

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

Philipp Lutz, Hans Dieter Nischalke, Christian P Strassburg, Ulrich Spengler

Philipp Lutz, Hans Dieter Nischalke, Christian P Strassburg, Ulrich Spengler, Department of Internal Medicine I, University of Bonn, D-53129 Bonn, Germany

Philipp Lutz, Christian P Strassburg, Ulrich Spengler, German Center for Infection Research, 38124 Braunschweig, Germany

**Author contributions:** Lutz P wrote the article; Nischalke HD, Strassburg CP and Spengler U critically revised the article.

**Conflict-of-interest:** No conflicts interest to declare.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Dr. Philipp Lutz, Department of Internal Medicine I, University of Bonn, Sigmund-Freud-Strasse 25, D-53129 Bonn, Germany. [philipp.lutz@ukb.uni-bonn.de](mailto:philipp.lutz@ukb.uni-bonn.de)  
 Telephone: +49-228-28715507

Fax: +49-228-28751419

Received: August 28, 2014

Peer-review started: August 29, 2014

First decision: November 14, 2014

Revised: November 30, 2014

Accepted: December 29, 2014

Article in press: December 31, 2014

Published online: March 27, 2015

### 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

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Spontaneous bacterial peritonitis (SBP) is a frequent infection in patients with liver cirrhosis which is associated with a poor prognosis. Portal hypertension leads to translocation of intestinal bacteria which cannot be eliminated due to immune defects caused by liver cirrhosis and genetic predisposition. Empirical antibiotic treatment has become less effective because of widespread antibiotic resistance. This review summarises key features of SBP and points out how diagnosis, treatment and prophylaxis may be improved in the future in order to reduce mortality.

Lutz P, Nischalke HD, Strassburg CP, Spengler U. Spontaneous bacterial peritonitis: The clinical challenge of a leaky gut and a

cirrhotic liver. *World J Hepatol* 2015; 7(3): 304-314 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i3/304.htm> DOI: <http://dx.doi.org/10.4254/wjh.v7.i3.304>

## 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<sup>[1]</sup>. Next to urinary tract infection, SBP is the most frequent infection in patients with advanced liver cirrhosis<sup>[2]</sup>. While it develops in up to 3.5% of patients that are treated as outpatients<sup>[3]</sup>, its prevalence is as high as 12% in hospitalized patients<sup>[2,4]</sup>. In patients at high risk, SBP incidence can be reduced by prophylactic antibiotic treatment<sup>[5-7]</sup>. However, efforts to decrease the high mortality associated with SBP, ranging between 16% and 52%, had to face disappointing limitations<sup>[2,8,9]</sup>. Concerning antibiotic treatment and prophylaxis, the rise of bacterial resistance to antibiotics commonly used in patients with liver cirrhosis has reduced the therapeutical options<sup>[10]</sup>. 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<sup>[11]</sup>. 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<sup>[12]</sup>. 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*)<sup>[13,14]</sup>. Upper gastrointestinal bleeding is the only major risk factor with sudden onset<sup>[15]</sup>. Usually, an external source of infection cannot be identified<sup>[16]</sup>. Taken together, these facts suggest that SBP is an endogenous infection, in general caused by transmigration of enteric bacteria to the ascites<sup>[17]</sup>.

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<sup>[18,19]</sup>, 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<sup>[20]</sup>. In addition, indirect signs of bacterial translocation, such as elevated levels of lipopolysaccharide binding protein (LBP)<sup>[21]</sup> or bacterial DNA<sup>[22]</sup> 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<sup>[23]</sup>. 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<sup>[24]</sup> or in a pet holder<sup>[25]</sup> and SBP by *Bacillus cereus*<sup>[26]</sup> 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<sup>[27]</sup>. 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<sup>[17]</sup>. 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<sup>[28]</sup>. In animal models, elevated levels of LPS or LBP can be induced by liver damage<sup>[29,30]</sup>. Markers of bacterial translocation have been linked to all major complications of liver cirrhosis, including ascites formation<sup>[21]</sup>, severe portal hypertension<sup>[31]</sup>, variceal bleeding<sup>[32]</sup>, hepatorenal syndrome, SBP<sup>[33]</sup> and hepatic encephalopathy<sup>[34]</sup>. 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<sup>[35]</sup>, a decreased barrier function of the intestine<sup>[36]</sup> and impaired host responses to translocating bacteria<sup>[37]</sup>.

In healthy subjects, the small bowel contains a relatively small number of bacteria<sup>[38]</sup>. By contrast, in patients with liver cirrhosis, bacterial overgrowth in the small bowel occurs<sup>[39,40]</sup>. 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<sup>[27]</sup>. In addition, it is not only the bacterial species present in the intestine that may lead to complications of liver cirrhosis<sup>[41]</sup>, but also the products of bacterial metabolism. In line with this, intake of rifaximin

improves cognition along with altering metabolites from intestinal bacteria, but does not influence the composition of the intestinal microbiome<sup>[42]</sup>. An intriguing question is in how far the intestinal microbiome is only the consequence of liver disease or - once pathologically changed - contributes to the development of more severe disease<sup>[35]</sup>.

It is important to note that the virulence of bacterial strains concerning onset and course of infection differs considerably. *E. coli* strains causing SBP display higher motility than *E. coli* causing urinary or biliary tract infections<sup>[43]</sup>. In addition, SBP by encapsulated *E. coli* is associated with more complications<sup>[44]</sup> and in the special case of the K1 antigen with lower survival<sup>[45]</sup>.

A decreased barrier function of the intestine in advanced liver disease has been found in animal models<sup>[46-48]</sup> and humans<sup>[31,49,50]</sup>. Recently, the farnesoid X receptor (FXR), a nuclear receptor for bile acids<sup>[51]</sup>, has emerged as an important molecule for maintaining the intestinal barrier. Bacterial translocation from the intestine is increased in FXR knock-out and in bile-duct ligated mice<sup>[52]</sup>. Synthetical FXR agonists block bacterial translocation in the latter<sup>[52]</sup> and decrease portal hypertension in animals models of cirrhosis<sup>[53]</sup>. In addition, a FXR polymorphism which leads to a reduced translation of FXR target genes is associated with the occurrence of SBP<sup>[54]</sup>. So far, it is not known if synthetic FXR agonists may reduce bacterial translocation in humans.

SBP is associated with polymorphisms in pattern recognition receptors, for example the nucleotide-binding oligomerization domain containing 2 (NOD2) gene<sup>[55,56]</sup>. The same NOD2 polymorphisms predispose for Crohn's disease<sup>[57]</sup>, which is also characterised by a leaky gut. Unfortunately, the mechanism by which these polymorphisms lead to increased bacterial translocation is still debated. Nevertheless, this joint association provides a clear hint for a shared mechanism and underlines the involvement of the innate immune system in bacterial translocation.

## CIRRHOTIC LIVER

Portal hypertension is a hallmark of advanced liver cirrhosis. Decreasing portal hypertension reduces bacterial translocation<sup>[31]</sup>. However, data on a possibly protective role of non-selective beta blockers, which reduce portal pressure, concerning the occurrence of SBP in patients with liver cirrhosis are contradictory<sup>[12,58]</sup>. Another treatment for portal hypertension is the placement of a transjugular intrahepatic portosystemic shunt (TIPS)<sup>[59]</sup>. A meta-analysis on TIPS for refractory ascites found no significantly decreased incidence of SBP in patients with TIPS<sup>[60]</sup>, but studies focussing directly on this issue are missing.

