Clinical and Experimental HEPATOLOGY

Clin Exp HEPATOL 2018; 4, 4: 224–231
DOI: https://doi.org/10.5114/ceh.2018.80123
Received: 22.07.2018, **Accepted:** 04.11.2018, **Published:** 03.12.2018

Review paper

Spontaneous bacterial peritonitis – therapeutic challenges in the era of increasing drug resistance of bacteria

Karolina Anna Rostkowska, Anna Szymanek-Pasternak, Krzysztof Adam Simon

Department of Hepatology and Infectious Diseases, Wrocław Medical University, Poland

Abstract

Spontaneous bacterial peritonitis (SBP) is one of the most common bacterial infections in patients with liver cirrhosis and it significantly contributes to the deterioration of the prognosis and increased risk of mortality. Previous data suggested that the most common pathogens causing SBP are G-negative aerobic bacteria and treatment recommended by the international guidelines (EASL, AASLD) is highly effective.

In recent years, due to the widespread use of antibiotic prophylaxis and the increased frequency of hospitalization along with the use of invasive procedures in patients with cirrhosis, the involvement of Gram-positive cocci and multi-drug resistant bacteria in the etiology of SBP is increasing. This is related to the lowering of the effectiveness of the first-line therapy used so far and worsening of the prognosis, increasing in-hospital mortality. In this work we summarize current data on the characteristics of pathogens responsible for SBP in the context of currently recommended treatment regimens.

Key words: drug resistance, ascites, MDR, cirrhosis, spontaneous bacterial peritonitis.

Address for correspondence

Dr. Karolina Anna Rostkowska, Department of Hepatology and Infectious Diseases, Wrocław Medical University, 5 Koszarowa St., 51-149 Wrocław, Poland, e-mail: karolinarostkowska01@gmail.com

Introduction

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of previously sterile ascitic fluid found in the peritoneal cavity. A prerequisite for the diagnosis of SBP is exclusion of an intra-abdominal source of infection requiring surgical intervention, referred to as secondary peritonitis. The development of SBP may occur in patients with ascites regardless of its etiology; however, the most common complication develops in cases of decompensated liver cirrhosis. Infectious diseases in patients with cirrhosis significantly contribute to the deterioration of the prognosis, increasing the mortality four-fold [1]. SBP, observed in 10-30% of hospitalized patients with cirrhosis and ascites [1], is one of the most common bacterial infections in this group of patients [2].

The pathomechanism of SBP is still not fully understood, but the factors that lie behind it may be identified. Cirrhosis results in abnormal small intestine motility, which in turn predisposes to intestinal bacterial overgrowth and translocation [3]. In addition, this phenomenon may be exacerbated by the frequent use of proton pump inhibitors in this group of patients, leading to a reduction in gastric acidity and increase in intestinal permeability which promotes bacterial translocation and colonization of mesenteric lymph nodes [4, 5]. Subsequent infection of the fluid in the peritoneal cavity is also facilitated by the impairment of the body defense mechanisms [3].

SBP-causing bacteria can also enter the peritoneal cavity via the blood circulation system or lymphatic system from extra-gastrointestinal foci such as the urinary tract, lungs, dermatitis and subcutaneous tissue, pharyngitis and often neglected odontogenic foci [4, 6]. The diagnosis confirms the finding of > 250 polymorphonuclear cells (PMNs) in a milliliter of ascitic fluid [7]. If additionally the ascitic fluid culture is positive,

as is observed in approximately 40% of SBP cases, we can diagnose a culture-positive SBP; otherwise the disease is called neutrocytic ascites. When the ascitic fluid culture is positive and the number of PMNs is < 250 in a milliliter of ascitic fluid the condition is called bacterascites [1]. As cirrhosis is a condition of immunosuppression, called cirrhosis-associated immune dysfunction (CAID) [8], the body's response to infection may be poorly expressed [1]. Therefore, in all patients with liver cirrhosis and even mild ascites, in the case of sudden deterioration of liver function, SBP should always be taken into account, even in the absence of obvious clinical symptoms or deviations in laboratory tests [7].

The risk of SBP increases with the progression of liver disease expressed as bilirubin > 3.2 mg/dl and PLT < 98 000/mm [3, 9]. Each additional point on the MELD scale (Model for End-Stage Liver Disease) increases the risk by 11% [10].

