Volume Resuscitation in Sepsis: The Albumin Debate

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Pharmacy Grand Rounds
January 23, 2018
Objectives

1. Describe the proven and theoretical roles of albumin in physiological homeostasis
2. Review the data supporting and refuting the use of albumin in sepsis
3. Recognize when albumin administration is appropriate in a patient with sepsis
Systemic Effects of Sepsis
Fluid Resuscitation Rationale

• Early-goal directed therapy significantly reduces in-hospital mortality in patients with septic shock

• Immediate fluid resuscitation is the standard of care for septic shock
  • Does not require central venous pressure monitoring
  • Administration guided by clinical assessment

The ProCESS Investigators. NEJM. 2014; 370(18): 1683-93.
The Ideal Resuscitation Fluid

• Effect on intravascular volume expansion
  • Predictable
  • Sustained
• Similar chemical properties of extracellular fluid
• No resultant adverse effects or sequelae
• Favorable patient outcomes
• Cost effective
• Readily available

Crystalloids and Colloids

Crystalloid

Colloid (Albumin)
Crystalloids For Fluid Resuscitation

- Effect on intravascular volume expansion
  - Predictable
  - Sustained
- Similar chemical properties of extracellular fluid
- No resultant adverse effects or sequelae
- Favorable patient outcomes
- Cost effective
- Readily available

Albumin Physiological Role

• Albumin is responsible for 75% of plasma colloid oncotic pressure.

• Albumin may also influence vascular permeability through interstitial matrix binding.

Albumin For Fluid Resuscitation

Effect on intravascular volume expansion
- Predictable
- Sustained
- Similar chemical properties of extracellular fluid
- No resultant adverse effects or sequelae
- Favorable patient outcomes
- Cost effective
- Readily available

Which of the Following is a Theoretical Role of Albumin in Fluid Resuscitation

1. Provides an predictable amount of volume per gram administered in sepsis
2. Inexpensive and widely available
3. Creates oncotic and osmotic pressure to provide intravascular volume without excess fluid
4. Has not been reported to cause any adverse effects following administration
### Serum Albumin and Mortality Risk - 1997

<table>
<thead>
<tr>
<th>Background</th>
<th>• Accumulating literature on inverse relationship between serum albumin level and risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Systematic review</td>
</tr>
</tbody>
</table>
| Main comparison | Serum Albumin:  
• Healthy subjects vs.  
• Individuals with acute/chronic illness |
| Primary outcome | Mortality |
| Results | • For each 2.5 g/dL decrease in serum albumin the estimated increase in mortality risk was 24% - 56% |
| Overall interpretation | • Low serum albumin may increase mortality risk  
• Lacks guidance on hypoalbuminemia management |

## Albumin Administration in Critically Ill Patients - 1998

<table>
<thead>
<tr>
<th>Background</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• It is unknown whether albumin replacement will affect patient outcomes in critical illness</td>
<td></td>
</tr>
<tr>
<td>• Due to the expense of albumin, its use should be restricted to patients that will derive benefit</td>
<td></td>
</tr>
<tr>
<td>Study type</td>
<td>Meta analysis</td>
</tr>
<tr>
<td>Main comparison</td>
<td>Albumin or Plasma Protein Fraction vs. Crystalloid or No Administration</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>All-cause mortality</td>
</tr>
</tbody>
</table>
# Albumin Administration in Critically Ill Patients - 1998

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>1.46 (0.97 to 2.22)</td>
</tr>
<tr>
<td>Burns</td>
<td>2.40 (1.11 to 5.19)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1.69 (1.07 to 2.67)</td>
</tr>
<tr>
<td>Pooled relative risk of death</td>
<td>1.61 (1.09 to 2.38)</td>
</tr>
</tbody>
</table>

Overall risk of death for albumin was 6% (3% to 9%)

### Albumin Administration in Critically Ill Patients - 1998

| Strengths | • Multiple trials for each treatment group  
|           | • Groupings used for risk classification were relevant to clinical practice |
| Weaknesses | • Limited subpopulations used for analysis  
|           | • Lack of well-defined mechanism for increased mortality |
| Overall Interpretation | • Despite the findings of this study, it remains unlikely that albumin administration truly increases mortality |

# Survival After Albumin Administration - 2001

## Background
Previous meta-analysis had significant limitations:
- Relevant trials weren’t included
- Omission of key patient groups
- Included studies with poor methodological quality

<table>
<thead>
<tr>
<th>Study type</th>
<th>Meta analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main comparison</td>
<td>Albumin vs. Crystalloid Therapy, No Albumin, Lower-Dose Albumin</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Relative risk of death</td>
</tr>
</tbody>
</table>

