A 5-day-old female infant who was born at 26 weeks' gestation with a birthweight of 850 g is in an incubator and receiving intensive phototherapy. She is not receiving respiratory support and is tolerating some enteral breast milk. Among today’s laboratory findings, the total serum bilirubin is 14 mg/dL (239 μmol/L). You discuss the risks and treatment options with the parents including exchange transfusion if the bilirubin continues to rise. The parents want to know if the serum bilirubin is the best indicator of risk for brain damage and what other tests might be conducted (assuming all are available to you).

Of the following, the MOST accurate risk assessment for bilirubin encephalopathy in a small premature infant would be:

- A. plasma free (unbound) bilirubin alone
- B. plasma free (unbound) bilirubin plus clinical status
- C. ratio of plasma bilirubin to albumin concentration
- D. total plasma bilirubin concentration alone
- E. total plasma bilirubin plus clinical status

The infant in the vignette represents a class of neonatal intensive care unit patients for whom we have had little guidance about the management of serum bilirubin concentrations. Her serum bilirubin concentration is rising despite treatment with intensive phototherapy.

The main host defense against bilirubin toxicity is the avid binding of unconjugated bilirubin to albumin. The binding capacity for an individual infant is dependent on the concentration of albumin and the presence or absence of molecules that compete for the same binding site (eg, free fatty acids, sulfonamides, diuretics, salicylates, nonsteroidal analgesics). Bilirubin neurotoxicity occurs when albumin-binding capacity is exceeded and lipid-soluble unconjugated bilirubin diffuses across the blood-brain barrier and accumulates in neurons. Bilirubin interferes with many cellular and membrane functions including respiration, which can lead to the death of cells. Premature infants tend to have lower concentrations of plasma albumin compared with older infants. In addition, conditions such as sepsis, hypoglycemia, and hypothermia can increase endogenous free fatty acid concentrations and reduce bilirubin-binding capacity.

A 2008 publication from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network provides some guidance on the prevention of bilirubin encephalopathy in premature infants who weigh less than 1,000 g at birth (extremely low birthweight [ELBW] infants). Almost 2,000 ELBW infants were randomized to groups receiving “aggressive phototherapy” (AP) or “conservative phototherapy” (CP). Those randomized to AP began receiving phototherapy around 24 hours of age when the average serum bilirubin concentration was about 5 mg/dL (86 μmol/L). Infants randomized to CP began receiving phototherapy around 58 hours of age when serum bilirubin concentration reached 10 mg/dL (171 μmol/L).
they were more than 750 g at birth or 8 mg/dL (137 µmol/L) if less than or equal to 750 g at birth. Infants met criteria for exchange transfusion when their serum bilirubin concentration exceeded 15 mg/dL (257 µmol/L) for those more than 750 g at birth and 13 mg/dL (222 µmol/L) for the smaller group. Exchange transfusion was rare in both groups and incidences did not differ (P=.69).

The primary outcome for the NICHD study was the incidence of death or neurodevelopmental impairment. The incidences of this combined outcome were 52% for the AP group and 55% for the CP group (relative risk 0.94, 95% confidence limits 0.87-1.02, not statistically different). The study did find a significant decrease in the incidence of neurodevelopmental impairment (AP 26% vs CP 30%) at 18 to 22 months' corrected age follow-up. The relative risk for neurodevelopmental impairment was 0.86 with 95% confidence limits between 0.74 and 0.99 (P<.05). Mental Development Index Scores lower than 85 and 70 were more prevalent in the CP group. The incidence of profound impairment (defined as severe mental or severe motor impairment) was also significantly lower. The kinds of impairment typical of bilirubin encephalopathy were also different between groups, including severe hearing loss and athetosis. The study did not note early signs of bilirubin encephalopathy among enrolled infants.

About half of the infants in the recent NICHD study were assessed for free or unbound bilirubin. High concentrations of unbound bilirubin were associated with higher risks than lower concentrations for death or neurodevelopmental impairment, death or cerebral palsy, death or hearing loss, and death prior to follow up. The clinical stability of the infant was analyzed to determine whether degree of illness affected the risk of poor clinical outcomes in the group treated with the "aggressive" phototherapy protocol. Clinical condition was deemed unstable if the infant had acidosis (pH<7.15) or sepsis, required resuscitation and/or vasopressor medication, or mechanical ventilation at the time of sampling. The results indicated that unbound bilirubin alone predicted outcome independent of clinical status.

Total plasma bilirubin concentration also correlated positively with death or neurodevelopmental impairment, death or cerebral palsy, death or hearing loss, and death before follow-up in unstable ELBW infants, but not in stable infants like the infant in the vignette.

Importantly, increased unbound bilirubin was associated with much larger effects on the incidences of these outcomes than total bilirubin concentration. For instance, as the unbound bilirubin concentration increased from 0.5 µg/dL (0.009 µmol/L) to 2 µg/dL (0.03 µmol/L), the probability of death or hearing loss increased from about 10% to 55% regardless of whether the infant was stable or not at the time of sampling. This is a larger change in probability than when total bilirubin increased from 3 mg/dL (51 µmol/L) to 15 mg/dL (257 µmol/L) in unstable infants (10%-40%). Total bilirubin did not predict outcomes in infants who were stable at the time of sampling.

The ratio of total serum bilirubin concentration divided by the serum albumin concentration has been shown to correlate with the unbound bilirubin concentration in previous studies. Studies of the biologic effects of bilirubin in infants (eg, brain-stem auditory evoked response measurements) have shown a relatively poor correlation with total bilirubin concentration, a better correlation with the bilirubin-albumin concentration ratio, and the best correlation with unbound bilirubin concentration.

References


American Board of Pediatrics Content Specification(s)

Bilirubin: Know the factors affecting the binding of bilirubin to albumin and know the pharmacologic agents which affect binding

Bilirubin: Know the mechanisms by which bilirubin enters the brain and causes damage

Bilirubin: Know the factors that increase the risk of the development of kernicterus