

Efficacy of current guidelines for the treatment of spontaneous bacterial peritonitis in the clinical practice

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evaluating its efficacy. The initial treatment with cefotaxime failed more frequently than expected. An increase in healthcare-related infections with antibiotic-resistant pathogens may explain this finding. A different first-line antibiotic treatment should be investigated.

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Key words: Spontaneous bacterial peritonitis; Cefotaxime; Antibiotic-resistant pathogens; Ascitic polymorphonuclear count; Cirrhosis

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Abstract

AIM: To verify the validity of the International Ascites Club guidelines for treatment of spontaneous bacterial peritonitis (SBP) in clinical practice.

METHODS: All SBP episodes occurring in a group of consecutive cirrhotics were managed accordingly and included in the study. SBP was diagnosed when the ascitic fluid polymorphonuclear (PMN) cell count was > 250 cells/mm³, and empirically treated with cefotaxime.

RESULTS: Thirty-eight SBP episodes occurred in 32 cirrhotics (22 men/10 women; mean age: 58.6 ± 11.2 years). Prevalence of SBP, in our population, was 17%. Ascitic fluid culture was positive in nine (24%) cases only. Eleven episodes were nosocomial and 71% community-acquired. Treatment with cefotaxime was successful in 59% of cases, while 41% of episodes required a modification of the initial antibiotic therapy because of a less-than 25% decrease in ascitic PMN count at 48 h. Change of antibiotic therapy led to the resolution of infection in 87% of episodes. Among the cases with positive culture, the initial antibiotic therapy with cefotaxime failed at a percentage (44%) similar to that of the whole series. In these cases, the isolated organisms were either resistant or with an inherent insufficient susceptibility to cefotaxime.

CONCLUSION: In clinical practice, ascitic PMN count is a valid tool for starting a prompt antibiotic treatment and

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INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a frequent and severe complication of cirrhotic patients with ascites^[1]. It is defined as an infection of ascites in the absence of a contiguous source of infection, such as abdominal abscesses or intestinal perforations.

The prevalence of SBP in unselected, hospitalized, cirrhotic patients with ascites has been reported to range between 10% and 30%^[1,2-6]. Following the first episode of SBP, the cumulative recurrence rate within one year of follow up is approximately 70%^[7].

In an initial series published in the 1970s, when SBP was first described, the mortality rate associated with an episode of SBP exceeded 80%^[8]. This short-term prognosis has, however, considerably improved during the last decades. In more recent prospective studies, in fact, the mortality rate related to this complication was estimated to be around 20%-30%^[9-11]. An early diagnosis and the promptness of an effective therapy are the most likely rea-

sons for this improvement in prognosis.

Symptoms of SBP may be insidious; in addition, by using conventional culture techniques, the ascitic fluid culture outcome is negative in up to 60% of patients with SBP. Since a rapid diagnosis and an early treatment have a crucial role, the antibiotic treatment cannot, therefore, be delayed to the moment when the microbiological results are available^[12,13].

In 2000, the International Ascites Club published the guidelines for the diagnosis and treatment of SBP in cirrhotic patients^[12]. These guidelines suggested that a diagnosis of SBP should be based on polymorphonuclear (PMN) cell count in the ascitic fluid and that a PMN cell count greater than 250 cells/mm³ should be considered highly suspicious of SBP, thus representing an indication to empirically initiate an antibiotic treatment. The gold standard treatment consists of third-generation cephalosporins, especially cefotaxime, given intravenously at a dose of 4-8 g/d for a minimum duration of 5 d. A repeat diagnostic paracentesis to document the response by a greater-than 25% decrease in ascitic fluid neutrophil count at 48 h after initiation of antibiotics is recommended. With this regimen, resolution of SBP is achieved in approximately 90% of patients and 30-d survival is at least 80%^[12]. This recommendation is, however, based on the results of randomized controlled trials and its validity and applicability need to be verified in the clinical practice. Moreover, there have been suggestions that the type and etiology of bacterial infections in cirrhosis may have changed during recent years^[14,15]. An increasing incidence of SBP caused by Gram-positive bacteria in cirrhotic patients with ascites has been observed by different authors^[16,17]. In addition, an increased frequency of bacteria resistant to multiple antibiotics has been shown^[18]. This may be due to the extensive use of quinolones, and, in particular, to the employment of norfloxacin for SBP prophylaxis, as well as an increasing use of invasive procedures for the complications of cirrhosis.

