Spontaneous bacterial peritonitis: recent guidelines and beyond

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INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is the most frequent and life-threatening infection in patients with liver cirrhosis requiring prompt recognition and treatment. It is defined by the presence of >250 polymorphonuclear cells (PMN)/mm^3 in ascites in the absence of an intra-abdominal source of infection or malignancy. In this review we discuss the current opinions reflected by recent guidelines (American Association for the Study of Liver Diseases, European Association for the Study of the Liver, Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten),[1–4] with particular focus on controversial issues as well as open questions that need to be addressed in the future. First, diagnostic criteria and tools available for rapid and accurate diagnosis are reviewed. Second, since prophylaxis is of crucial relevance when trying to improve survival, we discuss who should be treated, when, how and for how long to prevent episodes of SBP. Identification of risk factors and individualisation of timing and selection of prophylactic measures are the key to success without major development of resistant bacteria. Finally, effective therapy is essential since treatment failure is associated with poor outcome. Since the emergence and spread of drug-resistant bacteria has accelerated, criteria for the choice of antibiotic regimen in the individual patient are pivotal for optimising therapy.

EPIDEMIOLOGY AND PROGNOSIS OF SBP

SBP is the most frequent bacterial infection in cirrhosis, accounting for 10–30% of all reported bacterial infections in hospitalised patients.[5–7] In outpatients without symptoms the prevalence is low (3.5%[8] or lower[9 10]), but the prevalence increases in the nosocomial setting, ranging from 8% to 36%.[11 12] Bacterascites, defined as positive culture results but no increase in the PMN count in the ascitic fluid, occurs with a prevalence of 2–3% in outpatients[8–10] and in up to 11% in hospitalised patients.[11 13] In-hospital mortality for the first episode of SBP ranges from 10% to 50%, depending on various risk factors.[7 14–18] One-year mortality after a first episode of SBP has been reported to be 31% and 93%.[8 17 19–21] In fact, the occurrence of SBP or other severe bacterial infections markedly worsens the prognosis in patients with cirrhosis and it has been proposed that a new prognostic stage of cirrhosis not reflected in current staging systems should be defined, the so-called 'critically ill cirrhotic'.[22] Patients at this late stage have to be evaluated for the possibility of liver transplantation. Predictive factors reported for a poor prognosis in various cohorts of patients with SBP are summarised in figure 1 and include age,[16 20] Child score,[18 20 23] intensive care,[16 18] nosocomial origin,[18 24] hepatic encephalopathy,[25] elevated serum creatinine and bilirubin,[26] lack of infection resolution/need to escalate treatment and culture positivity[27–29] as well as the presence of bacteraemia[30] and CARD15/NOD2 variants as a genetic risk factor.[31] It is important to stress in this context that the only factors that are modifiable in this scenario are timely diagnosis and effective first-line treatment.

Bacterial translocation (BT) and pathophysiology

Bacterial translocation (BT) is the most common cause of SBP.[32 33] However, particularly in nosocomial SBP, other sources such as transient bacteraemia due to invasive procedures can lead to SBP. Limited BT to mesenteric lymph nodes (MLN) is a physiological phenomenon, whereas any increase in the rate and severity of BT may be deleterious for the patient and thus should be termed 'pathological BT'. Only a few intestinal bacteria are able to translocate into MLN, including *Escherichia coli*, *Klebsiella pneumoniae* and other Enterobacteriaceae.[34] Interestingly, these species most frequently cause SBP, and DNA sequencing studies reveal genotypic identity of bacteria in MLN and ascites in the vast majority of cases.[35 36] This suggests that pathological BT is the underlying cause and source of SBP in cirrhosis and supports the view that the route of pathological BT leading to SBP is largely lymphatic. Three factors have been implicated in the development of pathological BT in liver cirrhosis[32]: (1) alterations in gut microbiota; (2) increased intestinal permeability; and (3) impaired immunity.

