

# Management of Adult Patients With Ascites Due to Cirrhosis

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## Preamble

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic (Medline search); (2) the American College of Physicians' *Manual for Assessing Health Practices and Designing Practice Guidelines*<sup>1</sup>; (3) policy guidelines, including the American Association for the Study of Liver Diseases' Policy Statement on Development and Use of Practice Guidelines and the American Gastroenterological Association's Policy Statement on the Use of Medical Practice Guidelines,<sup>2,3</sup> and (4) the author's 22 years of experience in the clinical and laboratory investigation of, and care of patients with, this problem, including 7 years' experience in a liver unit in which approximately 60% of patients have ascites.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventative aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies designed to be followed in every case. Specific recommendations are based on relevant published information. Cost-effectiveness and cost-benefit data should be incorporated in the appropriate setting. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases requires a grade to be assigned and reported with each recommendation (Table 1).

These guidelines were developed for the care of adult patients with clinically detectable ascites. Although the general approach may be applicable to children, the pedi-

atric data base is much smaller and there may be unanticipated differences between adults and children. Patients with ascites that is detected by imaging modalities but is not yet clinically evident are not included because of the lack of published information regarding the natural history of this entity.

## Background

Cirrhosis was the tenth leading cause of death in the United States, according to a 2000 Vital Statistics Report, in which data was collected through 1998.<sup>4</sup> Ascites is the most common of the 3 major complications of cirrhosis; the other complications are hepatic encephalopathy and variceal hemorrhage.<sup>5</sup> Approximately 50% of patients with "compensated" cirrhosis, *i.e.*, without having developed one of these complications, develop ascites during 10 years of observation.<sup>5</sup> Development of fluid retention in the setting of cirrhosis is an important landmark in the natural history of chronic liver disease: approximately 50% of patients with ascites succumb in 2 years.<sup>6</sup> Many patients are referred for liver transplantation after development of ascites.

## Literature Review

A Medline search from 1966 through 2002 was performed; search terms included ascites, diet therapy, drug therapy, radiotherapy, surgery, and therapy. The search involved only papers published in English and involving humans. A manual search of the author's files was also performed. The search yielded 1,867 papers including 411 published since a similar search was performed in 1997 in preparation for writing the previous guideline on ascites.<sup>7</sup>

## Evaluation and Diagnosis

### History

Most patients (approximately 85%) with ascites in the United States have cirrhosis.<sup>8</sup> In about 15% of patients with ascites, there is a nonhepatic cause of fluid retention. Successful treatment is dependent on an accurate diagnosis of the cause of ascites; *e.g.*, peritoneal carcinomatosis does not respond to diuretic therapy. Patients with ascites should be questioned about risk factors for liver disease. Those who lack an apparent cause for cirrhosis should also

Abbreviations: SAAG, serum-ascites albumin gradient; PMN, polymorphonuclear leukocyte; TIPS, transjugular intrahepatic portosystemic stent-shunt; SBP, spontaneous bacterial peritonitis.

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**Table 1. Quality of Evidence on Which a Recommendation Is Based\***

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities; descriptive epidemiology

\*Data from Woolf and Sox.<sup>3</sup>

be questioned about lifetime body weight; nonalcoholic steatohepatitis has been concluded to be causative in many of these patients.<sup>9</sup> Past history of cancer, heart failure, or tuberculosis is also relevant. Hemophagocytic syndrome can masquerade as cirrhosis with ascites.<sup>10</sup> These patients have fever, jaundice, and hepatosplenomegaly, usually in the setting of lymphoma or leukemia.<sup>10</sup>

### Physical Examination

The presence of a full, bulging abdomen should lead to percussion of the flanks. If the amount of flank dullness is greater than usual (i.e., if the percussed air-fluid level is higher than normally found on the lateral aspect of the abdomen with the patient supine), one should test for "shifting." Approximately 1,500 mL of fluid must be present before flank dullness is detected.<sup>11</sup> If no flank dullness is present, the patient has less than a 10% chance of having ascites.<sup>11</sup> The fluid wave and puddle sign are not useful.<sup>11</sup> Ascites due to alcoholic cardiomyopathy can mimic that due to alcoholic cirrhosis. Jugular venous distension is present in the former but not in the latter.

The physical examination for detecting ascites in the obese patient is problematic. An abdominal ultrasound may be required to determine with certainty if fluid is present.

The diagnosis of new-onset ascites is suspected on the basis of the history and physical examination and usually confirmed by successful abdominal paracentesis and/or ultrasound. The diagnosis of the cause of ascites formation is based on the results of the history, physical, and ascitic fluid analysis. In general, few other tests are required. However, the liver is commonly imaged (usually with ultrasound) to screen for hepatocellular carcinoma, portal vein thrombosis, and hepatic vein thrombosis.

### Abdominal Paracentesis

Abdominal paracentesis with appropriate ascitic fluid analysis is probably the most rapid and cost-effective method of diagnosing the cause of ascites.<sup>12,13</sup> Fluid due to portal hypertension can be readily differentiated from fluid due to other causes.<sup>8</sup> Also, in view of the high prevalence of ascitic fluid infection at the time of admission to

the hospital, an admission surveillance tap may detect unexpected infection.<sup>14</sup>

Although older published series reported a relatively high morbidity, and even mortality, when trocars were used for paracentesis, more recent studies regarding paracentesis complications in patients with ascites documented no deaths or infections caused by the paracentesis.<sup>15</sup> Complications were reported in only about 1% of patients (abdominal wall hematomas), despite the fact that 71% of the patients had an abnormal prothrombin time.<sup>15</sup> Although more serious complications (hemoperitoneum or bowel entry by the paracentesis needle) occur,<sup>16</sup> they are sufficiently unusual (<1/1,000 paracenteses) that they should not deter performance of this procedure. It is the practice of some physicians to give blood products (fresh frozen plasma and/or platelets) routinely before paracentesis in cirrhotic patients with coagulopathy. This policy is not data-supported. The risks and costs of prophylactic transfusions exceed the benefit.

In the past, the midline was usually chosen as the site for paracentesis. However, the abdominal wall in the left lower quadrant, 2 finger breadths cephalad and 2 finger breadths medial to the anterior superior iliac spine, has been shown to be thinner and with a larger pool of fluid than the midline.<sup>17</sup> If the fluid is difficult to localize by examination because of obesity, ultrasonography can be useful.

There are few contraindications to paracentesis. Coagulopathy should preclude paracentesis only when there is clinically evident fibrinolysis or clinically evident disseminated intravascular coagulation.<sup>15</sup> These conditions occur in less than 1 per 1,000 procedures. There is no data-supported cutoff of coagulation parameters beyond which paracentesis should be avoided.<sup>15</sup>

### Recommendations

1. Abdominal paracentesis should be performed and ascitic fluid should be obtained from inpatients and outpatients with clinically apparent new-onset ascites. (Grade II-3)
2. Since bleeding is sufficiently uncommon, the prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended. (Grade III)

### Ascitic Fluid Analysis

Future outcomes studies are required to determine the optimal testing strategy. Meanwhile, an algorithm approach seems preferable to ordering a large number of tests on most specimens. If uncomplicated cirrhotic ascites is suspected, only screening tests (e.g., cell count and differential, albumin and total protein concentration) are

performed on the initial specimen. If the results of these tests are unexpectedly abnormal, further testing can be performed on another ascitic fluid sample. Also, many laboratories save an aliquot of fluid for a few days; this fluid can be tested if the specimen has been handled properly. However, since most specimens are consistent with uncomplicated cirrhotic ascites, no further testing will be needed in the majority of patients.

