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Special Article

Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document

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SPONTANEOUS bacterial peritonitis (SBP) is a frequent and severe complication of cirrhotic patients with ascites. Much information regarding SBP has appeared during recent years, particularly on aspects involving the management of this complication. Therefore, the International Ascites Club (IAC) commissioned a panel of experts to prepare a consensus on the diagnosis, therapy and prophylaxis of SBP. A draft consensus document, drawn up by the panel members, was presented and discussed at the regular Meeting of the IAC held during the 33rd Annual Meeting of the European Association for the Study of the Liver, in Lisbon in April 1998, after which a final consensus was reached.

This article represents the final consensus document and is divided into three separate sections concerning the diagnosis, treatment and prophylaxis of SBP. Specific recommendations are formulated and each recommendation is rated on the basis of strength and quality according to guidelines from the Practice Guidelines Committee of the American Association for the Study of Liver Diseases, with some modifications (1). The rating system is summarized in Table 1.

Diagnosis of SBP

Diagnostic paracentesis: in whom and when

Background

All cirrhotic patients with ascites can develop SBP. The prevalence of SBP in unselected cirrhotic patients with ascites admitted to a hospital ranges between 10 and 30% (2–6). Approximately half the episodes of SBP are present at the time of hospital admission and the remainder are acquired during hospitalization (7–9).

Most patients with SBP have symptoms and/or signs clearly suggestive of peritoneal infection, especially abdominal pain, fever and alterations in gastrointestinal motility. In other patients the development of SBP may be clinically manifested by impairment of liver function (e.g. development of hepatic encephalopathy) or renal failure as the predominant or only features (7,8,10–15). However, SBP may be asymptomatic or there may be minor symptoms only. This is particularly so when the diagnosis of the infection is made at hospital admission (7,8,10–15).

Recommendations (Table 2)

A diagnostic paracentesis should be performed on hospital admission in all cirrhotic patients with ascites to investigate the presence of SBP, even in patients admitted for reasons other than ascites.

A diagnostic tap should also be performed in hospitalized patients with ascites if and when they develop any of the following: a) local symptoms or signs suggestive of peritoneal infection, such as abdominal pain, rebound tenderness or clinically relevant alterations of gastrointestinal motility (i.e. vomiting, diarrhea, ileus); b) systemic signs of infection, such as fever, leukocytosis or septic shock, and c) hepatic encephalopathy or rapid impairment in renal function without any clear precipitating factor.

Paracentesis should also be performed routinely in patients with ascites and gastrointestinal hemorrhage before the administration of prophylactic antibiotics (see below, *Prophylaxis of SBP*).

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TABLE 1

Rating appraisal of the strength of recommendation and the quality of evidence for recommendation (adapted from the Practice Guidelines Committee of the American Association for the Study of Liver Diseases, with some modifications; ref. 1)

Strength of recommendation:
- A: Survival benefit
- B: Improved diagnosis
- C: Improvement in quality of life
- D: Relevant improvement in pathophysiological knowledge
- E: Impact on health care cost

Quality of evidence for recommendation:
- I: Evidence from at least one properly randomized, controlled trial
- II: Evidence from at least one:
  - Well-designed clinical trial without randomization
  - Cohort or case-control study
  - Well-designed meta-analysis
- III: Evidence from:
  - Clinical experience
  - Descriptive studies
  - Reports of expert committees
- IV: No rating

Ascitic fluid cell count

Background

Peritoneal infection causes an inflammatory reaction that results in an increased number of polymorphonuclear leukocytes (PMN) in ascitic fluid. Despite the use of sensitive methods, ascites culture is negative in approximately 40% of patients with clinical manifestations suggestive of SBP and increased ascites PMN (15–21). Moreover, treatment cannot be delayed until microbiological results are available. Therefore, empirical antibiotic treatment for SBP is started when objective evidence of a local inflammatory reaction is present, i.e. an elevated ascites PMN count. On the basis of currently available data, the greatest sensitivity for the diagnosis of SBP is reached with a cutoff PMN count of 250/ mm^3, although the greatest specificity is reached with a cutoff of 500 PMN/mm^3 (3,22–30). In patients with bloody ascitic fluid (i.e. ascites red blood cell count >10 000/mm^3, as the result of a traumatic tap or conditions causing hemorrhage into ascites, such as concomitant neoplasm or severe coagulopathy) (31), a correction factor of 1 PMN per 250 red blood cells (RBC) has been proposed, since this is the maximum expected ratio of PMN to RBCs normally present in peripheral blood (31,32).

Although some physicians still establish the diagnosis of SBP on the basis of both the ascites total leukocyte count and the percentage of PMNs, there is no rationale for the use of this criterion in the diagnosis of SBP (3,33,34).