Microbiota

Liver cirrhosis is associated with distinct changes in faecal microbial composition[37 38] including an increased prevalence of potentially pathogenic bacteria such as Enterobacteriaceae. Moreover, small intestinal bacterial overgrowth (SIBO), defined as >10^5 colony forming units/ml jejunal aspirate and/or colonic-type species, is frequently present in advanced stages of liver cirrhosis and has been linked with pathological BT, SBP and endotoxinaemia.[39–41] In cirrhosis, factors promoting these changes may include deficiencies in paneth cell defensins,[41a] reduced intestinal motility, decreased pancreatobiliary secretions and portal-hypertensive enteropathy. In experimental cirrhosis, in the absence of SIBO, BT occurs rarely (0–11%) and at rates comparable to healthy

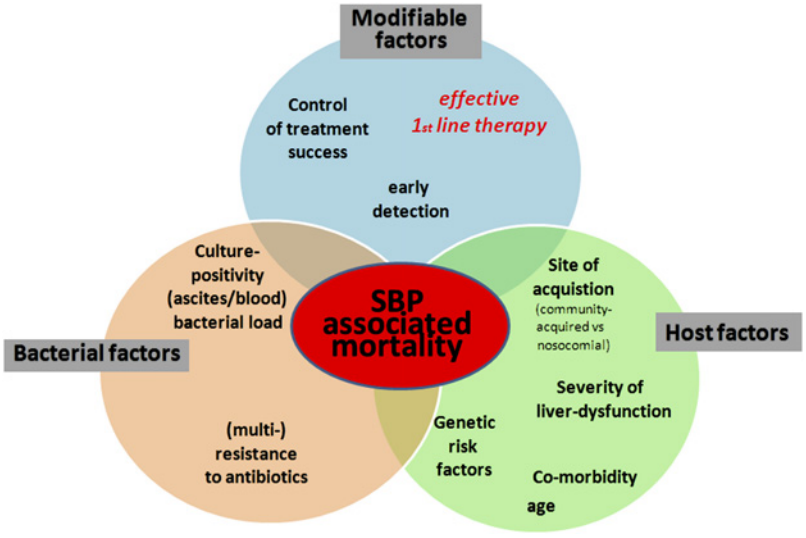

Figure 1 Spontanous bacterial peritonitis (SBP)-associated mortality. Reported risk factors for poor prognosis in SBP are categorised into fixed or modifiable factors as well as host and bacterial factors, respectively. The most relevant for survival is resolution of infection which is best influenced by effective first-line therapy since other factors are not modifiable.

conditions. However, BT does not occur in up to half of the animals with SIBO and, thus, SIBO is necessary but not sufficient for BT to occur.

Intestinal permeability

Cirrhosis is associated with structural and functional alterations in the intestinal mucosa that increase permeability to bacteria and bacterial products. In particular, changes in enterocyte mitochondrial function and increased oxidative stress of the intestinal mucosa have been identified.[42 43]

Host defence

For translocation to become clinically significant—that is, for it to lead to SBP or bacteraemia—a failure of local and systemic immune defences appears to be the most important prerequisite (see below).

Local ascitic-peritoneal host defence in peritonitis

The peritoneal cavity probably has the most severe lack of host defence compared with other compartments in decompensated cirrhosis. In fact, ascites per se may be considered a risk factor for the development of peritonitis. In healthy conditions, peritoneal host defence mechanisms are very efficient and intraperitoneal injection of various numbers of single organisms does not cause peritonitis unless adjuvant substances or ascites are present.[44] In cirrhosis, deficiencies in local defence mechanisms against bacteria, including dysfunction of cellular and humoral immunity, limit peritoneal bacterial clearance.

