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Drug Shortage Alert
Albumin
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Recommendations and information provided in this Drug Shortage Alert are compiled by experts in the field. Practitioners are advised to consult with their institution's staff to ensure that response to any drug shortage is in line with internal policies and procedures.

INTRODUCTION

- Albumin has previously and sporadically been affected by shortages due to manufacturer discontinuation and/or increased demand. Depending on current availability, routine usage should be evaluated, and restrictive criteria may need to be implemented to conserve existing supply for critical patients and certain indications.
- Albumin shortages in the ICU can have several implications for patients. This alert is for the following albumin solutions:
    - Albumin 5% solutions
    - Albumin 25% solutions
- This summary provides potential management strategies, pharmacotherapeutic considerations, and safety implications.
- The recommendations are based on both current evidence and the need for conservation during this shortage.

MANAGEMENT STRATEGIES

Depending on your institution's supply, considerations for reserving albumin for the following scenarios, which have literature supporting benefit over alternatives, is prudent:

- **Albumin 25%**
    - Large volume paracentesis
    - Spontaneous bacterial peritonitis
    - Hepatorenal syndrome/acute kidney injury (AKI)
- **Albumin 5%**
    - Sepsis and septic shock*
    - Burn hypovolemia*
    - Cardiac surgery*
    - Therapeutic apheresis

    *Reserve for selected patients (**Table 1**)

Table 1 describes selected indications for the above-mentioned drug shortage, specifically in critically ill patients. Data suggest that restricting albumin to indications with the strongest data for support is associated with decreased albumin use, decreased costs, and no change in clinical outcomes.[1,2]

Table 1. Potential Management Strategies for Albumin Drug Shortage

Indication in critically ill patients	Suggested strategies	Key points
Indications with strongest data to support use of albumin		

LVP[3,4]	• > 5L LVP
	  ○ Administer 6 to 8 g of albumin for every L of fluid removed
	• ≤ 5L LVP
	  ○ Consider albumin replacement only in setting of hypotension (SBP < 90 mm Hg), hyponatremia (Na < 130 mmoL/L) and/or AKI
	• Round dose to nearest 12.5 g; utilize 25%
		• Risk of post-paracentesis circulatory dysfunction (PPCD) increases with LVP > 8 L
		  ○ PPCD presents as renal impairment, hyponatremia, hepatic encephalopathy, and potentially death
		• Albumin replacement reduces the risk of renal impairment and mortality
		• Suggest against performing LVP (>4L) in critically ill patients with SBP, due to volume shifts

Spontaneous bacterial peritonitis treatment[3]	• Day 1: 1.5 g/kg albumin once • Day 3: 1 g/kg albumin once • Round dose to nearest 12.5 g; utilize 25%. A maximum dose of 100 g has been suggested.	• Use albumin in combination with antibiotics • Highest benefit of albumin is in those with AKI (BUN > 30 mg/dL or SCr > 1 mg/dL) or jaundice (bilirubin > 5 mg/dL)
HRS/AKI (previously type I HRS)[3]	• Preferred treatment with a vasoconstrictor is recommended first line (terlipressin preferred, although norepinephrine or oral midodrine combined with IV/SQ octreotide may be used if needed) in combination with albumin • Dose: albumin 1 g/kg on day 1 followed by 40-50 g/day for up to 14 days	• Multiprofessional team should be involved for the initiation of vasopressor/albumin therapy and/or RRT • Monitor for development of pulmonary edema from albumin • If no improvement in SCr by day 4, vasoconstrictor/albumin therapy should be discontinued
Therapies requiring albumin (apheresis, plasmapheresis, plasma exchange)[5]	• Albumin 5% is used as replacement fluid in several types of therapeutic apheresis • Other replacement fluids such as FFP or crystalloids may be used in certain types of therapeutic apheresis	• Albumin dose is variable and depends on the plasma volume removed
Indications with data to support use of albumin in selected patients		

Sepsis and septic shock[6-8]	• First-line treatment is with crystalloids for fluid resuscitation
	  ○ Balanced crystalloids are suggested over normal saline
		• Crystalloid therapy is first-line for resuscitation (strong recommendation, moderate quality of evidence).
		  ○ A quantity of 30 mL/kg is suggested in the first 3 hours, although this

