Spontaneous bacterial peritonitis: The clinical challenge of a leaky gut and a cirrhotic liver

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Abstract

Spontaneous bacterial peritonitis (SBP) is a frequent, life-threatening bacterial infection in patients with liver cirrhosis and ascites. Portal hypertension leads to increased bacterial translocation from the intestine. Failure to eliminate invading pathogens due to immune defects associated with advanced liver disease on the background of genetic predisposition may result in SBP. The efficacy of antibiotic treatment and prophylaxis has declined due to the spread of multi-resistant bacteria. Patients with nosocomial SBP and with prior antibiotic treatment are at a particularly high risk for infection with resistant bacteria. Therefore, it is important to adapt empirical treatment to these risk factors and to the local resistance profile. Rifaximin, an oral, non-absorbable antibiotic, has been proposed to prevent SBP, but may be useful only in a subset of patients. Since novel antibiotic classes are lacking, we have to develop prophylactic strategies which do not induce bacterial resistance. Farnesoid X receptor agonists may be a candidate, but so far, clinical studies are not available. New diagnostic tests which can be carried out quickly at the patient’s site and provide additional prognostic information would be helpful. Furthermore, we need tools to predict antibiotic resistance in order to tailor first-line antibiotic treatment of spontaneous bacterial peritonitis to the individual patient and to reduce mortality.

Key words: Ascites; Cirrhosis; Farnesoid X receptor; Liver; Nucleotide-binding oligomerization domain containing 2; Rifaximin; Prophylaxis; Spontaneous bacterial peritonitis; Toll-like receptor 2
INTRODUCTION

Patients in advanced stages of liver cirrhosis tend to develop bacterial peritonitis without evident source of infection, a form of infection which has been termed spontaneous bacterial peritonitis (SBP) in 1963[1]. Next to urinary tract infection, SBP is the most frequent infection in patients with advanced liver cirrhosis[2]. While it develops in up to 3.5% of patients that are treated as outpatients[3], its prevalence is as high as 12% in hospitalized patients[4,5]. In patients at high risk, SBP incidence can be reduced by prophylactic antibiotic treatment[6-8]. However, efforts to decrease the high mortality associated with SBP, ranging between 16% and 52%, had to face disappointing limitations[2,8,9]. Concerning antibiotic treatment and prophylaxis, the rise of bacterial resistance to antibiotics commonly used in patients with cirrhosis has reduced the therapeutic options[10]. In addition, attempts to decrease the prevalence of the indispensable underlying condition of SBP, liver cirrhosis, by modern antiviral treatment of viral hepatitis B and C, will probably be counterbalanced by the rising number of patients with non-alcoholic fatty liver disease[11]. Furthermore, SBP is recognised as an important marker of liver disease progression which might be the decisive watershed in the management of advanced liver disease[12]. It can be conceived as the clinically evident manifestation of bacterial translocation from the intestine, linking intestinal microbiome, genetic and acquired immune defects to the development of infection. Thus, SBP stays not only at the centre of liver disease pathophysiology, but also remains a challenge in clinical management. Neither reduction of the burden of liver disease nor development of new antibiotics to overcome bacterial resistance will occur in near future. Therefore, the challenge is to define subgroups of patients for optimal therapy in order to decrease failure of empirical therapy and exert low selection pressure on bacteria.

LEAKY GUT

The usual bacteria causing SBP in patients without prior antibiotic treatment or frequent hospitalisations are enteric bacteria, mostly *Escherichia coli* (*E. coli*)[13,14]. Upper gastrointestinal bleeding is the only major risk factor with sudden onset[15]. Usually, an external source of infection cannot be identified[16]. Taken together, these facts suggest that SBP is an endogenous infection, in general caused by transmigration of enteric bacteria to the ascites[17].

Apart from these clinical observations, experimental data also support this hypothesis. Bacterial translocation of enteric bacteria to mesenterial lymph nodes was not only observed in animal models[18,19] but also in patients with liver cirrhosis, in whom the prevalence of bacterial translocation increased with liver disease severity assessed by the Child-Pugh-Score[20]. In addition, indirect signs of bacterial translocation, such as elevated levels of lipopolysaccharide binding protein (LBP)[21] or bacterial DNA[22] are frequently found in patients with liver cirrhosis.

