Leadership Project Final Paper:  
Infant Bilirubin Levels and Adverse Developmental Outcomes 
by Dennis O’dell, MD; Rachel Duchoslav, MS; Erin Clark, MD; and Rena Vanzo, MS

Introduction: Adverse outcomes as a consequence of hyperbilirubinemia in neonates have been a recognized problem for decades. The most important recognized potential adverse outcome from high bilirubin levels is kernicterus, an outcome leading to either death, or severe neurologic sequelae, including mental retardation, seizures, and hearing loss. Attempts to limit the risk of acquiring kernicterus have driven protocols for monitoring bilirubin levels in neonates, and interventions include either phototherapy or exchange transfusion when it appears that bilirubin levels will reach a critical level. Much controversy has occurred over the definition of a safe bilirubin level, and the impact that added risk factors have on the development of kernicterus. These risk factors include hemolytic disease, prematurity, infection, and certain drugs, among others.

It is unclear if there are additional sequelae of hyperbilirubinemia beyond kernicterus. Some studies have found evidence that the incidence of certain developmental disorders, such as autism, ADHD, and learning disabilities is higher in children who had elevated bilirubin levels as neonates. Other studies that have investigated this question have not found differences in these disorders based on bilirubin levels.

There are a number of problems with interpreting research findings related to these questions. Almost all outcome studies include results that are based on peak serum bilirubin levels. Bilirubin levels are typically only obtained on infants with either risk factors or the presence of clinical jaundice. There is very poor correlation between peak bilirubin levels and outcome, and current treatment recommendations are based on preventing the bilirubin level from reaching a level above which most, but not all, cases of kernicterus occur. This level is generally considered to be 20 to 25 mg/dL. However, many, if not most, children who have bilirubin that is elevated beyond this level have no evident adverse outcomes.

Peak serum bilirubin level is known to be associated with, but is a very poor predictor of, kernicterus. Bilirubin is bound to serum albumin, and it is thought that it is the free unbound bilirubin that crosses the blood-brain barrier that potentially damages certain areas in the brain, leading to kernicterus. Free bilirubin is not, however, generally measured, and the measurement of total bilirubin does not necessarily reflect the free bilirubin level. It appears that the above mentioned risk factors increase free bilirubin levels. It also appears that hemolysis is a major contributor to kernicterus. For many years it was felt that kernicterus did not occur without significant hemolysis, such as seen in Rh or ABO incompatibility. In recent years, cases of non-hemolytic hyperbilirubinemia leading to kernicterus have been documented.

Complicating the issue further is the fact that in neonates there are a number of mechanisms designed to keep bilirubin levels high. In most mammals the end byproduct of heme metabolism is biliverdin, which is non toxic and easily excreted. In humans there is an additional step, requiring significant energy expenditure; the conversion of biliverdin to bilirubin. Additionally, after bilirubin is conjugated in the liver, it is normally excreted in stool. But in neonates, deconjugation occurs in the intestinal tract, allowing unconjugated bilirubin to be reabsorbed, thus increasing serum bilirubin levels. It has therefore been hypothesized that bilirubin serves some as-yet-unknown protective purpose in the neonate. One suggestion is that bilirubin serves as an additional
antioxidant, protecting neonates from the damaging consequences of oxidative stress. So it is not an insignificant question to ask if we are potentially doing harm in some infants by keeping bilirubin levels artificially low by treating with phototherapy or exchange transfusion. Furthermore, it is not entirely clear whether phototherapy actually prevents kernicterus or that the photoisomer byproducts of phototherapy are harmless.

Because of new protocols and technology, we are in a position to add to our current understanding of sequelae of hyperbilirubinemia. First, in the Intermountain Healthcare system, a protocol has been in place to measure serum bilirubin levels on all neonates since 2002. All previous outcome studies were done with bilirubin results in only a subset of neonates with additional risk factors. Second, Intermountain, over the same time period, has instituted state of the art electronic medical records, allowing relatively easy access to all records in the system. Third, through the direction of researchers at Utah State University (USU), initially at Logan Regional Hospital and now throughout the country, newborn hearing screening is now performed on all newborns. Statewide registries on those with hearing problems are accessible. Fourth, in virtually all communities in Utah, a developmental treatment program exists (called the “0 to 3” program or Baby Watch) where most children with developmental problems are assessed and treated. Finally, at USU, we see many children with developmental disabilities in the Cache Valley community. Because of these new resources, we have a unique opportunity to re-explore the above issues, and potentially answer some outstanding questions related to the proper management and follow up of infants who have high bilirubin levels.

Research Questions: During the proposed study, the following research questions will be investigated:
1) Is the risk of acquiring autism, ADHD, or learning disabilities increased with a bilirubin level over 20 mg/dL compared to those with levels under 20 mg/dL?
2) Do other risk factors emerge as being significantly correlated to autism, ADHD, or learning disabilities that are related to high bilirubin levels in neonates?
   a. These risk factors would include causes of hemolysis that are not now routinely screened for, but yet are somewhat common, such as G6PD deficiency and spherocytosis.
   b. Other risk factors that need exploring are gestational age, maternal and fetal/neonatal medication exposure, breast feeding, neonatal weight loss and dehydration, Rh and ABO incompatibility, and perinatal and neonatal complications (such as abnormal fetal heart rate tracings, low APGAR scores, ICU admission, infection, etc).
3) Is there any evidence of a protective effect of bilirubin on certain conditions, such as retinopathy of prematurity (ROP), risk of bleeding and stroke, or other? Are low bilirubin levels also associated with increased risk of adverse developmental outcomes?
4) What is the association of bilirubin levels and hearing problems (with delayed or late onset) and/or auditory neuropathy?
5) Is phototherapy associated with decreased levels of problematic outcomes (including kernicterus)? Is phototherapy associated with adverse developmental outcomes?

