

Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012

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Preamble

This guideline has been approved by the American Association for the Study of Liver Diseases 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 Guidelines¹; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the AGA Policy Statement on Guidelines²; and (4) the experience of the author in the specific topic.

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 not dealt with in detail because of the lack of published information regarding the natural history of this entity. These patients should probably be reimaged after an interval of perhaps 3 months or when the fluid becomes clinically apparent. Once the fluid is clinically detectable or other signs or symptoms, e. g. pain or fever, develop, paracentesis should be performed and the approach outlined in this guideline then applies.

An updated Medline search from 2007-2012 was performed; search terms included ascites, hepatorenal syndrome, diet therapy, drug therapy, radiotherapy, surgery, and therapy. The search involved only papers published in English and involving humans. The search yielded 479 papers published since a similar search was performed in 2007 in preparation for writing the previous guideline on ascites.

Introduction

Cirrhosis is the eighth leading cause of death in the United States, if expanded liver diagnosis codes are used.⁵ Ascites is the most common of the 3 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.

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

This is a revised and updated guideline based on the previously published version (Hepatology 2009;49:2087-107).

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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.
<i>Level of Evidence</i>	<i>Description</i>
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.

Evaluation and Diagnosis

History. Most patients (approximately 85%) with ascites in the United States have cirrhosis (Table 2).¹⁰ In about 15% of patients with ascites, there is a non-hepatic 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 (to determine the number of years of overweight or obesity) and diabetes as nonalcoholic steatohepatitis has been concluded to be causative in many of these patients.¹¹ Past history of cancer, heart failure, renal disease, thyroid 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 1,500 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 cardiomyopathy can mimic that due to alcoholic cirrhosis. Pulmonary hypertension can also lead to heart failure and ascites. 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 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. Polycystic liver can rarely cause portal hypertension and ascites. 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, and ascitic fluid analysis. In general, few other tests are required. However, the liver is commonly imaged to screen for morphologic evidence of cirrhosis and portal hypertension, tumors, portal vein thrombosis, and hepatic vein thrombosis.

Abdominal Paracentesis. Abdominal paracentesis with appropriate ascitic fluid analysis is probably the

Table 2. Differential Diagnosis of Ascites

Cirrhosis
Alcoholic Hepatitis
Heart Failure
Cancer (peritoneal carcinomatosis, massive liver metastases, etc)
“Mixed” Ascites, <i>i. e.</i> Cirrhosis Plus Another Cause for Ascites
Pancreatitis
Nephrotic Syndrome
Tuberculous Peritonitis
Acute Liver Failure
Budd-Chiari Syndrome
Sinusoidal Obstruction Syndrome
Postoperative Lymphatic Leak
Myxedema

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 paracentesis 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 (<1/1,000 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 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 pre-procedure or used it only if the INR 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 per 1,000 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



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.

hemorrhagic complications despite a) no prophylactic transfusions, b) platelet counts as low as 19,000 cells/mm³ ($19 \times 10^6/L$) (54% <50,000) and c) 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.²⁷ Now, as 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 (Figure 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.²⁸ 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.²⁹

A 1 or 1.5 inch 21 or 22 gauge needle can be used for diagnostic paracentesis in lean patients; a 3.5 inch 22 gauge needle can be used in obese patients.²⁷ Larger caliber (15 or 16 gauge), multi-hole needles can

Table 3. Ascitic Fluid Laboratory Data*

Routine	Optional (When There is Suspicion of Infection)	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.

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be used for therapeutic paracentesis. Plastic-sheathed catheters can be shaved off into the peritoneal cavity and can lead to the need for laparoscopy or laparotomy to retrieve the piece that was shaved off.³⁰

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

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, since most specimens are consistent with uncomplicated cirrhotic ascites, no further testing will be needed in the majority of patients.

The gross appearance of the fluid should be noted. This can range from water-clear to frankly purulent,

bloody, or chylous.²⁷ If ascitic fluid infection is suspected (fever, abdominal pain, or unexplained encephalopathy, acidosis, azotemia, hypotension, or hypothermia), bacterial culture of the fluid in aerobic and anaerobic 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 3 minutes.³¹ However, the largest study of a urine dipstick (2133 paracenteses) demonstrated a sensitivity of only 45%.³² Urine dipsticks would not be expected to be sensitive in detecting neutrophils in ascitic fluid. An ascites-specific dipstick has been developed and calibrated to 100% sensitivity in detecting a neutrophil count greater than or equal to 250 cells/mm³ [$0.25 \times 10^9/L$].³³

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.³⁴ Additional testing, *e.g.*, lactate dehydrogenase, and glucose to assist in differentiating spontaneous from secondary bacterial peritonitis, can be performed on the initial specimen based on clinical judgment.³⁵ 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.³⁶

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.^{10,37} 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.¹⁰ Patients who have portal hypertension plus a second cause for ascites formation also have a SAAG greater than or equal to 1.1g/dL. The SAAG retains accuracy despite fluid infusion and diuretic use.³⁸

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 [unpublished observations]).^{39,40} Bacterial culture is not necessary in asymptomatic patients undergoing serial large-volume paracenteses; false-positives may exceed true positives.^{39,40} Repeating tests of total protein and SAAG on fluid removed therapeutically is also usually not needed.

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.⁴¹ The sensitivity of cytology in detecting peritoneal carcinomatosis is 96.7% if 3 samples (from different paracentesis procedures) 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%.⁴¹ In this study, 50 mL of fresh warm ascitic fluid were hand-carried to the laboratory for immediate processing. If the first sample is diagnostic of malignancy, no further search for malignant cells is needed. Use of DNA cytometry or magnetic enrichment may improve the sensitivity of cytology further.^{42,43} Patients with peritoneal carcinomatosis usually have a history of a breast, colon, gastric, or pancreatic primary carcinoma. The sensitivity of smear of ascitic fluid for mycobacteria approaches zero; the sensitivity of fluid culture for mycobacteria is approximately 50%.⁴⁴ Only patients at high risk for tuberculous peritonitis (*e.g.*, recent immigration from an endemic area or acquired immunodeficiency syndrome)⁴⁵ should have testing for mycobacteria on the first ascitic fluid specimen. Polymerase chain reaction testing for mycobacteria or 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 250 cells/mm³ ($0.25 \times 10^9/L$) 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.^{46,47} A single dose of an effective antibiotic usually leads to a negative bacterial culture.³⁵

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 2 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 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.

