PREVALENCE AND CLINICAL OUTCOME OF SPONTANEOUS BACTERIAL PERITONITIS IN HOSPITALIZED PATIENTS WITH LIVER CIRRHOSIS: A PROSPECTIVE OBSERVATIONAL STUDY IN CENTRAL PART OF CROATIA

Ivan Gunjača¹, Ivan Francetić²

¹Division of Gastroenterology, Department of Medicine, Karlovac General Hospital, Karlovac, ²Department of Clinical Pharmacology, University Department of Medicine, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – Spontaneous bacterial peritonitis (SBP) is a serious complication of liver cirrhosis and is defined as infected ascites in the absence of any recognizable secondary cause of infection. The aim of the study was to evaluate the prevalence, incidence, pathogens and clinical outcome of SBP. This prospective observational study included 108 cirrhotic patients with ascites treated during 18 months. Patients were divided into two groups according to diagnostic criteria of SBP: SBP group (n=23) and non-SBP group (n=85). Differences in clinical outcomes between the two groups were analyzed, including mortality rate, incidence of gastrointestinal bleeding, bacteremia/sepsis and frequency of rehospitalization. The pathogens responsible for SBP were analyzed in SBP group. The prevalence of SBP was 21% and incidence 14.1% per year. Statistically significant between-group differences were recorded in mortality (26% vs. 4.7%; P=0.017), incidence of gastrointestinal bleeding (39% vs. 11.7%; P=0.015) and rehospitalization frequency (47.8% vs. 20%; P=0.05). The incidence of sepsis following episode of gastrointestinal bleeding was similar in both groups (55.5% vs. 50%; P=0.892). The following pathogens were responsible for SBP: Escherichia coli (n=7), MRSA (n=2), Acinetobacter spp. (n=2), Staphylococcus aureus (n=1), Streptococcus spp. (n=1), Staphylococcus epidermidis (n=1) and Enterococcus faecalis (n=1). As indicated by study results, the incidence and mortality of SBP were high. Patients with liver cirrhosis and gastrointestinal hemorrhage were found to be at a high risk of developing sepsis with or without clinically proven SBP. The pathogens responsible for SBP were mostly gram-negative microorganisms; however, there were also a significant proportion of gram-positive microorganisms and hospital infections with antibiotic-resistant bacteria. Study results suggested the spectrum of pathogens to change due to the selection of antibiotic-resistant bacteria within the hospital setting.

Key words: Liver cirrhosis – complications; Liver cirrhosis – microbiology; Peritonitis – etiology; Peritonitis – microbiology; Bacterial infections – etiology; Bacterial infections – diagnosis; Croatia

Introduction

Spontaneous bacterial peritonitis (SBP) is a serious complication in cirrhotic patients with ascites. In 1971, Conn and Fessel described a syndrome of infected ascitic fluid in patients with hepatic cirrhosis,
which they named SBP\textsuperscript{1}. SBP is by definition an infection of previously sterile ascitic fluid, without any apparent intra-abdominal source of infection\textsuperscript{2}. The pathophysiology of SBP is not completely understood, but evidence suggests that bacteria translocate from the intestinal lumen to the systemic circulation, causing bacteremia and subsequent colonization of the ascitic fluid\textsuperscript{3,4}.

Recent studies using newer diagnostic criteria and improved culture techniques have estimated the prevalence of SBP to 10%-30% of cirrhotic patients with ascites admitted to hospitals. Since clinical manifestations of SBP are non-specific, the diagnosis of SBP is established by the polymorphonuclear cell count in ascitic fluid of 250 cells/mm\textsuperscript{3} (culture-positive neutrophytic ascites)\textsuperscript{6}. The organism responsible for the infection is isolated in 60%-70% of cases if using improved culture methods. The ascitic fluid obtained from paracentesis should be inoculated in blood culture bottle. Compared with conventional culture techniques, this procedure significantly increases the detection rate of responsible microorganism\textsuperscript{7-9}. In patients with SBP, studies based on quantitative cultures of ascitic fluid have shown a median bacterial concentration of one to 70% of cirrhotic patients with ascites admitted to hospitals. Since clinical manifestations of SBP are non-specific, the diagnosis of SBP is established by the polymorphonuclear cell count in ascitic fluid of 250 cells/mm\textsuperscript{3} (culture-positive neutrophytic ascites)\textsuperscript{6}. The organism responsible for the infection is isolated in 60%-70% of cases if using improved culture methods. The ascitic fluid obtained from paracentesis should be inoculated in blood culture bottle. Compared with conventional culture techniques, this procedure significantly increases the detection rate of responsible microorganism\textsuperscript{7-9}. In patients with SBP, studies based on quantitative cultures of ascitic fluid have shown a median bacterial concentration of one