If ascitic fluid infection is suspected (fever, abdominal pain, or unexplained encephalopathy), bacterial culture in blood culture bottles should be performed. Use of a urine dipstick to detect neutrophils in ascitic fluid takes only 90 seconds to 2 minutes; if confirmed by other studies, this may become a routine method of providing early suspicion of infection.<sup>18,19</sup> Automated cell counting has been shown to be accurate; the result is rapidly available and thus may replace the manual cell count.<sup>20</sup> Additional testing, *e.g.*, total protein, lactate dehydrogenase, and glucose to assist in differentiating spontaneous from secondary bacterial peritonitis, can be performed on the initial specimen based on clinical judgment.<sup>21</sup> An ascitic fluid carcinoembryonic antigen greater than 5 ng/mL or ascitic fluid alkaline phosphatase greater than 240 units/L has also been shown to be accurate in detecting gut perforation into ascitic fluid.<sup>22</sup>

The serum-ascites albumin gradient (SAAG) has been proved in prospective studies to categorize ascites better than the total-protein-based exudate/transudate concept and better than modified pleural fluid exudate/transudate criteria.<sup>8,23</sup> Calculating the SAAG involves measuring the albumin concentration of serum and ascitic fluid specimens obtained on the same day and subtracting the ascitic fluid value from the serum value. If the SAAG is greater than or equal to 1.1 g/dL (11g/L), the patient has portal hypertension, with approximately 97% accuracy.<sup>8</sup> Patients who have portal hypertension plus a second cause for ascites formation also have a SAAG greater than or equal to 1.1g/dL.

Patients undergoing serial outpatient therapeutic paracenteses probably should be tested only for cell count and differential (the author has detected 8 episodes of spontaneous bacterial peritonitis in approximately 400 paracenteses in a paracentesis clinic in 2 years [Zeid Kayali, Reza Khoshini, B.A.R., outpatient management of refractory ascites, unpublished observations, 2003]). Bacterial culture is not necessary in asymptomatic patients undergoing serial large-volume paracenteses.<sup>24,25</sup>

The most expensive tests are the cytology and smear and culture for mycobacteria; these tests should probably be ordered only when there is a high pretest probability of occurrence of the disease under consideration. The ascitic fluid cytology is positive only in the setting of peritoneal

carcinomatosis.<sup>26</sup> The sensitivity of cytology in detecting peritoneal carcinomatosis is 96.7% if 3 samples are sent and processed promptly; the first sample is positive in 82.8% and at least 1 of 2 samples is positive in 93.3%.<sup>26</sup> In this study, 50 mL of fresh warm ascitic fluid were hand-carried to the laboratory for immediate processing. Patients with peritoneal carcinomatosis usually have a history of a breast, colon, gastric, or pancreatic primary carcinoma. The sensitivity of smear for mycobacteria is approximately 0%; the sensitivity of fluid culture for mycobacteria is approximately 50%.<sup>27</sup> Only patients at high risk for tuberculous peritonitis (*e.g.*, recent immigration from an endemic area or acquired immunodeficiency syndrome)<sup>28</sup> should have testing for mycobacteria on the first ascitic fluid specimen. Laparoscopy with biopsy and mycobacterial culture of tubercles are the most rapid and accurate methods of diagnosing tuberculous peritonitis.

Multiple prospective trials have shown that bacterial growth occurs in only about 50% of instances when ascitic fluid with a polymorphonuclear leukocyte (PMN) count greater than or equal to 250cells/mm<sup>3</sup> ( $0.25 \times 10^9/L$ ) is cultured by older methods as compared to approximately 80% if the fluid is inoculated into blood culture bottles at the bedside.<sup>29,30</sup>

### Recommendations

3. The initial laboratory investigation of ascitic fluid should include an ascitic fluid cell count and differential, ascitic fluid total protein, and SAAG. (Grade II-2)
4. If ascitic fluid infection is suspected, ascitic fluid should be cultured at the bedside in blood culture bottles. (Grade II-2)
5. Other studies can be ordered based on pretest probability of disease (Table 2). (Grade III)

### Differential Diagnosis

Although cirrhosis is the cause of ascites formation in most patients, approximately 15% have a cause other than liver disease, including cancer, heart failure, tuberculosis, or nephrotic syndrome.<sup>8</sup> Approximately 5% of patients with ascites have 2 or more causes of ascites formation, *i.e.*, "mixed" ascites.<sup>8</sup> Usually, these patients have cirrhosis plus 1 other cause, *e.g.*, peritoneal carcinomatosis or peritoneal tuberculosis. Many patients with enigmatic ascites are eventually found to have 2 or even 3 causes for ascites formation (*e.g.*, heart failure, diabetic nephropathy, and cirrhosis due to nonalcoholic steatohepatitis). In this setting, the sum of predisposing factors leads to sodium and water retention when each individual factor might not be severe enough to cause fluid overload.

**Table 2. Ascitic Fluid Laboratory Data\***

Routine	Optional	Unusual	Unhelpful
Cell count and differential	Culture in blood culture bottles	AFB smear and culture	pH
Albumin	Glucose	Cytology	Lactate
Total protein	Lactate dehydrogenase	Triglyceride	Cholesterol
	Amylase	Bilirubin	Fibronectin
	Gram's stain		Glycosaminoglycans

Abbreviation: AFB, acid-fast bacteria.

\*Adapted from Runyon.<sup>13</sup> Reprinted with permission from W.B. Saunders.

## Treatment of Ascites

Appropriate treatment of patients with ascites depends on the cause of fluid retention. SAAG can be helpful diagnostically as well as in decision-making regarding treatment. Patients with low SAAG ascites usually do not have portal hypertension and, with the exception of nephrotic syndrome, do not respond to salt restriction and diuretics.<sup>13</sup> In contrast, patients with a high SAAG have portal hypertension and usually are responsive to these measures.<sup>13</sup>

The remainder of this guideline is applicable only to patients with cirrhosis as the cause of their ascites. Improvement in the outcome of patients with nonportal-hypertension-related ascites depends on successful treatment of the underlying disorder.

Alcohol-induced liver injury is perhaps the most reversible cause of liver disease that leads to high albumin gradient ascites.<sup>13</sup> One of the most important steps in treating ascites in this setting is to treat the underlying liver disease by convincing the patient to stop drinking alcohol. In a period of months, abstinence can result in dramatic improvement in the reversible component of alcoholic liver disease. One recent study demonstrates that patients who have Child-Pugh C cirrhosis due to alcohol and who stop drinking have an approximately 75% 3-year survival, but all those who continue to drink die in 3 years.<sup>31</sup> Ascites may resolve or become more responsive to medical therapy with abstinence and time. Nonalcoholic liver diseases are less reversible; by the time ascites is present, these patients may be better candidates for liver transplantation than protracted medical therapy.

