The Role of Albumin in the Management of Hepatorenal Syndrome: A Systematic Review
Prashant R. Mudireddy, MD, Rajender Agarwal, MD, MPH, and Kendal Williams, MD, MPH

ABSTRACT

- **Objective:** To evaluate the available evidence supporting the use of albumin for diagnosis and treatment of hepatorenal syndrome (HRS).
- **Methods:** We searched MEDLINE, EMBASE, and the Cochrane Library for articles published in English between 1966 and March 2013. To evaluate the role of albumin in the diagnosis of HRS, we looked for trials comparing albumin to other plasma expanders. To evaluate the role of albumin in the treatment of HRS, we looked for trials comparing vasoconstrictor plus albumin to vasoconstrictor alone.
- **Results:** There were no trials evaluating the efficacy of albumin versus other volume expanders in the diagnosis of HRS. There were 4 studies (all nonrandomized) with a total 169 patients comparing the improvement in creatinine in HRS patients treated with vasoconstrictor (terlipressin) plus albumin to vasoconstrictor alone. In the terlipressin plus albumin group, the response rate (defined as any improvement in creatinine from baseline) was 65.5% vs 46.8% in terlipressin alone group. In the only study (total 21 patients) where survival data was available, survival rate at 1 month was higher in the vasoconstrictor plus albumin group (92% vs. 25%). A formal meta-analysis was not performed due to the lack of randomized controlled studies and heterogeneity in study designs and outcome definition.
- **Conclusions:** The use of albumin along with terlipressin significantly improved the response rates (defined as any decrease in serum creatinine) in patients with HRS when compared with terlipressin alone. There is insufficient data to comment on HRS reversal rate (defined as decrease in serum creatinine to below 1.5 mg/dL) and impact on survival. We found no evidence to support use of albumin over normal saline for plasma expansion for diagnosis of HRS.

Hepatorenal syndrome (HRS) is a serious complication of end-stage liver disease seen mainly in patients with advanced cirrhosis with ascites, and in patients with acute liver failure [1]. The probability of HRS occurrence in cirrhotics with ascites is about 18% at 1 year and 39% at 5 years [2]. There are 2 types of HRS. Type 1 HRS consists of a severe and rapidly progressive renal failure, defined as a doubling of the serum creatinine, reaching a level greater than 2.5 mg/dL in less than 2 weeks. Without treatment, type 1 HRS has a poor prognosis with a median survival time after onset of renal failure of only 2 weeks. Type 2 HRS is characterized by a moderate and slowly progressive renal failure and a median survival of 6 months [3]. Patients with type 2 HRS show signs of liver failure and arterial hypotension, but to a lesser extent than those with type 1 HRS. The dominant clinical feature is severe ascites with poor or no response to diuretics. Type 2 HRS can evolve into type 1 HRS following infections or other precipitating events.

Vasoconstrictor agents (eg, terlipressin, norepinephrine, midodrine plus octreotide) along with albumin are recommended by guidelines as the first line of treatment for HRS, especially HRS type 1 [1,4,5]. The mechanism by which vasoconstrictors and albumin may improve the glomerular filtration rate in patients with HRS is incompletely understood. Albumin is thought to increase central blood volume, increase cardiac output, bind to vasoconstrictors, and increase arterial vasoconstriction and blood pressure [1]. Despite uncertainty regarding its mechanism of potential benefit, albumin has become central to both therapeutic management and diagnosis.

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Indeed, albumin has largely replaced normal saline as the diagnostic trial fluid of choice for initial plasma expansion in HRS patients [1].

For hospitals, the central question is whether the increased use of albumin and its associated cost is justified. Albumin is considerably more costly than crystalloid solutions, has limited availability, and there is theoretical risk of transmission of infections, risk of anaphylactic reactions, and development of pulmonary edema [6–9]. For over a decade, controversy has surrounded the question of whether albumin infusion causes harm. A Cochrane meta-analysis published in 1998 [10] concluded that mortality was increased in patients receiving albumin. A subsequent meta-analysis published by Wilkes et al [11] contradicted this and supported the safety of albumin. In another meta-analysis by Vincent et al [12], albumin was shown to reduce morbidity in acutely ill hospitalized patients. The Sepsis Occurrence in Acutely ill Patients (SOAP) study [13] indicated that albumin administration was associated with decreased survival in intensive care unit (ICU) patients, while the Saline versus Albumin fluid Evaluation (SAFE) study [14] showed that use of 4% albumin and normal saline for fluid resuscitation results in similar outcomes at 28 days.