Apart from portal hypertension, cirrhosis leads to the development of various immune defects and might unmask minor genetic immune defects. The importance of genetic predisposition is stressed by

the high recurrence rate of SBP after a first episode if no antibiotic prophylaxis is given. In addition to polymorphisms in the NOD2<sup>[55,56]</sup> gene, which have not only been linked to an impaired intestinal barrier but also to altered innate immune responses<sup>[57]</sup>, polymorphisms in the toll-like receptor 2 (TLR2) gene<sup>[61]</sup> and the monocyte chemotactic protein 1 (MCP1) gene<sup>[62,63]</sup> have been associated with the occurrence of SBP. TLR2 and NOD2 are pattern recognition receptors that sense bacterial components and trigger immune responses<sup>[64]</sup>. Patients carrying both a NOD2 and a TLR2 risk variant have a particularly high susceptibility for SBP<sup>[61]</sup>. Overall, patients with liver cirrhosis and ascites carrying a NOD2 risk variant display a higher mortality than patient with wild-type alleles<sup>[55,56]</sup>. MCP1 is a chemokine attracting immune cells, in particular monocytes, to the site of infection<sup>[65]</sup>. Monocytes from patients with the G allele at position -2518 produce more MCP1 than monocytes from patients with the A allele at this position<sup>[66]</sup>, 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<sup>[6,7]</sup>. In addition, defects in neutrophil<sup>[67]</sup>, monocyte<sup>[68]</sup>, T cell<sup>[69]</sup> and dendritic cell<sup>[70]</sup> 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<sup>[21]</sup>. 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<sup>[71]</sup>. 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

**Table 1 Important risk factors for spontaneous bacterial peritonitis**

Variceal bleeding <sup>[15]</sup>
Previous SBP <sup>[6]</sup>
Genetic polymorphisms in the <i>NOD2</i> <sup>[55,56]</sup> , <i>TLR2</i> <sup>[61]</sup> , <i>MCP1</i> <sup>[62,63]</sup> and <i>FXR</i> <sup>[54]</sup> gene
Low ascites protein content (below 1-1.5 g/dL) <sup>[7]</sup>
Advanced liver disease <sup>[116]</sup>
Intake of proton pump inhibitors <sup>[96,97]</sup>

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.

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<sup>[6,7]</sup> 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<sup>[7]</sup>.

A PMN count of 250 cells/μL has been chosen because it constitutes a sensitive diagnostic marker<sup>[16]</sup>. **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**<sup>[6,9]</sup>. 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**<sup>[72]</sup>. 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<sup>[73-76]</sup>. 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<sup>[77]</sup>. 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<sup>[78]</sup>, since failure of first-line treatment due to increasing rates of bacterial resistance is associated

with poor prognosis<sup>[79]</sup>. 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**<sup>[80]</sup>. **Calprotectin**, a **protein secreted by neutrophils**, is another candidate for a bedside test<sup>[81]</sup>.

## TREATMENT OF SBP

**Antibiotic therapy for 5 d with third generation cephalosporines** is the established treatment for SBP<sup>[6,7]</sup>. 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<sup>[7]</sup>. Treatment with **albumin reduces** the incidence of **renal failure** and **death**<sup>[82]</sup>. However, the rise in bacterial resistance has reduced the efficacy of third generation cephalosporines and quinolones, especially in nosocomial infections<sup>[78]</sup>. In addition, **enterococci**, which are **per se resistant to cephalosporines**, have become **more frequent** as a source of SBP<sup>[83]</sup>. Failure of first line treatment is associated with worse survival<sup>[84]</sup>. 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<sup>[78,85]</sup>. 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)<sup>[86]</sup> 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**<sup>[10]</sup>. 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 2 Randomised controlled trials concerning antibiotic treatment of spontaneous bacterial peritonitis**

Ref.	No. of patients	Study arms	Resolution of infection	P	Comment
Felisart <i>et al</i> <sup>[117]</sup>	73	Ampicillin + tobramycin <i>vs</i> cefotaxime	56% <i>vs</i> 85%	< 0.02	Also patients without SBP included
Rimola <i>et al</i> <sup>[118]</sup>	143	Cefotaxime 8 g/24 h <i>vs</i> 4 g/24 h	77% <i>vs</i> 79%	NS	Only patients with uncomplicated SBP included
Navasa <i>et al</i> <sup>[119]</sup>	123	Ofloxacin <i>po vs</i> cefotaxime <i>iv</i>	84% <i>vs</i> 85%	NS	
Ricart <i>et al</i> <sup>[120]</sup>	48	Amoxicillin-clavulanic acid <i>vs</i> cefotaxime	88% <i>vs</i> 83%	NS	Only patients with nosocomial SBP included
Terg <i>et al</i> <sup>[121]</sup>	80	Ciprofloxacin only <i>iv vs</i> 2 d <i>iv</i> then <i>po</i>	76 <i>vs</i> 78%	NS	
Piano <i>et al</i> <sup>[86]</sup> (NCT01455246) (preliminary results presented at the AASLD 2014, Abstract 574)	32	Daptomycin + meropenem <i>vs</i> ceftazidime	87% <i>vs</i> 25%	< 0.001	

NS: Not significant; SBP: Spontaneous bacterial peritonitis.

to give piperacillin/tazobactam or - in regions with high prevalence of multi-resistant bacteria - carbapenems in combination with glykopeptides<sup>[78]</sup>. In addition, a second paracentesis after 48 h of treatment should be performed<sup>[6]</sup>. 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<sup>[6]</sup>. 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<sup>[8,87]</sup>. 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<sup>[6,7]</sup>. Primary prophylaxis of SBP is recommended in all patients with gastrointestinal bleeding and mostly done with cephalosporines<sup>[78,88]</sup>. In this context, antibiotic prophylaxis has been reported to reduce SBP incidence about 70%<sup>[89]</sup>. Low ascites protein content has been identified early on as risk factor for SBP<sup>[90]</sup>, which has been explained by a low complement activity<sup>[91]</sup>. A randomised controlled trial<sup>[92]</sup> 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<sup>[6,7]</sup>. 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<sup>[6,7]</sup> based on the result of a clinical trial<sup>[93]</sup> and data from studies including patients with and without prior SBP<sup>[5,94]</sup>. However, an increase of infections with quinolone - resistant bacteria has been reported after the introduction of secondary prophylaxis into clinical practice<sup>[10,95]</sup>. 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<sup>[96,97]</sup>. Therefore, acid suppressive therapy should be prescribed only if a clear indication exists, which is not often the case<sup>[84]</sup>. Interestingly, this harmful side-effect of proton pump inhibitors seems to be caused rather by impaired oxidative burst of granulocytes and monocytes<sup>[98]</sup> than by inducing small bowel bacterial overgrowth<sup>[99]</sup>. Probiotics can reduce bacterial translocation and the associated inflammatory changes in animal models of liver cirrhosis<sup>[100,101]</sup>. However, clinical trials did not show a significant reduction of SBP incidence under treatment with probiotics<sup>[102,103]</sup>.

