernicterus the result (3, 4). In 2001, the AAP Subcommittee on Neonatal Hyperbilirubinemia issued a commentary that identified the common clinical risk factors for severe hyperbilirubinemia and the root causes for new cases of kernicterus. It emphasized key recommendations for management of jaundice from the 1994 practice parameter and identified areas in need of further research (5). In addition, the commentary mentioned that the AAP treatment recommendations were undergoing revision.

In preparation for these revised guidelines, the AAP requested the U.S. Agency for Healthcare Research and Quality (AHRQ) to commission an evidence review of several key questions about neonatal hyperbilirubinemia. This report (herein referred to as the AHRQ Report) was issued in January 2003. The AHRQ Report examined the relationship between severe hyperbilirubinemia and neurodevelopment (adjusting for the role of effect modifiers), the efficacy of phototherapy, the reliability of various strategies

for predicting hyperbilirubinemia, and the accuracy of transcutaneous bilirubin measurements (6). Various aspects of the diagnosis, management, and consequences of hyperbilirubinemia in the term and near-term newborn are summarized below.

Descriptors of Jaundice and Hyperbilirubinemia

There are no standardized definitions for neonatal hyperbilirubinemia and there is limited gestational age adjusted data on the distribution of bilirubin in the newborn period. Criteria for describing hyperbilirubinemia refer to absolute levels of bilirubin measured at any age in the neonatal period, and specific bilirubin levels linked to infant age in hours. "Physiologic jaundice" is a commonly used term implying that the bilirubin level is within the normal range for age, is not due to a pathologic risk factor such as hemolysis, and has traditionally not required medical intervention. The 1994 AAP Guidelines define jaundice present in the first 24 hours of life to be "pathologic" (2).

Predicting Risk for Severe Hyperbilirubinemia and Kernicterus

Several authors define "severe hyperbilirubinemia" as levels of bilirubin that are greater than the 95th percentile for chronological age. Clinical risk factors for that condition in term and near term infants include: jaundice in the first 24 hours of life; visible jaundice before hospital discharge; previous jaundiced sibling; gestational age of 35-38 weeks at birth; exclusive breastfeeding; East Asian race; bruising and/or cephalohematoma; maternal age of 25 years or more; and male gender (5)(7).

Underlying etiologies for severe hyperbilirubinemia include active hemolysis and inborn errors of metabolism. A recent case review by the AAP Subcommittee on Neonatal Hyperbilirubinemia identified the following root causes for kernicterus (5):

- Hospital discharge before 48 hours of life, with no early follow up (especially for infants born at 35 to 37 weeks gestational age);
- Failure to check the bilirubin level in an infant noted to be jaundiced in the first 24 hours;
- Failure to recognize the presence of risk factors for hyperbilirubinemia;
- Underestimating the severity of jaundice by clinical (visual) assessment;
- Lack of concern regarding the presence of jaundice;
- Delay in measuring serum bilirubin despite marked jaundice; and
- Failure to respond to parental concern regarding jaundice, poor feeding, or lethargy.

A recent study evaluated whether the level of total serum bilirubin (TSB) collected prior to hospital discharge could be used to model subsequent risk of clinically significant hyperbilirubinemia. The model assigned three levels of risk to postnatal age in hours specific TSB (8).

Screening and Diagnosis

The first screening method for jaundice is visual inspection of the infant's skin. Jaundice is usually visible when the total serum bilirubin level reaches 6 mg per deciliter (mg/dL) serum or more. Limitations of visual inspection include inter-observer variability, dark skin pigmentation in the infant that obscures the yellow hue, and infrequent physical examinations. In term and near term infants, peak bilirubin levels commonly occur in the second half of the first week of life, usually after hospital discharge. This peak may occur later in breast-fed infants and pre-term infants.

Early hospital discharge reduces the opportunity for frequent physical assessments. Discharge before 48 hours of age is now common among newborns delivered via an uncomplicated vaginal delivery and these infants may have only one physical examination before going home. The AAP and the American College of Obstetrics and Gynecology (ACOG) now recommend one physical examination within 24 hours of birth and a second within 24 hours prior to discharge – both of which should include an observation for jaundice (9). In addition, if an infant is discharged at less than 48 hours of age, the AAP and ACOG recommend a similar evaluation within 48 hours of discharge. In cases where there is no second inpatient exam and/or timely outpatient follow-up, progressive hyperbilirubinemia may escape recognition.