In order to guide decision making on the appropriate use of albumin at the University of Pennsylvania Health System (UPHS), the UPHS Center for Evidence-based Practice performed a systematic review to evaluate the evidence for the role of albumin in the diagnosis and treatment of HRS.

**METHODS**

We searched MEDLINE, EMBASE and the Cochrane Library for clinical trials published between 1966 and March 2013 using keywords and/or medical subject headings for HRS and albumin. The sample search strategy is presented in Table 1. Titles and abstracts of the references identified were screened, followed by full-text review of the articles meeting inclusion criteria. Additionally references lists of the selected articles were hand searched. The inclusion criteria are summarized in Table 2. We excluded non-English studies, case series, and studies published in abstract form only.

We extracted data on study design, intervention, patient population, size of the study sample and the outcome measures. Due to the heterogeneity in study designs and outcome definition, we elected not to perform a formal meta-analysis.

**RESULTS**

Our literature search initially yielded 1295 articles. We excluded 1177 articles that were not relevant to the review, leaving 118 articles retrieved for full text review plus 19 additional articles retrieved based on reference list searches. After excluding review articles, meta-analyses, case reports, and case series, we ultimately identified 4 studies [15–18] that met our pre-defined inclusion criteria.

**Study Characteristics**

We failed to identify a controlled study evaluating the role of albumin in the diagnosis of HRS. The 4 studies that met our criteria were all nonrandomized treatment studies comparing the improvement in creatinine in HRS patients treated with a vasoconstrictor drug plus albumin versus vasoconstrictor alone (Table 3). Of the included clinical trials, 1 was prospective [15] and 3 were retrospective [16–18]. The number of patients in each trial ranged from 18 to 112, totaling 169 patients for all the studies combined. Terlipressin, a drug not currently available in the United States, was the vasoconstrictor used in all studies. The dose of albumin used for treatment of HRS varied among the trials. In 2 studies, central venous pressure was used for albumin dosing [15,16]. All the studies used the International Ascites Club (IAC) 1996 definition of HRS [19] for selection of patients except the study by Triantos et al [18], which used IAC 2007 definition [1]. Patients with ongoing infection, known cardiac or respiratory diseases, and peripheral vascular disease were excluded. Two studies included only HRS type 1 patients [16,17], one included both type 1 and type 2 patients [15], and the remaining trial included patients with both type 1 and type 2 HRS and those with renal failure not fulfilling either type 1 or type 2 criteria [18].

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**Table 1. Sample Search Strategy (Ovid Medline)**

1. exp albumins
2. exp liver cirrhosis
3. exp liver diseases
4. exp hepatorenal syndrome
5. exp kidney diseases
6. exp acute kidney failure
7. exp kidney failure, chronic
8. or/2-7
9. 1 and 8
10. Limit 9 to (English language and humans)
The trials varied in their definitions of response to treatment (Table 3).

**Use of Albumin for Diagnosis of HRS**
As noted, there were no controlled clinical studies that evaluate the efficacy of albumin in the diagnosis of HRS.

**Use of Albumin in Treatment of HRS**
We found no randomized controlled trials comparing albumin to a comparison group that did not also receive albumin in the management of HRS. In the 1 prospective, uncontrolled nonrandomized study by Ortega et al [15], complete response rates (defined as decrease in serum creatinine to ≤ 1.5 mg/dL during treatment) were significantly higher in the terlipressin plus albumin group (10/13 patients or 77%) compared to terlipressin alone group (2/8 patients or 25%), suggesting that albumin may have added benefit in the treatment of HRS when used along with vasoconstrictor drug. Survival at 1 month and 3 months was also higher in terlipressin plus albumin group (12/13 patients or 92% and 7/13 or 54% respectively) compared to terlipressin alone group (2/8 patients or 25% and 1/8 or 12.5% respectively). However, in the retrospective studies by Moreau et al [17] and Colle et al [16], there were no significant differences in the dose of albumin between responders (defined as those with improvement in creatinine below 130 mmol/L or decrease in creatinine of at least of 20% from pretreatment value) and nonresponders. A retrospective study by Triantos et al [18] found that following

