



Thân thiện như chính ngôi nhà của bạn

Serum Albumin

VS

Outcomes in Critically Ill Children

CONTENT

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INTRODUCTION

- Serum albumin is a strong biomarker of disease severity and prognosis in adult patients.
- In contrast, its value as predictor of outcome in critically ill children has not been established.
- The question of whether to administer albumin in hypoalbuminemic patients remains largely unanswered.

Hypoalbuminemia in Acute Illness: Is There a Rationale for Intervention?

A Meta-Analysis of Cohort Studies and Controlled Trials

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Methods

A meta-analysis was conducted of 90 cohort studies with 291,433 total patients evaluating hypoalbuminemia as an outcome predictor by multivariate analysis and, separately, of nine prospective controlled trials with 535 total patients on correcting hypoalbuminemia.

Results

Hypoalbuminemia was a potent, dose-dependent independent predictor of poor outcome. Each 10-g/L decline in serum albumin concentration significantly raised the odds of mortality by 137%, morbidity by 89%, prolonged intensive care unit and hospital stay respectively by 28% and 71%, and increased resource utilization by 66%. The association between hypoalbuminemia and poor outcome appeared to be independent of both nutritional status and inflammation. Analysis of dose-dependency in controlled trials of albumin therapy suggested that complication rates may be reduced when the serum albumin level attained during albumin administration exceeds 30 g/L.

Conclusions

Hypoalbuminemia is strongly associated with poor clinical outcomes. Further well-designed trials are needed to characterize the effects of albumin therapy in hypoalbuminemic patients. In the interim, there is no compelling basis to withhold albumin therapy if it is judged clinically appropriate.

Hypoalbuminaemia in critically ill children: incidence, prognosis, and influence on the anion gap

A Durward, A Mayer, S Skellett, D Taylor, S Hanna, S M Tibby, I A Murdoch

Arch Dis Child 2003;88:419-422

Methods Prospective descriptive study of 134 critically ill children in the paediatric intensive care unit (ICU). Paired arterial blood samples were taken at ICU admission and 24 hours later, from which blood gases, electrolytes, and albumin were measured. The anion gap (including potassium) was calculated and then corrected for albumin using Figge's formula.

Results The incidence of admission hypoalbuminaemia was 57%, increasing to 76% at 24 hours. Neither admission hypoalbuminaemia, nor extreme hypoalbuminaemia (<20 g/l) predicted mortality; however, there was an association with increased median ICU stay (4.9 v 3.6 days). After correction for albumin the incidence of a raised anion gap (>18 mEq/l) increased from 28% to 44% in all samples (n = 263); this discrepancy was more pronounced in the 103 samples with metabolic acidosis (38% v 73%). Correction produced an average increase in the anion gap of 2.7 mEq/l (mean bias), with limits of agreement of ± 3.7 mEq/l.

Conclusion Admission hypoalbuminaemia is common in critical illness, but is not an independent predictor of mortality. However, failure to correct the anion gap for albumin may underestimate the true anion gap, producing error in the interpretation of acid-base abnormalities. This may have treatment implications.

Hypoalbuminemia in Critically Ill Children

Ira N. Horowitz, MD; Kenneth Tai, MD

Design: Retrospective medical record review.

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).

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)

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

Hypoalbuminemia in critically sick children

Lokesh K. Tiwari^{1,2}, Sunit Singhi¹, M. Jayashree¹, Arun K. Baranwal^{1,2}, Arun Bansal¹