Quantification of total serum bilirubin (TSB) is the current standard for diagnosing hyperbilirubinemia. Methods for assessing TSB include the following: bilirubin oxidase; 2.5.dichlorophenyldiazonium tretrafluoroborate diazo; direct spectrophotometry; high performance liquid chromatography (HPLC); and reflectance spectrophotometry (10). Methods differ in their ability to fractionate bilirubin, effects of the pH of the sample on the test result, and utility of the test based on the postnatal age of the infant. All tests are subject to impact of serum sample collection, due to the breakdown of bilirubin when it is exposed to light. Additionally, availability of these tests and turn around time for receiving results vary across the United States. Furthermore, intra- and even greater inter-laboratory variability exists (11).

Transcutaneous bilirubinometry (TcB) measurement has emerged as a non-invasive screening method that may reduce the number of blood collections needed to monitor change in TSB. The FDA has cleared the following devices to measure TcB: Abbott Nbil; Air Shields JM-102 Jaundice Meter; Air Shields JM-103 Jaundice Meter; Chromatics Colormate III; Chromatics Colormate TLC Bilitest; Ingram Icterometer; Instrumentation Laboratory Synthesis; Minolta Hill-Rom Air shields Bilirubinometer; Respironics Bilichek Non-Invasive Bilirubin Analyzer; and the SpectRx Bilicheck TM. The AHRQ Report found that the correlation coefficients for TcB compared to TSB in these devices ranged from 0.84 to 0.96. Factors such as the skin assessment site, the actual level of TSB, the degree of skin pigmentation, and hemoglobin level may influence the strength of correlation between TcB and TSB (6).

Utility of the end-tidal carbon monoxide measurement (Natus CO-STAT analyzer) in combination with a single TSB has also been investigated in order to potentially improve the predictive value of TSB measured in the first days of life (12).

Kernicterus

Kernicterus, or bilirubin encephalopathy, is a rare though serious complication of severe hyperbilirubinemia, occurring in fewer than 1 in 250,000 live births (19). In the acute phase, infants with kernicterus are lethargic with low tone and a poor suck. Infants with kernicterus may go on to develop clinical findings that include hypertonia, high-pitched cry, choreo-athetoid cerebral palsy, dental dysplasia, paralysis of upward gaze, and cognitive and other disabilities. The mortality rate for kernicterus is at least 10 percent, and long term morbidity at least 70 percent. The concentration and the exposure duration of bilirubin in the brain are determinants of bilirubin neurotoxicity (13). However, correlation between serum bilirubin concentration and encephalopathy is weak in infants without active hemolysis (13). The AHRQ Report found that the preponderance of kernicterus cases occurred in infants with serum bilirubin levels above 20 mg/dl. Whether that association is causal is not clear. This report further concludes that a single TSB was not sufficient to predict long-term behavioral or neurodevelopmental outcomes for hyperbilirubinemia.

As mentioned earlier, recent reports suggest that the frequency of kernicterus has increased in the last decade. However, no long-term population-based surveillance systems currently exist in the United States to answer that question. Efforts to establish kernicterus surveillance are ongoing through the Centers for Disease Control and Prevention National Center for Birth Defects and Developmental Disabilities.

Management

The 1994 AAP Management guidelines provide recommendations for intervention based on an infant's age in hours and total serum bilirubin (see Table below).

Table. Management of Hyperbilirubinemia in the Healthy Term Newborn (2)

Age in hours	*Total Serum Bilirubin Level, in mg/dL*			
	Consider phototherapy	Phototherapy	Exchange transfusion if intensive phototherapy fails	Exchange Transfusion and intensive phototherapy
≤ 24				
25-48	≥12	≥ 15	≥ 20	≥25
49-72	≥ 15	≥ 18	≥25	≥ 30
≥ 72	≥ 17	≥20	≥ 25	≥ 30

Phototherapy has been the standard of care for treatment of neonatal hyperbilirubinemia for approximately 40 years. Phototherapy acts by converting bilirubin to compounds that can avoid the hepatic conjugation system and be eliminated in the urine or the bile without further metabolism. Phototherapy is usually administered in the hospital setting during the post-partum stay, but also upon hospital re-admission. Phototherapy may also be used in the home setting.

Potential adverse effects of phototherapy – which include, but are not limited to, skin rash overheating, and dehydration – are usually mild if appropriate precautions are taken to assure proper thermal control, hydration, and covering of the eyes. The constraints imposed by the administration of phototherapy may reduce the opportunity for maternal-infant interaction, especially if the infant remains in the hospital after the mother is discharged. When administered in the home, phototherapy can be disruptive to the family/s adjustment to its new member. There is no evidence to suggest that phototherapy has any adverse long-term effect (6)(9).

