Albumin administration improves organ function in critically ill hypoalbuminemic patients: A prospective, randomized, controlled, pilot study*

Marc-Jacques Dubois, MD, FRCPC; Carlos Orellana-Jimenez, MD; Christian Melot, MD, PhD, Msc (Stat); Daniel De Backer, MD, PhD; Jacques Berre, MD; Marc Leeman, MD, PhD; Serge Brimioulle, MD, PhD; Olivier Appoloni, MD; Jacques Creteur, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCP, FCCM

Objective: **To test the hypothesis that administration of albumin to correct hypoalbuminemia might have beneficial effects on organ function in a mixed population of critically ill patients.**

Design: **Prospective, controlled, randomized study.**

Setting: **Thirty-one-bed, mixed medicosurgical department of intensive care.**

Patients: **All adult patients with a serum albumin concentration ≤30 g/L were assessed for eligibility. Principal exclusion criteria were expected length of stay <72 hrs, life expectancy <3 months or a do-not-resuscitate order, albumin administration in the preceding 24 hrs, or evidence of fluid overload.**

Interventions: **The 100 patients were randomized to receive 300 mL of 20% albumin solution on the first day, then 200 mL/day provided their serum albumin concentration was <31 g/dL (albumin group), or to receive no albumin (control group).**

Measurements and Main Results: **The primary outcome was the effect of albumin administration on organ function as assessed by a delta Sequential Organ Failure Assessment score from day 1 to day 7 (or the day of intensive care discharge or death, whichever came first). The two groups of 50 patients were comparable at baseline for age, gender, albumin concentration, and Acute Physiology and Chronic Health Evaluation II score. Albumin concentration did not change over time in the control group but increased consistently in the albumin group ($p < .001$). Organ function improved more in the albumin than in the control group ($p = .026$), mainly due to a difference in respiratory, cardiovascular, and central nervous system components of the Sequential Organ Failure Assessment score. Diuretic use was identical in both groups, but mean fluid gain was almost three times higher in the control group (1679 ± 1156 vs. 658 ± 1101 mL, $p = .04$). Median daily calorie intake was higher in the albumin than in the control group (1122 [935–1158] vs. 760 [571–1077] kcal, $p = .05$).**

Conclusions: **Albumin administration may improve organ function in hypoalbuminemic critically ill patients. It results in a less positive fluid balance and a better tolerance to enteral feeding. (Crit Care Med 2006; 34:2536–2540)**

KEY WORDS: albumin; hypoalbuminemia; randomized controlled clinical trial; intravenous fluid; multiple organ failure

Hypoalbuminemia occurs commonly in the intensive care unit (ICU) and may be due to decreased synthesis by the liver and/or to increased losses, either internally (in the interstitium as a result of increased capillary permeability) or externally (through blood losses or exudates or increased proteolysis and clearance) (1). The administration of albumin solutions to correct hypoalbuminemia has been debated over the years as it is not clear if hypoalbuminemia is simply a marker of the severity of disease or is causally linked to the development of complications. Moreover, albumin administration may have deleterious effects including altered coagulation, altered renal function, decreased myocardial contractility, immunosuppression, and worsened edema due to the passage of albumin into the interstitial compartment (2, 3).

The now famous Cochrane meta-analysis of clinical trials addressing albumin administration in the critically ill (4) indicated that the relative risk of death after albumin administration was 1.68 (95% confidence interval 1.26–2.23) in all patients and 1.69 (1.07–2.67) in hypoalbuminemic patients. A more recent meta-analysis on albumin administration showed no increased mortality rate in patients regardless of the indication for receiving it (5), although a recent observational study of 3,147 acutely ill patients (6) reported that albumin administration was independently associated with a lower 30-day survival, using a Cox proportional hazard model, and that, in 339 pairs matched according to a propensity score, ICU and hospital mortality rates were higher in patients who received albumin than in those who did not. However, the Saline vs. Albumin Fluid Evaluation (SAFE) study, an Australian randomized controlled trial that recruited >7,000 patients, showed no differences in outcome between patients treated with 4% albumin as their resuscitation fluid and those receiving saline (7).

