A Brief History of Neonatal Jaundice

William Cashore, MD

The authors of late 19th Century pediatric texts recognized *Icterus neonatorum* as a common finding in newborns. This condition was generally benign and self-limited. Since most newborns at the time were breast-fed, comparisons of the frequency of jaundice in breast and formula-fed infants were not immediately evident to medical observers until later, when formula-feeding was introduced in a larger and growing percentage of newborns (eventually, a majority). The first volume (1885-1891) of medical records from the original Providence Lying–in Hospital contains several observations of neonatal icterus, usually during the first week of what was then a 10-14 day length of stay.

Icterus gravis was also recognized as a more severe form of neonatal jaundice, often associated with profound anemia, abnormal neurological findings, and death. The cause of icterus gravis as an alloimmune hemolytic disorder was not recognized until years later when the immunology of human blood groups was elucidated. High parity rates led to recurrences within families, and recurrence rates after a first affected infant led clinicians to suspect a genetic basis for icterus gravis. The discovery of the Rh group of red cell antigens in 1940 confirmed the risk of recurrence within families.

Clinical research on hemolytic disease of the newborn in the 1940s and 1950s led to a better understanding of its pathogenesis and advances in its treatment. Increased understanding of the pathogenesis, diagnosis, and treatment of hemolytic disease contributed to advances in the whole field of perinatal and neonatal care. These advances included the development of systems for maternal screening which now includes prenatal diagnosis by maternal serology and amniocentesis. The early detection of hemolytic disease prenatally has led to invasive antenatal treatment by intrauterine fetal transfusion.[1] Not only have these advances led to antenatal interventions but they have improved the postnatal protocols for the management of neonatal Rh hemolytic disease, including close hematologic and biochemical monitoring of affected newborns and the invention of exchange transfusion[2] to correct anemia and to reduce and moderate bilirubin levels. The neonatal protocols for Rh erythroblastosis were in turn closely linked to the early development of neonatal intensive care, since many Rh-affected newborns were delivered prematurely and with respiratory distress.

Certain pediatricians of the 1940s-1960s incorporated the care of infants with Rh erythroblastosis into their practice, forming teams of consultants to monitor affected newborns and carry out the tedious procedure of exchange transfusion when indicated. In Providence, these included John Barrett, MD, Frank Giunta, MD, Edwin Forman, MD, and several others, many of whom had received special postgraduate training in Rh disease from specialists in the disorder at large academic centers such as the University of Pennsylvania and the Boston Lying-in Hospital. Some general pediatricians who learned to specialize in Rh disease management continued their careers in the newborn nursery, educating themselves and their close colleagues as the first generation of neonatal intensive care specialists.

The high birth rates and multiparity typical of the post war Baby Boom years resulted in thousands of cases of neonatal disease in this country and abroad. Development of Rh – immune antiglobulin in 1968[3] coincided with a contemporaneous fall in birth rates during the 1970s and thereafter, so that with screening, immunoglobulin prophylaxis during pregnancy, and smaller family size, neonatal Rh erythroblastosis has now become rare.

Lessons learned from the study and treatment of Rh disease have carried over into a more detailed understanding of the causes and consequences of non-hemolytic neonatal jaundice. Subcortical central nervous system injury, or kernicterus, can occur with extreme elevations of unconjugated bilirubin even without alloimmune mediated hemolysis. A small proportion of newborns either overproduce bilirubin or fail to conjugate and excrete it in their first few days or weeks, with early bilirubin levels at risk of exceeding 20 or even 25 mg/dl. These babies need to be monitored and some need to be treated postnatally, to avoid exposure to unconjugated bilirubin levels far in excess of the normal range, and potentially toxic. Conditions contributing to increased risk of, or from, hyperbilirubinemia include:

1. Prematurity, less than 37 weeks gestation
2. Breast feeding, with elevated bilirubin in 10-15% of breast fed newborns
3. ABO incompatibility, a cause of early hyperbilirubinemia in 1-2% of infants
4. G6-PD deficiency, whose frequency is unknown in the absence of a reliable neonatal screen

