Management of Adult Patients with Ascites Due to Cirrhosis: An Update

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Preamble

This guideline has been approved by the AASLD and represents the position of the Association. 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) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines[1]; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association Policy Statement on Guidelines[2]; and (4) the author's decades of experience caring for patients with cirrhosis and ascites.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. To more fully characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a Class (reflecting benefit versus risk) and Level (assessing strength or certainty) of Evidence to be assigned and reported with each recommendation (Table 1, adapted from the American College of Cardiology and the American Heart Association Practice Guidelines[3]).[4]

These guidelines were developed for the care of adult patients with clinically detectable ascites. Although the general approach may be applicable to children, the pediatric database is much smaller and there may be unanticipated differences between adults and children. Patients with ascites detected only by imaging modalities but not yet clinically evident are excluded because of the lack of published information regarding the natural history of this entity.

A Medline search from 1966 through 2007 was performed; search terms included ascites, hepatorenal syndrome, diet therapy, drug therapy, radiotherapy, surgery, and therapy. The search involved only articles published in English and involving humans. A manual search of the author's files and recent abstracts was also performed. The search yielded 2115 articles including 153 published since a similar search was performed in 2002 in preparation for writing the previous guideline on ascites.

Introduction

Cirrhosis was the twelfth leading cause of death in the United States, according to a 2006 Vital Statistics Report in which data were collected through 2004.[5] Ascites is the most common of the three major complications of cirrhosis; the other complications are hepatic encephalopathy and variceal hemorrhage.[6] Approximately 50% of patients with "compensated" cirrhosis, i.e., without having developed one of these complications, develop ascites during 10 years of observation.[6] Ascites is the most common complication of cirrhosis that leads to hospital admission.[7] The pathophysiology of ascites and hepatorenal syndrome have been reviewed elsewhere.[8] Development of fluid retention in the setting of cirrhosis is an important landmark in the natural history of chronic liver disease: approximately 15% of patients with ascites succumb in 1 year and 44% succumb in 5 years.[9] Many patients are referred for liver transplantation after development of ascites.

Evaluation and Diagnosis

History

Most patients (approximately 85%) with ascites in the United States have cirrhosis (Table 2).[10] In about 15% of

Abbreviations: AASLD, American Association for the Study of Liver Diseases; LDH, lactate dehydrogenase; PMN, polymorphonuclear leukocyte; SAAG, serum-ascites albumin gradient; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portasystemic stent-shunt.

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He began to serve on the scientific advisory board for Ikaria after the guideline was completed.

Table 1. Grading System for Recommendations

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard-of-care.

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 be questioned about lifetime body weight; nonalcoholic steatohepatitis has been concluded to be causative in many of these patients.[11] Past history of cancer, heart failure, renal disease, or tuberculosis is also relevant. Hemophagocytic syndrome can masquerade as cirrhosis with ascites.[12] These patients have fever, jaundice, and hepatosplenomegaly, usually in the setting of lymphoma or leukemia.[12]

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 tympany-dullness interface is higher than normally found on the lateral aspect of the abdomen with the patient supine), one should test for "shifting". The presence of shifting dullness has 83% sensitivity and 56% specificity in detecting ascites.[13] Approximately 1500 mL of fluid must be present before flank dullness is detected.[13] If no flank dullness is present, the patient has less than a 10% chance of having ascites.[13] The fluid wave and puddle sign are cumbersome and perform less well when compared to shifting dullness.[13] 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. Also measurement of a blood concentration of brain natriuretic peptide or pro–brain natriuretic peptide can help distinguish ascites due to heart failure from ascites due to cirrhosis.[14] The median pro–brain natriuretic peptide concentration is 6100 pg/mL in the former and only 166 pg/mL in the latter.[14]

Giant cysts or pseudocysts can rarely mimic ascites. Paracentesis may produce fluid with unusual characteristics. Imaging usually provides the correct diagnosis.[15]

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. Ascites usually is present for only a few weeks before the patient seeks medical attention. In contrast, a slowly enlarging abdomen over months to years is most likely due to obesity not ascites.

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 etiology of ascites formation is based on the results of the history, physical examination, and ascitic fluid analysis. In general, few other tests are required. However, the liver is commonly imaged 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.[16,17] Fluid due to portal hypertension can be readily differentiated from fluid due to other causes.[10] 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.[18]

Although older published series reported a relatively high morbidity, and even mortality, when trocars were used for paracentesis, more recent studies regarding para-

Table 2. Differential Diagnosis of Ascites

Cirrhosis
Alcoholic hepatitis
Heart failure
Cancer (peritoneal carcinomatosis, massive liver metastases, etc)
"Mixed" ascites, i. e., cirrhosis plus another cause for ascites
Pancreatitis
Nephrotic syndrome
Tuberculous peritonitis
Acute liver failure
Budd-Chiari syndrome
Sinusoidal obstruction syndrome
Postoperative lymphatic leak
Myxedema

centesis complications in patients with ascites documented no deaths or infections caused by the paracentesis.[19] 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.[19] Although more serious complications (hemoperitoneum or bowel entry by the paracentesis needle) occur,[20] they are sufficiently unusual (<1/1000 paracenteses) that they should not deter performance of this procedure. In a study of 4729 paracenteses, investigators reported that eight of nine bleeding complications occurred in patients with renal failure; perhaps the qualitative platelet abnormality in this setting predisposes to more bleeding.[21]

Although some physicians give blood products (fresh frozen plasma and/or platelets) routinely before paracentesis in patients with cirrhosis and coagulopathy, this policy is not data-supported.[19,22] Routine tests of coagulation also do not reflect bleeding risk in patients with cirrhosis; these patients regularly have normal global coagulation because of a balanced deficiency of procoagulants and anticoagulants.[23] In a recent survey of the use of blood products in relation to paracentesis, 50% of approximately 100 hepatologists attending a conference on coagulopathy in liver disease indicated that they either never used plasma before procedure or used it only if the international normalized ratio was >2.5.[24] The risks and costs of prophylactic transfusions may exceed the benefit. Coagulopathy should preclude paracentesis only when there is clinically evident hyperfibrinolysis (three-dimensional ecchymosis/hematoma) or clinically evident disseminated intravascular coagulation. A shortened (<120 minutes) euglobulin clot lysis time documents hyperfibrinolysis.[25] However, this test may not be routinely available. Epsilon aminocaproic acid can be used to treat hyperfibrinolysis; paracentesis can be performed after the lysis time has normalized on treatment.[26] Bleeding conditions occur in less than 1/1000 patients who require paracentesis. There is no data-supported cutoff of coagulation parameters beyond which paracentesis should be avoided.[19] In a study of 1100 large-volume paracenteses, there were no hemorrhagic complications despite (1) no prophylactic transfusions, (2) platelet counts as low as 19,000 cells/mm^3 (19×10^6/L) (54% <50,000), and (3) international normalized ratios for prothrombin time as high as 8.7 (75% >1.5 and 26.5% >2.0).[22]

