Management of Adult Patients With Ascites Caused by Cirrhosis

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Ascites is the most common of the major complications of cirrhosis. The development of ascites is an important landmark in the natural history of cirrhosis and has been proposed as an indication for liver transplantation. The initial evaluation of a patient with ascites should include a history, physical evaluation, and abdominal paracentesis with ascitic fluid analysis. Treatment should consist of abstinence from alcohol, sodium restricted diet, and diuretics. This regimen is effective in ≈90% of patients. The treatment options for the diuretic-resistant patients include serial therapeutic paracenteses, liver transplantation, and peritoneovenous shunting. (HEPATOLOGY 1998;27:264-272.)

PREAMBLE

These guidelines provide a data-supported approach to the care of patients with ascites. They are based on the following: 1) a formal review and analysis of the published world literature (1,045 papers) on ascites (Medline Search from 1966-1996, search terms included ascites, diet therapy, drug therapy, radiotherapy, surgery, and therapy); 2) the American College of Physician’s Manual for Assessing Health Practices and Designing Practice Guidelines; and 3) several published and draft guidelines, including the American Association for the Study of Liver Diseases’ Policy Statement on Development and Use of Practice Guidelines and American Gastroenterological Association’s Policy Statement on Guidelines; and 4) 15 years of experience on the part of the author in the clinical and laboratory investigations of and care for patients with this problem.

These guidelines, intended for use by physicians, suggest preferable approaches to the diagnostic, therapeutic, and preventative aspects of care. These guidelines are intended to be flexible, in contrast with “standards of care,” which are inflexible policies to be followed in almost every case.

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

Specific recommendations are based on relevant published information. In an attempt to standardize recommendations, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases modified the categories of the Infectious Diseases Society of America’s Quality Standards. These categories are reported with each recommendation, using the letters A through E to determine the strength of recommendation and roman numerals I through III to determine quality of evidence upon which recommendations are based, as follows: A, survival benefit; B, improved diagnosis; C, improvement in quality of life; D, relevant pathophysiologic parameters improved; E, impacts cost of health care; I, evidence from multiple well-designed randomized controlled trials, each involving a number of participants to be of sufficient statistical power; II, evidence from at least one large, well-designed clinical trial with or without randomization from cohort or case-control analytic studies or from well designed meta-analysis; III, evidence based on clinical experience, descriptive studies, or reports of expert committees; and IV, not rated.

Background

Cirrhosis was the eleventh leading cause of death, according to the 1994 Morbidity and Mortality Weekly Report. It is estimated that there are 3 million Americans with cirrhosis. Ascites is the most common of the three major complications of cirrhosis; the other complications include hepatic encephalopathy and variceal hemorrhage. Approximately 50% of patients with “compensated” cirrhosis, i.e., without having developed one of these complications, develop ascites during 10 years of observation. The development of fluid retention in the setting of cirrhosis is an important landmark in the natural history of chronic liver disease. Approximately 50% of patients with ascites succumb in two years, which has led to inclusion of ascites as one of the indications for initiating evaluation for liver transplantation.

Evaluation

History. Most patients (≈80%) with ascites in the United States have cirrhosis. There is a nonhepatic cause of fluid retention in about 20% of patients with ascites. Successful treatment depends 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, including alcohol, intravenous and recreational drug use, transfusions, homosexuality, acupuncture, tattoos, ear-piercing, country of origin, family history, history of jaundice or hepatitis, etc. Past history of cancer, heart failure, or tuberculosis is also relevant.

Physical Examination. The presence of a full, bulging abdomen should lead to percussion of the flanks. If the amount of
flank dullness is greater than usual, i.e., if the percussed air-fluid level is higher than that normally found on the lateral aspect of the abdomen with the patient supine, then “shifting” should be checked for. If there is no flank dullness, there is no reason to check for shifting. Approximately 1,500 mL of fluid must be present to detect dullness.9 If flank dullness is not present, the patient has less than a 10% chance of having ascites.9

An abdominal ultrasound may be required to determine with certainty if fluid is present. Ultrasonography can detect as little as 100 mL of fluid in the abdomen.10

**Diagnosis**

The diagnosis of recent onset ascites is suspected on the basis of the history and physical examination and is usually confirmed by successful abdominal paracentesis and/or ultrasound. The diagnosis of the cause of ascites formation is based on the results of the history, a physical, and of ascitic fluid analysis. In general, few other tests are required. Other radiologic or endoscopic procedures usually provide little information in the initial evaluation of the patient with ascites.

