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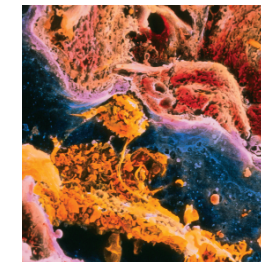

Spontaneous Bacterial Peritonitis

A Review of Treatment Options

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Educational Objectives

After reviewing this article, readers should be able to:

- Identify the pathogenesis of spontaneous bacterial peritonitis (SBP).
- Explain the clinical presentation of SBP.
- Describe the various types of diagnostic testing available for identifying and assessing a course of SBP.
- Differentiate between primary SBP and secondary peritonitis.
- Identify current pharmacological treatment guidelines and concerns regarding the use of third-generation cephalosporins as empirical therapy.
- Describe the role of prophylactic therapy in the management and prevention of SBP.

Introduction

Spontaneous bacterial peritonitis (SBP), an infection of ascitic fluid without a definitive intra-abdominal source that can be surgically treated,[1] is a common complication in patients with cirrhosis and ascites. Patients with ascites who have been followed prospectively for one year have a 10% to 25% incidence of having at least one episode of SBP during that time period. When patients with ascites underwent routine paracentesis, the incidence of active SBP ranged from 10% to 27% at the time of hospital admission.[2,3]

Because of an improved understanding of the disease, earlier detection of infection, and a larger armamentarium of safe and effective antibiotics from which to choose, infection-related mortality resulting from SBP declined markedly between the 1970s and the 1990s.[1] The prognosis is generally improved if antibiotics are begun before the onset of shock and renal failure.[4,5] However, because of the severe underlying liver disease that is usually a progenitor to the development of SBP, inpatient non–infection-related mortality rates have still been quite high at 20% to 40%.[4,5] If the patient survives that hospitalization, one-year and two-year mortality rates for those with SBP are approximately 70% and 80%, respectively.[3,6–10]

Further adding to the inherent morbidity of SBP is its proclivity for recurrence. After an episode of SBP has been successfully cleared with antibiotic therapy, recurrence rates range from 40% to 70% within the first year.[3,6]

In view of these data bearing a rather grim prognosis for those with SBP, further research and experience in the diagnosis and management of this disease have continued to progress. These new findings, together with ongoing education for health care providers, may bring hope of an improved prognosis to patients. In that spirit, this article reviews the pathophysiology, diagnosis, management, and prevention of SBP associated with ascites of cirrhosis.

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Pathogenesis

SBP is thought to result from a combination of factors inherent in cirrhosis and ascites, such as prolonged bacteremia secondary to compromised host defenses, intrahepatic shunting of colonized blood, and defective bactericidal activity within the ascitic fluid.[11] Contrary to earlier theories, transmucosal migration of bacteria from the gut to the ascitic fluid is no longer considered to play a major role in the etiology of SBP.[12]

With respect to compromised host defenses, patients with severe acute or chronic liver disease are often deficient in complement and may also have malfunctioning of the neutrophilic and reticuloendothelial systems.[13–16] Frequent and prolonged bacteremia are potential consequences of these defects in host defenses.

In terms of important predictors for identifying cirrhotic patients at greatest risk for SBP, both a high serum bilirubin (above 2.5 mg/dL) and a low ascitic fluid protein concentration (less than 1.0 g/dL) have been shown to be independent factors for both initial episodes of SBP as well as for recurrence.[7,17]

As to why a higher serum bilirubin might be linked to a greater risk of acquiring SBP, the association is probably indirect. Elevated serum bilirubin levels usually coincide with a more severe or advanced stage of liver disease. Serum bilirubin is one of five markers used to stage the severity of liver disease according to Child–Pugh rankings.[18] The higher the number in these rankings, the greater the risk of SBP.[1] This helps to explain why 70% of cases of SBP are seen in patients with Child–Pugh class C cirrhosis.[19]

As for the significance of ascitic fluid proteins, Runyon

demonstrated that cirrhotic patients with ascitic protein concentrations below 1 g/dL were 10 times more likely to develop SBP than individuals with higher concentrations.[17] It is thought that the antibacterial, or opsonic, activity of ascitic fluid is closely correlated with the protein concentration.[20] Thus, patients with low protein levels are at higher risk for SBP. Conversely, patients with ascitic fluid of typically high protein content, such as those with malignant ascites or congestive heart failure, are relatively resistant to SBP.[21,22] Additional studies have confirmed the validity of the ascitic fluid protein concentration as the best predictor of the first episode of SBP.[7,23]

In summary, the development of SBP probably involves a relatively prolonged case of bacteremia translocating to an opsonin-deficient site in the body. In the case of SBP, that site is ascitic fluid.[3]

Clinical Presentation and Diagnosis

The clinical presentation of SBP is highly variable. SBP may be manifested as a relatively insidious asymptomatic colonization (bacterascites), or it can quickly emerge as a sepsis syndrome with a high fatality rate.[24] Presenting signs and symptoms can include fever, changes in mental status, abdominal tenderness, gastrointestinal (GI) bleeding, chills, nausea, or vomiting. In one study, fever (68%), mental status alterations (61%), and abdominal tenderness (46%) were the most frequent observations in patients with SBP.[25] Yet some authors report that as many as 30% of patients with paracentesis-proven SBP may be completely asymptomatic.[19]

Because of the tremendous variability in presentations, and also because such presentations may overlap with other conditions often seen in cirrhosis (e.g., encephalopathy), a proper assessment, as described next, is essential in diagnosis.