Context: There is a paucity of data evaluating serum albumin levels and outcome of critically ill-children admitted to intensive care unit (ICU). **Aims:** The aim was to study frequency of hypoalbuminemia and examine association between hypoalbuminemia and outcome in critically ill-children. **Settings and Design:** Retrospective review of medical records of 435 patients admitted to 12 bedded pediatric ICU (PICU). **Materials and Methods:** Patients with hypoalbuminemia on admission or any time during PICU stay were compared with normoalbuminemic patients for demographic and clinical profile. Effect of albumin infusion was also examined. Odds ratio and 95% confidence interval were calculated using SPSS 16. **Results:** Hypoalbuminemia was present on admission in 21% (92 of 435) patients that increased to 34% at the end of 1st week and to 37% (164 of 435) during rest of the stay in PICU. Hypoalbuminemic patients had higher Pediatric Risk of Mortality scores (12.9 vs. 7.5, $P < 0.001$) and prolonged PICU stay (13.8 vs. 6.7 days, $P < 0.001$); higher likelihood of respiratory failure requiring mechanical ventilaton (84.8% vs. 28.8%, $P < 0.001$), prolonged ventilatory support, progression to multiorgan dysfunction syndrome (87.8% vs. 16.2%) and risk of mortality (25.6% vs. 17.7%). Though, the survivors among recipients of albumin infusion had significantly higher increase in serum albumin level (0.76 g/dL, standard deviation [SD] 0.54) compared with nonsurvivors (0.46 g/dL, SD 0.44; $P = 0.016$), albumin infusion did not reduce the risk of mortality. **Conclusions:** Hypoalbuminemia is a significant indicator of mortality and morbidity in critically sick children. More studies are needed to define role of albumin infusion in treatment of such patients.

Serum Albumin Is an Independent Predictor of Clinical Outcomes in Critically Ill Children*

Heitor Pons Leite, MD, PhD¹; Alessandra Vaso Rodrigues da Silva, MD, MSc²;
Simone Brasil de Oliveira Iglesias, MD, PhD³; Paulo Cesar Koch Nogueira, MD, PhD⁴

Design: Analysis of prospectively collected database.

Setting: PICU of a teaching hospital.

Patients: Two hundred seventy-one patients consecutively admitted. Neonates, patients with chronic liver or kidney disease, inborn errors of metabolism, those who received prior administration of albumin solution, and readmissions were excluded.

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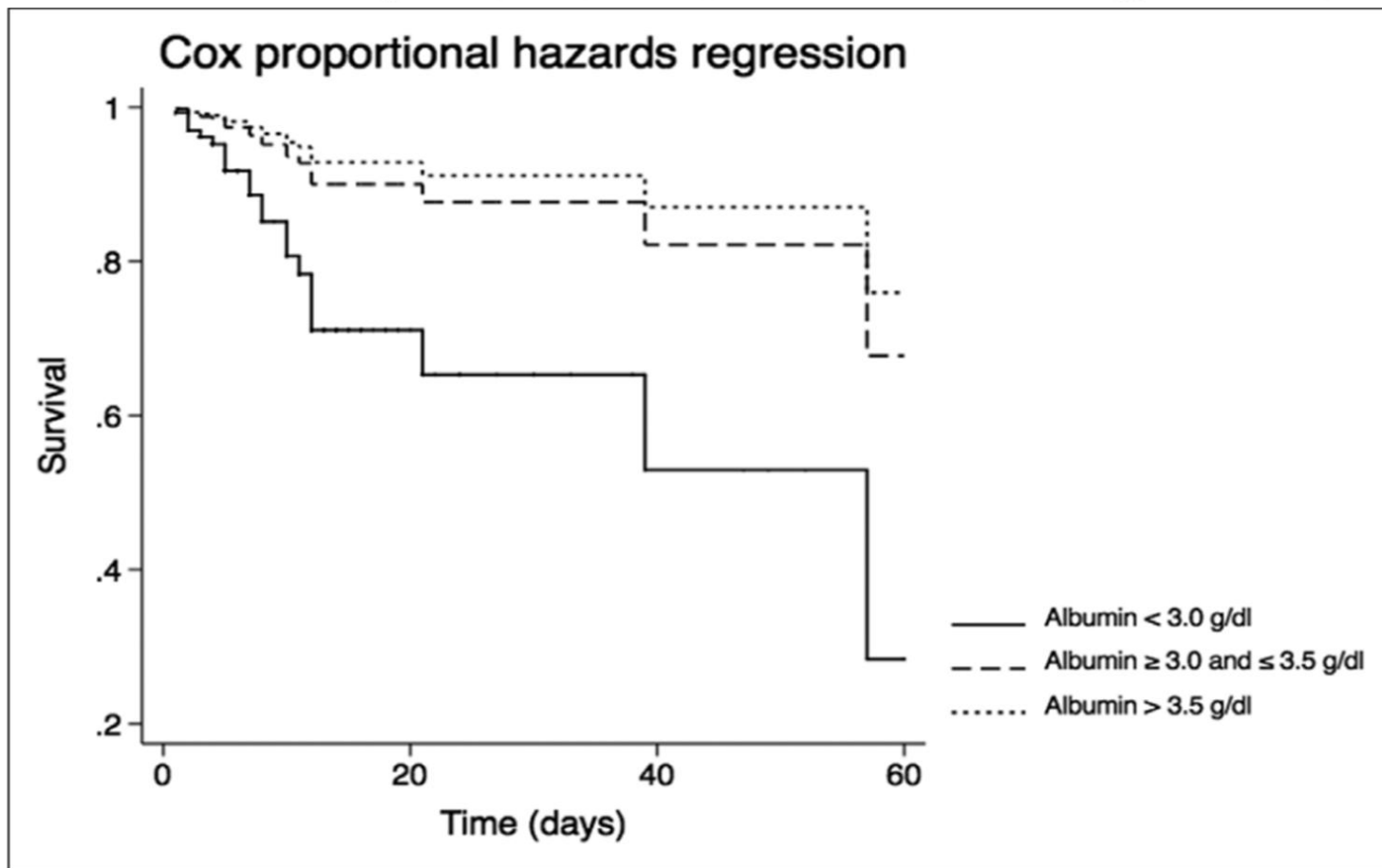