**Abdominal Paracentesis.** Abdominal paracentesis with appropriate ascitic fluid analysis is probably the most rapid and cost-effective method of diagnosing the cause of ascites.11 Also, in view of the 10% to 27% prevalence of ascitic fluid infection at the time of admission to the hospital, an admission ultrasound may detect unexpected infection.12

Although older published series have 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.13,14 Complications have been reported in only about 1% of patients (abdominal wall hematomas), despite the fact that 71% of the patients had an abnormal prothrombin time.13 Although more serious complications (hemoperitoneum or bowel entry by the paracentesis needle) occur, they are unusual enough (<1/1,000 paracenteses) that they should not deter performance of this procedure. It is the practice of some physicians to give blood products, such as fresh frozen plasma and/or platelets, routinely before paracentesis in cirrhotics with coagulopathy. This policy is not data-supported. Because a transfusion-requiring hematoma develops in only ≈1% of patients who undergo paracentesis without prophylactic transfusions of plasma or platelets, approximately 140 U of fresh frozen plasma and/or platelets must be administered to prevent the transfusion of ≈2 U of red cells. The risks and costs of prophylactic transfusions exceed the benefit.

There are few contra-indications to paracentesis. Although coagulopathy is a potential contraindication, most patients with cirrhotic ascites have coagulopathy. If mild coagulopathy was viewed as a contra-indication to paracentesis, few cirrhotics would undergo this procedure. Coagulopathy should preclude paracentesis only when there is clinically-evident fibrinolysis or clinically-evident disseminated intravascular coagulation.13,14 These conditions occur in less than 1 of 1,000 procedures. There is no data-supported cutoff for coagulation parameters beyond which paracentesis should be avoided;13,14

**Recommendations**

Abdominal paracentesis should be performed and ascitic fluid should be obtained from inpatients and outpatients with clinically-apparent new onset ascites. Bleeding is sufficiently uncommon to preclude the need for prophylactic fresh frozen plasma or platelets. (Rating, II BE.)

**ASCITIC FLUID ANALYSIS**

**Analysis**

Although future studies are required to determine an optimal testing strategy, meanwhile, an algorithm approach seems preferable to ordering a large number of tests on most specimens. If uncomplicated cirrhotic ascites is suspected, only screening tests, e.g., cell count and differential and albumin 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. However, as most specimens consist of uncomplicated cirrhotic ascites, no further testing will be needed in the majority of patients.

If ascitic fluid infection is suspected, cell count and differential, albumin concentration, and bacterial culture in blood culture bottles are performed. Additional testing, e.g., total protein, lactate dehydrogenase, and glucose to assist in differentiating spontaneous from secondary bacterial peritonitis, can be performed on the initial specimen based on clinical judgement.12

The serum-ascites albumin gradient has been proved in prospective studies to categorize ascites better than the total-protein based exudate/transudate concept and than the modified pleural fluid exudate/tranudate criteria.15-17 Calculating the serum-ascites albumin gradient involves measuring the albumin concentration of serum and ascitic fluid specimens and subtracting the ascitic fluid value from the serum value. With approximately 97% accuracy, a serum-ascites albumin gradient of ≧1.1 g/dL (11 g/L) indicates that the patient has portal hypertension.15 Conversely, a serum-ascites albumin gradient of <1.1 g/dL (11 g/L) with ≦97% accuracy that the patient does not have portal hypertension.

Patients undergoing serial outpatient therapeutic paracenteses probably should be tested only for cell count and differential; bacterial culture is not necessary in asymptomatic patients.18

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. Only ≦7% of ascitic fluid cytologies are positive and only in the setting of peritoneal carcinomatosis.19 These patients usually have a history of a breast, colon, gastric, or pancreatic primary. The sensitivity of smear for mycobacteria is ≈0%; the sensitivity of fluid culture for mycobacteria is ≈50%.20 Only patients at high risk for tuberculous peritonitis, e.g., recent immigration from an endemic area or acquired immunodeficiency syndrome, should have testing for mycobacteria on the first ascitic fluid specimen.21

Multiple prospective trials show that bacterial growth occurs in only about 50% of instances when ascitic fluid with a polymorphonuclear (PMN) count ≧ 250 cells/mm³ (0.25 × 10⁹/L) is cultured by “conventional” methods as compared with approximately 80% if the fluid is inoculated into blood culture bottles at the bedside.22-24
Recommendations

1. The initial ascitic fluid analysis should include a cell count and differential and serum-ascites albumin gradient. (Rating, II B.)