Microbiologic Testing

As with any patient suspected of having a serious infection, blood and urine cultures should be obtained before an antibiotic regimen is begun for patients thought to have contracted SBP. With SBP, blood cultures may be positive up to one-third of the time.[19] Routine urine cultures are also recommended in this situation; even if the patient lacks classic symptoms of a urinary tract infection, organisms colonizing in the urine have the potential to travel to the ascitic fluid. In fact, asymptomatic bacteriuria is an independent risk factor for SBP.[19]

Historically, Gram stain and culture of ascitic fluid, when performed by conventional microbiologic methods, have shown poor diagnostic yields in the effort to identify the pathogen. Conventional culture methods consisted of inoculating agar plates with approximately 2 mL of ascitic fluid, then incubating the sample in anticipation that an organism would colonize on the agar plate. With this method, even Gram staining of ascitic fluid has been useful in fewer than half of cases, and actual growth of identifiable bacteria on agar plates has appeared still less likely.[26]

What is the reason for such poor results with conventional culture methods? One must keep in mind that this process was accomplished after the ascitic fluid was transferred from the patient's room to the laboratory. Because the median bacterial concentration in ascitic fluid is approximately two organisms per milliliter—much lower than inocula found in most other types of infections—the probability of a culture's being positive with such fastidious prokaryotes with this method is indeed remote.[3]

In response to the futility of finding pathogens using conventional means, it was eventually discovered that inoculation of 10 to 20 mL of ascitic fluid into 100-mL blood culture bottles at the patient's bedside yielded much better results. A study comparing the efficacy of bedside inoculation with the conventional method showed a 40% improvement in sensitivity, increasing the yield from less than half to about 80% with the blood culture bottle inoculation method. These promising results were later affirmed, and current standards of practice now indicate that culture of ascitic fluid should be obtained at the bedside with the blood culture bottle method.[1,27,28]

Ascitic Fluid Analysis via Diagnostic Paracentesis

Even after pan-culturing is properly completed, some series show that 30% to 40% of all patients with SBP have negative cultures of both blood and ascitic fluid.[19] Furthermore, these culture methods take at least 24 to 48 hours to produce the desired results. Because of these shortcomings, paracentesis, when used to obtain an ascitic fluid cytologic analysis, remains the single most important test for identifying and assessing a course of SBP. Unlike the microbiologic cultures already mentioned, the paracentesis fluid analysis can be performed safely and can produce valuable results in just one to four hours.[1]

Of all the information gleaned from the ascitic fluid cytologic "tap," the neutrophil count remains the best test for making a presumptive diagnosis of SBP.[12,16] As shown in Table 1, polymorphonuclear neutrophilic leukocyte (PMN) counts, starting at 250 or 500 cells/mL (depending upon the culture results and the patient's clinical presentation), are considered valid markers for SBP.[16]

Other information included in the tap varies in its usefulness. For example, because of their unreliability, ascitic fluid pH and ascitic lactate concentrations should not be the only measures relied on for evaluating patients with presumed SBP. In fact, the ascitic fluid's pH is thought to be nothing more than an indirect marker of ascitic PMN counts.[3]

Table 1 Subsets of Ascitic Fluid Infections

	PMNs	Cultures
Spontaneous bacterial peritonitis	≥ 250 cells/mL	Positive
Culture-negative neutrocytic ascites	≥ 500 cells/mL	Negative
Monomicrobial non-neutrocytic bacterascites	< 250 cells/mL	Positive

PMN = polymorphonuclear neutrophilic leukocyte.
From Bhuva M, Ganger D, Jensen D. *Am J Med* 1994; 97:169–175. Reprinted with permission from Elsevier.[38]

Urine Reagent Strip Testing

An initially promising and practical bedside test for quickly diagnosing SBP has gained attention. Reagent strips are designed to detect the presence of the enzyme leukocyte esterase in urine obtained via a standard bedside urine-collection method. Leukocyte esterase is an intracellular enzyme contained within PMNs that is released into the environment when PMNs are lysed during the normal inflammatory cascade.[29]

Three studies of this test have been published, and results thus far show sensitivities, specificities, and negative predictive values of 90% or higher when the test is used as a screen for diagnosing SBP.[30–33] However, as practical as this method sounds in terms of allowing earlier use of antibiotics by a couple of hours or more, whether such testing would comply with current hospital accreditation standards remains questionable.[34] Furthermore, a critical review of the current literature concluded that, based on larger studies showing low sensitivity and a high risk of false positives, reagent strip testing cannot be recommended for confirming a diagnosis of SBP.[35]

Primary Spontaneous Bacterial Peritonitis versus Secondary Peritonitis: Differential Diagnosis and Pathogenicity

Another important consideration is differentiating SBP from secondary peritonitis. Depending upon the series of patients studied, approximately 5% to 15% of patients with infected ascites have an intra-abdominal source, such as a perforated bowel.[9,11] This differentiation is of paramount importance, because the mortality rate of SBP approaches 100% if treatment includes antibiotics without surgical intervention.[36] However, the mortality rate is about 80% if a patient with SBP receives an unnecessary exploratory laparotomy.[37]