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.^{48,49} 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 (since 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 aerobic and anaerobic blood culture bottles prior to initiation of antibiotics. (Class I, Level B)

5. Other studies of ascitic fluid can be ordered based on the 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. The 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 (≥ 1.1 g/dL) have portal hypertension and usually are responsive to these measures.¹⁷

Table 4. Treatment Options for Patients with Cirrhosis and Ascites

First-Line
Cessation of alcohol use, when present
Sodium restricted diet and diet education
Dual diuretics, usually spironolactone and furosemide, orally with single daily dosing
Discontinue non-steroidal anti-inflammatory drugs
Evaluation for liver transplantation
Second-Line
Discontinue beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers
Consider adding midodrine especially in the profoundly hypotensive patient
Serial therapeutic paracenteses
Evaluation for liver transplantation
Transjugular intrahepatic portosystemic stent-shunt (TIPS)
Third-Line
Peritoneovenous shunt

The remainder of this guideline is applicable only to patients with cirrhosis and portal (sinusoidal) hypertension 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.

First-Line Treatment

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 (Table 4). In a period of months, abstinence can result in dramatic improvement in the reversible component of alcoholic liver disease. One 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.⁵⁰ Ascites may resolve or become more responsive to medical therapy with abstinence and time.

Baclofen has been shown in a randomized trial, that included only patients with alcoholic liver disease, to reduce alcohol craving and alcohol consumption; it can be given at a dose of 5 mg orally tid for 3 days and then 10 mg tid.⁵¹ Ascites in decompensated hepatitis B cirrhosis and autoimmune hepatitis can also have a dramatic response to specific treatment.⁵² Liver diseases other than alcohol-related, 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.

Diet and Diuretics

The mainstays of first-line 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.^{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.^{53,54}

Urine Sodium Monitoring

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 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. Men with cirrhosis 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. Less creatinine is indicative of an incomplete collection. Total nonurinary sodium excretion is less than 10 mmol per day in afebrile patients with cirrhosis without diarrhea.⁵⁴ One of the goals of treatment is to increase urinary excretion of sodium so that it exceeds 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 and 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

well with a 24-hour sodium excretion.⁵⁵ This urine sodium/potassium ratio may replace the cumbersome 24-hour collection. When this ratio is >1 , the patient should be losing fluid weight. The higher the ratio, the greater the urine sodium excretion.

Fluid Restriction

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 unless it is rapidly corrected in the operating room at the time of liver transplantation.⁵⁶ A study of 997 patients with cirrhosis and ascites demonstrates that the serum sodium is less than or equal to 120 mmol/L in only 1.2% of patients and less than or equal to 125 mmol/L in only 5.7%.⁵⁷ Attempts to rapidly correct hyponatremia in this setting with hypertonic saline can lead to more complications than the hyponatremia itself.⁵⁸

Vaptans

Vaptans are a relatively new class of drugs — the vasopressin receptor antagonists — and have been studied predominantly in heart failure but also in the setting of cirrhosis.^{59,60} Their utility in treating hyponatremia and in reducing fluid overload have been studied. These drugs appear to correct mild hyponatremia. However correction of hyponatremia may not correlate with more important clinical outcomes. The intravenous agent conivaptan has been studied in patients with cirrhosis and is approved for use for treatment of “euvoletic and hypervolemic hyponatremia in hospitalized patients”.⁵⁹ Caution is advised by the manufacturer in the use of this drug in patients with cirrhosis. Rapid correction of hyponatremia can occur and have permanent clinical sequelae, such as demyelination. An oral preparation — tolvaptan — increases serum sodium in patients who have pretreatment values of <130 mmol/L.⁶⁰ Hyponatremia recurs when this drug is discontinued.⁶¹

The most recent oral agent, satavaptan, was specifically studied to determine its efficacy in treating ascites rather than hyponatremia and was found to be “not clinically beneficial in the long-term management of ascites in cirrhosis” in a study involving 1200 patients with cirrhosis.⁶² Satavaptan was also associated with higher mortality compared to placebo.⁶² These drugs can increase thirst.

Whether these agents will be safe and 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 consideration. 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 and no data-supported level of restriction. In reality, restrictions are seldom enforced. A serum sodium less than 120-125 mmol/L is a reasonable threshold. Patients with cirrhosis do not usually have symptoms from hyponatremia until the sodium is below 110 mmol/L or unless the decline in sodium is very rapid.

Bed Rest

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 and ascites. Theoretically, this may increase sodium avidity. This theoretical concern would have to translate into clinically relevant outcomes before bed rest could be advocated.

Diuretics

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.⁶³ Single-agent furosemide has been shown in a randomized controlled trial to be less efficacious than spironolactone.⁶⁴ 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.^{65,66} A randomized trial purports to demonstrate that spironolactone should be used as a single agent, with furosemide added only for refractory patients.⁶⁷ Diuresis was slower in the single-agent spironolactone group with a lesser need for dose adjustments; thus this approach may be useful for outpatients.⁶⁷ However another randomized trial indicates that initial combination treatment shortens the time to mobilization of moderate ascites.⁶⁸ Most patients require combination treatment eventually. The largest study ever performed (involving 3860 patients with cirrhosis and

ascites) used combination therapy from the beginning.⁶⁹ 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 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.^{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 post liver transplantation may tolerate less spironolactone than usual because of hyperkalemia.

Single morning dosing maximizes compliance. Dosing more than once daily reduces compliance and can cause nocturia.

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.⁷⁰ Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites.⁷¹⁻⁷³ Hydrochlorothiazide can also cause rapid development of hyponatremia when added to the combination of spironolactone and furosemide; it should be used with extreme caution or avoided.⁷³ Eplerenone is a newer aldosterone antagonist that has been used in heart failure.⁷⁴ It has not been studied in the setting of cirrhosis and ascites.

Other diuretics, such as torasemide and bumetanide, 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).⁷⁵ Another study has confirmed this observation.⁷⁶ This intravenous furosemide "test" may help speed detection of diuretic-resistant patients so that they can more rapidly be given second-line treatment options.⁷⁵ 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.⁶⁶

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.⁶⁹

Intravenous Albumin

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.⁷⁷ However further studies including cost-effectiveness analysis in the United States are required before this extremely expensive treatment can be advocated.

Hospitalization

Outpatient treatment can be attempted initially. However, some patients with cirrhosis and ascites also have gastrointestinal hemorrhage, hepatic encephalopathy, bacterial infection, hypotension, azotemia, 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. Diuretics should be withheld in the setting of active gastrointestinal bleeding, hepatic encephalopathy or renal dysfunction. Frequently, intensive education is required to ensure patient understanding that the diet and diuretics are actually effective and worth the effort.

Speed of Weight Loss

There is no limit to the daily weight loss of patients who have significant edema. Once the edema has resolved, 0.5 kg is probably a reasonable daily maximum.⁷⁸ Uncontrolled or recurrent encephalopathy, serum sodium less than 120 mmol/L despite fluid restriction, or serum creatinine greater than 2.0 mg/dL (180 μ mol/L) should lead to cessation of diuretics, reassessment of the situation, and consideration of second-line options (Table 4).

