

Hypoalbuminemia in Critically Ill Children

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Objective: To evaluate whether hypoalbuminemia on admission is a predictor of adverse outcome in critically ill children.

Design: Retrospective medical record review.

Setting: A 14-bed medical and surgical pediatric intensive care unit (PICU).

Participants: All patients admitted to the PICU from January 1, 1998, through December 31, 2000, under the care of the PICU team or trauma service and whose albumin level was measured were potential subjects. One hundred fifty-five patients were divided into 4 groups on the basis of age and appropriate albumin level for that age group. The groups of hypoalbuminemic patients were combined (hypoalbuminemia group) and compared with the combined group of patients with albumin levels above the reference cutoff (normal albumin level group).

Exposure: Serum albumin level.

Main Outcome Measures: Length of PICU and hospital stays, receipt and length of ventilatory support, survival, pediatric risk of mortality score, mortality risk, and number of organ failures.

Results: Controlling for mortality risk, the hypoalbuminemia group had a longer average stay in the PICU (8.08 vs 4.41 days; 95% confidence interval [CI] for difference, 1.02-6.32) and the hospital (11.36 vs 6.63 days; 95% CI for difference, 1.31-8.16) than did the normal albumin level group. The hypoalbuminemia group had a lower survival rate (odds ratio, 0.10; 95% CI, 0.02-0.46) and a higher number of organ failures (1.38 vs 0.65; 95% CI for difference, 0.40-1.04).

Conclusion: Admission hypoalbuminemia is a significant marker of morbidity and mortality in critically ill children.

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ALBUMIN IS THE MOST ABUNDANT protein in blood plasma, usually constituting up to two-thirds of total plasma protein.¹ It contributes about 80% of the plasma colloid osmotic pressure and is responsible for the transport and binding of many molecules. Albumin is highly water soluble and resides in the extracellular space, with one-third in the intravascular space and two-thirds in the extravascular space. Typically, hypoalbuminemia is ascribed to diminished synthesis (eg, malnutrition, malabsorption, or hepatic dysfunction) or increased losses (eg, urinary losses with nephropathy or protein-losing enteropathy). Diversion of synthetic capacity to other proteins (acute-phase reactants) is another cause of hypoalbuminemia. Inflammatory disorders can accelerate the catabolism of albumin while simultaneously decreasing its manufacture. During critical illness, capillary permeability increases dramatically and alters albumin

exchange between intravascular and extravascular compartments.

Hypoalbuminemia is associated with poor outcomes in adult critical illness, but whether this association exists in pediatric patients remains unclear.²⁻⁶ There is a paucity of data evaluating serum albumin level on admission as a predictor of outcome in critically ill children. Our goal was to evaluate whether hypoalbuminemia on admission is a marker of adverse outcome in this population.

METHODS

We performed a retrospective medical record review of data collected from January 1, 1998, through December 31, 2000, in the pediatric intensive care unit (PICU) at the Ronald McDonald Children's Hospital of Loyola University Medical Center. Any pediatric patient whose albumin level was measured was a potential subject. Patients were stratified by age and serum albumin level on admission. *Hypoalbuminemia* was defined as an albumin level

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Table 1. Criteria for Failure of Specific Organ Systems^a

Organ System	Criteria
Cardiovascular	MAP, < 40 mm Hg (infants aged < 12 mo) MAP, < 50 mm Hg (children aged ≥ 12 mo)
Respiratory	HR, < 50 beats/min (infants aged < 12 mo) HR, < 40 beats/min (children aged ≥ 12 mo) Cardiac arrest Continuous vasoactive drug infusion for hemodynamic support RR, > 90/min (infants aged > 12 mo) RR, > 70/min (children aged ≥ 12 mo) PaO ₂ , < 40 mm Hg (in absence of cyanotic heart disease) PaCO ₂ , < 65 mm Hg PaO ₂ :FIO ₂ , < 250 mm Hg Ventilatory support (> 24 h if postoperative) Tracheal intubation for airway obstruction or acute respiratory failure
Neurologic	Glasgow coma scale score, < 5 Fixed, dilated pupils Persistent (> 20 min) intracranial pressure > 20 mm Hg or need for therapeutic intervention
Hematologic	Hemoglobin level, < 5 g/dL WBC count, < 3 × 10 ³ cells/μL Platelet count, < 20 000/μL
Renal	Disseminated intravascular coagulopathy (PT > 20 s or aPTT > 60 s in presence of positive FSP assay results) SUN level, > 100 mg/dL Serum creatinine level, > 2 mg/dL Need for dialysis
Gastrointestinal Hepatic	Blood transfusions, > 20 mL/kg in 24 h because of gastrointestinal hemorrhage (endoscopic confirmation optional) Total bilirubin level, > 5 mg/dL and SGOT or LDH more than twice the reference value (without evidence of hemolysis) Hepatic encephalopathy ≥ grade II ¹⁰

Abbreviations: aPTT, activated partial thromboplastin time; FIO₂, fraction of inspired oxygen; FSP, fibrin split products; HR, heart rate; LDH, lactic dehydrogenase; MAP, mean arterial pressure; PT, prothrombin time; RR, respiratory rate; SGOT, serum glutamic oxaloacetic transaminase; SUN, serum urea nitrogen; WBC, white blood cell.

SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.104; creatinine to micromoles per liter, by 88.4; platelet count to number of cells × 10⁹ per liter, multiply by 10; urea nitrogen to millimoles per liter, by 0.357; and WBC count to number of cells × 10⁹ per liter, multiply by 0.001.

^aReproduced with permission from Wilkinson et al.⁹

of less than 3.4 g/dL for patients 7 months or older and less than 2.5 g/dL for patients younger than 7 months.⁷ (To convert albumin to grams per liter, multiply by 10.) All patient data were combined according to age-specific definitions of hypoalbuminemia. Our institutional review board approved the project and waived the need for consent.

INCLUSION CRITERIA

All patients admitted to the PICU under the care of the PICU team or trauma service whose albumin level was measured were potential subjects. Arrival to the PICU was required no later than the second hospital day, if the patient was initially admitted to the floor. A comprehensive metabolic profile or albumin level was obtained within 48 hours of admission to the hospital.

EXCLUSION CRITERIA

Patients who were not expected to have a normal albumin level (ie, a level above the reference cutoff value for their age) in their usual state of health were excluded. Therefore, patients who were malnourished (below the fifth percentile according to growth curve data) or who had lost weight (> 10% of their body weight in the premorbid state) were excluded. Other exclusion criteria included presence of a chronic disease affecting the growth and development of the gastrointestinal system (failure to thrive or inflammatory bowel disease) or the kidney (end-stage renal disease or proteinuria), receipt of home parenteral nutrition, or presence of a chromosomal, genetic, or inborn metabolic disorder. Patients who had undergone cardiac surgery,

experienced significant blood loss during surgery (> 10% of their blood volume), or received blood products or albumin before measurement of the albumin level were also excluded.

Data recorded included age, sex, diagnosis (categorized by organ system, eg, respiratory, infectious, neurologic, or cardiac), pediatric risk of mortality (PRISM) score,⁸ risk of mortality computed from the PRISM score, length of hospital stay, length of PICU stay, receipt and length of ventilatory support, number of organ failures⁹ (**Table 1**), outcome (survival), complications, and whether the patient received supplemental albumin. Except for death in an extremely ill child, complications were all unexpected, untoward events such as nosocomial pneumonia, decubitus ulcer, or reintubation.

DATA ANALYSIS

Mortality probability was used as a control variable when groups, which were divided according to their albumin level (hypoalbuminemic patients [hypoalbuminemia group] vs patients with a normal albumin level [normal albumin level group]) were compared on all outcome variables. Because both the PRISM and risk of mortality scores were highly skewed, we computed the logarithm of risk of mortality. Analyses of covariance were used to compare the groups on scaled variables (eg, number of organ failures) using the logarithm of mortality risk as a covariate. The Mantel-Haenszel test was used to compare the groups on categorical variables (eg, survival). In these categorical analyses, mortality risk was controlled with a dichotomy of the logarithm of mortality risk. A median split was used to define low and high risk.

Table 2. Diagnostic Groups

Diagnosis by Organ System	Patients Aged < 7 mo		Patients Aged ≥ 7 mo	
	Hypoalbuminemia ^a (n=10)	Normal Albumin Level (n=27)	Hypoalbuminemia ^b (n=41)	Normal Albumin Level (n=77)
Neurologic	0	6	9	27
Respiratory	1	10	8	13
Infectious disease	5	2	9	3
Cardiovascular	1	3	7	5
Metabolic	1	1	1	10
Toxicology	0	0	1	12
Hematology	0	2	6	3
Gastrointestinal	2	3	0	0
Trauma	0	0	0	2
Renal	0	0	0	1
Rheumatologic	0	0	0	1

^aIn patients younger than 7 months, hypoalbuminemia was defined as an albumin level of less than 2.5 g/dL (to convert to grams per liter, multiply by 10).

^bIn patients 7 months or older, hypoalbuminemia was defined as an albumin level of less than 3.4 g/dL.