Using the results of retrospective studies, Akriviadis and Runyon developed an algorithm for identifying patients with infection secondary to perforation and for distinguishing SBP from nonperforation secondary peritonitis depending on the patient's response to antibiotic therapy.[36]

An initial pretreatment ascitic fluid cytologic analysis can be helpful in distinguishing SBP from secondary peritonitis. Both types are characterized by PMN counts greater than 250 cells/mm^3, but secondary peritonitis often shows total protein concentrations above 1 g/dL, glucose concentrations lower than 50 mg/dL, and serum lactate dehydrogenase (LDH) levels above the upper limit of normal (ULN).[36]

Unlike secondary peritonitis, SBP tends to be monomicrobic about 92% of the time.[19] The most commonly occurring organisms are enteric gram-negative rods such as *Escherichia coli* and *Klebsiella* spp., which cause more than half of all infections. Gram-positive organisms cause about 25% of infections.[1] Although some series show *Streptococcus pneumoniae* as the most common streptococcal organism,[19,26] others find the *viridans* group as the predominant gram-positive pathogen.[19] *Enterococcus* spp. have been documented in 6% to 10% of cases. *S. aureus* is noted infrequently, representing only about only 2% to 4% of all SBP infections.[26] In one series quite representative of the literature, the most frequently isolated organisms included *E. coli,* streptococci, and *Klebsiella* spp.; these accounted for more than 80% of all cases of SBP (Table 2).[38]

Table 2 **Bacteriology of Spontaneous Bacterial Peritonitis**

Organism	No. of Isolates (%) (N = 263)
Escherichia coli	121 (46)
Streptococcus and group D streptococci	80 (30)
Klebsiella pneumoniae	24 (9)
Other aerobic gram-negative bacilli	22 (8)
Anaerobes	2 (<1)
Other *Staphylococus* spp., diphtheroids	15 (6)

From Bhuva M, Ganger D, Jensen D. *Am J Med* 1994;97:169–175. Reprinted with permission of Elsevier.[38]

There is another significant difference between SBP and secondary peritonitis. Although facultative anaerobic organisms such as Enterobacteriaceae and streptococci are common SBP pathogens, obligate anaerobes, such as *Bacteroides* spp., are rarely implicated as a cause of SBP. This observation is attributed to the relatively high oxygen content of ascitic fluid, an environment in which facultative anaerobes cannot proliferate as long as needed to attain pathogenicity.[39]

Summary

As a result of the nonspecific clinical presentation of patients with SBP, combined with the delay and lack of sensitivity in currently available microbiologic techniques, the early use of cytologic testing via paracentesis is crucial to the assessment of patients with suspected SBP. Empirical treatment of antibiotics would logically include coverage of *E. coli*, *Klebsiella* spp., and streptococcal species (see Management).

Management

Antibiotic Therapy

Since the 1985 seminal study, which showed better outcomes with cefotaxime (Claforan, Sanofi-Aventis) than with the combination of ampicillin and tobramycin (American Pharmaceutical Partners), third-generation cephalosporins have been the agents of choice in the management of SBP.[40] Subsequently, several studies have reinforced the role of third-generation cephalosporins in an effort to determine the optimal dose and duration of therapy.[5,41–44]

In 2000, The International Ascites Club published a consensus document on the diagnosis, management, and prophylaxis of SBP.[45] The guidelines suggested several antibiotics that might be used for empirical treatment, such as cefotaxime, cefonicid (Monocid, GlaxoSmithKline), ceftizoxime (Cefizox, Astellas), ceftriaxone (Rocephin, Roche), ceftazidime (Fortaz, GlaxoSmithKline; Tazicef, Hospira), and amoxicillin–clavulanic acid (Augmentin, GlaxoSmithKline). In some studies, these antibiotics showed similar rates of efficacy, ranging from 77% to 93%; yet because of the increased risk of nephrotoxicity, the use of extended-spectrum beta-lactam (ESBL) antibiotics, combined with aminoglycosides, was not recommended.

The duration of therapy, according to the guidelines, should be a minimum of five days. This recommendation is largely

derived from the comparative trial showing that a five-day course of cefotaxime (2 g every eight hours) was as effective as a 10-day course of therapy with respect to resolution of infection, recurrence of SBP, and hospital mortality rates.[5]

Rimola et al. subsequently demonstrated that cefotaxime at a dose of 2 g every 12 hours was as effective as 2 g every six hours.[41] Consequently, cefotaxime at a dose of 2 g every 12 hours was more cost-effective for treating SBP. In addition, the use of oral antibiotic therapy, namely ofloxacin (Floxin, PriCara) 400 mg every 12 hours, was recommended for patients with uncomplicated SBP who had not previously received quinolone prophylaxis. Uncomplicated SBP was defined as no shock, ileus, or GI hemorrhage; no profound hepatic encephalopathy; and no serum creatinine level above 3 mg/dL.

Finally, it was recommended that patients' responses to therapy be evaluated with a second diagnostic paracentesis after 48 hours. An inability to achieve a decrease of at least 25% in PMNs should be considered a therapeutic failure, and a switch to an alternative antibiotic therapy is required.