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. An outpatient appointment within 7 days of discharge from the hospital has been shown to correlate with lower readmission rates within 30 days in the setting of heart failure.⁷⁹

Drugs To Be Avoided or Used With Caution

Blood pressure in patients with cirrhosis and ascites is supported by elevated levels of vasoconstrictors such as vasopressin, angiotensin, and aldosterone; these vasoconstrictors are compensating for the vasodilatory effect of nitric oxide.⁸ Arterial pressure independently predicts survival in patients with cirrhosis; those with a mean arterial pressure >82 mmHg have a 1 year survival of 70% compared to 40% for those ≤ 82 mmHg.⁸⁰ Drugs that inhibit the effects of these vasoconstrictors would be expected to lower blood pressure; they have been documented to do so.⁸¹ Lowering blood pressure might worsen survival.

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be avoided or used with caution in patients with cirrhosis and ascites. The European Association for the Study of the Liver practice guideline on ascites recommends that "...they should generally not be used in patients with ascites".⁸² In the unusual situation when they are used, blood pressure and renal function must be monitored carefully to avoid rapid development of renal failure.

Propranolol has been shown to shorten survival in patients with refractory ascites in a prospective study.⁸³ This could be due to its negative impact on blood pressure and the increase in the rate of paracentesis-induced circulatory dysfunction that is seen in patients who are taking propranolol in the setting of refractory ascites.⁸⁴ Blood pressure and renal function should be monitored closely in patients who have refractory ascites. The risks versus benefits of beta blockers must be weighed carefully in each patient. Consideration should be given to discontinuing beta blockers or not initiating beta blockers in those patients with refractory ascites and those who develop worsening hypotension or worsening azotemia.

Prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs can reduce urinary sodium excretion in patients with cirrhosis and can induce azotemia.⁸⁵ These drugs should be avoided in this setting. Only the unusual patient whose risk of an ischemic cardiac or neurologic event exceeds the risk of worsening azotemia or gut bleeding should take low dose aspirin.

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.⁸⁶

Larger volumes of fluid have been safely removed with the administration of intravenous albumin (8 g/L of fluid removed) in patients with tense ascites whether it was diuretic-resistant or not.⁸⁷ 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).⁸⁸ A single large-volume paracentesis followed by diet and diuretic therapy is appropriate treatment for patients with tense ascites.^{87,88} 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. However this should be tested in the context of a randomized trial.⁷⁵ 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.⁸⁸ First-line therapy consists of dietary sodium restriction and diuretics and abstinence from alcohol, if relevant (Table 4).

In the outpatient clinic, body weight, blood pressure, 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 are consuming more sodium in their diet than 88 mmol per 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 less than 78 mmol sodium 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.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. Baclofen can be given to reduce alcohol craving and alcohol consumption in patients with ascites in the setting of alcoholic liver disease. (Class IIb, Level C)

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

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

11. Vaptans may improve serum sodium in patients with cirrhosis and ascites. However their use does not currently appear justified in view of their expense, potential risks, and lack of evidence of efficacy in clinically meaningful outcomes. (Class III, Level A)

12. 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)

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

14. Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in patients with cirrhosis and ascites may be harmful, must be carefully considered in each patient, monitoring blood pressure and renal function. (Class III, Level C)

15. The use of nonsteroidal anti-inflammatory drugs should be avoided in patients with cirrhosis and ascites, except in special circumstances. (Class III, Level C)

16. 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 per day of spironolactone and 160 mg per day furosemide), or (2) recurs rapidly after therapeutic paracentesis.⁸⁹

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 patients with cirrhosis and ascites are refractory to standard medical therapy.^{64,69}

Simple Medical Treatment Options

Beta blockers may shorten survival in refractory ascites;⁸³ therefore consideration should be given to discontinuing or not initiating these drugs in this setting.

Oral midodrine 7.5 mg three times daily has been shown in a randomized trial to increase urine volume, urine sodium, mean arterial pressure, and survival.⁹⁰ Nurses and care givers may be reluctant to provide diuretics to profoundly hypotensive patients. Midodrine can be added to diuretics to increase blood pressure and theoretically convert diuretic-resistant patients back to diuretic-sensitive.

Options for patients refractory to routine medical therapy after discontinuing beta blockers and adding midodrine include (a) serial therapeutic paracenteses, (b) liver transplantation, (c) transjugular intrahepatic portosystemic stent-shunt (TIPS), (d) peritoneovenous shunt, and (e) experimental medical therapy (Table 4).

Serial Therapeutic Paracenteses

Serial therapeutic paracenteses are effective in controlling ascites. Usually total paracentesis is performed to minimize the number of paracenteses. Controlled trials demonstrating the safety of this approach have now been published.⁸⁸ Even in patients with no urine sodium excretion, paracenteses performed approximately every 2 weeks control ascites.^{16,17} Diuretics have usually been discontinued once the patient is considered diuretic-resistant. The European guideline recommends discontinuing diuretics if the urine sodium is <30 mmol/day during diuretic therapy.⁸² Frequency of paracentesis provides insight into the patient's degree of compliance with the diet. Five liters has been considered a large-volume paracentesis.

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 therapeutic 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}

Although indwelling catheters and ports can be useful in malignancy-related ascites, their safety and efficacy in the setting of cirrhosis must be proved prior to advocating their use.

Colloid Replacement

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.⁹¹ Refractoriness to diuretic treatment was not a prerequisite for entry into this study; in fact, 31.4% of patients had not received diuretics.⁹¹ 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.⁹¹ 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 single study large enough to demonstrate decreased survival in patients given no plasma expander compared to patients given albumin after paracentesis.⁹²

Multiple other randomized trials have been conducted. A meta-analysis of 17 trials involving 1225 patients has been published, demonstrating a reduction in mortality with an odds ratio of death of 0.64 (95% CI, 0.41-0.98) in the albumin group.⁹³ Albumin was shown to be superior to other plasma expanders; the mean volume of ascitic fluid removed was 5.5-15.9 liters.⁹³ Studies have infused between 5 and 10 g of albumin per liter of fluid removed; 6-8 g/L have been the most common doses.⁹¹⁻⁹³ One study has compared albumin doses in 70 patients; the 4g/L group had similar paracentesis-induced circulatory dysfunction and renal impairment to the 8g/L group.⁹⁴

If albumin is infused, providing 6-8 g per liter of fluid removed seems appropriate. It is usually infused during and/or shortly after the paracentesis. In Europe only a 20% intravenous solution is available. In the

US 5% and 25% intravenous solutions are available. Both are isotonic. Infusion of the 5% solution increases the sodium load five-fold.

Terlipressin intravenously (1 mg at onset of paracentesis, 1 mg at 8 hrs and 1 mg at 16 hrs) and midodrine orally (for 72 hrs after paracentesis) appear to be as effective as albumin in suppressing plasma renin elevation in randomized trials; terlipressin is not currently available in the US.^{95,96}

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.

