Albumin Therapy in Critically Ill Patients
by Mihaela Popescu, Pharm.D.

Introduction: Serum albumin is the most abundant blood plasma protein and constitutes more than half of the intravascular protein mass. Albumin is synthesized in the liver, and it is responsible for up to 80% of the plasma osmotic pressure. Albumin has multiple physiologic functions including binding and transporting molecules, scavenging free radicals, inhibiting platelet function, antithrombotic effects, and contributing to the capillary membrane permeability. Normal serum albumin concentration is 4 g/dL, and its concentration in the interstitial space is usually half the concentration in the intravascular space. Albumin circulates from the intravascular space across the capillary wall into the interstitial compartment. It then returns to the intravascular space via the lymphatic system. Commercially available human albumin is derived from pooled human plasma and is available in 5% and 25% concentrations.

Albumin in Volume Resuscitation: The ideal fluid to use for volume resuscitation in critically ill patients has been an ongoing debate for many years. Isotonic crystalloid solutions (e.g., Lactated Ringer’s and 0.9% sodium chloride) distribute in the extracellular space (25% intravascular, 75% interstitial). They are linked to reducing colloid oncotic pressure and predisposing patients to pulmonary edema. It is hypothesized that colloids such as albumin, dextrans, or blood products (e.g., packed red blood cells or fresh frozen plasma) remain within the intravascular space and provide an oncotic gradient that favors the entry of water from the interstitial space. However, in patients with altered permeability (e.g., septic shock, ARDS), this benefit can be lost as albumin leaks from the intravascular to the interstitial space within hours.

Please refer to Table 1 for details on the distribution of various crystalloids and colloids in the body as well as select indications. Refer to Table 2 for cost information.

Albumin in Critically Ill Patients: In 1998, a Cochrane review investigated the effect of human albumin and plasma protein fraction (PPF) on mortality in critically ill patients suffering hypovolemia, burns, or hypoalbuminemia.
Thirty randomized trials were included, and patients administered albumin or PPF were compared to patients who received crystalloid solutions or no therapy. The pooled relative risk of death with albumin use was 1.68 (95% CI: 1.26 – 2.23). For all patient categories (i.e., critically ill patients with hypovolemia, burns or hypoalbuminemia), the mortality risk was higher with albumin use. In the subgroup of hypovolemic patients, the relative risk of death after albumin administration was 1.46 (95% CI: 0.97-2.22, p>0.2). The authors suggested the increased risk was attributable to albumin’s anticoagulant properties, alteration in interstitial oncotic pressure, and the adverse effects associated with rapid volume replacement. The authors concluded that there was no evidence suggesting that albumin reduces mortality; furthermore, the authors hypothesized that albumin may have the potential to increase mortality in select patients.

Horsey commented on the limitations of the 1998 Cochrane review, suggesting it lacked a homogenous patient population, consistency in severity of illness, treatment regimens, correlation between time of death, and time of albumin administration. Additionally, mortality was not the primary endpoint in many of the studies included in the 1998 review.

An updated Cochrane review was published in 2004, but it only included one additional study [Saline versus Albumin Fluid Evaluation (SAFE) trial]. The review reached the same conclusions as the 1998 review. The pooled relative risk of death with albumin was 1.04 (95% CI: 0.96-1.13, p=0.34). In the subgroup of hypovolemic patients, the relative risk of death with albumin was 1.01 (95% CI: 0.93-1.11, p=0.76).

### Table 1: Fluid Distribution and Major Indications

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Intracellular</th>
<th>Interstitial</th>
<th>Intravascular</th>
<th>Major Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% sodium chloride or Lactated Ringer’s</td>
<td>None</td>
<td>750 mL</td>
<td>250 mL</td>
<td>Intravascular repletion in hemodynamically unstable patients</td>
</tr>
<tr>
<td>3% sodium chloride</td>
<td>→</td>
<td>750 mL +</td>
<td>250 mL +</td>
<td>Small amounts (e.g., 250 mL) by intermittent infusion have been used in conjunction with 0.9% sodium chloride or Lactated Ringer’s for intravascular depletion in patients with head trauma</td>
</tr>
<tr>
<td>5% dextrose/0.45% sodium chloride</td>
<td>333 mL</td>
<td>500 mL</td>
<td>167 mL</td>
<td>Maintenance fluid in euvolement or dehydrated (sodium and water loss) patients with mild signs/symptoms of volume depletion</td>
</tr>
<tr>
<td>5% dextrose</td>
<td>667 mL</td>
<td>250 mL</td>
<td>83 mL</td>
<td>Dehydration (primarily water loss) in patients with mild signs/symptoms of volume depletion</td>
</tr>
<tr>
<td>6% hetastarch with electrolytes (Hextend®)</td>
<td>None</td>
<td>None</td>
<td>1,000 mL</td>
<td>Treatment of hypovolemia</td>
</tr>
<tr>
<td>5% albumin</td>
<td>None</td>
<td>None</td>
<td>1,000 mL</td>
<td>Intravascular repletion in symptomatic patients</td>
</tr>
<tr>
<td>25% albumin</td>
<td>→</td>
<td>→</td>
<td>1,000 mL +++</td>
<td>Usually given by intermittent infusion of small volumes (e.g., 50–100 mL) or by continuous infusion titrated to response in hypovolemic patients with excess interstitial fluid accumulation</td>
</tr>
</tbody>
</table>