A new approach for SBP prophylaxis is to consider non-absorbable antibiotics that might reduce the intestinal bacterial load without systemic side effects<sup>[16]</sup>. The main candidate is rifaximin<sup>[104]</sup>, which prevents

**Table 3** Randomised controlled trials concerning antibiotic prophylaxis of spontaneous bacterial peritonitis

Ref.	No. of patients	Study arms	Kind of prophylaxis	Occurrence of SBP	P
Ginés <i>et al</i> <sup>[93]</sup>	80	Norfloxacin <i>vs</i> placebo	Secondary	12% <i>vs</i> 35%	0.014
Soriano <i>et al</i> <sup>[122]</sup>	63	Norfloxacin <i>vs</i> control	Primary/secondary	0% <i>vs</i> 23%	< 0.05
Singh <i>et al</i> <sup>[123]</sup>	60	Trimethoprim-sulfamethoxazole <i>vs</i> control	Primary/secondary	3% <i>vs</i> 27%	0.025
Grangé <i>et al</i> <sup>[124]</sup>	107	Norfloxacin <i>vs</i> placebo	Primary	0% <i>vs</i> 9%	NS
Rolachon <i>et al</i> <sup>[125]</sup>	60	Ciprofloxacin <i>vs</i> placebo	Primary/secondary	4% <i>vs</i> 22%	< 0.05
Novella <i>et al</i> <sup>[126]</sup>	109	Norfloxacin permanently <i>vs</i> only during hospitalisation	Primary	2% <i>vs</i> 17%	< 0.01
Fernández <i>et al</i> <sup>[92]</sup>	68	Norfloxacin <i>vs</i> placebo	Primary	7% <i>vs</i> 61%	< 0.001
Terg <i>et al</i> <sup>[127]</sup>	100	Ciprofloxacin <i>vs</i> placebo	Primary	4% <i>vs</i> 14%	0.076

NS: Not significant; SBP: Spontaneous bacterial peritonitis.

hepatic encephalopathy<sup>[105,106]</sup> 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<sup>[107]</sup>. 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<sup>[108]</sup>. 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<sup>[109]</sup>. 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<sup>[110]</sup>. 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<sup>[111-113]</sup>, 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<sup>[52,54]</sup>. FXR agonist have already been tested for non-alcoholic fatty liver disease and primary biliary cirrhosis and show a good safety profile<sup>[114,115]</sup>. 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.

## REFERENCES

- Conn HO. Spontaneous peritonitis and bacteremia in laennec's cirrhosis caused by enteric organisms. a relatively common but rarely recognized syndrome. *Ann Intern Med* 1964; **60**: 568-580 [PMID: 14138877 DOI: 10.7326/0003-4819-60-4-568]
- Singal AK, Salameh H, Kamath PS. Prevalence and in-hospital mortality trends of infections among patients with cirrhosis: a nationwide study of hospitalised patients in the United States. *Aliment Pharmacol Ther* 2014; **40**: 105-112 [PMID: 24832591 DOI: 10.1111/apt.12797]
- Evans LT, Kim WR, Poterucha JJ, Kamath PS. Spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhotic ascites. *Hepatology* 2003; **37**: 897-901 [PMID: 12668984 DOI: 10.1053/jhep.2003.50119]
- Cadranel JF, Noursbaum JB, Bessaguet C, Nahon P, Nguyen-Khac E, Moreau R, Thévenot T, Silvain C, Bureau C, Nouel O, Pilette C, Paupard T, Pauwels A, Sapey T, Grangé JD, Tran A. Low incidence of spontaneous bacterial peritonitis in asymptomatic cirrhotic outpatients. *World J Hepatol* 2013; **5**: 104-108 [PMID: 23556041 DOI: 10.4254/wjh.v5.i3.104]
- Saab S, Hernandez JC, Chi AC, Tong MJ. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *Am J Gastroenterol* 2009; **104**: 993-1001; quiz 1002 [PMID: 19277033 DOI: 10.1038/ajg.2009.3]
- European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]
- Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 2013; **57**: 1651-1653 [PMID: 23463403 DOI: 10.1002/hep.26359]
- Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2011; **9**: 260-265 [PMID: 21145427 DOI: 10.1016/j.cgh.2010.11.038]
- Tandon P, Kumar D, Seo YS, Chang HJ, Chaulk J, Carbonneau M, Qamar H, Keough A, Mansoor N, Ma M. The 22/11 risk prediction model: a validated model for predicting 30-day mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *Am J Gastroenterol* 2013; **108**: 1473-1479 [PMID: 23877350 DOI: 10.1038/ajg.2009.3]

- 10.1038/ajg.2013.204]
- 10 **Fernández J**, Acevedo J, Castro M, García O, de Lope CR, Roca D, Pavesi M, Sola E, Moreira L, Silva A, Seva-Pereira T, Corradi F, Mensa J, Ginès P, Arroyo V. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012; **55**: 1551-1561 [PMID: 22183941 DOI: 10.1002/hep.25532]
  - 11 **Karlas T**, Wiegand J, Berg T. Gastrointestinal complications of obesity: non-alcoholic fatty liver disease (NAFLD) and its sequelae. *Best Pract Res Clin Endocrinol Metab* 2013; **27**: 195-208 [PMID: 23731881 DOI: 10.1016/j.beem.2013.02.002]
  - 12 **Mandorfer M**, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, Hagmann M, Blacky A, Ferlitsch A, Sieghart W, Trauner M, Peck-Radosavljevic M, Reiberger T. Nonselective  $\beta$  blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. *Gastroenterology* 2014; **146**: 1680-90.e1 [PMID: 24631577 DOI: 10.1053/j.gastro.2014.03.005]
  - 13 **Piroth L**, Pechinot A, Minello A, Jaulhac B, Patry I, Hadou T, Hansmann Y, Rabaud C, Chavanet P, Neuwirth C. Bacterial epidemiology and antimicrobial resistance in ascitic fluid: a 2-year retrospective study. *Scand J Infect Dis* 2009; **41**: 847-851 [PMID: 19922067 DOI: 10.3109/00365540903244535]
  - 14 **Cheong HS**, Kang CI, Lee JA, Moon SY, Joung MK, Chung DR, Koh KC, Lee NY, Song JH, Peck KR. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *Clin Infect Dis* 2009; **48**: 1230-1236 [PMID: 19302016 DOI: 10.1086/597585]
  - 15 **Lee YY**, Tee HP, Mahadeva S. Role of prophylactic antibiotics in cirrhotic patients with variceal bleeding. *World J Gastroenterol* 2014; **20**: 1790-1796 [PMID: 24587656 DOI: 10.3748/wjg.v20.i7.1790]
  - 16 **Wiest R**, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. *Gut* 2012; **61**: 297-310 [PMID: 22147550 DOI: 10.1136/gutjnl-2011-300779]
  - 17 **Wiest R**, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol* 2014; **60**: 197-209 [PMID: 23993913 DOI: 10.1016/j.jhep.2013.07.044]
  - 18 **Guarner C**, González-Navajas JM, Sánchez E, Soriando G, Francés R, Chiva M, Zapater P, Benlloch S, Muñoz C, Pascual S, Balanzó J, Pérez-Mateo M, Such J. The detection of bacterial DNA in blood of rats with CCl<sub>4</sub>-induced cirrhosis with ascites represents episodes of bacterial translocation. *Hepatology* 2006; **44**: 633-639 [PMID: 16941689 DOI: 10.1002/hep.21286]
  - 19 **Llovet JM**, Bartoli R, March F, Planas R, Viñado B, Cabré E, Arnal J, Coll P, Ausina V, Gassull MA. Translocated intestinal bacteria cause spontaneous bacterial peritonitis in cirrhotic rats: molecular epidemiologic evidence. *J Hepatol* 1998; **28**: 307-313 [PMID: 9580278 DOI: 10.1016/S0168-8278(88)80018-7]
  - 20 **Cirera I**, Bauer TM, Navasa M, Vila J, Grande L, Taurá P, Fuster J, García-Valdecasas JC, Lacy A, Suárez MJ, Rimola A, Rodés J. Bacterial translocation of enteric organisms in patients with cirrhosis. *J Hepatol* 2001; **34**: 32-37 [PMID: 11211904 DOI: 10.1016/S0168-8278(00)00013-1]
  - 21 **Albillos A**, de la Hera A, González M, Moya JL, Calleja JL, Monserrat J, Ruiz-del-Arbol L, Alvarez-Mon M. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. *Hepatology* 2003; **37**: 208-217 [PMID: 12500206 DOI: 10.1053/jhep.2003.50038]
  - 22 **Such J**, Francés R, Muñoz C, Zapater P, Casellas JA, Cifuentes A, Rodríguez-Valera F, Pascual S, Sola-Vera J, Carnicer F, Uceda F, Palazón JM, Pérez-Mateo M. Detection and identification of bacterial DNA in patients with cirrhosis and culture-negative, nonneutrocytic ascites. *Hepatology* 2002; **36**: 135-141 [PMID: 12085357 DOI: 10.1053/jhep.2002.33715]
  - 23 **Rogers GB**, van der Gast CJ, Bruce KD, Marsh P, Collins JE, Sutton J, Wright M. Ascitic microbiota composition is correlated with clinical severity in cirrhosis with portal hypertension. *PLoS One* 2013; **8**: e74884 [PMID: 24086392 DOI: 10.1371/journal.pone.0074884]
  - 24 **Ashley BD**, Noone M, Dwarakanath AD, Malnick H. Fatal *Pasteurella dagmatis* peritonitis and septicaemia in a patient with cirrhosis: a case report and review of the literature. *J Clin Pathol* 2004; **57**: 210-212 [PMID: 14747455 DOI: 10.1136/jcp.2003.7419]
  - 25 **Lutz P**, Parcina M, Bekeredjian-Ding I, Hoerauf A, Strassburg CP, Spengler U. Spontaneous bacterial peritonitis by *Pasteurella multocida* under treatment with rifaximin. *Infection* 2014; **42**: 175-177 [PMID: 23526308 DOI: 10.1007/s15010-013-0449-4]
  - 26 **Lee YL**, Shih SD, Weng YJ, Chen C, Liu CE. Fatal spontaneous bacterial peritonitis and necrotizing fasciitis with bacteraemia caused by *Bacillus cereus* in a patient with cirrhosis. *J Med Microbiol* 2010; **59**: 242-244 [PMID: 19850708 DOI: 10.1099/jmm.0.011056-0]
  - 27 **Qin N**, Yang F, Li A, Prifti E, Chen Y, Shao L, Guo J, Le Chatelier E, Yao J, Wu L, Zhou J, Ni S, Liu L, Pons N, Batto JM, Kennedy SP, Leonard P, Yuan C, Ding W, Chen Y, Hu X, Zheng B, Qian G, Xu W, Ehrlich SD, Zheng S, Li L. Alterations of the human gut microbiome in liver cirrhosis. *Nature* 2014; **513**: 59-64 [PMID: 25079328 DOI: 10.1038/nature13568]
  - 28 **Seki E**, Schnabl B. Role of innate immunity and the microbiota in liver fibrosis: crosstalk between the liver and gut. *J Physiol* 2012; **590**: 447-458 [PMID: 22124143 DOI: 10.1113/jphysiol.2011.219691]
  - 29 **Su GL**, Rahemtulla A, Thomas P, Klein RD, Wang SC, Nanji AA. CD14 and lipopolysaccharide binding protein expression in a rat model of alcoholic liver disease. *Am J Pathol* 1998; **152**: 841-849 [PMID: 9502426]
  - 30 **Nakatani Y**, Fukui H, Kitano H, Nagamoto I, Tsujimoto T, Kuriyama S, Kikuchi E, Hoppou K, Tsujii T. Endotoxin clearance and its relation to hepatic and renal disturbances in rats with liver cirrhosis. *Liver* 2001; **21**: 64-70 [PMID: 11169075 DOI: 10.1034/j.1600-0676.2001.210110.x]
  - 31 **Reiberger T**, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, Lammert F, Trauner M, Peck-Radosavljevic M, Vogelsang H. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. *J Hepatol* 2013; **58**: 911-921 [PMID: 23262249 DOI: 10.1016/j.jhep.2012.12.011]
  - 32 **Fukui H**, Matsumoto M, Tsujita S, Takaya A, Kojima H, Matsumura M, Tsujii T. Plasma endotoxin concentration and endotoxin binding capacity of plasma acute phase proteins in cirrhotics with variceal bleeding: an analysis by new methods. *J Gastroenterol Hepatol* 1994; **9**: 582-586 [PMID: 7532449 DOI: 10.1111/j.1440-1746.1994.tb01565.x]
  - 33 **El-Naggar MM**, Khalil el-SA, El-Daker MA, Salama MF. Bacterial DNA and its consequences in patients with cirrhosis and culture-negative, non-neutrocytic ascites. *J Med Microbiol* 2008; **57**: 1533-1538 [PMID: 19018026 DOI: 10.1099/jmm.0.2008/001867-0]
  - 34 **Jain L**, Sharma BC, Sharma P, Srivastava S, Agrawal A, Sarin SK. Serum endotoxin and inflammatory mediators in patients with cirrhosis and hepatic encephalopathy. *Dig Liver Dis* 2012; **44**: 1027-1031 [PMID: 22883217 DOI: 10.1016/j.dld.2012.07.002]
  - 35 **Schnabl B**, Brenner DA. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology* 2014; **146**: 1513-1524 [PMID: 24440671 DOI: 10.1053/j.gastro.2014.01.020]
  - 36 **Pijls KE**, Jonkers DM, Elamin EE, Masclee AA, Koek GH. Intestinal epithelial barrier function in liver cirrhosis: an extensive review of the literature. *Liver Int* 2013; **33**: 1457-1469 [PMID: 23879434 DOI: 10.1111/liv.12271]
  - 37 **Sipeki N**, Antal-Szalmás P, Lakatos PL, Papp M. Immune dysfunction in cirrhosis. *World J Gastroenterol* 2014; **20**: 2564-2577 [PMID: 24627592 DOI: 10.3748/wjg.v20.i10.2564]
  - 38 **Dukowicz AC**, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol Hepatol (N Y)* 2007; **3**: 112-122 [PMID: 21960820]
  - 39 **Pande C**, Kumar A, Sarin SK. Small-intestinal bacterial overgrowth in cirrhosis is related to the severity of liver disease. *Aliment Pharmacol Ther* 2009; **29**: 1273-1281 [PMID: 19302262 DOI: 10.1111/j.1365-2036.2009.03994.x]
  - 40 **Bauer TM**, Schwacha H, Steinbrückner B, Brinkmann FE, Ditzén AK, Aponte JJ, Pelz K, Berger D, Kist M, Blum HE. Small intestinal bacterial overgrowth in human cirrhosis is associated with