Serial paracenteses also deplete proteins, may aggravate malnutrition and predispose to infection.⁹⁷

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.⁹⁸ Referral should not be delayed in patients with refractory ascites.

TIPS

Transjugular intrahepatic portosystemic stent-shunt (TIPS) is a side-to-side portacaval shunt that is usually placed by an interventional radiologist using local anesthesia.⁹⁹⁻¹⁰⁴ 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, included patients with advanced liver disease, and took place very early in our experience with this relatively new technique.¹⁰¹ Four large-scale, multicenter randomized controlled trials comparing TIPS to sequential large-volume paracentesis have been completed and published.^{99,100,102,103} (Table 5). 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.⁹⁹ 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.¹⁰⁰ 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.¹⁰² The most recently published study reports a survival advantage

Table 5. Large-Scale Randomized Controlled Trials of TIPS Versus Serial Large-Volume Paracenteses

Ref No	Inclusion Criteria	Method of Randomization and Analysis	N	Control of Ascites	Survival	Encephalopathy
99	Tense ascites & failure of 4 weeks of therapy	No details	60	61% vs. 18% ($P = .006$)	69% vs. 52% ($P = .11$)	58% vs. 48%*
100	Ascites refractory to medical therapy	Sealed opaque envelope Intention to treat	70	51% vs. 17% ($P = .003$)	41% vs. 35%* ($P = .29$)	All 77% vs. 66% Severe 60% vs. 34% ($P = .03$)
102	Refractory ascites	No details Intention to treat	109	58% vs. 16% ($P < .001$)	40% vs. 37%*	Moderate-Severe 38% vs. 12% ($P = .058$)
103	Refractory or recidivant	No details	66	79% vs. 42% ($P = .0012$)	77% vs. 52% ($P = .021$)	Severe ($P = .039$)

* P value not significant.

in the TIPS group with similar hospitalization rates but more severe encephalopathy with TIPS.¹⁰³

Multiple meta-analyses have been published regarding these trials.¹⁰⁴⁻¹⁰⁸ 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 meta-analysis which used individual patient data reports significantly ($P = 0.035$) improved transplant-free survival with TIPS and similar cumulative probability of developing first episode of encephalopathy.¹⁰³

Only one trial required a specific cutoff of cardiac ejection fraction (>50%) for eligibility for enrollment.¹⁰² Due to their hyperdynamic circulation, the ejection fraction of the patient with cirrhosis is usually greater than 70-75%.¹⁰⁹ 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% and those with diastolic dysfunction may have a higher risk of post-TIPS heart failure and reduced survival.^{110,111}

Patients with parenchymal renal disease, especially those on dialysis, may not respond as well to TIPS as those with functional renal insufficiency.¹¹²

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 two-year survival than that seen with uncoated stents in a retrospective multi-center study.^{113,114} This covered stent has been the standard for many years. Also, a scoring system, Model for End-Stage Liver Disease (MELD), has been developed and validated to predict 3-month mortality after TIPS¹¹⁵ All of the trials mentioned above were initiated before the coated shunt was available and most were performed 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 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.¹¹⁶

Peritoneovenous Shunts

The peritoneovenous Denver shunt (and the discontinued LeVeen shunt) was popularized in the 1970s as a physiologic treatment of ascites.^{69,117} However, the poor long-term patency, excessive complications, and no survival advantage compared to medical therapy in controlled trials have led to the near abandonment of this procedure.^{69,117} Peritoneovenous shunting should now be reserved for diuretic-resistant patients who are not candidates for transplant or TIPS, and who are not candidates for serial paracenteses because of multiple abdominal scars or distance from a physician willing to perform and capable of performing paracenteses. Interventional radiologists have reported the possibility of performing a peritoneovenous shunt without the participation of a surgeon.¹¹⁸

Experimental Options

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.^{77,119} 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 bid 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.¹²⁰ 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.¹²¹

Radiologists and surgeons have collaborated to develop a device that drains ascitic fluid into the urinary bladder.¹²² 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.

Genes in the renin-angiotensin-aldosterone system have been reported to correlate with refractory ascites and decreased survival; this discovery could lead to “personalized medicine” for patients with cirrhosis and ascites.¹²³

Recommendations

17. The risks versus benefits of beta blockers must be carefully weighed in each patient with refractory ascites. Systemic hypotension often complicates their use. Consideration should be given to discontinuing or not initiating these drugs in this setting. (Class III, Level B)

18. The use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be avoided in patients refractory ascites. Systemic hypotension often complicates their use.. (Class III, Level B)

19. Oral midodrine has been shown to improve clinical outcomes and survival in patients with refractory ascites; its use should be considered in this setting. (Class IIa, Level B)

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

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

22. For large-volume paracenteses, an albumin infusion of 6-8 g per liter of fluid removed appears to improve survival and is recommended (Class IIa, Level A)

23. Referral for liver transplantation should be expedited in patients with refractory ascites, if the patient is otherwise a candidate for transplantation. (Class IIa, Level C)

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

25. Peritoneovenous shunt, performed by a surgeon or interventional radiologist 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)

Spontaneous Bacterial Peritonitis

Diagnosis. Ascitic fluid infection is sufficiently common (12% in an older series) at the time of admission of a patient with cirrhosis and ascites to justify a diagnostic paracentesis.¹⁸ The incidence is lower now due to prevention in high-risk subgroups. The diagnosis of spontaneous bacterial peritonitis (SBP) is made in the presence of an elevated ascitic fluid absolute polymorphonuclear leukocyte (PMN) count (*i.e.*, ≥ 250 cells/mm³ [0.25×10^9 /L]) without an evident intra-abdominal, surgically treatable source of infection.¹²⁴ 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; the clinician’s clinical impression that infection is unlikely does not rule out infection.¹²⁵ 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 if paracentesis is repeated 6 hrs after the dose is given in 86% of cases; only resistant flora are detected.³⁵ Dipstick testing of ascitic fluid and automated cell counts may improve early detection of this infection, literally within 2-3 minutes.³¹⁻³³ Older studies used urine dipsticks that were not calibrated to 250 cells/mm³ [0.25×10^9 /L]; not surprisingly these studies report poor sensitivity, <50%.³² A newer dipstick specifically designed for ascitic fluid and calibrated to 250 cells/mm³ [0.25×10^9 /L]) reports

100% sensitivity,³³ but requires confirmation before it can be widely recommended.