<table>
<thead>
<tr>
<th>Table 2. Inclusion Criteria for Articles</th>
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<tr>
<td><strong>Objective</strong></td>
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<tr>
<td>To evaluate efficacy of albumin in the diagnosis of hepatorenal syndrome</td>
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<td>To evaluate efficacy of albumin in the treatment of hepatorenal syndrome</td>
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<th>Table 3. Study Characteristics and Results</th>
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<tbody>
<tr>
<td><strong>Study</strong></td>
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<tr>
<td>Ortega 2002 [15]</td>
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<tr>
<td>Colle 2002 [16]</td>
</tr>
<tr>
<td>Moreau 2002 [17]</td>
</tr>
<tr>
<td>Triantos 2010 [18]</td>
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</tbody>
</table>

*All results terlipressin + albumin vs. terlipressin alone. CVP = central venous pressure; NR = not reported; SCr = serum creatinine.*
the start of terlipressin, the continuation of albumin infusions had no bearing on the final outcomes.

**DISCUSSION**

Currently, the International Ascites Club, American Association for Study of Liver Diseases, and European Association for the Study of the Liver recommend vasoconstrictor agents (terlipressin, norepinephrine, midodrine plus octreotide) along with albumin as the first line of treatment for HRS, especially HRS type 1 [1,4,5]. Several meta-analyses [20–24] have been performed on the role of vasoconstrictors plus albumin (especially terlipressin) in the management of HRS. Some of the most recent meta-analyses are summarized in Table 4. From these meta-analyses, it can be concluded that terlipressin plus albumin is superior to albumin monotherapy in the treatment of HRS type 1 and improves short-term survival. However, it is unclear if vasoconstrictors alone are inferior to combination therapy of vasoconstrictor plus albumin in the treatment of HRS. To our knowledge, this is the first systematic review evaluating this question.

We conclude that, based on evidence of low-quality, albumin when used along with terlipressin significantly improved the response rates (defined as any decrease in serum creatinine from pretreatment value) in patients with HRS when compared with terlipressin alone. However, there is limited evidence that terlipressin plus albumin leads to increased HRS reversal rate (defined as decrease in serum creatinine to below 1.5 mg/dL from pretreatment value) or improves survival compared to terlipressin alone.

In order to more conclusively demonstrate that albumin provides additive value to the vasoconstrictor drug in the treatment of HRS, randomized studies comparing vasoconstrictor drug alone versus vasoconstrictor drug plus albumin need to be performed. There are as yet no published randomized controlled studies on this issue and the 1 prospective nonrandomized controlled trial by Ortega et al [15] is limited by a small number of patients. The remainder of the evidence base consists of retrospective controlled studies and these studies were not designed to study the difference in response rate between vasoconstrictor plus albumin and albumin alone.

We found no evidence to support use of albumin over normal saline as a volume expander for the diagnosis of HRS. The accepted definition of HRS requires a fluid challenge with either albumin or saline. The decision to use albumin instead of 1.5 L normal saline is based on hypothesis that albumin is a better plasma expander and will prevent misdiagnosing patients with true volume depletion as HRS. As an example, in a study by Peron et al, 11/20 (55%) HRS patients treated with albumin and furosemide showed response to treatment (either increase in creatinine clearance above 40 mL/min or serum creatinine fell under 132 µmol/L) after they had had no response to 1.5 L intravenous saline, suggesting that patients were not adequately plasma expanded with normal saline alone [25]. But the results of this study should be interpreted with caution: First, patients received diuretic along with albumin and this might have a confounding effect. Second, most of the patients needed albumin for more than 2 days to respond to treatment.

However, the literature suggests heterogeneity in both practice and agents used for volume expansion in diagnosis of HRS. In the studies of pharmacological treatment of HRS, we found that 9 studies [15,18,26–32] used albumin, 3 studies [25,33,34] used normal saline, 3 studies [35–37] used both albumin and normal saline, and 1 study used albumin plus fresh frozen plasma [38] for the diagnosis of HRS. The dose of albumin and the number of days of albumin infusion for initial plasma expansion varied among the studies. In 5 trials, albumin use for diagnosis of HRS was based on central venous pressure [26,27,29,30,38].

