Effect of Albumin on Diuretic Response to Furosemide in Patients with Hypoalbuminemia

By Thitima Doungngern, PharmD, BCPS, Yvonne Huckleberry, PharmD, BCPS, John W. Bloom, MD, and Brian Erstad, PharmD.

Background
Albumin is broadly prescribed for critically ill patients although it does not have a mortality benefit over crystalloids. One common use of albumin is to promote diuresis.

Objectives
To compare urine output in patients treated with furosemide with and without albumin and to assess other variables possibly associated with enhanced diuresis.

Methods
A retrospective study was conducted on patients in a medical intensive care unit who received furosemide therapy as a continuous infusion with and without 25% albumin for more than 6 hours. Primary end points were urine output and net fluid loss.

Results
A total of 31 patients were included in the final analysis. Mean urine output in patients treated with furosemide alone did not differ significantly from output in patients treated with furosemide plus albumin at 6, 24, and 48 hours: mean output, 1119 (SD, 597) mL vs 1201 (SD, 612) mL, $P = .56$; 4323 (SD, 1717) mL vs 4615 (SD, 1741) mL, $P = .42$; and 7563 mL (SD, 2766) vs 7432 (SD, 2324) mL, $P = .94$, respectively. Additionally, net fluid loss did not differ significantly between the 2 groups at 6, 24, and 48 hours. Higher concentrations of serum albumin did not improve urine output. The only independent variable significantly associated with enhanced urine output at 24 and 48 hours was increased fluid intake.

Conclusion
Volume overload, a common problem in critically ill patients, is typically treated with fluid restriction and diuretics. Furosemide is the loop diuretic most often prescribed to enhance urine output in these patients. Compared with bolus administration, continuous infusion of furosemide may improve diuresis with fewer adverse effects. However, furosemide resistance may occur in critically ill patients despite alterations in dosing regimens, making it difficult to achieve goals for fluid output.

The mechanism of diuretic resistance remains unclear, but hypoalbuminemia may be one of the causes. A preliminary study by Inoue et al. indicated that the combination of furosemide and albumin, given as a single bolus, was as effective as the same dose of furosemide alone in improving urine output in patients with diuretic resistance. Maximal urine output occurred within 1 hour in both groups of patients. Patients had various diagnoses, and the clinical design of the study is not well described. In subsequent studies with improved designs, the effects of furosemide plus albumin in specific populations of patients such as those with nephrotic syndrome and cirrhosis with ascites were conflicting. Most recently, Martin et al. suggested that furosemide plus albumin may be better than furosemide alone for the treatment of adult respiratory distress syndrome. Because of the large number of patients needed to show potential mortality differences with the use of albumin, investigators have focused on more specific benefits of albumin related to oxygenation or diuresis.

Because of periodic shortages, high cost, and potential adverse effects of albumin, studies of the effectiveness of albumin in enhancing diuresis in critically ill patients are needed. Our study was designed to determine if continuous infusions of 25% albumin enhanced urine output when given with continuous infusions of furosemide. We had a unique opportunity to study this issue because cotherapy with albumin and furosemide infusions that may precede or follow furosemide infusions alone are often used in the medical intensive care unit (ICU) at Arizona Health Sciences Center, Tucson, Arizona. The primary objective of the study was to compare urine output in patients given furosemide alone with output in patients given both furosemide and albumin. The secondary objective was to identify other variables that might be associated with enhanced diuresis.

**Methods**

**Study Design**

Adult patients in the medical ICU who received a continuous furosemide infusion with and without 25% albumin were studied retrospectively. The study was conducted at Arizona Health Sciences Center, a tertiary care, academic medical center. The local institutional review board reviewed and approved the study. Primary end points were urine output and net fluid loss.

The diuretic effect of a continuous infusion of furosemide peaks approximately 3 hours after the infusion is started. Therefore, cumulative urine output at 6 hours was chosen as the initial and primary end point to ensure measurement of the full diuretic effect of the furosemide infusion.

**Selection of Patients**

Any adult patient admitted to the medical ICU between January 1, 2007, and August 31, 2010, who received a sequential continuous furosemide infusion for at least 6 hours and a combined furosemide plus 25% albumin infusion for at least 6 hours was included in the study. The order of infusion did not matter so long as no gap occurred between the 2 sequential infusions. Patients were excluded if they did not have sequential infusions of furosemide.
and furosemide plus albumin, received furosemide or furosemide plus albumin before the sequential infusions, had incomplete intake and output records, or had renal dysfunction (defined as serum creatinine level greater than 1.5 mg/dL; to convert creatinine levels greater than 1.5 mg/dL and/or acute tubular necrosis. Therefore, data on 31 patients were included in the final analysis. Of the 31 patients, 17 initially received furosemide infusions; the other 14 patients initially received infusions of furosemide plus albumin.

