Critical Review Form
Therapy
[Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999.](#)

Objectives: "to determine whether plasma volume expansion with albumin could prevent the impairment of renal function and reduce mortality in patients with spontaneous bacterial peritonitis [SBP]." (p. 403)

Methods: This multicenter randomized controlled trial was conducted at 7 university hospitals in Spain between November 1995 and September 1997. Adults aged 18-80 years with cirrhosis and SBP, defined as an ascitic polymorphonuclear (PMN) cell count > 250/mm^3, were eligible for enrollment. Exclusion criteria included findings suggestive of secondary peritonitis, antibiotics within the week prior to SBP diagnosis (except prophylactic norfloxacin), the presence of other infections, shock, GI bleeding, grade 3 or 4 hepatic encephalopathy, cardiac failure, organic nephropathy, HIV, any disease that would affect short term prognosis, a serum creatinine > 3 mg/dL, and the presence of a potential cause of dehydration.

All patients received IV cefotaxime, dosed according to renal function. Patients were randomized to either receive albumin or not receive albumin. Patients in the albumin group were given a dose of 1.5 g/kg in the first 6 hours after enrollment, followed by 1 g/kg on day 3. The primary endpoints of the study were mortality and renal impairment. Renal failure at the time of enrollment was defined as a BUN > 30 mg/dL or a creatinine > 1.5 mg/dL. In patients without renal failure at the time of enrollment, renal impairment was defined as an increase in either BUN or creatinine by more than 50% to a level higher than 30 mg/dL or 1.5 mg/dL, respectively. In patients with renal failure at the time of enrollment, renal impairment was defined as an increase in BUN or creatinine by more than 50% from baseline.

A total of 126 eligible patients were enrolled during the study, with 63 randomized to cefotaxime alone and 63 randomized to cefotaxime plus albumin. Patients were randomized based on a computer generated randomization scheme, and allocation was concealed using sealed envelopes.

	Guide	Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Randomization was performed independently at each hospital with the use of sealed envelopes containing the treatment assignments, which were based on random numbers generated by the SAS statistical package." (p. 404)
2.	Was randomization concealed (blinded)?	Likely yes. Randomization was concealed using sealed envelopes, however it is made explicit that these were opaque.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. The authors to not mention any crossover. Additionally, three patients withdrawn from the study due to failure to meet inclusion criteria were included in the final analysis. One patient in the cefotaxime-plus-albumin group was over 80 years of age, one in this group had received antibiotics in the previous week, and one patient in the cefotaxime only group had cardiac failure. An intention to treat analysis was therefore used.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Patients were similar with respect to age, gender, percent with alcohol as the cause of cirrhosis, presence of hepatocellular carcinoma, serum albumin level, prothrombin time, isolated organism, renal failure, and Child-Pugh score. Patients in the cefotaxime only group had higher baseline white blood cell counts and higher serum bilirubin levels (mean 6 ± 1 vs. 4 ± 1).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes. The authors do not mention blinding of patients or the use of a placebo. It is doubtful that performance bias on the part of the patients would affect outcomes.
2.	Were clinicians aware of group allocation?	Yes. The authors do not mention blinding of clinicians or the use of a placebo. It is possible that performance bias on the part of the clinicians would affect outcomes.
3.	Were outcome assessors aware of group allocation?	No. The investigators were unaware of treatment assignment. Additionally, the outcomes measured in the study were objectively defined.
4.	Was follow-up complete?	No. Patients were followed throughout their

		hospitalization. After discharge they were followed weekly for the first month and then monthly until 90 days after enrollment. The exact method of follow-up was not well defined. A total of 7 patients (6%) were lost to follow-up after hospital discharge: 4 in the cefotaxime only group, 3 in the cefotaxime-plus-albumin group.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	<u>Renal Impairment</u> • BUN and serum creatinine levels were lower in patients in the cefotaxime-plus-album group compared to the cefotaxime only group on days 3, 6, and 9. • The incidence of renal impairment was significantly lower in the cefotaxime-plus-albumin group compared to the cefotaxime only group (10% vs. 33%, p = 0.002; OR 0.21, 95% CI 0.08-0.57[†]). <u>Mortality</u> • In-hospital mortality was significantly lower in the cefotaxime-plus-albumin group compared to the cefotaxime only group (10% vs. 29%, p = 0.01; OR 0.26, 95% CI 0.10-0.72[†]). • 90-day mortality was significantly lower in the cefotaxime-plus-albumin group compared to the cefotaxime only group (22% vs. 41%, p = 0.03; OR 0.41, 95% CI 0.19-0.89[†]) <u>Secondary Outcomes</u> • There was no significant difference in the incidence of resolution of infection (94% vs. 98%, p = 0.36), duration of antibiotic therapy (6 ± 1 vs. 5 ± 1 days, p = 0.83), or duration of hospital stay (13 ± 1 vs. 14 ± 1, p = 0.48) between the cefotaxime only group and the cefotaxime-plus-albumin group. † Calculated using http://www.neoweb.org.uk/Additions/compare.htm
2.	How precise was the estimate of the treatment effect?	See above. For the primary outcomes of the study (mortality and renal impairment), the 95% CIs for the ORs do not cross 1.0, and hence achieve statistical significance.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	

1.	Were the study patients similar to my patient?	Yes. Although this study was conducted in Spain, it was conducted in university hospitals and enrolled patients with cirrhosis and SBP. A significant proportion of these patients (~30%) had cirrhosis due to alcoholism, which I suspect would be similar to our patient population. Patient management is likewise quite similar between the US and Spain for cirrhosis and SBP. The incidence of major comorbidities is not know from this study, and could represent a difference between our patients and those in the study. Careful application of the study's exclusion criteria would be necessary to ensure appropriate external validity of the study results.
2.	Were all clinically important outcomes considered?	Yes. The authors considered the most clinically relevant patient-important outcomes, namely renal failure and death. They did not consider cost or quality of life.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. Albumin is a relatively inexpensive therapy and there were no adverse events related to its administration in this study. The study demonstrated a significant reduction in in the incidence of renal impairment and death. In appropriate patients with SBP meeting inclusion criteria, albumin should be administered in addition to antibiotics in order to improve outcomes.

Limitations:

1. There was a baseline difference in serum bilirubin levels between the two groups, with a higher level in the cefotaxime only group (mean 6 ± 1 vs. 4 ± 1). Baseline serum bilirubin level was found to be an independent predictor for the development of renal impairment and mortality. Despite randomization, the cefotaxime-only group began the study with a worse prognosis.

2. The authors do not discuss the study's limitations.

3. Patients and clinicians were not blinded to group allocation.

Bottom Line:

In this nonblinded randomized controlled trial comparing cefotaxime alone to cefotaxime plus albumin administration in patients with cirrhosis and SBP, death and renal impairment occurred less frequently when albumin was administered (OR 0.26, 95% CI 0.10-0.72 and OR 0.21, 95% CI 0.08-0.57). Despite a baseline difference in serum bilirubin levels (which was shown to be an independent predictor of both mortality and renal impairment), it seems reasonable to administer albumin to patients with SBP meeting the study's inclusion criteria.