Hypothesis: Restrictive albumin use guidelines in the surgical intensive care unit (SICU) will not increase mortality and will result in cost savings.

Design: Prospective cohort study.

Setting: Tertiary teaching hospital.

Patients: All patients admitted to the SICU from July 1, 2004, through July 1, 2005, were included in this study.

Interventions: Patients in the first 3 quarters of the study were treated with no restriction on albumin use. An organized educational program was initiated by the new intensivist-led critical care team and directed toward the residents, nursing staff, and primary surgical teams. Appropriate albumin use guidelines were instituted in the last quarter.

Main Outcome Measures: Prospective clinical and outcome data were collected. Albumin use data and costs were obtained from the pharmacy prospective database.

Results: A total of 1361 patients were included in the study. A statistically significant reduction in albumin use (54%) was found in the fourth quarter \((P = .004)\), and a substantial cost saving was realized (56% reduction in cost) with the albumin use guidelines. Restrictive use of albumin had no negative impact on ICU mortality. Mean Acute Physiology and Chronic Health Evaluation III scores on ICU day 1 were not different. No significant difference in mean ICU length of stay was noted. Maintained reduction in the use of albumin was documented during the next 6 quarters.

Conclusions: The implementation of albumin use guidelines during critical care resuscitation using an educational approach in a SICU is associated with reduced albumin use, significant cost savings, and no negative impact on ICU outcome. Continued educational efforts promoting evidence-based practices in the ICU are warranted.

Arch Surg. 2008;143(10):935-939

The administration of intravenous fluids to maintain or increase intravascular volume is a common intervention in the surgical intensive care unit (SICU). The choice of whether to use crystalloid (eg, isotonic sodium chloride solution, Ringer lactate) or colloid (eg, albumin, hetastarch) for fluid resuscitation in the ICU continues to be debated.1-3 Costs associated with colloid fluid resuscitation are significantly higher than costs associated with crystalloid fluid resuscitation.

Compared with other colloid and crystalloid solutions, albumin solutions are expensive.4 Volume for volume, human albumin solution is more than twice as expensive as hydroxyethyl starch and more than 30 times more expensive than crystalloid solutions, such as sodium chloride or Ringer lactate. Because of the high cost, the limited availability of human albumin, and the potential for associated adverse events,5 it is imperative that its use be restricted to indications for which it is efficacious, and hypoalbuminemia and critical illness are controversial indications.6,7

See Invited Critique at end of article

The recent publication of the Saline versus Albumin Fluid Evaluations (SAFE) study8 in 6997 critically ill patients randomized to receive 4% albumin vs isotonic sodium chloride solution documented no difference in 28-day all-cause mortality, ICU or hospital length of stay, or duration of mechanical ventilation or renal replacement therapy. This study9 further documented that albumin has no clear benefit in the fluid resuscitation of most

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critically ill patients. We therefore sought to assess the effect of implementation of an albumin use guideline in the SICU to reduce albumin use on risk-adjusted ICU mortality and cost savings.

METHODS

This prospective cohort study was conducted from July 1, 2004, to July 1, 2005. All patients admitted to the University of Michigan SICU (general surgical, transplantation, vascular, specialty surgery, and trauma patients) were included in this study. There was no restriction on albumin use in the first 3 quarters of the year. Before the beginning of the final quarter an organized educational program was initiated by the new intensivist-led critical care team in March 2005, which included the following: journal clubs (review of SAFE trial and other studies), didactic sessions (review of appropriate indications for albumin), discussion during patient care rounds, and an educational program directed toward the SICU resident team, nursing staff, and primary surgical teams. Appropriate albumin use guidelines, adapted from the University Health Consortium albumin guidelines,10 were instituted in the fourth quarter. Prospective clinical and risk-adjusted outcome data were collected by Acute Physiology and Chronic Health Evaluation (APACHE) III dedicated personnel. Albumin use data and costs were obtained from the pharmacy prospective database. Follow-up data were collected through the end of calendar year 2006.