Recommendations *(Table 2)*

Diagnosis of SBP must be based on the PMN cell count in ascitic fluid. A PMN count of more than 250/ mm^3 is highly suspicious of SBP and constitutes an indication to empirically initiate antibiotic treatment. Although an ascitic fluid PMN count greater than 500/ mm^3 is more specific for the diagnosis of SBP, the risk of not treating the few patients with SBP who have an ascites PMN count between 250 and 500/mm^3 is unacceptable. An ascitic fluid PMN count of less than 250/mm^3 excludes the diagnosis of SBP.

In patients with hemorrhagic ascites (i.e. ascites RBC count >10 000/mm^3), a subtraction of one PMN per 250 RBC should be made to adjust for the presence of blood in ascites.

A diagnosis of SBP established on the basis of symptoms and signs is not acceptable.

Ascitic fluid culture

Background

Using conventional culture techniques, ascitic fluid cultures are negative in up to 60% of patients with clinical manifestations suggestive of SBP and an increased ascites PMN count (18–21). The low proportion of positive ascitic fluid cultures is probably due to the relatively low concentration of bacteria in ascitic fluid compared to infections in other organic fluids (e.g. urine). Prospective comparative trials have shown that culture of ascitic fluid directly into blood culture bottles (aerobic and anaerobic media) at the bedside increases the yield of bacteria up to 90% (18–21). However, outside of these trials that were specifically designed to investigate different culture methods, and even using the method of inoculating ascites into blood culture bottles, cultures are still negative in approximately 30–50% of patients with an increased ascites PMN count (8,9,15). The condition of increased PMN count in ascites and negative culture has been known as "culture-negative neutrocytic ascites", which is considered as a variant of SBP, since the short- and long-term course of patients with either condition is the same (16,17,35). In a significant proportion of patients with SBP, blood cultures are positive (3,16); in these cases, bacteria isolated from peripheral blood are presumably the same bacteria causing SBP.

At present, the Gram stain of a smear of sediment obtained after centrifugation of ascitic fluid is positive in only a few cases, probably because SBP is usually diagnosed at very early stages of the infection, when the concentration of organisms in ascites is very low (19).

Recommendations *(Table 2)*

Culture of ascitic fluid should be performed at the bedside using blood culture bottles, including both aerobic

TABLE 2

Recommendations on diagnosis of SBP

Recommendation	Rating
Diagnosis of SBP:	
1. Diagnostic paracentesis in cirrhotics with ascites:	
At hospital admission	AB, III
Whenever patients develop any of the following:	AB, III
• Local signs of peritonitis (pain, vomiting, diarrhea, ileus)	
• Systemic signs of infection (fever, leukocytosis, septic shock)	
• Hepatic encephalopathy without any clear precipitating factor	
• Rapid renal function impairment without an apparent cause	
Prior to antibiotic prophylaxis, if gastrointestinal bleeding	B, II
2. Diagnosis of SBP based on ascitic fluid PMN count >250/mm^3; in patients with bloody ascites: substract 1 PMN per 250 RBC	B, III
3. Cultures:	
Ascitic fluid culture: bedside inoculation into blood culture bottles; minimum amount: 10 ml	B, I
Blood cultures simultaneous to ascitic fluid cultures	B, III
Special conditions:	
1. Bacterascites:	
Definition criteria: positive ascitic fluid culture, ascites PMN <250/mm^3, and no evidence of local or systemic infection	B, III
Once bacterascites is diagnosed, repeat paracentesis; if:	BE, III
• Ascites PMN >250/mm^3: initiate antibiotic treatment	
• Ascites PMN <250/mm^3, but culture continues to be positive: initiate antibiotic treatment	
• Ascites PMN <250/mm^3 and negative culture: bacterascites is resolved, no more action is required	
In patients with positive ascitic fluid culture, ascites PMN <250/mm^3 and evidence of local or systemic infection: initiate antibiotic treatment	A, IV
2. Secondary peritonitis:	
Suspected when any of the following:	AB, III
• Lack of response to antibiotic treatment	
• Two or more organisms isolated (particularly anaerobes or fungi)	
• At least two of the following findings in ascitic fluid:	
Glucose <50 mg/dl	
Protein >10 g/l	
Lactic dehydrogenase >normal serum levels	
Once secondary peritonitis is suspected:	AB, III
• Initiate appropriate radiological investigation	
• Add antibiotics against anaerobes and enterococci	

and anaerobic media. The minimum amount of ascitic fluid inoculated in each bottle should be 10 ml.

Since blood cultures increase the possibility of identifying the infecting organisms, blood cultures should also be obtained in patients with increased ascitic fluid PMN count before initiating antibiotic administration.