Figure 1. Kaplan-Meier survival estimate for patients according to tertiles of serum albumin concentration (< 3.0 g/dL; ≥ 3.0 and ≤ 3.5 g/dL; > 3.5 g/dL).

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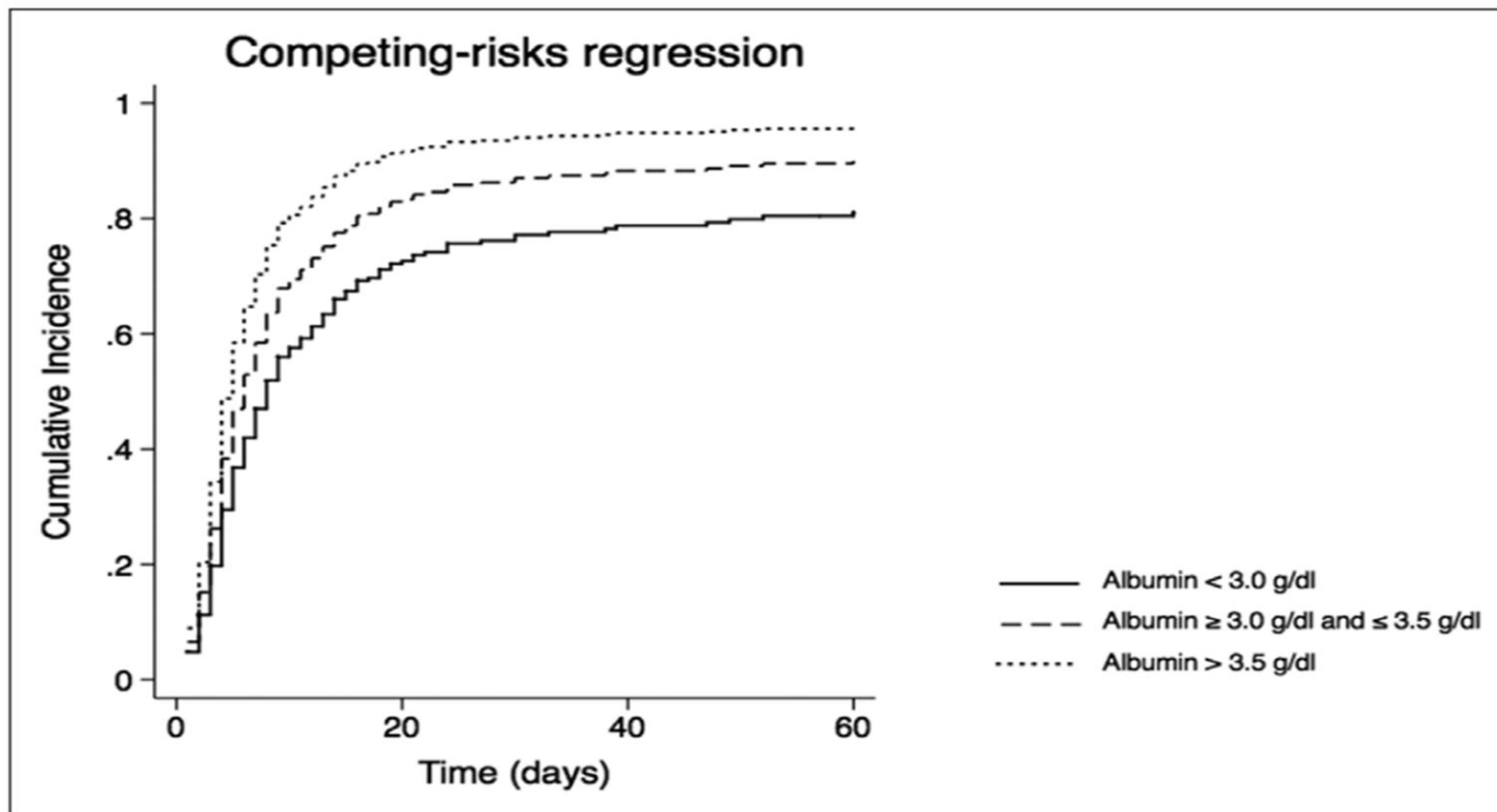