In addition, it has been shown that the risk is higher in patients with ascitic fluid protein concentration < 1.5 mg/ml [11] and in the case of bleeding from esophageal varices [12].

The frequent occurrence of SBP is often associated with an impaired immune response in patients with cirrhosis, expressed by reduced activity of mononuclear phagocytes and deficiency of complement components in the blood, especially in ascitic fluid [13, 14].

Among the iatrogenic factors, the risk of SBP development is increased by proton pump inhibitors in the mechanism of enhancing the bacterial translocation [15], and additionally by impairing the respiratory burst generated by phagocytes, as demonstrated in a number of studies [16, 17]. However, these observations were not confirmed in a multi-center prospective study carried out in Argentina [18]. Further studies are needed to assess the dependence of proton pump inhibitors and the incidence of SBP.

Prognosis in spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is one of the most common infectious diseases in patients with cirrhosis and is associated with a serious prognosis [7]. The 30-day mortality rate is estimated at 26-48.7% [19-21].

Resistance to third generation cephalosporins, ineffectiveness of empiric therapy and nosocomial infection are factors that increase 30-day in-hospital mortality [21, 22]. In addition, this relationship was demonstrated for acute renal failure, severe sepsis, shock, hemodynamic instability, severity of liver disease and HCC [21, 23].

Death in the course of SBP may occur directly in the course of the disease or in connection with the decompensation of liver function provoked by the infection and manifested as hepatic encephalopathy or hepatorenal syndrome. Bleeding from esophageal varices may also occur more often [12, 24].

SBP, accounting for 22.5% of infectious etiology of acute on chronic liver failure (ACLF), is one of its most frequent causes [25].

After the SBP episode, the 1-year survival rate is estimated at 30% to 50% and 5-year survival at 15.2% [26, 27]; therefore the past disease history is an indication for qualification for liver transplantation [7].

The hepatorenal syndrome develops in 33% of patients with SBP and is the strongest predictor of in-hospital mortality in this group [28], which can reach as high as 67%. Treatment of SBP with antibiotic administered with albumins compared to antibiotic alone was associated with decreased incidence of renal impairment (10% vs. 33%) [29]. Infection may be manifested as the systemic inflammatory response syndrome (SIRS), sepsis, multiple organ failure, acute on chronic liver failure and death [30].

In patients with ascites in the course of cirrhosis, controlled in conditions outside the hospital, SBP was found in 1.3-3.5% [31, 32]. In hospitalized patients, the disease is present upon admission or develops already during hospitalization in 25-35% [2, 33]. The risk of recurrence of SBP within one year from the first episode is estimated at 34-70% [27, 34].

The risk factors for recurrent disease include female sex, hepatic encephalopathy, urinary tract infection and protein concentration in ascitic fluid < 1 g/dl [27, 34].

In addition, a higher relapse rate was observed in patients with advanced liver disease expressed by elevated bilirubin (> 1 or > 4 mg/dl) and hypoprothrombinemia < 45%. In a study conducted on 238 people in Pakistan, the protective effect of hepatitis B was demonstrated [27, 34].

Etiological factors responsible for the development of spontaneous bacterial peritonitis

In studies conducted in the last century in positive cultures of ascitic fluid in patients with SBP, G-negative intestinal bacteria sensitive to third generation cephalosporins were most commonly cultured. G-positive bacteria were responsible for about 1/4 episodes of SBP [35, 36]. However, with increasing frequency of hospitalization, the use of invasive procedures, increased exposure to broad-spectrum antibiotics and

the widespread SBP antibiotic prophylaxis with fluoroquinolones, the profile of pathogens causing spontaneous bacterial peritonitis began to change. Currently, multi-drug resistant pathogens – that is, resistant to antibiotics from 3 or more groups, including β-lactams – are increasingly isolated [20]. Based on the site of infection, SBP was divided into nosocomial (hospital acquired – HA), health-care associated (HCA) and community acquired (CA) – this division commonly reflects antibiotic resistance of the pathogens.