Since the absolute number of PMN per mm^3 ascitic fluid defines SBP, the mechanisms of chemotaxis mediating PMN influx into the peritoneal cavity are important. The degree of PMN migration and accumulation in the peritoneal cavity combating invading bacteria depends on a number of factors. Resident macrophages are the first to phagocytose bacteria, they further help to attract PMN by release of chemotactic factors and activate complement. For instance, monocyte chemotactic protein 1 is one of the most potent chemokines, and a functional polymorphism has been proposed as a risk factor for SBP in alcoholic cirrhosis.[45] A chemotactic gradient is necessary to achieve appropriate neutrophil recruitment into the peritoneal cavity. In fact, PMN chemoattractants such as zymosan are very effective in preventing the death of animals with *E coli*-induced peritonitis when administered locally but not systemically.[46] Unfortunately, little is known about the influx, efflux and kinetics of neutrophils in ascitic fluid in cirrhosis and its dependency on type, extent and duration of bacterial stimulus as well as host factors.

Besides influx of PMN, bacterial clearance is determined by the overall killing capacity which is dependent on opsonisation, burst activity and inflammatory response. A marked reduction in opsonic and bactericidial activity is well-known in cirrhosis. In particular, low C3 levels in cirrhotic ascites correlate strongly with opsonic activity[47] and have been shown to predispose to SBP.[48] However, the total protein content aslo mirrors opsonic activity and has been shown to be predictive of the development of SBP.[49] At a protein level of >1.5 g/dl ascitic fluid, the incidence rates of SBP have been consistently reported to be lower than 1%. In contrast, at protein levels <1.5 g/dl ascitic fluid, the risk of SBP increases, parallelling the decrease in protein content and reaching incidence rates of 27–41% at levels <1.0 g/dl.[19 50 51] Other factors that may contribute but have not been addressed thoroughly include compartmentalisation via activation of coagulatory systems or the omentum (called the 'abdominal policeman') and visceral fat. The latter is a relevant source of adipokines known to modulate the inflammatory response. In fact, significant levels of, for example, adiponectin, visfatin and resistin are observed in ascites and the latter is increased in the presence of SBP.[52]

Liver dysfunction and systemic risk factors

Cirrhosis is accompanied by deficits in innate and adaptive intrahepatic, intestinal and systemic immunity. Patients with cirrhosis with decreased reticuloendothelial system (RES) activity develop SBP at a higher rate than those with close to normal RES activity.[23] Accordingly, markers of advanced liver dysfunction have been identified as independent risk factors for a first episode of SBP. A bilirubin level of >3.2 mg/dl and platelet count of <98 000/mm^3 significantly increase the likelihood of SBP,[53] and each model for end-stage liver disease (MELD) point increases the risk of SBP by about 11%.[54] However, circulating mononuclear cells also present with alterations in Toll-like receptor (TLR)[55] and HLA expression[56 57] as well as reduced

chemotactic, opsonic, phagocytic and killing capacity.[58 59] Furthermore, genetic variants influencing host defence mechanisms such as CARD15/NOD2[31 60] and TLR2[61] have been reported to be associated with an enhanced probability of acquiring SBP. TLR2 polymorphisms and NOD2 variants seem to represent supplementary risk factors since the simultaneous presence of both unfavourable polymorphisms markedly increases the risk of SBP.[61] This underlines the known interaction of NOD2 and TLRs, in particular the modulation of TLR2-dependent cytokine responses by NOD2.[62]

Medication can also affect the chances of developing SBP. The use of proton pump inhibitors (PPI) has been proposed to facilitate SIBO and thus to contribute to pathological BT. In fact, retrospective case–control studies reveal a potential association between the use of PPI and development of SBP.[63 64] Considering the frequently inadequate overuse of PPI in patients with cirrhosis, we therefore recommend restricting their use to indications of proven benefit. In contrast, non-selective β-blockers (NSBB) may prevent SBP.[65 66] It is tempting to speculate that this benefit relates to an improvement in chemotaxis, proinflammatory cytokine release and killing capacity reported for β-adrenergic antagonists in various experimental settings.[67 68] Since the sympathetic nervous system affects PMN chemotaxis, the question arises as to how treatment with NSBB affects the validity of diagnosing SBP based on PMN count in the ascitic fluid.