- systemic endotoxemia. *Am J Gastroenterol* 2002; **97**: 2364-2370 [PMID: 12358257 DOI: 10.1111/j.1572-0241.2002.05791.x]
- 41 **Bajaj JS**, Hylemon PB, Ridlon JM, Heuman DM, Daita K, White MB, Monteith P, Noble NA, Sikaroodi M, Gillevet PM. Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G675-G685 [PMID: 22821944 DOI: 10.1152/ajpgi.00152.2012]
  - 42 **Bajaj JS**, Heuman DM, Sanyal AJ, Hylemon PB, Sterling RK, Stravitz RT, Fuchs M, Ridlon JM, Daita K, Monteith P, Noble NA, White MB, Fisher A, Sikaroodi M, Rangwala H, Gillevet PM. Modulation of the metabiome by rifaximin in patients with cirrhosis and minimal hepatic encephalopathy. *PLoS One* 2013; **8**: e60042 [PMID: 23565181 DOI: 10.1371/journal.pone.0060042]
  - 43 **Kao CY**, Lin WH, Tseng CC, Wu AB, Wang MC, Wu JJ. The complex interplay among bacterial motility and virulence factors in different *Escherichia coli* infections. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 2157-2162 [PMID: 24957011 DOI: 10.1007/s10096-014-2171-2]
  - 44 **Soriano G**, Coll P, Guarner C, Such J, Sánchez F, Prats G, Vilardell F. *Escherichia coli* capsular polysaccharide and spontaneous bacterial peritonitis in cirrhosis. *Hepatology* 1995; **21**: 668-673 [PMID: 7875665 DOI: 10.1002/hep.1840210311]
  - 45 **Wang MC**, Lin WH, Tseng CC, Wu AB, Teng CH, Yan JJ, Wu JJ. Role of K1 capsule antigen in cirrhotic patients with *Escherichia coli* spontaneous bacterial peritonitis in southern Taiwan. *Eur J Clin Microbiol Infect Dis* 2013; **32**: 407-412 [PMID: 23052990 DOI: 10.1007/s10096-012-1757-9]
  - 46 **Fouts DE**, Torralba M, Nelson KE, Brenner DA, Schnabl B. Bacterial translocation and changes in the intestinal microbiome in mouse models of liver disease. *J Hepatol* 2012; **56**: 1283-1292 [PMID: 22326468 DOI: 10.1016/j.jhep.2012.01.019]
  - 47 **White JS**, Hoper M, Parks RW, Clements WD, Diamond T. Patterns of bacterial translocation in experimental biliary obstruction. *J Surg Res* 2006; **132**: 80-84 [PMID: 16154151 DOI: 10.1016/j.jss.2005.07.026]
  - 48 **Inamura T**, Miura S, Tsuzuki Y, Hara Y, Hokari R, Ogawa T, Teramoto K, Watanabe C, Kobayashi H, Nagata H, Ishii H. Alteration of intestinal intraepithelial lymphocytes and increased bacterial translocation in a murine model of cirrhosis. *Immunol Lett* 2003; **90**: 3-11 [PMID: 14611901 DOI: 10.1016/j.imlet.2003.05.002]
  - 49 **Campillo B**, Pernet P, Bories PN, Richardet JP, Devanlay M, Aussel C. Intestinal permeability in liver cirrhosis: relationship with severe septic complications. *Eur J Gastroenterol Hepatol* 1999; **11**: 755-759 [PMID: 10445796 DOI: 10.1097/00042737-199907000-00013]
  - 50 **Pascual S**, Such J, Esteban A, Zapater P, Casellas JA, Aparicio JR, Girona E, Gutiérrez A, Carnices F, Palazón JM, Sola-Vera J, Pérez-Mateo M. Intestinal permeability is increased in patients with advanced cirrhosis. *Hepatogastroenterology* 2003; **50**: 1482-1486 [PMID: 14571769]
  - 51 **Modica S**, Gadaleta RM, Moschetta A. Deciphering the nuclear bile acid receptor FXR paradigm. *Nucl Recept Signal* 2010; **8**: e005 [PMID: 21383957 DOI: 10.1621/nrs.08005]
  - 52 **Inagaki T**, Moschetta A, Lee YK, Peng L, Zhao G, Downes M, Yu RT, Shelton JM, Richardson JA, Repa JJ, Mangelsdorf DJ, Kliewer SA. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *Proc Natl Acad Sci USA* 2006; **103**: 3920-3925 [PMID: 16473946 DOI: 10.1073/pnas.0509592103]
  - 53 **Verbeke L**, Farre R, Trebicka J, Komuta M, Roskams T, Klein S, Elst IV, Windmolders P, Vanuytsel T, Nevens F, Laleman W. Obeticholic acid, a farnesoid X receptor agonist, improves portal hypertension by two distinct pathways in cirrhotic rats. *Hepatology* 2014; **59**: 2286-2298 [PMID: 24259407 DOI: 10.1002/hep.26939]
  - 54 **Lutz P**, Berger C, Langhans B, Grünhage F, Appenrodt B, Nattermann J, Lammert F, Hoerauf A, Sauerbruch T, Strassburg CP, Spengler U, Nischalke HD. A farnesoid X receptor polymorphism predisposes to spontaneous bacterial peritonitis. *Dig Liver Dis* 2014; **46**: 1047-1050 [PMID: 25086996 DOI: 10.1016/j.dld.2014.07.008]