Despite negative ascitic fluid and blood cultures, patients with increased ascites PMN count should be considered as having SBP. It is proposed to use the term "culture-negative SBP" or simply "SBP" for this condition, similarly to other types of infection, such as meningitis, arthritis or pneumonia, in which a proportion of cultures are also negative but the name of the infection is not changed for this reason.

Bacterascites

Background

The term "bacterascites" refers to the colonization of ascitic fluid by bacteria, in the absence of an inflammatory reaction in the peritoneal fluid. Therefore, the diagnosis of bacterascites is currently made when there is a positive ascitic fluid culture in the setting of an ascitic fluid PMN count <250/mm^3 (11,12,36–38). However, patients with bacterascites so defined do not constitute a homogeneous population. In some patients bacterascites is the result of secondary bacterial colonization of ascites from a concomitant extraperitoneal infection (e.g. pneumonia or urinary tract infection) (36–38). These patients usually present with general and local (extraperitoneal) symptoms and signs of infection. In other patients, the growth of bacteria from the ascitic fluid corresponds to the spontaneous colonization of ascites, and they can either be clinically asymptomatic or have abdominal pain or fever (11,12,36–38). The course of untreated bacterascites is also variable. While in some patients, particularly in those who are asymptomatic, bacterascites represents a transient and spontaneously reversible colonization of ascites, in other patients, mainly those who are symptomatic, bacterascites is the first step in the development of SBP (36–39).

Recommendations *(Table 2)*

The term "bacterascites" should be reserved for patients fulfilling the following criteria: positive ascitic fluid culture, ascites PMN count <250 cells/mm^3 and absence of any evidence of systemic or local infection.

Once the diagnosis of bacterascites is made (usually 2–3 days after the paracentesis, when the microbiological results are available), it is recommended that paracentesis for PMN count and culture be repeated and treated accordingly. Three possible scenarios are then possible: a) ascites PMN >250/mm^3: antibiotic therapy should be initiated as bacterascites has probably evolved into SBP; b) ascitic fluid PMN <250/mm^3 and ascitic fluid culture continues to be positive: initiation of antibiotic therapy appears to be the most judicious option, although further investigations are necessary to properly assess this recommendation, and c) ascitic fluid PMN <250/mm^3 and ascitic fluid culture is now negative: no further action is required as bacterascites has spontaneously resolved.

Patients with positive ascitic fluid culture and ascitic fluid PMN count <250/mm^3, but with symptoms and signs of an extraperitoneal infection (e.g. pneumonia, urinary tract infection), should receive antibiotic treatment according to the *in vitro* susceptibility of the organism(s) isolated in ascites since it is likely that this organism(s) is also responsible for the extraperitoneal infection. Similarly, because most patients with positive ascitic fluid culture, ascitic PMN count <250/mm^3 and clinical signs of peritoneal infection develop SBP within a few days, these patients should also receive appropriate antibiotic therapy.

Spontaneous versus *secondary bacterial peritonitis*

Background

The vast majority of cirrhotic patients with ascites and peritoneal infection have SBP. However, a small group of patients have bacterial peritonitis secondary to perforation or acute inflammation of intra-abdominal organs, abdominal wall infections or previous abdominal surgical procedures (11,40,41). With the exception of peritonitis secondary to the two latter conditions, in which the precise nature of peritoneal infection can easily be established, the differential diagnosis between spontaneous (primary) and secondary peritonitis can occasionally be difficult. The differentiation is important because secondary peritonitis usually does not resolve unless patients are treated surgically. Conversely, surgical therapy may be accompanied by significant deterioration in the clinical status of cirrhotic patients with spontaneous peritoneal infection (42).

Although clinical and laboratory characteristics of secondary peritonitis have been reported in only a small number of patients, it has been suggested that secondary peritonitis should be suspected when at least one of the following features is present (41,43):

a) No response to antibiotic therapy, that is, lack of a significant decrease (or even an increase) in ascitic fluid PMN cell count in follow-up paracenteses performed during therapy (see below, *Treatment of SBP*).

b) More than one organism isolated from ascites (particularly when the growth of anaerobic bacteria or fungi is observed).

c) At least two of the following findings in the ascitic fluid: glucose levels <50 mg/dl, protein concentration >10 g/l, lactic dehydrogenase concentration >normal serum levels.

These criteria seem to be very sensitive in the detection of secondary peritonitis but their specificity is low (44). Studies involving large series of patients are necessary to improve the clinical approach to the differential diagnosis between spontaneous and secondary peritonitis.

Recommendations *(Table 2)*

Secondary peritonitis should be suspected when there is a lack of response to antibiotic treatment and/or in the presence of the aforementioned ascitic fluid alterations.