DIAGNOSIS OF SBP

Symptoms and signs are frequently absent in patients with SBP,[69] so a diagnostic paracentesis should be performed in all patients with ascites admitted to hospital regardless of whether or not there is clinical suspicion. Diagnosis should be prompt and treatment must not be delayed until the microbiology results are available. Thus, in all the available guidelines, diagnosis is based on a fixed defined cut-off PMN count in the ascitic fluid.[1–4] In patients with haemorrhagic ascites (ie, red blood cell count >10 000/mm^3), subtraction of one PMN per 250 red blood cells should be made to adjust for the presence of blood in ascites. Owing to the short lifespan of PMN, their ascitic count is independent of diuretics and/or other modulations of ascites volume. In contrast, lymphocytes which have a long lifespan increase in concentration during diuresis.[70] Moreover, differential diagnoses of predominant lymphocytosis in ascitic fluid include tuberculous peritonitis, neoplasms, congestive heart failure, pancreatitis and myxedema, but not usually SBP. PMN are therefore used to define SBP, and the greatest sensitivity is reached at a cut-off value of 250 PMN/mm^3, although the best specificity has been reported with a cut-off of 500 PMN/mm^3.[71–74] However, since it is important not to miss a case of SBP, the most sensitive cut-off value is used. Nonetheless, this upper limit has been set quite arbitrarily since it was tested in the setting of culture-positive peritonitis. Thus, the range of PMN in truly non-infected ascites—that is, the ascitic PMN count that is clinically relevant for the patient—is not known. Moreover, SBP caused by Gram-positive cocci has been reported frequently to have a PMN count below the threshold of 250/mm^3.[75] Interestingly, bactDNA from Gram-negative bacteria in ascitic fluid is associated with a higher ascitic PMN count than bactDNA from Gram-positive bacteria,[76] underscoring the differences in stimulatory capacity for PMN migration depending on the type of bacteria.

Microscopy versus automated cell counter

Ascitic PMN cell counts can be determined either by a traditional haematological method using a light microscope and a manual counting chamber or by automated cell counters.[77–79] Current guidelines either do not state specifically the method to be used[2 4] or recommend microscopy as the preferred method.[1] However, microscopic evaluation is labour-intensive, time-consuming and has high intraoperator and interoperator variability. In contrast, automated cell counters, if available, are easily accessible in emergencies and provide results within minutes at low cost. Their use has recently been validated in patients with cirrhotic ascites,[77 79] revealing sufficient sensitivity for detection of SBP, and thus should be recommended. However, it is important to stress that not all automated cell counters fulfil the quality criteria. These include sufficient functional sensitivity, test precision and accuracy, particularly for automated leucocyte counts in ascites even with low cell concentrations (eg, XE-5000 (Sysmex, Mundelein, IL, USA), Advia 120 (Erlangen, Germany), Iris iQ200 (Chatsworth, CA, USA), CellDyn-4000 (Wiesbaden, Germany)).

None of the recent guidelines recommends the use of reagent test strips to assess leucocyte esterase activity of activated PMNs for the diagnosis of SBP owing to unacceptable rates of false negative results.[80] However, most of the strips used to date have been developed for urinary tract infections with a threshold of >50 PMN/mm^3.[81] Recently, a reagent strip test has been calibrated for ascitic fluid with a cut-off of 250 PMN/mm^3.[82] Validity scores achievable were reported to be 100% sensitivity and 100% negative predictive value. However, this needs to be confirmed in large multicentre trials and, furthermore, the test was not interpretable in bloody, chylous or bilious ascitic fluid.