	• Consider albumin only after use of large volume of crystalloid for resuscitation • Guidelines recommend against using starches (e.g., hetastarch) or gelatin	quantity should be dependent on patient comorbidities (e.g., heart failure, anuria) (weak, low quality of evidence) • There is no consensus regarding crystalloid volume at which to consider albumin nor the dose of albumin to use • Albumin may confer some hemodynamic benefits over crystalloid, but there is no associated mortality benefit ○ The ALBIOS trial evaluating albumin 20% replacement to 3 g/dL plus crystalloid versus crystalloid alone in patients with severe sepsis demonstrated a higher mean arterial pressure and lower fluid balance at 7 days in the albumin arm without difference in 28-day or 90-day mortality • Measures of fluid responsiveness and perfusion should be assessed to guide fluid administration after initial bolus
Burn hypovolemia[9-13]	• First-line treatment with crystalloids (lactated Ringer solution) for resuscitation • Albumin use should be reserved for patients with > 20% TBSA after failing crystalloid resuscitation	• Failing crystalloid resuscitation or under-resuscitation is defined as fluid resuscitation volume exceeding the Parkland formula calculation by more than 1.5 to 2 times (6 mL/kg/%TBSA) after 8 to 12 hours from the time of injury ○ This phenomenon is also known as "fluid creep" • Albumin dose or volume should be calculated as a proportion of the hourly fluid rate ○ Albumin is usually started at 1/3 of the current hourly fluid rate and lactated Ringer solution at 2/3 • Limit albumin use to 48 hours
Cardiac surgery[14-19]	• First-line treatment with crystalloids • Reserve albumin for patients with pulmonary edema or other clinically important edema • Albumin may be used in patients who received large volume of crystalloids (e.g., 2L)	• Recently published ALBICS trial did not show a difference in major adverse events between 4% albumin and Ringer acetate in patients undergoing on-pump cardiac surgery ○ Secondary outcomes demonstrated patients who received 4% albumin had less myocardial injury but had a

		higher risk of infection, bleeding, and need for reoperation ○ A before-and-after study found that utilizing use criteria for albumin postcardiac surgery resulted in significant decrease in albumin use without increase in complications. • An Australian retrospective study including approximately 1200 postcardiac surgery patients found that patients exposed to albumin had more complications. Patients who received albumin were more likely to need reoperations and receive blood transfusions. These finding are similar to the finding in the ALBICS trial. • The use of albumin in cardiac surgery remains a highly debatable issue, as the evidence is mainly retrospective and the outcomes are conflicting. The ALBICS trial provides more clarity, but the single center design, exclusion of high-risk patients, and use of 4% albumin and Ringer acetate may limit its generalizability
Hypotension in hemodialysis[20-24]	• Recommend using crystalloids as a first line therapy for IDH • Mannitol 20% or 25% may be used as a second-line therapy after crystalloids • Mannitol 20% or 25% infused at a rate of 25 g/h (0.25 g/kg/h) up to total maximum of 75 g	• Albumin 5% should not be used to treat IDH • Albumin 25% may be considered in patients with contraindication to mannitol, including patients who are anuric or severely hypovolemic or who have intracranial bleed or preexisting severe pulmonary edema • Utilizing an algorithm for IDH may minimize the use of albumin for IDH treatment
ECMO[25-28]	• First-line treatment with crystalloids for fluid resuscitation • Circuits can be primed with crystalloid solutions and/or blood products • Albumin 25% may be added to the crystalloid-primed circuit	• Evidence for the use of albumin for resuscitation in patients on ECMO is scarce • Available evidence comprises small retrospective studies with conflicting results
Hemorrhagic shock[29-32]	• Balanced transfusions of plasma, red blood cells, and platelets are preferred	• There is no benefit of albumin over crystalloid if IV fluids are used • Albumin should be avoided in traumatic brain injury due to potential