The question of whether to administer albumin in hypoalbuminemic patients, however, remains largely unanswered. It is difficult to imagine how hypoalbumin-

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From the Department of Intensive Care, Erasme Hospital, Free University of Brussels, Brussels, Belgium.

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emia could be beneficial. For example, hypoproteinemia has been shown to correlate with the development of acute respiratory distress syndrome and other complications (8), and hypoalbuminemia has been associated with worse outcomes from cardiac surgery (9). Indeed, a meta-analysis of 90 cohort studies and nine prospective controlled studies showed that hypoalbuminemia was an independent predictor of poor outcome (10). This association between hypoalbuminemia and poor outcome appeared to be independent of both nutritional status and inflammation. Analysis of serum albumin concentration in the controlled trials of albumin therapy suggested that complication rates may be reduced when the serum albumin concentration reached during albumin administration exceeds 30 g/L (10). Also of concern is that mortality, the usual end point of these trials, may be insensitive in a critical care setting (11), and many have argued that morbidity may be a more sensitive end point. In a recent multiple-center trial (12), 40 mechanically ventilated patients with acute lung injury or acute respiratory distress syndrome who had total protein concentrations <6.0 g/dL were randomized to receive furosemide with placebo or furosemide with albumin for 72 hrs. Patients who received albumin had improved oxygenation, with greater net negative fluid balance and better maintenance of hemodynamic stability.

In this pilot study, we used the concept of delta Sequential Organ Failure Assessment (SOFA) (13), recently also used to assess effects of activated protein C on organ function in patients of the PROWESS study (14), to assess the effects of albumin therapy on morbidity, and we prospectively tested the hypothesis that administration of albumin to correct hypoalbuminemia might have beneficial effects on organ function in a mixed population of critically ill patients.

METHODS

Experimental Design and Study Organization. This prospective, controlled, randomized, open, single-center study was performed in the 31-bed Department of Intensive Care of the Erasme Hospital, the academic hospital of the Free University of Brussels. Every patient hospitalized in the department with a serum albumin concentration ≤30 g/L was assessed for eligibility. Exclusion criteria were age <18 yrs, expected length of stay <72 hrs (as assessed by the admitting physician), life expectancy <3 months (as assessed by the admitting physician) or a do-not-resuscitate order, previous adverse reaction to the administration of albumin, administration of albumin in the preceding 24 hrs, or the presence of any of the following: fluid overload (as assessed by the admitting physician), acute head injury with a Glasgow Coma Scale score <7, end-stage liver disease, third degree-burn, nephrotic syndrome, and need for plasmapheresis.

The protocol was approved by the Hospital Ethics Committee, which felt that written informed consent was not necessary in view of the clear lack of evidence for or against albumin administration in this situation. However, an information sheet describing the study was given to the patients or their relatives explaining that they were free to withdraw from the study at any time.

Randomization. Eligible patients were randomized in a 1:1 ratio using sealed envelopes. When a patient was assigned to one group, he or she remained in that group whether or not he or she received the planned treatment (intention-to-treat analysis).

Treatment. As part of their standard fluid management, patients randomized to the albumin group received 300 mL of 20% albumin solution (furnished by the Plasma Protein Therapeutics Association, Brussels, Belgium) on day 1 and 200 mL on subsequent days, each unit being given over a 2- to 3-hr period, provided that their serum albumin concentration was <31 g/L. Serum albumin was measured daily (by immunonephelometry); if it was >31 g/L, albumin was not administered but was given as soon as the albumin level was below this target value. The administration of albumin was restricted to emergency use in the control patients, who received Ringer's lactate as their standard fluid. In both groups, synthetic colloids were avoided. Blood components such as blood and fresh frozen plasma were given when needed. Diuretics were used as indicated. Enteral nutrition was started as soon as possible to meet a 20- to 30-kcal/kg/day goal.

End Points. The primary outcome of the study was to determine whether albumin, given to correct hypoalbuminemia, could improve organ dysfunction as assessed by a change in the SOFA score (15) (Table 1) from baseline to day 7 (or before if the patient was discharged from the ICU or died). Secondary outcomes were the mortality rate at day 28; organ dysfunction as assessed by SOFA score at days 14, 21, and 28; the ICU length of stay; use of diuretics; fluid balance; and mean caloric intake from days 1 to 7.