Bacterial DNA detection and culture techniques

Detection of bacterial DNA (bactDNA) using various approaches has recently been proposed in the ascitic fluid of patients with cirrhosis.[83–85] The advantage of such a system would be the immediate identification of the causative bacteria, thus enabling more accurately targeted antibiotic treatment. BactDNA is found in the ascitic fluid of about 40% of patients with cirrhosis, being derived mainly from Gram-negative bacteria.[84 85] However,

detection of bactDNA in ascites or serum was not associated with an enhanced incidence of SBP and does not appear to predict the development of bacterial infections.[86]

Culture techniques

Gram staining of peritoneal fluid is rarely helpful[87] and is not recommended. In contrast, culture is the recommended procedure. Although only a few species and genera are found to cause SBP, more than 70 different microbial species have been isolated from the ascitic fluid of patients with bacteriologically-confirmed SBP.[88] Classical culture techniques fail to grow bacteria in up to 65% of neutrocytic ascites. Bedside inoculation of ascites into blood culture bottles has been shown to increase the sensitivity to nearly 80%.[89–91] In this regard, non-radiometric (eg, colorimetric BacTec) systems in particular have improved the time to diagnosis since they are faster than conventional blood culture bottles.[89] Handling processes influence culture results and delay in transport increases false negative results.[92] Separate and simultaneous blood cultures should be collected since 30–58% of SBP cases are associated with bacteraemia.[30 93]

Other markers of inflammation and secondary peritonitis

Other markers found to be indicative of SBP include ascitic pH, lactate dehydrogenase, lactate (and corresponding arterial–ascitic gradients), but none of these is sufficiently predictive or discriminative and may be increased in malignancy-related ascites.[72 74 94 95] Proteins such as granulocyte elastase[96] and lactoferrin[97] released by PMN upon activation have likewise been shown to be increased in SBP. Lactoferrin was reported to give rates of sensitivity and specificity of 95.5% and 97%, respectively, using a cut-off value of 242 ng/ml and to decrease to below the cut-off value in patients responding to treatment.[97] However, because of the small number of SBP cases in this investigation, confirmation is required in multicentre trials including assessment of its accuracy in haemorrhagic and coexisting malignant ascites.

Differentiation of SBP from secondary peritonitis due to perforation or inflammation of an intra-abdominal organ is clinically very relevant as the associated mortality is exceedingly high.[98] In fact, all patients with perforated secondary peritonitis not undergoing timely surgery have been reported to die during hospitalisation and, thus, delayed diagnostic investigation is fatal. However, the proposed criteria to suspect secondary peritonitis (eg, inadequate response to therapy, multiple organisms)[1 3] are identified too late and therefore rapid and accurate 'chemical' parameters available at the time of paracentesis are needed. Parameters proposed by Runyon *et al* are neutrocytic ascites with at least two of the following three criteria: ascitic fluid total protein >1 g/dl (in contrast to SBP), glucose <50 mg/dl (due to bacterial glucose utilisation) or lactate dehydrogenase >225 mU/ml.[99] The sensitivity of these criteria can be less than 68%[98 99] and thus can be optimised. In addition, Wu *et al* reported that ascitic fluid with either alkaline phosphatase >240 U/l or carcinoembryonic antigen >5 ng/ml in 80% of cases reflects peritonitis of secondary origin.[100] Although no data are available on the diagnostic accuracy of the combined criteria (ie, those of either Wu *et al* or Runyon *et al*), they are likely to improve sensitivity and should be tested prospectively. In the meantime, we strongly recommend performing an abdominal CT scan as soon as any of these features are present.[101]

Box 1

Key messages established unequivocally

- Clinical judgement does not rule out SBP and thus a diagnostic paracentesis should be performed in all patients with cirrhosis and ascites at hospital admission and/or in case of gastrointestinal bleeding, shock signs of inflammation, worsening of liver/renal function or hepatic encephalopathy.
- SBP is defined by >250 PMN/mm^3 and bacterascites by positive culture results of ascitic fluid in the absence of PMN >250/mm^3.
- Ascitic fluid culture is important to guide antibiotic therapy and should be performed in all patients before starting antibiotic treatment by inoculation of ascites into blood culture bottles at the patient's bedside.