In the past, the avascular midline, midway between the pubis and the umbilicus, was usually chosen as the site for paracentesis. Now, because many paracenteses are performed to remove a large volume of fluid and abdominal obesity increases the midline wall thickness, the left lower quadrant is the preferred location (Fig. 1). The abdominal wall in the left lower quadrant, 2 finger breadths (3 cm) 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 and is usually a good choice for needle insertion for performance of a therapeutic paracentesis.[27] The right lower quadrant may be a suboptimal choice in the setting of a dilated cecum (due to lactulose) or an appendectomy scar. The area of the inferior epigastric arteries should be avoided; these vessels are located midway between the pubis and anterior superior iliac spines and then run cephalad in the rectus sheath. Visible collaterals should also be avoided. A laparoscopic study found that collaterals can be present in the midline and thus present a risk for rupture during paracentesis.[28]

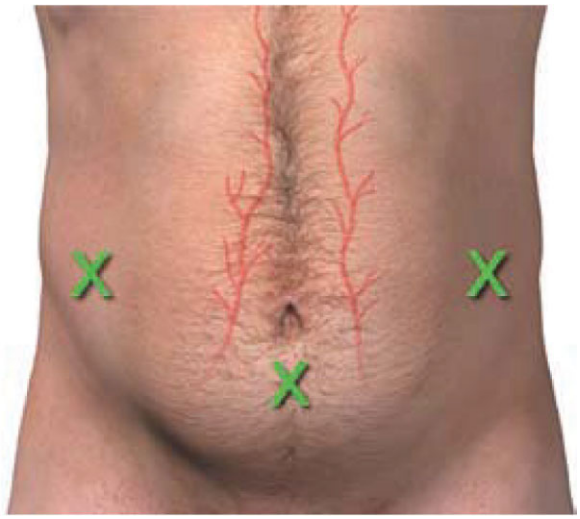

Fig. 1. Diagram of the abdomen showing the three usual sites for abdominal paracentesis. The author prefers the left lower quadrant site. Reproduced from Thomsen TW, Shaffer RW, White B, Setnik GS. Paracentesis. N Engl J Med 2006;355:e21, with permission from the Massachusetts Medical Society. Copyright (2006) Massachusetts Medical Society. All rights reserved.

If the fluid is difficult to localize by examination because of obesity, ultrasonography can be a useful adjunct in locating fluid and visualizing the spleen and other structures to be avoided. There are few contraindications to paracentesis. The procedure should be performed by a provider who has been trained in its performance.

Recommendations:

1. Abdominal paracentesis should be performed and ascitic fluid should be obtained from inpatients and outpatients with clinically apparent new-onset ascites. (Class I, Level C)

2. Because bleeding is sufficiently uncommon, the routine prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended. (Class III, Level C)

Table 3. 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.[17] Reprinted with permission from W.B. Saunders.

Ascitic Fluid Analysis

An algorithm approach seems preferable to ordering a large number of tests on most specimens (Table 3). If uncomplicated ascites due to cirrhosis 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, because 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, unexplained encephalopathy, acidosis, azotemia, hypotension, or hypothermia), bacterial culture of the fluid in blood culture bottles inoculated at the bedside should be performed. Use of a urine dipstick to detect neutrophils in ascitic fluid takes only 90 seconds to 2 minutes.[29,30] However, the largest study of a urine dipstick (2123 paracenteses) demonstrated a sensitivity of only 45%.[31] Development of an ascites-specific dipstick in contrast to a urine dipstick is needed. Automated cell counting has been shown to be accurate in one study; the result is rapidly available and could replace the manual cell count if it is further validated.[32] Additional testing, e.g., for total protein, lactate dehydrogenase (LDH), and glucose to assist in differentiating spontaneous from secondary bacterial peritonitis, can be performed on the initial specimen based on clinical judgment.[33] An ascitic fluid carcinoembryonic antigen >5 ng/mL or ascitic fluid alkaline phosphatase >240 U/L has also been shown to be accurate in detecting gut perforation into ascitic fluid.[34]

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.[11,35] 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 ≥ 1.1 g/dL (11 g/L), the patient has portal hypertension, with approximately 97% accuracy.[11] Patients who have portal hypertension plus a second cause for ascites formation also have a SAAG ≥ 1.1 g/dL.

Patients undergoing serial outpatient therapeutic paracenteses probably should be tested only for cell count and differential[36,37] (the author has detected eight episodes of spontaneous bacterial peritonitis [SBP] in approximately 400 paracenteses in a paracentesis clinic in 2 years [unpublished observations]). Bacterial culture is not necessary in asymptomatic patients undergoing serial large-volume paracenteses.

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.[38] The sensitivity of cytology in detecting peritoneal carcinomatosis is 96.7% if three samples are sent and processed promptly; the first sample is positive in 82.8% and at least one of two samples is positive in 93.3%.[38] In this study, 50 mL of fresh warm ascitic fluid were hand-carried to the laboratory for immediate processing. Use of DNA cytometry or magnetic enrichment may improve the sensitivity of cytology further.[39,40] 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%.[41] Only patients at high risk for tuberculous peritonitis (e.g., recent immigration from an endemic area or acquired immunodeficiency syndrome)[42] 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 ≥ 250 cells/mm^3 (0.25×10^9/L) is cultured by older methods, i.e., sending a syringe or tube of fluid to the laboratory, as compared to approximately 80% if the

fluid is inoculated into blood culture bottles at the bedside and prior to administration of antibiotics.[43,44]

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 (Table 3).[10] Approximately 5% of patients with ascites have two or more causes of ascites formation, i.e., "mixed" ascites.[10] Usually, these patients have cirrhosis plus one other cause, e.g., peritoneal carcinomatosis or peritoneal tuberculosis. Many patients with enigmatic ascites are eventually found to have two or even three 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.