Enterobacteriaceae producing ESBL (extended spectrum β-lactamases) are a particular problem, especially in HA infections, as in addition to resistance to third generation cephalosporins they often contain genes that cause resistance to other antibiotic groups, e.g. quinolones and tetracyclines [37]. The number of infections caused by G-positive bacteria, including enterococci and MRSA, is also increasing, which is particularly affected by the prophylactic use of fluoroquinolones [38]. This phenomenon results in the ever-lower effectiveness of the empirical first-line therapy applied so far and the outdated guidelines being followed (Table 1).

In a prospective study, carried out in 2 stages, Fernandez *et al*. analyzed bacterial infections in patients with liver cirrhosis and ascites, hospitalized in 2005-2007 and 2010-2011, taking into account the place of acquisition of infection (HA, HCA, and CA). In the first group of 507 infections in 223 patients, multi-drug resistant strains were detected in 4%, 14% and 35% of patients with CA, HCA and HA infection, respectively. In addition, there was a significantly higher incidence of septic shock (25% vs. 10%) and higher mortality in infections caused by multi-drug resistant bacteria than other pathogens (25 vs. 12%) [33].

Similar results were obtained in a study conducted in Germany on 311 patients with liver cirrhosis and ascites. Tests of ascitic fluid confirmed SBP in 197 patients, and positive cultures were found in 114 patients. Gram-positive bacteria accounted for 47.8%, of which *Enterococcus* represented 26.1%, and *Staphylococcus* spp. 13.8%. Third generation cephalosporins were effective in 70.2% of CA infections, but only in 56.3% of HA infections. Positive ascites and MELD score were associated with shorter survival. Piperacillin with tazobactam was found to be a high-activity antibiotic both in HA and CA SBP (85.1% and 92.5%, respectively) [39].

In the study carried out in the Central European region similar results were obtained, with 89% of bacteria causing SBP (in 4 out of 5 cases) proving to be G-positive. With piperacillin-tazobactam used as a drug of first choice a therapeutic response was achieved in 78% of patients [40].

In another study conducted on a large group of patients in France, there was a definite preponderance of Gram-positive bacteria, which accounted for 70% of cultivated pathogens from HA infections, including MRSA (24.8%). The analyzed group also had higher mortality among patients infected with *Staphylococcus*, older age and with more advanced liver disease expressed by a higher Child-Pugh score [41].

The profile of SBP-inducing bacteria varies depending on the geographical region and can be different even between individual hospitals in a given country – *Enterobacteriaceae* producing ESBL dominate in Eastern Europe and Asia, while methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) dominate in the US and South America. Carbapenemase-producing *Klebsiella pneumoniae* is increasingly isolated in Italy [42] – therefore first-line empirical antibiotic therapy should be chosen according to the local epidemiology.

Characteristics of SBP-inducing pathogens vary depending on where the infection was acquired. In hospital-acquired infections, multi-drug resistant pathogens are more often cultivated, which in turn contributes to less effective treatment and worse prognosis [21, 33]. Other risk factors for multi-drug resistant bacteria infection include long-term prophylactic use of norfloxacin, previous multi-drug resistant bacterial infection, recent treatment with β-lactams and advanced liver disease expressed by the MELD score [19, 33, 43-45].

Therapeutic treatment in spontaneous bacterial peritonitis in the era of increasing drug resistance of pathogens

According to the current guidelines of the European Association for the Study of the Liver (EASL) in the treatment of SBP in empiric antibiotic therapy, a third-generation cephalosporin, cefotaxime, is recommended 2.0 g every 12 h or every 8 h for a minimum period of 5 days. As alternatives, amoxicillin with clavulanic acid and fluoroquinolones – ciprofloxacin/ofloxacin are proposed, but not for patients using norfloxacin prophylactically and from areas with high rates of resistance to fluoroquinolones. The American Association for the Study of Liver Diseases (AASLD) guidelines additionally take into account the place of acquisition of the infection and previously used antibiotic therapy. In HA infections and in the use of β-lactams, we recommend a personalized therapy based on the local profile of antibiotic susceptibility in patients with cirrhosis. Ofloxacin used orally (400 mg every 12 hours) is proposed as a second-line drug but only

Table 1. Characterization of pathogens cultivated from cultures of body fluids in patients with cirrhosis [2, 20, 22, 30, 35-39]