2. When culture is performed, ascitic fluid should be cultured at the bedside in blood culture bottles. (Rating, II B.)

Differential Diagnosis

Although cirrhosis is the cause of ascites formation in most patients, approximately 20% of patients with ascites have a cause other than liver disease. Approximately 5% of patients with ascites have two or more causes of ascites formation, i.e., “mixed” ascites.15,25 Usually these patients have cirrhosis plus one other cause, e.g., peritoneal carcinomatosis or peritoneal tuberculosis. Many patients with enigmatic ascites are eventually reported to have 2 or even 3 causes for ascites formation, such as heart failure and diabetic nephropathy. 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.

TREATMENT OF ASCITES

Treatment

Appropriate treatment of patients with ascites depends on the cause of fluid retention. The serum-ascites albumin gradient can be helpful diagnostically, as well as in therapeutic decision making. Patients with low serum-ascites albumin gradient ascites usually do not have portal hypertension and do not respond to salt restriction and diuretics,8 except when patients have nephrotic syndrome. In contrast, patients with a high serum-ascites albumin gradient have portal hypertension and usually are responsive to these measures.7

The remainder of these guidelines applies only to patients in which ascites is caused by cirrhosis.

Alcohol with or without hepatitis C is the most common cause of liver disease that leads to high albumin gradient ascites.11,26 One of the most important steps in treating this form of ascites is to treat the underlying liver disease by convincing the patient to abstain from alcohol. In a period of months, abstinence can result in the improvement of the reversible component of alcoholic liver disease. In a prospective study, abstinence has been shown to normalize portal pressure in some, but not in all, patients.27 Ascites may resolve or become more responsive to medical therapy during this time. Non-alcoholic liver diseases are less reversible, and by the time ascites is present, these patients may be better candidates for liver transplantation than for protracted medical therapy.

The mainstays of treatment of patients with cirrhosis and ascites include the following: 1) education regarding dietary sodium restriction (2,000 mg/day [88 mmol/day]); and 2) oral diuretics.7,11 More stringent dietary sodium restriction can speed weight loss. Fluid loss and weight changes are directly related to sodium balance in patients with portal hypertension-related ascites. It is sodium restriction, not fluid restriction, that results in weight loss as fluid passively follows sodium.28 The measurement of urinary sodium excretion is a helpful parameter to follow in these patients. Random urinary sodium concentrations are of value when they are 0 mmol/L or > 100 mmol/L; however, random urinary sodium concentrations 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 > 3,000 mL. Urine samples collected for twenty-four hours to determine sodium excretion are much more informative than are random specimens; however, full-day collections are clumsy. Providing patients with verbal and written instructions, a container, and a lab order slip to turn in with the completed specimen will help to insure patient compliance. The completion of the 24-hour specimen collection can be assessed by measuring the levels of urinary creatinine. Cirrhotic men should excrete 15 to 20 mg of creatinine per kilogram body weight per day, and women should excrete 10 to 15 mg/kg per day. Lower excretions of creatinine are indicative of an incomplete collection. Total non-urinary sodium excretion is < 10 mmol/day in afebrile cirrhotics without diarrhea.29 One of the goals of treatment is to increase the urinary excretion of sodium so that it is > 78 mmol/day (88 mmol/day of intake − 10 mmol/day of non-urinary excretion). Only the 10% to 15% of patients who have spontaneous natriuresis (> 78 mmol/day) can be considered for dietary sodium restriction alone, i.e., without diuretics; however, when given a choice, most patients prefer to take diuretics and to have a more liberal sodium intake rather than to abstain from diuretics and to have a more severe sodium restriction.

Fluid restriction is not a necessity when treating most patients with cirrhotic ascites. The chronic hyponatremia that is usually seen in patients with cirrhotic ascites is seldom morbid. Rapid attempts to correct hyponatremia in this setting can lead to more complications than can the hyponatremia itself.

The rapid correction of asymptomatic hyponatremia in the patients with cirrhosis is probably only appropriate in the immediate pre-liver transplant setting. Severe hyponatremia, e.g., serum sodium < 120 mmol/L, does warrant fluid restriction in the cirrhotic ascites patient. Cirrhotic patients do not usually have symptoms from hyponatremia until their sodium levels fall below 110 mmol/L or unless the decline in sodium is very rapid.