The cancer antigen 125 (CA125) warrants mention. Essentially all patients, including men with ascites or pleural fluid of any cause, have an elevated serum CA125; when ascites is controlled, the CA125 level decreases dramatically.[45,46] This test is elevated when mesothelial cells are under pressure from the presence of fluid; it is very nonspecific. When this test is found to be abnormal, the female patient may be unnecessarily referred for gynecologic surgery even if the ovaries were removed decades earlier; cirrhosis is regularly detected at laparotomy as the cause for ascites formation (because it is most common cause) rather than ovarian cancer, and the patient may die postoperatively. Patients with ascites should not have serum tested for CA125.

Recommendations:

3. The initial laboratory investigation of ascitic fluid should include an ascitic fluid cell count and differential, ascitic fluid total protein, and SAAG. (Class I, Level B)

4. If ascitic fluid infection is suspected, ascitic fluid should be cultured at the bedside in blood culture bottles prior to initiation of antibiotics. (Class I, Level B)

5. Other studies of ascitic fluid can be ordered based on pretest probability of disease (Table 3). (Class IIa, Level C)

6. Testing serum for CA125 is not helpful in the differential diagnosis of ascites. Its use is not recommended in patients with ascites of any type. (Class III, Level B)

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 ($<$1.1 g/dL) ascites usually do not have portal hypertension and, with the exception of nephrotic syndrome, do not respond to salt restriction and diuretics.[17] In contrast, patients with a high SAAG ($\geq$1.1 g/dL) have portal hypertension and usually are responsive to these measures.[17]

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 one of the most reversible causes of liver disease that leads to high SAAG ascites.[17] One of the most important steps in treating ascites in this setting is to treat the underlying liver disease by ceasing alcohol consumption. 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 class 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.[47] Ascites may resolve or become more responsive to medical therapy with abstinence and time. Decompensated hepatitis B cirrhosis can also have a dramatic response to antiviral treatment.[48] Liver diseases other than those that are related to alcohol, hepatitis B, and autoimmune hepatitis are less reversible; by the time ascites is present, these patients may be best served by referral for liver transplantation evaluation rather than protracted medical therapy.

The mainstays of treatment of patients with cirrhosis and ascites include (1) education regarding dietary sodium restriction (2000 mg/day [88 mmol/day]) and (2) oral diuretics.[16,17] More stringent dietary sodium restriction can speed mobilization of ascites, but is not recommended because it is less palatable and may further worsen the malnutrition that is usually present in these patients. 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, as fluid follows sodium passively.[49] Measurement of urinary sodium excretion is a helpful parameter to follow when rapidity of weight loss is less than desired.[16,17] Random urinary sodium concentrations are of value when they are 0 mmol/L or $>$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. Men with cirrhosis should excrete more than 15 mg creatinine per kilogram of body weight per day, and women with cirrhosis should excrete more than 10 mg/kg/day. Less creatinine is indicative of an incomplete collection. Total nonurinary sodium excretion is less than 10 mmol/day in afebrile patients with cirrhosis without diarrhea.[50] One of the goals of treatment is to increase urinary excretion of sodium so that it exceeds 78 mmol/day (88 mmol intake/day − 10 mmol nonurinary excretion per day). Only the 10%-15% of patients who have spontaneous natriuresis >78 mmol/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/day with approximately 90% accuracy.[51] 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 patients with cirrhosis and ascites is seldom morbid unless it is rapidly corrected in the operating room at the time of liver transplantation.[52] A study of 997 patients with cirrhosis and ascites demonstrates that the serum sodium is ≤120 mmol/L in only 1.2% of patients and ≤125 mmol/L in only 5.7%.[53] Attempts to rapidly correct hyponatremia in this setting with hypertonic saline can lead to more complications than the hyponatremia itself.[54] Preliminary data suggest that aquaretic drugs have the promise of correcting hyponatremia. The intravenous aquaretic agent conivaptan has been studied in patients with cirrhosis and is approved for use for treatment of "euvolemic and hypervolemic hyponatremia in hospitalized patients".[55] Caution is advised by the manufacturer in the use of this drug in patients with cirrhosis. An oral preparation tolvaptan increases serum sodium in patients who have pretreatment values <130 mmol/L.[56] However, whether these agents will be effective without side effects in the subset of patients with cirrhosis who are more in need of correction of hyponatremia (serum sodium ≤120 mmol/L) remains unproven. Cost-effectiveness also warrants investigation. Unfortunately, many drugs that have theoretical promise in treating ascites, e.g., angiotensin-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 <120-125 mmol/L is a reasonable threshold. Patients with cirrhosis do not usually have symptoms from hyponatremia until the sodium is <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 patients with cirrhosis 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.[16,17] 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.[57] Single-agent furosemide has been shown in a randomized controlled trial to be less efficacious than spironolactone.[58] The good oral bioavailability of furosemide in the patient with cirrhosis, together with the acute reductions in glomerular filtration rate associated with intravenous furosemide, favor use of the oral route of administration.[59,60] A randomized trial purports to demonstrate that spironolactone should be used as a single agent, with furosemide added only for refractory patients.[61] Diuresis was slower in the single-agent spironolactone group with a lesser need for dose adjustments; thus, this approach may be useful for outpatients.[61] However, another randomized trial indicates that initial combination treatment shortens the time to mobilization of moderate ascites.[62] Most patients require combination treatment eventually. The largest study ever performed (involving 3860 patients with cirrhosis and ascites) used combination therapy from the beginning.[63] Starting with both drugs appears to be the preferred approach in achieving rapid natriuresis and maintaining normokalemia. An alternative approach would be to start with single-agent spironolactone, in particular in the outpatient setting.

The doses of both oral diuretics can be increased simultaneously every 3-5 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/day of spironolactone and 160 mg/day of furosemide.[16,17] Furosemide can be temporarily withheld in patients presenting with hypokalemia; this is very common in the setting of alcoholic hepatitis. Patients with parenchymal renal disease (e.g., diabetic nephropathy or immunoglobulin A nephropathy or those having undergone liver transplantation) may tolerate less spironolactone than usual because of hyperkalemia. Single morning dosing maximizes compliance. Amiloride (10-40 mg/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.[64] Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites.[65-67] Hydrochlorothiazide can also cause rapid development of hyponatremia when added to the combination of spironolactone and furosemide.[67] Eplenerone is a new aldosterone antagonist that has been used in heart failure.[68] It has not been studied in the setting of cirrhosis and ascites.