Note: All amounts are based on the assumption that 1000 mL of each respective fluid was administered.

→ direction of fluid shift (from the intracellular space to the intravascular space)

+ fluid pulled from other compartments
Wilkes and colleagues performed a meta-analysis of 55 trials (n=3504) comparing the use of albumin with crystalloid therapy, lower doses of albumin, or no albumin. Regimens in the control group included crystalloids, but not synthetic colloids, blood products, or PPF. There was no difference in mortality between the groups. The relative risk of death for all trials was 1.11 (95% CI: 0.95 – 1.28, p>0.2).

Haynes and colleagues performed a meta-analysis of 79 randomized trials (n=4755) in the following seven categories of clinical indications: cardiac surgery, non-cardiac surgery, hypoalbuminemia, ascites, sepsis, burns, and brain injury. The use of albumin was compared to the use of different crystalloid fluids for volume expansion. In cardiac surgery (31 trials, n=1559), albumin administration led to lower fluid requirements, higher oncotic pressure, and lower incidence of pulmonary edema (p<0.05). The same effects on fluid requirements and pulmonary edema occurrence were noted in non-cardiac surgery (17 trials, n=999), but there was no effect on increasing oncotic pressure. In ascites (10 trials, n=942), albumin reduced hemodynamic instability, morbidity and length of stay, and improved survival after spontaneous bacterial peritonitis (p<0.05). In sepsis (4 trials, n=104), albumin decreased the incidence of pulmonary edema and respiratory dysfunction compared with crystalloid (p<0.05). The authors concluded that albumin may be favorable in various clinical settings, however, further investigation is needed to assess the proper dose and administration schedule.

Another meta-analysis analyzed the morbidity of critically ill patients who received albumin in comparison to those patients who received crystalloids, low dose albumin, or no albumin. The study included 71 trials (n = 3782) and patients with various albumin indications, such as surgery or trauma, burns, or hypoalbuminemia. The authors concluded that patients receiving albumin had a lower rate of morbidity with a relative risk of 0.92 (95% CI: 0.86 – 0.98, p=.002). The number needed to treat with albumin (mean follow-up: 4 days) to avoid one complication was 44 patients.

Finfer and colleagues performed a randomized, double-blind trial to investigate the effects of fluid resuscitation with 4% albumin or saline on mortality in patients (n=7000) admitted to the intensive care unit (ICU). Patients with trauma, severe sepsis, or ARDS were followed for 28 days. The authors found no significant difference in mortality, morbidity, length of stay in the ICU, length of hospital stay, frequency of need for mechanical ventilation, renal replacement therapy, or time until death. The study supports the hypothesis that albumin and normal saline are clinically equivalent as therapy for intravascular volume resuscitation in critically ill patients.

### Table 2: Average Wholesale Prices of Select Crystalloids and Colloids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
<th>Average Wholesale Price (AWP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% sodium chloride</td>
<td>1000 mL</td>
<td>$9</td>
</tr>
<tr>
<td>6% Hextend®</td>
<td>500 mL</td>
<td>$40</td>
</tr>
<tr>
<td>5% albumin</td>
<td>250 mL</td>
<td>$100</td>
</tr>
<tr>
<td>25% albumin</td>
<td>100 mL</td>
<td>$100</td>
</tr>
</tbody>
</table>

**Conclusion:** At the Cleveland Clinic, due to a nationwide shortage, 5% albumin is restricted to pediatrics, the operating rooms, and neurosurgery intensive care unit (for severe or critical cerebral vasospasm after subarachnoid hemorrhage). There are currently no specific formulary restrictions for 25% albumin, however, the CC Pharmacy and Therapeutics Committee monitors its utilization. Based on evidence available, albumin and crystalloids are clinically equivalent as there are no substantial data to support a difference in survival or morbidity.