When secondary peritonitis is suspected, antibiotic treatment should include antimicrobial agents against anaerobic organisms and enterococci, and the presence of secondary peritonitis should be properly investigated.

Treatment of SBP

Empirical antibiotic therapy

Background

Empirical antibiotic therapy must be initiated immediately after the diagnosis of the infection is made, without prior knowledge of the causative organisms and their *in vitro* susceptibility. Since Gram-negative aerobic bacteria from the family of *Enterobacteriaceae* and non-enterococcal *Streptococcus* spp. are the most common causative organisms (2,3,5,12), the initial empirical antibiotic therapy of SBP should cover these organisms. Furthermore, the pharmacokinetic properties of the antibiotics selected should be adequate to treat peritoneal infection (i.e. antibiotic concentrations in ascitic fluid >MIC_{90} of causative microorganisms). The efficacy and safety of different antimicrobial agents as initial empirical antibiotic therapy in SBP have been investigated with the following results.

a) Cefotaxime: This antibiotic has been the most ex-

tensively investigated in patients with SBP. In the first randomized, comparative study (45), cefotaxime was more effective in achieving the resolution of SBP and other infections than ampicillin plus tobramycin and, whereas no patient treated with cefotaxime developed nephrotoxicity and superinfections, these two complications occurred in more than 10% of the patients treated with ampicillin plus tobramycin. Two other randomized, controlled trials assessing the optimal duration of therapy and dosage of cefotaxime in cirrhotic patients with SBP have been reported. One of these trials showed that 5-day therapy with cefotaxime (2 g/8 h) was as effective as 10-day therapy in relation to the rate of resolution of the infection, recurrence of SBP during hospitalization, and hospital mortality (46). The other trial reported similar rates of SBP resolution and patient survival in patients with SBP receiving cefotaxime at a dose of either 2 g/6 h or 2 g/12 h (15). The results of these two studies suggest that the high efficacy of cefotaxime in SBP can be maintained with short-course administration of this antimicrobial agent and with doses lower than those formerly used, with a significant reduction in the cost of the antibiotic. Cefotaxime at the above doses achieves adequate concentrations in ascitic fluid in patients with SBP (15,47,48). The cost of cefotaxime therapy in SBP is moderate, particularly if low doses are used. As an example, in Spain the market price of 2 g cefotaxime b.i.d is ∈32.56 per day.

b) Other cephalosporins: The rate of SBP resolution and patient survival has been found to be very high with the use of other cephalosporins, including cefonicid, ceftriaxone, ceftizoxime and ceftazidime (49–53), with no significant differences as compared to that reported with the use of cefotaxime.

c) Combinations of aminoglycosides and beta-lactam antibiotics: As mentioned above, the usefulness of the association of ampicillin and tobramycin has been assessed in cirrhotic patients with severe infections (45). Other combinations included cephalothin with either gentamicin or tobramycin (54), and mezlocillin with netilmicin (53). The efficacy of these combinations is only moderate and, importantly, they are associated with a high incidence of nephrotoxicity. Therefore, these antibiotic associations are not recommended as initial empirical antibiotic therapy in cirrhotic patients with SBP.

d) Aztreonam: Aztreonam is a monocyclic beta-lactam antibiotic with efficacy against enterobacteria but not against Gram-positive cocci. In a comparative study, aztreonam (associated with other antibiotics active against Gram-positive bacteria) was less effective than cefotaxime in the treatment of SBP (55). This study concluded that aztreonam was not adequate for the empirical treatment of SBP.

e) Amoxicillin plus clavulanic acid: In a pilot study, the administration of 1 g of amoxicillin associated with 200 mg of clavulanic acid, q.i.d., was effective in 85% of 27 episodes of SBP (56). In a recent comparative trial, amoxicillin-clavulanic acid was as effective as cefotaxime in the treatment of SBP (57). In both studies, amoxicillin-clavulanic acid therapy was not associated with relevant adverse effects. The low cost is one important advantage of this antibiotic regimen (market price of 1 g iv, q.i.d.: ∈17.64 per day).

f) Oral antibiotics: In most cases, patients with SBP are in relatively good clinical condition and may be treated orally. This has been assessed in two studies. In one of these studies (58), the oral administration of pefloxacin (alone or in combination with other oral antibiotics: cotrimoxazole, amoxicillin, cefadroxil, and cotrimoxazole plus metronidazole) achieved the following results: 87% rate of resolution of SBP, 13% incidence of superinfections, and 60% survival rate. The second study (9) consisted of a randomized, controlled trial involving patients with uncomplicated SBP (no shock, ileus, gastrointestinal hemorrhage, profound hepatic encephalopathy or serum creatinine >3 mg/dl). It compared oral ofloxacin (400 mg/12 h) *versus* intravenous cefotaxime (2 g every 6 h). The rate of infection resolution, length of antibiotic treatment and patient survival were similar in the two groups. No adverse effects related to oral ofloxacin administration were observed, and the cost of ofloxacin treatment was very much lower than the cost of cefotaxime treatment (market price of oral ofloxacin, 400 mg/12 h: ∈4.44 per day).