Figure 2. Cumulative incidence of ICU discharge for patients according to serum albumin concentration (< 3.0 g/dL; ≥ 3.0 and ≤ 3.5 g/dL; > 3.5 g/dL).

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TABLE 5. Univariate and Multivariable Linear Regression Analyses of the Association Between Serum Albumin and Ventilator-Free Days

Explanatory Variable	Univariate Analysis		Multivariable Analysis	
	Coefficient (95% CI)	<i>p</i>	Coefficient (95% CI)	<i>p</i>
Revised Pediatric Index of Mortality 2 score	-0.36 (-0.42 to -0.3)	< 0.001	-0.34 (-0.40 to -0.28)	< 0.001
Malnutrition	-2.52 (-4.58 to -0.46)	0.016	-0.06 (-1.81 to 1.70)	0.95
Age (mo)	0.01 (-0.01 to 0.03)	0.27	–	
Serum albumin (g/dL)	3.00 (1.46–4.54)	< 0.001	1.86 (0.56–3.16)	0.005
C-reactive protein	-0.01 (-0.03 to 0.00)	0.067	0.00 (-0.013 to 0.012)	0.96
Lactate	-0.05 (-0.11 to -0.12)	0.12	–	
Severe sepsis/septic shock at admission	-6.71 (-9.80 to -3.62)	< 0.001	-2.23 (-4.94 to 0.47)	0.105

Blank cells indicate *p* > 0.10 in Univariate Analysis, so these variables were not included in the Multivariable Analysis.

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Conclusions Hypoalbuminemia at admission to a PICU is associated with higher 60-day mortality, longer duration of mechanical ventilation, and lower probability of ICU discharge. These associations are independent of the magnitude of inflammatory response, clinical severity, and nutritional status. (*Pediatr Crit Care Med* 2016; 17:e50–e57)

DISCUSSION

Hypoalbuminaemia in critically ill children: incidence, prognosis, and influence on the anion gap

A Durward, A Mayer, S Skellett, D Taylor, S Hanna, S M Tibby, I A Murdoch

Arch Dis Child 2003;**88**:419–422

Hypoalbuminaemia is a frequent occurrence in critically ill adults, with spontaneous normalisation of values often only occurring late in the recovery phase of the disease.¹³ The aetiology of hypoalbuminaemia in critical illness is complex and may involve a number of mechanisms such as an imbalance between albumin synthesis and degradation, increased capillary leakage, and altered intravascular and tissue albumin distribution.¹³ A low serum albumin concentration may be associated with a poor outcome independent of the underlying disease process¹³; furthermore, correction by administration of intravenous albumin does not decrease mortality.^{5 14}

Serum Albumin Is an Independent Predictor of Clinical Outcomes in Critically Ill Children*

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that occurs in systemic inflammation. The increased capillary permeability leading to redistribution from the intravascular to the interstitial compartment is probably the most important mechanism of hypoalbuminemia in patients with metabolic stress (31, 32). In our study, malnutrition and the magnitude of systemic inflammation were both associated with decreased serum albumin. However, these factors accounted for only a small fraction of the decrease in albumin serum concentrations.