The recent changes in its microbial etiology may have several important implications for the management and treatment of SBP and suggest the need for verifying the efficacy of current guidelines.

The aim of our study was, therefore, to verify validity, applicability, and efficacy of the International Ascites Club guidelines for the treatment of SBP and assess the results of such approach in an unselected group of consecutive cirrhotic patients with SBP admitted to our Gastroenterology Unit during a three-year period (January 2004-January 2007).

MATERIALS AND METHODS

Materials

All the episodes of SBP occurring in cirrhotic patients admitted to our Gastroenterology Unit from January 2004 to January 2007 were managed according to the International Ascites Club guidelines^[12] and included in the study.

The diagnosis of liver cirrhosis was based on clinical, biochemical, and/or histopathological data. The severity

of the liver disease was classified in each patient at entry according to the Child-Pugh's^[19] and the model for end-stage liver disease's (MELD) scores^[20]. The MELD score was assessed using the Mayo Clinic website calculator. The main cause of admission was recorded for each patient.

According to our routine clinical practice, a detailed medical history, a complete physical examination, standard laboratory tests (including a complete blood cell count, prothrombin time, biochemical tests of liver and kidney function, and fresh urine sediment), a chest x-ray film, a diagnostic paracentesis, and an ascitic fluid culture were performed in all the cirrhotic patients with ascites on the day of admission and whenever they developed symptoms and signs suspicious for SBP (i.e. fever, change in mental status, abdominal pain, peripheral leukocytosis, development of renal failure, hypotension, *etc.*) during hospitalization. In some patients re-admitted for recurrent ascites, a diagnostic paracentesis was also repeated.

The ascitic fluid samples were collected under aseptic conditions in tubes containing ethylenediamine tetraacetic acid anticoagulant and then tested to determine white blood cell (WBC) and PMN counts by automated cell blood counter (Technicon System H*1; Bayer Diagnostics, Milan, Italy), as described elsewhere^[21]. All the specimens were analyzed within one hour. Additional samples of ascitic fluid were collected for the determination of glucose, albumin, and total protein concentrations. Moreover, 10 mL of ascitic fluid were inoculated directly at the patient's bedside into aerobic and anaerobic blood culture bottles for bacteriological examination^[22]. Bacterial identification and antimicrobial susceptibility testing were carried out by the VITEK2 system (bioMérieux SA, Marcy-l'Etoile, France). Double-disk synergy tests were used for the confirmation of extended-spectrum-lactamase (ESBL) producers.

Patients' management

Those patients with a diagnosis of SBP (when the PMN cell count in the ascitic fluid was greater than 250 cells/mm³) were included in the study. Those with bacteriascites (i.e. positive ascitic fluid culture with < 250 neutrophils/mm³) or with clinical and laboratory data suggesting secondary peritonitis were excluded. All the patients were managed according to the International Ascites Club guidelines^[12]. SBP was empirically treated with third-generation cephalosporins (intravenous cefotaxime, 2 g/8 h, for a minimum of 5 d), regardless of the positivity of the culture. The antibiotic dosage was adjusted to the renal function throughout the treatment period.

In those cases not responding to the initial antibiotic regimen, the therapy was appropriately changed, either according to the *in vitro* susceptibility of the isolated bacteria, or empirically. For this purpose, a further paracentesis was always performed 2 d after the beginning of the antibiotic treatment. Treatment failure was established when the condition of the patients rapidly deteriorated within the first hour of the antibiotic therapy (i.e. with development of shock), or when no significant decrease in the ascitic PMN count was observed in the follow-up paracentesis. A reduction in the PMN count of

less than 25% as compared with the pre-treatment value was considered as suggestive of failure of the antibiotic treatment.

Clinical signs and symptoms of infection (fever, abdominal pain, mental status change, hypotension, *etc.*) were recorded daily. Arterial pressure, heart rate, body temperature, and weight were measured daily. WBC count, serum urea, creatinine, and sodium levels were determined before the initiation of treatment, every 2 d during treatment, and 24 h after therapy completion.

Diuretics were routinely withdrawn at the time of diagnosis of SBP and therapeutic paracenteses were not allowed until the resolution of infection.

SBP was considered resolved when all the clinical signs of infection disappeared, the PMN count in the ascitic fluid decreased to less than 250 cells/mm³, total and differential WBC count normalized, and blood and ascitic fluid cultures were negative.