Nevertheless, bacteria from other sources are also found in ascites. Pyrosequencing of ascitic DNA for viable bacteria revealed that a substantial amount of non-enteric bacteria have access to the peritoneal cavity[23]. In patients, SBP may be caused by bacteria not known from the intestine: examples like SBP by *Pasteurella multocida* after a scratch of a pet dog[24] or in a pet holder[25] and SBP by bacillus *cereus*[26] indicate that any kind of bacteremia in cirrhotic patients might end up in ascites infection. In addition, a recent study in Chinese patients suggested that the intestinal microbiome of patients with liver cirrhosis, in contrast to healthy controls, might contain bacteria which normally reside in the oral cavity[27]. Therefore, it is difficult to distinguish the source of infection by identifying the causative microorganism. It is not known to which extent different routes of infection contribute to the development of SBP.

In general, intestinal bacterial translocation is conceived as a key feature of liver cirrhosis[28]. However, measuring bacterial translocation directly is not feasible, so surrogate parameters like lipopolysaccharide (LPS) - a component of the wall of Gram-negative bacteria - bacterial DNA or LPS binding protein (LBP) are used[29]. In animal models, elevated levels of LPS or LBP can be induced by liver damage[29,30]. Markers of bacterial translocation have been linked to all major complications of liver cirrhosis, including ascites formation[21], severe portal hypertension[31], variceal bleeding[32], hepatorenal syndrome, SBP[33] and hepatic encephalopathy[34]. Three factors are considered as key mechanisms to increase bacterial translocation in patients with liver cirrhosis: changes in the amount and composition of the intestinal microbiome[21], a decreased barrier function of the intestine[36] and impaired host responses to translocating bacteria[37].

In healthy subjects, the small bowel contains a relatively small number of bacteria[38]. By contrast, in patients with liver cirrhosis, bacterial overgrowth in the small bowel occurs[39,40]. With the advances in microbiome research, the composition of intestinal bacteria in patients with liver cirrhosis can now be assessed in more detail. Significant differences compared to healthy subjects have been found[27]. In addition, it is not only the bacterial species present in the intestine that may lead to complications of liver cirrhosis[41], but also the products of bacterial metabolism. In line with this, intake of rifaximin
The high recurrence rate of SBP after a first episode if no antibiotic prophylaxis is given. In addition to polymorphisms in the NOD2 gene, which have not only been linked to an impaired intestinal barrier but also to altered innate immune responses, polymorphisms in the toll-like receptor 2 (TLR2) gene and the monocyte chemotactic protein 1 (MCP1) gene have been associated with the occurrence of SBP. TLR2 and NOD2 are pattern recognition receptors that sense bacterial components and trigger immune responses. Patients carrying both a NOD2 and a TLR2 risk variant have a particularly high susceptibility for SBP. Overall, patients with liver cirrhosis and ascites carrying a NOD2 risk variant display a higher mortality than patient with wild-type alleles. MCP1 is a chemokine attracting immune cells, in particular monocytes, to the site of infection. Monocytes from patients with the G allele at position -2518 produce more MCP1 than monocytes from patients with the A allele at this position, so that patients with the A allele are probably more prone to SBP because of a deficit to raise adequate levels of MCP1. Taken together, these genetic studies point at an eminent role of the innate immune system in the development of SBP. Determination of these polymorphisms has no diagnostic impact, because not all patients carrying these mutations will develop SBP, probably due to the presence of so far unknown protective genetic variations and competing risk factors, e.g. death from variceal bleeding or hepatocellular carcinoma. In addition, the presence of these polymorphisms does not predict the onset of SBP - while some patients will develop SBP at first decompensation, other patients receive several large-volume paracentesis till SBP occurs.

Synthesis of proteins by a cirrhotic liver is reduced and fluid accumulates, leading to lower ascites protein concentration, which has been described as one of the major risk factors for SBP. In addition, defects in neutrophil, monocyte, T cell and dendritic cell function have been shown in patients with liver cirrhosis. It is probable that these immune defects impair the normal clearance of translocated bacteria, leading to a state of permanent immune activation and inflammation. The most common causes of liver cirrhosis, viral hepatitis and alcoholic abuse, differ by the mechanisms of liver damage. However, studies demonstrating differences in immune function of ascites cells between these two etiologies are rare. One study found that ascites macrophages are more pro-inflammatory in alcoholic liver disease than in liver cirrhosis induced by hepatitis C virus. Nevertheless, the scarcity of such studies rather seems to indicate that alterations in the immune system concerning the susceptibility to bacterial infections in chronic liver disease are determined mainly by liver failure in general, while the cause of liver disease is secondary.