Table 3. Descriptive Statistics Study Variables

Variable	Hypoalbuminemia Group (n=51)	Normal Albumin Level Group (n=104)	Mean Difference, 95% CI
Albumin level, mean±SE, g/dL	2.45±0.10	3.77±0.06	...
Length of stay, mean±SE, d ^a			
PICU	8.08±1.08	4.41±0.74	1.02 to 6.32
Hospital	11.36±1.40	6.63±0.96	1.31 to 8.16
Length of ventilatory support, mean±SE, d ^{a,b}	7.82±1.62	5.50±1.67	-2.44 to 7.08
Organ failures, mean±SE, No. ^a	1.38±0.13	0.65±0.09	0.40 to 1.04
Risk of ventilatory support, OR (95% CI)	4.12 (1.95 to 8.72)
Survival rate, OR (95% CI)	0.10 (0.02 to 0.46)

Abbreviations: CI, confidence interval; PICU, pediatric intensive care unit; OR, odds ratio; ellipses, not applicable.

SI conversion factor: To convert albumin to grams per liter, multiply by 10.

^aVariable is adjusted for risk of mortality.

^bThe numbers of patients receiving ventilatory support were 35 and 33 for the hypoalbuminemia and normal albumin level groups, respectively.

RESULTS

The medical records of 225 patients with an admission albumin level measurement were initially reviewed. Seventy patients were excluded. Of the 155 patients remaining, 10 patients younger than 7 months had hypoalbuminemia (mean±SE albumin level, 1.64±0.46 g/dL), as did 41 patients 7 months or older (mean±SE albumin level, 2.65±0.62 g/dL). Twenty-seven patients younger than 7 months had a normal albumin level (mean±SE albumin level, 3.19±0.37 g/dL) in addition to 77 patients 7 months or older (mean±SE albumin level, 3.97±0.49 g/dL). Our group of 155 patients had a mean concentration of 3.33 g/dL. Of the 51 patients in the hypoalbuminemia group, 25 were male and 26 were female; of the 104 patients with a normal albumin level, 59 were male and 45 were female ($P=.39$). The mean age of the hypoalbuminemia group was 57.0 months (range, 0-214 months) and that of the normal albumin level group was 67.7 months (range, 0-211 months) ($P=.36$).

The diagnostic categories of the 155 patients are given in **Table 2**. The Mantel-Haenszel test results showed that children in the hypoalbuminemia group were more likely

to have an infectious disease diagnosis (odds ratio [OR], 7.27; 95% confidence interval [CI], 2.34-22.56; $P=.001$, controlling for mortality risk), but the differences observed between the groups in terms of neurologic diagnoses were not significant (OR, 0.53; 95% CI, 0.23-1.23; $P=.20$). Complications included chylothorax, reintubation, pneumothorax, adult respiratory distress syndrome, nosocomial bacteremia, panhypopituitarism, skin burn (intravenous infiltration), and venous thrombosis.

An analysis of covariance indicated that children in the hypoalbuminemia group had a higher mean number of organ failures compared with those in the normal albumin level group (1.38 vs 0.65; 95% CI for difference, 0.40 to 1.04; $F_{1,152}=19.99$; $P<.001$, adjusting for mortality risk). Our group of 155 patients had a mean concentration of 3.33 g/dL. Similarly, the hypoalbuminemia group had a significantly longer adjusted length of stay in the hospital (11.36 vs 6.63 days; 95% CI for difference, 1.31 to 8.16; $F_{1,152}=7.47$; $P=.007$) and the PICU (8.08 vs 4.41 days; 95% CI for difference, 1.02 to 6.32; $F_{1,152}=7.51$; $P=.007$). However, no significant difference was found in length of ventilatory support (7.82 vs 5.50 days; 95% CI for difference, -2.44 to 7.08; $F_{1,63}<1$; $P=.33$) (**Table 3**).

The PRISM score (11.69 vs 6.03; $P < .001$) and risk of mortality score (0.166 vs 0.038; $P < .001$) were increased in the hypoalbuminemia group compared with the normal albumin level group. Controlling for mortality risk, the Mantel-Haenszel test showed that children with hypoalbuminemia were more likely to receive ventilatory support, (OR, 4.12; 95% CI, 1.95-8.72; $P < .001$), less likely to survive (OR, 0.10; 95% CI, 0.02-0.46; $P = .002$), more likely to have complications (OR, 3.54; 95% CI, 1.41-8.88; $P = .009$), and more likely to receive albumin (OR, 9.89; 95% CI, 1.19-82.08; $P = .03$).