Center/Author/Year	Number of patients	Drug-resistant bacteria	G+	G–	Prognosis
Spain/Fernandez *et al.*/1998-2000	405 persons 572 infections 138 SBP	Norfloxacin prophylactically 50% – resistant to ciprofloxacin Without norfloxacin 16%	53%		
Greece/Alexopoulou *et al.*/2008-2011	47 SBP	9-19% MDR carbapenemase producing *K. pneumoniae* – 4 ESBL *E. coli* – 3 *P. aeruginosa* – 2 67% – patients using quinolone prophylaxis (24% without prophylaxis)	55% *Streptococcus* – 10 *Enterococcus* – 9 *K. pneumoniae* – 5	*E. coli* – 8%	
Germany/Friedrich/ 2007-2013	113 SBP		47.8% *Enterococcus* spp. – 26.1% *Staphylococcus* – 13.8%	44.9% *Enterobacter* spp. – 40.6%	
Greece/Alexopoulou/ 2012-2014	130 SBP	20.8% XDR – 10% *P. aeruginosa* – 5	*Enterococcus* spp. – 30 *Streptococcus* spp. – 25 *S. aureus* – 8	*E. coli* – 33 *K. pneumoniae* – 16	37.7% – 30-day mortality Factor associated with mortality – XDR infection
Portugal/Oliveira/ 2009-2014	139 SBP	MDR – 17% Resistance to quinolones – 33%	42%		Mortality dependent of CRP, MELD
Korea/Cheong/ 2000-2007	236 SBP	Resistance to cef. III gen. – 41% HA 19% CA Resistance to quinolones 50% HA 30.9% CA	*Streptococcus* – 9.8%	*E. coli* – 43.2% *Klebsiella* spp. – 14%	30-day mortality HA – 58.7% CA – 37.3% Risks: HCC, AKI, HA, shock, resistance to cef. III gen.
France/Bert/ 1998-1999	70 persons 78 pathogens SBP	48.7% HA resistant to amox-clav vs. 18.4% CA 33.3% HA resistant to cefotaxime vs. 13.2% CA	57.1% *Streptococcus* – 48.5% *S. aureus* – 8.5%	50% *E. coli* – 32.8%	
France/Piroth/ 2010-2011	57 episodes of SBP 140 – bacterascites	12.68% 4.8% – VRE 1.11% – MRSA (3) 3.73% ESBL *E. coli*	64.9% *Enterococcus* – 24%	33.9% *E. coli* – resistant to amox-clav 37.5% resistant to cef. III gen. 10.5%	26.8% died
Spain/Fernandez/ 2005-2007, 2010-2011	223 persons 507 infections 110 persons 162 infections	18% – 35% HA *Enterobacteriaceae* ESBL – 43 persons *P. aeruginosa* – 17 persons MRSA – 14 *Enterococcus faecium* – 14			

XDR – extensively drug resistant – pathogens insensitive to at least one drug from all but two or fewer groups of available drugs; HA – hospital acquired; CA – community acquired

with no exposure to quinolones, vomiting, shock, grade II or higher encephalopathy, or an increase in creatinine greater than 3 mg/dl [7, 46].

According to the above recommendations, this therapy was effective in 77-98% of cases, and most often G-negative aerobic bacteria, sensitive to β-lactams, were the bacteria responsible for SBP.

Along with the change in the characteristics of pathogens inducing SBP, the efficacy of previously recommended therapeutic regimens has ceased to be sufficient (Table 2).

Comparing the efficacy of 7-day meropenem and daptomycin therapy to ceftazidime therapy, where the regression of ascitic fluid changes was considered as

Table 2. Comparison of efficacy of SBP treatment with third generation cephalosporins [21, 23, 30, 35-37]

Country/author/year	Number of patients	% efficacy HA	% efficacy HCA	% efficacy CA
Spain/Fernandez *et al.*/2005-2007	507 infections in 223 patients	40%	73%	83%
Spain/Ariza *et al.*/2001-2009	200 persons 246 cases of SBP	59.1%*	78.9%*	92.9%*
Germany/Friedrich *et al.*/2007-2013	113	56.3%	70.2%	
Italy/Angeloni/2004-2006	38		59%	
France/Piroth/2010-2011	57 cases of SBP 140 bacterascites		39.5%	
Greece/Alexopoulou/2008-2011	47		51%*	

