Critical Review Form
Meta-analysis

Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012.

Objectives: **"to determine the comparative effectiveness of albumin and alternative treatments in minimizing PCD [postparacentesis circulatory dysfunction], hyponatremia, and mortality among ascites patients undergoing LVP [large volume paracentesis]." (p. 1173)**

Methods: **A search was performed of MEDLINE, EMBASE, the Cochrane Library, ClinicalTrials.gov, Google, and abstract databases from major meetings in hepatology. Randomized controlled trials that compared LVP plus albumin to either LVP without adjunctive treatment or LVP plus another volume expander or vasoconstrictor were eligible as long as they reported data for one or more of the primary outcomes. Reference lists of primary articles and review articles were examined, as were the tables of contents of major hepatology journals. Eligibility was determined independently by at least 2 investigators who then performed data extraction.**

The primary outcomes of the analysis were PCD, mortality, and hyponatremia. Secondary endpoints were recurrent ascites, renal impairment, hepatic encephalopathy, portal hypertensive bleeding, and hospital readmission. Trial results were combined using a fixed-effects model. Trial quality was assessed by evaluation of randomization method, allocation concealment, and blinding.

Seventeen studies met inclusion criteria, comprising a total of 1225 patients. In 3 of the trials, albumin was compared to paracentesis alone; in 9 trials albumin was compared to an artificial colloid or hypertonic saline; in 5 trials, albumin was compared to a vasoconstrictor. The mean age in the studies ranged from 46.9 to 61.4 years and the mean proportion of male patients was 73.6% (range 60.0% to 90.0%). Alcohol was the etiology of cirrhosis in a pooled mean of 71.3% of patients (range 38.9% to 94.1%). All studies excluded patients with renal dysfunction or GI bleeding, and 16 studies excluded patients with spontaneous bacterial peritonitis or sepsis. The mean volume removed during paracentesis ranged from 5.5 to 15.9 L.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. Patients with cirrhosis undergoing large volume paracentesis are at risk for circulatory dysfunction, renal failure, and death as a result of large fluid shifts. Given the frequency of hypoalbuminemia in such patients, it is reasonable to assess whether the administration of albumin in such patients to increase oncotic pressure and restore circulatory volume could reduce adverse events.
2.	Was the search for relevant studies details and exhaustive?	Yes. The authors searched all of the major databases, conference abstracts, article bibliographies, and tables of content from relevant journals.
3.	Were the primary studies of high methodological quality?	No. Study quality varied greatly. Only 2 of the studies blinded patients and clinicians to group allocation, while 1 blinded the laboratory. Blinding was not described in the remaining 14 trials. Randomization was conducted using a table or a computer-generated sequence in 10 trials; the method of randomization was not reported in the other 7 trials. Allocation concealment was adequate in 5 trials and unspecified in the remaining 12.
4.	Were the assessments of the included studies reproducible?	Yes. The authors assessed study quality by looking at three criteria: randomization method, allocation concealment, and blinding. They did not assess for selective outcome reporting or incomplete outcome data.
II.	***What are the results?***	
1.	What are the overall results of the study?	Postparacentesis Circulatory Dysfunction (PCD) • Data for PCD were available in 16 trials, with an I^2 statistic of 12.8%. The results, broken down by control, are provided in Table 1. Albumin significantly reduced the risk of PCD compared to no control (NNT = 2) and compared to an alternative volume expander. Compared to vasoconstrictors, there was a trend towards benefit with albumin, but this did not achieve statistical significance.

Table 1. Effect of albumin on incidence of PCD

Control	# of trials	# of events/# in albumin group	# of events/# in control group	OR (95% CI)
None	3	7/41	31/44	0.07 (0.02-0.22)
Volume expander	8	46/303	135/391	0.34 (0.23-0.51)
Vasocon-strictor	5	12/83	13/80	0.79 (0.32-1.92)

Hyponatremia

- Data for hyponatremia were available for all 17 trials, though one trial could not be included because there were no events in either group. For the 16 trials included in the meta-analysis, the I^2 statistic was 0%. The results, broken down by control, are provided in Table 2. Albumin significantly reduced the risk of PCD compared to no control and compared an alternative volume expander. Compared to vasoconstrictors, there was a trend towards benefit with albumin, but this did not achieve statistical significance.