At present, some patients developing SBP are receiving prophylaxis with quinolones (see below, *Prophylaxis of SBP*). In these patients, SBP is commonly caused by Gram-positive cocci or quinolone-resistant Gram-negative bacilli (59,60). Cefotaxime is very effective in these cases (60,61).

Recommendations *(Table 3)*

Antibiotic therapy must be empirically initiated in cirrhotic patients with an ascitic fluid PMN cell count >250/mm^3.

Several antibiotics can be used for the initial empirical therapy of SBP with similar efficacy: cefotaxime, other cephalosporins (cefonicid, ceftizoxime, ceftriaxone and ceftazidime), or amoxicillin-clavulanic acid. The optimal cost-effective dosage has only been investigated for cefotaxime. For this antibiotic, a minimum dose of 2 g/12 h should be administered. In addition, a minimum duration of 5 days of cefotaxime therapy

TABLE 3

Recommendations on treatment of SBP

Recommendation	Rating
1. Antibiotic therapy must be empirically initiated in patients with ascitic fluid PMN count >250/mm^3	A, II
2. Recommended antibiotics for initial empirical therapy:	
Cefotaxime; minimum dose 2 g/12 h, minimum duration 5 days	A, I
Other: ceftizoxime, cefonicid, ceftriaxone, ceftazidime, amoxicillin-clavulanic acid; standard dosage	AE, II
In patients with uncomplicated SBP and not under quinolone prophylaxis: oral ofloxacin is another option	E, I
In patients under quinolone prophylaxis: cefotaxime	A, III
In patients with beta-lactam hypersensitivity: quinolones	A, IV
Aminoglycosides should be avoided	A, I
3. Assessment of response to antibiotic therapy:	
Periodical clinical evaluation and, at least, one follow-up paracentesis (i.e. after 2 days of antibiotic therapy) to determine ascitic fluid PMN count	AB, III
Treatment failure when one of the following:	A, IV
• Deterioration of clinical condition within the first hours of antibiotic therapy	
• Less than 25% decrease in ascitic fluid PMN in follow-up paracentesis as compared to pre-treatment value	
If treatment failure:	A, III
• Modify antibiotic therapy according to *in vitro* susceptibility of isolated organisms or empirically	
• Consider the possibility of secondary peritonitis	

is recommended. For the remaining antibiotic agents, standard dosage for severe infections is recommended. Since most of these antibiotic agents are predominantly excreted in the urine, dose adjustments are necessary in patients with severe renal impairment.

Patients with uncomplicated SBP and not receiving prophylaxis with quinolones can be treated orally with ofloxacin, at a minimum dose of 400 mg/12 h.

For patients developing SBP while under quinolone prophylaxis, cefotaxime administration appears as the most adequate antibiotic regimen.

There are no studies in patients with beta-lactam antibiotic hypersensitivity. Nevertheless, the administration of quinolones seems an adequate therapeutic alternative in these cases.

Aminoglycosides should be avoided as initial empirical antibiotic therapy.

Assessment of response to antibiotic therapy

Background

Resolution of SBP is achieved in approximately 90% of patients with the above regimens. The resolution of the infection is associated with the disappearance of all systemic and local symptoms and signs of infection, reduction of the PMN count in ascitic fluid below 250/mm^3, normal WBC count and negative ascitic fluid culture (7,15,62,63). However, for those patients who do not improve the mortality rate is very high, even when antibiotic treatment is appropriately modified (7,15). Therefore, assessing the course of the infection is important to recognize treatment failure as early as possible. It has been suggested that the changes in the PMN count in ascitic fluid after 2 days of antibiotic therapy in relation to the pre-treatment values constitute the best marker of the therapeutic response in patients with SBP. In a prospective investigation the drop in the ascitic fluid PMN count during this time was 92±9% in patients who survived at the end of hospitalization and 66±38% in those who did not (62).

Recommendations (Table 3)

The response to treatment should be assessed by periodically evaluating the symptoms and signs of infection and at least one follow-up paracentesis after 2 days of antibiotic therapy to determine the PMN count in ascitic fluid. Treatment failure can be established when the condition of the patients rapidly deteriorates within the first hours of antibiotic therapy (i.e. with development of shock) or no significant decrease in ascitic PMN count is observed in the follow-up paracentesis. Although no specific cutoff has been established, a reduction in the PMN count of less than 25% in relation to the pre-treatment value may reasonably be considered as suggestive of failure of the antibiotic treatment.