RESULTS

All patients (n = 1361) admitted to the SICU during the study period were included in this study. The implementation of albumin use guidelines resulted in a statistically significant reduction in albumin use (54%, P = .004, Figure 1). Similarly, a significant cost savings of 56% was found (Figure 2). The cost of albumin was calculated directly based on the unit cost of 12.5 g (25%) of albumin ($43 per 50-mL vial). No difference was seen in mean APACHE III scores on ICU day 1 in all 4 quarters. No difference in ICU mortality was identified with the reduction in albumin use, despite a higher APACHE III score and predicted ICU mortality in that quarter. The ICU mortality was significantly lower than the predicted ICU mortality during all quarters (Table 1). No difference in mean ICU length of stay was noted. Follow-up data for albumin use documented a persistent reduction in albumin use in the SICU during the next 6 quarters (2005-2006, Table 2).

COMMENT

Fluid resuscitation for hypovolemia is integral to the short-term medical management of critically ill patients. When it comes to selecting the resuscitation fluid, physicians are faced with a range of options. At the most basic level, the choice is between a colloid and crystalloid solution. Colloids are widely used, having been recommended in a number of resuscitation guidelines and intensive care management algorithms.11

The American Hospital Consortium Guidelines recommend that colloids be used in hemorrhagic shock until blood products become available and in nonhemorrhagic shock after an initial infusion with crystalloid. A 1995 survey of American academic health centers, however, found that the use of colloids far exceeded these recommendations.12 There is, however, no scientific evidence for this widespread practice, with the most recent systematic review13 of 19 trials and 7576 patients concluding that “there is no evidence from randomized controlled trials that resuscitation with colloids reduces the risk of death compared to resuscitation with crystalloids in patients with trauma, burns or following surgery.”

Controversy surrounding the efficacy and potential harm of albumin use in a variety of clinical settings is long-standing.14 A meta-analysis published by the Cochrane Injuries Group15 in 1998 documented an increased mortality rate in patients randomized to albumin supplementation in 30 controlled trials (1419 patients). They concluded that “albumin should not be used outside the context of a properly conceived and rigorously controlled trial with mortality as the endpoint.” An accompanying editorial suggested that “the administration of albumin should be halted.”16
Significant criticism of the Cochrane analysis ensued, given that it had excluded a number of trials that had shown reduced mortality with albumin administration. A subsequent, more inclusive (not just critically ill patients) meta-analysis of 55 trials that involved surgery or trauma, burns, hypoaalbuminemia, high-risk neonates, ascites, and other indications was published. This analysis concluded that “no effect of albumin on mortality was detected.”

An update to the Cochrane review of albumin use in critically ill patients was published in 2004, including 32 trials and 8452 patients,18 and concluded that “there is no evidence that albumin reduces mortality in critically ill patients.” The authors again recommended that “albumin should only be used within the context of a well concealed and adequately powered randomized controlled trial.”

This landmark trial of the safety of albumin in intensive care, performed by the Australian and New Zealand Intensive Care Society Clinical Trials Group, has recently been published. The SAFE study is a prospective trial of 6,997 critically ill patients randomized to 4% albumin or isotonic sodium chloride solution for fluid resuscitation during the 28 days after ICU admission. No differences in 28-day all-cause mortality (relative risk [RR], 0.99; 95% confidence interval [CI], 0.91-1.09; \(P = .87\)), ICU or hospital length of stay, or duration of mechanical ventilation or renal replacement therapy were identified.

A subgroup analysis of the SAFE study documented that among patients with trauma (n = 1,186), albumin was associated with a trend toward increased mortality (RR, 1.36; 95% CI, 0.99-1.86), particularly in patients with traumatic brain injury. Another subgroup analysis of patients with severe sepsis (n = 1,218) documented that albumin use was associated with a trend toward reduced mortality (RR, 0.87; 95% CI, 0.74-1.02). These results must be interpreted with caution, particularly in light of emerging data documenting that albumin administration in sepsis is associated with a rapid reduction in serum albumin concentration and decreased volume expansion.19 The study cohort was also analyzed to determine the effect of baseline serum albumin concentration (\(\leq 2.5\) vs \(> 2.5\) g/dL) on outcome of resuscitation in the SAFE study, and no difference was identified in 28-day all-cause mortality, ICU or hospital length of stay, or duration of renal replacement therapy or mechanical ventilation.20