INCREASED VASCULAR PERMEABILITY: A MAJOR CAUSE OF HYPOALBUMINAEMIA IN DISEASE AND INJURY

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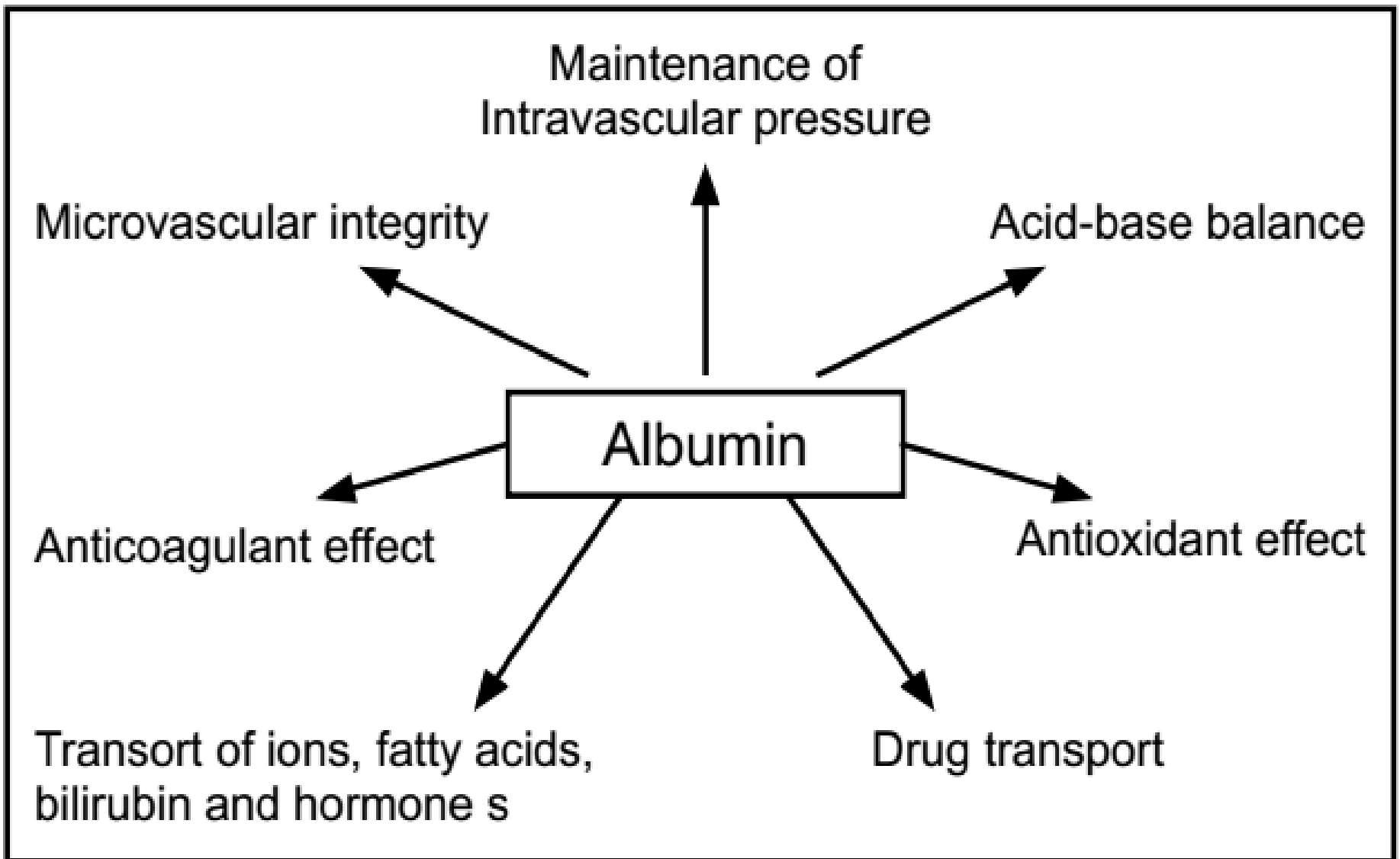
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Summary

The rate of loss of albumin to the tissue spaces (measured as transcapillary escape rate) rose by more than 300% in patients with septic shock, and the average increase within 7 h of cardiac surgery was 100%. The transcapillary escape rate in cachectic cancer patients was twice that of a group of healthy individuals. The rate of loss of albumin to the tissue spaces is normally 5%/h, which is more than 10 times the rates of synthesis and catabolism, and these large rate increases indicate that increased vascular permeability is an important cause of the lowered concentration of albumin commonly seen in acute and chronic disease.