A total of 19 patients (61%) were women, and the mean age was 54.3 years. The 3 most common underlying illnesses were cancer (36%), most often skin cancer; cardiovascular disease (23%); and liver disease (16%), mostly due to hepatitis C. A total of 26 patients (84%) had a ratio of PaO₂ to fraction of inspired air less than 300. Other baseline characteristics are presented in Table 1.

Table 1 shows data for the patients who received furosemide alone and furosemide plus albumin. The infusion rate for furosemide was initiated at 2 to 5 mg/h and titrated in an attempt to achieve a urine output 50 to 100 mL/h greater than fluid intake. The infusion rate for 25% albumin was 8 or 10 mL/h in all but 3 patients (rates of 5 mL/h for 2 patients and 12 mL/h for 1 patient). The median initial furosemide dose was 4 mg/h in patients who received furosemide alone and 5 mg/h in patients who received furosemide plus albumin. Differences in furosemide dose between the 2 groups at 6 hours (P = .33) and 24 hours (P = .50) were not significant. At 48 hours, the patients who received furosemide plus albumin received more furosemide than did the patients who received furosemide alone (P = .04).

Urine output did not differ significantly between the 2 groups at 6, 24, or 48 hours (P values: .56, .42, and .94, respectively). Similarly, urine output did not differ significantly within the furosemide-alone group (P = .09) and the furosemide-plus-albumin

Table 1
Baseline characteristics (N = 31)

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<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
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<tr>
<td>Age, y</td>
<td>54.3 (17.8)</td>
<td>21-84</td>
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<td>Weight at admission, kg</td>
<td>78.2 (24.3)</td>
<td>46.5-142</td>
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<tr>
<td>Height, cm</td>
<td>167.2 (10.1)</td>
<td>148-188</td>
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<tr>
<td>Serum creatinine, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.8 (0.3)</td>
<td>0.5-1.5</td>
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<tr>
<td>Serum albumin, g/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.1 (0.5)</td>
<td>1.3-3.2</td>
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<tr>
<td>APACHE II score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20.6 (5)</td>
<td>13-31</td>
</tr>
<tr>
<td>SOFA score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.6 (2.5)</td>
<td>2-12</td>
</tr>
<tr>
<td>Ratio of PaO₂ to fraction of inspired oxygen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>174 (103.9)</td>
<td>80-465</td>
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</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

<sup>a</sup> Day 0, the day that continuous furosemide infusion alone was started. To convert to micromoles per liter, multiply by 88.4.

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Statistics

On the basis of data on urine output in critically ill medical patients, it was estimated that 22 patients would be needed to detect a 30% difference in urine output between the furosemide-alone and the albumin-plus-furosemide groups with 80% power and α = .05. However, it was decided to enroll at least 30 patients to decrease the risk of a type II error.

Continuous data for comparison of the 2 groups of patients were evaluated by using paired t tests or repeated-measures analysis of variance. A 2-sample t test was used to evaluate unpaired data. Linear regression analysis was used to investigate relationships between the dependent variable urine output and demographic independent variables (age, weight, severity of illness) and other independent variables (ie, furosemide or albumin dose, fluid intake, and serum albumin concentrations) at 24 and 48 hours for both groups of patients. Significance was defined as P < .05 unless otherwise noted (Bonferroni correction for post hoc testing). All data are reported as mean and standard deviation.

At 48 hours, those receiving furosemide/albumin received more furosemide than those who received furosemide alone.
group ($P = .89$) according to the order in which the infusions were administered as the primary end point. Additionally, net fluid loss did not differ significantly between the 2 groups at 6, 24, or 48 hours ($P$ values: .42, .47, and .82, respectively).

Table 3 shows the relationship between urine output and independent variables according to simple regression analysis. Fluid intake was the only significant predictor of increased urine output for both the furosemide-alone group ($P = .02; R^2 = 0.27$) and the furosemide-plus-albumin group ($P = .004; R^2 = 0.29$) at 24 and 48 hours. In the patients given furosemide plus albumin, serum levels of albumin increased from 6 to 24 hours (mean, 2.0 g/dL [SD, 0.46] to 2.4 g/dL [SD, 0.47]; $P = .04$) and from 24 to 48 hours (mean, 2.4 g/dL [SD, 0.47] to 2.8 g/dL [SD, 0.45]; $P = .02$), but only the 6 to 48 hour increase (mean, 2.0 g/dL [SD, 0.46] to 2.8 g/dL [SD, 0.45]; $P < .001$) was significant with post hoc adjustment of $P$ values.