Because these and several other risk conditions have been associated with case reports of extreme bilirubin elevations and occasional kernicterus, early screening of all newborns for early or persistent jaundice is recommended.[4] Visible jaundice on Day 1 or early on Day 2 should prompt a laboratory determination of total and direct bilirubin concentration. A rate of increase > 0.25 mg/dl/hr should be followed with repeat determinations until stable or responding to ordered treatment. This rate of increase approximates to daily bilirubin levels > 5-6 mg/dl on Day 1, > 10-12 mg/dl on Day 2, or > 17-18 mg/dl on Day 3. Infants with bilirubin levels > 20mg/dl should be treated with high intensity light from multiple sources, positioned to expose most of the skin. Those with levels of 25 mg/dl or higher should be treated aggressively with frequent re-samplings in centers with the ability to potentially provide exchange transfusions. The bilirubin levels treated with effective doses of phototherapy should decline to acceptable levels within 12-24 hours. Most recently the American Academy of Pediatrics recommended treatment of hyperbilirubinemia based on hour specific nomogram findings of Vinod Bhutani et al.[4,5]

Infants with rising bilirubin levels in the nursery, close to but not exceeding the high risk guidelines, should be followed as outpatients within 1-3 working days of hospital discharge.[5] Follow up should include a weight check and feeding history, a detailed inspection for the extent and

intensity of jaundice, and if needed a follow-up bilirubin determination as indicated by the history and exam.

Since the 1980s phototherapy has superseded exchange transfusion as the treatment of choice for non-hemolytic hyperbilirubinemia.[6,7] (Phototherapy is helpful in cases of hemolytic hyperbilirubinemia, but may not be sufficient to correct the anemia or control the jaundice). Guidelines for both phototherapy and exchange transfusion, now a rare procedure, may be found in standard pediatric and neonatal texts, manuals for newborn care from various academic centers, and practice guidelines from the American Academy of Pediatrics.

Conclusion

Hyperbilirubinemia is a universal problem in newborn nurseries, increasing in North America as rates of breast feeding and borderline prematurity have increased in recent years. Neonatal jaundice is the most common reason to order laboratory tests in an otherwise well newborn. Although self-limited and benign in most cases, neglected or untreated severe hyperbilirubinemia can have dire neurodevelopmental consequences for the newborn.

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The author and spouse/significant other have no financial interests to disclose.

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Health By Numbers

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Health Status and Health Care Utilization Among Children In Rhode Island, 2007: Comparing Children With Public Insurance and Children With Private Insurance

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Health status and health care utilization among children are profoundly influenced by health insurance coverage. Uninsured and underinsured children are less likely than adequately insured children to receive preventive health care, have a usual source of care, and receive health care within a medical home that addresses their comprehensive needs. Gaps in health insurance coverage may lead to delayed or unmet health care needs among children.[1]

This report describes 1) the distribution of health insurance type among Rhode Island children, and 2) the health status and health care utilization disparities between children with public health insurance and children with private health insurance.

Methods

Data from the 2007 National Survey of Children's Health (NSCH-2007) were analyzed. The NSCH-2007, a random digit

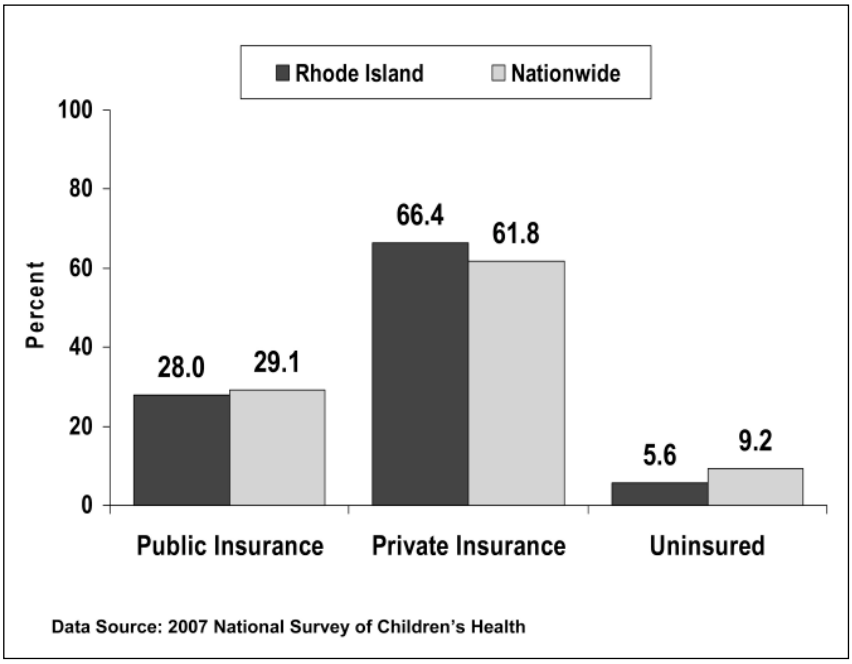

Figure 1. Distribution of Health Insurance Type
Children 0-17 Years of Age, Rhode Island vs. United States, 2007