If signs or symptoms of infection developed after discontinuation of antibiotics, a paracentesis for PMN cell count was also repeated.

SBP was considered as "community-acquired" when it was present at admission, and as "nosocomial" when it developed during hospitalization in patients with a normal ascitic fluid at admission^[14].

SBP-related mortality was defined as a death caused by bacterial infection of the ascitic fluid, with clinical and bacteriologic evidence of uncontrolled infection.

After discharge from the hospital, most of the patients were followed as outpatients for continued care. All were prescribed norfloxacin for prophylaxis of SBP recurrence.

Statistical analysis

Results are expressed as mean \pm SD. The differences between groups were determined by student's *t* test. The chi-square test was used when appropriate to determine the differences in proportions. The independent role of factors selected by the univariate analysis was assessed by stepwise regression analysis. The statistical significance was established at a *P* value of less than 0.05. Calculations were performed by using a statistical software program (Number Cruncher Statistical System 97, Kaysville, Utah, USA).

RESULTS

From January 1, 2004 through December 31, 2006, 38 consecutive episodes of SBP occurred in 32 cirrhotic patients with ascites (22 men and 10 women, mean age 58.6-11.2 years) hospitalized in our Gastroenterology Unit.

In the same period, a total of 228 diagnostic paracenteses were performed in 129 cirrhotic patients with ascites consecutively admitted to our Unit. The prevalence of SBP, in our patient population, was therefore calculated as 17%.

Demographic and clinical characteristics of our patient population are reported in Table 1. The etiology of cirrhosis was alcoholic in 13 (41%) cases. All the patients had advanced cirrhosis with high serum bilirubin (9.5-10.5 mg/dL), low prothrombin activity (57%-18.8%), and high Child-Pugh's (10.2-1.9) and MELD's (19.4-8.5) scores.

SBP presented without symptoms and signs in most

Table 1 Demographic, clinical, and biochemical characteristics of the patients (mean \pm SD)

	Patients
<i>n</i>	32
Age (yr)	58.6 \pm 11.2
Gender (male/female)	22/10
Alcoholic origin (yes/no)	13/19
MELD score	19 \pm 9
Child-Pugh class (A/B/C)	0/11/21
Bilirubin (mg/dL)	9.5 \pm 10.5
Albumin (g/dL)	2.6 \pm 0.5
Prothrombin time (%)	55.7 \pm 18.8
Creatinine (mg/dL)	1.3 \pm 0.5
Serum sodium (mEq/L)	133.4 \pm 5.4
WBC (mm ³)	8867.1 \pm 6504

cases: at the time of hospital admission, fever was present in 12 cases, abdominal pain in six, and blood leukocyte counts were higher than 10 000/mm³ in only 11 cases. At hospitalization, renal failure was recorded in 14 (37%) cases and hepatic encephalopathy in eight (21%).

In 16 of the 38 episodes, the presence of a risk factor for SBP occurrence was identified: there were seven cases with a previous episode of SBP (six of them were receiving antibiotic prophylaxis for SBP at inclusion), three patients had gastrointestinal bleeding, and six had undergone invasive procedures.

The ascitic fluid culture was positive in only nine (24%) of the 38 SBP episodes. The isolated organisms were Gram-negative bacilli in five cases (two *E. coli*, two *Klebsiella pneumoniae*, and one *Enterobacter*) and Gram-positive cocci in four (two *Enterococcus* species, one *Staphylococcus aureus*, and one *Streptococcus viridans*).

Eleven (29%) episodes were nosocomial and 71% were community-acquired. There was no significant difference in terms of resolution of infection and mortality between these two sub-groups.

Cefotaxime was used as an initial empirical therapy in 29 cases. In the remaining nine cases, a different antibiotic therapy was started for the following reasons: five developed SBP despite the antibiotic treatment with cephalosporins initiated for other reasons (i.e. as a prophylaxis before an invasive procedure or for bleeding), and four patients were allergic to cephalosporins. These nine patients were included only in the analysis for the identification of predictors of mortality.

The treatment was successful in 17 of the 29 episodes initially treated with cefotaxime (59%), while in 12 (41%) episodes the initial antibiotic therapy with cefotaxime was changed because of a less-than 25% decrease in the ascitic fluid of PMN cell count at paracentesis performed after 48 h. In these patients, the antibiotic therapy was changed to imipenem-cilastatin in six cases, piperacillin-tazobactam in two, ampicillin-sulbactam in two and amoxicillin-clavulanic acid in one. The last patient died 48 h after the beginning of the antibiotic therapy. In five cases, a further change in the antibiotic treatment was necessary.