Empiric Treatment. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm³ ($0.25 \times 10^9/L$) in a clinical setting compatible with ascitic fluid infection should receive empiric antibiotic therapy (Table 5).^{17,124} An elevated ascitic fluid PMN count probably represents evidence of failure of the first line of defense, the peritoneal macrophages, to kill invading bacteria. Isolation of bacteria from fluid samples will be maximized 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.^{17,41,44} The patients who meet the above criteria but have negative cultures have been labeled with a diagnosis of culture-negative neutrocytic ascites.¹²⁶ The initial threshold PMN count for making this diagnosis was 500 cells/mm³ ($0.5 \times 10^9/L$).¹²⁶ However, subsequent studies have revised this threshold to 250 cells/mm³ ($0.25 \times 10^9/L$).¹²⁷ Patients with culture-negative neutrocytic ascites have similar signs, symptoms, and mortality as patients with SBP and warrant empiric antibiotic treatment.¹²⁴ 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.¹²⁸ 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.¹²⁸ 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.¹²⁸

The ascitic fluid PMN count is more rapidly available than the culture (with dipstick results available within 2-3 minutes) and appears to be accurate in determining who really needs empiric antibiotic treatment.^{33,124} 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/mm³ ($0.25 \times 10^9/L$); this has been labeled monomicrobial nonneutrocytic bacterascites.¹²⁹ Most patients — 62% in one study — resolve the colonization without antibiotics and without a neutrophil response.¹²⁹

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.¹²⁹ 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 leukocytosis¹³⁰; 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.¹³¹ Cefotaxime or a similar third-generation cephalosporin appears to be the treatment of choice for suspected SBP; it used to cover 95% of the flora including the 3 most common isolates: *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcal pneumoniae* (Table 6).¹³¹ 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.¹³² 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).¹³³

An uncontrolled study demonstrated that 5 days of ceftriaxone 1 g intravenously twice a day was effective in treating culture-negative neutrocytic ascites.¹³⁴

Widespread use of quinolones to prevent SBP in high-risk subgroups of patients as well as frequent hospitalizations and exposure to broad-spectrum antibiotics (see below) have led to a change in flora with more gram-positives and extended-spectrum *B*-lactamase-producing *Enterobacteriaceae* in recent years.¹³⁵⁻¹³⁷ Risk factors for multiresistant infections include: nosocomial origin of infection, long-term norfloxacin prophylaxis, recent infection with multiresistant bacteria, and recent use of *B*-lactam antibiotics.¹³⁵

Table 6. Treatment of Spontaneous Bacterial Peritonitis (SBP)

Ref No.	Study Design	Method of Randomization and Analysis	N	Results	P	Mortality	P
131	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%	NS
						Hospitalization mortality 33% vs 43%	NS
132	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
139	Oral ofloxacin vs. Cefotaxime for SBP	Sealed envelope	123	Resolution 84 vs 85%	NS	Hospitalization mortality 19% vs 19% NS	NS
141	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

Infections with these resistant organisms are associated with a higher mortality¹³⁵ and can impact and complicate post-transplant care.¹³⁸ We may encounter bacteria for which we have no effective treatment.¹³⁷ In order to minimize bacterial resistance, it is prudent to limit prophylactic antibiotics to patients who meet the inclusion criteria of randomized trials (see below), minimize duration of antibiotic treatment of infections, and narrow the spectrum of coverage, once susceptibility testing results are available. "Susceptibility of bacteria causing infections in cirrhosis should therefore be periodically tested in each hospital, and the empirical antibiotic schedule should be properly adapted".¹³⁵

Oral Treatment. Oral ofloxacin (400 mg bid for an average of eight 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 greater than 3 mg/dL.¹³⁹ Only 61% of patients with SBP met study inclusion criteria. All treatment was given in hospitalized patients.¹³⁹ 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.¹⁴⁰ 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 kg body weight within 6 hours

of enrollment and 1.0 g/kg on day 3.¹⁴¹ A decrease in mortality from 29% to 10% was reported.¹⁴¹ Improving control of a complication of advanced cirrhosis is commonly reported; however, dramatically improving survival is seldom shown.¹⁴² 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.¹⁴³ Albumin has been shown to be superior to hydroxyethyl starch in spontaneous bacterial peritonitis.¹⁴⁴

Distinguishing Spontaneous From Secondary Bacterial Peritonitis. Secondary bacterial peritonitis, *i.e.*, ascitic fluid infection caused by a surgically treatable intra-abdominal source, can masquerade as SBP.³⁵ Less than 5% of infected ascites is due to a intra-abdominal surgically treatable source.¹⁴⁵ 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.*, peri-appendiceal abscess).³⁵ 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.³⁵ In contrast, the initial ascitic fluid analysis and the response to treatment can assist with this important distinction.³⁵ The characteristic analysis in the setting of free perforation is PMN count greater than or equal to 250 cells/mm³ (usually many thousands), multiple organisms (frequently including fungi and enterococcus) 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.³⁵

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/mm³. These criteria have been shown to have 100% sensitivity but only 45% specificity in detecting perforation in an older prospective study.³⁵ A more recent study has confirmed 96% sensitivity of the above 3 criteria and/or polymicrobial culture; a computerized tomographic scan was diagnostic in 85% of patients with secondary peritonitis.¹⁴⁵

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.³⁶ Patients who fulfill either set of criteria for gut perforation should undergo emergent computed tomographic scanning.^{35,36}

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.³⁵ 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 perforation and nonperforation secondary peritonitis.³⁵

Patients documented to have free perforation or nonperforation secondary peritonitis should receive anaerobic coverage in addition to a third-generation cephalosporin and may require laparotomy.^{35,145} The mortality of secondary peritonitis treated with antibiotics and surgery is similar to that of SBP treated with antibiotics.³⁵

Follow-up Paracentesis. A follow-up ascitic fluid analysis is not needed in many patients with infected ascites.¹⁴⁶ The majority of patients have SBP in the typical setting (*i.e.*, advanced cirrhosis) with typical symptoms, typical ascitic fluid analysis (total protein ≤ 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.^{5,146} 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.³⁵

Recommendations

26. 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)

27. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm³ ($0.25 \times 10^9/L$) in a community-acquired setting in the absence of recent B-lactam antibiotic exposure should receive empiric antibiotic therapy, e.g., an intravenous third-generation cephalosporin, preferably cefotaxime 2 g every 8 hours. (Class I, Level A)

28. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm³ ($0.25 \times 10^9/L$) in a nosocomial setting and/or in the presence of recent B-lactam antibiotic exposure should receive empiric antibiotic therapy based on local susceptibility testing of bacteria in patients with cirrhosis. (Class IIa, Level B)

29. 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 greater than 3 mg/dL. (Class IIa, Level B)

30. Patients with ascitic fluid PMN counts less than 250 cells/mm³ ($0.25 \times 10^9/L$) 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. (Class I, Level B)

31. When the ascitic fluid of a patient with cirrhosis is found to have a PMN count greater than or equal to 250 cells/mm³ ($0.25 \times 10^9/L$) and there is high suspicion of secondary peritonitis, it should also be tested for protein, LDH, glucose, Gram's stain, carcinoembryonic antigen, and alkaline phosphatase to assist with the distinction of SBP from secondary peritonitis. Computed tomographic scanning should also be performed. (Class IIa, Level B)

32. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm³ ($0.25 \times 10^9/L$) in a nosocomial setting and/or in the presence of recent B-lactam antibiotic exposure and/or culture an atypical organism(s) or have an atypical clinical response to treatment, should undergo a follow-up

Table 7. Meta-Analyses of Trials of Prevention of Spontaneous Bacterial Peritonitis (SBP)

Ref No.	Type of Trials	Number of Trials/Patients	Results	P	Mortality	P
158	Gastrointestinal bleeding	5/534	32% Reduction in infections	0.01	9.1% Reduction	0.004
161	Primary prophylaxis When AFTP <1.5 g/dL	4/190	OR 0.18 (95% CI 0.10-0.32)	0.000	OR 0.60 (95% CI 0.37-0.97)	0.036
160	Oral prophylaxis	8/647	RR 0.32 (95% CI 0.20-0.51)	0.00001	RR 0.65 (95% CI 0.48-0.88)	0.006

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not available; AFTP, ascitic fluid total protein; RR, relative risk.

paracentesis after 48 hrs of treatment to assess the response in PMN count and culture. (Class IIa, Level C)

33. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm³ ($0.25 \times 10^9/L$) 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 per kg body weight within 6 hours of detection and 1.0 g/kg on day 3. (Class IIa, Level B)

Prevention of SBP

Use of proton pump inhibitors has been associated with an increased rate of SBP.¹⁴⁷ In one study 68% of patients had no documented indication for their use.¹⁴⁷ Restricting use of these drugs to data-supported indications may help prevent SBP.

The identification of other risk factors for development of SBP (including ascitic fluid total protein concentration less than 1.0 g/dL or 1.5 g/dL, variceal hemorrhage, and prior episode of SBP) has led to randomized controlled trials of prophylactic antibiotics¹⁴⁸⁻¹⁵⁴ (Table 7). Recurrence of SBP has been reported to be 69% in 1 year.¹⁵⁵ Norfloxacin 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.^{149,150} Norfloxacin 400 mg orally twice per day for 7 days helps prevent infection in patients with variceal hemorrhage.¹⁵¹ An antibiotic can be given intravenously while the patient is actively bleeding; ofloxacin (400 mg per day) has been validated for this purpose; however this drug is no longer on many formularies.¹⁵² Ceftriaxone intravenously 1 g/d for 7 days has been shown to be superior to oral norfloxacin in a randomized trial.¹⁵³

Administering 5 doses of double-strength trimethoprim/sulfamethoxazole or a single oral dose of 750 mg of ciprofloxacin per week has also been reported to be effective in preventing SBP in patients with cirrhosis and ascites.^{154,156} However, intermittent dosing may select resistant flora more rapidly.¹⁵⁷ Daily dosing of this drug combination may be better than intermittent dosing.

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.¹⁵⁸ Four randomized trials of primary prophylaxis of SBP in patients with cirrhosis and an ascitic fluid total protein less than 1.5 g/dL have demonstrated in a meta-analysis, a reduction in bacterial infections and as well as a reduction in mortality (odds ratio 0.60, 95% CI, 0.37-0.97).^{159,160} A meta-analysis of 8 oral antibiotic trials involving 647 patients demonstrates a 72% reduction in mortality at 3 months; only 6 patients need to be treated to prevent one additional death.¹⁶¹

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.¹⁶²

Selective intestinal decontamination does select resistant gut flora, which can subsequently cause spontaneous infection. 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.¹³⁵ 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.^{163,164}

Based on the available literature, it is reasonable to give norfloxacin (or trimethoprim/sulfamethoxazole) continuously to patients who have experienced an episode of SBP and to patients who meet the inclusion criteria of the most restrictive randomized trial, i. e. patients with an ascitic fluid total protein less than 1.5 g/dL and with impaired renal function (creatinine ≥ 1.2 , BUN ≥ 25 or serum Na ≤ 130) or liver failure (Child score ≥ 9 and bilirubin ≥ 3).^{150,154,156,159,160,161} More liberal use of these antibiotics would be predicted to lead to colonization with, and subsequent infection by, resistant flora.¹³⁵

In a report of liver transplant infections, one risk factor for post-transplant fungal infection was “prolonged therapy with ciprofloxacin”.¹⁶⁵ 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 and in the absence of an ascitic fluid total protein less than 1.5 g/dL is not data-supported.

Parenteral antibiotics to prevent sclerotherapy-related infections do not appear to be warranted, based on a controlled trial.¹⁶⁶ It is the active bleeding that appears to be the risk factor for infection, not sclerotherapy.¹⁶⁷ Variceal banding has largely replaced sclerotherapy; antibiotics would be even less likely to be of benefit in the setting of banding.

Recommendations

34. 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). Perhaps parenteral antibiotic, while the patient is bleeding and oral antibiotic after oral intake is resumed, for a total of 7 days, is a practical treatment regimen.

35. Patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin (or trimethoprim/sulfamethoxazole). (Class I, Level A)

36. In patients with cirrhosis and ascites, long-term use of norfloxacin (or trimethoprim/sulfamethoxazole) can be justified if the ascitic fluid protein <1.5 g/dL along with impaired renal function (creatinine \geq 1.2, BUN \geq 25 or serum Na \leq 130) or liver failure (Child score \geq 9 and bilirubin \geq 3). (Class I, Level A)

37. 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)

Hepatorenal Syndrome

Diagnosis. The major criteria for the diagnosis of hepatorenal syndrome (HRS) in the setting of cirrhosis were updated in 2007 and include (1) cirrhosis with ascites; (2) serum creatinine greater than 1.5 mg/dL; (3) no improvement of serum creatinine (decrease to a level of 1.5 mg/dL or less) after at least two days with

diuretic withdrawal and volume expansion with albumin¹⁶⁸ (The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/d); (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.¹⁶⁸ 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.¹⁶⁹ 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 and is commonly associated with death in patients who do not die of other complications of cirrhosis.¹⁶⁸

Older studies excluded patients with bacterial infection; newer studies permit inclusion of such patients.¹⁶⁸ Hepatorenal syndrome has been a diagnosis of exclusion. Only a minority of patients with azotemia in cirrhosis have hepatorenal syndrome.¹⁷⁰ In one study (involving 463 patients) that appears to exclude patients with acute kidney injury/acute tubular necrosis, only 13% had hepatorenal syndrome.¹⁷⁰ An additional category that perhaps should have been included as hepatorenal syndrome, involved 46% of the 463 patients—those with bacterial infection-related azotemia.¹⁷⁰

There are also new biomarkers that may assist with diagnosis and may make it less of a diagnosis of exclusion.¹⁷¹ Urinary neutrophil gelatinase-associated lipocalin is 20 ng/mL creatinine in normal controls, 20 ng/mL in pre-renal azotemia, 50 ng/mL in chronic kidney disease, 105 ng/mL in hepatorenal syndrome, and 325ng/mL in acute kidney injury.¹⁷¹

This test has been shown to be superior to three other urine biomarkers.¹⁷² It is not surprising that this test would have intermediate values between pre-renal azotemia and acute kidney injury. This test was readily available in the US; recently the manufacturer ceased production.