Data Collection. Demographic data (age and gender) and Acute Physiology and Chronic Health Evaluation II (16) and SOFA scores were obtained at randomization. Data needed to compute the SOFA score were re-

Table 1. The Sequential Organ Failure Assessment (SOFA) score (15)

SOFA Score	0	1	2	3	4
				With Respiratory Support	
Respiration, Pao_2/FIo_2, mm Hg	>400	≤400	≤300	≤200	≤100
Coagulation, platelets × $10^3/mm^3$	>150	≤150	≤100	≤50	≤20
Liver, bilirubin, mg/dL (μmol/L)	<1.2 (<20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (>204)
Cardiovascular, hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or no repinephrine >0.1[a]
Central nervous system, Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal, creatinine, mg/dL, (μmol/L)	<1.2 (<110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (>440)
Or urine output				or <500 mL/day	or <200 mL/day

MAP, mean arterial pressure.
[a]Adrenergic agents administered for ≥1 hr (doses given are in μg/kg/min).

corded daily for the first 7 days and then on days 14, 21 and 28. They included Pao_2 and FIo_2 (to calculate Pao_2/FIo_2 ratio), platelet count, bilirubin concentration, mean arterial pressure and need for vasoactive drugs, Glasgow Coma Scale score, creatinine concentration, and urine output. In addition, use of diuretics and caloric intake were recorded daily for the first 7 days following inclusion. ICU length of stay was also noted and patients were followed up to day 28 for mortality. Adverse effects related to albumin administration presenting at any time during the study period were assessed and noted.

Statistical Analysis. All data were analyzed on an intent-to-treat basis. Data are expressed as mean (and SD or confidence interval). Student's *t*-test was used to compare difference between groups for the continuous variables and Fisher's exact test for categorical variables. For the primary outcome, namely the change in SOFA scores, the independent Student's test was confirmed by a nonparametric test (Mann-Whitney's test).

A p value $<.05$ was needed for statistical significance.

RESULTS

Enrollment and Patients at Baseline. During a 9-month period (March to December 2001), 1,985 consecutive ICU patients were screened, of whom 1,880 were not enrolled because they had at least one exclusion criteria: 887 (47%) were not hypoalbuminemic on admission or during their stay, 506 (27%) had an expected length of stay <72 hrs, 179 (10%) had a medical condition precluding inclusion (73 with fluid overload, 30 with acute head injury with a Glasgow Coma Scale score <7, 25 with end-stage liver disease, and 51 with other diagnoses), 140 (7%) had a life expectancy <3 months or a do-not-resuscitate order, 89 (5%) were <18 yrs old, and 79 (4%) had received albumin in the previous 24 hrs. Of the 105 remaining patients, five had an albumin concentration >30 g/L and were immediately excluded.

Patients were comparable at baseline in terms of age, gender, type of admission, Acute Physiology and Chronic Health Evaluation II and SOFA scores, and albumin serum concentration (Table 2). There was no difference in the number of red blood cell transfusions between the groups during the study period (albumin group, 2.3 ± 1.2 units packed red blood cells; control group, 2.5 ± 1.4 units; p = not significant).

Albumin Serum Concentration. The mean amount of albumin received by the treatment group was 111 ± 12.5 g/day. Albumin serum concentration did not change in the control group but rapidly increased in the albumin group from days 1 to 7 (Fig. 1).

SOFA and Sub-SOFA Scores. The delta SOFA, established from the last and baseline SOFA values (Table 3), was greater in the albumin group than in the control group (3.1 vs. 1.4 vs. $p = .03$), a difference mainly due to respiratory (Pao_2/FIo_2 ratio), cardiovascular, and central nervous system components. The respiratory score component increased significantly from baseline to last SOFA in the albumin group (215 ± 59 to 257 ± 62) compared with the control group (238 ± 73 to 248 ± 66, $p = .0058$). For the cardiovascular score component, patients in the albumin group showed a decrease from 1 to 0 that was statistically different from the control group (0–0, $p = .01$). For the central nervous component, Glasgow Coma Scale score increased from 13 to 15 ($p = .03$) in the albumin group compared with 14 to 15 in the control group ($p = .48$)

Secondary End Points. Twelve (24%) patients in the albumin group and 15 patients (30%) in the control group died during the 28-day study period ($p = .65$). No differences in organ function were noted at days 14, 21, and 28, but only 23, 14, and 3 patients, respectively, were still part of the study at these times, the rest having died or been discharged. The length of stay was 8 ± 2 days in the albumin group and 7 ± 2 days in the control group ($p = .13$).