Among the nine episodes of SBP in whom the culture of ascitic fluid was positive, the initial antibiotic therapy

with cefotaxime failed in four cases, a percentage (44%) similar to that of the whole series. In these four episodes, the isolated organisms were either resistant to cefotaxime (ESBL-positive *E. coli*, *Enterobacter*, and *Enterococcus*), or had an inherent insufficient susceptibility to cefotaxime (*Staphylococcus aureus*).

SBP resolved in 26/29 episodes initially treated with cefotaxime, while three patients died with signs of active infection. Two further deaths due to SBP occurred among the nine patients not treated initially with cefotaxime. At multivariate analysis, the only variables that showed an independent relationship with mortality for SBP were the presence, at entry, of renal failure (defined as an increase in serum urea and/or creatinine to greater-than 30 mg/dL or 1.2 mg/dL respectively) and a mean arterial pressure < 70 mmHg (R-squared = 0.35).

DISCUSSION

The aim of our study was to verify the validity, applicability, and efficacy of the guidelines proposed in 2000 by the International Ascites Club for the treatment of SBP. The applicability in the clinical practice of a guideline derived from randomized controlled investigations is very important. Moreover, such analysis is also justified by the evidence that the type and etiology of bacterial infections in cirrhosis may have changed during recent years^[14-18]. For this purpose, the results of patients' management according to these guidelines were evaluated in an unselected group of cirrhotic patients with SBP consecutively observed in the last three-year period.

Our study suggests that, in clinical practice, an approach to SBP based on ascitic fluid PMN cell count is correct and valid for starting the antibiotic treatment and evaluating its efficacy as well. On the other hand, the suggestion of using third-generation cephalosporins (cefotaxime) as the first-line antibiotic treatment is not equally valid, since a switch to another antibiotic was necessary in more than 40% of our cases.

Infections may frequently occur in patients with liver cirrhosis, especially when decompensated, and may be a cause of death *per se*; but, they can also act as a trigger for a number of severe complications, such as hepatic encephalopathy and renal failure^[23]. Moreover, infection has been related to variceal bleeding both in terms of pathogenesis of portal pressure increment and severity of bleeding episodes^[24,25], since the related mortality was reduced by prompt antibiotic therapy^[26]. SBP is one of the most frequent infections in patients with cirrhosis^[6]. Fever, leukocytosis, and abdominal symptoms are rare (recorded in 20% only of our series); the identification of the infection of ascitic fluid is, therefore, based only on the result of the diagnostic paracentesis. A PMN cell count > 250 cell/mm³ has been proposed as the most important parameter for the diagnosis of SBP, as we isolated responsible bacteria in the ascitic fluid culture very infrequently (recorded in only 24% of the episodes observed in our cohort). The low proportion of positive ascitic fluid cultures is probably due to the relatively low concentration of bacteria in the ascitic fluid as compared with the infections in other organic flu-

ids (e.g. urine)^[12]. For the same reason, a therapy based on the isolation of the responsible bacteria is seldom achievable and the antibiotic treatment cannot be delayed to the moment when microbiological results are available^[12,13]. In these conditions, the efficacy of the empiric antibiotic treatment can rarely be based on the amelioration of the symptoms or on microbiological results. Therefore, a reduction of PMN cell count below 250 cell/mm³ or of 25% of the initial value has been suggested as the main criterion for establishing the efficacy of the antibiotic and the need for switching the therapy. Our study confirms the validity of such an approach. Based on PMN cell count, we were, in fact, able to identify the failure of the initial therapy on time, and the consequent change of the antibiotic therapy allowed us to control the infection in the majority of cases, with in-hospital mortality rate of less than 15%. This result is similar to that reported in the literature and is particularly good when considering the severe conditions of our patients.

In our study, the presence of arterial hypotension or renal failure at admission was the only independent predictor of mortality for SBP. To our knowledge, this observation is similar to the findings of other studies^[27]. According to the 2000 Ascites Club guidelines the use albumin, as suggested by the paper of Sort *et al*^[28], was not included in our protocol for SBP management. Even the most recent guidelines for the prevention and treatment of HRS^[29] suggest that albumin administration may reduce the incidence of renal failure and mortality in patients with SBP, but recommended further studies to define the optimal doses and the subgroup of patients for whom albumin is highly indicated. In our study, renal dysfunction was independently related with mortality and this finding supports the importance of improving the systemic hemodynamics and, thus, of renal function during the treatment of SBP.