Material and Methods

The study was a hospital based prospective cohort study of 18 month duration (January 2006 to June 2007). The study was conducted at a regional hospital in Karlovac, situated in central Croatia. Karlovac General Hospital has a catchment population of 150 000. The aim of the study was to assess the prevalence and incidence of SBP and clinical outcome of study patients. The study included 108 patients with liver cirrhosis admitted to Department of Medicine and Intensive Care Unit (ICU). Inclusion criteria were clinical liver cirrhosis with ascites and upper GI hemorrhage in patients with clinical signs of liver cirrhosis and ascites. Exclusion criteria were ascites due to renal, cardiac, tubercular or malignant pathology and secondary peritonitis.

Cirrhosis was diagnosed clinically, using laboratory tests, sonographic and endoscopic methods. Each patient was classified according to Child-Pugh classification\textsuperscript{8} as a scoring system grading the severity of chronic liver disease. The Child-Pugh score is calculated by assigning 1 point for any feature in column 1, 2 points for any feature in column 2, and 3 points for any feature in column 3; class A ≤6; class B 7-9; and class C ≥10 (Table 1). Patients were not selected according to sociodemographic characteristics, education and clinical status. Patients were included irrespective of their hepatitis B or C viral status. The patients with appropriate indication were also subjected to abdominal paracentesis with ascites evacuation. With all aseptic precautions by inserting a 22- or 18-gauge needle in the left iliac fossa or midline just below the umbilicus, abdominal paracentesis was performed and samples referred to the laboratory. Ascitic fluid was collected into ethylene diamine tetracetic
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Acid (EDTA) tube for total leukocyte count and differential leukocyte count; into plain vial for biochemical analysis; and 10 mL of ascitic fluid were inoculated in standard microbiological culture (which was a standard procedure at our hospital in 2006) or in blood culture bottle (BacT/ALERT® FA, Biomerieux Inc., Durham, USA; standard procedure at our hospital in 2007). We used the usual biochemical, microbiologic and cytologic analytical methods to determine specific weight, total protein, glucose, LDH, and total leukocyte and neutrophil counts per mm$^3$. Total leukocyte count and differential leukocyte count were determined on a Cell- DYN 3200® (Abbott Diagnostics International).

Cases with ascites were labeled as having SBP and were enrolled in the study if the ascitic fluid analysis showed either or both of the following: total polymorphonuclear count $>$250 cells/mm$^3$ and ascitic fluid culture positive without surgical cause of infection. SBP was diagnosed using standard criteria, i.e. absolute neutrophil count $>$250 cells/mm$^3$ (neutrocytic ascites) in the absence of an intra-abdominal source of infection; and ascitic fluid cultures positive and neutrophil count $>$250 cells/mm$^3$ (culture-positive neutrocytic ascites). If the ascitic fluid cultures were negative in the presence of neutrocytic ascites, these patients were characterized as having culture-negative neutrocytic ascites (CNNA). Patients with positive ascitic fluid cultures but without neutrocytic ascites were classified as having bacterascites.

Paracentesis was performed as early as possible after hospitalization, before starting antibiotics. Antibiotics (ceftriaxone 2x1 g, 12 hourly, intravenously for five to seven days, alternative regimes were ciprofloxacin 2x400 mg or amoxicillin with clavulanic acid 3x1, 2 g) were started in those patients that had the ascitic fluid polymorphonuclear count of more than 250/mm$^3$. Antibiotic therapy was modified empirically or on the basis of culture sensitivity result (if available).

The patients were clinically treated for decompensated liver cirrhosis. In case of complications, treatment was administered according to literature recommendations$^{10}$. All the aforementioned pertinent data (clinical parameters, laboratory findings, ultrasonography findings, and microbiologic specimens) were then fed into a Microsoft Excel spreadsheet and statistically processed using the Statistica 7.0 software (Statsoft Inc., Tulsa, USA).

