Prevalence of Hypoalbuminemia and Elevated Bilirubin/Albumin Ratios in a Large Cohort of Infants in the Neonatal Intensive Care Unit

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Objective To provide descriptive data on serum albumin levels and the bilirubin to albumin (B/A) ratio in neonates admitted to the neonatal intensive care unit, assess the effect of gestational and chronological age on serum albumin and the B/A ratio, and evaluate the association between extreme values and mortality.

Study design Using a retrospective cohort design, we queried the Pediatrix clinical data warehouse for all infants born between 23 and 41 weeks of gestation from 1997 to 2014 who had a report of both a serum albumin and total serum bilirubin (TSB) level on the same day between birth and 14 days of life.

Results There were 382 190 paired albumin and bilirubin levels across 164 401 neonates (15% of the 1 072 682 infants in the clinical data warehouse). Both gestational age and postnatal age were independent factors that influenced the values for serum albumin, TSB, and B/A ratio (ANOVA; $P < .0001$). TSB and B/A ratios values above birth weight–specific thresholds for exchange transfusions were uncommon (<6% of infants). Hypoalbuminemia (<2.5 mg/dL) was common (29% of infants). Neonates with serum albumin levels <2.5 g/dL or with B/A ratio levels exceeding exchange thresholds were at higher risk of death compared with infants who did not exceed these levels. This association was independent of other risk factors (estimated gestational age, birth weight, sex, and the presence of a major anomaly).

Conclusion Both gestational age and postnatal age influence TSB, albumin, and B/A ratios; hypoalbuminemia and extreme B/A ratios are associated with an increased risk of death. *(J Pediatr 2017;188:280-6).*

Low serum albumin may potentiate the risk of bilirubin-induced brain injury by limiting albumin-bilirubin binding capacity. Hypoalbuminemia, defined as a serum albumin <2.5 g/dL in preterm and <3.0 g/dL in term neonates, is a risk factor for bilirubin neurotoxicity.[1-5] Concentrations <2.0 g/dL accompanied by an elevated bilirubin/albumin (B/A) ratio have been associated with some cases of low-bilirubin kernicterus.[6,7] The B/A ratio correlates with unbound bilirubin.[1,8] Although an imperfect surrogate of central nervous system bilirubin exposure, it may nevertheless serve as a meaningful proxy of bilirubin neurotoxicity risk during hypoalbuminemia.[1,6,7,9] Accordingly, serum albumin measurement, identification of hypoalbuminemia, and calculation of the B/A ratio have been recommended to assess the need for a double volume exchange transfusion (DVET) in the hyperbilirubinemic neonate,[1,4,5,10] an approach endorsed by the American Academy of Pediatrics in their 2004 Hyperbilirubinemia Practice Guideline.[5]

The risk for bilirubin encephalopathy is largely confined to the first 2 weeks of postnatal life. This vulnerable period is characterized by developmental red blood cell, hepatic, and gastrointestinal immaturities that produce an imbalance favoring bilirubin production over hepatic–enteric bilirubin clearance with resultant hyperbilirubinemia.

Reports on serum albumin concentrations in neonates during the first 2 weeks of postnatal life, however, are limited by their sample size and temporal scope, and have shown variable results.[11-16] Many reports date from 1990 or earlier[11-13,17-20] and none have substantial numbers of extremely low birth weight neonates. Descriptive data on the B/A ratio are far more limited.

The aims of the current study were to provide descriptive data on serum albumin levels and the B/A ratio in a large cohort of neonates admitted to the neonatal intensive care unit (NICU), assess the effect of gestational and chronological age on serum albumin and the B/A ratio, determine the prevalence of hypoalbuminemia as a bilirubin neurotoxicity risk factor, determine the prevalence of B/A ratios that exceed reported birth weight–specific DVET treatment thresholds,[1,10] and evaluate the association between extreme values and mortality.

B/A	Bilirubin/albumin (ratio)
CDW	Clinical data warehouse
DVET	Double volume exchange transfusion
NICU	Neonatal intensive care unit
TSB	Total serum bilirubin

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Methods

This descriptive review analyzed data from the Pediatrix Medical Group clinical data warehouse (CDW).[21] The CDW is a large multicenter, deidentified dataset that is compliant with the Health Insurance Portability and Accountability Act and from a diverse group of 330 NICUs in 34 states and Puerto Rico that represents approximately 20% of all NICU admissions in the United States. The CDW is generated by Pediatrix Medical Group clinicians using a proprietary software system (BabySteps, MEDNAX Inc, Sunrise, Florida) that captures medical documentation (eg, admission, progress, and discharge notes), billing worksheets, and the CDW dataset. Data are added and modified by providers as they make their daily assessments. The gestational age assignment is based on the best obstetrical estimate before delivery and recorded as completed weeks. To maximize validity, data for the CDW are extracted at the end of the infant's NICU stay, so providers have multiple opportunities to review and verify the documentation. The Western Institutional Review Board has approved the use of this deidentified warehouse data for the study.