Contrary to popular belief, there is a histologic lesion associated with hepatorenal syndrome, glomerular tubular reflux.¹⁷³ This would be predicted to lead to leakage of a tubular biomarker from the damaged tubule. Kidney biopsy can be performed in cirrhosis.

However the risks must be carefully weighed against the benefits. Biomarkers should help prevent the need for biopsy.

Prevention. Albumin infusion has been shown in a randomized trial to prevent HRS and improve survival in the setting of spontaneous bacterial peritonitis.¹⁴¹ Pentoxifylline has been shown in a randomized trial to be superior to placebo in preventing hepatorenal syndrome in patients with cirrhosis, ascites, and creatinine clearances between 41 and 80 mL/min.¹⁷⁴ Many of such patients have refractory ascites. This drug has also been shown to prevent hepatorenal syndrome and improve survival in patients with severe alcoholic hepatitis.¹⁷⁵

Treatment. Hemodialysis is frequently used to control azotemia and maintain electrolyte balance before liver transplantation.¹⁷⁶ Many patients require it for a variable interval after transplantation. Hypotension during dialysis is a common problem. However, without transplantation survival is dismal; one older series reported no survivors out of 25 patients.¹⁷⁷ A more recent study reports that eight of 30 patients with HRS survived 30 days with use of hemodialysis or continuous venovenous hemodialysis in the intensive care unit setting.¹⁷⁸ Continuous venovenous hemofiltration/hemodialysis causes less hypotension but requires the continuous involvement of a dialysis nurse.¹⁷⁹

Many pharmaceutical treatments, predominantly vasoconstrictors, including some that are not available in the United States have been studied. Recently, treatments have been much more successful for type I hepatorenal syndrome. The drug combination along with albumin infusion, that has been reported from Europe and the United States is octreotide and midodrine.^{180,181} In the initial study, 5 patients received 10 to 20 grams of intravenous albumin per day for 20 days, plus octreotide with a target dose of 200 μ 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.¹⁸⁰ Results were superior to those of 8 patients treated with dopamine and albumin.¹⁸⁰ This regimen can be administered outside of an intensive care unit and can even be given at home.¹⁸⁰ A retrospective study from the United States involving 60 octreotide/midodrine/albumin-treated patients and 21 concurrent nonrandomized albumin treated controls reported reduced mortality in the treatment group (43% vs 71%, $P < 0.05$).¹⁸¹

An uncontrolled pilot study of this drug combination followed by TIPS in 14 patients reported

improved renal function and natriuresis.¹⁸² Two studies, including one with randomization and crossover design, demonstrate that octreotide alone is not beneficial for HRS; midodrine appears to be required in addition.^{183,184} Two randomized trials comparing norepinephrine to terlipressin, report equal efficacy in reversing type I or II hepatorenal syndrome in the former study and type I in the latter study; this treatment requires that the patient be in an intensive care unit.^{185,186}

Terlipressin has been the subject of the most intense investigation. A US 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.¹⁸⁷ A European multicenter, randomized, controlled trial of terlipressin and albumin versus albumin alone in 46 patients with type I or type II demonstrated an improvement in renal function but no survival advantage at three months.¹⁸⁸ The most recent meta-analysis of 8 studies involving 320 patients demonstrated $\sim 50\%$ efficacy and an odds ratio of 7.5 in reversing hepatorenal syndrome.¹⁸⁹ Terlipressin is not available in the United States.

TIPS alone has also been reported to be effective in type I hepatorenal syndrome in an uncontrolled pilot study of 7 patients.¹⁹⁰ There are too few patients in these uncontrolled pilot studies of TIPS treatment of HRS with or without vasoconstrictors to make a strong statement about where to place it in the treatment algorithm.

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 9; renal function improved significantly compared to pretreatment levels.¹⁹¹ 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 ten patients.¹⁹²

A meta-analysis of vasoconstrictor treatment (including terlipressin, octreotide/midodrine, and norepinephrine) of type I and type II hepatorenal syndrome reports that vasoconstrictor drugs with or without albumin, reduced mortality compared with no intervention or albumin alone (relative risk 0.82, 95% confidence interval 0.40-1.39).¹⁹³ Terlipressin plus albumin reduced mortality compared to albumin alone (relative risk 0.81, 95% confidence interval 0.68-0.97) with a

reduction in mortality in type I but not type II HRS.¹⁹³

Enthusiasm is high for these new treatments.¹⁹⁴ There are ongoing randomized controlled trials that should help 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. Albumin and norepinephrine or vasopressin can be considered in the intensive care unit.

It has been known for >30 years that liver transplantation can be an effective treatment for hepatorenal syndrome.¹⁹⁵ However if the patient has been dialysed for greater than or equal to 8 weeks prior to liver transplantation, simultaneous kidney transplantation may be needed to avoid post-transplant dialysis.¹⁹⁶

Recommendations

38. Urinary biomarkers such as neutrophil gelatinase associated lipocalin may assist in the differential diagnosis of azotemia in patients with cirrhosis. (Class IIa, Level B)

39. 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)

40. Albumin infusion plus administration of norepinephrine should also be considered in the treatment of type I hepatorenal syndrome, when the patient is in the intensive care unit. (Class IIa, Level A)

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

Additional Considerations

Umbilical Hernias in Patients with Cirrhosis and Ascites

Prevalence. Abdominal wall hernias are common in patients with cirrhosis and ascites. Umbilical hernias are the most common with a prevalence of up to 20%.¹⁹⁷ These hernias develop in patients with long-standing ascites that is either refractory to medical therapy or associated with non-compliance. Hernias can be prevented or minimized by optimal control of fluid and minimization of pressure on the abdominal wall. Strangulation can occur within hours to days after a large-volume paracentesis, peritoneovenous shunt, or TIPS.^{198,199} Strangulated omentum

can have an unusual appearance on imaging and even resemble a malignant mass. If bowel or omentum is present in the hernia when fluid rapidly exits the hernia, the bowel or omentum can be trapped in the hernia ring.

Treatment. Patients can be advised to wear an appropriately-sized abdominal binder, and to manually support the hernia when coughing or straining, to minimize pain and minimize growth of the hernia. Patients can also be alerted to the possibility of incarceration and to manually try to reduce the hernia or urgently seek medical attention if it is not easily reducible incarceration occurs and.