The mainstays of treatment of patients with cirrhosis and ascites include (1) education regarding dietary sodium restriction (2000 mg per day [88 mmol per day]) and (2) oral diuretics.<sup>12,13</sup> More stringent dietary sodium restriction can speed mobilization of ascites. Fluid loss and weight change are directly related to sodium balance in patients with portal-hypertension-related ascites. It is sodium restriction, not fluid restriction, which results in weight loss; fluid follows sodium passively.<sup>32</sup> Measurement of urinary sodium excretion is a helpful parameter

to follow when rapidity of weight loss is less than desired.<sup>12,13</sup> Random urinary sodium concentrations are of value when they are 0 mmol/L or greater than 100 mmol/L but are much less helpful when they are intermediate because of lack of uniformity of sodium excretion during the day and lack of knowledge of total urine volume, which may vary from 300 mL to greater than 3000 mL. Twenty-four-hour collections of urine for determination of sodium excretion are much more informative than random specimens; however, full-day collections are cumbersome. Providing patients with verbal and written instructions, a container, and a lab order slip to turn in with the completed specimen helps insure compliance. Completeness of collection of the 24-hour specimen can be assessed by measurement of urinary creatinine. Cirrhotic men should excrete more than 15 mg of creatinine per kilogram of body weight per day, and women should excrete more than 10 mg/kg per day.<sup>33</sup> Less creatinine is indicative of an incomplete collection. Total nonurinary sodium excretion is less than 10 mmol per day in afebrile cirrhotic patients without diarrhea.<sup>34</sup> One of the goals of treatment is to increase urinary excretion of sodium so that it is greater than 78 mmol per day (88 mmol intake per day – 10 mmol nonurinary excretion per day). Only the 10% to 15% of patients who have spontaneous natriuresis greater than 78 mmol per day can be considered for dietary sodium restriction alone (*i.e.*, without diuretics). However, when given a choice, most patients would prefer to take some diuretics and have a more liberal sodium intake than take no pills and have a more severe sodium restriction.

A random “spot” urine sodium concentration that is greater than the potassium concentration correlates with a 24-hour sodium excretion greater than 78 mmol per day with approximately 90% accuracy.<sup>35</sup> This urine sodium/potassium ratio may replace the cumbersome 24-hour collection.

Fluid restriction is not necessary in treating most patients with cirrhosis and ascites. The chronic hyponatremia usually seen in cirrhotic ascites patients is seldom morbid. Attempts to rapidly correct hyponatremia in this setting with hypertonic saline can lead to more complica-

tions than the hyponatremia itself.<sup>36</sup> Preliminary data suggest that aquaretic drugs have the promise of correcting hyponatremia. However, these agents have been under investigation for more than 10 years in the setting of cirrhosis and are not yet approved in the United States.<sup>37</sup> Efficacy without side effects in the subset of patients who are in need of correction of hyponatremia remains unproven. Unfortunately, many drugs that have theoretical promise in treating ascites, *e.g.*, angiotension-converting enzyme inhibitors, have been shown to aggravate hypotension and have not been clinically useful. Severe hyponatremia does warrant fluid restriction in the patient with cirrhosis and ascites; however, there is no data-supported specific threshold for initiating fluid restriction. A serum sodium less than 120–125 mmol/L is a reasonable threshold. Cirrhotic patients do not usually have symptoms from hyponatremia until the sodium is below 110 mmol/L or unless the decline in sodium is very rapid.

Although it is traditional to recommend bed rest (based on extrapolation from heart failure), this is impractical and there are no controlled trials to support this practice. Upright posture may aggravate the plasma renin elevation found in cirrhotic patients with ascites. Theoretically, this may increase sodium avidity. This theoretical concern would have to translate into clinically relevant outcomes before bed rest could be advocated.

The usual diuretic regimen consists of single morning doses of oral spironolactone and furosemide, beginning with 100 mg of the former and 40 mg of the latter.<sup>12,13</sup> Previously, single-agent spironolactone was advocated, but hyperkalemia and the long half-life of this drug have resulted in its use as a single agent only in patients with minimal fluid overload.<sup>38</sup> Single-agent furosemide has been shown in a randomized controlled trial to be less efficacious than spironolactone.<sup>39</sup> The good oral bioavailability of furosemide in the cirrhotic patient, together with the acute reductions in glomerular filtration rate associated with intravenous furosemide, favor use of the oral route of administration.<sup>40,41</sup>

The doses of both oral diuretics can be increased simultaneously every 3 to 5 days (maintaining the 100 mg:40 mg ratio) if weight loss and natriuresis are inadequate. In general, this ratio maintains normokalemia. Usual maximum doses are 400 mg per day of spironolactone and 160 mg per day of furosemide.<sup>12,13</sup> Furosemide can be temporarily withheld in patients presenting with hypokalemia. Patients with parenchymal renal disease (*e.g.*, diabetic nephropathy or immunoglobulin A nephropathy) may tolerate less spironolactone than usual because of hyperkalemia. Single morning dosing maximizes compliance. Amiloride (10–40 mg per day) can be substituted

for spironolactone in patients with tender gynecomastia. However, amiloride is more expensive and has been shown to be less effective than an active metabolite of spironolactone in a randomized controlled trial.<sup>42</sup>

Newer loop diuretics must be proven to be superior to current drugs before their expense can be justified. Although an intravenous dose of 80 mg of furosemide can cause an acute reduction in renal perfusion and subsequent azotemia in patients with cirrhosis and ascites, this same dose has been shown in one study to separate diuretic-resistant (<50 mmol urine sodium in 8 hours) from diuretic-sensitive patients (>50 mmol).<sup>43</sup> This intravenous furosemide “test” may help speed detection of diuretic-resistant patients so that they can more rapidly be given second-line treatment options.<sup>43</sup>

In the largest, multicenter, randomized controlled trial performed in patients with ascites, this approach (dietary sodium restriction and dual diuretic regimen) has been shown to be effective in more than 90% of patients in achieving a reduction in the volume of ascites to acceptable levels.<sup>44</sup>

Outpatient treatment can be attempted initially. However, some patients with cirrhosis and ascites also have gastrointestinal hemorrhage, hepatic encephalopathy, bacterial infection, and/or hepatocellular carcinoma, and may require hospitalization for definitive diagnosis and management of their liver disease as well as management of their fluid overload. Frequently, intensive education is required to convince the patient that the diet and diuretics are actually effective and worth the effort.

There is no limit to the daily weight loss of patients who have massive edema. Once the edema has resolved, 0.5 kg is probably a reasonable daily maximum.<sup>45</sup> Encephalopathy, serum sodium less than 120 mmol/L despite fluid restriction, or serum creatinine greater than 2.0 mg/dL (180  $\mu$ mol/L) should lead to cessation of diuretics, reassessment of the situation, and consideration of second-line options.

In the past, patients with ascites frequently occupied hospital beds for prolonged periods of time because of confusion regarding diagnosis and treatment and because of iatrogenic problems. Although an abdomen without clinically detectable fluid is a reasonable ultimate goal, it should not be a prerequisite for discharge from the hospital. Patients who are stable, with ascites as their major problem, can be discharged to the clinic after it has been determined that they are responding to their medical regimen. However, in order for patients to be discharged early from the hospital, they should be seen in the outpatient setting promptly, ideally within approximately 1 week of discharge.