Although conventional recommendations suggest bed rest, based on extrapolation from heart failure, this recommendation is impractical and is not supported by controlled trials. An upright posture may aggravate the plasma renin elevation found in cirrhotic patients with ascites; theoretically, this may increase sodium avidity. This theoretical concern must be translated into clinically relevant outcomes before bed rest could be advocated.

The usual diuretic regimen consists of single morning doses of oral spironolactone and furosemide, beginning with 100 mg of the former and 40 mg of the latter.13 Previsously, 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.30,31 A randomized controlled trial has revealed a two-week interval before the onset of action of single-agent spironolactone.31 Single-agent furosemide has been shown in a randomized controlled trial to be less efficacious than spironolactone.32 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 the use of the oral administration.33,34
The dose of both oral diuretics can be increased simultaneously, maintaining the 100 mg:40 mg ratio, if weight loss and natriuresis are inadequate on the lower doses. In general, this ratio maintains normokalemia. Maximum doses are 400 mg/day of spironolactone and 160 mg/day of furosemide. Furosemide can be temporarily withheld in patients presenting with hypokalemia. Patients with parenchymal renal disease, e.g., diabetic nephropathy or immunoglobulin A nephropathy, may tolerate less spironolactone than usual because of hyperkalemia. Single morning dosing maximizes compliance. Amiloride can be substituted for spironolactone, but it is more expensive and has been shown to be less effective in a randomized controlled trial.

New loop diuretics must be proven to be superior to current drugs before their expense can be justified.

This approach, dietary sodium restriction and dual diuretic regimen, has been shown to be effective in 90% of patients in the largest, multicenter, randomized controlled trial performed in patients with ascites.

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

There is no limit to the daily weight loss of patients who have massive edema. Once the edema has resolved, 0.5 kg is probably a reasonable daily maximum. Encephalopathy, serum sodium < 120 mmol/L despite fluid restriction, or serum creatinine > 2.0 mg/dL should result in the cessation of diuretics, the reassessment of the situation, and the consideration of second-line options (see Refractory Ascites later in paper).

In the past, patients with ascites frequently occupied hospital beds for prolonged periods of time because of confusion regarding diagnosis and treatment and also 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, for patients to be discharged early from the hospital, they should be observed in the outpatient setting promptly, ideally within approximately one week of discharge.

Large volume paracentesis rapidly relieves tense ascites. A study performed more than two decades ago showed that paracentesis in this setting is hemodynamically beneficial to the patient. A more recent study shows that a single 4 to 6 L of paracentesis can be performed safely without post-paracentesis colloid infusion in the patient with diuretic-resistant tense ascites. However, large volume paracentesis does nothing to correct the underlying cause of ascites formation, i.e., sodium retention. Large volume paracentesis predictably removes the fluid more rapidly, in minutes, than does careful diuresis, which may take from days to week. However, to prevent reaccumulation of fluid, sodium intake should be reduced and urinary sodium excretion should be increased with diuretics. The determination of optimal diuretic doses for each patient takes time as it involves the process of titrating the doses upward until natriuresis and weight loss are achieved. Although a controlled trial shows that large volume paracentesis is faster than diuretic therapy for patients with cirrhosis and tense ascites, it should not be viewed as first line therapy for all patients with ascites.

In the outpatient clinic, body weight, orthostatic symptoms, serum electrolytes, urea, and creatinine are monitored. Random urine sodium concentration is measured if the weight loss is inadequate. If urinary sodium concentration is intermediate or if refractory ascites or non-compliance with diet are suspected, 24-hour urine specimens can be collected to assist with management decisions. Patients who are excreting > 78 mmol/day and who are not losing weight should be further counselled about restricting sodium in their diets. These patients should not be labelled as diuretic-resistant and should not proceed to second line therapy (see later) until it is documented that they are compliant with the sodium-restricted diet.

Patients who are excreting more than 78 mmol/day of sodium in the urine with stable or increasing weight are consuming more sodium in the diet than 88 mmol. Patients who do not lose weight and who excrete < 78 mmol/day should receive an attempt at a higher dose of diuretics. Frequency of follow-up is determined by response to treatment and by patient stability. Some patients warrant evaluation every two to four weeks until it is clear that they are responding to treatment and not developing problems; in these patients, further evaluation every few months may be appropriate. Intensive outpatient treatment, in particular diet education, may help prevent subsequent hospitalizations.