Patients who are candidates for liver transplantation probably should wait to have the hernia repaired during or after the transplant. The risks *versus* the benefits of repair must be carefully weighed in patients who are not transplant candidates. Every effort should be made to control ascites prior to elective repair. If ascites is present at the time of repair, the hernia recurs in up to 73%.²⁰⁰

In the past hernia repair was associated with significant morbidity and mortality, especially when the repair was done urgently.¹⁹⁷ More recently, minimally invasive techniques, such as fibrin-based tissue adhesive, and laparoscopic repair have been reported.^{201,202} In transplant centers, a multidisciplinary approach to incarcerated or spontaneously ruptured hernias with consideration of pre or post-operative TIPS, has been reported to lead to operative mortality as low as 5%.²⁰³ The use of mesh has been advocated, but this is largely based on data collected in patients without cirrhosis.²⁰⁴ The risk of infection of the mesh may be too high in patients with cirrhosis, especially when the repair is done for incarceration or rupture. Postoperative dietary sodium should be restricted to 2000 mg/day and intravenous maintenance fluids should be eliminated or minimized, in order to minimize fluid accumulating in the abdomen and to minimize the risk of dehiscence or leakage of fluid from the fresh wound. The baseline hypotension that is common in these patients need not be treated with fluid boluses. Elective TIPS can be considered in patients with thin-walled umbilical hernias to prevent spontaneous rupture and the associated morbidity and mortality.^{203,204}

Recommendations

42. The risks versus benefits of hernia repair must be weighed carefully in patients with cirrhosis and ascites. Elective repair can be performed during or after liver transplantation. (Class IIa, Level C)

43. Elective repair of a hernia in a patient with cirrhosis is best performed after ascites has been controlled by medical treatment, the patient's overall condition has been optimized, and a multidisciplinary approach with consideration of perioperative TIPS is utilized. (Class IIa, Level C)

44. Emergent repair of a strangulated or perforated umbilical hernia is best performed by a surgeon who is experienced in the care of patients with cirrhosis. (Class IIa, Level C)

Hepatic Hydrothorax

Prevalence. Hepatic hydrothorax is defined as a large pleural effusion (usually unilateral and right-sided) that occurs in a patient with cirrhosis and ascites.²⁰⁵ Although ascites may occasionally not be clinically obvious, there is essentially always some fluid in the abdomen radiographically.²⁰⁶ Fluid passes from the peritoneal cavity to the pleural space through a small defect in the diaphragm.²⁰⁵ If the defect is large, so much fluid is pulled into the chest with each breath that little accumulates in the abdomen. These effusions are found in ~5% of patients with cirrhosis and ascites.²⁰⁵ Contrary to popular belief, the results of analysis of the pleural fluid and ascitic fluid are not identical. The protein concentration of the pleural fluid is usually higher than that of the ascitic fluid, due to differences in the hydrostatic forces in the abdomen versus the chest.²⁰⁵ Also the pleural fluid can become infected with bacteria, i. e. spontaneous bacterial empyema, in the absence of spontaneous bacterial peritonitis.²⁰⁷ Sixteen (13%) of 120 patients with hepatic hydrothorax developed bacterial infection of the pleural fluid over 4 years' time in one study.²⁰⁷

Thoracentesis can be performed without transfusion of platelets or plasma.²⁰⁸ There is no data-supported upper limit of volume that is removed. In one study "pleural fluid was drained by gravity until no more fluid could be obtained".²⁰⁸ Pneumothorax occurred in 4% in this study.²⁰⁸ Left-sided pleural effusions in cirrhosis and ascites can be due to tuberculosis, cancer, or pancreatitis.²⁰⁹

An abdominal origin of the pleural fluid can be confirmed by injecting technetium-radiolabeled sulfur colloid into the abdomen and detecting rapid passage of isotope into the chest cavity.^{205,206} Occasionally this test is falsely negative due to high pressure in the chest cavity; in this circumstance, the test can be repeated after a large-volume thoracentesis. Fluid reaccumulates

rapidly after thoracentesis and can lead to a positive test result.

Treatment. Although multiple studies have documented the morbidity (94-100%) and mortality (12-100%) associated with chest tube placement in patients with hepatic hydrothorax, these tubes are frequently placed before it is known that the patient has cirrhosis, especially if there is no clinically detectable ascites.^{210,211} Chest tube insertion may lead to a rapid deterioration in the patient's condition, resulting in death or necessitating urgent TIPS or transplant.^{210,211} Spontaneous bacterial empyema can be treated with appropriate antibiotics, without chest tube insertion.²⁰⁷

First-line treatment of hepatic hydrothorax is similar to that of ascites in the setting of cirrhosis 2000 mg/day sodium diet and dual diuretics.²⁰² This can be effective, especially if the patient has a reversible component to their liver injury, e. g. alcohol. Therapeutic thoracentesis should be performed for dyspnea. TIPS is the most commonly used second-line treatment.^{114,202}

Recommendations

45. Chest tube insertion is contraindicated in patients with hepatic hydrothorax. (Class III, Level B)

46. First-line therapy of hepatic hydrothorax consists of dietary sodium restriction and diuretics. (Class IIa, Level B)

47. TIPS can be considered as second-line treatment for hepatic hydrothorax, once it becomes refractory. (Class IIb, Level B)

Cellulitis. Cellulitis of the lower extremity(ies) or abdominal wall can be the cause of fever and pain in patients with cirrhosis.^{135,212} This soft-tissue infection is an under-recognized and increasing problem in patients with cirrhosis and fluid retention, perhaps in part due to the obesity epidemic and the brawny edema present in many obese patients.²¹² Patients with brawny edema plus pitting edema may be unusually predisposed to bacterial infection. Risk factors for cellulitis in cirrhosis include skin trauma/puncture, obesity, homelessness, and subjective degree of edema.²¹² In one series cellulitis was more common than spontaneous bacterial peritonitis.²¹² In another series 13% of infections in cirrhosis were diagnosed as cellulitis.¹³⁵ Treatment should include diuretics to reduce edema and either a first-generation cephalosporin, if the cellulitis is community-acquired and involves no recent exposure to antibiotics, or a third-generation cephalosporin plus vancomycin or cloxacillin if the cellulitis

occurs in a patient who has received antibiotics in the recent past.^{135,212}

Recommendation

48. Cellulitis can explain pain and fever in patients with cirrhosis and ascites and should be treated with diuretics and antibiotic(s). (Class IIb, Level B)

Percutaneous Endoscopic Gastrostomy. Percutaneous endoscopic gastrostomy should be avoided in patients with cirrhosis, especially when ascites is present. One study has shown a 38.5% 30-day mortality; 9 of the 10 patients who died within 30 days had ascites at the time of tube placement.²¹³ Although a practice guideline on nutrition suggests that it may be placed if reaccumulation of fluid can be prevented for 7-10 days, it provides no reference for this statement and no method of preventing reaccumulation.²¹⁴

Recommendation

49. Percutaneous endoscopic gastrostomy should be avoided in patients with cirrhosis and ascites. (Class IIb, Level B)

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