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 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).[69] Another study has confirmed this observation.[70] This intravenous furosemide "test" may help speed detection of diuretic-resistant patients so that they can more rapidly be given second-line treatment options.[69] However, intravenous furosemide can cause azotemia (see below), and its repeated use should probably be minimized until its safety and efficacy are evaluated in randomized trials.

In the largest, multicenter, randomized controlled trial performed in patients with ascites, dietary sodium restriction and a dual diuretic regimen with spironolactone and furosemide has been shown to be effective in more than 90% of patients in achieving a reduction in the volume of ascites to acceptable levels.[63]

An unblinded randomized controlled trial in patients with new-onset ascites demonstrates that weekly 25 g infusions of albumin for 1 year followed by infusions every 2 weeks improved survival compared to diuretics alone.[71] However, further studies including cost-effectiveness analysis in the United States are required before this extremely expensive treatment can be advocated.

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 ensure patient understanding 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.[72] Uncontrolled or recurrent encephalopathy, serum sodium $<$120 mmol/L despite fluid restriction, or serum creatinine $>$2.0 mg/dL (180 μmol/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.[73] Larger volumes of fluid have been safely removed with the administration of intravenous albumin (8 g/L of fluid removed).[74] 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).[75] A single large-volume paracentesis followed by diet and diuretic therapy is appropriate treatment for patients with tense ascites.[73,75] 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 op-

timal diuretic doses for each patient, by 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. However, this should be tested in the context of a randomized trial.[69] Although a controlled trial has demonstrated that large-volume paracentesis is predictably 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.[75]

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 >1 or 24-hour urine sodium >78 mmol/day and are not losing weight are consuming more sodium in their diet than 88 mmol/day and should be counseled further about dietary 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 do not lose weight and excrete <78 mmol sodium/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 2-4 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.[9] Liver transplantation should be considered in the treatment options for these patients.

Recommendations:

7. Patients with ascites who are thought to have an alcohol component to their liver injury should abstain from alcohol consumption. (Class I, Level B)

8. First-line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol/day [2000 mg/day]) and diuretics (oral spironolactone with or without oral furosemide). (Class IIa, Level A)

9. Fluid restriction is not necessary unless serum sodium is less than 120-125 mmol/L. (Class III, Level C)

10. An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. (Class IIa, Level C)

11. Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses. (Class IIa, Level C)

12. Liver transplantation should be considered in patients with cirrhosis and ascites. (Class I, Level B)

Refractory Ascites

Refractory ascites is defined as fluid overload that (1) is unresponsive to sodium-restricted diet and high-dose diuretic treatment (400 mg/day spironolactone and 160 mg/day furosemide) or (2) recurs rapidly after therapeutic paracentesis.[76] Prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs can reduce urinary sodium excretion in patients with cirrhosis and can induce azotemia.[77] 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/day) urinary sodium excretion despite diuretics or (2) development of clinically significant complications of diuretics, e.g., encephalopathy, serum creatinine >2.0 mg/dL, serum sodium <120 mmol/L, or serum potassium >6.0 mmol/L. Randomized trials have shown that fewer than 10% of patients with cirrhosis and ascites are refractory to standard medical therapy.[58,63] Options for patients refractory to routine medical therapy include (1) serial therapeutic paracenteses, (2) liver transplantation, (3) transjugular intrahepatic portasystemic stent-shunt (TIPS), (4) peritoneovenous shunt, and (5) experimental medical therapy.

Serial therapeutic paracenteses are effective in controlling ascites. This has been known since the time of the ancient Greeks. Controlled trials demonstrating the safety of this approach have now been published.[75] Even in patients with no urine sodium excretion, paracenteses performed approximately every 2 weeks control ascites.[16,17] 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 mmol/L × 6 L = 780 mmol). A 10-L paracentesis removes 1300 mmol. Patients consuming 88 mmol of sodium per day, excreting approximately 10 mmol/day in nonurinary losses, and excreting no urinary sodium retain a net of 78 mmol/day. Therefore, a 6-L paracentesis removes 10 days (780 mmol or 78 mmol/day) of retained sodium and a 10-L paracentesis removes approximately 17 days of retained sodium (1300 mmol or 78 mmol/day = 16.7 days) in patients with no urinary sodium excretion. Patients with some urinary sodium excretion should require para-

centeses 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 and a pump) has become available that may improve the ease and speed of paracentesis. Although one might predict that therapeutic paracentesis would have a higher complication rate than diagnostic paracentesis, this has not been borne out by prospective studies.[19,22]

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.[78] Being refractory to diuretic treatment was not a prerequisite for entry into this study; in fact, 31.4% of patients had not received diuretics.[78] 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.[78] 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 who are given no plasma expander compared to patients given albumin after paracentesis.[79] Furthermore, the activation in vasoconstrictor systems that can follow large-volume paracentesis may not be related to a decreased intravascular volume.[80] Also, albumin infusions markedly increase albumin degradation, and albumin is very expensive.[74,81-83] In a study performed more than 40 years ago, 58% of infused albumin was accounted for by increased degradation, and a 15% increase in serum albumin led to a 39% increase in degradation.[81] Additionally, in vitro studies have shown that increasing albumin concentration in cell culture media has been shown to decrease albumin synthesis.[83]

A systematic review of 79 randomized trials of albumin use in multiple settings, including 10 trials in patients with ascites, did not make definitive statements about its use except in the setting of SBP (see section below).[84] The American Thoracic Society's consensus statement included the 7000-patient Saline versus Albumin Fluid Evaluation (SAFE) trial, which demonstrated no difference in 28-day mortality in the critical care setting.[85] 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.[78]

Studies have infused between 5 and 10 g of albumin per liter of fluid removed.[78-80] No study has compared doses. If albumin is infused, providing 6-8 g/L of fluid removed seems appropriate. In Europe, only a 20% intravenous solution is available. In the United States, 5% and 25% intravenous solutions are available. Both are isotonic. Infusion of the 5% solution increases the sodium load five-fold.