Since the publication of the guidelines in 2000, little has changed in the antibiotic recommendations for SBP.[46,47] Indeed, the antibiotic regimen of cefotaxime 2 g every 12 hours, found to be cost-effective in the mid-1990s, continues to be advocated as a regimen of first choice.[46] However, the availability of generic formulations of several cephalosporins suggests that clinicians have other options at their disposal.

Franca et al. examined the efficacy of a short course of ceftriaxone therapy for the management of SBP.[48] Thirty-three patients received ceftriaxone 1 g every 12 hours for five days. The diagnosis of SBP was confirmed on the basis of ascitic fluid PMN counts above 250 cells/mL. Patients received a follow-up diagnostic paracentesis on days 5, 7, 10, and 15 to assess resolution. The infection was considered to have resolved when all signs of infection disappeared and the ascitic fluid PMN count was below 250 cells/mL. SBP resolved after five days of therapy in 73% of patients. Total resolution after prolonged therapy was achieved in 94% of patients. The in-hospital mortality rate was 12%. A companion editorial commented not only on the outstanding efficacy of ceftriaxone but also on the effective strategy using surveillance of ascitic fluid PMN counts to assist in establishing duration of antibiotic therapy.[49]

Angelini and colleagues evaluated the efficacy of ciprofloxacin (Cipro, Bayer) (from IV to oral step-down therapy), compared with ceftazidime in 116 patients with SBP.[50] Ciprofloxacin was given at 200 mg IV twice daily and was changed to 500 mg orally twice daily when clinical signs of infection disappeared. Ceftazidime was administered at a dose of 2 g twice daily. The dose of both antibiotics was adjusted in patients with renal insufficiency. Infection resolved in 80% of patients receiving ciprofloxacin and in 84% receiving ceftazidime. Step-down therapy was achieved in 82% of the patients receiving ciprofloxacin after a mean duration of 5.2 days, and it enabled early discharge from the hospital, or a mean of six fewer days of hospitalization and a mean cost savings of 1,150 Euros (€) (approximately $1,400).

In an effort to validate the recommendations of the International Ascites Group, Angeloni et al. evaluated 38 episodes of SBP in 32 patients.[50] In accordance with the guidelines, patients were treated empirically with cefotaxime at a dose of 2 g every eight hours for a minimum of five days. Patients who did not respond to treatment were switched according to their culture data or empirical results. Cefotaxime was unsuccessful in 41% of the cases, necessitating a switch to an alternative therapy. Culture data were able to be obtained in nine episodes of SBP, four of which were isolates with known resistance to ceftaxime (ESBL-positive *E. coli*, *Enterobacter*, and *Enterococcus*) or insufficient susceptibility (*Staphylococcus aureus*). The investigators suggested that their findings supported the possibility that the microbial etiology of SBP changes over time. Consequently, empirical therapy for SBP might need to be determined by patterns of local bacterial resistance. Therefore, the initial use of third-generation cephalosporins might no longer be optimal.

In 1994, investigators explored the potential emergence of resistance in patients who received prophylaxis with norfloxacin (Noroxin, Merck) 400 mg daily to prevent SBP.[51] After observing quantitative stool cultures in 31 patients, they noted that no resistant organisms were isolated in 15 patients; however, fluoroquinolone-resistant organisms were isolated in 16 patients between days 14 and 43, including *S. aureus*, coagulase-negative *Staphylococcus* spp., *Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca,* and *Proteus rettgeri*. The authors cautioned against routinely giving prophylactic antibiotics to patients with cirrhosis.

Subsequent studies documented the changing epidemiology associated with antibiotic prophylaxis for SBP.[52,53] Yet another study has demonstrated emergence of resistant pathogens over time in patients with SBP, irrespective of antibiotic prophylaxis.[54] In examining two time frames (1991 to 1995 and 1996 to 2000), Singh et al. showed that the incidence of multidrug-resistant organisms in patients with SBP who were admitted to a liver transplant unit increased from 8.3% to 38.5%.[54] Most resistant pathogens (71%) were either ESBL-producing organisms or methicillin-resistant *S. aureus* (MRSA). The researchers noted that asymptomatic colonization of the GI tract with ESBL-producing organisms normally precedes clinical disease; for every clinically overt infection with an ESBL-producing organism, three additional patients have asymptomatic GI tract colonization.[55] With the emergence of resistant gram-positive organisms (MRSA) and of ESBL-producing gram-negative bacteria, it seems prudent to assess patients with SBP for resistant pathogens.

Thus, if patients with SBP who have been previously receiving fluoroquinolone prophylaxis are not responding to therapy after 48 hours, vancomycin (Vancocin, Viro Pharma) should be added.[46] Local epidemiologic findings might also support switching from antibiotics to an agent with activity against ESBL-producing organisms, such as ertapenem (Invanz, Merck) or tigecycline (Tigacil, Wyeth).

The empirical treatment of SBP consists of any of a number of cephalosporins, such as cefotaxime (Claforan), ceftriaxone (Rocephin), ceftizoxime (Cefizox), or amoxicillin–clavulanic acid (e.g., an IV formulation in Europe). Because the relative efficacy of these agents is similar, cost should be the mitigating factor. Caution should be exercised if patients present with SBP and have been receiving prophylactic therapy with a fluoroquinolone. Lack of a response at 48 hours suggests a

potential resistant pathogen such as MRSA or an ESBL-producing organism, and the addition of vancomycin or an alternative therapy is required.