Methods: A sample of children in the Cache Valley community with adverse developmental outcomes will be identified through records from the Biomedical Division of the Center for Persons with Disabilities (Utah State University) and the Up-to-3 Early Intervention Program in Logan, Utah. The medical records of these children will subsequently be reviewed through the electronic...
medical records IHC database. Records will be reviewed in this order to prevent removal of identifying/confidential information from IHC records. The control group will consist of children who have been identified through well child checkups to have no developmental disabilities, and to be age/gender/ethnicity matched to our case cohort; we will compare bilirubin levels and other risk factors between the case and control groups. The goal is to have from 50-100 cases and from 50-100 controls. All record reviews will be coded with no identifying information recorded. The analyses of data from these children will emphasize only variables present within the IHC database, thereby again precluding risk of identity disclosure. Records will be reviewed in order to capture specific risk factors according to a chart review form (attached on pages 6 and 7). Not all of the items in the record review form will be available, but if present will be included.

After data collection, statistical analysis will be used to evaluate any correlations between peak bilirubin level and developmental outcomes. We will also consider the duration of elevated bilirubin levels. Adverse developmental outcomes will include diagnoses of autism spectrum disorders, ADHD, speech and language problems, other learning disabilities, and hearing loss.

Based on results from this preliminary study, we anticipate identifying factors that will lead to future productive research into the complexity of management of hyperbilirubinemia in the neonate, and to the possibility of preventing some adverse developmental outcomes. Additionally we hope to identify risk factors that increase the likelihood of adverse developmental outcomes.

**Procedures:** This project was initiated in April 2009 at USU by a multidisciplinary team, including Dennis O’dell from Pediatrics and Rachel Duchoslav from Psychology. Development processes included initial brainstorming, literature review, hypothesis generation and drafting the research protocol. This proposal was submitted to the Intermountain Healthcare Institutional Review Board (IRB) in August 2009. At this time, additional multidisciplinary team members from the University of Utah, including Erin Clark from Obstetrics and Gynecology and Rena Vanzo from Genetics, joined the team as a part of the Utah Regional Leadership Education in Neurodevelopmental Disabilities (URLEND) leadership research project.

The research methodology was reviewed in detail and modified according to research questions deemed most pertinent to the URLEND project. The chart review form was also reviewed and modified according to our specific aims. Team members collaborated over email and phone consultation, combining and modifying proposal ideas, potential infant and pre-natal risk factors, and outcome measurements. Every member took an active role in hypothesis generation, creation of specific aims, and finalization of research methods.

During this process, a parent and family consultant, Tina Persels, was also added to the team. Tina has experience in the field of developmental disability in two capacities: she is the mother of a 10-year-old boy with autism and other disabilities, and also works for the non-profit organization Utah Family Voices as a family advocate. We determined that she would be an invaluable team member, especially for purposes of communication with the general public. This is because her background provides a unique ability to help predict how the results will be received and interpreted by the families who have been and will be confronted with autism and other developmental disabilities (i.e. those who will be critically reading and evaluating our results).

The IRB process took longer than anticipated. Originally, IHC IRB application materials were completed in August 2009, but after many questions, clarifications, and email discussions, IHC IRB
approval was granted in December 2009. Most of the clarification needed centered on the archival nature of the study, specifically applied to Health Insurance Portability and Accountability Act (HIPAA) regulations and medical record reviews. Additionally, the study also needed USU IRB approval, as the study involves medical record review from multiple sites, some of which are on the campus of USU. This IRB approval process also took longer than anticipated, and focused also on HIPAA regulations and the intricacies of medical record reviews. The proposal was revised so that parents of identified children were contacted with a letter stating the purpose of the study, as well as the archival nature of the research. Parents will be given a chance to ‘opt out’ of the study.

As of April 2010, the project has been approved by both IRBs. The team’s collaboration has been interesting and has generated some new ideas regarding the focus of the project. Currently, participants are being identified, letters of information are being sent to those who are identified, and the ‘opt out’ forms are being mailed. The next step will be to conduct the actual records review and data collection.

References:


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CHART REVIEW

Case #: Age: Physician:
Dx:

Records Available: MBI or BIF Other Provider:
CS School Records

Gender: M or F # of Sibs Birth order
Place of Birth Travel

Stressors:

Adopted: Y or N
Age of mother at birth: Age of Father at birth:

PREGNANCY
# of pregnancies: Live births: Miscarriages:
Problems during pregnancy:
Medications:

Birth weight: Gestational age: SGA/LGA/AGA
Complications after birth:

Jaundice: Y or N Details:

Diet in first year:

Developmental Concerns:

PMHx:
Hand Preference: Physical findings: (parents report)

Response to Vaccines: Normal NA Abnormal: details-

Environmental Exposures:

Sleep Problems: Severity: Hours of Sleep:
Family History:
ASD:
MH:
Auto-immune:
Other:

PEx:
Ht%: Wt%: OFC%: Hearing: Vision:
General: Neuro:

Psycho-ED Testing: (source)

Speech and Language:

CBCL:
  Mother:
  Father:
  Teacher:

Vanderbilt:
  Mother:
  Father:
  Teacher:

IHC-MHI:
IVA:
SCQ:
ADOS:
GADS:
M-CHAT:
GARS:
YSR:
Treatments: