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PREVENTION OF COMPLICATIONS WITH SPONTANEOUS BACTERIAL PERITONITIS WITH LIVER CIRRHOSIS OF VIRAL ETIOLOGY

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Abstract
Spontaneous bacterial peritonitis (SBP) is defined as a bacterial infection of the ascitic fluid without a surgically treatable intra-abdominal infection source. SBP is a common, severe complication in cirrhosis patients with ascites, and if left untreated, in-hospital mortality may exceed 90%. However, the incidence of SBP has been lowered to approx. 20% through early diagnosis and antibiotic therapy. Clinical awareness, prompt diagnosis, and immediate treatment are advised when caring for these patients to reduce mortality and morbidity.

Keywords: Cirrhosis, infection, spontaneous bacterial peritonitis, multidrug-resistant bacteria, antibiotics.

Introduction

Among persons with ascites who have been followed for a year, spontaneous bacterial peritonitis (SBP) develops in approximately 10 to 30% and has an estimated in-hospital mortality rate of 20% [1,2,3]. Among persons with cirrhosis, the prevalence of SBP is 1.5 to 3.5% in an outpatient setting and approximately 10% in an inpatient setting. In most instances, SBP results from translocation of bacteria from the intestinal lumen [4,5]. Less often, SBP results from bacteremia that originates at a distant site, such as a urinary tract infection. The majority of cases of SBP are caused by gram-negative enteric organisms, such as Escherichia coli and Klebsiella pneumoniae, but in recent years the proportion of SBP caused by gram-positive cocci, such as Streptococcus pneumoniae, Staphylococcus species, and Enterococcus species, has increased significantly [1,7]. Risk factors associated with the development of SBP include cirrhosis, ascitic fluid total protein less than 1 g/dL, total serum bilirubin greater than 2.5 mg/dL, variceal hemorrhage, and a previous episode of SBP [9,10]. The use of proton pump inhibitors may slightly increase the risk of developing SBP in persons with cirrhosis and ascites; therefore, in this setting, proton pump inhibitors should be prescribed only in persons who have a clear indication.

In a person with ascites, the presence of new-onset fever (temperature greater than 37.8°C or 100°F), abdominal pain, hepatic encephalopathy, metabolic acidosis, renal failure, hypotension, diarrhea, paralytic ileus, hypothermia, leukocytosis, or other signs or symptoms of infection should prompt a diagnostic paracentesis for ascitic fluid analysis and culture [14]. Approximately 13% of individuals with SBP present without any symptoms. For persons with cirrhosis and ascites who are admitted to the hospital, approximately 10 to 15% have evidence of SBP [15]. Thus, all persons

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with cirrhosis and ascites should undergo a diagnostic paracentesis at the time of hospital admission [14]. In addition, paracentesis should be repeated in persons who develop signs or symptoms of infection. There is no need for transfusion of plasma or platelets prior to a diagnostic paracentesis, given the extremely low risk of hemorrhagic complications, except in the setting of disseminated intravascular coagulation or clinically apparent hyperfibrinolysis [16,17,18].

Cirrhotic patients have an altered defense against bacteria associated with reduced bacterial clearance [1]. This immune defect facilitates bacterial translocation induced by increased intestinal permeability and gut bacterial overgrowth [2]. Therefore, bacterial infection is either present on admission or develops during hospitalization in about 30% of patients with cirrhosis, and the most common form of these infections is spontaneous bacterial peritonitis (SBP) [3].

SBP is diagnosed upon positive ascites culture and/or absolute neutrophil count (polymorphonuclear cell or PMN) within ascites fluid (AF) of ≧250 cells/mm3 [7,8]. Diagnosis is distinct from secondary peritonitis and hence is made in the absence of an intra-abdominal source of infection or other causes of an elevated ascites neutrophil count, such as hemorrhage, pancreatitis, peritoneal tuberculosis, and carcinomatosis [7], or an evident intra-abdominal, surgically treatable source [9,10].