Although many aspects of bacterial translocation...
are known, it is still not fully understood how and when bacterial translocation finally leads to SBP. Important risk factors for SBP are listed in Table 1.

### DIAGNOSIS OF SBP

This limitation in our understanding led to simplified diagnostic criteria, which are easy to use in clinical practice, but may not reflect differences in disease. Diagnosis of SBP is made according to international guidelines[6,7] in patients with liver cirrhosis if the ascites polymorphonuclear (PMN) cell count exceeds 250 cells/μL and other forms of peritonitis have been excluded. Among others, differential diagnosis comprises malignant ascites, bowel perforation, intraabdominal abscess formation, pancreatitis and peritonitis due to special bacteria like mycobacterium tuberculosis or chlamydia. Hints for secondary bacterial peritonitis due to bowel perforation are polymicrobial culture growth in combination with two of the following findings in the ascites: a total protein above 1 g/dL, lactate dehydrogenase above the normal for serum and glucose levels below 50 mg/dL[7,7].

A PMN count of 250 cells/μL has been chosen because it constitutes a sensitive diagnostic marker[16]. Growth of bacteria in the ascites culture does not establish the diagnosis of SBP, since bacteria are detected only in about 40% of SBP cases[7,9]. Conversely, detectable bacteria in ascites samples with a PMN count below 250 cells/μL lead only in 38% to SBP, because most patients eliminate the bacteria without therapeutic intervention[7]. Attempts to improve the sensitivity of microbiological ascites analysis had limited success. Overall, detection of bacteria in the ascites by PCR-based methods failed to improve test accuracy[73-76]. A pilot study using in-situ hybridisation in ascites leukocytes detected bacteria in 10/11 SBP cases, but this study is limited by the small sample size and by the fact that species identification was not possible[77]. However, even if a molecular method could prove superior to traditional culture methods regarding detection rate, a problem of increasing importance is rapid detection of resistance to antibiotics[78], since failure of first-line treatment due to increasing rates of bacterial resistance is associated with poor prognosis[79]. However, reliable determination of resistance profiles can so far only be done by phenotypical tests after conventional culture.

One of the advantages of the current diagnostic definition of SBP is its simplicity. However, a differential leukocyte count of the ascites can be obtained only in some clinical settings. Therefore, alternative tests that can be performed easily, rapidly and reliably are needed. The most advanced form of these tests is a urinary dipstick that is calibrated especially to ascites[80]. Calprotectin, a protein secreted by neutrophils, is another candidate for a bedside test[81].

### TREATMENT OF SBP

Antibiotic therapy for 5 d with third generation cephalosporines is the established treatment for SBP[6,7]. Randomised trials concerning the antibiotic treatment of SBP are summarised in Table 2. In addition to antibiotics, substitution of albumin to prevent occurrence of hepatorenal syndrome is recommended, in particular for patients that present with total bilirubin > 4 mg/dL or creatinine > 1 mg/dL or urea nitrogen > 30 mg/dL[7]. Treatment with albumin reduces the incidence of renal failure and death[82]. However, the rise in bacterial resistance has reduced the efficacy of third generation cephalosporines and quinolones, especially in nosocomial infections[78].

In addition, enterococci, which are per se resistant to cephalosporines, have become more frequent as a source of SBP[83]. Failure of first line treatment is associated with worse survival[84]. Therefore, it would be necessary to replace cephalosporines with a more effective empiric therapy. The regional variability of antibacterial resistance limits a general approach. Considering isolates from culture-positive SBP, only combinations of modern broad spectrum antibiotics like carbapenems and glykopeptides are considered as reliably effective first line therapy in all patients[78,85].

Renal toxicity, costs and concerns about induction of even more multi-resistant microorganisms are drawbacks of such a treatment. First results of a randomised trial comparing ceftazidime vs meropenem + daptomycin (NCT01455246) presented at the congress of the American Association for the Study of Liver Diseases 2014 (poster 574) indicate a benefit for the combination therapy.