The duration of therapy should be a minimum of five days. For fluoroquinolone-naive patients, switching from parenteral antibiotic therapy to an oral fluoroquinolone usually allows for early discharge from the hospital.

Albumin

Acute renal failure is the single most important predictor of death in patients with SBP. Two studies had shown that plasma volume expansion with colloids decreased the incidence of renal failure in cirrhotic patients undergoing large-volume paracentesis.[56,57] A randomized, controlled study of patients with uncomplicated SBP showed a decreased incidence of renal failure (33% with cefotaxime/albumin vs. 10% with cefotaxime alone) and a decrease in mortality (29% vs. 10%, respectively).[56]

Albumin 1.5 g/kg was administered on the first day, and 1 g/kg was given on the third day. The study has been criticized for not providing details on fluid management in the control group; such information might have influenced the outcome. Patients in the study who were most likely to benefit from albumin had serum bilirubin levels above 4 mg/dL, serum creatinine above 1 mg/dL, and blood urea nitrogen (BUN) concentrations above 30 mg/dL.

This observation was confirmed in a subsequent study.[58] Consequently, albumin should be reserved for this subgroup of patients with SBP. It has also been suggested that the albumin dose be limited to 100 g per dose.[46] Because the study excluded patients with complicated SBP, the benefit of albumin in this group of patients has not been determined. Patients from the community with SBP without compromised renal function and no evidence of encephalopathy should not receive albumin.[46]

Prophylaxis

Antibiotic prophylaxis in patients with cirrhosis is intended to selectively decontaminate the GI tract in order to decrease the risk of SBP. With the advent of resistant organisms associated with prophylaxis, therapy should be reserved only for patients at highest risk of SBP. The three patient populations for whom prophylaxis might be indicated include those with a history of SBP, those presenting with an upper GI hemorrhage, and those with a low total protein level in ascitic fluid.

Patients who have had an episode of SBP have a one-year recurrence rate of 40% to 70% and a one-year mortality rate of 50% to 70%.[46] In the Gines study, norfloxacin 400 mg daily decreased the incidence of SBP from 68% to 20%.[59] Once-weekly ciprofloxacin has also been evaluated but is not considered to be as effective as daily antibiotic therapy.[47] Trimethoprim–sulfamethoxazole (Bactrim, Women First) has been studied in a small number of patients and is equivalent to norfloxacin.[60] Concerns about development of resistance with the use of fluoroquinolones may help make trimethoprim–sulfamethoxazole become a reasonable option for SBP prophylaxis.

Lastly, antibiotic cycling may provide another option for prophylaxis while minimizing risks for resistance, but prospective trials are needed.[61] Prophylaxis should begin after the completion of antibiotic therapy for SBP (norfloxacin 400 mg daily) and should continue until resolution of ascites, liver transplantation, or death.[45]

Patients with cirrhosis who are admitted for upper GI hemorrhage should also receive antibiotic prophylaxis. The incidence of infection in these patients approaches 45%.[46] Further, the development of infection increases the failure to control bleeding, the rate of rebleeding (caused by sepsis-related coagulopathy), and mortality rates.[62–66]

Several studies have documented a decreased incidence of infection with the use of short-term antibiotic prophylaxis.[67–70] Similar to secondary prophylaxis, the drug of choice in setting of upper GI hemorrhage has been norfloxacin 400 mg daily; however, there is increasing concern about the role of fluoroquinolones because of the potential for resistant pathogens.

Fernandez and associates compared norfloxacin with ceftriaxone in the prophylaxis of infection in patients with advanced cirrhosis and GI hemorrhage.[71] Patients who received ceftriaxone had significantly fewer episodes of infection (26% vs. 11% receiving norfloxacin, $P = 0.03$) and fewer episodes of SBP (12% vs. 2%, respectively, $P = 0.03$). There were seven gram-negative bacterial isolates in the norfloxacin group, six of which were quinolone-resistant. The investigators attributed the poor efficacy of norfloxacin to the changing epidemiology of bacterial infections in cirrhosis and to the likely delayed onset of selective intestinal decontamination with oral antibiotic therapy. Local epidemiologic patterns should be considered during the process of selecting prophylactic antibiotics.

Prophylaxis has also been considered for cirrhotic patients with low ascitic fluid total protein levels. In a prospective study, patients with ascitic fluid protein concentrations below 1 g/dL had a higher rate of SBP (20% over a one-year period) than patients with protein concentrations above 1 g/dL (0% over two years).[72] Several early studies examined the potential role of prophylaxis in these patients with low ascitic fluid protein, but results were largely inconclusive and definitive recommendations could not be made.[46]

Another study by Fernandez et al., published in 2007, examined the use of prophylactic norfloxacin 400 mg daily in patients with the following pathology:[73]

- advanced cirrhosis (Child–Pugh score, 9 or above; bilirubin, above 3 mg/dL), or
- impaired renal function (serum creatinine, 1.2 mg/dL or above, blood urea nitrogen, 25 mg/dL or above; or serum sodium, 130 mEq/L or below)
- ascitic fluid protein below 1.5 g/dL

At one year, norfloxacin prophylaxis was associated with a significant decrease in the probability of SBP (7% with norfloxacin vs. 61% with placebo; $P < 0.001$) and in hepatorenal syndrome (28% vs. 41%, respectively, $P = 0.02$) and an improved probability of survival (60% vs. 48%, respectively, $P = 0.05$).