### Management of Tense Ascites

An initial large-volume paracentesis rapidly relieves tense ascites. A prospective study has demonstrated that a single 5-L paracentesis can be performed safely without post-paracentesis colloid infusion in the patient with diuretic-resistant tense ascites.<sup>46,47</sup> Larger volumes of fluid have been safely removed with the administration of intravenous albumin (8 g/L of fluid removed).<sup>48</sup> However, large-volume paracentesis does nothing to correct the underlying problem that led to ascites formation, *i.e.*, sodium retention. Large-volume paracentesis predictably removes the fluid more rapidly (minutes) than does careful diuresis (days to weeks).<sup>49</sup> A single large-volume paracentesis followed by diet and diuretic therapy is appropriate treatment for patients with tense ascites.<sup>46,49</sup> In the diuretic-sensitive patient, to serially remove fluid by paracentesis when it could be removed with diuretics seems inappropriate.

In order to prevent reaccumulation of fluid, sodium intake should be reduced and urinary sodium excretion should be increased with diuretics. Determining the optimal diuretic doses for each patient—titrating the doses upward every 3–5 days until natriuresis and weight loss are achieved—can take some time. The intravenous furosemide “test” may shorten this time; this should be tested in the context of a randomized trial.<sup>43</sup> Although a controlled trial has demonstrated that large-volume paracentesis is faster than diuretic therapy for patients with cirrhosis and *tense* ascites, it should not be viewed as first-line therapy for all patients with ascites.<sup>49</sup>

In the outpatient clinic, body weight, orthostatic symptoms, and serum electrolytes, urea, and creatinine are monitored. If weight loss is inadequate, a random spot urine sodium/potassium ratio or 24-hour urine sodium can be measured. Patients who are excreting urine sodium/potassium greater than 1 or 24-hour urine sodium greater than 78 mmol per day and not losing weight should be counseled further about diet sodium restriction. These patients should not be labeled as diuretic-resistant and should not proceed to second-line therapy until it is documented that they are compliant with the diet. Patients who are excreting more than 78 mmol per day of sodium in the urine with unchanged or increasing weight are consuming more sodium in the diet than 88 mmol per day.

Patients who do not lose weight and excrete less than 78 mmol per day should receive an attempt at a higher dose of diuretics. Frequency of follow-up is determined by response to treatment and stability of the patient. Some patients warrant evaluation every 2 to 4 weeks until it is clear that they are responding to treatment and not developing problems. Thereafter, evaluation every few

months may be appropriate. Intensive outpatient treatment, in particular with regard to diet education, may help prevent subsequent hospitalizations.

Development of ascites as a complication of cirrhosis is associated with a poor prognosis, approximately a 50% 2-year survival.<sup>6</sup> Liver transplantation should be considered in the treatment options for these patients.

### Recommendations

6. Patients with ascites who are thought to have an alcohol component to their liver injury should abstain from alcohol consumption. (Grade II-2)

7. First-line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol per day [2000 mg per day]) and diuretics (oral spironolactone and furosemide). (Grade I)

8. Fluid restriction is not necessary unless serum sodium is less than 120–125 mmol/L. (Grade III)

9. An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. (Grade II-3)

10. Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses. (Grade III)

11. Liver transplantation should be considered in patients with cirrhosis and ascites. (Grade II-3)

### Refractory Ascites

Refractory ascites is defined as fluid overload that (1) is unresponsive to sodium-restricted diet and high-dose diuretic treatment (400 mg per day of spironolactone and 160 mg per day furosemide), or (2) recurs rapidly after therapeutic paracentesis.<sup>50</sup> Prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs can reduce urinary sodium excretion in patients with cirrhosis and can induce azotemia.<sup>51</sup> These drugs can convert patients from diuretic-sensitive to refractory and should be avoided in this setting. Failure of diuretic therapy may be manifested by (1) minimal to no weight loss together with inadequate (<78 mmol per day) urinary sodium excretion despite diuretics, or (2) development of clinically significant complications of diuretics, *e.g.*, encephalopathy, serum creatinine greater than 2.0 mg/dL, serum sodium less than 120 mmol/L, or serum potassium greater than 6.0 mmol/L. Randomized trials have shown that less than 10% of cirrhotic ascites patients are refractory to standard medical therapy.<sup>39,44</sup> Options for patients refractory to routine medical therapy include (1) serial therapeutic paracenteses, (b) liver transplantation, (c) transjugular intrahepatic portosystemic stent-shunt (TIPS), and (d) peritoneovenous shunt.<sup>12,13,44,52,53</sup>

Serial therapeutic paracenteses are effective in controlling ascites. This has been known since the time of the ancient Greeks. However, only relatively recently have controlled trials demonstrating the safety of this approach been published.<sup>49</sup> Even in patients with no urine sodium excretion, paracenteses performed approximately every 2 weeks control ascites.<sup>12,13</sup> Frequency of paracentesis provides insight into the patient's degree of compliance with the diet. The sodium concentration of ascitic fluid is approximately equivalent to that of plasma in these patients: 130 mmol/L. A 6-L paracentesis removes 780 mmol of sodium ( $130 \text{ mmol/L} \times 6 \text{ L} = 780 \text{ mmol}$ ). A 10-L paracentesis removes 1300 mmol. Patients consuming 88 mmol of sodium per day, excreting approximately 10 mmol per day in nonurinary losses, and excreting no urinary sodium retain a net of 78 mmol per day. Therefore, a 6-L paracentesis removes 10 days ( $780 \text{ mmol} / 78 \text{ mmol per day}$ ) of retained sodium and a 10-L paracentesis removes approximately 17 days of retained sodium ( $1300 \text{ mmol} / 78 \text{ mmol per day} = 16.7 \text{ days}$ ) in patients with no urinary sodium excretion. Patients with some urinary sodium excretion should require paracenteses even less frequently. Patients requiring paracenteses of approximately 10 L more frequently than every 2 weeks are clearly not complying with the diet.

In recent years, new paracentesis equipment (*e.g.*, multihole, large-bore needle) has become available that may improve the ease and speed of paracentesis.

One controversial issue regarding therapeutic paracentesis is that of colloid replacement. In one study, 105 patients with tense ascites were randomized to receive albumin (10 g/L of fluid removed) versus no albumin, after therapeutic paracentesis.<sup>54</sup> Refractoriness to diuretic treatment was not a prerequisite for entry into this study; in fact, 31.4% of patients had not received diuretics.<sup>54</sup> The group that received no albumin developed statistically significantly more (although asymptomatic) changes in electrolytes, plasma renin, and serum creatinine than the albumin group, but no more clinical morbidity or mortality.<sup>54</sup> Although another study has documented that the subset of patients who develop a rise in plasma renin after total paracentesis have decreased life expectancy, there has been no study large enough to demonstrate decreased survival in patients given no plasma expander compared to patients given albumin after paracentesis.<sup>55</sup> Furthermore, the activation in vasoconstrictor systems that can follow large-volume paracentesis may not be related to a decreased intravascular volume.<sup>56</sup> Also, albumin infusions markedly increase albumin degradation, and albumin is very expensive.<sup>47,57,58</sup> In a study performed almost 40 years ago, 58% of infused albumin was accounted for by increased degradation, and a 15% in-

crease in serum albumin led to a 39% increase in degradation.<sup>57</sup> Increasing albumin concentration in cell culture media has been shown to decrease albumin synthesis.<sup>59</sup>

The University Hospital Consortium is a not-for-profit alliance of academic medical centers in the United States; its 1995 update of the National Institutes of Health consensus conference on albumin recommends no intravenous fluid infusion after paracenteses of less than 4 L and recommends crystalloid as a first-line agent and albumin as a second-line agent for larger paracenteses.<sup>60</sup> In view of the extremely high cost of albumin, future studies also should include cost analyses. Nevertheless, albumin is being used after therapeutic paracentesis. While more studies are awaited, it is reasonable although not mandatory to give it for paracenteses greater than 5 L.<sup>54</sup>

Studies have infused between 5 and 10 g of albumin per liter of fluid removed.<sup>52,54,55</sup> No study has compared doses.