The use of diuretics was identical in both groups (1.5 days in the control group vs. 1 day in the albumin group, $p = .87$), but the mean daily fluid gain was almost three times higher in the control

Table 2. Baseline characteristics of patients in albumin and control groups

	Control Group (n = 50)	Albumin Group (n = 50)	*p* Value
Age, yrs	65.2 ± 13.7	63.0 ± 14.3	.43
Gender, male/female, n	30/20	31/19	1.00
Type of admission			1.00
Medical, n (%)	28 (56)	29 (58)	
Surgical, n (%)	22 (44)	21 (42)	
APACHE II score	21.3 ± 11.8	22.4 ± 10.6	.63
SOFA score	5.7 ± 0.8	6.3 ± 0.8	.31
Receiving mechanical ventilation, %	78	80	1.00
Receiving vasopressor agents, %	44	48	.66
Albumin, g/L	23.7 ± 3.7	23.2 ± 4.4	.47

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Data are expressed as mean ± SD for age, APACHE II and SOFA scores, and serum albumin concentration.

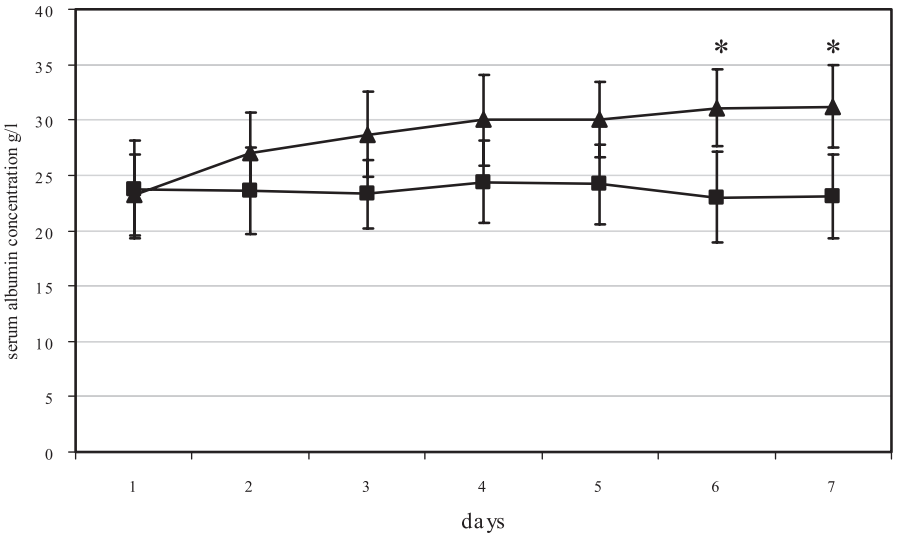

Figure 1. Serum albumin concentration (in g/L ± SD) from day 1 to day 7. *Triangles*, albumin group; *squares*, control group. *$p < .001$.

Table 3. Baseline, last, and delta Sequential Organ Failure Assessment (SOFA) values in control and albumin groups

	Control Group (n = 50)	Albumin Group (n = 50)	*p* Value
Baseline SOFA	5.7 ± 0.8	6.3 ± 0.8	.31
Last SOFA	4.6 ± 1.2	4.1 ± 1.1	.65
Delta SOFA	1.4 ± 1.1	3.1 ± 1.0	.03

Last SOFA, SOFA score at day 7 or before if patient discharged or died; delta SOFA, difference between baseline and last SOFA.

Data are expressed as mean ± SD.

group than in the albumin group (1679 ± 1156 vs. 658 ± 1101 mL, $p = .04$).