Terg and colleagues conducted a double-blind, randomized study comparing outcomes in cirrhotic patients with ascitic protein concentrations below 1.5 g/dL. Patients received either ciprofloxacin 500 mg daily or placebo.[74] The ciprofloxacin patients had a greater probability of remaining free of bacter-

ial infections (80% vs. 55% receiving placebo, $P = 0.05$) and survival at 12 months (86% vs. 66% with placebo, $P < 0.04$). These studies support the role of fluoroquinolone prophylaxis for low ascitic protein levels (below 1.5 g/dL).

Conclusion

SBP is a common malady in patients with cirrhosis-related ascites, and it often occurs so insidiously that it is sometimes discovered only serendipitously when paracentesis is performed. The ascitic fluid acquired by paracentesis cytologic analysis remains the gold standard for diagnosis, and more than 250 to 500 PMNs/mL is considered pathognomonic for SBP. Because of the low bacterial inoculum found in most of these infections, a special microbiologic procedure, whereby ascitic fluid is collected in a series of 100-mL blood culture bottles, is necessary to improve yields on pathogen identification. Enteric gram-negative rods and streptococci make up the preponderance of SBP pathogens.

Management of SBP consists of several antibiotic options, including cefotaxime and ceftriaxone. Patients should be evaluated after 48 hours to determine whether expanded antibiotic therapy is warranted. Clinicians should also consider local epidemiologic patterns that might suggest a risk of ESBL-producing organisms.

Prophylaxis should be administered to all patients who have had an episode of SBP and to patients admitted to a health center with GI hemorrhage. The data also suggest a role for primary prophylaxis with fluoroquinolones in patients with a low ascitic fluid protein concentration.