In case of treatment failure, antibiotic therapy should be rapidly modified either according to the *in vitro* susceptibility of isolated bacteria in patients with culture-positive SBP or empirically in patients with culture-negative SBP (according to the physician or center experience). Furthermore, the possibility of secondary peritonitis should be considered and appropriate investigations initiated.

Since despite these measures mortality remains high in patients with failure to respond to the initial antibiotic treatment, methods for more rapidly and accurately assessing therapeutic response should be further investigated.

Prophylaxis of SBP

The efficacy and safety of prophylaxis for SBP (and other infections) has been investigated in two populations of cirrhotic patients: a) hospitalized patients with gastrointestinal hemorrhage, and b) non-bleeding cirrhotic patients with ascites.

Cirrhotic patients with gastrointestinal hemorrhage

Background

All cirrhotic patients with upper gastrointestinal bleeding, independent of the presence or absence of ascites, are at a high risk of developing severe bacterial infections, including SBP, within the first days of the hemorrhagic episode (64–70). Approximately 20% of these patients are already infected at admission, and 50% develop an infection during hospitalization.

Because most microorganisms causing infection in cirrhotic patients are of enteric origin, the initial investigations addressed the effectiveness of prophylactic intestinal decontamination in these patients. Two randomized, controlled studies have demonstrated that selective intestinal decontamination with oral administration of antibiotics is effective in preventing bacterial infection in cirrhotic patients with gastrointestinal hemorrhage. In the first study (64) the administration of different combinations of oral, non-absorbable antibiotics (either gentamicin, vancomycin and nystatin, or neomycin, colistin and nystatin) significantly reduced the incidence of infection from 35% in the control group to 16% in the treated group (incidence of spontaneous bacteremia and/or SBP reduced from 21% to 9%). In the second controlled trial (65), treated patients received oral norfloxacin, a quinolone partially absorbed after oral administration and very active *in vitro* against bacteria commonly causing infection in cirrhotic patients. Patients who received norfloxacin, 400 mg twice daily for 7 days, developed less infections than controls: 10% versus 37%, respectively. The incidence of bacteremia and/or SBP was 3% in the treated group and 17% in the control group. In these two studies there was a marked reduction of infections caused by enteric bacteria, without any significant change in the incidence of infections caused by bacteria of a probable extraintestinal source.

The usefulness of systemic administration of prophylactic antibiotic agents in cirrhotic patients with gastrointestinal hemorrhage has also been investigated in three more recent controlled studies. In these studies the treated groups received ofloxacin (initially intravenously and then orally) plus amoxicillin-clavulanic acid (iv, before each endoscopy), ciplofloxacin plus amoxicillin-clavulanic acid (first intravenously and then orally once the bleeding was controlled), and oral ciprofloxacin, respectively (66,68,70). The incidence of bacterial infections was significantly lower in the treated groups (10–20%) than in the corresponding control groups (45–66%).

No serious adverse events were associated with any of the above prophylactic regimes and there was no increase in the incidence of infection caused by resistant organisms. A recent meta-analysis has also reported that antibiotic prophylaxis was significantly effective in improving survival in cirrhotic patients with gastrointestinal hemorrhage (71). In this meta-analysis no differences were found between orally-administered *versus* intravenously-administered antibiotics.

A relative limitation in these studies was the inability to assess the effect of antibiotic prophylaxis specifically on SBP since the incidences of both SBP and bacteremia were analyzed together. This was mainly due to the small number of patients with ascites included in these studies, which precluded an analysis of the incidence of SBP alone. Nevertheless, the marked decrease in the rate of overall infections (SBP and other infectious complications) and the improvement of survival in the

TABLE 4

Recommendations on prophylaxis of SBP

Recommendation	Rating
In cirrhotics with upper gastrointestinal hemorrhage:	
1. Oral administration of norfloxacin, 400 mg/12 h, over a minimum period of 7 days	AE, I
2 Alternative regimes: combinations of systemic antibiotics (ciprofloxacin, ofloxacin, amoxicillin-clavulanic acid)	A, II
3. Exclusion of SBP and other infections before starting prophylaxis	A, III
In non-bleeding cirrhotic patients with ascites:	
1. In patients recovering from an SBP episode:	
Continuous oral administration of norfloxacin, 400 mg/day	AE, I
Consider liver transplantation	AC, III
2. In patients without past history of SBP and with:	
High ascitic fluid protein (i.e. >10 g/l): prophylaxis unnecessary	E, III
Low ascitic fluid protein (i.e.<10 g/l): no consensus on the necessity of prophylaxis	IV

groups receiving antibiotic prophylaxis support such prophylaxis being strongly recommended in cirrhotic patients with gastrointestinal hemorrhage independently of their specific risk of SBP. Furthermore, the meta-analysis by Bernard et al. (71) included only SBP cases and showed a significant benefit in this subset of patients: 95% of patients were free of SBP in the treated group *versus* 87% in the control group.