The median daily caloric intake (nonnormal distribution) was higher in the albumin group than in the control group (1122 [935–1158] vs. 760 [571–1077] kcal, $p = .05$).

Adverse Events and Crossover. One patient in the albumin group developed pulmonary edema on day 1 of randomization that was attributed to a concurrent acute coronary syndrome; he responded well to diuretics and was later discharged to the ward.

Only one patient in the control group received albumin because of profound hypoalbuminemia (17 g/L) and an inadequate hemodynamic response to crystalloid infusion.

DISCUSSION

The present pilot study suggests that administration of hyperoncotic albumin to hypoalbuminemic critically ill patients may lead to an improvement in organ function. Many studies have been conducted on the correction of hypoalbuminemia in various populations including newborns (17–20), patients receiving total parenteral nutrition (21–23), and surgical patients (24, 25). These small studies dealt with mortality as an end point and showed no benefit with albumin administration. Here we focused on the effects of albumin administration on morbidity and specifically on organ dysfunction, rather than on mortality, in critically ill patients with hypoalbuminemia.

As expected, patients in both groups experienced an improvement in organ function, but the improvement was greater in the albumin group, particularly for the respiratory, cardiovascular, and central nervous system components of the SOFA score. We found a lesser positive fluid balance in the albumin group. This observation is supported by recent results from Martin and colleagues (12), who also showed better hemodynamic stability and Pao_2/Fio_2 ratios in hypoproteinemic patients with acute lung injury or acute respiratory distress syndrome who received furosemide plus albumin compared with those who received furosemide plus normal saline. Also of interest, albumin administration has been shown to prevent decreased cardiomyocyte contractility in an endotoxemic model (26) and to improve neurologic function and decrease brain edema following cerebral ischemia (27). Our study also suggests better tolerance to enteral feeding in patients who received albumin resulting in greater daily caloric intake. Hypoalbuminemia has been associated with intolerance to enteral feeding due to mucosal interstitial edema (28) and the greater associated incidence of diarrhea (29, 30).

In healthy patients, albumin contributes up to 80% of the normal colloid oncotic pressure (COP). In critically ill patients, COP is reduced, in part due to hypoalbuminemia occurring as a result of movement of albumin from the vascular to interstitial space during acute inflammation. Since the classic experiments by Guyton et al. (31), it has been well established that a low oncotic pressure is an important factor for the development of edema when hydrostatic pressure is elevated, as is commonly observed in the critically ill patient. Correcting hypoalbuminemia with hyperoncotic 20% albumin infusions may thus be expected to mobilize interstitial fluid and improve organ function compared with patients who receive crystalloid only therapy. Indeed, the fluid gain was greater in the control group than in the albumin treated group, and one explanation for the observed effects on organ function may be that they were due to the effects of albumin on COP and may equally have been seen with an artificial colloid solution. However, the relation between COP and serum albumin concentration is not straightforward (32), and albumin possesses other effects besides its action on oncotic pressure. As a binder of endogenous and exogenous substances, albumin can influence the plasma levels of drugs (33), including antibiotics (34) and anticoagulants (35). Albumin also possesses antioxidant and scavenger properties in part by its potential to replete thiol stores (36–38), and it can modulate apoptosis (39, 40). Albumin administration may also improve microcirculatory blood flow, increase mesenteric blood flow, decrease leukocyte rolling and adherence, and reduce the inflammatory response (41). Few studies have looked at the clinical relevance of these properties, and in this pilot study we did not examine markers of inflammation or microcirculatory blood flow. Nevertheless, these characteristics of albumin may help explain the possible benefits observed following correction of hypoalbuminemia. Comparison of albumin infusion with an artificial colloid solution may have helped tease out whether the effects observed were due simply to the influence of albumin on COP or to some of its other qualities.

The pharmacoeconomic dimension of albumin administration was not studied in this pilot study. However, it is reasonable to think that even if albumin solutions are expensive, they may be cost-effective if they can influence organ dysfunction (42), as was shown here. However, albumin administration did not influence length of stay in this pilot study.