### Discussion

This study is the first one done to determine whether or not continuous infusion of 25% albumin enhances furosemide-induced diuresis in critically ill patients. We found that the effect of coadministration of furosemide and albumin was no greater than that of continuous infusion of furosemide alone.

Various beneficial mechanisms of the action of albumin beyond simple volume expansion have been described. For example, an early evaluation of furosemide mixed with an equimolar solution of albumin in analbuminemic rats suggested that albumin might play an important role in delivering furosemide to its site of action in the kidneys, thereby enhancing diuresis. In contrast, in a study in rats with nephrotic syndrome, the response to furosemide was compromised when the drug was given with albumin, suggesting that furosemide binding to albumin reduced the availability of the active compound. When medications were added that displaced furosemide from its albumin binding site, an improved diuretic response occurred. These conclusions suggest that the relationship between albumin and furosemide is not well understood.

The method of administration may influence the efficacy of albumin for diuresis. For example, results in normal and analbuminemic rats suggest that albumin and furosemide administered together form a complex that carries the furosemide to the kidney for uptake by renal tubular cells. Our study is the first to investigate the diuretic effects of a continuous infusion of albumin in medical ICU patients. In previous studies focused on specific populations of patients to whom albumin was administered via

### Table 2

<table>
<thead>
<tr>
<th>Time, h</th>
<th>Furosemide alone</th>
<th>Furosemide plus albumin</th>
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<tr>
<td></td>
<td>Fluid intake, mL</td>
<td>Fluid intake, mL</td>
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<td></td>
<td>Urine output, mL</td>
<td>Net fluid loss, mL</td>
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<tr>
<td>0-6 (N = 31)</td>
<td>43 (42)</td>
<td>937 (441)</td>
</tr>
<tr>
<td>0-24 (n = 15)</td>
<td>148 (120)</td>
<td>3136 (1114)</td>
</tr>
<tr>
<td>0-48 (n = 5)</td>
<td>265 (246)</td>
<td>6072 (2814)</td>
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</table>

*All values are mean (SD).*

### Table 3

**Simple regression analysis of independent variables with urine output at 24 or 48 hours**

<table>
<thead>
<tr>
<th>Variable</th>
<th>$P$ ($R^2$ if significant)</th>
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<tr>
<td>Age (24 hours)</td>
<td>.14</td>
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<tr>
<td>Weight in kilograms (24 hours)</td>
<td>.22</td>
</tr>
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<td>APACHE II score (24 hours)</td>
<td>.44</td>
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<tr>
<td>SOFA score (24 hours)</td>
<td>.94</td>
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<tr>
<td>Furosemide dose in furosemide-alone group (24 hours)</td>
<td>.77</td>
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<tr>
<td>Furosemide dose in furosemide-alone group (48 hours)</td>
<td>.047 (0.37)</td>
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<tr>
<td>Furosemide dose in combined albumin group (24 hours)</td>
<td>.35</td>
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<tr>
<td>Furosemide dose in combined albumin group (48 hours)</td>
<td>.23</td>
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<tr>
<td>Albumin dose in combined albumin group (24 hours)</td>
<td>.36</td>
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<tr>
<td>Albumin dose in combined albumin group (48 hours)</td>
<td>.48</td>
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<tr>
<td>Albumin concentration in albumin group (24 hours)</td>
<td>.90</td>
</tr>
<tr>
<td>Albumin concentration in albumin group (48 hours)</td>
<td>.047 (0.34)</td>
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<tr>
<td>Fluid intake in furosemide-alone group (24 hours)</td>
<td>.02 (0.27)</td>
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<tr>
<td>Fluid intake in furosemide-alone group (48 hours)</td>
<td>.02 (0.45)</td>
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<tr>
<td>Fluid intake in combined albumin group (24 hours)</td>
<td>.004 (0.29)</td>
</tr>
<tr>
<td>Fluid intake in combined albumin group (48 hours)</td>
<td>.03 (0.37)</td>
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</table>

**Abbreviations:** APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.
The method of administration may influence the efficacy of albumin for diuresis.