Nonalbumin plasma expanders such as dextran 70, hydroxyethylstarch, and even saline have been advocated, also without demonstration of a survival advantage.[79,86] Hydroxyethylstarch can fill Kupffer cells and cause portal hypertension even in patients without underlying liver disease.[87] Terlipressin appears to be as effective as albumin in suppressing plasma renin elevation in a randomized trial; this drug is not currently available in the United States.[88]

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 preparacentesis identification of the subset of patients who are at higher risk of postparacentesis circulatory dysfunction. Serial paracenteses also deplete proteins, may aggravate malnutrition, and predispose to infection.[89]

Liver transplantation should be considered in the treatment options of patients with ascites. Once patients become refractory to routine medical therapy, 21% die within 6 months.[90] Referral should not be delayed in patients with refractory ascites.

TIPS is a side-to-side portacaval shunt that is usually placed by an interventional radiologist using local anesthesia.[91-96] In some centers, especially in Europe, the procedure may be performed by hepatologists. General anesthesia is used in some centers. One randomized trial comparing TIPS to large-volume paracentesis demonstrated higher mortality in the TIPS group, but this study was very small and took place very early in our experience with this relatively new technique.[93] Four large-scale, multicenter randomized controlled trials comparing TIPS to sequential large-volume paracenteses have been completed and published.[91,92,94,95] (Table 4). 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.[91] Another reports prevention of hepatorenal syndrome but with higher costs in the

Table 4. Large-Scale Randomized Controlled Trials of TIPS Versus Serial Large-Volume Paracenteses

Ref. Number	Inclusion Criteria	Method of Randomization and Analysis	N	Control of Ascites	Survival	Encephalopathy
91	Tense ascites and failure of 4 weeks of therapy	No details	60	61% vs. 18% ($P = 0.006$)	69% vs. 52% ($P = 0.11$)	58% vs. 48%*
92	Ascites refractory to medical therapy	Sealed opaque envelope; Intention to treat	70	51% vs. 17% ($P = 0.003$)	41% vs. 35%*	All 77% vs. 66% ($P = 0.29$) Severe 60% vs. 34% ($P = 0.03$)
94	Refractory ascites	No details; Intention to treat	109	58% vs. 16% ($P < 0.001$)	40% vs. 37%*	Moderate-severe 38% vs. 12% ($P = 0.058$)
95	Refractory or recidivant	No details	66	79% vs. 42% ($P = 0.0012$)	77% vs. 52% ($P = 0.021$)	Severe ($P = 0.039$)

*P value not significant.

TIPS group: there were similar rates of encephalopathy overall but more severe hepatic encephalopathy in the TIPS group.[92] Another study shows no survival advantage with TIPS, but a trend ($P = 0.058$) toward more moderate or severe encephalopathy in the TIPS group and no effect on quality of life.[94] The most recently published study reports a survival advantage in the TIPS group with similar hospitalization rates but more severe encephalopathy with TIPS.[95] Multiple meta-analyses have been published regarding these trials.[96-101] They all report better control of ascites and more encephalopathy in the TIPS group. Unfortunately recurrent tense ascites is frequently a manifestation of noncompliance on the part of the patient rather than refractory ascites. The most recent meta-analysis, which used individual patient data, reports significantly ($P = 0.035$) improved transplant-free survival with TIPS and similar cumulative probability of developing a first episode of encephalopathy.[101]

Only one trial required a specific cutoff of cardiac ejection fraction (>50%) for eligibility for enrollment.[94] Due to their hyperdynamic circulation, the ejection fraction of the patient with cirrhosis is usually greater than 70%-75%.[102] An ejection fraction of greater than 60% may be more appropriate as an inclusion criterion for entry into a TIPS study, because patients with an ejection fraction between 50% and 60% and those with diastolic dysfunction may have a higher risk of post-TIPS heart failure and reduced survival.[103,104]

Patients with parenchymal renal disease, especially those on dialysis, may not respond as well to TIPS as those with functional renal insufficiency.[105]

Meanwhile, a polytetrafluoroethylene-covered stent has been developed that has more than twice the interval of patency of the uncoated stent at 1 year in a randomized trial; this shunt is associated with a greater 2-year survival than that seen with uncoated stents in a retrospective multicenter study.[106,107] Also, a scoring system, Model for End-Stage Liver Disease (MELD), has been developed and validated to predict 3-month mortality after TIPS.[108] All of the trials mentioned above were initiated before the coated shunt was available and 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, the level of sophistication of patient screening improves (e.g., ejection fraction and MELD), and the technology of the stent itself improves, the results of future trials may be better than past trials. More randomized trials are planned. Meanwhile, TIPS should be second-line therapy. There is a more detailed discussion of TIPS in the practice guideline on this topic.[109]

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.[63,110] 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.[70,110] A randomized controlled trial of uncoated TIPS versus peritoneovenous shunt reports better long-term efficacy in the TIPS group.[111] There are no trials of coated TIPS versus peritoneovenous shunt. Shunt-related fibrous adhesions and even "cocoon" formation after peritoneous shunt 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. Peritoneovenous shunting could also be considered before transplant in patients who are not candidates for TIPS, with the realization that surgery in the right upper quadrant can make subsequent transplant more difficult. 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.[112] Radiologists are also placing plastic subcutaneous access ports for paracentesis.[113] Radiologists and surgeons have collaborated to develop a device that drains ascitic fluid into the urinary bladder.[114] None of these new techniques has been studied in randomized trials. We await the results of such studies before placing these innovations into our algorithm.

There are several experimental treatment options for patients with refractory ascites. In addition to the unblinded randomized controlled trial (mentioned above) of regular albumin infusion in patients with new-onset ascites, there is a retrospective study demonstrating efficacy of weekly albumin infusions of 50 g in reducing body weight in patients with refractory ascites who were not candidates for TIPS.[71,115] Regular infusions of albumin for treatment of new-onset or refractory ascites should be considered experimental until more studies demonstrate efficacy and cost-effectiveness. A pilot randomized trial of 0.075 mg of oral clonidine twice per day versus placebo in patients with cirrhosis, ascites, and a plasma norepinephrine level of >300 pg/mL demonstrated more rapid mobilization of ascites with fewer complications.[116] Another pilot randomized trial of paracentesis plus albumin versus clonidine plus spironolactone in patients with cirrhosis, refractory ascites, and a plasma norepinephrine level of >300 pg/mL demonstrated fewer hospitalizations in the latter group.[117] A pilot study of subcutaneous octreotide in two patients with refractory ascites demonstrated an improvement in renal function and hemodynamics and a reduction in renin and aldosterone.[118] Clearly, more data are needed before these experimental options can be placed in the treatment algorithm.