Therefore, it seems more adequate to identify risk factors for resistance to standard treatment in order to select patients who profit from broader antibiotic treatment. Known risk factors are nosocomial infection, previous antibiotic prophylaxis with norfloxacin, use of beta-lactams during the past 12 wk and a history of infection by multi-resistant bacteria[10]. For patients with these risk factors, treatment adapted to the local resistance profiles is recommended. However, therapy should be started immediately after diagnosis of SBP, and most clinicians might not know the local resistance profiles. A more general recommendation is

| Table 1 Important risk factors for spontaneous bacterial peritonitis |
|---------------------------------------------------------------|
| Variceal bleeding[58] |
| Previous SBP[9] |
| Genetic polymorphisms in the NOD2[15-16], TLR2[17], MCP1[18,19] and FXR[20-23] gene |
| Low ascites protein content (below 1-1.5 g/dL)[7] |
| Advanced liver disease[24] |
| Intake of proton pump inhibitors[25-27] |

SBP: Spontaneous bacterial peritonitis; NOD2: Nucleotide-binding oligomerization domain containing 2; TLR2: Toll like receptor 2; MCP1: Monocyte chemotactic protein 1; FXR: Farnesoid X receptor.
to give piperacillin/tazobactam or - in regions with high prevalence of multi-resistant bacteria - carbapenems in combination with glykopeptides\textsuperscript{[78]}. In addition, a second paracentesis after 48 h of treatment should be performed\textsuperscript{[6]}. Based on the results from a first study, a decrease of less than 25% of PMN indicates treatment failure and should prompt a change in treatment\textsuperscript{[86]}. Recognizing treatment failure as early as possible is essential to reduce mortality. Thus, studies to define more and better parameters of treatment response are needed. Of course, rapid microbiological analysis and communication of the results to the clinician is another important factor to guide therapy. However, it is not only response to antibiotic treatment that reduces mortality, but also prevention of renal failure, which might be the most important prognostic factor\textsuperscript{[8,87]}. Albumin substitution to prevent renal failure in the context of SBP was already discussed above.

In summary, the challenges of SBP therapy are various given the rise in resistant bacteria. New classes of antibiotics need to be developed. More knowledge about distinguishing patients who can be treated with standard antibiotics from those who need special treatment is required. Last but not least, failure of first line treatment must be detected as early and as reliably as possible. Still, effective prophylaxis of SBP might alleviate all these problems.

**PROPHYLAXIS OF SBP**

Primary and secondary prophylaxis of SBP has been established based on some of the known risk factors for SBP: gastrointestinal bleeding, previous SBP and low ascites protein content\textsuperscript{[6,7]}. Primary prophylaxis of SBP is recommended in all patients with gastrointestinal bleeding and mostly done with cephalosporines\textsuperscript{[78,88]}. In this context, antibiotic prophylaxis has been reported to reduce SBP incidence about 70\%\textsuperscript{[89]}. Low ascites protein content has been identified early on as risk factor for SBP\textsuperscript{[90]}, which has been explained by a low complement activity\textsuperscript{[91]}. A randomised controlled trial\textsuperscript{[92]} in 68 patients with low ascites protein and advanced liver failure or impaired renal function showed that prophylaxis with norfloxacin significantly reduced the occurrence of SBP and improved 3-mo survival, so that primary antibiotic prophylaxis for such patients should be considered according to current guidelines\textsuperscript{[6,7]}. So far, no study has investigated if the rise in resistant bacteria counterbalances the benefit of primary prophylaxis in these patients.

Secondary prophylaxis of SBP with quinolones is widely recommended\textsuperscript{[6,7]} based on the result of a clinical trial\textsuperscript{[93]} and data from studies including patients with and without prior SBP\textsuperscript{[5,94]}. However, an increase of infections with quinolone - resistant bacteria has been reported after the introduction of secondary prophylaxis into clinical practice\textsuperscript{[10,95]}. Again, data from randomised trials to evaluate the efficacy of secondary prophylaxis in the context of a high prevalence of antibiotic resistance are missing. Naturally, long term prophylaxis has to be carried out with oral antibiotics, so that not only parenteral, but also oral new antibiotic classes are needed. Randomised studies on primary and secondary antibiotic prophylaxis of SBP are summarized in Table 3.