The development of ascites as a complication of cirrhosis is associated with a poor prognosis, with approximately a 50% 2-year survival. Liver transplantation should be considered in the treatment options for these patients, especially when local waiting times exceed 12 months.

Recommendations

1. Patients who drink alcohol and develop ascites should be encouraged to abstain from alcohol consumption. (Rating, III ACDE.)

2. A sodium restricted (88 mmol/day = 2,000 mg/day) diet, together with oral spironolactone and furosemide, is effective in controlling fluid overload in 90% of patients with cirrhosis and ascites and is also the mainstay of treatment. (Rating, I CD.)

3. Fluid restriction is not necessary unless serum sodium is < 120 mmol/L. (Rating, III D.)

4. Bedrest is not recommended. (Rating, III C.)

5. A single 4-to-6 L abdominal paracentesis should be performed in patients with tense ascites. Sodium restricted diet and oral diuretics should then be administered. (Rating, I CD.)

6. Urine sodium excretion can assist in determining patient compliance with diet and diuretic-resistance. (Rating, III DE.)

7. Diuretic-sensitive patients should preferably be treated with sodium-restricted diet and oral diuretics rather than with serial paracenteses. (Rating, III CD.)

8. Liver transplantation should be considered in eligible patients with cirrhosis and ascites. (Rating, III ACD.)
REFRACTORY ASCITES

Background

Refractory ascites is defined as fluid overload that is nonresponsive to sodium-restricted diet and high-dose (400 mg/d of spironolactone and 160 mg/d furosemide) diuretic treatment, in the absence of prostaglandin inhibitors, such as non-steroidal anti-inflammatory drugs. Failure of diuretic therapy may be manifested by the following: 1) minimal to no weight loss, together with inadequate (< 78 mmol/d) urinary sodium excretion, despite diuretics; or 2) development of clinically significant complications of diuretics. Several randomized trials have shown that < 10% of patients with cirrhotic ascites are refractory to standard medical therapy. Options for patients refractory to routine medical therapy include the following: 1) serial therapeutic paracenteses; 2) liver transplantation; 3) paracentesis and peritoneovenous shunt; and 4) transjugular intrahepatic portosystemic stent-shunt.

Serial therapeutic paracenteses are effective in controlling ascites, a fact which has been known since the time of the ancient Greeks. However, only recently have controlled trials demonstrating the safety of this approach been published. Even in patients without urine sodium excretion, ascites can be controlled by paracenteses performed approximately every 2 weeks. The frequency of paracentesis provides insight into a patient's degree of compliance with the diet. The sodium concentration of ascitic fluid is approximately equivalent to that of plasma, which is 130 mmol/L in these patients. A 6-liter paracentesis removes 780 mmol of sodium (130 mmol/L x 6 L = 780 mmol). A ten-liter paracentesis removes 1,300 mmol. Patients who consume 88 mmol of sodium per day, excreting ≈10 mmol/day in non-urinary losses and excreting no urinary sodium, retain a net of 78 mmol/day; therefore a 6-liter paracentesis removes 10 days (780 mmol:78 mmol/day) of retained sodium and a ten-liter paracentesis removes ≈17 days of retained sodium (1,300 mmol:78 mmol/day = 16.7 days) in patients without urinary sodium excretion. Patients with urinary sodium excretion greater than zero should require paracenteses even less frequently. Patients requiring paracenteses of ≈10 liters more frequently than every 2 weeks are clearly not complying with the diet.

In recent years, new paracentesis equipment has become available that may improve the ease and speed of paracentesis. One controversial issue regarding therapeutic paracentesis is that of colloid replacement. In one study patients with tense ascites were randomized to receive albumin (10 g per liter of fluid removed) versus no albumin, after therapeutic paracentesis. Refractoriness to diuretic treatment was not a prerequisite for entry into this study; in fact, 31.4% of patients had not received diuretics. The group that received no albumin developed statistically significantly more changes, although asymptomatic, in electrolytes, plasma renin, and serum creatinine than did the albumin group, but no more clinical morbidity or mortality. Although another study has documented that the subset of patients who develop a post-paracentesis rise in plasma renin have decreased life expectancy, there has been no study large enough to show decreased survival in patients who did not receive any plasma expander compared with patients administered albumin after paracentesis.