Recommendations *(Table 4)*

Antibiotic prophylaxis should be administered to cirrhotic patients with upper gastrointestinal hemorrhage, independently of the presence or absence of ascites, because this measure is effective in preventing bacterial infections and improving survival.

Although several antibiotic regimens are useful in these patients, oral administration (*per os* or through a nasogastric tube) of norfloxacin, 400 mg/12 h, appears to be the first-choice antibiotic prophylaxis due to its simpler administration and lower cost. This prophylaxis should be administered over a minimum period of 7 days.

Since most cirrhotic patients are infected at the time of the hemorrhagic episode, the possible existence of SBP or other infections should be excluded before starting prophylactic antibiotic administration.

Non-bleeding cirrhotic patients with ascites

Background

Risk of SBP in different subgroups of non-bleeding cirrhotic patients with ascites:

Increased risk of SBP has been found in the following subsets:

a) Patients with previous episodes of SBP. These patients have a 1-year probability of SBP recurrence of 40–70% (72,73).

b) Patients who have never had SBP and have increased serum bilirubin and/or low total ascitic fluid protein concentration. In one study, the 1-year probability of the first episode of SBP in patients with serum bilirubin >2.5 mg/dl was 43% (74). However, this incidence may have been an overestimate since antibiotic prophylaxis was not administered during episodes of gastrointestinal hemorrhage occurring during the study. In another investigation, 15% of patients admitted with low ascitic fluid protein content (<10 g/l) developed SBP during hospitalization (75). Other studies have reported 1-year probabilities of SBP of 20% (in patients who received antibiotic prophylaxis if and when they develop gastrointestinal hemorrhage) (76) and of 40% (in patients who did not receive this prophylaxis) (74). The risk of SBP in patients without a previous history of SBP and high ascitic fluid protein concentration is negligible, provided antibiotic prophylaxis is administered during episodes of gastrointestinal bleeding, with 1-year and 3-year probabilities of 0% and 3%, respectively (76).

Prophylaxis of SBP in non-bleeding cirrhotic patients with ascites:

a) Selective intestinal decontamination by oral administration of norfloxacin: Three randomized, controlled studies have investigated the usefulness of norfloxacin prophylaxis in several populations of non-bleeding cirrhotic patients with ascites. In the first study, which involved patients who had had a previous episode of SBP, the continuous administration of norfloxacin, at a dose of 400 mg/day, reduced the 1-year probability of SBP recurrence from 68% in the placebo-treated group to 20% in the norfloxacin-treated group, with a reduction of the probability of recurrent SBP caused by aerobic Gram-negative bacilli from 60% to 3% (59).

The second study included cirrhotic patients with a protein concentration in ascitic fluid <15 g/l, some of whom had had a previous episode of SBP. In this inhomogeneous population, the administration of norfloxacin, 400 mg/day throughout the hospitalization period, decreased the in-hospital incidence of SBP from 22% in the control group to 0% in the treated group (77).

The third controlled study included cirrhotic patients with ascitic fluid protein concentration <15 g/l and no previous episodes of SBP. In this study the 6-month incidence of SBP was 0% in the group of patients prophylactically treated with norfloxacin, 400 mg/day for 6 months, compared to 9% in patients treated with placebo (78). Nevertheless, the incidence of SBP caused by Gram-negative organisms (the only one which theoretically can be prevented by norfloxacin prophylaxis) in the two groups was not statistically significant: 0% in the norfloxacin-treated group and 5% in the placebo-treated group. The relatively short period of study, the narrow difference between the treated and the placebo groups and, more importantly, the low rate of SBP by Gram-negative bacteria in the control group casts some doubts on the convenience of norfloxacin prophylaxis in this specific group of patients.

b) Other antibiotic regimes: A placebo-controlled study demonstrated that 6-month prophylaxis with ciprofloxacin, 750 mg weekly, was effective in reducing the incidence of SBP in cirrhotic patients with low ascitic fluid protein concentration: 4% in the treated group and 22% in the placebo-control group (79). In this study, patients with and without a prior history of SBP were included together and no attempt was made

to evaluate the development of SBP in these two subgroups of patients separately.