Materials and Methods

This article aims to help clinicians and other healthcare professionals in reviewing, studying, and assisting with the management of SBP patients. Key terms in our search include SBP, bacterial peritonitis, antibiotics, antibiotic resistance, ascites, paracentesis, microbiology, treatment, and prophylaxis. Randomized controlled trials and meta-analyses conducted for the treatment of SBP were also identified.

The 2013 American Association for the Study of Liver Diseases (AASLD) guidelines on the management of adult patients with ascites due to cirrhosis suggests antibiotic therapy for patients with an AF PMN count of ≧250 cells/mm3 or <250 cells/mm3 but with signs of infection [8]. This recommendation implies that all three types of SBP warrant immediate treatment once symptoms become known.

BACTERIAL CULTURE

Prior to administering antibiotics, ascitic fluid (at least 10 mL) should be obtained and then directly inoculated into a blood culture bottle at the bedside, instead of sending the fluid to the laboratory in a syringe or container, since immediate inoculation improves the yield on bacterial culture from approximately 65 to 90%, when the ascitic fluid cell count is at least 250 cells/mm3 (0.25 × 109/L) [14,20,21]. Separate and simultaneous blood cultures should also be obtained, as up to 50% of persons with SBP have concomitant bacteremia.

CRITERIA FOR TREATMENT

Individuals with suspected spontaneous bacterial peritonitis (SBP) and ascitic fluid PMN greater than or equal to 250 cells/mm3 (0.25 × 109/L) should promptly receive empiric antibiotic therapy. Further, persons with culture-negative neutrocytic ascites have similar mortality rates as persons with culture-positive spontaneous bacterial peritonitis and benefit from antibiotic treatment, which should not be delayed while awaiting bacterial culture results (Figure 2) [14,19]. Antimicrobial

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therapy should be given as soon as ascitic fluid has been obtained for culture and should not be delayed while awaiting culture results.

TREATMENT REGIMENS

Broad-spectrum antibiotic therapy is recommended for treatment of proven or suspected SBP and may be narrowed when susceptibility results become available [1,14]. Studies have demonstrated resistance rates of approximately 30% in gram-negative infections to fluoroquinolones and trimethoprim-sulfamethoxazole, with particularly high rates in persons who have received fluoroquinolone prophylaxis; on the other hand, more than 90% of isolates in persons who have received fluoroquinolone prophylaxis still remain susceptible to cefotaxime. Extended-spectrum antibiotics, such as carbapenems, may even be considered in nosocomial cases. The choice of treatment will depend on location of acquisition (community versus nosocomial), local resistance patterns, and culture sensitivity results when available. The following summarizes recommended and commonly used antimicrobial regimens to treat SBP [14].

Cefotaxime: Intravenous cefotaxime administered 2 grams every 8 hours (or similar third-generation cephalosporin) for a total course of 5 days is the treatment of choice for SBP, as it achieves excellent ascitic fluid levels covers the most common causative microorganisms: Escherichia coli, Klebsiella pneumoniae, and Streptococcus pneumonia [17]. Cefotaxime has been shown to be successful in treating SBP in 77 to 98% of cases [18,19].

Ceftriaxone: Intravenous ceftriaxone 1 gram every 12 hours or 2 grams every 24 hours for 5 days can be used in place of cefotaxime [12,13].

Ciprofloxacin: In a randomized trial involving adults diagnosed with SBP, intravenous ciprofloxacin 200 mg every 12 hours for 2 days, followed by oral ciprofloxacin (500 mg PO every 12 hours for 5 days) was effective and more cost-effective than intravenous ceftazidime; participants were excluded from the trial if they were receiving a fluoroquinolone for SBP prophylaxis [16]. Fluoroquinolones should not be used to treat SBP in persons taking a fluoroquinolone for SBP prophylaxis.

Ofloxacin: Oral ofloxacin 400 mg orally twice a day for an average of 8 days was shown in one randomized, controlled trial to be as effective as intravenous cefotaxime for individuals hospitalized with SBP who do not have vomiting, shock, grade II or greater hepatic encephalopathy, or serum creatinine greater than 3 mg/dL [20]. Further trials are needed before ofloxacin can be recommended as an outpatient therapy for SBP. In addition, fluoroquinolones should not be used to treat SBP in any setting when a person is taking a fluoroquinolone for SBP prophylaxis.