Study patients were divided into two groups. Group 1 (SPB group) included patients with clini-

| Table 1. Child-Pugh classification of cirrhosis |
|-----------------|-----------|-----------|
| Factor          | 1         | 2         | 3         |
| Encephalopathy  | None      | Stage I-II| Stage III-IV |
| Ascites         | None      | Easily controlled | Poorly controlled |
| Bilirubin (mg/dL) | $<$2     | 2-3       | $>$3       |
| Albumin (g/dL)  | $>$3.5    | 3-3.5     | $<$3       |
| Prothrombin time (second prolonged) | 0-4 | 4-6 | $>$6 |

| Table 2. Results according to patient groups |
|-----------------|-----------|-----------|
| Patient group   | SBP  | Non-SBP | Total |
| No. of patients | n=23 (21.2%) | n=85 (78.8%) | N 108 |
| No. of deceased | 6 | 4 | 10 |
| Total mortality rate per year | 26% | 4.7% | 9.2% |
| Average Child-Pugh class | C (11.7) | B (8.2) | B |
| No. of rehospitalized patients per year | 11/23 (47.8%) | 17/85 (20%) | 27/108 (25%) |
| No. of patients with gastrointestinal bleeding with/without endoscopic interventions | 9/23 (39%) | 10/85 (11.7%) | 19/108 (17.5%) |
| Sepsis/bacteremia after endoscopic intervention | 5/9 (55.5%) | 5/10 (50%) | 10/19 (52.6%) |

SBP = spontaneous bacterial peritonitis
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Introduction

The prevalence of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis has been found to be between 10% and 50%. The incidence of SBP in patients with cirrhosis is 14.1% per year. The leading etiology of chronic liver disease was alcohol related cirrhosis, followed by virus related cirrhosis, hemochromatosis, idiopathic hepatitis, primary biliary cirrhosis, and autoimmune hepatitis. Eighteen patients had a past history of ascitic fluid paracentesis, but none of them had documented SBP and/or having received SBP prophylaxis.

Methods

Study results are presented in Table 2. Our prospective study included 108 patients (74 male and 34 female), mean age 57.4±15.1 years, with decompensated liver cirrhosis with ascites, hospitalized at Department of Medicine, Karlovac General Hospital. Study patients were divided into two groups: SBP group (n=23; 21.2%) and non-SBP group (n=85; 78.8%) (Fig. 1). The prevalence of SBP during the 18-month study period was 21.2%. It is interesting to note that the prevalence of SBP among patients included in the study in 2007 was as high as 33%. The incidence of SBP in our cirrhotic patients was 14.1% per year. The leading etiology of chronic liver disease was alcohol related cirrhosis (n=90), followed by virus related cirrhosis (n=12), hemochromatosis (n=2), idiopathic hepatitis related cirrhosis (n=2), primary biliary cirrhosis (n=1), and autoimmune hepatitis (n=1). Eighteen patients had a past history of ascitic fluid paracentesis, but none of them had documented SBP and/or having received SBP prophylaxis.

Results

Six deaths (mortality rate of 26%) were recorded in the SBP group and four deaths (mortality rate of...
The prevalence of SBP in hospitalized patients with liver cirrhosis ranged from 10% to 30% in unselected cirrhotic patients with ascites admitted to the hospital. Our study found a 21% prevalence of SBP in patients hospitalized with the clinical diagnosis of decompensated liver cirrhosis. The incidence of developing SBP in our cirrhotic patients was 14.1% per year. According to Navasa et al., the 1-year probability of developing a first episode of SBP in cirrhotic patients with ascites is approximately 10%. In a series of 127 patients admitted to the hospital for the treatment of an episode of ascites, Llach et al. showed the probability of developing a first episode of SBP to be 11% at 1 year and 15% at 3-year follow-up.

When the patients enrolled in the study in 2007 were analyzed separately, the prevalence increased to up to 33%, which could be explained by the diagnosis and management of SBP at our hospital. The present study was carried out by different clinicians according to a standardized protocol. Paracentesis and ascitic fluid biochemistry were performed in line with a uniform protocol, thus reducing variability in handling the ascitic fluid samples. During the study, we improved the microbiologic protocol for ascites. In 2007, the ascitic fluid obtained by paracentesis was inoculated into blood culture bottles. Compared with conventional culture techniques used in 2006, this procedure significantly increased the rate of detection of the responsible microorganisms. In our clinical practice, this improvement may have reflected on better results recorded in 2007. The variation in patient management due to the availability of the ascitic fluid analysis results reflected the practice in the ‘real world’.