The substantial differences in the wholesale costs of these 2 therapies is notable ($232 for 1 L of 5% albumin vs $2.32 for 1 L of isotonic sodium chloride solution), with the cost for each patient treated in the SAFE study estimated at $521.30 for albumin compared with $6.90 for isotonic sodium chloride solution, a 75-fold difference.21 These cost differences suggested that the routine use of albumin is hard to justify because crystalloid use is associated with similar outcomes at a lower cost. However, some physicians may interpret the SAFE study to have documented an absence of harm associated with albumin and will continue to use it based on presumed potential benefit in select patients.22

More recently, the results of the Sepsis Occurrence in Acutely Ill Patients study, a prospective, multicenter, observational cohort study (n = 3,147) conducted in Europe, examined albumin use and outcomes. Interestingly, 354 patients (11.2%) received albumin, and most (157, 44.4%) received it during the first 24 hours after ICU admission. Albumin administration was independently associated with decreased 30-day survival (hazard ratio, 1.57; 95% CI, 1.11-2.22; \(P = .01\)) in this population of critically ill patients, of whom 1,388 (44.1%) were surgical patients. Furthermore, surgical patients were the largest cohort to receive albumin, comprising 218 of the 354 patients who received albumin during the study period.

The rationale for giving albumin solutions rather than crystalloid solutions in cases of hypovolemic shock is that fluid reabsorption from the interstitial space is enhanced, and fluid therefore remains in the vascular system longer as predicted by the Starling principle that governs hydrostatic and oncotic pressures within the capillaries. However, the Starling principle may not appropriately reflect the microcirculation in critically ill patients, especially under conditions of capillary leakage, as may happen in sepsis, burns, and other acute ill-

### Table 1. Reduction in Albumin Use in the Fourth Study Quarter Was Associated With No Difference in ICU Mortality (Despite Higher APACHE III Score and Predicted ICU Mortality) or ICU LOS

<table>
<thead>
<tr>
<th>Quarter</th>
<th>No. of Patients (N = 1,361)</th>
<th>Albumin Use, Unit of 12.5 g (25%)</th>
<th>Albumin Cost ($43 per Vial), $a</th>
<th>Mean ICU Mortality, %</th>
<th>Predicted ICU Mortality, %</th>
<th>APACHE III Score on Day 1</th>
<th>Mean ICU LOS, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>356</td>
<td>813</td>
<td>34,064</td>
<td>4.62</td>
<td>6.43</td>
<td>46.6</td>
<td>4.29</td>
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<tr>
<td>2</td>
<td>325</td>
<td>790</td>
<td>33,101</td>
<td>3.23</td>
<td>5.68</td>
<td>48.6</td>
<td>4.41</td>
</tr>
<tr>
<td>3</td>
<td>358</td>
<td>866</td>
<td>36,285</td>
<td>3.62</td>
<td>5.93</td>
<td>48.9</td>
<td>4.34</td>
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<tr>
<td>4</td>
<td>322</td>
<td>464</td>
<td>19,441</td>
<td>3.31</td>
<td>6.62</td>
<td>49.3</td>
<td>4.54</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; LOS, length of stay.

aData The cost of albumin was calculated directly based on the unit cost of 12.5 g (25%) of albumin ($43 per 50-mL vial).

### Table 2. Total Albumin Use and Cost in Subsequent 6 Quarters (2005-2006)

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Albumin Use, No. of Patients</th>
<th>Albumin Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>July-September 2005</td>
<td>770</td>
<td>16,826</td>
</tr>
<tr>
<td>October-December 2005</td>
<td>448</td>
<td>10,524</td>
</tr>
<tr>
<td>January-March 2006</td>
<td>422</td>
<td>10,379</td>
</tr>
<tr>
<td>April-June 2006</td>
<td>595</td>
<td>17,966</td>
</tr>
<tr>
<td>July-September 2006</td>
<td>496</td>
<td>16,303</td>
</tr>
<tr>
<td>October-December 2006</td>
<td>467</td>
<td>15,777</td>
</tr>
</tbody>
</table>
ness. Additional preclinical studies have documented that albumin protects against gut-induced lung injury in vitro and in vivo. Small studies have confirmed some potential benefits, particularly with the more concentrated 25% solution for restoration of colloidal osmotic pressure. Additional trials are under way (Early Albumin Resuscitation During Septic Shock, Albumin in Acute Ischemic Stroke, and Treatment of Subarachnoid Hemorrhage With Human Albumin) to further investigate the efficacy of albumin.