So where does this evidence base lead us in making utilization decisions about albumin’s appropriateness? For diagnosis of HRS, the risk of underdiagnosis and its associated poor prognosis is likely too great to justify not using an albumin challenge when the diagnosis is in question and patients have failed to response to crystalloids alone. For the therapeutic management of HRS, the evidence base is conflicting and of low quality. Given the severity of HRS type 1, however, low-quality evidence may be sufficient at this stage to justify the use of albumin. The situation is akin to the utilization of heparin in the management of ST-elevation myocardial infarction where the studies defining the evidence base have used it in both the intervention and placebo arms, therefore its use is recommended as standard of care by the ACC/AHA guidelines even though there is little evidence of heparin providing independent value.

As with any systematic review, our results are limited by the quality of the included studies. We found no ran-
We excluded studies published in languages other than English and did not search for unpublished evidence.

In conclusion, evidence of low quality supports the use of albumin along with vasoconstrictor agents in the treatment of HRS. Future research should include adequately powered randomized controlled trials evaluating the efficacy, dose and duration of albumin treatment for the treatment of HRS. Vasoconstrictor agents other than terlipressin (like midodrine plus octreotide, norepinephrine) should also be evaluated, as these are the agents used in the US population.

### Table 4. Recent Meta-analyses of Pharmacological Treatment of Hepatorenal Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. of Studies/Patients</th>
<th>Study vs Control</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Fabrizi 2006</td>
<td>Systematic review with meta-analysis—pooled rate random effects model</td>
<td>10/154</td>
<td>Terlipressin ± plasma expander</td>
<td>Pooled rate of HRS reversal 0.52 (95% CI, 0.42-0.61, P &lt; 0.001). Pooled OR for mortality non-responders to responders 5.746 (95% CI, 1.5-21.9).</td>
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<tr>
<td>Fabrizi 2009</td>
<td>Systematic review with meta-analysis of controlled clinical trials—random effects model</td>
<td>5/243</td>
<td>Terlipressin vs placebo (albumin used in both study and control groups in all but 1 study)</td>
<td>Pooled OR ratio of HRS reversal 8.09 (95% CI, 3.521-18.59; P &lt; 0.001). Pooled OR of survival 2.064 (95% CI, 0.939-4.538; P = 0.07)</td>
</tr>
<tr>
<td>Sagi 2009</td>
<td>Meta-analysis</td>
<td>4/223</td>
<td>Terlipressin+ albumin vs albumin ± placebo</td>
<td>HRS reversal in type 1 46% vs 11.6% RR 3.66 (95% CI, 2.15-6.23; P &lt; 0.001). Overall survival 41% vs 27.6% RR 1.43, 95% CI, 0.87-2.35; P = 0.16). Transplant-free survival @90 days 24.8% vs 12.4% RR 1.85 (95% CI 1.3-4.1; P = 0.05)</td>
</tr>
<tr>
<td>Dobre 2010</td>
<td>Systematic review and meta-analysis—random effects model</td>
<td>8/320</td>
<td>Terlipressin + albumin vs albumin ± placebo</td>
<td>HRS reversal terlipressin vs placebo OR 7.47 (95% CI, 3.17-17.59; P &lt; 0.001). Terlipressin vs noradrenaline OR 1.23 (95% CI, 0.43-3.54; P = 0.7)</td>
</tr>
<tr>
<td>Gluud 2010</td>
<td>Systematic review with meta-analysis—intention to treat random effects</td>
<td>10/376</td>
<td>Terlipressin vs no intervention (2 trials)</td>
<td>Reversal of HRS (terlipressin + albumin vs albumin) RR 3.76 (95% CI 2.21-6.39)</td>
</tr>
<tr>
<td></td>
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<td>Terlipressin + albumin vs albumin (4 trials)</td>
<td>Improved renal function (terlipressin + albumin vs albumin) RR 2.00 (95% CI 1.11-3.62).</td>
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<tr>
<td></td>
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<td>Terlipressin + albumin vs noradrenaline + albumin (2 trials)</td>
<td>Mortality Overall vasoconstrictors alone or with albumin reduced mortality RR 0.82 (95% CI, 0.70-0.96). In subgroup analysis effect on mortality seen at 15 days but not beyond. Subgroup analysis stratified by the treatments assessed showed terlipressin + albumin reduced mortality compared to albumin, RR 0.81 (95% CI, 0.68-0.97)</td>
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CI = confidence interval; OR = odds ratio; RR = relative risk.

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REFERENCES

7. Burroughs AK. Is the use of albumin of value in cirrhosis? the case not so in favour, or is there an alternative?. Dig Liver Disease 2003;35:664-7.

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