The organisms cultured were predominantly gram-negative (60%); however, there were a significant proportion of gram-positive microorganisms (40%) and hospital infections with MRSA and *Acinetobacter baumanii* (26.6%). The spectrum of bacteria cultured in the study included *Escherichia coli* (n=7), MRSA (n=2), *Acinetobacter* species (n=2), *Staphylococcus aureus* (n=1), *Streptococcus* spp. (n=1), *Staphylococcus epidermidis* (n=1) and *Enterococcus faecalis* (n=1) (Table 3).

**Table 3. Organisms detected in spontaneous bacterial peritonitis culture positive cases**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>7</td>
<td>43.7</td>
</tr>
<tr>
<td>MRSA</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td><em>Acinetobacter</em> species</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td><em>Streptococcus</em> group A and B</td>
<td>1</td>
<td>6.2</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>1</td>
<td>6.2</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>1</td>
<td>6.2</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>1</td>
<td>6.2</td>
</tr>
</tbody>
</table>

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in this study differed from those reported from some previous studies in hospitalized patients with cirrhotic ascites. In a study by Fernandez et al., gram-positive organisms cultured were explained by norfloxacine prophylaxis or previous interventions. Different studies evaluated the emergence of antibiotic-resistant bacteria in cirrhotic patients undergoing selective intestinal decontamination for the prevention of SBP. 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. More recently, the prevalence of such infections has been found to have increased. A recent study 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 in patients receiving quinolone prophylaxis were mostly due to gram-positive organisms (79%). This study also showed the emergence of severe nosocomial staphylococcal infections due to methicillin-resistant strains.

Although our patients did not receive antimicrobial prophylaxis, a high number of hospital acquired infections was explained by the use of broad-spectrum antibiotics for urinary infections, pneumonia, cutaneous abscesses, sepsis, etc. Many of our patients had prolonged stay at Intensive Care Unit (ICU) and were intubated with vascular and other catheters, which could be an independent risk factor for developing nosocomial SBP.

The significant proportion of gram-positive microorganisms and hospital infections recorded in our study suggested that the selection of antibiotic-resistant bacteria led to dissemination within the hospital setting. The results of our study point to the need of additional investigation of the risk factors for developing nosocomial SBP.

The outcome in cirrhotic patients with SBP has improved dramatically during the last 20 years. In studies published before 1980, the rate of SBP resolution ranged between 25% and 50% and patient survival between 0% and 20%. In recent studies, the respective figures are 70%-90% and 50%-70%. In our study, the 1-year mortality was 26% in liver cirrhosis patients with SBP and 4.7% in patients without SBP (*P*<0.017). According to the literature, the 1- and 2-year probability of survival after an episode of SBP is 30% and 20%, respectively.

SBP recurrence is common in patients that have recovered from an episode of SBP, estimated to 43% at 6 months and 69% at 1 year. In our study, the frequency of cirrhotic patient rehospitalization within a year was significantly higher in SBP group (47.8% vs. 20.0%; *P*=0.05) (Fig. 3).

During hospital stay, cirrhotic patients with SBP suffered from GI bleeding and were subjected to endoscopic interventions more frequently than those without SBP (39% vs. 11.7%; *P*=0.015) (Fig. 4). These results support the conclusion that bacterial infections are frequently associated with upper GI bleeding in cirrhotic patients. Recent reports on advances in clinical practice suggest that bacterial infections are frequently associated with upper GI bleeding in cirrhotic patients, which develops in up to 66% (20% within the first 48 hours and 35%-66% within two weeks). About two thirds of these infections are present at hospital admission, whereas the remaining third develop during admission as compared with 5% to 7% in the general hospital population. Our results suggest a similar conclusion.