1. Figure 1 – Physiological effects of exogenous albumin.

BENEFIT OF ALBUMIN ADMINISTRATION

Year Event

- 1941 First clinical use of human albumin solution in a patient with multiple trauma and circulatory shock
- 1943 One of the first published reports of human albumin use in 200 patients
- 1975 First randomized controlled trial of human albumin in 16 patients undergoing abdominal aortic surgery
- 1998 Cochrane meta-analysis including 30 randomized controlled trials and reporting increased mortality rates in critically ill patients who received albumin
- 1998 US Food and Drug Administration issued a 'Dear Doctor' letter to all healthcare providers expressing serious concern over the safety of albumin administration in the critically ill population, based on the findings of the Cochrane meta-analysis, and urging physicians to exercise discretion in its use
- 1999 Expert Working Party of the Committee on Safety of Medicines in UK concluded that there was insufficient evidence of harm to warrant withdrawal of albumin products but large, purpose-designed, randomized, controlled clinical trials should be conducted to answer questions about mortality effects
- 1999 Study in 126 patients with cirrhosis and spontaneous bacterial peritonitis randomized to treatment with intravenous cefotaxime or cefotaxime and intravenous albumin; hospital and 3-month mortality rates were lower in the patients who received albumin
- 2001 Wilkes and Navickis' meta-analysis including 55 trials and reporting no overall effect of albumin on mortality
- 2003 Meta-analysis of 90 cohort studies evaluating hypoalbuminemia as an outcome predictor by multivariate analysis and nine prospective controlled trials evaluating use of albumin to correct hypoalbuminemia; results showed hypoalbuminemia to be a dose-dependent predictor of poor outcome and correction of serum albumin to >30 g/l associated with reduced complications

Year Event

- 2004 Large SAFE study randomizing 6,997 patients to 4% albumin or normal saline when fluid challenge needed; results showed no difference in mortality rates among groups, and subgroup analyses suggested benefit in patients with severe sepsis and harm in those with traumatic brain injury
- 2005 US Food and Drug Administration issued a notice stating that the SAFE study had resolved the prior safety concerns raised by the Cochrane Injuries Group in 1998
- 2005 Results of SOAP observational study showing that albumin use was associated with decreased mortality in critically ill patients using a Cox proportional hazard model and a propensity case-matching analysis
- 2006 Pilot study of 100 patients with serum albumin ≤ 30 g/l randomized to receive 300 ml of 20% albumin solution on the first day and then 200 ml/day if their serum albumin concentration remained < 31 g/l, or to receive no albumin; organ function was improved in patients treated with albumin
- 2011 Meta-analysis including 17 studies in patients with sepsis reporting a survival benefit for patients who received albumin
- 2012 ESICM taskforce Consensus statement suggesting that albumin may be included in the resuscitation of severe sepsis patients (grade 2B)
- 2013 Surviving Sepsis Campaign guidelines for the first time specifically suggest (grade 2C) use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids
- 2013 EARSS randomized controlled multicenter study comparing 100 ml 20% albumin with normal saline in patients with early severe sepsis, showing no differences in mortality rates between groups
- 2014 ALBIOS randomized controlled multicenter study comparing 20% albumin plus crystalloid or crystalloid alone and then continuing albumin infusions to maintain serum albumin ≥ 30 g/l; no overall difference in 28-day or 90-day mortality rates but survival benefit at 90 days in patients with septic shock

Fluid Resuscitation in Sepsis

A Systematic Review and Network Meta-analysis

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Data Sources: MEDLINE, EMBASE, *ACP Journal Club*, CINAHL, HealthSTAR, the Allied and Complementary Medicine Database, and the Cochrane Central Register of Controlled Trials through March 2014.