Table 2. Effect of albumin on incidence of hyponatremia

Control	# of trials	# of events/# in albumin group	# of events/# in control group	OR (95% CI)
None	3	3/77	13/79	0.20 (0.05-0.74)
Volume expander	9	37/404	79/499	0.61 (0.40-0.93)
Vasocon-strictor	4	2/54	7/58	0.37 (0.09-1.49)

Mortality

- Data on mortality were available in 13 studies, though one trial could not be included because there were no deaths in either group. For the 12 trials included in the meta-analysis, the I^2 statistic was 0%. Only 1 trial reported mortality data when comparing albumin with no treatment, hence a meta-analysis could not be performed. Compared to both alternative volume expanders and vasoconstrictors, there was a trend towards decreased mortality, but neither result achieved statistical significance.

<table>
<tr><td></td><td></td><td>
Table 3. Effect of albumin on mortality
<table>
<tr><th>Control</th><th># of trials</th><th># of events/# in albumin group</th><th># of events/# in control group</th><th>OR (95% CI)</th></tr>
<tr><td>Volume expander</td><td>8</td><td>49/371</td><td>71/472</td><td>0.65 (0.42-1.01)</td></tr>
<tr><td>Vasocon-strictor</td><td>3</td><td>1/43</td><td>3/41</td><td>0.45 (0.08-2.60)</td></tr>
</table>
<u>Secondary endpoints</u>
"Albumin administration was associated with 15%-19% reductions in the odds of ascites recurrence, renal impairment, and hospital readmission. Smaller reductions were observed for hepatic encephalopathy and portal hypertensive bleeding. However, none of these effects with respect to secondary endpoints were statistically significant." (p. 1176)
</td></tr>
<tr><td>2.</td><td>How precise are the results?</td><td>See above.</td></tr>
<tr><td>3.</td><td>Were the results similar from study to study?</td><td>Yes. The authors provide I^2 statistics for groups of studies based on outcomes assessed rather than groups of studies whose results were pooled. Despite this, results within each pooled group were similar from study to study and visual inspection of the Forest plots reveals no obvious evidence of heterogeneity.</td></tr>
<tr><td>III.</td><td>Will the results help me in caring for my patients?</td><td></td></tr>
<tr><td>1.</td><td>How can I best interpret the results to apply them to the care of my patients?</td><td>The administration of albumin in patients with cirrhosis undergoing a large volume paracentesis seems to result in decreased risk of post-paracentesis circulatory dysfunction and hyponatremia when compared to both no treatment and compared to other volume expanders, with a trends towards benefit compared to vasoconstrictors. There was also a trend towards reduced mortality when albumin was compared to other volume expanders and vasoconstrictors, though these results did not achieve statistical significance.</td></tr>
<tr><td>2.</td><td>Were all patient important outcomes considered?</td><td>Yes. The authors considered the most clinically relevant outcomes, including mortality, renal impairment, and circulatory dysfunction. They also considered hospital readmission, ascites recurrence, hepatic encephalopathy, and postal hypertensive bleeding. They were not able to assess cost or length of stay.</td></tr>
<tr><td>3.</td><td>Are the benefits worth the costs and potential risks?</td><td>Yes. The administration of albumin in patients undergoing large volume paracentesis seems to result in a significant decrease in the risk of circulatory dysfunction and hyponatremia. In addition, albumin performed as well as (or better than) alternative volume</td></tr>
</table>

		expanders and vasoconstrictors. Albumin has few adverse effects when administered in the appropriate patients and is relatively inexpensive.

Limitations:

1. **The authors provide I^2 statistics for groups of studies based on outcomes assessed rather than based on groups of studies whose results were pooled.**

2. **The authors chose to combine data from various studies using a fixed-effects model. Given the high degree of clinical and methodological heterogeneity between studies, a random effects model would probably have been a better choice.**

3. **The relatively small number of studies pooled for each outcome makes an assessment of publication bias very limited.**

Bottom Line:

The administration of albumin in patients undergoing large volume paracentesis seems to result in a significant decrease in the risk of circulatory dysfunction (OR 0.07, 95% CI 0.02-0.22) and hyponatremia (OR 0.20, 95% CI 0.05-0.74) when compared to no intervention. In addition, albumin performed as well as (or better than) alternative volume expanders and vasoconstrictors. No significant effect on mortality was observed. Given that albumin has few adverse effects when administered in the appropriate patients and is relatively inexpensive, it seems reasonable to administer albumin to patients undergoing large volume paracentesis who do not have significant contraindications.