**percentage of strains susceptible to third generation cephalosporins*

Table 3. Proposed antibiotic therapy in SBP

	In-hospital	Out-of-hospital
Low percentage of MDR	Piperacillin + tazobactam	Cefotaxime/ceftriaxone or amoxicillin + clavulanic acid
High percentage of *Enterobacteriaceae* ESBL +	Meropenem	–
High percentage of VSE/MRSA	Meropenem + vancomycin/teicoplanin	–

effective therapy, a significant advantage of the first regimen was demonstrated – 86.7% compared to 25%.

In addition, the ineffectiveness of initial antibiotic therapy was a prognostic factor decreasing the 90-day survival time without the need for liver transplant [47]. Comparable results were obtained in the aforementioned study by Fernandez *et al*. The effectiveness of currently recommended first-line therapies in the treatment of HA infections in cirrhotic patients was only 40%, with HCA 73% and CA 83%. The effectiveness of 3rd generation cephalosporins in SBP was 26% [33].

In infectious diseases, especially in patients with cirrhosis, including SBP, it is of fundamental importance to quickly diagnose and implement effective antibiotic therapy. Delay in the implementation of adequate treatment is associated with therapeutic failures and increased mortality [7, 42].

Considering the high percentage of multi-drug resistant pathogens in HA infections, it is reasonable to make the choice of empirical therapy dependent on the place of acquisition of the infection. The local profile of antibiotic resistance should also be considered in the selection of the initial antibiotic therapy. According to EASL recommendations from 2013, developed at a conference in Barcelona, dedicated to infections in liver cirrhosis, in patients with HA infections, treatment depends on the local profile of drug resistance of pathogens. Piperacillin/tazobactam is the preferred first-line treatment, with a low percentage of drug-resistant bacteria. In hospitals with a high percentage of positive ESBL Enterobacteria, meropenem is recommended additionally with a glycopeptide (vancomycin or teicoplanin) with high prevalence of MRSA or VSE (vancomycin-susceptible *Enterococcus*). For the treatment of VRE (vancomycin-resistant *Enterococcus*), it is recommended to administer linezolid (Table 3).

Third generation cephalosporins – ceftriaxone or cefotaxime, or amoxicillin/clavulanic acid – are recommended in CA and HCA infections. However, in the case of a severe course of infection or a high percentage of drug-resistant pathogens in a given center, in HCA infections treatment is recommended as in hospital-acquired infections [42].

This approach is confirmed by the results of a study conducted in Italy on 94 patients with liver cirrhosis and HA infections. Patients were divided into two groups, one of which was treated with broad-spectrum antibiotics – imipenem/cilastatin ± vancomycin, azithromycin, tigecycline depending on the location of infection and standardized cephalosporins of the 3rd generation in SBP, bacteremia and cholecystitis or amoxicillin/clavulanic acid ± azithromycin at other infection locations. In-hospital mortality in the group treated with broad-spectrum antibiotics was 6% compared to 24% in the second group of patients. Similarly, the percentage of therapeutic failures was lower in the first group (18% vs. 51%) [48].

With a positive result of ascitic fluid culture, which is obtained in 50-65% of cases, it is necessary to appropriately modify antibiotic therapy, if possible with antibiotics with a narrower spectrum in order to reduce the risk of developing drug-resistant strains [7, 42].

It was not proven that the prolongation of antibiotic therapy would improve the effectiveness of treatment; therefore a 5-day treatment is recommended. On the second day of therapy, a check-up of ascitic fluid should be performed – an effective treatment is demonstrated by the reduction of the PMN amount by at least 25% of the initial value [1].

Patients with SBP have an increased incidence of hepatorenal syndrome, which may be associated with secondary to infection reduction of the effective volume of blood reaching the kidneys. It is a factor significantly worsening the prognosis; therefore, in addition to antibiotic therapy in the treatment of SBP, intravenous infusions of albumin in a dose of 1.5 g/kg on the day of diagnosis and 1 g/kg on the third day should be used [29]. This has been shown to reduce in-hospital mortality and prolong survival in patients at higher risk of death defined as creatinine concentration < 88 μmol/l and bilirubin < 68 μmol/l. This procedure is recommended for everyone, in the absence of unambiguous data demonstrating the ineffectiveness of such a procedure in a group of patients with a lower risk of death [7, 49]. Additionally, administration of albumins in SBP was associated with decreased concentration of proinflammatory cytokines and inflammatory response mediators such as nitric oxide, tumor necrosis factor α and interleukin 6 [49].