The one consistent factor significantly related to increased urine output was increased fluid intake.

intermittent boluses or short-term infusions, the results were conflicting. In a trial of 8 patients with nephrotic syndrome, Akcicek et al. administered furosemide as a 60-mg intravenous bolus followed by a 4-hour intravenous infusion of furosemide with and without 20% albumin. Maximal diuretic and natriuretic responses occurred during the drug infusions for all groups. The addition of albumin had no diuretic benefit. In contrast, Fliser et al. conducted a randomized, double-blind, placebo, controlled trial in 9 patients with nephrotic syndrome. Patients received a 60-mg furosemide bolus plus placebo, a 60-mg furosemide bolus plus 200 mL of 20% albumin, or placebo given as a bolus plus 200 mL of 20% albumin. The increase in urine output between the 3 groups during the 8-hour monitoring period were significant. Fliser et al noted that the same result could possibly be achieved by optimizing the dose of furosemide alone rather than by adding albumin.

The combination of furosemide plus albumin for the management of ascites in patients with cirrhosis has also had conflicting results. Gentilini et al. performed a randomized, controlled trial of 126 patients with cirrhosis and ascites. Patients were randomized to receive escalating doses of diuretics with or without 25% albumin. End points of the inpatient phase of the trial included disappearance of ascites and duration of hospital stay. The benefits of furosemide plus albumin were significantly better than the benefits of furosemide alone for both end points. In contrast to these findings, Chalasani et al. found a lack of benefit with furosemide plus albumin. They performed a randomized crossover study in 13 patients with cirrhosis and ascites to evaluate the effects of albumin on the response to furosemide as indicated by urinary excretion of sodium and urine volume. Patients received each of the following intravenously over 30 minutes: 40 mg of furosemide alone, 25 g of albumin alone, 40 mg of furosemide mixed with 25 g of albumin, and 40 mg of furosemide and 25 g of albumin infused simultaneously in different arms. Urine output for furosemide alone was similar to that for either combination. The diuretic and natriuretic responses returned to normal within 6 hours of drug administration in all arms of the study. Chalasani et al. concluded that coadministration of furosemide and albumin does not improve diuresis in patients with cirrhosis with ascites and most likely does not enhance diuresis in other populations of patients.

Martin et al. studied furosemide plus albumin in patients with hypoproteinemia and acute lung injury treated with mechanical ventilation. In this randomized, double-blind, placebo-controlled, multicentered trial, change in oxygenation over 24 hours was the primary end point. Net fluid loss was a secondary outcome. A total of 40 patients received furosemide with either a placebo or albumin. The control group received a furosemide bolus of 20 mg followed by a titrated infusion of up to 10 mg/h of furosemide for 72 hours with a normal saline placebo substituted for an equivalent volume of albumin. The treatment group received 25 g of 25% albumin immediately before the furosemide bolus and every 8 hours thereafter for the same duration. The improvement in oxygenation and net negative fluid balance in patients who received furosemide plus albumin was significantly greater than the changes in patients given furosemide plus placebo. These data are the most compelling to date that suggest albumin may enhance the effectiveness of furosemide in a specific population of patients.

Although a large percentage of our patients had a ratio of PaO_2 to fraction of inspired oxygen less than 300, we did not observe a beneficial diuretic effect with the addition of albumin. One difference in design between our study and that of Martin et al. is that we used continuous infusions of albumin rather than boluses. Also, we cannot exclude a relationship between increasing albumin concentrations and increased diuretic response. This possibility might account for the net fluid loss noted at 72 hours in the study by Martin et al.

In our regression analysis, albumin concentration at 48 hours was associated with urine output, but this finding was based on data from only 5 patients. Furthermore, by 48 hours, significantly more furosemide had been administered to patients receiving furosemide plus albumin than to patients given furosemide alone, a situation that could also explain the increased urine output at this time. In our study, the one consistent factor significantly related to increased urine output was increased fluid intake.