Survival After Albumin Administration - 2001

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled</td>
<td>1.11 (0.95 to 1.28)</td>
</tr>
<tr>
<td>Surgery or trauma</td>
<td>1.12 (0.85 to 1.46)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1.59 (0.91 to 2.78)</td>
</tr>
<tr>
<td>Ascites</td>
<td>0.93 (0.67 to 1.28)</td>
</tr>
<tr>
<td>&lt; 100 patients</td>
<td>1.37 (1.10 to 1.70)</td>
</tr>
<tr>
<td>≥ 100 patients</td>
<td>0.94 (0.77 to 1.14)</td>
</tr>
</tbody>
</table>
## Survival After Albumin Administration - 2001

| **Strengths** | • Included higher-quality trials for analysis  
|              | • Multiple sub-analyses to aid in clinical interpretation |
| **Weaknesses** | • Albumin often compared to no intervention  
|              | • Fluid management regimens varied significantly  
|              | • Analysis was not specific to sepsis |
| **Overall Interpretation** | • Albumin administration does not appear to harm patients, but comparative data is lacking regarding its utility as an alternative fluid |

## Saline and Albumin for Fluid Resuscitation in the ICU (SAFE Trial) - 2004

### Background
- Previous RCTs have been inadequately powered to assess survival
- Previous meta-analyses have found varying impact of albumin on mortality, limiting clinical utility

### Study type
Randomized controlled trial

### Patient population
- Critically ill patients requiring fluid resuscitation to maintain or increase intravascular volume

### Main comparison
Albumin 4% (n = 3,499) vs. Normal Saline (n = 3,501)

### Primary outcome
28 day all-cause mortality
Saline and Albumin for Fluid Resuscitation in the ICU (SAFE Trial) - 2004

<table>
<thead>
<tr>
<th>Results</th>
<th>Primary Outcome: Death at 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin group:</td>
<td>Outcome (95% CI)</td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.99 (0.91 to 1.09)</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>-0.2% (-2.1% to +1.8%)</td>
</tr>
</tbody>
</table>
## Subgroup Analyses: Death at 28 days

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe sepsis</td>
<td>0.87 (0.74 to 1.02)</td>
</tr>
<tr>
<td>No severe sepsis</td>
<td>1.05 (0.94 to 1.17)</td>
</tr>
</tbody>
</table>

Test for a common relative risk ($p = 0.06$)
Saline and Albumin for Fluid Resuscitation in the ICU (SAFE Trial) - 2004

| Strengths                  | • Randomized controlled trial  
|                           | • Investigated a variety of subpopulations |
| Weaknesses                | • Subpopulation analyses were not powered to drive clinical decisions |
| Overall Interpretation    | • Similar mortality outcomes at 28 days  
|                           | • Possible benefit of albumin with severe sepsis |

# Albumin Replacement in Critically Ill Hypoalbuminemic Patients - 2006

## Background
- Uncertain role of hypoalbuminemia
  - Cause of complications?
  - Marker of disease severity?
- Uncertain benefit of albumin replacement

## Study type
Randomized controlled trial

## Patient population
Critically ill patients with serum albumin ≤ 3.0 g/dL

## Main comparison
- 300 mL 20% albumin (D1) and 200 mL/d thereafter while serum albumin remains < 3.1 g/dL vs. No albumin

## Primary outcome
Change in SOFA score from baseline to day 7

SOFA Score

• Sequential Organ Failure Assessment (SOFA)
• Quantifies number and severity of organ failures
• Composite of:
  • Respiration, Pao2/FIo2
  • Platelet count
  • Bilirubin level
  • Blood pressure (hypotension)
  • Glasgow Coma Scale score
  • Serum creatinine or urine output

# Albumin Replacement in Critically Ill Hypoalbuminemic Patients - 2006

## Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Primary Outcome</th>
<th>Control (n=50)</th>
<th>Albumin (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SOFA</td>
<td></td>
<td>5.7 ± 0.8</td>
<td>6.3 ± 0.8</td>
<td>0.31</td>
</tr>
<tr>
<td>Final SOFA</td>
<td></td>
<td>4.6 ± 1.2</td>
<td>4.1 ± 1.1</td>
<td>0.65</td>
</tr>
<tr>
<td>Δ SOFA</td>
<td></td>
<td>(-) 1.4 ± 1.1</td>
<td>(-) 3.1 ± 1.0</td>
<td><strong>0.03</strong></td>
</tr>
</tbody>
</table>

Δ SOFA was favorably greater the albumin group

### Albumin Replacement in Critically Ill Hypoalbuminemic Patients - 2006

<table>
<thead>
<tr>
<th>Results</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 day mortality</td>
<td>Control 30%</td>
</tr>
<tr>
<td>No difference</td>
<td>Albumin 24%</td>
</tr>
<tr>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Use of diuretics</td>
<td>Control 1.5 D;</td>
</tr>
<tr>
<td>No difference</td>
<td>Albumin 1 D</td>
</tr>
<tr>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Daily fluid balance</td>
<td>Control 1.6 L ± 1.1 L</td>
</tr>
<tr>
<td>~3x higher in control</td>
<td>Albumin 0.6 L ± 1.1 L</td>
</tr>
<tr>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Albumin Replacement in Critically Ill Hypoalbuminemic Patients - 2006

| Strengths                        | • Focus on organ dysfunction rather than mortality  
|                                 | • Evaluated effect of albumin on fluid balance  
| Weaknesses                      | • No assessment of the cause of hypoalbuminemia  
|                                 | • Assessed only replacement, not fluid resuscitation  
| Overall Interpretation          | • Albumin administration in critically ill hypoalbuminemic patients improved SOFA scores  
|                                 | • It is unclear whether these findings apply to specific disease states such as sepsis  