The efficacy of continuous administration of trimethoprim-sulfamethoxazole (one double-strength tablet, 5 days a week) in cirrhotic patients with ascites was investigated in another controlled study (80). The incidence of SBP during the study period was 3% in the treated group and 27% in the control group. Nevertheless, the relatively small number of patients studied (30 in each arm) and the fact that patients with different risks for SBP were analyzed together (patients with low and high ascitic fluid protein, and patients who did and did not have had previous SBP episodes) make the interpretation of these results difficult and their applicability questionable.

c) Other investigations: A recent meta-analysis, which grouped four randomized, controlled trials investigating the efficacy of long-term administration of quinolones or trimethoprim-sulfamethoxazole in cirrhosis with ascites, indicated that antibiotic prophylaxis against SBP in these patients is associated with increased survival (81). After a mean follow-up period of 5 months, survival in patients who did and did not receive prophylaxis was 82% and 73%, respectively. However, in this meta-analysis patients with and without prior SBP were also included together. On the other hand, two recent economic analyses have calculated that long-term antibiotic prophylaxis in cirrhotic patients with ascites is associated with a reduced cost compared with the "diagnosis and treat" strategy, suggesting that prophylaxis in patients with a high risk of developing SBP in fact reduces the total antibiotic burden for these patients (82,83).

A concern with the use of prolonged antibiotic prophylaxis is that it will lead to selection of antibiotic-resistant bacteria which can be disseminated within the general community, and in particular hospital environments (84–90). These bacteria may then go on to cause infection in susceptible populations and may not be amenable to treatment. Although fluoroquinolone prophylaxis in a variety of indications has been shown to reduce the carriage of aerobic Gram-negative bacteria within the gut, it can also increase the number of Gram-positive bacteria, particularly *Staphylococcus aureus* and enterococci, and select fluoroquinolone-resistant Gram-negative bacteria, such as organisms from the *Enterobacteriaceae* family and *P. aeruginosa* (59,78,91–97). In countries and institutions where the prevalence of fluoroquinolone-resistant bacteria is high, prophylaxis with quinolones should be questioned, as fluoroquinolone-resistant organisms may already be present in the fecal flora of those individuals for whom prophylaxis is proposed. With specific regard to SBP, emergence of fecal quinolone-resistant bacteria in cirrhotic patients receiving long-term norfloxacin prophylaxis has been increasingly reported (78,92,95,97). Although the development of SBP or other infections caused by quinolone-resistant organisms, mainly *Pseudomonas* spp. and Gram-positive bacteria, in cirrhotic patients on quinolone prophylaxis was scarcely reported in initial controlled trials (i.e. the incidence of these infections in norfloxacin-treated patients was similar to that found in control patients) (59,77,79), the frequency of such infections has been found to be increased more recently (61,98). One recent study (98) showed clear differences in the type of bacteria causing infections in cirrhotic patients on chronic quinolone prophylaxis; while 67% of infections in untreated cirrhotic patients were due to Gram-negative organisms, infections that developed in patients receiving prophylaxis were mostly due to Gram-positive organisms (79%), with special mention for methicillin-resistant *Staphylococcus aureus*. This concern about the safety of this prophylaxis reinforces the necessity of restricting the administration of prophylactic antibiotics to those patients at the greatest risk of SBP. Knowledge of the prevalence of antibiotic-resistant bacteria in the clinical environment is required so that clinical judgment can be made as to whether norfloxacin prophylaxis is appropriate in that country or institution. It is also suggested that the carriage and/or development of fluoroquinolone-resistant fecal bacteria should be monitored in studies investigating the effect of quinolone prophylaxis.

Survival after SBP:

Survival expectancy after one episode of SBP has been reported to be very short, with a 1-year and 2-year probability of survival of 30–50% and 25–30%, respectively (72,73,99,100). Since survival expectancy after liver transplantation is currently much higher (101,102), patients recovering from an episode of SBP should be considered as potential candidates for liver transplantation.

Recommendations *(Table 4)*

Continuous oral administration of norfloxacin, 400 mg/day, is recommended in cirrhotic patients recovering from an episode of SBP.

Since survival probability is very much reduced after SBP, cirrhotic patients who have recovered from an episode of SBP should be evaluated for liver transplantation.

In cirrhotic patients without a past history of SBP and with a high ascites protein content (i.e. >10 g/l), long-term prophylactic administration of antibiotics is

not necessary since the risk of SBP in these patients is negligible provided adequate prophylaxis is administered if and when gastrointestinal hemorrhage develops in the course of the disease.

For cirrhotic patients who have never had SBP and in whom ascitic fluid protein concentration is low (i.e. <10 g/l), no consensus was reached by the panel of experts and IAC members on the necessity of antibiotic prophylaxis, during either hospitalization or as an outpatient regimen. The main reason for the lack of consensus was that, despite the positive results of all the studies investigating different antibiotics in the prophylaxis of SBP in patients with cirrhosis, they have been unable to identify the subsets of patients that clearly benefit from this therapy.

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