Non-albumin plasma expanders such as dextran 70, hydroxyethylstarch, and even saline have been advocated, also without demonstration of a survival advantage.<sup>55,61</sup> Hydroxyethylstarch can fill Kupffer cells and cause portal hypertension even in patients without underlying liver disease.<sup>62</sup> Part of the controversy regarding post-paracentesis plasma expanders relates to study design. More studies are needed, in particular studies that target survival as the specific study endpoint in patients with truly diuretic-resistant ascites. Chronic therapeutic paracenteses should be reserved for the 10% of patients who truly fail diuretic treatment. Some patients may benefit from albumin infusion after large-volume paracentesis. What are needed are risk factors that permit pre-paracentesis identification of the subset of patients who are at higher risk of post-paracentesis circulatory dysfunction.

Liver transplantation should be considered in the treatment options of patients with ascites. Once patients become refractory to routine medical therapy, 50% die within 6 months and 75% die within 1 year.<sup>63</sup> Referral should not be delayed in patients with refractory ascites.

TIPS is a side-to-side portacaval shunt that is placed by an interventional radiologist usually under local anesthesia<sup>52,53,64-66</sup>; in some European centers, TIPS is placed by hepatologists. General anesthesia is used in some centers. One randomized trial demonstrated higher mortality in the TIPS group compared to the medically treated group, but this study was very small and took place very early in our experience with this relatively new technique.<sup>64</sup> Four large-scale, multicenter randomized controlled trials comparing TIPS to sequential large-volume paracentesis have been undertaken<sup>52,53,65,66</sup> (Table 3). Three of these are completed and published.<sup>52,53,65</sup> The remaining study

**Table 3. Large-Scale Randomized Controlled Trials of TIPS Versus Serial Large-Volume Paracenteses**

Reference No.	Status	Inclusion Criteria	Method of Randomization and Analysis	N	Control of Ascites	Survival	Encephalopathy
52	Completed	Tense ascites & failure of 4 weeks of therapy	No details	60	61% vs. 18% (P = .006)	69% vs. 52% 1 year (P = .11 by univariate analysis)/(P = .02 by multivariate analysis)	58% vs. 48%*
53	Completed	Ascites refractory to medical therapy	Sealed opaque envelope Intention to treat	70	51% vs. 17% (P = .003)	41% vs. 35% 1 year*	All 77% vs. 66% (P = .29) Severe 60% vs. 34% (P = .03)
65	Completed	Refractory ascites	No details Intention to treat	109	58% vs. 16% (P < .001)	40% vs. 37%*	Moderate-Severe 38% vs. 12% (P = .058)
66	Ongoing	Refractory or recidivant ascites	No details	57	74% vs. 35% (P = .008)	71% vs. 35% (P = .017)	55% vs. 46% (P = .29)

\*P value not significant.

is ongoing and has been published only in abstract form.<sup>66</sup> All of these report better control of ascites in the TIPS group. One reports no survival advantage by univariate analysis but a statistically significant survival advantage for the TIPS group by multivariate analysis.<sup>52</sup> Another reports prevention of hepatorenal syndrome but with higher costs in the TIPS group: there were similar rates of encephalopathy overall but more severe hepatic encephalopathy in the TIPS group.<sup>53</sup> Another shows no survival advantage, with a trend (P = .58) toward more moderate or severe encephalopathy in the TIPS group and no effect on quality of life.<sup>65</sup> This study is the first to provide a specific cutoff of cardiac ejection fraction (>50%) for eligibility for enrollment.<sup>65</sup> The ejection fraction of the patient with cirrhosis is usually greater than 60%.<sup>67</sup> An ejection fraction of greater than 60% may be more appropriate as an inclusion criterion for entry into a TIPS study, since patients with an ejection fraction between 50% and 60% may have a higher risk of post-TIPS heart failure.<sup>68</sup> The abstract of the ongoing study reports a survival advantage in the TIPS group with similar hospitalization and encephalopathy rates.<sup>66</sup> Meanwhile, a polytetrafluoroethylene-covered stent has been developed that has more than twice the patency of the uncoated stent at 1 year in a randomized trial.<sup>69</sup> Also, there is a new scoring system, Model for End-Stage Liver Disease, to predict 3-month mortality after TIPS.<sup>70</sup> All of these trials were initiated before this scoring system was popularized. Furthermore, some investigators and some trials have withheld diuretics after TIPS. This further limits its efficacy. TIPS usually converts diuretic-resistant patients into diuretic-sensitive patients. Giving diuretics after TIPS and titrating the doses to achieve natriuresis is appropriate.

As the experience with TIPS continues, and the level of sophistication of patient screening improves (*e.g.*, ejection fraction), and the technology of the stent itself improves, the results of future trials may be better than past trials.

More randomized trials are planned. Their results are needed before the position of TIPS in the algorithm of treatment of patients with ascites can be finalized.

Peritoneovenous shunt, *e.g.*, LeVeen or Denver, was popularized in the 1970s as a physiologic treatment of ascites. Shunt placement has been shown in controlled trials to decrease the duration of hospitalization, decrease the number of hospitalizations, and decrease the dose of diuretics.<sup>44,71</sup> However, poor long-term patency, excessive complications, and no survival advantage compared to medical therapy in controlled trials have led to near abandonment of this procedure.<sup>44,71</sup> Shunt-related fibrous adhesions and even “cocoon” formation can make subsequent liver transplantation difficult. Peritoneovenous shunting should probably now be reserved for diuretic-resistant patients who are not candidates for transplant or TIPS—and who are not candidates for serial therapeutic paracenteses—because of multiple abdominal surgical scars or distance from a physician willing to perform and capable of performing paracenteses. Recent experience in shunt insertion by the surgeon may also be a factor in optimizing results in the rare patient who is selected to undergo this procedure.

Interventional radiologists have reported the possibility of performing a peritoneovenous shunt without the participation of a surgeon.<sup>72</sup> Radiologists are also placing plastic subcutaneous access ports for paracentesis.<sup>73</sup> Radiologists and surgeons have collaborated to develop a device that drains ascitic fluid into the urinary bladder.<sup>74</sup> None of these new techniques have been studied in randomized trials. We await the results of such studies before placing these innovations into our algorithm.