	• If IV fluids are needed, use crystalloids • Crystalloid administration should be limited to no more than 3L in the first 6 hours	increase in mortality and worse neurologic outcomes • Albumin may be used as a plasma-expansion therapy if accepted by patients who decline blood transfusions (e.g. Jehovah's Witnesses)
Liver transplant[3]	• When volume replacement is needed intraoperatively during liver transplant, albumin is suggested over crystalloids • Recommend against starches due to renal failure and coagulopathy	• No studies exist comparing crystalloids versus colloids on graft survival or mortality in liver transplant. Indirect evidence suggests a potential reduction in mortality in a meta-analysis of critically ill patients.
Diuresis[33-36]	• Routine use of albumin in patients with diuretic resistance is not recommended • Albumin might be considered in patients with diuretic resistance (failure to increase fluid and sodium output sufficiently to relieve volume overload, edema or congestion despite a full dose of a loop diuretic) and serum albumin concentration of less than 2.5 g/dL	• Evidence is limited to small, low-quality studies • Meta-analyses have found an improvement in urine output with the combination of albumin and loop diuretics; however, the meta-analyses used small, low-quality studies with some moderate or high risk of bias • If albumin is used in combination with diuretics, albumin should be discontinued if the fluid balance goals were not achieved in 24 hours

AKI, acute kidney injury; BUN, blood urea nitrogen; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; HRS, hepatorenal syndrome; IDH, intradialytic hypotension; LVP, large-volume paracentesis; RRT, renal replacement therapy; SCr, serum creatinine; SBP, systolic blood pressure; SQ, subcutaneous; TBSA, total burn surface area.

PHARMACOTHERAPEUTIC CONSIDERATIONS

- The use of both albumin 5% and albumin 25% in the setting of drug shortages is indication dependent. Please refer to the above review for more information regarding indications and specific dosing.
- Monitoring daily use for assessment of appropriate indication/dosing may reduce usage in times of shortage.
- Clinician education on indications as well as on alternate strategies is warranted.
- If necessary, albumin 25% can be diluted with dextrose 5% in water or normal saline.
    - This practice should be avoided unless significant shortage exists due to medication safety implications with compounding as well as shorter expiration date.
    - Risk of fatal hemolysis and AKI exist if albumin is diluted with sterile water for injection.
- **Table 2** lists some alternatives to albumin therapy including other colloid solutions such as hetastarch, dextran, frozen plasma, and crystalloids.

Table 2. Alternative Products for Albumin Drug Shortage

Product	Dosing	Monitoring	Key points

• Crystalloids • Lactated Ringer solution • Normal saline	500 to 1000 mL, repeated as needed based on intravascular volume	Monitor closely for fluid overload	If a patient has a contraindication to crystalloid therapy due to need for fluid restriction, acid-base imbalance, or electrolyte disorders, an alternative colloid should be considered
• HES • Hetastarch	500 to 1000 mL, repeated as needed based on intravascular volume status	• Use of HES products has been shown to increase risk of mortality, kidney injury, and coagulopathy • Starches have several contraindications, including congestive heart failure, renal failure, liver failure, coagulopathy, hyperviscosity, and previous reaction to starches	• Not recommended for use in critically ill patients, those with sepsis or septic shock, or those undergoing cardiopulmonary bypass or with kidney impairment • May consider in selected patients in volume replacement with plasma exchange and apheresis
Dextran 40 (LMD)	500 to 1000 mL (approximately 10 mL/kg)	• Monitor closely for fluid overload • Bleeding • Renal impairment • Thrombocytopenia	• Crystalloids are recommended as initial fluid of choice in resuscitation
Fresh frozen plasma	>30% TBSA • 0.5 mL/kg/% TBSA/24 hours in patients with burn >30% TBSA Plasma volume expansion in hemorrhagic shock • 37.5mL/kg or 1 unit (approximately 250mL)	• Urine output	• Reserve only for selected patients with volume overload • Consider only for selected patients • Consider benefit vs. risks

HES, hydroxyethyl starch; TBSA, total burn surface area.