  - 55 **Appenrodt B**, Grünhage F, Gentemann MG, Thyssen L, Sauerbruch T, Lammert F. Nucleotide-binding oligomerization domain containing 2 (NOD2) variants are genetic risk factors for death and spontaneous bacterial peritonitis in liver cirrhosis. *Hepatology* 2010; **51**: 1327-1333 [PMID: 20087966 DOI: 10.1002/hep.23440]
  - 56 **Bruns T**, Peter J, Reuken PA, Grabe DH, Schuldes SR, Brenmoehl J, Schölmerich J, Wiest R, Stallmach A. NOD2 gene variants are a risk factor for culture-positive spontaneous bacterial peritonitis and monomicrobial bacterascites in cirrhosis. *Liver Int* 2012; **32**: 223-230 [PMID: 21745302 DOI: 10.1111/j.1478-3231.2011.02561.x]
  - 57 **Strober W**, Watanabe T. NOD2, an intracellular innate immune sensor involved in host defense and Crohn's disease. *Mucosal Immunol* 2011; **4**: 484-495 [PMID: 21750585 DOI: 10.1038/mi.2011.29]
  - 58 **Senzolo M**, Cholongitas E, Burra P, Leandro G, Thalheimer U, Patch D, Burroughs AK. beta-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *Liver Int* 2009; **29**: 1189-1193 [PMID: 19508620 DOI: 10.1111/j.1478-3231.2009.02038.x]
  - 59 **Rössle M**. TIPS: 25 years later. *J Hepatol* 2013; **59**: 1081-1093 [PMID: 23811307 DOI: 10.1016/j.jhep.2013.06.014]
  - 60 **Salerno F**, Cammà C, Enea M, Rössle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. *Gastroenterology* 2007; **133**: 825-834 [PMID: 17678653 DOI: 10.1053/j.gastro.2007.06.020]
  - 61 **Nischalke HD**, Berger C, Aldenhoff K, Thyssen L, Gentemann M, Grünhage F, Lammert F, Nattermann J, Sauerbruch T, Spengler U, Appenrodt B. Toll-like receptor (TLR) 2 promoter and intron 2 polymorphisms are associated with increased risk for spontaneous bacterial peritonitis in liver cirrhosis. *J Hepatol* 2011; **55**: 1010-1016 [PMID: 21356257 DOI: 10.1016/j.jhep.2011.02.022]
  - 62 **Gäbele E**, Mühlbauer M, Paulo H, Johann M, Meltzer C, Leidl F, Wodarz N, Wiest R, Schölmerich J, Hellerbrand C. Analysis of monocyte chemotactic protein-1 gene polymorphism in patients with spontaneous bacterial peritonitis. *World J Gastroenterol* 2009; **15**: 5558-5562 [PMID: 19938194 DOI: 10.3748/wjg.15.5558]
  - 63 **Salama MK**, Sabry D, Al-Ghoussein MA, Ahmed R, AbdAllah S, Taha FM, Fathy W, Wadie MS, Nabih M, Abul-Fotouh A, Darwish T. Molecular detection of monocyte chemotactic protein-1 polymorphism in spontaneous bacterial peritonitis patients. *World J Gastroenterol* 2014; **20**: 11793-11799 [PMID: 25206284 DOI: 10.3748/wjg.v20.i33.11793]
  - 64 **Kawai T**, Akira S. The roles of TLRs, RLRs and NLRs in pathogen recognition. *Int Immunol* 2009; **21**: 317-337 [PMID: 19246554 DOI: 10.1093/intimm/dxp017]
  - 65 **Gu L**, Rutledge B, Fiorillo J, Ernst C, Grewal I, Flavell R, Gladue R, Rollins B. In vivo properties of monocyte chemoattractant protein-1. *J Leukoc Biol* 1997; **62**: 577-580 [PMID: 9365111]
  - 66 **Rovin BH**, Lu L, Saxena R. A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. *Biochem Biophys Res Commun* 1999; **259**: 344-348 [PMID: 10362511 DOI: 10.1006/bbrc.1999.0796]
  - 67 **Taylor NJ**, Manakkat Vijay GK, Abeles RD, Auzinger G, Bernal W, Ma Y, Wendon JA, Shawcross DL. The severity of circulating neutrophil dysfunction in patients with cirrhosis is associated with 90-day and 1-year mortality. *Aliment Pharmacol Ther* 2014; **40**: 705-715 [PMID: 25060167 DOI: 10.1111/apt.12886]
  - 68 **Ono Y**, Watanabe T, Matsumoto K, Ito T, Kunii O, Goldstein E. Opsonophagocytic dysfunction in patients with liver cirrhosis and low responses to tumor necrosis factor-alpha and lipopolysaccharide in patients' blood. *J Infect Chemother* 2004; **10**: 200-207 [PMID: 15365859 DOI: 10.1007/s10156-004-0321-7]
  - 69 **Schirren CA**, Jung MC, Zachoval R, Diepolder H, Hoffmann R, Riethmüller G, Pape GR. Analysis of T cell activation pathways in patients with liver cirrhosis, impaired delayed hypersensitivity and other T cell-dependent functions. *Clin Exp Immunol* 1997; **108**: 144-150 [PMID: 9097923 DOI: 10.1046/j.1365-2249.1997.d01-985.x]
  - 70 **Kakazu E**, Ueno Y, Kondo Y, Fukushima K, Shiina M, Inoue J, Tamai K, Ninomiya M, Shimosegawa T. Branched chain amino