Despite the lack of a proven survival advantage, albumin is being used after therapeutic paracentesis. However, albumin infusions markedly increase albumin degradation, and albumin is very expensive. In a study performed more than 30 years ago, 58% of infused albumin was accounted for by increased degradation, and a 15% increase in serum albumin led to a 39% increase in degradation. Increasing albumin concentration in cell culture media has recently been shown to decrease albumin synthesis. In view of the cost, i.e., $4 to $25 per gram x 50 g/tap = $200 to $1,250/tap, it is difficult to justify the expense of routine albumin infusion based on the data at hand.

Non-albumin plasma expanders, such as dextran-70, heparin, and even saline, have been advocated but without demonstration of a survival advantage. 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. A single paracentesis followed by diet and diuretic therapy is appropriate for tense ascites. In the diuretic-sensitive patient, to serially remove fluid by paracentesis, when it can be removed with diuretics, seems inappropriate. Probably, only patients with diuretic-resistant ascites should be treated with repeated large-volume paracenteses. In addition, patients with early cirrhosis seem to be more sensitive to volume changes than do patients with advanced cirrhosis; this may also help to explain the changes in plasma renin when patients with early cirrhosis receive large-volume paracenteses. Patients with early cirrhosis and diuretic-sensitive ascites should be treated with diuretics and not with paracentesis; these patients may be more sensitive to paracentesis-related volume depletion. Chronic therapeutic paracenteses should be reserved for the 10% of patients who truly fail diuretic treatment; these patients may be less sensitive to paracentesis-related volume depletion.

In addition, the most recent studies advocate giving 50% of the plasma expander immediately after the tap and the other half after 6 hours. This approach converts a brief outpatient procedure into a full-day clinic visit or an overnight hospitalization, which seems unwarranted. More convincing data involving appropriate groups of patients and regarding clinically relevant issues, rather than asymptomatic laboratory abnormalities, are required before albumin or other plasma expanders can be recommended.

Liver transplantation should be considered in the treatment options of patients with ascites. In some areas, patients wait 12 to 18 months for liver transplants; deaths are becoming increasingly common in patients awaiting transplantation. In this setting transplant must be considered very early after decompensation first becomes evident. The 24-month survival of patients with cirrhosis and ascites is 50%. Once patients become refractory to routine medical therapy, 50% die within 6 months. The 12-month survival of patients with ascites refractory to medical therapy is only 25%.

Peritoneovenous shunt, e.g., LeVeen or Denver, was popularized in the 1970s as a physiologic treatment of ascites. Shunt placement has been shown in controlled trials to decrease the duration of hospitalization, to decrease the number of hospitalizations, and to decrease the dose of diuretics; however, poor long-term patency, excessive complications, and no survival advantage compared with medical therapy in controlled trials have led to preferred abandonment of this procedure. Shunt-related fibrous adhesions,
and even “cocoon” formation, can make subsequent liver transplantation difficult.\(^{58}\) Peritoneovenous shunting should probably now be reserved for diuretic-resistant patients who are not transplant candidates and who are not candidates for serial therapeutic paracenteses because of multiple abdominal surgical scars or distance from a physician who is willing and capable of performing paracenteses. Recent experience in shunt insertion by the surgeon may also be a factor in optimizing results in the rare patient who is selected to undergo this procedure.

Transjugular intrahepatic portasystemic stent-shunt is a side-to-side portacaval shunt that is placed by an interventional radiologist, usually under local anesthesia.\(^{43,44}\) A randomized trial has reported higher mortality in the transjugular intrahepatic portasystemic stent-shunt group compared with the medically treated group.\(^{59}\) More randomized trials are in progress, and their results are needed before the position of transjugular intrahepatic portasystemic stent-shunt in the treatment algorithm of patients with ascites can be finalized. A recent National Institutes of Health Consensus Conference has listed transjugular intrahepatic portasystemic stent-shunt as “unproven” for treatment of refractory ascites or hepatic hydrothorax.\(^{44}\)

**Recommendations**

Treatment options for the 10% of patients with cirrhosis and ascites who are truly diuretic-resistant include the following:

1. Serial therapeutic paracenteses should be performed as needed, approximately every two weeks. Post-paracentesis albumin infusion is expensive and unproven to decrease morbidity or mortality; it appears to be unnecessary for paracenteses of \(< 5 \text{ L.} \) For larger volume paracenteses, an albumin infusion of \(\geq 50 \text{ g} \) can be considered. (Rating, I CE.)