Recommendations

13. Serial therapeutic paracenteses are a treatment option for patients with refractory ascites. (Class I, Level C)

14. Postparacentesis albumin infusion may not be necessary for a single paracentesis of less than 4-5 L. (Class I, Level C)

15. For large-volume paracenteses, an albumin infusion of 6-8 g/L of fluid removed can be considered. (Class IIa, Level C)

16. Referral for liver transplantation should be expedited in patients with refractory ascites. (Class IIa, Level C)

17. TIPS may be considered in appropriately selected patients who meet criteria similar to those of published randomized trials. (Class I, Level A)

18. Peritoneovenous shunt, performed by a surgeon experienced with this technique, should be considered for patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS. (Class IIb, Level A)

Hepatorenal Syndrome

Diagnosis

The major criteria for the diagnosis of hepatorenal syndrome in the setting of cirrhosis were updated in 2007 and include (1) cirrhosis with ascites; (2) serum creatinine >1.5 mg/dL; (3) no improvement of serum creatinine (decrease to a level of 1.5 mg/dL or less) after at least 2 days with diuretic withdrawal and volume expansion with albumin[119] (The recommended dose of albumin is 1 g/kg body weight/day up to a maximum of 100 g/day); (4) absence of shock; (5) no current or recent treatment with nephrotoxic drugs; and (6) absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field), and/or abnormal renal ultrasonography.[119] Many of the older studies did not involve measurement of cardiac filling pressures to exclude the possibility of intravascular volume depletion. A more recent study used albumin to achieve a central venous pressure of >3 cm of water.[120] 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 >2.5 mg/dL or a 50% reduction of the initial 24-hour creatinine clearance to a level <20 mL/minute in less than 2 weeks. Type II does not have a rapidly progressive course and is a common cause of death in patients who do not die of other complications of cirrhosis.[119]

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.[121] A more recent study reports that eight of 30

patients with hepatorenal syndrome survived 30 days with use of hemodialysis or continuous venovenous hemodialysis in the intensive care unit setting.[122] Continuous venovenous hemofiltration/hemodialysis causes less hypotension but requires the continuous involvement of a dialysis nurse.[123] In a study that screened 3860 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, there were only 33 patients with hepatorenal syndrome, and a type II error could not be excluded.[63] Furthermore, this study was performed before the types of hepatorenal syndrome were delineated.

Many pharmaceutical treatments, predominantly vasoconstrictors, including some that are not available in the United States, have been studied. Usually, short case series with or without historical controls are reported. Recently, treatments have been much more successful for type I hepatorenal syndrome. Dopamine is the traditional drug that has been used clinically. The drug combination, along with albumin infusion, that has been reported from Europe and the United States is octreotide and midodrine.[124,125] In the initial study, five patients received 10-20 g intravenous albumin per day for 20 days, plus octreotide with a target dose of 200 μg subcutaneously three times per day, and midodrine titrated up to a maximum of 12.5 mg orally three times per day to achieve an increase in mean blood pressure of 15 mm Hg.[124] Results were superior to those of eight patients treated with dopamine and albumin.[124] This regimen can be administered outside of an intensive care unit and can even be given at home.[124] A retrospective study from the United States involving 60 patients treated with octreotide/midodrine/albumin and 21 concurrent nonrandomized albumin-treated controls reported reduced mortality in the treatment group (43% versus 71%, $P < 0.05$).[125] An uncontrolled pilot study of this drug combination followed by TIPS reported improved renal function and natriuresis.[126] Two studies, including one with randomization and crossover design, demonstrate that octreotide alone is not beneficial for hepatorenal syndrome; midodrine appears to be required in addition.[127,128] 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.[129] An uncontrolled trial using terlipressin (not available in the United States) also reports success with type I hepatorenal syndrome.[130] A U.S. multicenter, randomized, controlled trial of terlipressin versus placebo in 112 patients with type I hepatorenal syndrome nearly achieved significance ($P = 0.059$) in its primary endpoint (survival at 14 days with serum creatinine <1.5 mg/dL on two occasions); unfortunately, there was no survival advantage.[131] A European multicenter, randomized, controlled trial of terlipressin and albumin versus albumin alone in 46 patients with type I or type II hepatorenal syndrome demonstrated an improvement in renal function but no survival advantage at 3 months.[132] A meta-analysis of studies of terlipressin demonstrated a 52% efficacy in reversing hepatorenal syndrome.[133] Whether terlipressin will become available in the United States remains to be seen. TIPS alone has also been reported to be effective in treatment of type I hepatorenal syndrome in an uncontrolled study of seven patients.[134]

Two studies have now been published involving patients with type II hepatorenal syndrome. One uncontrolled study involved terlipressin treatment of 11 patients followed by TIPS in nine; renal function improved significantly compared to pretreatment levels.[135] Another pilot uncontrolled study of TIPS in 18 patients awaiting liver transplantation reported "total remission of ascites" in eight patients and "partial response. . .without the need of paracentesis" in 10 patients.[136]

Enthusiasm is high for these new treatments.[137] What are needed are more well-designed, randomized controlled trials before we know where to place these options in the treatment algorithm. Until further data are available, albumin, octreotide, and midodrine should be considered in the treatment of type I hepatorenal syndrome.