Beta-Lactam Hypersensitivity: Intravenous ciprofloxacin 400 mg every 12 hours or intravenous levofloxacin 750 mg every 24 hours can be used in persons with a beta-lactam allergy, but should be avoided in those who have been receiving a fluoroquinolone for SBP prophylaxis [17].

INDICATIONS FOR SPONTANEOUS BACTERIAL PERITONITIS PROPHYLAXIS

Most episodes of SBP are thought to result from bacterial translocation from the gut [4,5,6]. Given the risk of resistance and alteration of gut flora, this long-term antibiotic prophylaxis should be reserved only for persons at high risk of developing SBP. Identified risk

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factors for the development of SBP include ascitic fluid total protein less than 1 g/dL, a history of gastrointestinal hemorrhage, and a previous history of SBP.

PRIMARY PROPHYLAXIS OF SPONTANEOUS BACTERIAL PERITONITIS

Persons with cirrhosis who have with low-protein ascites (less than 1.0 g/dL) and either impaired renal or liver function are at increased risk of developing SBP [14]. Although controversy exists regarding the use of prophylactic antibiotics in persons without and prior history of SBP (primary prophylaxis), in one randomized trial, daily oral norfloxacin in persons with more advanced liver disease prevented the development of spontaneous bacterial peritonitis and hepatorenal syndrome and improved survival at 3 months when compared with those who received placebo [20]. The American Association for the Study of Liver Diseases (AASLD) guidelines suggest using long-term antibiotic prophylaxis in persons who have 194scetic fluid total protein less than 1.5 g/dL and at least one of the following: impaired renal function (serum creatinine greater than or equal to 1.2 mg/dL, blood urea nitrogen greater than or equal to 25 mg/dL, or serum sodium less than or equal to 130 mEq/L), or liver failure (Child-Turcotte-Pugh greater than or equal to 9 points and total bilirubin greater than or equal to 3 mg/dL) [14]. Accordingly, most experts recommend daily long-term antimicrobial prophylaxis for persons with a history of one or more episodes of SBP.

Several studies have shown that oral norfloxacin 400 mg daily prevents SBP in persons with low-protein ascites and those with previous history of SBP [15]. Alternative regimens that have been studied include oral double-strength trimethoprim-sulfamethoxazole 5 doses per week or oral ciprofloxacin 750 mg once a week [20,21]. Prolonged use antibiotic prophylaxis in this setting has led to the development of gram-negative bacterial resistance (to fluoroquinolones and trimethoprim-sulfamethoxazole), as well as an increased likelihood of developing gram-positive infections [18]. Therefore, prophylaxis should be reserved for persons at high risk of developing SBP and daily dosing regimens are preferred. Daily long-term dosing with norfloxacin has proved superior to hospital-only administration of norfloxacin in the prevention of the first episode of SBP in persons with cirrhosis who have a serum total bilirubin greater than 2.5 mg/dL or ascitic fluid protein less than or equal to 1.5 g/dL [19]. The preferred prophylaxis regimen has been oral norfloxacin 400 mg daily, but given that norfloxacin is no longer available in the United States, reasonable alternatives include trimethoprim-sulfamethoxazole one double-strength tablet daily, oral ciprofloxacin 500 mg daily, or oral levofloxacin 250 mg daily [14].

Conclusion

High-risk patients must be treated for infections in a more aggressive way. Patients with cirrhosis who are infected, especially those with SBP, should be treated promptly and properly. Infections caused by MDR bacteria should be a current concern, and new antibiotic strategies are needed for this special population. Individualized antibiotic treatment based on local epidemiology is the key for success, not neglecting the urge to preserve renal function of these complex patients. It is important to keep pursuing new forms of prophylaxis against SBP, so that, in the future, antibiotics might no longer be necessary in this context, decreasing the risk of development of MDR bacteria.

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