Most risk factors for SBP cannot be modified easily. However, use of acid suppressive therapy, in particular with proton pump inhibitors, has been shown to increase the risk for SBP\textsuperscript{[96,97]}. Therefore, acid suppressive therapy should be prescribed only if a clear indication exists, which is not often the case\textsuperscript{[84]}. Interestingly, this harmful side-effect of proton pump inhibitors seems to be caused rather by impaired oxidative burst of granulocytes and monocytes\textsuperscript{[98]} than by inducing small bowel bacterial overgrowth\textsuperscript{[99]}. Probiotics can reduce bacterial translocation and the associated inflammatory changes in animal models of liver cirrhosis\textsuperscript{[100,101]}. However, clinical trials did not show a significant reduction of SBP incidence under treatment with probiotics\textsuperscript{[102,103]}.

A new approach for SBP prophylaxis is to consider non-absorbable antibiotics that might reduce the intestinal bacterial load without systemic side effects\textsuperscript{[104]}. The main candidate is rifaximin\textsuperscript{[105]}, which prevents

| Table 2  Randomised controlled trials concerning antibiotic treatment of spontaneous bacterial peritonitis |
|---|---|---|---|---|
| Study arms | Resolution of infection | Study arms | Resolution of infection | Study arms |
| **Ref.** | **No. of patients** | | **P** | **Comment** |
| | | | | |
| Felisart et al\textsuperscript{[121]} | 73 | Ampicillin + tobramycin vs cefotaxime | 56\% vs 85\% | < 0.02 | Also patients without SBP included |
| | | | | | |
| Nava\textsuperscript{[23,24]} | 143 | Cefotaxime 8 g/24 h vs 4 g/24 h | 77\% vs 79\% | NS | |
| | | | | | |
| Ricart et al\textsuperscript{[6,7]} | 48 | Amoxicillin-clavulanic acid vs cefotaxime | 88\% vs 83\% | NS | |
| | | | | | |
| Piano et al\textsuperscript{[96]} | 32 | Daptomycin + meropenem vs cefazidime | 87\% vs 25\% | < 0.001 | Only patients with nosocomial SBP included |

NS: Not significant; SBP: Spontaneous bacterial peritonitis.
and is widely used in patients with liver cirrhosis. In addition, it belongs to a class of antibiotics which is normally not used in therapy of SBP and was originally reported to induce no bacterial resistance\(^{107}\). A small study reported that patients who responded to rifaximin treatment by reduction of hepatic venous pressure gradient displayed a significant reduced rate of complications from liver cirrhosis including SBP over 5 years of follow-up\(^{108}\). Another retrospective study comprising 404 patients with liver cirrhosis and ascites requiring paracentesis described a significant reduction of SBP by rifaximin. However, patients with prior SBP or SBP occurring in the course of gastrointestinal bleeding had been excluded\(^{109}\). In addition, a prospective observational study of 152 patients with advanced liver cirrhosis found a reduction of SBP incidence only by quinolones, but not by rifaximin\(^{110}\). The different results of these studies may be explained by variations in the risk for SBP and severity of liver disease, suggesting that rifaximin might be effective only in the subgroup of patients who have relatively low risk for SBP and less severe liver disease. In summary, rifaximin cannot be recommended for SBP prophylaxis until prospective, randomised studies are available.

An ongoing clinical trial investigates if primary antibiotic prophylaxis with quinolones is beneficial in patients with a genetically determined high risk (EudraCT number 2013-001626-26).

Nevertheless, all antibiotics, including rifaximin\(^{111-113}\) will lead to the emergence of bacterial resistance. Therefore, strategies avoiding the use of antibiotics might be more promising on the long term. Potential candidates are FXR agonists, since reduced FXR function is associated with increased bacterial translocation\(^{52,54}\). FXR agonist have already been tested for non-alcoholic fatty liver disease and primary biliary cirrhosis and show a good safety profile\(^{114,115}\). Thus, this new class of drugs may become a novel tool to decrease bacterial translocation in the future.

**CONCLUSION**

SBP occurs frequently in patients with liver cirrhosis, because liver disease leads to increased rates of bacterial translocation from the gut, but is also associated with a compromised immune system. Mortality of SBP has remained high and bacterial resistance to antibiotics threatens to increase mortality even more in the future. The challenge is to improve treatment efficacy by understanding the pathophysiology of SBP in more detail, by tailoring the therapy to the needs of the individual patient and by identifying new approaches for prophylaxis.

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