Albumin administration has been shown to be as safe as saline when used as a resuscitation fluid in critically ill patients. The recent SAFE trial (7), a multiple-center, randomized, double-blind study that included almost 7,000 patients, showed no difference in outcome when a 4% albumin solution was compared with normal saline as the standard resuscitation fluid. One may argue that there was no beneficial effect either, but the study was not designed to investigate possible beneficial effects of albumin and the amount of study fluid was relatively limited. However, the somewhat lower mortality rate in the subgroup of septic patients who received albumin may be an indication that in such patients, who are more likely to be hypoalbuminemic, albumin administration may be beneficial. The current pilot study also suggests that in the specific group of hypoalbuminemic critically ill patients, albumin may have beneficial effects on organ function, although the exact mechanisms remain

undefined. A larger trial is needed to extend these observations and to indicate whether albumin should be viewed more as a replacement or substitutive therapy than a resuscitative fluid.

REFERENCES

1. Doweiko JP, Nompleggi DJ: Role of albumin in human physiology and pathophysiology. *JPEN J Parenter Enteral Nutr* 1991; 15: 207–211
2. Johnson SD, Lucas CE, Gerrick SJ, et al: Altered coagulation after albumin supplements for treatment of oligemic shock. *Arch Surg* 1979; 114:379–383
3. Pulimood TB, Park GR: Debate: Albumin administration should be avoided in the critically ill. *Crit Care* 2000; 4:151–155
4. Cochrane Injuries Group: Human albumin administration in critically ill patients: Systematic review of randomized controlled trials. *BMJ* 1998; 317:235–240
5. Wilkes MM, Navickis RJ: Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; 135:149–164
6. Vincent JL, Sakr Y, Reinhart K, et al: Is albumin administration in the acutely ill associated with increased mortality? Results of the SOAP study. *Crit Care* 2005; 9:R745–R754
7. Finfer S, Bellomo R, Boyce N, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
8. Mangialardi RJ, Martin GS, Bernard GR, et al: Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis. Ibuprofen in Sepsis Study Group. *Crit Care Med* 2000; 28:3137–3145
9. Fritz HG, Brandes H, Bredle DL, et al: Postoperative hypoalbuminaemia and procalcitonin elevation for prediction of outcome in cardiopulmonary bypass surgery. *Acta Anaesthesiol Scand* 2003; 47:1276–1283
10. Vincent JL, Dubois MJ, Navickis RJ, et al: Hypoalbuminemia in acute illness: Is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. *Ann Surg* 2003; 237:319–334
11. Vincent JL: Search for effective immunomodulating strategies against sepsis. *Lancet* 1998; 351:922–923
12. Martin GS, Moss M, Wheeler AP, et al: A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2005; 33:1681–1687
13. Lopes Ferreira F, Peres Bota D, Bross A, et al: Serial evaluation of the SOFA score to predict outcome. *J A M A* 2001; 286:1754–1758
14. Ely EW, Laterre PF, Angus DC, et al: Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003; 31:12–19
15. Vincent JL, de Mendonça A, Cantraine F, et al: Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicentric, prospective study. *Crit Care Med* 1998; 26: 1793–1800
16. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
17. Kanarek KS, Williams PR, Blair C: Concurrent administration of albumin with total parenteral nutrition in sick newborn infants. *JPEN J Parenter Enteral Nutr* 1992; 16: 49–53
18. McMurray LG, Roe JH, Sweet LK: Plasma protein studies on normal newborn and premature infants. I. Plasma protein values for normal full term and normal premature infants. II. Use of concentrated normal human serum albumin in treatment of premature infants. *Am J Dis Child* 1948; 75:265–278
19. Smith CA, Phillips KG, Roth RO: Effects and fate of human serum albumin administered intravenously and orally to premature infants. *J Clin Invest* 1950; 29:218–226