References

1. Such J, Runyon A. Spontaneous bacterial peritonitis. *Clin Infect Dis* 1998;27:669–676.
2. Gines P, Arroyo V, Rodes J. Therapy of ascites and spontaneous bacterial peritonitis. *In:* Cohen S, Davis GL, Gianella RA, et al., eds. *Therapy of Digestive Disorders: A Companion to Sleisenger and Fortran's Gastrointestinal and Liver Disease*. Philadelphia: WB Saunders, 2000:373–384.
3. Runyon A. Spontaneous bacterial peritonitis: An explosion of information. *Hepatology* 1988;8:171–175.
4. Navasa M, Follo A, Llovet JM, et al. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. *Gastroenterology* 1996:111:1011–1014.
5. Runyon BA, McHutchinson JG, Antillon MR, et al. Short course vs. long course antibiotic treatment of spontaneous bacterial peritonitis: A randomized controlled trial of 100 patients. *Gastroenterology* 1991;100:1737–1742.
6. Tito L, Rimola A, Gines P, et al. Recurrence of spontaneous bacterial peritonitis in cirrhosis: Frequency and predictive factors. *Hepatology* 1988;8:27–31.
7. Andreu M, Sola, R, Sitges-Serra A, et al. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Gastroenterology* 1993;104:1133–1138.
8. Conn HO, Fessel JM. Spontaneous bacterial peritonitis in cirrhosis: Variations on a common theme. *Medicine* 1971;50:161–197.
9. Pinzello G, Simonetti RG, Craxi A, et al. Spontaneous bacterial peritonitis: A prospective investigation in predominantly nonalcoholic cirrhotic patients. *Hepatology* 1983;3:545–549.
10. Weinstein MP, Iannini PB, Stratton CW, et al. Spontaneous bacterial peritonitis: A review of 28 cases with emphasis on improved survival and factors influencing prognosis. *Am J Med* 1978;64: 592–598.
11. Hoefs JC, Runyon BA. Culture-negative neutrocytic ascites: A variant of spontaneous bacterial peritonitis. *Hepatology* 1984;4: 1209–1211.
12. Runyon BA. Patients with deficient ascitic fluid opsonic activity are predisposed to spontaneous bacterial peritonitis. *Hepatology* 1988; 8:632–635.
13. Fox RA, Dudley FS, Sherlock S. The serum concentrations of the third component of complement in liver disease. *Gut* 1971;12: 574–578.
14. Kourilsky O, LeRoy C, Peltier AP. Complement and liver cell function in 53 patients with liver disease. *Am J Med* 1973;55: 783–790.
15. Rajkovic IA, Williams R. Abnormalities of neutrophil phagocytosis, intracellular killing, and metabolic activity in alcoholic cirrhosis and hepatitis. *Hepatology* 1986;6:252–262.
16. Rimola A, Soto R, Bory F, et al. Reticuloendothelial system phagocytic activity in cirrhosis and its relation to bacterial infections and prognosis. *Hepatology* 1984;4:53–58.
17. Runyon BA. Low-protein-concentration ascitic fluid is predisposed to spontaneous bacterial peritonitis. *Gastroenterology* 1986;91:1343–1346.
18. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the esophagus for bleeding esophageal varices. *Br J Surgery* 1973;60: 646–649.
19. Bandy SM, Tuttle A. Spontaneous bacterial peritonitis. E-medicine from WebMD. Updated July 16, 2008.
20. Runyon BA, Morrisey R, Hoefs JC, et al. Opsonic activity of human ascitic fluid: A potentially important protective mechanism against spontaneous bacterial peritonitis. *Hepatology* 1985;5: 634–637.
21. Kurtz RC, Bronzo RL. Does spontaneous bacterial peritonitis occur in malignant ascites? *Am J Gastroenterol* 1982;77:146–148.
22. Runyon BA. Spontaneous bacterial peritonitis associated with cardiac ascites. *Am J Gastroenterol* 1984;79:796.
23. Llach J, Rimola A, Navasa M, et al. Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: Relevance of ascitic fluid protein concentration. *Hepatology* 1992;16:724–727.
24. Hoefs JC, Canawati HN, Sapico FC, et al. Spontaneous bacterial peritonitis. *Hepatology* 1982;2:399–407.
25. Carey WD, Boayke A, Leatherman J. Spontaneous bacterial peritonitis: Clinical and laboratory features with reference to hospital-acquired cases. *Am J Gastroenterol* 1986;81:1156–1161.
26. Johnson CC, Baldessarre J, Levison ME. Peritonitis: Update on pathophysiology, clinical manifestations, and management. *Clin Infect Dis* 1997;24:1035–1047.
27. Runyon BA, Antillon MR, Akriviadis EA, et al. Bedside inoculation of blood culture bottles with ascitic fluid is superior to delayed inoculation in the detection of spontaneous bacterial peritonitis. *Clin Microbiol* 1990;28:2811–2812.
28. Wong CL, Holroyd-Leduc J, Thorpe KE, et al. Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? *JAMA* 2008;299: 1166–1178.
29. Roberts GH, Ramsey MK. Guidelines for interpretation of the routine urinalysis. *Consultant Pharmacist* 1990;5:748–756.
30. Castellote J, Lopez C, Gornals J, et al. Rapid diagnosis of spontaneous bacterial peritonitis by use of reagent strips. *Hepatology* 2003;37:893–896. Erratum in *Hepatology* 2003;37(6):1503.
31. Vanbiervliet G, Rakotoarisoa C, Filippi J, et al. Diagnostic accuracy of a rapid urine-screening test (Multistix8SG) in cirrhotic patients with spontaneous bacterial peritonitis. *Eur J Gastroenterol Hepatol* 2002;14(11):1257–1260.
32. Butani RC, Shaffer RT, Szyjkowski RD, et al. Rapid diagnosis of infected ascitic fluid using leukocyte esterase dipstick testing. *Am J Gastroenterol* 2004:99:532–537.
33. Sapey T, Mena E, Fort E, et al. Rapid diagnosis of spontaneous bacterial peritonitis with leukocyte esterase reagent strips in a European and American center. *J Gastroenterol Hepatol* 2005;20: 187–192.
34. Runyan BA, Kaplan MM, Bonis PAL. Diagnosis of spontaneous bacterial peritonitis. UpToDate.com. Available at: www.uptodate.com. May 28, 2008.
35. Nguyen-Khac E, Cadranel JF, Thevenot T, Nousbaum J-B. Review