In a study cohort of almost 70,000 babies during 1992-1994, rehospitalization for jaundice was associated with race/ethnicity (Caucasian and Asian more likely than African-American and Hispanic); primaparity; preterm birth; breast-feeding; and suspicion of jaundice during the initial hospitalization (14). The median pre-admission TSB was 20.6mg/dl, and almost 90% of the re-admitted babies received phototherapy.

The AHRQ Report evaluated the ability of phototherapy to prevent the serum bilirubin from exceeding 20mg/dl and the effect of this treatment on neurodevelopmental outcome (6). The authors concluded that between six and 10 healthy newborns with bilirubin levels above 15 mg/dl needed to be treated with phototherapy, to prevent one occurrence

of a bilirubin level above 20mg/dl. Phototherapy combined with cessation of breastfeeding and substitution with formula was found to be the most efficient treatment protocol.

Use of exchange transfusion has decreased largely due to the prevention of Rh iso-immunization and use of phototherapy interventions in infants considered at high risk for developing kernicterus. Exchange transfusion is utilized when phototherapy fails, and has become an uncommon procedure in the U.S. Exchange transfusion to treat hyperbilirubinemia is now rare in the U.S.

Metalloporphyrin Heme Oxygenase Inhibitors

There are no approved drugs for the treatment or prevention of neonatal hyperbilirubinemia. Metalloporphyrin (Mps) heme oxygenase inhibitors have been studied in animals and humans for these indications and act by inhibiting the heme oxygenase enzyme, thereby limiting the conversion of heme to bilirubin. Tin mesoporphyrin has been studied in preterm infants, full term infants, and those with G-6-P-D deficiency (15)(16)(17). Treated infants required less phototherapy compared to controls. A transient erythematous rash was the most common adverse event reported in human newborns receiving tin mesoporphyrin. In addition, Mps are photosensitizers, suggesting a potentially harmful interaction with phototherapy.

In animal models, the half-life for tin mesoporphyrin was at least nine months, with long-term deposition of the drug in the reticulo-endothelial system. In vitro studies demonstrate inhibition by Mps of a variety of metabolic and enzymatic processes (18). The human safety data base for tin mesoporphyrin is limited. Limitations of the human safety data include the timing and duration of safety monitoring and the specific safety assessment parameters collected and evaluated. In addition, the safety monitoring to date has not addressed the potential long-term safety signals present in the animal toxicology literature. For example, it is unknown whether there is human health impact from long-term deposition of this drug in the reticulo-endothelial system.

Closing Thoughts

In summary, the management of hyperbilirubinemia in the term and near-term newborn remains controversial, with a continuing need to find an appropriate balance between the risk of the rare occurrence of kernicterus and the potential adverse events of therapeutic interventions to prevent it. The 1994 AAP guidelines strove for that balance, yet subsequent reports suggested an increase in the frequency of kernicterus – a rare and serious life-long disability. Adding to this complexity is the change in routine hospital discharge practices for healthy newborn infants, with short hospital stays of 24 to 48 hours becoming the norm. The consequences of earlier newborn discharge are less frequent screening for jaundice and the potential for a newborn infant with a rapidly rising bilirubin level to go unrecognized.

Following release of the 1994 AAP guidelines, a variety of research efforts have attempted to address remaining controversies about the description, screening, diagnosis, and treatment of hyperbilirubinemia in the term and near-term newborn. The prospect for widespread pharmacological treatment to prevent hyperbilirubinemia in this population is one new development that raises many research and ethical quandaries. These complex issues will be the substance of your discussion on June 11th, 2003.

Currently, this research paradigm recommends the prophylactic use of drugs to prevent hyperbilirubinemia and the need for phototherapy. This approach inevitably will lead to treatment of individual healthy newborns that in the past would receive no treatment at all for their transient jaundice. In that research context, what knowledge about safety, in both the short and long term, must be known about the drug before clinical trials proceed? What safety issues should be addressed during and after any clinical trial of a drug to prevent hyperbilirubinemia? Since the major adverse consequence of severe untreated hyperbilirubinemia remains kernicterus--a condition that is still so rare that its prevalence is difficult to estimate--how does one measure efficacy of any preventive drug therapy? Is prevention of phototherapy an appropriate endpoint? Are there subpopulations that might be at especially high risk for kernicterus and would be appropriate candidates for a preventive drug therapy trial? These and related issues will be the focus of our discussion on June 11th.

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