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.[138]

Recommendations:

19. Albumin infusion plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type I hepatorenal syndrome. (Class IIa, Level B)

20. Patients with cirrhosis, ascites, and type I hepatorenal syndrome should have an expedited referral for liver transplantation. (Class I, Level B)

Spontaneous Bacterial Peritonitis

Diagnosis

Ascitic fluid infection is sufficiently common (12% in a recent series) at the time of admission of a patient with cirrhosis and ascites to justify a diagnostic paracentesis.[18] The diagnosis of 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^3 [0.25×10^9/L]) without an evident intra-abdominal, surgically treatable source of infection.[139] An abdominal paracentesis

Table 5. Treatment of Spontaneous Bacterial Peritonitis (SBP)

Ref No.	Study Design	Method of Randomization and Analysis	N	Results	P	Mortality	P
145	Cefotaxime vs. ampicillin/ Tobramycin for severe infections	Random number table	73	Cure of infection 85% vs 56%	<0.02	Infection-related mortality 19% vs 31% Hospitalization mort 33% vs 43%	NS NS
148	Cefotaxime 5 days vs. 10 days For SBP	Sealed opaque envelope Intention to treat	100	Cure 93% vs. 91% Recurrence 12% vs 13%	NS	Infection-related mortality 0% vs 4% Hospitalization Mortality 33% vs. 43%	NS NS NS
150	Oral ofloxacin vs Cefotaxime for SBP	Sealed envelope	123	Resolution 84 vs 85%	NS	Hospitalization mortality 19% vs 19%	NS NS
152	Cefotaxime with or without albumin for SBP	Sealed envelope	126	Resolution 98% vs 94% Renal failure 0.002 10% vs 33%	NS	Hospitalization mortality 10% vs 29%	<.01

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

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. Empiric treatment of suspected infection without a sample for testing does not permit narrowing the spectrum of coverage compared to the situation when an organism is cultured that is susceptible to a narrow-spectrum antibiotic. Even a single dose of an effective broad-spectrum drug causes the culture to produce no growth in 86% of cases; only resistant flora are detected.[33] Dipstick testing of ascitic fluid and automated cell counts may improve early detection of this infection.[29-32]

Empiric Treatment

Patients with ascitic fluid PMN counts ≥250 cells/mm^3 (0.25×10^9/L) in a clinical setting compatible with ascitic fluid infection should receive empiric antibiotic therapy (Table 5).[17,139] 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.[17,43,140] The patients who meet the above criteria but have negative cultures have been labeled with a diagnosis of culture-negative neutrocytic ascites.[140] The initial threshold PMN count for making this diagnosis was 500 cells/mm^3 (0.5×10^9/L).[140] However, subsequent studies have revised this threshold to 250 cells/mm^3 (0.25×10^9/L).[141] Patients with culture-negative neutrocytic ascites have similar signs, symptoms, and mortality as patients with SBP and warrant empiric antibiotic treatment.[140] A prospective study in which two 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.[142] 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.[142] 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.[143]

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.[17,139] 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., <250 cells/mm^3 (0.25×10^9/L); this has been labeled monomicrobial nonneutrocytic bacterascites.[143] Most patients—62% in one study—resolve the colonization without antibiotics and without a neutrophil response.[143] 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.[142,143] Therefore, patients with cirrhosis and ascites who have convincing signs or symptoms of infection (fever, abdominal pain, or unex-

plained 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[144]; 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.[145] 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 three most common isolates: *Escherichia coli*, *Klebsiella pneumoniae*, and pneumococci[145] (Table 5). Widespread use of quinolones to prevent SBP in high-risk subgroups of patients (see below) has led to a change in flora with more gram-positives and quinolone-resistant bacteria in recent years.[146] Dosing of cefotaxime 2 g intravenously every 8 hours has been shown to result in excellent ascitic fluid levels (20-fold killing power after one dose).[147] 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.[148] An uncontrolled study demonstrated that 5 days of ceftriaxone 1 g intravenously twice per day was effective in treating culture-negative neutrocytic ascites.[149] Ceftriaxone is highly protein bound; this is a potential limitation in its ability to penetrate low protein ascitic fluid.

Oral Treatment. Oral ofloxacin (400 mg twice per day for an average of 8 days) 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 >3 mg/dL.[150] Only 61% of patients with SBP met study inclusion criteria. All treatment was given in hospitalized patients.[150] Intravenous ciprofloxacin followed by oral administration of this drug was found to be more cost-effective compared to intravenous ceftazidime in a randomized trial in patients who had not received quinolone prophylaxis.[151] Patients who have received quinolone prophylaxis may become infected with flora resistant to quinolones and should be treated with alternative agents.

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 kilogram body weight within 6 hours of enrollment and 1.0 g/kg on day 3.[152] A decrease in mortality from 29% to 10% was reported.[152] Improving control of a complication of advanced cirrhosis is commonly reported; however, dramatically improving survival is seldom shown. A more recent study has shown that albumin should be given when the serum creatinine is >1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL, but is not necessary in patients who do not meet these criteria.[153] Albumin has been shown to be superior to hydroxyethylstarch in treatment of SBP.[154]

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 two 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.[33] In contrast, the initial ascitic fluid analysis and the response to treatment can assist with this important distinction.[33] The characteristic analysis in the setting of free perforation is PMN count ≥ 250 cells/mm^3 (usually many thousands), multiple organisms (frequently including fungi and enterococcus) on Gram stain and culture, and at least two of the following criteria: total protein >1 g/dL, lactate dehydrogenase greater than the upper limit of normal for serum, and glucose <50 mg/dL.[33] It is useful to order an ascitic fluid Gram stain, culture, total protein, LDH, and glucose in patients with cirrhosis and ascites and an ascitic fluid PMN count ≥ 250 cells/mm^3. These criteria have been shown to have 100% sensitivity but only 45% specificity in detecting perforation in a prospective study.[33] An ascitic fluid carcinoembryonic antigen >5 ng/mL or ascitic fluid alkaline phosphatase >240 U/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.[34] 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/or computed tomographic scanning.[33,34]

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.[33] 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.[21]

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.[33] The mortality of secondary peritonitis treated with antibiotics and surgery is similar to that of SBP treated with antibiotics.[33]

Follow-Up Paracentesis

A follow-up ascitic fluid analysis is not needed in many patients with infected ascites.[155] The majority of patients have SBP in the typical setting (i.e., advanced cirrhosis) with typical symptoms, typical ascitic fluid analysis (total protein $\leq$1 g/dL, LDH less than the upper limit of normal for serum, and glucose $\geq$50 mg/dL), a single organism, and a dramatic clinical response.[17,155] 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.[33]

Recommendations:

21. 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). (Class I, Level B)

22. Patients with ascitic fluid PMN counts $\geq$250 cells/mm^3 (0.25 $\times$ 10^9/L) should receive empiric antibiotic therapy, e.g., an intravenous third-generation cephalosporin, preferably cefotaxime 2 g every 8 hours. (Class I, Level A)