**References:**

**Formulary Update**

The CC Pharmacy and Therapeutics (P&T) Committee met on Tuesday, October 13, 2009, and the following decisions were made:

**Additions:**
1. **Prasugrel (Effient®):** Prasugrel is FDA-approved to reduce the rate of thrombotic cardiovascular (e.g., stent thrombosis) events in patients with unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI) managed with percutaneous coronary intervention (PCI). For acute coronary syndromes, the dose is administered orally. For patients ≥60 kg, the loading dose is 60 mg and the maintenance dose is 10 mg once daily (in combination with aspirin 75-325 mg/day). Prasugrel use is **restricted** to CC Cardiology Service for initiation of therapy, but there is no restriction for continuation of therapy.

   For both initiation and continuation of therapy, absolute contraindications must be reviewed:
   Per CC Guidelines, there is an **absolute contraindication** to the use of prasugrel:
   - Any previous history of stroke or transient ischemic attack
     See Warning Bleeding Risk below
   Per CC Guidelines, there are **relative contraindications** to the use of prasugrel:
   - Age ≥75 years old (unless high-risk for ischemic complications)
   - Weight <60 kg
   - Strongly suspect surgical coronary disease
   - Currently receiving clopidogrel (Plavix®) or ticlopidine (Ticlid®)
   - Patients who require long-term anticoagulation [e.g., warfarin (Coumadin®)]

   **PER PRASUGREL PRESCRIBING INFORMATION: WARNING- BLEEDING RISK**

   Prasugrel can cause significant, sometimes fatal bleeding. Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients ≥75 years of age, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior myocardial infarction), where its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue prasugrel at least 7 days prior to any surgery.

   Additional risk factors for bleeding include:
   - body weight <60 kg
   - propensity to bleed
   - concomitant use of medications that increase the risk of bleeding

   Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures in the setting of prasugrel. If possible, manage bleeding without discontinuing prasugrel. Stopping prasugrel particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.
2. **Dronedarone (Multaq®):** Dronedarone is FDA-approved to reduce the risk of hospitalization related to paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL) in patients with a recent episode of AF/AFL and associated cardiovascular risk factors (e.g., age >70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm, or left ventricular ejection fraction <40%), who are in normal sinus rhythm or will be cardioverted. Dronedarone has been proven to be more efficacious than placebo but less efficacious than amiodarone in clinical trials. However, it has less side effects than amiodarone but similar drug interactions (i.e., there are drugs that are contraindicated, such as potent CYP3A4 inhibitors, drugs that prolong the QT interval, and grapefruit juice). The dose is 400 mg orally twice a day with meals. Dronedarone use is **restricted** to CC Electrophysiology Service (EPS) for initiation of therapy, but there is no restriction for continuation of therapy.

   There is a **Black Box Warning** for dronedarone: “In patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms, patients receiving dronedarone had a greater than two-fold increase in mortality; use is contraindicated in patients with NYHA Class IV Heart Failure or NYHA Class II-III Heart Failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic. If patients develop new or worsening heart failure symptoms (e.g., weight gain, dependent edema, or increasing shortness of breath) while on therapy, consider suspension or discontinuation of dronedarone.”

3. **Dexamethasone Intravitreal Implant (Ozurdex®):** Ozurdex® is FDA-approved for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central vein occlusion (CRVO). The implant contains dexamethasone 0.7 mg in the NOVADUR solid polymer drug delivery system and re-administration may need to occur at 3 months. It is contraindicated in ocular or periocular infections and in advanced glaucoma. The most common adverse reactions reported by >20% of patients included increased ocular pressure and conjunctival hemorrhage. Its use is **restricted** to outpatients at the Cole Eye Institute.

### Changes to Formulary Restrictions:

**Dexmedetomidine (Precedex®):** The formulary restrictions for dexmedetomidine will be expanded to include use in the adult MICU for failure to wean from the ventilator due to agitation.

**Dofetilide (Tikosyn®):** If a dofetilide order is received by a pharmacist to verify in EPIC during off hours, and it is ordered by a non-authorized dofetilide prescriber for **continuation of therapy from home**, then the pharmacist can verify and dispense **one dose**. The primary service will need to consult EPS the next day for approval of the continuation of therapy.