### Recommendations

12. Serial therapeutic paracenteses may be performed in patients with refractory ascites. (Grade III)

13. Post-paracentesis albumin infusion may not be necessary for a single paracentesis of less than 4 to 5 L. For large-volume paracenteses, an albumin infusion of 8 to 10 g per liter of fluid removed can be considered. (Grade II-2)

14. Referral for liver transplantation should be expedited in patients with refractory ascites. (Grade II-3)

15. TIPS should be considered in appropriately selected patients who meet criteria similar to those of published randomized trials. (Grade I)

16. Peritoneovenous shunt should be considered for patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS. (Grade I)

## Hepatorenal Syndrome

### Diagnosis

Major criteria include (1) advanced chronic or acute liver failure with portal hypertension; (2) serum creatinine greater than 1.5 mg/dL or 24-hour creatinine clearance less than 40 mL per minute; (3) absence of shock, ongoing bacterial infection, recent treatment with nephrotoxic drugs, or massive gastrointestinal or renal fluid losses; (4) no sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline; and (5) less than 500 mg/dL proteinuria and no ultrasonographic evidence of obstructive uropathy or parenchymal kidney disease.<sup>50</sup> Two types of hepatorenal syndrome have been described. Type I is characterized by rapidly progressive reduction in renal function as defined by a doubling of the initial serum creatinine to a level greater than 2.5 mg/dL or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 mL per minute in less than 2 weeks; type II does not have a rapidly progressive course.<sup>50</sup>

### Treatment

Hemodialysis is frequently used to control azotemia and maintain electrolyte balance before liver transplantation. Many patients require it for a variable interval after transplant. Hypotension during dialysis is a common problem. However, without transplantation survival is dismal; one older series reported no survivors out of 25 patients.<sup>75</sup> Continuous venovenous hemofiltration causes less hypotension but requires the continuous involvement of a dialysis nurse.<sup>76</sup> In a study that screened 3,860 patients with cirrhosis and ascites and included an arm for patients with hepatorenal syndrome, peritoneovenous shunting was not shown to improve survival in hepatorenal syndrome; however, a type II error could not be excluded.<sup>44</sup> Furthermore, this study was performed before the types of hepatorenal syndrome were delineated.

Many pharmaceutical treatments, including some that are not available in the United States, have been tried.

Usually, short case series with or without historical controls are reported, followed by a flurry of enthusiasm. Then the option disappears from the literature without publication of a randomized trial. Whether a randomized trial with negative results remains unpublished is unknown. Recently, treatments have been much more successful for type I hepatorenal syndrome, albeit without randomized data. Dopamine is the traditional drug that has been used clinically. The drug combination, along with albumin infusion, that has been reported from Europe but is also available in the United States is octreotide and midodrine.<sup>77</sup> In one study, 5 patients received 10 to 20 grams of intravenous albumin per day for 20 days, plus octreotide with a target dose of 200  $\mu$ grams subcutaneously 3 times per day, and midodrine titrated up to a maximum of 12.5 mg orally 3 times per day to achieve an increase in mean blood pressure of 15 mm Hg.<sup>77</sup> Results were superior to those of 8 patients treated with dopamine and albumin.<sup>77</sup> This regimen can be administered outside of an intensive care unit and can even be given at home.<sup>77</sup> Many liver units in the United States are reporting anecdotal success with this strategy. Another pilot study, this one using norepinephrine plus albumin, reports 83% (10 of 12 patients) success in reversing type I hepatorenal syndrome; this treatment requires that the patient be in an intensive care unit.<sup>78</sup> An uncontrolled trial using terlipressin (not available in the United States) also reports success with type I hepatorenal syndrome.<sup>79</sup> TIPS has also been reported to be effective in type I hepatorenal syndrome in an uncontrolled study of 7 patients.<sup>80</sup> Enthusiasm is high for these new treatments.<sup>81</sup> Whether they will be effective in patients with type II hepatorenal syndrome remains to be seen. What are needed are well-designed, randomized controlled trials.

It has been known for 30 years that liver transplantation is an effective treatment for hepatorenal syndrome; this will probably never be studied in a randomized trial.<sup>82</sup>

### Recommendations

17. Albumin infusion plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type I hepatorenal syndrome. (Grade II-1)

18. Patients with cirrhosis, ascites, and type I hepatorenal syndrome should have an expedited referral for liver transplantation. (Grade II-3)

## Spontaneous Bacterial Peritonitis

### Diagnosis

Ascitic fluid infection is sufficiently common at the time of admission of a patient with cirrhosis and ascites to justify a diagnostic paracentesis.<sup>14</sup> The diagnosis of spon-

taneous bacterial peritonitis (SBP) is made when there is a positive ascitic fluid bacterial culture and an elevated ascitic fluid absolute PMN count (*i.e.*,  $\geq 250$  cells/mm<sup>3</sup> [ $0.25 \times 10^9$ /L]) without an evident intra-abdominal, surgically treatable source of infection.<sup>83</sup> An abdominal paracentesis must be performed and ascitic fluid must be analyzed before a confident diagnosis of ascitic fluid infection can be made. A “clinical diagnosis” of infected ascitic fluid without a paracentesis is not adequate. Dipstick testing of ascitic fluid and automated cell counts may improve early detection of this infection.<sup>18–20</sup>

### **Empiric Treatment**

Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm<sup>3</sup> ( $0.25 \times 10^9$ /L) in a clinical setting, compatible with ascitic fluid infection, should receive empiric antibiotic therapy.<sup>13,83</sup> An elevated ascitic fluid PMN count probably represents evidence of failure of the first line of defense, the peritoneal macrophages, to kill invading bacteria. Most of the bacterial cultures of these fluid samples will grow bacteria if (1) the fluid is cultured in blood culture bottles, (2) there has been no prior antibiotic treatment, and (3) there is no other explanation for an elevated PMN count, *e.g.*, hemorrhagic ascites, peritoneal carcinomatosis, pancreatitis, or peritoneal tuberculosis.<sup>13,29,84</sup> The patients who meet the above criteria but have negative cultures have been labeled with a diagnosis of culture-negative neutrocytic ascites.<sup>84</sup> The initial threshold PMN count for making this diagnosis was 500 cells/mm<sup>3</sup> ( $0.25 \times 10^9$ /L).<sup>84</sup> However, subsequent studies have revised this threshold to 250 cells/mm<sup>3</sup> ( $0.25 \times 10^9$ /L).<sup>85</sup> Patients with culture-negative neutrocytic ascites have similar signs, symptoms, and mortality as patients with SBP and warrant empiric antibiotic treatment.<sup>84</sup> A prospective study in which 2 paracenteses were performed in rapid sequence (approximately 8 hours apart) before initiation of antibiotic therapy has demonstrated that only 8% of patients with culture-positive ascitic fluid with an elevated PMN count become culture-negative spontaneously.<sup>86</sup> The majority of patients with culture-positive neutrocytic ascites demonstrate rising bacterial counts and rising PMN counts when serial samples are obtained in rapid sequence before initiation of antibiotic therapy.<sup>86</sup> The majority of patients with culture-negative neutrocytic ascites continue with this pattern of ascitic fluid analysis when serial samples are obtained in rapid sequence before initiation of antibiotic therapy; 34.5% become culture-positive.<sup>86</sup>

The ascitic fluid PMN count is more rapidly available than the culture and appears to be accurate in determining who really needs empiric antibiotic treatment.<sup>13,83</sup> Delaying treatment until the ascitic fluid culture grows

bacteria may result in the death of the patient from overwhelming infection. In some patients, infection is detected at the bacterascites stage before there is a neutrophil response, *i.e.*, less than 250 cells/mm<sup>3</sup> ( $0.25 \times 10^9$ /L); this has been labeled monomicrobial nonneutrocytic bacterascites.<sup>87</sup> Most patients—62% in one study—resolve the colonization without antibiotics and without a neutrophil response.<sup>87</sup> Patients with bacterascites who do not resolve the colonization and who progress to SBP have signs or symptoms of infection at the time of the paracentesis that documents bacterascites.<sup>86,87</sup> Therefore, patients with cirrhosis and ascites who have convincing signs or symptoms of infection (fever, abdominal pain, or unexplained encephalopathy) should receive empiric treatment until the culture results are known regardless of the PMN count in ascitic fluid.