23. Oral ofloxacin (400 mg twice per day) can be considered a substitute for intravenous cefotaxime in inpatients without prior exposure to quinolones, vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine >3 mg/dL. (Class IIa, Level B)

24. Patients with ascitic fluid PMN counts <250 cells/mm^3 (0.25 $\times$ 10^9/L) and signs or symptoms of infection (temperature >100°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. (Class I, Level B)

25. When the ascitic fluid of a patient with cirrhosis is found to have a PMN count $\geq$250 cells/mm^3 (0.25 $\times$ 10^9/L) and there is high suspicion of secondary peritonitis, it should also be tested for total protein, LDH, glucose, Gram stain, carcinoembryonic antigen, and alkaline phosphatase to assist with the distinction of SBP from secondary peritonitis. (Class IIa, Level B)

26. Patients with ascitic fluid PMN counts $\geq$250 cells/mm^3 (0.25 $\times$ 10^9/L) and clinical suspicion of SBP, who also have a serum creatinine >1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL should receive 1.5 g albumin/kg body weight within 6 hours of detection and 1.0 g/kg on day 3. (Class IIa, Level B)

Prevention of SBP

The identification of risk factors for development of SBP (including ascitic fluid protein concentration <1.0 g/dL, variceal hemorrhage, and prior episode of SBP) has led to randomized controlled trials of prophylactic antibiotics[156-162] (Table 6). Norfloxacin 400 mg/day orally has been reported to successfully prevent SBP in (1) patients with low-protein ascites and (2) patients with prior SBP.[157-158] Norfloxacin 400 mg orally twice per day for 7 days helps prevent infection in patients with variceal hemorrhage.[159] An antibiotic can be given intravenously while the patient is actively bleeding; ofloxacin (400 mg/day) has been validated for this purpose.[160] Ceftriaxone given intravenously 1 g/day for 7 days has been shown to be superior to oral norfloxacin in a randomized trial.[161] Administering five doses of double-strength trimethoprim/sulfamethoxazole or a single oral dose of 750 mg ciprofloxacin per week has also been reported to be effective in preventing SBP in patients with cirrhosis and ascites.[162,163] However, intermittent dosing may select resistant flora more rapidly.[164] Daily dosing of this drug combination 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 five trials in patients with cirrhosis

Table 6. Prevention of Spontaneous Bacterial Peritonitis (SBP)

Ref No.	Study Design	Method of Randomization and Analysis	N	Results	P	Mortality	P
157	Norfloxacin vs. no drug In inpatients with AFTP	No details	63	SBP 0% vs. 23%	<0.05	Infection-related mortality (0% vs. 13%) Hospitalization mortality (6% vs. 16%)	NS NS
158	Norfloxacin vs. placebo in patients with prior SBP	No details	80	SBP recurrence 12% vs. 35%	0.014	18% vs. 25%	NS
159	Norfloxacin vs. no drug in patients with cirrhosis and gut hemorrhage	No details	119	Infection 10% vs. 37%	0.001	7% vs. 12%	NS
161	Norfloxacin vs ceftriaxone In patients with cirrhosis and gut hemorrhage	Computer-generated envelopes	111	Infection 33% vs 11%	0.003	9% vs 11%	NS
162	Trimethoprim/sulfamethoxazole vs. no drug in patients with cirrhosis and ascites	No details	67	SBP or bacteremia (3% vs. 27%)	0.025	7% vs. 20%	.15
165	Meta-analysis of antibiotic prevention of infection in patients with cirrhosis and gut hemorrhage	Meta-analysis	534	32% reduction in infection	<0.001	9% increase in survival	.004
171	Norfloxacin vs placebo in patients who met criteria	Computer-generated envelopes	68	SBP 7% vs 61% HRS 28% vs 7%	0.001 0.02	3-mo 94% vs 62% 12-mo 60% vs 48%	0.003 0.05

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

and gastrointestinal bleeding has shown a survival advantage of 9.1% in the treated group.[165]

A group in France reported a reduction in hospitalization mortality for patients with variceal hemorrhage from 43% 20 years ago to 15% recently; much of the reduced mortality was attributed to use of antibiotics to prevent infections.[166]

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.[167] A report from a center in which selective intestinal decontamination has been routine in high-risk patients for many years documents a 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.[146] 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.[168,169]

One trial in which patients with low-protein ($\leq$1 g/dL) ascitic fluid or bilirubin $>$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.[170] However, patients receiving continuous norfloxacin had a higher risk of resistant flora when they did develop infection.[170] A more recent randomized trial of daily norfloxacin versus placebo in patients with ascitic fluid protein $<$1.5 g/dL and at least one of the following: serum creatinine $\geq$1.2 mg/dL, blood urea nitrogen $\geq$25 mg/dL, serum sodium $\leq$130 mEq/L or Child-Pugh $\geq$9 points with bilirubin $\geq$3 mg/dL demonstrated prevention of SBP as well as hepatorenal syndrome and a survival advantage in the norfloxacin group.[171] Based on the available literature, it is reasonable to give norfloxacin (or trimethoprim/sulfamethoxazole) continuously to patients who meet these criteria.[162,170,171]

In a report of liver transplant infections, one risk factor for posttransplant fungal infection was "prolonged therapy with ciprofloxacin".[172] 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.[173] It is the active bleeding that appears to be the risk factor for infection, not sclerotherapy.[174] Variceal banding has largely replaced sclerotherapy; antibiotics would be even less likely to be of benefit in the setting of banding.

Recommendations:

27. Intravenous ceftriaxone for 7 days or twice-daily norfloxacin for 7 days should be given to prevent bacterial infections in patients with cirrhosis and gastrointestinal hemorrhage. (Class I, Level A)

28. 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. (Class I, Level A)

29. In patients with cirrhosis and ascites but no gastrointestinal bleeding, long-term use of norfloxacin (or trimethoprim/sulfamethasoxazole) can be justified if the ascitic fluid protein <1.5 g/dL and at least one of the following is present: serum creatinine ≥1.2 mg/dL, blood urea nitrogen ≥25 mg/dL, serum sodium ≤130 mEq/L or Child-Pugh ≥9 points with bilirubin ≥3 mg/dL. (Class I, Level B)

30. Intermittent dosing of antibiotics to prevent bacterial infections may be inferior to daily dosing (due to the development of bacterial resistance) and thus daily dosing should preferentially be used. (Class IIb, Level C)

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