- acids enhance the maturation and function of myeloid dendritic cells *ex vivo* in patients with advanced cirrhosis. *Hepatology* 2009; **50**: 1936-1945 [PMID: 19885880 DOI: 10.1002/hep.23248]
- 71 **Tapia-Abellán A**, Martínez-Esparza M, Ruiz-Alcaraz AJ, Hernández-Caselles T, Martínez-Pascual C, Miras-López M, Such J, Francés R, García-Peñarrubia P. The peritoneal macrophage inflammatory profile in cirrhosis depends on the alcoholic or hepatitis C viral etiology and is related to ERK phosphorylation. *BMC Immunol* 2012; **13**: 42 [PMID: 22866973 DOI: 10.1186/1471-2172-13-42]
  - 72 **Runyon BA**. Monomicrobial nonneutrocytic bacterascites: a variant of spontaneous bacterial peritonitis. *Hepatology* 1990; **12**: 710-715 [PMID: 2210672 DOI: 10.1002/hep.1840120415]
  - 73 **Sugihara T**, Koda M, Maeda Y, Matono T, Nagahara T, Mandai M, Ueki M, Murawaki Y. Rapid identification of bacterial species with bacterial DNA microarray in cirrhotic patients with spontaneous bacterial peritonitis. *Intern Med* 2009; **48**: 3-10 [PMID: 19122350 DOI: 10.2169/internalmedicine.48.1539]
  - 74 **Bruns T**, Sachse S, Straube E, Assefa S, Herrmann A, Hagel S, Lehmann M, Stallmach A. Identification of bacterial DNA in neutrocytic and non-neutrocytic cirrhotic ascites by means of a multiplex polymerase chain reaction. *Liver Int* 2009; **29**: 1206-1214 [PMID: 19602138 DOI: 10.1111/j.1478-3231.2009.02073.x]
  - 75 **Appenrodt B**, Lehmann LE, Thyssen L, Gentemann M, Rabe C, Molitor E, Trebicka J, Stüber F, Sauerbruch T. Is detection of bacterial DNA in ascitic fluid of clinical relevance? *Eur J Gastroenterol Hepatol* 2010; **22**: 1487-1494 [PMID: 21048463 DOI: 10.1097/MEG.0b013e328340c43a]
  - 76 **Soriano G**, Esparcia O, Montemayor M, Guarner-Argente C, Pericas R, Torras X, Calvo N, Román E, Navarro F, Guarner C, Coll P. Bacterial DNA in the diagnosis of spontaneous bacterial peritonitis. *Aliment Pharmacol Ther* 2011; **33**: 275-284 [PMID: 21083594 DOI: 10.1111/j.1365-2036.2010.04506.x]
  - 77 **Enomoto H**, Inoue S, Matsuhisa A, Aizawa N, Imanishi H, Saito M, Iwata Y, Tanaka H, Ikeda N, Sakai Y, Takashima T, Shimomura S, Iijima H, Nakamura H, Nishiguchi S. Development of a new in situ hybridization method for the detection of global bacterial DNA to provide early evidence of a bacterial infection in spontaneous bacterial peritonitis. *J Hepatol* 2012; **56**: 85-94 [PMID: 21835139 DOI: 10.1016/j.jhep.2011.06.025]
  - 78 **Jalan R**, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, Stadlbauer V, Gustot T, Bernardi M, Canton R, Albillos A, Lammert F, Wilmer A, Mookerjee R, Vila J, Garcia-Martinez R, Wendon J, Such J, Cordoba J, Sanyal A, Garcia-Tsao G, Arroyo V, Burroughs A, Ginès P. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014; **60**: 1310-1324 [PMID: 24530646 DOI: 10.1016/j.jhep.2014.01.024]
  - 79 **Ariza X**, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, Ariza J, Xiol X. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. *J Hepatol* 2012; **56**: 825-832 [PMID: 22173153 DOI: 10.1016/j.jhep.2011.11.010]
  - 80 **Mendler MH**, Agarwal A, Trimzi M, Madrigal E, Tsushima M, Joo E, Santiago M, Flores E, David G, Workman A, Runyon B. A new highly sensitive point of care screen for spontaneous bacterial peritonitis using the leukocyte esterase method. *J Hepatol* 2010; **53**: 477-483 [PMID: 20646775 DOI: 10.1016/j.jhep.2010.04.011]
  - 81 **Burri E**, Schulte F, Muser J, Meier R, Beglinger C. Measurement of calprotectin in ascitic fluid to identify elevated polymorphonuclear cell count. *World J Gastroenterol* 2013; **19**: 2028-2036 [PMID: 23599621 DOI: 10.3748/wjg.v19.i13.2028]
  - 82 **Sort P**, Navasa M, Arroyo V, Aldeguez X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-409 [PMID: 10432325 DOI: 10.1056/NEJM199908053410603]
  - 83 **Reuken PA**, Pletz MW, Baier M, Pfister W, Stallmach A, Bruns T. Emergence of spontaneous bacterial peritonitis due to enterococci - risk factors and outcome in a 12-year retrospective study. *Aliment Pharmacol Ther* 2012; **35**: 1199-1208 [PMID: 22449290 DOI: 10.1111/j.1365-2036.2012.05076.x]
  - 84 **Umgielter A**, Reindl W, Miedaner M, Schmid RM, Huber W. Failure of current antibiotic first-line regimens and mortality in hospitalized patients with spontaneous bacterial peritonitis. *Infection* 2009; **37**: 2-8 [PMID: 19169633 DOI: 10.1007/s15010-008-8060-9]
  - 85 **Fernández J**, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol* 2012; **56** Suppl 1: S1-12 [PMID: 22300459 DOI: 10.1016/S0168-8278(12)60002-6]
  - 86 **Piano S**, Salinas F, Morando F, Cavalin M, Romano A, Rosi S, Stanco M, Fasolato S, Sticca A, Senzolo M, Burra P, Gringeri E, Cillo U, Gatta A, Angeli P. Poster Session 1: Infections and Acute on Chronic Liver Failure. Abstract 574: The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis: results of a randomized controlled clinical trial. *Hepatology* 2014; **60**: 478A-501A [DOI: 10.1002/hep.27505]
  - 87 **Wong F**, O'Leary JG, Reddy KR, Patton H, Kamath PS, Fallon MB, Garcia-Tsao G, Subramanian RM, Malik R, Maliakkal B, Thacker LR, Bajaj JS. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. *Gastroenterology* 2013; **145**: 1280128-8.e1 [PMID: 23999172 DOI: 10.1053/j.gastro.2013.08.051]
  - 88 **Fernández J**, Ruiz del Arbol L, Gómez C, Durandez R, Serradilla R, Guarner C, Planas R, Arroyo V, Navasa M. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology* 2006; **131**: 1049-1056; quiz 1285 [PMID: 17030175 DOI: 10.1053/j.gastro.2006.07.010]
  - 89 **Chavez-Tapia NC**, Barrientos-Gutierrez T, Tellez-Avila FI, Soares-Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010; **(9)**: CD002907 [PMID: 20824832 DOI: 10.1002/14651858.CD002907.pub2]
  - 90 **Andreu M**, Sola R, Sitges-Serra A, Alia C, Gallen M, Vila MC, Coll S, Oliver MI. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Gastroenterology* 1993; **104**: 1133-1138 [PMID: 8462803]
  - 91 **Such J**, Guarner C, Enriquez J, Rodriguez JL, Seres I, Vilardell F. Low C3 in cirrhotic ascites predisposes to spontaneous bacterial peritonitis. *J Hepatol* 1988; **6**: 80-84 [PMID: 3279108 DOI: 10.1016/S0168-8278(88)80465-3]
  - 92 **Fernández J**, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, Vila C, Pardo A, Quintero E, Vargas V, Such J, Ginès P, Arroyo V. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007; **133**: 818-824 [PMID: 17854593 DOI: 10.1053/j.gastro.2007.06.065]
  - 93 **Ginès P**, Rimola A, Planas R, Vargas V, Marco F, Almela M, Forné M, Miranda ML, Llach J, Salmerón JM. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990; **12**: 716-724 [PMID: 2210673 DOI: 10.1002/hep.1840120416]
  - 94 **Segarra-Newnham M**, Henneman A. Antibiotic prophylaxis for prevention of spontaneous bacterial peritonitis in patients without gastrointestinal bleeding. *Ann Pharmacother* 2010; **44**: 1946-1954 [PMID: 21098755 DOI: 10.1345/aph.1P317]
  - 95 **Tandon P**, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. *Clin Gastroenterol Hepatol* 2012; **10**: 1291-1298 [PMID: 22902776 DOI: 10.1016/j.cgh.2012.08.017]
  - 96 **Deshpande A**, Pasupuleti V, Thota P, Pant C, Mapara S, Hassan S, Rolston DD, Sferra TJ, Hernandez AV. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *J Gastroenterol Hepatol* 2013; **28**: 235-242 [PMID: 23190338 DOI: 10.1111/jgh.12065]
  - 97 **Bajaj JS**, Zadornova Y, Heuman DM, Hafeezullah M, Hoffmann RG, Sanyal AJ, Saeian K. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Am J Gastroenterol* 2009; **104**: 1130-1134 [PMID: 19337238 DOI: 10.1038/ajg.2009.80]