According to the PMN cell count carried out at 48-h diagnostic paracentesis, cefotaxime-suggested as the first-line empiric antibiotic treatment—failed in more than 40% of SBP episodes. The need for changing antibiotic treatment is higher than that reported in previous studies^[30-35].

Although the cases with a positive culture were few (only 9 out of 29 patients), in these episodes the percentage of treatment failure of the initial therapy with cefotaxime was similar to that of the entire series (44%). In these patients, cefotaxime failed because the isolated organisms were intrinsically resistant to cefotaxime (as enterococci) or capable of degrading the expanded-spectrum cephalosporins (as ESBL-producing *E. coli* or Amp C β -lactamase producing *Enterobacter* species) or bacteria with an inherent insufficient susceptibility to cefotaxime (as *Staphylococcus aureus*). If this small subgroup is to be considered representative of the organisms currently involved in the development of SBP, our study supports the possibility that, in recent years, the microbial etiology of SBP is changing, as it seems to have more generally occurred for bacterial infections of these kinds of patients^[14]. In our hospital, a recent survey^[36] on 4769 samples collected for bacterial isolation from April to September 2006, showed a high prevalence of ESBL-producing enterobacteriaceae as an emergent cause of infections. In particular, among the ESBL-positive

E. coli, strains with CTX-M β -lactamases, specifically able to hydrolyze cefotaxime, were the most diffused. It is interesting to note that, although in the majority of our patients SBP was defined as “community-acquired” and nosocomial infections—defined as an infection of ascitic fluid diagnosed after a first negative ascitic fluid analysis—were not prevalent in the group resistant to cefotaxime, the above organisms are typically nosocomial. In other words, the episodes of SBP resistant to cefotaxime may be considered as healthcare-related infections^[37], probably due to the fact that compromised patients, as the cirrhotic patients included in the present study, have the frequent need of hospital assistance including outpatient visits, diagnostic invasive examinations, day-hospital admissions, *etc.*, which may facilitate contact with nosocomial antibiotic-resistant pathogens. These considerations should induce a change in our approach aimed not only at changing the first line antibiotic therapy in SBP, but also at reducing and making the patients’ access to the hospital more appropriate and rational.

In conclusion, an approach to SBP based on ascitic fluid PMN cell count is correct and valid in the clinical practice for both starting promptly the antibiotic treatment and evaluating its efficacy. However, the initial treatment with cefotaxime failed more frequently than expected. These results should promote investigations aimed at identifying different approaches. The antibiotics used for the empiric initial treatment should be chosen among those able to control infections which are often healthcare-related and thus sustained by antibiotic-resistant bacteria. The characteristics of bacterial infection in a given geographical area and community should be taken into account. Therefore, the generalization of our findings, which are derived by a monocentric study, deserves further investigations.

COMMENTS

Background

Spontaneous bacterial peritonitis (SBP) is a severe complication of cirrhotic patients with ascites. A prompt diagnosis and an early treatment are crucial for the outcome of these patients.

Research frontiers

In 2000, the International Ascites Club published the guidelines for the diagnosis and treatment of SBP in cirrhotic patients. This recommendation is, however, based on the results of randomized controlled trials and its validity and applicability need to be verified in clinical practice.

Innovations and breakthroughs

In agreement with the International Ascites Club guidelines, the study confirms the importance of performing a second paracentesis at 48 h after the initiation of the antibiotic therapy as well as the utility of the cut-off of PMN count in ascitic fluid for establishing treatment failure. The suggestion of using third-generation cephalosporins (cefotaxime) as the first-line antibiotic treatment is arguable, since a switch to another antibiotic was necessary in more than 40% of cases.

Applications

The study supports the possibility that, in recent years, the microbial etiology of SBP is changing as well as the sensibility of pathogens to antibiotic therapy. The characteristics of bacterial infection in a given geographical area and community should, therefore, be taken into account and each hospital should performed studies on bacterial sensibility and design their antibiotic strategy for SBP.

Peer review

It is a well-designed and well-written paper. The study adds important information on the management of cirrhotic patients with SBP.

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