Data Synthesis: 14 studies (18 916 patients) were included with 15 direct comparisons. Network meta-analysis at the 4-node level showed higher mortality with starches than with crystalloids (high confidence) and lower mortality with albumin than with crystalloids (moderate confidence) or starches (moderate confidence). Network meta-analysis at the 6-node level showed lower mortality with albumin than with saline (moderate confidence) and low-molecular-weight starch (low confidence) and with balanced crystalloids than with saline (low confidence) and low- and high-molecular-weight starches (moderate confidence).

Conclusion: Among patients with sepsis, resuscitation with balanced crystalloids or albumin compared with other fluids seems to be associated with reduced mortality.

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).

Randomized Trial of Volume Expansion with Albumin or Saline in Children with Severe Malaria: Preliminary Evidence of Albumin Benefit

Kathryn Maitland,^{1,2} Allan Pamba,¹ Michael English,^{1,4} Norbert Peshu,¹ Kevin Marsh,^{1,5} Charles Newton,^{1,3} and Michael Levin²

Background. Metabolic acidosis is the best predictor of death in children with severe falciparum malaria; however, its treatment presents a therapeutic dilemma, because acidosis and hypovolemia may coexist with coma, which can be associated with elevated intracranial pressure. We postulated that volume resuscitation with albumin might correct acidosis and hypovolemia with a lower risk of precipitating cerebral edema than crystalloid. In an open-label, randomized, controlled trial, we compared the safety of resuscitation with albumin to saline in Kenyan children with severe malaria.

Methods. We randomly assigned children with severe malaria and metabolic acidosis (base deficit, >8 mmol/L) to receive fluid resuscitation with either 4.5% albumin or normal saline. A control (maintenance only) group was only included for patients with a base deficit of <15 mmol/L. The primary outcome measure was the percentage reduction in base deficit at 8 h. Secondary end points included death, the requirement for rescue therapies, and neurological sequelae in survivors.

Results. Of 150 children recruited for the trial, 61 received saline, 56 received albumin, and 33 served as control subjects. There was no significant difference in the resolution of acidosis between the groups; however, the mortality rate was significantly lower among patients who received albumin (3.6% [2 of 56 patients]) than among those who received saline (18% [11 of 61]; relative risk, 5.5; 95% confidence interval, 1.2–24.8; $P = .013$).

Conclusions. In high-risk children with severe malaria and acidosis, fluid resuscitation with albumin may reduce mortality. Our study design did not enable us to determine whether saline administration is preferable to fluid restriction or whether saline administration is actually hazardous. Further studies are needed to confirm our findings before definitive treatment recommendations can be made.

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Mortality after Fluid Bolus in African Children with Severe Infection

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METHODS

We randomly assigned children with severe febrile illness and impaired perfusion to receive boluses of 20 to 40 ml of 5% albumin solution (albumin-bolus group) or 0.9% saline solution (saline-bolus group) per kilogram of body weight or no bolus (control group) at the time of admission to a hospital in Uganda, Kenya, or Tanzania (stratum A); children with severe hypotension were randomly assigned to one of the bolus groups only (stratum B). All children received appropriate antimicrobial treatment, intravenous maintenance fluids, and supportive care, according to guidelines. Children with malnutrition or gastroenteritis were excluded. The primary end point was 48-hour mortality; secondary end points included pulmonary edema, increased intracranial pressure, and mortality or neurologic sequelae at 4 weeks.

CONCLUSIONS

Fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in these resource-limited settings in Africa. (Funded by the Medical Research Council, United Kingdom; FEAST Current Controlled Trials number, ISRCTN69856593.)

Safety of human albumin—serious adverse events reported worldwide in 1998–2000[†]

J.-L. Vincent^{1*}, M. M. Wilkes² and R. J. Navickis²

Methods All serious adverse event reports received, and total doses of albumin distributed worldwide from the beginning of 1998 to the end of 2000 by 10 major suppliers of therapeutic human albumin were compiled.

Conclusions Although the observed incidence of adverse events is likely to be an underestimate, nevertheless both non-fatal and fatal serious adverse events in albumin recipients appear to be rare. These results add further support to the excellent safety record of human albumin.

Update on the Comparative Safety of Colloids: A Systematic Review of Clinical Studies

*A.B. Johan Groeneveld, MD, PhD, FCCP, FCCM**, *Roberta J. Navickis, PhD†*, and *Mahlon M. Wilkes, PhD†*

Methods Clinical studies reported since 2002 with safety data for acutely ill patients receiving HES, gelatin, dextran, or albumin were sought by computer searches and other methods. Safety endpoints included mortality, morbidity, bleeding and impaired coagulation, and acute kidney injury (AKI). Data extracted from the included study reports were qualitatively summarized.