Dubois et al. *Crit Care Med.* 2006; 34(10): 2536-40..
## Albumin Replacement in Severe Sepsis or Septic Shock (ALBIOS Trial) - 2014

<table>
<thead>
<tr>
<th><strong>Background</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• The SAFE trial suggested a trend towards mortality benefit from albumin in severe sepsis</td>
<td></td>
</tr>
<tr>
<td>• Subsequent studies showed benefit to maintaining albumin levels &gt; 3.0 g/dL</td>
<td></td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>Critically ill patients with severe sepsis</td>
</tr>
<tr>
<td><strong>Main comparison</strong></td>
<td>20% Albumin + Crystalloid Solution vs. Crystalloid Solution</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>28 day all-cause mortality</td>
</tr>
</tbody>
</table>

### Fluids Administered and Treatment Effects

<table>
<thead>
<tr>
<th>Results</th>
<th>Albumin: 3.7 L (IQR 3.2 to 4.4 L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No difference in total daily fluid administration during the first 7 days</td>
<td>Control: 3.8 L (IQR 3.2 to 4.5 L)</td>
</tr>
<tr>
<td></td>
<td>P = 0.10</td>
</tr>
</tbody>
</table>

CI: Confidence interval  
IQR: Interquartile range  
LOS: Length of stay

## Albumin Replacement in Severe Sepsis or Septic Shock (ALBIOS Trial) - 2014

### Primary Outcome: 28 Day Mortality

<table>
<thead>
<tr>
<th>Results</th>
<th>Control</th>
<th>Albumin</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32.0%</td>
<td>31.8%</td>
<td>1.00 (0.87 to 1.14)</td>
</tr>
</tbody>
</table>

### Subgroup Outcomes: Death at 90 Days

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative risk (95% CI), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>0.87 (0.77 to 0.99), p = 0.03</td>
</tr>
<tr>
<td>No septic shock</td>
<td>1.13 (0.92 to 1.39), p = 0.25</td>
</tr>
</tbody>
</table>

### Albumin Replacement in Severe Sepsis or Septic Shock (ALBIOS Trial) - 2014

| Strengths | • Analyzed albumin use in both sepsis and low albumin  
|           | • Assessed both mortality and organ function |
| Weaknesses | • Potentially underpowered due to low mortality rate  
|           | • Risk for type 1 error |
| Overall Interpretation | • Albumin administration did not provide a mortality benefit at 28 days in patients with severe sepsis  
|           | • Difference found in septic shock was not sufficiently powered and may have been due to chance |

## Evidence Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAFE Trial, 2004</td>
<td>• Albumin had similar mortality outcomes at 28 days</td>
</tr>
<tr>
<td>Albumin Replacement, 2006</td>
<td>• Albumin improved SOFA scores in critically ill hypoalbuminemic patients</td>
</tr>
<tr>
<td>ALBIOS Trial, 2014</td>
<td>• Albumin replacement provided similar mortality outcomes at 28 days in patients with sepsis</td>
</tr>
</tbody>
</table>

Surviving Sepsis Campaign: Guidelines for Sepsis and Septic Shock, 2016

- Fluid resuscitation recommendations
  - Continue fluids as long as clinical status improves
  - Crystalloids are the fluid of choice
  - Use albumin + crystalloids in patients that require substantial amounts of crystalloids

Application Question 1

QL is a 59 year old male admitted to your service with sepsis. He does not have any medical comorbidities.

QL does not have vasopressor requirements.

Current labs and vitals

- HR: 116  
- MAP: 58  
- Serum albumin: 3.2 g/dL  
- Lactate: 2.5 mEq/dL
Application Question 1

You have been asked to select a resuscitation fluid for QL. Which of the following would be the most appropriate?

1) 5% albumin
2) 20% albumin
3) Lactated ringers
4) 5% dextrose in water
Application Question 2

QL has now received 9 liters of lactated ringers for fluid resuscitation.

His hemodynamic status remains unstable and the team would like to continue to administer fluids.

You notice that QL has developed significant anasarca since the initiation of fluid resuscitation and the team questions if they should make a change to his resuscitation fluid.
Application Question 3

What do you suggest for additional fluid resuscitation for QL?

1) Continue with lactated ringers
2) Switch to normal saline
3) Switch to 25% albumin
4) Switch to 5% albumin
Summary

• In most instances crystalloids are preferred to albumin for fluid resuscitation in sepsis
  • Equivalent outcomes even when albumin is replaced to goal
  • Albumin expense

• Preexisting data does not cover all patient circumstances and clinical judgement must be used
  • Fluid overload and edema
  • Liver dysfunction
Future

• Albumin vs. crystalloids in septic shock
• Albumin vs. crystalloids in hepatic impairment
• Predictive utility of ischemia-modified albumin
• Volume-expanding effect of albumin and alterations in infusion rate
Volume Resuscitation in Sepsis: The Albumin Debate

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