COMMENT

Hypoalbuminemia is not an infrequent event in the critically ill child. Not every child admitted to our PICU undergoes a comprehensive metabolic profile or albumin level determination; therefore, the true incidence of hypoalbuminemia in our population is not known. There is a paucity of data in this regard. In the only other comparable study, Durward et al⁴ found a hypoalbuminemia incidence of 56.7%. Whatever the cause of low albumin levels, the decreased plasma colloid osmotic pressure compromises the intravascular volume, placing the child at risk for inadequate blood flow to vital organs. This is especially true of capillary leak, in which the albumin escapes to the interstitial space, pulling fluid along. Thus, it would be expected that a low serum albumin level would be associated with poor outcome.

The adult literature has documented hypoalbuminemia as a marker for disease severity, prolonged ventilatory support, and extended length of intensive care unit (ICU) stay. In their meta-analysis, Vincent and colleagues³ found hypoalbuminemia to be a dose-dependent independent predictor of poor outcome. Each 1.0-g/dL decline in serum albumin concentration significantly raised the odds of mortality by 137%, morbidity by 89%, and prolonged ICU and hospital stay by 28% and 71%, respectively, and increased resource utilization by 66%. In the trauma population, patients with a lower serum albumin level (< 2.6 g/dL) were found to have significantly longer ICU (17.1 vs 14.2 days; $P < .001$) and hospital (17.3 vs 20.1 days; $P = .003$) lengths of stay, more days receiving ventilatory support (11.1 vs 13.5 days; $P = .003$), and greater mortality ($P = .002$) when matched for age and injury severity.⁶ The relative risks of infection and mortality increased greater than 2.5-fold in patients with increased age and a low serum albumin level when analyzed by multilinear regression analysis.⁶ However, other investigators from China found that, in medical and surgical patients, serum albumin level had low sensitivity and specificity for predicting hospital mortality.¹¹

In the pediatric prognostic scoring systems PRISM III and PIM,¹² albumin level is not a variable used to determine the percentage. However, in the recent effort to develop and then prospectively validate a multiple organ dysfunction scoring system in a large population of critically ill children, significant differences were observed in all variables studied for the hepatic/pancreatic organ system between survivors and nonsurvivors.¹³ This included albumin level, although the bilirubin level provided higher

validity.¹³ The study by Durward et al⁴ measuring anion gap in hypoalbuminemic children found that hypoalbuminemia on admission was common but not an independent predictor of mortality; mean albumin levels were similar between survivors and nonsurvivors. In contrast, our patients in the hypoalbuminemia group, when compared with the normal albumin level group, had a higher severity of illness, greater likelihood of ventilatory support, higher predicted rate of mortality, and higher rate of actual mortality. Our 2 groups may be much more disparate because there is no intermediate care unit in our institution, and much less acutely ill patients may have composed our normal albumin level group. This proposed difference between our hypoalbuminemia and normal albumin level groups compared with the patients studied by Durward et al is suggested by the larger discrepancy in severity of illness scores ($P = .001$) and rates of ventilatory support ($P < .001$) between our 2 groups. In addition, the medical condition of the patients in the study by Durward et al may have been more critical, as evidenced by the inclusion criteria of an indwelling arterial line, higher rate of ventilatory support in the control group, and a mean albumin concentration of 2.98 g/dL for their 134 patients. (Our group of 155 patients had a mean concentration of 3.33 g/dL.)

Some indications for which albumin therapy is considered include hypovolemia, shock, burns, hypoalbuminemia, surgery or trauma, cardiopulmonary bypass graft, acute respiratory distress syndrome, plasmapheresis, hemodialysis, and sequestration of protein-rich fluids.^{14,15} In the critically ill patient, in whom the endothelium may be damaged, treatment with colloids and crystalloids could conceivably increase interstitial fluid volume: crystalloids by virtue of their usual distribution throughout the extracellular space, and colloids by increasing oncotic pressure within the interstitium if there is substantial transcapillary leak. The use of albumin as a fluid for volume replacement or as a treatment for hypoalbuminemia has been an ongoing debate and has been the subject of evidenced-based reviews.¹⁶ The use of albumin replacement as a volume expander for the critically ill adult was investigated during the SAFE (Saline vs Albumin Fluid Evaluation) Study from New Zealand and Australia, a randomized double-blind study of nearly 7000 patients.¹⁷ In that study, investigators found that 4% albumin treatment for hypotension did not result in decreased mortality or morbidity.¹⁷

In summary, we found that hypoalbuminemia was a significant marker of morbidity and mortality in critically ill children. Additional pediatric studies are needed to confirm this, although the adult literature is in agreement. Replacement is very likely to be beneficial in some circumstance (eg, for septic shock)¹⁸ and not of value (for burns¹⁹) or detrimental (eg, for head trauma) in others.¹⁴ The physician, as always, needs to tailor the treatment on the basis of the disease process and the serum albumin concentration.

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