2. Liver transplantation should be considered if the patient is an acceptable candidate. (Rating, III CD.)

3. Peritoneovenous shunt might be an option for patients who are not transplant candidates. (Rating, I CD.)

**SPONTANEOUS BACTERIAL PERITONITIS**

**Background**

**Diagnosis.** This diagnosis is made when there is a positive ascitic fluid bacterial culture, which is an elevated ascitic fluid polymorphonuclear leukocyte count, i.e., \(\geq 250 \text{ cells/mm}^3 (0.25 \times 10^9/\text{L}) \) without an evident intra-abdominal and surgically treatable source of infection.\(^ {12}\) 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 inadequate.

**Empiric Treatment.** Patients with ascitic fluid polymorphonuclear leukocyte counts \(\geq 250 \text{ cells/mm}^3 (0.25 \times 10^9/\text{L}) \), in a clinical setting that is compatible with ascitic fluid infection, should receive empiric antibiotic therapy.\(^ {12}\) An elevated ascitic fluid polymorphonuclear leukocyte count probably represents evidence of failure of the first line of defense, the peritoneal macrophages, to kill invading bacteria.\(^{40}\) A prospective study in which two paracenteses were performed in rapid sequence (\(= 4 \text{ hours apart} \)), before the initiation of antibiotic therapy, shows that only 8% of patients with culture-positive ascitic fluid with an elevated PMN count become culture-negative spontaneously.\(^ {61}\) The majority of patients with culture-positive neutrocytic ascites show rising bacterial and PMN counts when serial samples are obtained in rapid sequence before initiation of antibiotic therapy.\(^ {61}\)

The ascitic fluid PMN count is more rapidly available than is the culture and seems to be accurate in determining who really needs empiric antibiotic coverage.\(^ {12}\) 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 bacterasites stage before there is a neutrophil response.\(^ {62}\) Most patients with bacterasites who do not resolve the colonization and who progress to SBP have signs or symptoms of infection at the time of the tap, which documents bacterasites.\(^ {61,62}\) Therefore, patients with cirrhotic ascites who have convincing signs or symptoms of infection should receive treatment, regardless of the PMN count in ascitic fluid.

The patient with alcoholic hepatitis represents a special case. These patients regularly develop fever, leukocytosis, and abdominal pain which can masquerade as spontaneous bacterial peritonitis (SBP). In addition, they can develop SBP. These patients do not develop false-positive elevated ascitic fluid PMN counts because of peripheral leukocytosis;\(^ {63}\) it must be presumed that an elevated PMN count represents 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 cultures, and urine cultures show no bacterial growth.

A 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 in combination with tobramycin in a controlled trial.\(^ {64}\) Cefotaxime or a similar third-generation cephalosporin appears to be the treatment of choice for suspected SBP, as it covers 95% of the flora, including the three most common isolates, which are Escherichia coli, Klebsiella pneumoniae, and the pneumococcus.\(^ {12,64}\) IV dosing of 2 g cefotaxime every 8 hours results in excellent ascitic fluid levels, 20-fold killing power after one dose.\(^ {65}\) After sensitivities are known, the spectrum of coverage can usually be narrowed. In a randomized controlled trial involving 100 patients, it has been reported that 5 days of treatment is as efficacious as 10 days in the treatment of carefully characterized patients with SBP.\(^ {66}\)

**Distinction From Secondary Bacterial Peritonitis.** Secondary bacterial peritonitis, i.e., ascitic fluid infection caused by a surgically-treatable intra-abdominal source, can masquerade as SBP. Secondary peritonitis can be divided into two subsets: those with free perforation of a viscus, e.g., duodenal ulcer, and those with loculated abscesses in the absence of perforation, e.g., perinephric abscess. Signs and symptoms do not aid in the separation of patients who need surgical intervention (both subsets of secondary peritonitis) from those who have SBP and who need only antibiotic treatment.\(^ {67}\) In contrast, the initial ascitic fluid analysis and the response to treatment can assist with this important distinction.\(^ {67}\) The characteristic analysis in the setting of free perforation is PMN count \(\geq 250/\text{cu mm} \) (usually many thousands), multiple organisms on gram stain and culture, and two or three of the following criteria: total protein > 1 g/dL, lactate dehydrogenase greater than the upper limit of normal for serum, and glucose < 50 mg/dL.\(^ {67}\) It has been reported that these criteria have 100% sensitivity but only 45% specificity in detecting perforation in
a prospective study. Patients who fulfill these criteria should undergo emergent plain and upright films, water-soluble contrast studies of the gut, and computed tomographic scanning. These criteria are only 50% sensitive in detecting non-perforation peritonitis; the follow-up PMN count after 48 hours of treatment assists in detecting these patients. The 48-hour PMN count is essentially always below the pretreatment value in SBP when an appropriate antibiotic is used; in contrast, in non-perforation peritonitis the PMN count rises despite treatment. Patients reported to have free perforation or non-perforation peritonitis should receive anaerobic coverage in addition to a third-generation cephalosporin and laparotomy.