SAFETY IMPLICATIONS

- Lack of availability of albumin for patients at risk for volume overload may put the patient at risk for further edema and volume overload when alternative products are utilized in place of albumin.
- Patients at risk for volume overload should be monitored more closely, including those with renal disease, congestive heart failure, and other comorbidities with predisposition to volume overload.
    - Edema and fluid overload risk depend on the volume and rate of fluid infusion and clinical scenario.
- Because albumin is a human-derived blood product, adverse effects are rare (< 0.1%), but include:
    - Anaphylactoid reactions
    - Flushing
    - Urticaria
    - Fever or chills
    - Nausea or vomiting
    - Tachycardia
    - Hypotension
- Albumin administration is associated with a significant sodium load (e.g., 145 mEq/L of either preparation), so it is important to consider when substituting products and concentrations.

IMPACT ON ICU CARE

- Albumin shortages may necessitate careful resource allocation decisions with clinicians evaluating the most critical cases for albumin administration. This can pose challenges in balancing the needs of different patients and optimizing treatment options based on available resources.
    - Multiprofessional teams should evaluate current available alternatives by indication and potentially obtaining increased stock of alternatives.
- Aside from crystalloids, there are few safe and effective alternatives available as a substitute for albumin.
- Albumin should be reserved for the above indications in patients who are not appropriate candidates for crystalloid therapy or where data prefer albumin.

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REFERENCES

1. Charles A, Purtill M, Dickinson S, et al. Albumin use guidelines and outcome in a surgical intensive care unit. *Arch Surg*. 2008 Oct;143(10):935-939; discussion 939.
2. Buckley MS, Knutson KD, Agarwal SK, et al. Clinical pharmacist-led impact on inappropriate albumin use and costs in the critically ill. *Ann Pharmacother.* 2020 Feb;54(2):105-112.
3. Nanchal R, Subramanian R, Alhazzani W, et al. Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU: neurology, peri-transplant medicine, infectious disease, and gastroenterology considerations. *Crit Care Med*. 2023 May 1;51(5):657-676.
4. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021 Aug;74(2):1014-1048.
5. Connelly-Smith L, Alquist CR, Aqui NA, et al. Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the Writing Committee of the American Society for Apheresis: the ninth special issue. *J Clin Apher*. 2023 Apr;38(2):77-278.
6. Martin GS, Bassett P. Crystalloids vs. colloids for fluid resuscitation in the intensive care unit: a systematic review and meta-analysis. *J Crit Care*. 2019 Apr;50:144-154.
7. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021 Nov 1;49(11):e1063-e1143.
8. Caironi P, Tognoni G, Gattinoni L. Albumin replacement in patients with severe sepsis or septic shock. *N Eng J Med.* 2014 Jul 3;371(1):84.
9. Saffle JIL. The phenomenon of “fluid creep” in acute burn resuscitation. *J Burn Care Res*. 2007 May-Jun;28(3):382-395.
10. Pruitt BA Jr. Protection from excessive resuscitation: “pushing the pendulum back.” *J Trauma*. 2000 Sep;49(3):567-568.
11. Pham TN, Cancio LC, Gibran NS; American Burn Association. American Burn Association practice guidelines burn shock resuscitation. *J Burn Care Res*. 2008 Jan-Feb;29(1):257-266.
12. Lawrence A, Faraklas I, Watkins H, et al. Colloid administration normalizes resuscitation ratio and ameliorates “fluid creep.” *J Burn Care Res*. 2010 Jan-Feb;31(1):40-47.
13. Cartotto R, Callum J. A review of the use of human albumin in burn patients. *J Burn Care Res*. 2012 Nov-Dec;33(6):702-717.
14. Russell JA, Navickis RJ, Wilkes MM. Albumin versus crystalloid for pump priming in cardiac surgery: meta-analysis of controlled trials. *J Cardiothorac Vasc Anesth*. 2004 Aug;18(4):429-437.
15. Podgoreanu MV, Mamoun N. Albumin vs crystalloid fluid for resuscitation in cardiac surgery: new evidence and arguments in the timeless debate. *JAMA*. 2022 Jul 19;328(3):246-248.
16. Pesonen E, Vlasov H, Suojaranta R, et al. Effect of 4% albumin solution vs Ringer acetate on major adverse events in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized clinical trial. *JAMA*. 2022 Jul 19;328(3):251-258.
17. Matebele MP, Ramanan M, Thompson K, Cornmell G, Naidoo RV, Shekar K. Albumin use after cardiac surgery. *Crit Care Explor*. 2020 Jul;2(7):e0164.
18. Kingeter AJ, Raghunathan K, Munson SH, et al. Association between albumin administration and survival in cardiac surgery: a retrospective cohort study. *Can J Anaesth*. 2018 Nov;65(11):1218-1227.
19. Fink RJ, Young A, Yanez ND, et al. Cohort study of albumin versus lactated Ringer’s for postoperative cardiac surgery fluid resuscitation in the intensive care unit. *Pharmacotherapy*. 2018 Dec;38(12):1241-1249.