All infants of $23^{0/7}$ to $41^{6/7}$ weeks of gestation born from 1997 through 2014 who had a report of both a serum albumin and total serum bilirubin (TSB) level on the same day between birth and 14 days of life were included. There were 382 190 such levels across 164 401 neonates (15% of the 1 072 682 infants in the CDW). Most infants had only 1 serum albumin and TSB value reported on any given day; in those who had >1 value, the maximum TSB and the minimum albumin levels were used for that day. In general, there were at least 1000, and frequently several thousand, subjects recorded at each postnatal day in every gestational age range (**Table I**; available at www.jpeds.com).

Serum albumin, TSB, and B/A ratio levels were analyzed as a function of gestational age and postnatal age within each gestational age cohort. The prevalence of hypoalbuminemia was determined as a function of gestational age and defined as a serum albumin <2.5 g/dL for infants of <35 weeks of gestation and <3.0 g/dL for infants ≥35 weeks of gestation. These serum albumin concentrations represent gestational age–specific thresholds at which hypoalbuminemia might increase the risk of brain injury ("neurotoxicity risk factor") in infants with hyperbilirubinemia.[3-5]

The prevalence of a B/A ratio (mg/g) or TSB (mg/dL) that exceeded DVET treatment thresholds in high-risk neonates was also assessed using birth weight specific criteria set forth by Ahlfors[1] and include the following: for a birth weight <1250 g, B/A ratio ≥4.0 or TSB ≥10 mg/dL; birth weight 1250-1499 g, B/A ratio ≥5.2 or TSB ≥13 mg/dL; birth weight 1500-1999 g, B/A ratio ≥6.0 or TSB ≥15 mg/dL; birth weight 2000-2499 g, B/A ratio ≥6.8 or TSB >17 mg/dL; and birth weight ≥2500 g, B/A ratio ≥7.2 or TSB ≥18 mg/dL.[1] These B/A ratio thresholds were derived from the birth weight–specific TSB DVET treatment threshold and a single critical hypoalbuminemia level ≤2.5 g/dL,[1] and were used for analysis purposes only; medical care, including hyperbilirubinemia management, was left to the discretion of the NICU team.

Because low serum albumin levels have been reported as an independent predictor of mortality in preterm neonates in small cohort studies,[15,16] we assessed the relationship between hypoalbuminemia, TSB, and B/A ratio and death during the birth NICU hospitalization. For this analysis, transported infants were excluded (n = 19 715, 12%). Mortality was calculated as the number of deaths divided by the total number of patients (ie, died/[died + discharged home]).

Statistical Analyses

Categorical variables were evaluated by 2-tailed χ^2 and Fisher exact tests. Continuous variables were compared using a 2-tailed ANOVA for parametrically distributed data and Kruskal-Wallis analysis of variance for nonparametrically distributed data. The changes in values by age (days since birth) were evaluated using analysis of variance within each estimated gestational age group. A comparison for all possible pairs was done using Tukey–Kramer tests. All graphically displayed values are presented as median (10th-90th percentile). To correct for multiple comparisons, we accepted a P value of <.001 as significant.

To evaluate the association between mortality, serum albumin <2.5 g/dL, and birth weight–specific TSB concentrations or B/A ratios greater than the DVET thresholds as defined previously, we used logistic regression, correcting for gestational age, birth weight, and major anomalies within each birth weight group. We calculated the unadjusted and adjusted OR for each variable. In the calculation of the adjusted OR, we used 2 models. In the first model, each variable was entered independently. In the second model, all 3 variables (albumin <2.5 g/dL, TSB > DVET threshold, and B/A ratio > DVET threshold) were included. We searched from day 0 to day 7 and found the maximum B/A ratio, the minimum albumin level, and the maximum TSB levels reported. This period was selected because it represented the time frame during which the lowest serum albumin, highest TSB, and highest B/A ratios were seen. Statistical analyses were performed using JMP 11 (SAS Institute, Cary, North Carolina).

Results

Both gestational age and postnatal age were independent factors that significantly influenced the values for serum albumin, TSB, and B/A ratio (**Figure**, A-C, ANOVA; $P < .0001$). Post hoc analysis showed that significant differences between gestational age groups in all 3 measures were present on each day. Similarly, within each gestational age group, there were significant differences between days in all 3 measures.

Figure, A shows that, within each gestational age group, TSB levels increased as a function of gestational age, as well as during the first few days of postnatal life. Thereafter, TSB declined to a relative plateau in 23- to 30-week' gestation neonates, and decreased more steadily in infants between 31 and 41 weeks.