In the aftermath of GI bleeding and endoscopic interventions, sepsis with proven bacteremia was recorded in five SBP and non-SBP patients each (55.5% vs. 50%; *P*=0.892) (Fig. 5). This result supports a conclusion that bacteremia and systemic infection are often complications of GI bleeding in cirrhotic patients. Sepsis in cirrhotic patients with proven bacteremia was found in both groups in similar proportion. Development of SBP after an episode of bacteremia was in correlation with the stage of liver disease. The mean Child score was 11.7 (Child C) in SBP group and 8.2 (Child B) in non-SBP group. It is concluded that the development of sepsis and SBP after GI bleeding episode are two independent risk factors. The strong association between infection and variceal bleeding in cirrhotic patients has been confirmed in several studies, including association with failure to control bleeding, early rebleeding and mortality.

In conclusion, spontaneous bacterial peritonitis is a frequent and severe complication in cirrhotic patients...
with ascites. Although SBP prognosis has improved in recent years, the complications and mortality rate associated with this bacterial infection are still high. Patients with cirrhosis and SBP have numerous complications and consequently invasive procedures and ICU treatment are often needed. Our results showed the gram-negative microorganisms to predominate in SBP infections; however, there also were a significant proportion of gram-positive microorganisms and hospital infections with antibiotic-resistant bacteria. The significant proportion of gram-positive and hospital acquired infections raise concern about the selection of antibiotic-resistant bacteria in cirrhotic patients and their dissemination within the hospital environment.

References

Sažetak

UČESTALOST I KLINIČKI ISHOD SPONTANOG BAKTERIJSKOG PERITONITISA U BOLNIČKI LIJEČENIH BOLESNIKA S JETRENOM CIROZOM: PROSPEKTIVNO OPSERVACIJSKO ISPITIVANJE U SREDIŠNJOJ HRVATSKOJ

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Spontani bakterijski peritonitis (SBP) je ozbiljna komplikacija izazvana cirozom jetre, a definira se kao inficirani ascites u odsutnosti bilo kakvog prepoznatljivog sekundarnog uzroka infekcije. Cilj ove studije bio je utvrditi učestalost, incidenciju, patogene i klinički ishod. U ovoj prospektivnoj studiji procijenjeno je 108 bolesnika s jetrenom cirozom i ascitesom liječenih u razdoblju od 18 mjeseci. Bolesnici su bili podijeljeni u dvije skupine prema dijagnostičkim kriterijima za SBP: skupina SBP (n=23) i skupina ne-SBP (n=85). Analizirale su se razlike među dvjema skupinama u kliničkom ishodu, odnosno stopa smrtnosti, incidencija gastrointestinalnog krvaenja, bakteremija/sepsa i učestalost ponovnog prijma u bolnicu. U skupini SBP analizirali su se i uzročnici odgovorni za SBP. Učestalost SBP kod naših bolesnika bila je 21%, a rizik incidencije 14,1% na godinu. Utvrđena je statistički značajna razlika među dvjema skupinama u smrtnosti (26% prema 4,7%; \(P=0,017\)), incidenciji gastrointestinalnog krvaenja (39% prema 11,7%; \(P=0,015\)) i učestalosti ponovnog prijma u bolnicu (47,8% prema 20%; \(P=0,05\)). Incidencija sepse nakon epizode gastrointestinalnog krvaenja bila je slična u dvjema skupinama (55,5% prema 50%; \(P=0,892\)). Za SBP su bili odgovorni slijedeći uzročnici: *Escherichia coli* (n=7), MRSA (n=2), *Acinetobacter* spp. (n=2), *Staphylococcus aureus* (n=1), *Streptococcus* spp. (n=1), *Staphylococcus epidermidis* (n=1) i *Enterococcus faecalis* (n=1). U našim bolesnicima bilježi se visoka incidencija i smrtnost od SBP. Bolesnici s jetrenom cirozom i gastrointestinalnim krvaenjem imaju visok rizik za razvoj sepse s klinički dokazanim SBP ili bez njega. Među patogenima odgovornim za SBP prevladavaju gram-negativni mikroorganizmi, no zabilježen je i značajan udio gram-pozitivnih mikroorganizama i bolničkih infekcija bakterijama otpornim na antibiotike. Rezultati ovog ispitivanja ukazuju na promjene u spektru patogena uslijed selekcije bakterija otpornih na antibiotike u bolničkoj sredini.

Ključne riječi: Ciroza jetre – komplikacije; Ciroza jetre – mikrobiologija; Peritonitis – etiologija; Peritonitis – mikrobiologija; Bakterijske infekcije – etiologija; Bakterijske infekcije – dijagnostika; Hrvatska