The lack of demonstrable evidence in improvement of mortality with the use of albumin in fluid resuscitation, coupled with the availability of equally effective lower-cost alternatives, emphasizes the need for a published set of guidelines to ensure the safe and cost-effective use of albumin. Several studies have previously shown discrepancies in albumin use even in the presence of set guidelines, with the variability dependent on the individual ordering physician’s preconceived bias, usually based on experience and not on factual evidence of superior efficacy. Fan et al showed that the most common indications for albumin use were hypotension in hemodialysis (18.9%), volume replacement or expansion (1.5%), and hypoalbuminemia (14.8%). No indication for albumin use was identified in 9.4% of patients. Albumin use was dependent on the specialty of the ordering physician, with surgeons and nephrologists accounting for most use. Additional educational efforts are therefore warranted.

Few data exist regarding the use of albumin and outcome in SICU patients. An administrative database study in patients undergoing coronary artery bypass graft surgery (n = 19,578) who received colloids (albumin vs non-protein colloids [hetastarch or dextran]) identified that albumin use in 8084 cases (41.3% of the study cohort) was associated with lower all-cause in-hospital mortality (2.47% vs 3.03%, P = .02). In the multivariable logistic regression analysis, albumin use was associated with 25% lower odds of mortality compared with nonprotein colloid use (OR, 0.80; 95% CI, 0.67-0.96). Whether this study documented the improved efficacy of albumin or the adverse effects of nonprotein colloids in this patient population is controversial. Most importantly, this study’s major limitation was that there was no crystalloid control group. Additional studies in burn shock resuscitation document the lack of efficacy of albumin on the incidence of multiple organ dysfunction or other outcome measures.

Our current study documented that the implementation of albumin use guidelines and educational efforts was effective in significantly reducing albumin use in a SICU. During the first 3 quarters of this study, no attempt was made to assess the appropriateness of albumin use, in terms of either indication or dosage, but it is evident that albumin was used contrary to the established evidence-based guidelines. This is a common occurrence, with an evaluation of albumin use in 53 hospitals in the United States confirming that albumin was inappropriately prescribed for 57.8% of adult patients and 52.2% of pediatric patients.

The absence of any demonstrable negative impact of reduction in albumin use on risk-adjusted ICU mortality or ICU length of stay in SICU patients further supports the use of crystalloids as the first-line fluid during resuscitation in the critical care setting. Additional efforts are required to further reduce albumin use in SICUs, and ongoing efforts are under way. Institutions should implement guidelines that focus on responsible use of albumin in an increasingly cost-conscious health care environment, and continued educational efforts promoting evidence-based practices in the ICU are warranted.

Accepted for Publication: July 5, 2007.
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Financial Disclosure: None reported.

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(Reprinted) Arch Surg/Vol 143 (No. 10), Oct 2008 www.archsurg.com 938

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Charles et al have nicely shown that implementation of clinical guidelines derived from evidence-based medicine can change physician behavior. Indeed, evidence-based medicine is slowly being adopted in areas where such data exist. The crystalloid-colloid argument for resuscitation of trauma and burn patients has long been over, with the exception of instances in which lower volumes would be logistically helpful on the battlefield. However, the use of colloid has its proponents, now mostly anesthesiologists, who use it in the intraoperative and perioperative periods. Hextend rather than albumin is used because of the expense of the latter. The idea that colloid administration would result in less tissue edema has not been borne out experimentally because third spacing of colloids eventually occurs. The Cochrane database has repeatedly shown no difference in mortality with albumin use, and more recently the SAFE trial has also shown no benefit from albumin in the critical care patient. Despite these data, albumin use has been excessive in some centers. Following an educational program that included discussion during rounds, journal clubs, and didactic sessions, albumin use was reduced without any change in ICU mortality during the study period of 1 year. Associated costs were reduced as well, and illness severity, as measured by APACHE III scores, was similar during the observation period. This study is an excellent example of how such evidence-based medicine can be implemented locally, but it takes a champion of the cause and a team concept as well for institutional change. Although the study was reliant on historical controls and not randomized, it was prospective and demonstrated a marked reduction in albumin use that persisted during the following year. One wonders if there will be much use for albumin in this setting now that the data are compelling against its use in the ICU.

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Financial Disclosure: None reported.