The patient with alcoholic hepatitis represents a special case. These patients may have fever, leukocytosis, and abdominal pain that can masquerade as SBP. In addition, they can develop SBP. These patients do not develop false-positive elevated ascitic fluid PMN counts because of peripheral leukocytosis<sup>88</sup>; an elevated PMN count must be presumed to represent SBP. Empiric antibiotic treatment (for presumed ascitic fluid infection) of patients with alcoholic hepatitis who have fever and/or peripheral leukocytosis can be discontinued after 48 hours if ascitic fluid, blood, and urine cultures demonstrate no bacterial growth.

Relatively broad-spectrum therapy is warranted in patients with suspected ascitic fluid infection until the results of susceptibility testing are available. Cefotaxime, a third-generation cephalosporin, has been shown to be superior to ampicillin plus tobramycin in a controlled trial.<sup>89</sup> Cefotaxime or a similar third-generation cephalosporin appears to be the treatment of choice for suspected SBP; it covers 95% of the flora including the 3 most common isolates: *Escherichia coli*, *Klebsiella pneumoniae*, and pneumococci<sup>89</sup> (Table 4). Dosing of cefotaxime 2 g intravenously every 8 hours has been shown to result in excellent ascitic fluid levels (20-fold killing power after 1 dose).<sup>90</sup> After sensitivities are known, the spectrum of coverage can usually be narrowed. A randomized controlled trial involving 100 patients has demonstrated that 5 days of treatment is as efficacious as 10 days in the treatment of carefully characterized patients with SBP.<sup>91</sup>

**Oral Treatment.** Oral ofloxacin has been reported in a randomized controlled trial to be as effective as parenteral cefotaxime in the treatment of SBP in patients without vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine greater than 3 mg/dL.<sup>92</sup> Only 61% of patients with SBP met study inclusion criteria. All treatment was given in hospitalized patients.<sup>92</sup>

**Table 4. Treatment of Spontaneous Bacterial Peritonitis (SBP)**

Reference No.	Study Design	Method of Randomization and Analysis	N	Results	P	Mortality	P
89	Cefotaxime vs. ampicillin/tobramycin for severe infections	Random number table	73	Cure of infection 85% vs. 56% Superinfection 0% vs. 16%	<.02	Infection-related mortality 19% vs. 31% Hospitalization mortality 27% vs. 39%	NS
91	Cefotaxime 5 days vs. 10 days for SBP	Sealed opaque envelope Intention to treat	100	Cure 93% vs. 91% Recurrence 12% vs. 13%	NS NS	Infection-related mortality 0% vs. 4% Hospitalization mortality 33% vs. 43%	NS NS
92	Oral ofloxacin vs. cefotaxime for SBP	Sealed envelope	123	Resolution 84% vs. 85%	NS	Hospitalization mortality 19% vs. 19%	NS
93	Cefotaxime with or without albumin for SBP	Sealed envelope Intention to treat	126	Resolution 98% vs. 94% Renal failure 10% vs. 33%	NS .002	Hospitalization mortality 10% vs. 29%	<.01

Abbreviation: NS, not significant.

**Intravenous Albumin Infusion in Addition to Cefotaxime.** One controlled trial randomized patients with SBP to receive cefotaxime alone versus cefotaxime plus 1.5 g albumin per kg body weight within 6 hours of enrollment and 1.0 g/kg on day 3.<sup>93</sup> A decrease in mortality from 29% to 10% was reported.<sup>93</sup> This is the lowest hospitalization mortality ever reported in a randomized trial of SBP.<sup>94</sup> Improving control of a complication of advanced cirrhosis is commonly reported; however, dramatically improving survival is seldom shown. This study warrants confirmation. While confirmation is awaited, it is reasonable to give albumin in this dose in this setting.

#### **Distinction From Secondary Bacterial Peritonitis**

Secondary bacterial peritonitis, *i.e.*, ascitic fluid infection caused by a surgically treatable intra-abdominal source, can masquerade as SBP. Secondary peritonitis can be divided into 2 subsets: those with free perforation of a viscus (*e.g.*, duodenal ulcer) and those with loculated abscesses in the absence of perforation (*e.g.*, perinephric abscess). Signs and symptoms do not help separate patients who need surgical intervention (both subsets of secondary peritonitis) from those who have SBP and need only antibiotic treatment.<sup>21</sup> In contrast, the initial ascitic fluid analysis and the response to treatment can assist with this important distinction.<sup>21</sup> The characteristic analysis in the setting of free perforation is PMN count greater than or equal to 250 cells/mm<sup>3</sup> (usually many thousands), multiple organisms on Gram's stain and culture, and at least two of the following criteria: total protein greater than 1g/dL, lactate dehydrogenase greater than the upper limit of normal for serum, and glucose less than 50 mg/dL.<sup>21</sup> It is useful to order an ascitic fluid Gram's stain, culture, total protein, LDH, and glucose in patients with cirrhosis

and ascites and an ascitic fluid PMN count greater than or equal to 250 cells/mm<sup>3</sup>. These criteria have been shown to have 100% sensitivity but only 45% specificity in detecting perforation in a prospective study.<sup>21</sup> An ascitic fluid carcinoembryonic antigen greater than 5 ng/mL or ascitic fluid alkaline phosphatase greater than 240 units/L has also been shown to be accurate in detecting gut perforation into ascitic fluid with a sensitivity of 92% and specificity of 88%; these criteria would not be predicted to be useful in nonperforation secondary peritonitis.<sup>22</sup> Patients who fulfill either set of criteria for gut perforation should undergo emergent plain and upright films, water-soluble contrast studies of the gut, and computed tomographic scanning.<sup>21,22</sup>

The total protein, LDH, and glucose criteria are only 50% sensitive in detecting nonperforation secondary peritonitis; the follow-up PMN count after 48 hours of treatment assists in detecting these patients.<sup>21</sup> The 48-hour PMN count is essentially always below the pretreatment value in SBP when an appropriate antibiotic is used; in contrast, the PMN count rises despite treatment in nonperforation secondary peritonitis.<sup>21</sup>

Patients documented to have free perforation or nonperforation secondary peritonitis should receive anaerobic coverage in addition to a third-generation cephalosporin and should undergo laparotomy.<sup>21</sup> The mortality of secondary peritonitis treated with antibiotics and surgery is similar to that of SBP treated with antibiotics.<sup>21</sup>

#### **Follow-up Paracentesis**

A follow-up ascitic fluid analysis is not needed in all patients with infected ascites.<sup>95</sup> The majority of patients have SBP in the typical setting (*i.e.*, advanced cirrhosis) with typical symptoms, typical ascitic fluid analysis (total