Although probiotics might be helpful with restoring the intestinal microflora, they were not proven to reduce SBP incidence [5].

Spontaneous bacterial peritonitis prophylaxis

According to the EASL guidelines, the use of antibiotic prophylaxis due to the induction of drug-resistant strain selection must be reserved only for patients with the highest risk of SBP. Three groups of patients at high risk of developing the disease were distinguished: patients with acute gastrointestinal bleeding, with low total protein concentration in ascitic fluid – even without a previous SBP episode – and patients with a previous SBP episode [7].

The EASL guidelines, in prophylaxis of SBP, recommend that patients from the last two groups be administered a fluoroquinolone antibiotic, norfloxacin, as the first-line drug. Prophylactic use of norfloxacin on the one hand prevents the occurrence of SBP recurrence in patients with risk factors, while on the other hand, it contributes to the development of antibiotic-resistant strains [2]. Long-term use of norfloxacin increases the risk of infection with ESBL-producing *Enterobacteriaceae* by 4 times. This relationship was not found for antibiotics not absorbed from the gastrointestinal tract, including rifaximin [42, 50]. A study in Egypt on 262 people comparing the efficacy of rifaximin and norfloxacin in the prevention of SBP recurrence demonstrated a significant advantage of rifaximin. The relapse rate in the rifaximin group was 3.88% in comparison to 14.13% in the norfloxacin group. There was also a lower mortality rate in the first group of patients, and an additional positive effect, i.e. less frequent occurrence of hepatic encephalopathy [51].

Rifaximin is proposed as an alternative to fluoroquinolones for use in the prophylaxis of SBP. However, more randomized, multi-center studies are needed, including comparing the efficacy of rifaximin with norfloxacin in the prevention of SBP.

The relationship between bleeding from esophageal varices – a common complication of liver cirrhosis – and portal hypertension and bacterial infection has been confirmed in numerous studies. The presence of bacterial endotoxins in the systemic circulation stimulates the production of pro-inflammatory cytokines, which contribute to increased pressure in the portal system and exacerbate hemostasis disorders, increasing the risk of bleeding. On the other hand, due to bleeding from esophageal varices, the patient undergoes numerous invasive procedures, and hypovolemia caused by bleeding increases the bacterial translocation and additionally impairs the functioning of the mononuclear phagocytic system, increasing the risk of infection. Prophylactic antibiotic therapy when diagnosing bleeding from esophageal varices increases the effectiveness of bleeding treatment and reduces mortality. According to the EASL guidelines, ceftriaxone is recommended as a drug of choice in patients with advanced liver disease defined as the presence of 2 of the following: ascites, significant malnutrition, encephalopathy, bilirubin concentration above 3 mg/dl. On the other hand, norfloxacin 500 mg every 12 hours for 7 days or another fluoroquinolone antibiotic is recommended in patients with less advanced disease [7, 12].

Conclusions

In Poland, no broader studies assessing the pathogen characteristics of SBP have been carried out so far. However, data on drug-resistant pathogens in Poland, as in other European countries, are alarming. The percentage of *Klebsiella pneumoniae* strains resistant to 3rd generation cephalosporins, as well as fluoroquinolones and aminoglycosides, is increasing; in 2016 in Poland it exceeded 50%. The percentage of *Escherichia coli* resistant to third generation cephalosporins in Poland in 2016 was 10-25% and with additional resistance to

fluoroquinolones and aminoglycosides 5-10%, MRSA 10-25% [52]. These data indicate that also in Poland there is a risk of reduced effectiveness of previously recommended first line antibiotic therapy in SBP and this should be taken into account in clinical practice.

Determining the profile of the etiological factors of SBP in a given treatment entity seems to be crucial for the development of appropriate, individualized therapeutic standards in the era of increasing drug resistance of bacteria.

Disclosure

The authors report no conflict of interest.

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