20. McCausland FR, Prior LM, Heher E, Waikar SS. Preservation of blood pressure stability with hypertonic mannitol during hemodialysis initiation. *Am J Nephrol*. 2012;36(2):168-174.
21. Knoll GA, Grabowski JA, Dervin GF, O'Rourke K. A randomized, controlled trial of albumin versus saline for the treatment of intradialytic hypotension. *J Am Soc Nephrol*. 2004 Feb;15(2):487-492.
22. Kanbay M, Ertuglu LA, Afsar B, et al. An update review of intradialytic hypotension: concept, risk factors, clinical implications and management. *Clin Kidney J*. 2020 Jul 8;13(6):981-993.
23. Fortin PM, Bassett K, Musini VM. Human albumin for intradialytic hypotension in haemodialysis patients. *Cochrane Database Syst Rev*. 2010 Nov 10;(11):CD006758.
24. Emili S, Black NA, Paul RV, Rexing CJ, Ullian ME. A protocol-based treatment for intradialytic hypotension in hospitalized hemodialysis patients. *Am J Kidney Dis*. 1999 Jun;33(6):1107-1114.
25. Wengenmayer T, Schroth F, Biever PM, et al. Albumin fluid resuscitation in patients on venoarterial extracorporeal membrane oxygenation (VA-ECMO) therapy is associated with improved survival. *Intensive Care Med*. 2018 Dec;44(12):2312-2314.
26. Prucha J, Peitz G, Blais M. 1491: Hemodynamic and ECMO flow response to albumin versus crystalloid therapy. Abstract 1491. *Crit Care Med*. 2022 Jan;50(1):749.
27. Jeon JB, Lee CH, Lim Y, et al. Hypoalbuminemia and albumin replacement during extracorporeal membrane oxygenation in patients with cardiogenic shock. *J Chest Surg*. 2023 Jul 5;56(4):244-251.
28. Gajkowski EF, Herrera G, Hatton L, Velia Antonini M, Vercaemst L, Cooley E. ELSO guidelines for adult and pediatric extracorporeal membrane oxygenation circuits. *ASAIO J*. 2022 Feb 1;68(2):133-152.
29. Shafi S, Collinsworth AW, Richter KM, et al. Bundles of care for resuscitation from hemorrhagic shock and severe brain injury in trauma patients: translating knowledge into practice. *J Trauma Acute Care Surg*. 2016 Oct;81(4):780-794.
30. Rashid M, Kromah F, Cooper C. Blood transfusion and alternatives in Jehovah's Witness patients. *Curr Opin Anaesthesiol*. 2021 Apr 1;34(2):125-130.
31. Melia D, Post B. Human albumin solutions in intensive care: a review. *J Intensive Care Soc*. 2021 Aug;22(3):248-254.
32. Cannon JW. Hemorrhagic shock. *N Engl J Med*. 2018 Jan 25;378(4):370-379.
33. Lee TH, Kuo G, Chang CH, et al. Diuretic effect of co-administration of furosemide and albumin in comparison to furosemide therapy alone: an updated systematic review and meta-analysis. *PLoS One*. 2021 Dec 1;16(12):e0260312.
34. Kitsios GD, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. *J Crit Care*. 2014 Apr;29(2):253-259.
35. Itagaki Y, Yoshida N, Banno M, Momosaki R, Yamada K, Hayakawa M. Efficacy of albumin with diuretics in mechanically ventilated patients with hypoalbuminemia: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2022 Sep 16;101(37):e30276.
36. Ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. *Nat Rev Cardiol*. 2015 Mar;12(3):184-192.

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