Results Sixty-nine clinical studies were included. Of those, 42 were randomized controlled trials (RCTs) with 10,382 total patients. New safety data, since 2002, predominantly concerned albumin or HES. A large RCT of intensive care unit patients showed that albumin does not adversely affect survival. Acute kidney injury and a dose-dependent increase in mortality were observed in a large RCT of patients with severe sepsis or septic shock receiving HES. Impaired coagulation and clinical bleeding were frequently reported after HES infusion, especially in cardiac surgery. In head-to-head randomized comparisons of different HES solutions, observed effects on coagulation and renal function were similar. Gelatin showed less impairment of coagulation than HES. Very few safety data related to dextran were identified.

Conclusions Albumin displayed a more favorable safety profile than HES. Available evidence does not support the existence of consistent safety differences between HES solutions.

The COASST study: Cost-effectiveness of albumin in severe sepsis and septic shock[☆]

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Gaël Priol MD^d, Philippe Aegerter MD^e

Abstract

Introduction: The cost-effectiveness of albumin-based fluid support in patients with severe sepsis is not known.

Methods We compared standard medical practice and systematic albumin infusion. The study population consisted of patients with severe sepsis and/or septic shock admitted to one of the 35 intensive care units belonging to the Cub-Réa regional database between 1 January 1998 and 31 December 2002. Only stays longer than 24 hours and only patients with a minimum of circulatory, renal, or respiratory failure were considered. Cost estimates were based on French diagnosis-related groups and fixed daily prices. A 4.6% reduction in mortality was expected in the albumin arm, as observed in the Saline vs Albumin Fluid Evaluation (SAFE) Study. Life expectancy was estimated with the declining exponential approximation of life expectancy method, based on age, sex, Simplified Acute Physiology Score II, and McCabe score.

Results: The number of lives saved among the 11 137 patients was 513. The average life expectancy of the 5156 patients who left the hospital alive was estimated to be 9.78 years. The costs per life saved and per year life saved were €6037 and €617, respectively. Sensitivity analyses confirmed the robustness of the results.

Conclusion The application of the SAFE Study results to CUB-Réa data shows that albumin infusion is cost-effective in severe sepsis.

Choice of Fluids in Severe Septic Patients - A Cost-effectiveness Analysis Informed by Recent Clinical Trials

Albert Farrugia^{1,2,3,*}, Megha Bansal¹, Sonia Balboni¹, Mary Clare Kimber¹, Gregory S. Martin⁴ and Josephine Cassar⁵

Abstract: Fluid resuscitation with colloids is an established second line therapy for septic patients. Evidence of relative efficacy outcomes is tempered by considerations of the relative costs of the individual fluids. An assessment of recent large clinical trials was performed, resulting in a ranking in the efficacy of these therapies. Probabilities for mortality and the need for renal replacement therapy (RRT) were derived and used to inform a decision analysis model comparing the effect of crystalloid, albumin and hydroxyethyl starch solutions in severe septic patients followed from hospital admission to 90 days in intensive care. The US payer perspective was used. Model inputs for costs and efficacy were derived from the peer-reviewed literature, assuming that all fluid preparations are bio-equivalent within each class of these therapies. Probabilities for mortality and the need for renal replacement therapy (RRT) data were synthesized using a Bayesian meta-analysis. Relative to crystalloid therapy, 0.21 life years were gained with albumin and 0.85 life years were lost with hydroxyethyl starch. One-way sensitivity analysis showed that the model's outcomes were sensitive to the cost of RRT but not to the costs of the actual fluids or any other costs. We conclude that albumin may be the most cost-effective treatment in these patients when the total medical costs and iatrogenic morbidities involved in treating sepsis with fluids are considered. These results should assist and inform decision making in the choice of these drugs.

CONCLUSION

- Serum Albumin Is an Independent Predictor of Clinical Outcomes in Critically Ill Children.
- We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock, when patients require substantial amounts of crystalloids. Albumin infusion is safe and cost-effective in severe sepsis and septic shock.

