Albumin. *Its place in critical care practice*

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Most critically ill patients have a common pathophysiological process. Infection, trauma, or major surgery initiates an inflammatory cascade leading to the release of various inflammatory mediators (for example, cytokines) and activation of leukocytes. This is a self-perpetuating cascade, which results in damaged endothelial integrity, increasing microvascular permeability and promotes extravasations of fluids (including albumin) into the tissue. Moreover, there are several reasons why albumin supplementation might make things worse for critically ill patients.[1] Cost containment is becoming an increasingly important factor in medical decision making. Human albumin solutions are more expensive than other colloids and crystalloids. An acceptable alternative to albumin would be favorable. The impact of albumin infusion on survival has long been a subject of debate and several investigations. It is very difficult to comment on the rational of use of albumin in clinical practice. Variations in patients, targets, additive therapy, and other factors make interpretation of the literature difficult. Interestingly, despite advice not to use albumin, use of this product continues. There is no convincing data justifying administration of albumin either for treating hypovolemia or for correcting hypo-albuminemia. In this report, we will summarize what the literature states on the use of albumin for the critically ill patient.

Despite a growing body of systematic reviews and evidence based medicine analyses, the safety profile of albumin is still under dispute. Two meta-analysis of randomized trials have broadly assessed the effects of albumin on survival.[2,3] None showed a significant overall survival benefit. Indeed, the Cochrane Injuries Group Albumin Reviewers meta-analyses even indicated increased mortality amongst albumin recipients (6.8%). A major limitation of both meta-analyses is the reliance on survival as the end point. More than half of the included randomized trials were not designed to assess this end point. Another meta-analysis included only studies using purified albumin and a wide spectrum of patients. It included 55 trials involving 3,504 patients. Overall, this analysis detected no difference in mortality between patients treated with albumin and other fluids.[4] A more recent systematic review included 79 randomized trials with a total of 4,755 patients.[5] It showed definite beneficial effects of albumin in both cardiac and non cardiac surgery. They analyzed the use of albumin administration in diverse clinical settings, such as hypoalbuminemia, ascites, sepsis, burn patients and outcomes after brain injury. They concluded that albumin does bestow benefit in terms of decreased morbidity in a wide array of clinical settings. However, the optimal dose and administration schedule for albumin remain to be delineated. Further investigations are warranted to address these issues.

The Saline versus Albumin Fluid Evaluation (SAFE) study is the largest ever multicentric, double blind, randomized controlled trial of SAFE for fluid resuscitation of critically ill patients in intensive care from 16 intensive care units in Australia and New Zealand over an 18 month period. Of the 6,997 patients who underwent randomization, 3,497 were assigned to receive 4% albumin and 3,500 to receive saline.[6] There were 726 deaths in the albumin group compared to 729 deaths in the saline group (relative risk of death, 0.99; 95% confidence interval: 0.91-1.09; p=0.87). The 2 groups of patients had a similar proportion of new single-organ and multiple-organ failure (p=0.85). There were no significant differences between the groups in the mean numbers of days spent in the ICU, days spent in the hospital, days of mechanical ventilation, or days of renal-replacement therapy. Subgroup analysis of the albumin-treated group revealed a trend towards decreased mortality in patients with septic shock, and a trend towards increased mortality in trauma patients, especially those with traumatic brain injury. This study had conclusive evidence that 4% albumin is as safe as saline for resuscitation, although no overall benefit of albumin use was seen. The commonly used higher albumin concentrations require rigorous evaluation in clinical trials.

The Cochrane Injuries Group Albumin Reviewers continuously publishes an update of the original meta-analysis. Their last search was updated in August 2004.[7] The conclusion was that there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline in critically ill patients with burns and hypoalbuminemia or hypovolemia **(Table 1)**. Very recently, Vincent et al[8] looked at the effect of albumin administration on morbidity (including death) in acutely ill hospitalized patients. In their meta-analysis, they analyzed a nonselective, transparent large data sampling of 71 trials. They concluded that albumin reduces morbidity in a broad category of acutely ill hospitalized patients. To make a recommendation from this study, one needs to study the data carefully, as the median duration of follow-up for all included trials was only 4 days. Also, the number needed to treat to avoid one complication was 44 patients. Using such costly therapy in this meta-analysis, there was no evidence that this was

Table 1 - Cochrane Database Systematic Review result on albumin use in critically ill patients from 32 trials (updated August 2004)*:

Patients category	Relative risk of death	95% Confidence interval
Hypovolemia	1.01	0.92 - 1.1
Burns	2.4	1.11 - 5.19
Hypoalbuminemia	1.38	0.94 - 2.03

*The pooled relative risk of death with albumin administration was 1.04.

translated to a better outcome in terms of shorter ICU/hospital stay or hospital discharge. Furthermore, the albumin used by the trials included varied from 2-25% albumin concentration. Although they calculated the total amount of albumin received in grams, the question remains whether it is the concentration of albumin preparation used, the target serum albumin level or the total grams of albumin received, that matters? Albumin has been used for over 50 years for fluid resuscitation in the ICU, despite the lack of any adequately powered randomized clinical trials. As yet, there is no evidence to support the widespread use of albumin. There is no convincing data justifying administration of albumin either for treating hypovolemia or for correcting hypoalbuminemia. Until convincing data pro albumin is presented, injudicious use of albumin is not to be recommended. Further trials are required to form optimal fluid regimens, and indications. That use of albumin in critically ill patients should urgently be reviewed by the critical care practitioner. It should not be used outside the context of rigorously conducted randomized controlled trials.

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Use of adrenaline as an adjunct to local anesthetic agent. *A cause of concern for the anesthesiologist*

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Adrenaline is an endogenous catecholamine. It is a sympathomimetic agent that has both α and β adrenergic effects. Physicians mainly use it as a bronchodilator, during cardiopulmonary resuscitation and in the treatment of acute anaphylactic reactions. We often use adrenaline in a concentration of 5 µgm/ml (1:200,000) to reduce blood flow and slow the rate of absorption of the local anesthetic agent, thus reducing the plasma concentration and prolonging the duration of action.[1] It has been recognized for a long time that halothane and, to a lesser extent, other volatile anesthetics sensitize myocardium to the arrhythmogenic effects of adrenaline. Sensitization is the interaction between volatile anesthetics and catecholamines that leads to reductions in the threshold for both atrial and ventricular arrhythmias. Sequentially escalating doses of adrenaline produce premature ventricular contractions and sustained ventricular tachyarrhythmias during halothane anesthesia. Pretreatment with thiopentone attenuates halothane-adrenaline induced arrhythmias, presumably via effects on the atrioventricular node or the upper bundle of His. The doses of adrenaline required to produce ventricular arrhythmias during desflurane or sevoflurane anesthesia are similar to, but significantly less than those observed during administration of isoflurane and halothane.[2] However, Katz and Katz[3] made 3 suggestions for