20. Greenough A, Emery E, Hird MF, et al: Randomised controlled trial of albumin infusion in ill preterm infants. *Eur J Pediatr* 1993; 152:157–159
21. Brown RO, Bradley JE, Bekemeyer WB, et al: Effect of albumin supplementation during parenteral nutrition on hospital morbidity. *Crit Care Med* 1988; 16:1177–1182
22. Wojtysiak SL, Brown RO, Roberson D, et al: Effect of hypoalbuminemia and parenteral nutrition on free water excretion and electrolyte-free water resorption. *Crit Care Med* 1992; 20:164–169
23. Rubin H, Carlson S, DeMeo M, et al: Randomized, double-blind study of intravenous human albumin in hypoalbuminemic patients receiving total parenteral nutrition. *Crit Care Med* 1997; 25:249–252
24. Ford EG, Jennings LM, Andrassy RJ: Serum albumin (oncotic pressure) correlates with enteral feeding tolerance in the pediatric surgical patient. *J Pediatr Surg* 1987; 22: 597–599
25. Golub R, Sorrento JJ Jr, Cantu R Jr, et al: Efficacy of albumin supplementation in the surgical intensive care unit: A prospective, randomized study. *Crit Care Med* 1994; 22: 613–619
26. Walley KR, McDonald TE, Wang Y, et al: Albumin resuscitation increases cardiomyocyte contractility and decreases nitric oxide synthase II expression in rat endotoxemia. *Crit Care Med* 2003; 31:187–194
27. Belayev L, Liu Y, Zhao W, et al: Human albumin therapy of acute ischemic stroke: Marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. *Stroke* 2001; 32:553–560
28. Lobo DN, Bjarnason K, Field J, et al: Changes in weight, fluid balance and serum albumin in patients referred for nutritional support. *Clin Nutr* 1999; 18:197–201
29. Brinson RR, Kolts BE: Hypoalbuminemia as an indicator of diarrheal incidence in critically ill patients. *Crit Care Med* 1987; 15: 506–509
30. Hwang TL, Lue MC, Nee YJ, et al: The incidence of diarrhea in patients with hypoalbuminemia due to acute or chronic malnutrition during enteral feeding. *Am J Gastroenterol* 1994; 89:376–378
31. Guyton AC, Granger HJ, Taylor AE: Interstitial fluid pressure. *Physiol Rev* 1971; 51: 527–563
32. Margarson MP, Soni N: Serum albumin: Touchstone or totem? *Anaesthesia* 1998; 53: 789–803
33. Burt M, Anderson DC, Kloss J, et al: Evidence-based implementation of free phenytoin therapeutic drug monitoring. *Clin Chem* 2000; 46:1132–1135
34. Mimoz O, Soreda S, Padoin C, et al: Ceftriaxone pharmacokinetics during iatrogenic hydroxyethyl starch-induced hypoalbuminemia: A model to explore the effects of decreased protein binding capacity on highly bound drugs. *Anesthesiology* 2000; 93:735–743
35. Tincani E, Mazzali F, Morini L: Hypoalbuminemia as a risk factor for over-anticoagulation. *Am J Med* 2002; 112:247–248
36. Quinlan GJ, Margarson MP, Mumby S, et al: Administration of albumin to patients with sepsis syndrome: A possible beneficial role in plasma thiol repletion. *Clin Sci (Lond)* 1998; 95:459–465
37. Lang JD Jr, Figueroa M, Chumley P, et al: Albumin and hydroxyethyl starch modulate oxidative inflammatory injury to vascular endothelium. *Anesthesiology* 2004; 100:51–58
38. Quinlan GJ, Mumby S, Martin GS, et al: Albumin influences total plasma antioxidant capacity favorably in patients with acute lung injury. *Crit Care Med* 2004; 32:755–759
39. Zoellner H, Hofler M, Beckmann R, et al: Serum albumin is a specific inhibitor of apoptosis in human endothelial cells. *J Cell Sci* 1996; 109(Pt 10):2571–2580
40. Zoellner H, Hou JY, Lovery M, et al: Inhibition of microvascular endothelial apoptosis in tissue explants by serum albumin. *Microvasc Res* 1999; 57:162–173
41. Horstick G, Lauterbach M, Kempf T, et al: Early albumin infusion improves global and local hemodynamics and reduces inflammatory response in hemorrhagic shock. *Crit Care Med* 2002; 30:851–855
42. Vincent JL: Fluid management: The pharmacoeconomic dimension. *Crit Care* 2000; 4(Suppl 2):S33–S35