**Table 5. Prevention of Spontaneous Bacterial Peritonitis (SBP)**

Reference No.	Study Design	Method of Randomization and Analysis	N	Results	P	Mortality	P
97	Norfloracin vs. no drug in inpatients with AFTP <1.5 g/dL	No details	63	SBP 0% vs. 23%	<.05	Infection-related mortality (0% vs. 13%) Hospitalization mortality (6% vs. 16%)	NS NS
98	Norfloracin vs. placebo in patients with prior SBP	No details	80	SBP recurrence 12% vs. 35%	.014	18% vs. 25%	NS
99	Norfloracin vs. no drug in cirrhotics with gut hemorrhage	No details	119	Infection 10% vs. 37%	.001	7% vs. 12%	NS
101	Trimethoprim/sulfamethoxazole vs. no drug in cirrhotics with ascites	No details	67	SBP or bacteremia (3% vs. 27%)	.025	7% vs. 20%	.15
102	Meta-analysis of antibiotic prevention of infection in cirrhotics with gut hemorrhage	Meta-analysis	534	32% reduction in infection	<.001	9% increase in survival	.004

Abbreviations: AFTP, ascitic fluid total protein; NS, not significant.

protein  $\leq 1$  g/dL, LDH less than the upper limit of normal for serum, and glucose greater than or equal to 50 mg/dL, a single organism, and a dramatic clinical response.<sup>13,95</sup> Repeat paracentesis can be performed to document sterility of culture and dramatic decrease in PMN count in patients with SBP; however, it is not necessary. In contrast, if the setting, symptoms, analysis, organism(s), or response are atypical, repeat paracentesis can be helpful in raising the suspicion of secondary peritonitis and prompting further evaluation and surgical intervention when appropriate.<sup>21</sup>

### Recommendations

19. Patients with ascites admitted to the hospital should undergo abdominal paracentesis. Paracentesis should be repeated in patients (whether in the hospital or not) who develop signs or symptoms or laboratory abnormalities suggestive of infection (*e.g.*, abdominal pain or tenderness, fever, encephalopathy, renal failure, acidosis, or peripheral leukocytosis). (Grade III)

20. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm<sup>3</sup> ( $0.25 \times 10^9/L$ ) should receive empiric antibiotic therapy, *e.g.*, intravenous cefotaxime 2 g every 8 hours. (Grade I)

21. Patients with ascitic fluid PMN counts less than 250 cells/mm<sup>3</sup> ( $0.25 \times 10^9/L$ ) and signs or symptoms of infection (temperature  $>100^\circ F$  or abdominal pain or tenderness) should also receive empiric antibiotic therapy, *e.g.*, intravenous cefotaxime 2 g every 8 hours, while awaiting results of cultures. (Grade II-3)

22. When the ascitic fluid of a patient with cirrhosis is found to have a PMN count greater than or equal to 250 cells/mm<sup>3</sup> ( $0.25 \times 10^9/L$ ), it should also be tested for total

protein, LDH, glucose, and Gram's stain to assist with the distinction of SBP from secondary peritonitis. (Grade II-2).

23. Oral ofloxacin (400 mg twice per day.) can be considered a substitute for intravenous cefotaxime in inpatients without vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine greater than 3 mg/dL. (Grade I)

24. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm<sup>3</sup> ( $0.25 \times 10^9/L$ ) and clinical suspicion of SBP should receive 1.5 g albumin per kg body weight within 6 hours of detection and 1.0 g/kg on day 3. (Grade I)

### Prevention of SBP

The identification of risk factors for development of SBP (including ascitic fluid protein concentration less than 1.0 g/dL, variceal hemorrhage, and prior episode of SBP) has led to randomized controlled trials of prophylactic antibiotics<sup>96-101</sup> (Table 5). Norfloracin 400 mg per day orally has been reported to successfully prevent SBP in (1) patients with low-protein ascites and (2) patients with prior SBP.<sup>97-98</sup> Norfloracin 400 mg orally twice per day for 7 days helps prevent infection in patients with variceal hemorrhage.<sup>99</sup> An antibiotic can be given intravenously while the patient is actively bleeding; ofloxacin (400 mg per day) has been validated for this purpose.<sup>100</sup> Administering 5 doses of double-strength trimethoprim/sulfamethoxazole per week has also been reported to be effective in preventing SBP in patients with cirrhosis and ascites.<sup>101</sup> However, intermittent dosing may select resistant flora more rapidly. Daily dosing of this drug combi-

nation may be better than intermittent dosing. Selective intestinal decontamination with norfloxacin or trimethoprim/sulfamethoxazole has not been shown to prolong survival in humans in individual trials. However, these studies were not designed to detect a survival advantage. A meta-analysis of 5 trials in patients with cirrhosis and gastrointestinal bleeding has shown a survival advantage of 9.1% in the treated group.<sup>102</sup>

Selective intestinal decontamination does select resistant gut flora, which can subsequently cause spontaneous infection; fortunately, infection-causing bacteria that are resistant to quinolones are usually sensitive to cefotaxime.<sup>103</sup> A report from a center in which selective intestinal decontamination has been routine in high-risk patients for many years documents a recent change in the flora of bacterial infections with a predominance of gram-positive organisms, compared to a predominance of gram-negative organisms in the past.<sup>104</sup> This is cause for concern and emphasizes the importance of limiting selective intestinal decontamination to patients at high risk. Selective intestinal decontamination with norfloxacin or trimethoprim/sulfamethoxazole in patients with prior SBP or low-protein ascitic fluid does appear to be cost-effective.<sup>105,106</sup>

One trial in which patients with low-protein ( $\leq 1$ g/dL) ascitic fluid or bilirubin greater than 2.5 mg/dL were randomized either to continuous norfloxacin or to inpatient-only norfloxacin demonstrated that continuous norfloxacin reduced SBP compared to inpatient-only prophylaxis.<sup>107</sup> However, patients receiving continuous norfloxacin had a higher risk of resistant flora when they did develop infection.<sup>107</sup> Based on the available literature, it is reasonable to give norfloxacin (or trimethoprim/sulfamethoxazole) (1) to inpatients who meet these criteria with discontinuation of the drug at the time of discharge or (2) continuously to patients who meet these criteria.<sup>101,107</sup>

In a report of liver transplant infections, one risk factor for post-transplant fungal infection was "prolonged therapy with ciprofloxacin" (pg. 1328).<sup>108</sup> There are no published randomized trials of selective intestinal decontamination versus placebo in preventing infections in patients awaiting liver transplantation. Use of long-term selective intestinal decontamination in this setting in the absence of prior SBP is not data-supported.

Parenteral antibiotics to prevent sclerotherapy-related infections do not appear to be warranted, based on a controlled trial.<sup>109</sup> It is the active bleeding that appears to be the risk factor for infection, not sclerotherapy.<sup>110</sup> Variceal banding has largely replaced sclerotherapy; antibiotics would be even less likely to be of benefit in the setting of banding.

## Recommendations

25. Short-term (7 days) inpatient twice-daily norfloxacin (or trimethoprim/sulfamethoxazole) should be given to prevent bacterial infections in patients with cirrhosis and gastrointestinal hemorrhage; a quinolone antibiotic can be given intravenously while the patient is actively bleeding. (Grade I)

26. Patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin (or trimethoprim/sulfamethoxazole) because this is the most data-supported indication for long-term outpatient prophylaxis. (Grade I)

27. In patients with cirrhosis and ascites but no gastrointestinal bleeding, either short-term (inpatient-only) or long-term outpatient use of daily norfloxacin (or trimethoprim/sulfamethoxazole) can be justified when the ascitic fluid total protein is less than or equal to 1g/dL or serum bilirubin greater than 2.5 mg/dL. (Grade I)

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