Follow-Up Paracentesis. A follow-up ascitic fluid analysis is not needed in all infected ascites patients. The majority of patients have SBP in the typical setting, e.g., advanced cirrhosis, with typical symptoms, typical ascitic fluid analysis (total protein \( < 1 \text{ g/dL} \), lactate dehydrogenase less than the upper limit of normal for serum, and glucose \( \geq 50 \text{ mg/dL} \)), a typical single organism, and a typical dramatic clinical response. Repeat paracentesis can be performed to document a culture's sterility 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 suspicion of secondary peritonitis and prompting further evaluation and surgical intervention when appropriate.

Possible Oral Treatment. Oral ofloxacin has been reported in a randomized controlled trial to be as effective as parenteral cefotaxime in the treatment of SBP in patients who are not vomiting and not in shock. Confirmatory trials are awaited before oral treatment of this life-threatening infection can be enthusiastically recommended.

Recommendations
1. Patients admitted to the hospital with ascites 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). (Rating, III B.)
2. Patients with ascitic fluid PMN counts \( \geq 250 \text{ cells/mm}^3 \) (0.25 \( \times \) 10\(^9/L\)) should receive empiric antibiotic therapy, e.g., 2 g of cefotaxime iv every 8 hours. (Rating, II BD.)
3. Patients with ascitic fluid PMN counts \( < 250 \text{ cells/mm}^3 \) (0.25 \( \times \) 10\(^9/L\)) and signs or symptoms of infection (temperature \( > 100^\circ\text{F} \), abdominal pain or tenderness) should also receive empiric antibiotic therapy, e.g., 2 g of cefotaxime iv every 8 hours, while awaiting results of cultures. (Rating, II BD.)

Prevention
The identification of risk factors for development of SBP, including ascitic fluid protein concentration \( < 1.0 \text{ g/dL} \), variceal hemorrhage, and prior episode of SBP, has led to randomized controlled trials of prophylactic antibiotics. The oral administration of 400 mg/d of norfloxacin has been reported to successfully prevent SBP in the following: 1) in patients with low-protein ascites; and 2) patients with prior SBP. The oral administration of 400 mg/d of norfloxacin twice per day for seven days helps to prevent infection in patients with variceal hemorrhage; however, oral antibiotics do not prolong survival and do select resistant gut flora, which can subsequently cause spontaneous infection. In a report of liver transplant infections, one risk factor for fungal infection was described as “prolonged therapy with ciprofloxacin.” Intermittent dosing, such as the following: 1) a single weekly dose of 750 mg of ciprofloxacin; 2) five doses of trimethoprim/sulfamethoxazole per week; or 3) restricting use of norfloxacin to inpatients only, with discontinuation of the drug at the time of discharge, may be the best compromises in preventing infection without selecting resistant flora, according to three randomized trials. However, studies reporting substantial cost savings and/or survival advantages for treated patients will be required before prophylaxis can be enthusiastically recommended.

There are no published randomized trials of antibiotic versus placebo in preventing infections in patients awaiting liver transplantation.

To prevent sclerotherapy-related infections, parenteral antibiotics do not seem to be warranted, based on a controlled trial; rather, active bleeding seems to be the risk factor for infection, not sclerotherapy. Variceal banding may replace sclerotherapy. Antibiotics would be even less likely to be of benefit in the setting of banding.

Recommendations
1. Short-term inpatient quinolone should be considered in the prevention of bacterial infections in patients with the following: 1) low-protein (< 1 g/dL) ascites; 2) variceal hemorrhage; and 3) prior SBP. (Rating, I CD.)
2. Long-term outpatient use probably can be reserved for patients who have survived an SBP episode. (Rating, I CD.)

APPENDIX
These guidelines were developed under the auspices of, and approved by, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. They are intended to suggest preferable approaches to the clinical management of liver diseases. They are flexible and are not intended as the only acceptable approach to treatment. As the appropriate level of skill or course of treatment will vary in light of the relevant facts and circumstances surrounding each individual case, these guidelines are not intended to define the applicable standard of medical care and may be updated periodically as new information becomes available.

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REFERENCES