Although hyperoncotic albumin may have potential benefits in specific populations of patients, we conclude that the addition of a 25% albumin infusion to continuous infusion with furosemide does not improve diuresis in critically ill patients with hypoalbuminemia. In agreement...
with previous studies, we recommend optimizing the furosemide dosing before considering the addition of colloid. Furthermore, if diuretic resistance occurs, the addition of a thiazide diuretic may produce a better result and be more cost-effective in achieving diuresis in patients with volume overload whose hemodynamic status is stable.²

Our study had some limitations. Because the study was retrospective, incorrectly recorded information and uncontrolled confounders are possible. For example, details of patients’ characteristics that might have influenced the response to furosemide or the combination regimen may have been missed. Because of limited enrollment, we did not perform subgroup analyses to evaluate whether albumin is beneficial in specific populations of patients in the ICU. Furthermore, the limited number of patients at the final 48-hour end point prohibits firm conclusions about an effect or lack of effect of albumin in enhancing furosemide diuresis with more prolonged administration. Finally, we evaluated the use of continuous infusions of albumin and furosemide at only a single institution, so our results may not be generalizable to other ICUs.

Conclusions

Compared with continuous infusion of furosemide alone, administration of furosemide plus albumin given as a continuous infusion did not improve urine output in critically ill patients. Furthermore, cumulative fluid loss did not differ between the 2 groups. Enhanced urine output was associated solely with increased fluid intake and not with other independent variables such as serum levels of albumin.

ACKNOWLEDGMENTS

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REFERENCES


FINANCIAL DISCLOSURES

None reported.

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1. Which of the following is the most frequently used treatment for volume overload in critically ill patients?
   a. Thiazide diuretics and fluid restriction
   b. Fluid restriction and albumin
   c. Fluid restriction and loop diuretics
   d. Albumin and thiazide diuretics

2. Which of the following is the primary objective of this study?
   a. To compare urinary output in patients given furosemide and albumin injections every 6 hours
   b. To compare urinary output in patients given furosemide alone with output in patients given both furosemide and albumin
   c. To compare urinary output in patients given furosemide alone with output in patients given furosemide and thiazide diuretic
   d. To compare urinary output in patients given furosemide alone with output in patients given furosemide and thiazide diuretics

3. Which of the following statements best describes the study design?
   a. Adult patients in a medical intensive care unit (ICU) receiving a continuous furosemide infusion with and without 25% albumin; diuretic effect measured at 30-minute increments
   b. All adult ICU patients receiving a continuous thiazide infusion with and without 25% albumin; diuretic effect measured at 3 hours and 6 hours
   c. Adult patients in an MICU receiving a continuous furosemide infusion with and without 25% albumin; diuretic effect measured at 6 hours for primary endpoint
   d. All adult patients in an MICU receiving a continuous furosemide infusion with and without 25% albumin; diuretic effect measured at 30-minute increments

4. Which patients were excluded from the study?
   a. Those who did not have sequential infusions of albumin and furosemide; renal dysfunction, hypokalemia
   b. Those who had sequential infusions of albumin and furosemide; incomplete intake and output records, serum creatinine 1.0
   c. Those who did not have sequential infusions of albumin and furosemide; renal dysfunction, current renal disease
   d. Those who had sequential infusions of albumin and furosemide; renal dysfunction, current renal disease

5. Which of the following baseline data points were collected on all patients?
   a. Age, sex, height, weight, urine creatinine, cardiac medications, ICU diagnosis
   b. Age, sex, height, weight, urine creatinine, diuretic medications, ICU diagnosis
   c. Fluid restriction, current renal disease
   d. Add thiazide diuretic

6. How many patients would be needed to detect a 30% difference in urine output between furosemide alone and the albumin plus furosemide group?
   a. 53
   b. 67
   c. 170
   d. 22

7. How many patients were in the final study?
   a. 170
   b. 31
   c. 36
   d. 14

8. What were the 3 most common underlying illnesses seen in the patients in this study?
   a. Skin cancer, respiratory disease, cardiovascular disease
   b. Skin cancer, pancreatitis, hepatitis C
   c. Skin cancer, liver disease, respiratory disease
   d. Skin cancer, cardiovascular disease, liver disease

9. Which of the following was the only significant predictor of increased urinary output for both the furosemide and the furosemide plus albumin group at 24 and 48 hours?
   a. Fluid intake
   b. Rate of furosemide infusion
   c. Rate of albumin infusion
   d. Time interval between furosemide and albumin infusion

10. Which of the following statements best describes the effect of coadministration of furosemide and albumin?
    a. Effect was greater than the continuous infusion of furosemide alone
    b. Effect was the same for furosemide infusion alone and furosemide and albumin administration
    c. Effect was no greater than the continuous infusion of furosemide alone
    d. Effect was significantly greater than the continuous infusion of furosemide alone

11. Which of the following is the recommended treatment if loop diuretic resistance continues?
    a. Add 20% albumin
    b. Add loop diuretic
    c. Add fluid
    d. Add thiazide diuretic

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