- 98 **Garcia-Martinez I**, Francés R, Zapater P, Giménez P, Gómez-Hurtado I, Moratalla A, Lozano-Ruiz B, Bellot P, González-Navajas JM, Such J. Use of proton pump inhibitors decrease cellular oxidative burst in patients with decompensated cirrhosis. *J Gastroenterol Hepatol* 2015; **30**: 147-154 [PMID: 25039465 DOI: 10.1111/jgh.12667]
- 99 **Bauer TM**, Steinbrückner B, Brinkmann FE, Ditzén AK, Schwacha H, Aponte JJ, Pelz K, Kist M, Blum HE. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. *Am J Gastroenterol* 2001; **96**: 2962-2967 [PMID: 11693333 DOI: 10.1111/j.1572-0241.2001.04668.x]
- 100 **Zhang W**, Gu Y, Chen Y, Deng H, Chen L, Chen S, Zhang G, Gao Z. Intestinal flora imbalance results in altered bacterial translocation and liver function in rats with experimental cirrhosis. *Eur J Gastroenterol Hepatol* 2010; **22**: 1481-1486 [PMID: 20739895 DOI: 10.1097/MEG.0b013e32833eb8b0]
- 101 **Sánchez E**, Nieto JC, Boullousa A, Vidal S, Sancho FJ, Rossi G, Sancho-Bru P, Oms R, Mirelis B, Juárez C, Guarner C, Soriano G. VSL#3 probiotic treatment decreases bacterial translocation in rats with carbon tetrachloride-induced cirrhosis. *Liver Int* 2015; **35**: 735-745 [PMID: 24750552 DOI: 10.1111/liv.12566]
- 102 **Pereg D**, Kotliroff A, Gadoth N, Hadary R, Lishner M, Kitay-Cohen Y. Probiotics for patients with compensated liver cirrhosis: a double-blind placebo-controlled study. *Nutrition* 2011; **27**: 177-181 [PMID: 20452184 DOI: 10.1016/j.nut.2010.01.006]
- 103 **Pande C**, Kumar A, Sarin SK. Addition of probiotics to norfloxacin does not improve efficacy in the prevention of spontaneous bacterial peritonitis: a double-blind placebo-controlled randomized-controlled trial. *Eur J Gastroenterol Hepatol* 2012; **24**: 831-839 [PMID: 22522141 DOI: 10.1097/MEG.0b013e3283537d61]
- 104 **Scarpignato C**, Pelosini I. Rifaximin, a poorly absorbed antibiotic: pharmacology and clinical potential. *Chemotherapy* 2005; **51** Suppl 1: 36-66 [PMID: 15855748 DOI: 10.1159/000081990]
- 105 **Bass NM**, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, Sigal S, Sheikh MY, Beavers K, Frederick T, Teperman L, Hillebrand D, Huang S, Merchant K, Shaw A, Bortey E, Forbes WP. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; **362**: 1071-1081 [PMID: 20335583 DOI: 10.1056/NEJMoa0907893]
- 106 **Eltawil KM**, Laryea M, Peltekian K, Molinari M. Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis. *World J Gastroenterol* 2012; **18**: 767-777 [PMID: 22371636 DOI: 10.3748/wjg.v18.i8.767]
- 107 **DuPont HL**, Jiang ZD. Influence of rifaximin treatment on the susceptibility of intestinal Gram-negative flora and enterococci. *Clin Microbiol Infect* 2004; **10**: 1009-1011 [PMID: 15522005 DOI: 10.1111/j.1469-0691.2004.00997.x]
- 108 **Vlachogiannakos J**, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J Gastroenterol Hepatol* 2013; **28**: 450-455 [PMID: 23216382 DOI: 10.1111/jgh.12070]
- 109 **Hanouneh MA**, Hanouneh IA, Hashash JG, Law R, Esfeh JM, Lopez R, Hazratjee N, Smith T, Zein NN. The role of rifaximin in the primary prophylaxis of spontaneous bacterial peritonitis in patients with liver cirrhosis. *J Clin Gastroenterol* 2012; **46**: 709-715 [PMID: 22878533 DOI: 10.1097/MCG.0b013e3283182506dbb]
- 110 **Lutz P**, Parcina M, Bekeredian-Ding I, Nischalke HD, Nattermann J, Sauerbruch T, Hoerauf A, Strassburg CP, Spengler U. Impact of rifaximin on the frequency and characteristics of spontaneous bacterial peritonitis in patients with liver cirrhosis and ascites. *PLoS One* 2014; **9**: e93909 [PMID: 24714550 DOI: 10.1371/journal.pone.0093909]
- 111 **Valentin T**, Leitner E, Rohn A, Zollner-Schwetz I, Hoenigl M, Salzer HJ, Krause R. Rifaximin intake leads to emergence of rifampin-resistant staphylococci. *J Infect* 2011; **62**: 34-38 [PMID: 21073894 DOI: 10.1016/j.jinf.2010.11.004]
- 112 **Kothary V**, Scherl EJ, Bosworth B, Jiang ZD, Dupont HL, Harel J, Simpson KW, Dogan B. Rifaximin resistance in *Escherichia coli* associated with inflammatory bowel disease correlates with prior rifaximin use, mutations in *rpoB*, and activity of Phe-Arg- $\beta$ -naphthylamide-inhibitable efflux pumps. *Antimicrob Agents Chemother* 2013; **57**: 811-817 [PMID: 23183443 DOI: 10.1128/AAC.02163-12]
- 113 **Carman RJ**, Boone JH, Grover H, Wickham KN, Chen L. In vivo selection of rifamycin-resistant *Clostridium difficile* during rifaximin therapy. *Antimicrob Agents Chemother* 2012; **56**: 6019-6020 [PMID: 22908175 DOI: 10.1128/AAC.00974-12]
- 114 **Silveira MG**, Lindor KD. Obeticholic acid and budesonide for the treatment of primary biliary cirrhosis. *Expert Opin Pharmacother* 2014; **15**: 365-372 [PMID: 24382005 DOI: 10.1517/14656566.2014.873404]
- 115 **Mudaliar S**, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, Adorini L, Sciacca CI, Clopton P, Castellote E, Dillon P, Pruzanski M, Shapiro D. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. *Gastroenterology* 2013; **145**: 574-582.e1 [PMID: 23727264 DOI: 10.1053/j.gastro.2013.05.042]
- 116 **Obstein KL**, Campbell MS, Reddy KR, Yang YX. Association between model for end-stage liver disease and spontaneous bacterial peritonitis. *Am J Gastroenterol* 2007; **102**: 2732-2736 [PMID: 17714556 DOI: 10.1111/j.1572-0241.2007.01485.x]
- 117 **Felisart J**, Rimola A, Arroyo V, Perez-Ayuso RM, Quintero E, Gines P, Rodes J. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. *Hepatology* 1985; **5**: 457-462 [PMID: 3888810 DOI: 10.1002/hep.1840050319]
- 118 **Rimola A**, Salmerón JM, Clemente G, Rodrigo L, Obrador A, Miranda ML, Guarner C, Planas R, Solà R, Vargas V. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. *Hepatology* 1995; **21**: 674-679 [PMID: 7875666 DOI: 10.1002/hep.1840210312]
- 119 **Navasa M**, Follo A, Llovet JM, Clemente G, Vargas V, Rimola A, Marco F, Guarner C, Forné M, Planas R, Bañares R, Castells L, Jimenez De Anta MT, Arroyo V, Rodés J. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. *Gastroenterology* 1996; **111**: 1011-1017 [PMID: 8831596 DOI: 10.1016/S0016-5085(96)70069-0]
- 120 **Ricart E**, Soriano G, Novella MT, Ortiz J, Sàbat M, Kolle L, Sola-Vera J, Miñana J, Dedéu JM, Gómez C, Barrio JL, Guarner C. Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. *J Hepatol* 2000; **32**: 596-602 [PMID: 10782908 DOI: 10.1016/S0168-8278(00)80221-4]
- 121 **Terg R**, Cobas S, Fassio E, Landeira G, Ríos B, Vasen W, Abecasis R, Ríos H, Guevara M. Oral ciprofloxacin after a short course of intravenous ciprofloxacin in the treatment of spontaneous bacterial peritonitis: results of a multicenter, randomized study. *J Hepatol* 2000; **33**: 564-569 [PMID: 11059861 DOI: 10.1016/S0168-8278(00)80008-2]
- 122 **Soriano G**, Guarner C, Teixidó M, Such J, Barrios J, Enríquez J, Vilardell F. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. *Gastroenterology* 1991; **100**: 477-481 [PMID: 1985045]
- 123 **Singh N**, Gayowski T, Yu VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. *Ann Intern Med* 1995; **122**: 595-598 [PMID: 7887554 DOI: 10.7326/0003-4819-122-8-199504150-00007]
- 124 **Grangé JD**, Roulot D, Pelletier G, Pariente EA, Denis J, Ink O, Blanc P, Richardet JP, Vinel JP, Delisle F, Fischer D, Flahault A, Amiot X. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: a double-blind randomized trial. *J Hepatol* 1998; **29**: 430-436 [PMID: 9764990 DOI: 10.1016/S0168-8278(98)80061-5]
- 125 **Rolachon A**, Cordier L, Bacq Y, Noursbaum JB, Franza A, Paris JC, Fratte S, Bohn B, Kitmacher P, Stahl JP. Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial. *Hepatology* 1995; **22**: 1171-1174 [PMID: 7557868]
- 126 **Novella M**, Solà R, Soriano G, Andreu M, Gana J, Ortiz J, Coll

S, Sàbat M, Vila MC, Guarner C, Vilardell F. Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. *Hepatology* 1997; **25**: 532-536 [PMID: 9049193 DOI: 10.1002/hep.510250306]

127 Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R,

Landeira C, Romero G, Dominguez N, Muñoz A, Levi D, Míguez C, Abecasis R. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. *J Hepatol* 2008; **48**: 774-779 [PMID: 18316137 DOI: 10.1016/j.jhep.2008.01.024]

**P- Reviewer:** Al-Shamma S, Kaya M, Liaskou E, Sira MM

**S- Editor:** Tian YL **L- Editor:** A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