article: Utility of reagent strips in diagnosis of infected ascites in cirrhotic patients. *Aliment Pharmacol Ther* 2008;28:282–288.
36. Akriviadis EA, Runyon BA. Utility of an algorithm in differentiation spontaneous from secondary bacterial peritonitis. *Gastroenterology* 1990;98:127–133.
37. Garrison RN, Cryer HM, Howard DA, et al. Clarification of risk factors for abdominal operations in patients with hepatic cirrhosis. *Ann Surg* 1984;199:648–655.
38. Bhuva M, Ganger D, Jensen D. Spontaneous bacterial peritonitis: An update on evaluation, management, and prevention. *Am J Med* 1994;97:169–175.
39. Scheckman P, Onderdonk AB, Bartlett JG. Anaerobes in spontaneous peritonitis (letter). *Lancet* 1977;2:1223.
40. Felisart J, Rimola A, Arroyo V, et al. Cefotaxime is more effective than is ampicillin–tobramycin in cirrhotics with severe infections. *Hepatology* 1985;5:457–462.
41. Rimola A, Salmeron JM, Clemente G, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: Results of a prospective, randomized, multicenter study. *Hepatology* 1995;21:674–679.
42. Mercader J, Gomez J, Ruiz J, et al. Use of ceftriaxone in the treatment of bacterial infections in cirrhotic patients. *Chemotherapy* 1989;35:23–26.
43. Gomez-Jimenez J, Ribera E,Gasser I, et al. Randomized trial comparing ceftriaxone with cefonicid for treatment of spontaneous bacterial peritonitis in cirrhotic patients. *Antimicrob Agents Chemother* 1993;37:1587–1592.
44. Mesquita MA, Balbino EPS, Albuquerque RS, et al. Ceftriaxone in the treatment of spontaneous bacterial peritonitis: Ascitic fluid polymorphonuclear count response and short-term prognosis. *Hepatogastroenterology* 1997;44:1276–1280.
45. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: A consensus document. *J Hepatol* 2000;32:142–153.
46. Ghassemi H, Garcia-Tsao G. Prevention and treatment of infections in patients with cirrhosis. *Best Pract Res Clin Gastroenterol* 2007;21:77–93.
47. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis and multiorgan failure in cirrhosis. *Semin Liver Dis* 2008;28:26–42.
48. Franca AVC, Giordano HM, Seva-Pereira T, Soares EC. Five days of ceftriaxone to treat spontaneous bacterial peritonitis in cirrhotic patients. *J Gastroenterol* 2002;37:119–122.
49. Suzuki K, Takikawa Y. Marked improvement in the resolution of, and survival rates in, spontaneous bacterial peritonitis (editorial). *J Gastroenterol* 2002;37:149–150.
50. Angeloni S, Leboffe C, Parente A, et al. Efficacy of current guidelines for the treatment of spontaneous bacterial peritonitis in the clinical practice. *World J Gastroenterol* 2008;14:2757–2762.
51. Dupeyron C, Mangeney N, Sedrati L, et al. Rapid emergence of quinolone resistance in cirrhotic patients treated with norfloxacin to prevent spontaneous bacterial prophylaxis. *Antimicrob Agents Chemo* 1994;38:340–344.
52. Campillo B, Dupeyron C, Ricardet J-P, et al. Epidemiology of severe hospital-acquired infections in patients with liver cirrhosis: Effects of long-term administration of norfloxacin. *Clin Infect Dis* 1998;26:1066–1070.
53. Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: Epidemiologic changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002;35:140–148.
54. Singh N, Wagener MM, Gayowski T. Changing epidemiology and predictors or mortality in patients with spontaneous bacterial peritonitis at a liver transplant unit. *Clin Microbiol Infect* 2003;9:531–537.
55. Patterson DL, Mudder RR, Squier C, et al. Outbreak of infection with *E. coli* harboring extended-spectrum beta-lactamase (ESBL) in a liver transplant unit: Could norfloxacin administration to carriers contribute to control? *Clin Infect Dis* 2001;33:126–128.
56. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403–409.
57. Gines P, Guevara M, De Las Heras D, Arroyo V. Review article: Albumin for circulatory support in patients with cirrhosis. *Aliment Pharmacol Ther* 2002(16 Suppl 5):24–31.
58. Sigal SH, Stanca CM, Fernandez J, et al. Restricted use of albumin for spontaneous bacterial peritonitis. *Gut* 2007;56:597–599.
59. Gines P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: Results of a double-blind, placebo-controlled trial. *Hepatology* 1990;12:716–724.
60. Lontos S, Gow PJ, Vaughan RB, Angus PW. Norfloxacin and trimethoprim–sulfamethoxazole have similar efficacy in the prevention of spontaneous bacterial peritonitis. *Hepatology* 2008; 23:252–255.
61. Assy N, Schlessinger S, Miron D, Hussein O. Cycling of antibiotics for the prophylaxis of recurrent spontaneous bacterial peritonitis in a cirrhotic patient. *World J Gastroenterol* 2005;11: 6407–6408.
62. Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1998; 27:1207–1212.
63. Vivas S, Rodríguez M, Palacio MA, et al. Presence of bacterial infection in bleeding cirrhotic patients is independently associated with early mortality and failure to control bleeding. *Dig Dis Sci* 2001;46:2752–2757.
64. Bernard B, Cadranel JF, Valla D, et al. Prognostic significance of bacterial infection in bleeding cirrhotic patients: A prospective study. *Gastroenterology* 1995;108:1828–1834.
65. Pohl J, Pollmann K, Sauer P, et al. Antibiotic prophylaxis after variceal hemorrhage reduces incidence of early rebleeding. *Hepatogastroenterology* 2004;51:541–546.
66. Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. *Cochrane Database Syst Rev* 2002;CD002907.
67. Rimola A, Bory F, Teres J, et al. Oral, non-absorbable antibiotics prevent infection in cirrhotics with gastrointestinal hemorrhage. *Hepatology* 1985;5:463–467.
68. Soriano G, Guarner C, Tomas A, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. *Gastroenterology* 1992;103:1267–1272.
69. Blaise M, Pateron D, Trinchet JC, et al. Systemic antibiotic therapy prevents bacterial infection in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1994;20:34–38.
70. Hsieh WJ, Lin HC, Hwang SJ, et al. The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. *Am J Gastroenterol* 1998; 93:962–966.
71. Fernandez J, Ruiz del Arbol L, Gomez C, et al. Norfloxacin vs. ceftriaxone in the prophylaxis of infection in patients with advanced cirrhosis and hemorrhage. *Gastroenterol* 2006;131: 1049–1056.
72. Llach J, Rimola A, Navasa M, et al. Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: Relevance of ascitic fluid protein concentration. *Hepatology* 1992;16:724–727.
73. Fernandez J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007;133: 818–824.
74. Terg R, Fassio E, Guevara M, et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: A randomized, placebo-controlled study. *J Hepatol* 2008;48:774–779. ■

Conflict of Interest (COI) Statement

The authors have no relationships to disclose. This article contains discussion of off-label use. The content of this article has been reviewed under Jefferson's Continuing Medical Education COI policy.