Controversial but proposed

- PMN count in ascitic fluid can be determined either by microscope OR appropriate automated cell counters. Reagent strips currently cannot be recommended for rapid diagnosis of SBP but ascites-calibrated sticks may become available.
- Bacterial DNA is not useful in detecting or predicting the occurrence of SBP.

Questions to be addressed in the future

- Are there potential differences in the detection of SBP dependent on the use of β-blockers and the type of causative bacteria (Gram-positive vs Gram-negative)?
- Is the fixed cut-off PMN count used for defining SBP the best choice, or is the chemotactic capacity of each individual patient relevant?
- Which parameters are sufficiently sensitive to guide rapid imaging for detection of secondary peritonitis?

TREATMENT OF SBP

Treatment has to be started immediately after diagnosis of SBP and therefore is empirical since culture results are not available at this time point. The strain of bacteria causing SBP mainly depends on the site of acquisition. However, none of the international guidelines to date differentiates

between nosocomial and community-acquired SBP with regard to the type of antibiotic regimen to use. This may be deleterious since nosocomial infections are associated with high rates of bacterial multiresistance and mortality (J G Acevedo, personal communication, 2009).[24 102] Patients with cirrhosis are also at increased risk of healthcare-associated infections,[103] but studies are needed to determine the associated risk for multiresistant bacteria causing SBP.

Community-acquired SBP: complicated and uncomplicated cases

Historically, Gram-negative bacteria—almost exclusively Enterobacteriaceae—have been isolated in the overwhelming majority of SBP cases. More recently, several studies have found an increasing rate of infections with Gram-positive bacteria and resistant microorganisms (J G Acevedo, personal communication, 2009).[24 29 102] However, in patients with no previous hospitalisation and no prior antibiotic treatment, the causative bacteria still usually belong to the easily treatable Enterobacteriaceae family of bacteria. Several antibiotics have been recommended for the initial treatment of SBP in these cases including cefotaxime or other third-generation cephalosporins, amoxicillin-clavulanic acid or quinolones. Although earlier trials have shown comparable efficacy of intravenous amoxicillin/clavulanic acid (1/0.2 g every 8 h) and intravenous cefotaxime in the treatment of SBP, recent increases in resistance to aminopenicillin/β-lactamase inhibitors[104] may limit their usefulness. In patients presenting without complicating factors that may worsen therapeutic efficacy, oral treatment with quinolones appears sufficient in countries with a relatively low rate of quinolone-resistant strains of *E coli*. Possible complicating factors include shock, ileus, gastrointestinal bleeding, severe hepatic encephalopathy or renal dysfunction (serum creatinine >3 mg/dl).[105]

Nosocomial SBP: treatment failure, risk factors and recommendations

In nosocomial SBP, use of the antibiotics recommended above (third-generation cephalosporins, amoxicillin/clavulanic acid or quinolones) has recently led to disappointing and unacceptably low rates of resolution (J G Acevedo, personal communication, 2009).[29 106] Resistance to third-generation cephalosporins and quinolones has been reported to increase continuously and to reach levels of 23–44% and 38–50%, respectively, in some institutions and countries (J G Acevedo, personal communication, 2009).[24 29 106 107] In addition, the incidence of extended-spectrum β-lactamase (ESBL)-producing bacteria as well as multiresistant Gram-positive bacteria such as *Enterococcus faecium* or methicillin-resistant *Staphylococcus aureus* (MRSA) causing nosocomial SBP is alarming (table 1). MRSA has been found in 24–27% of cases of SBP, with detection of *S aureus* in ascites several years ago.[75 112] Fortunately, the numbers are decreasing in most European countries.[113] In contrast, the Study for Monitoring Antimicrobial Resistance Trends reported that hospital-acquired ESBL-positive *E coli* in any intra-abdominal infection have increased in Europe from 4.3% in 2002 to 11.8% in 2008.[114 115] ESBLs cause resistance to various types of newer β-lactam antibiotics including third-generation cephalosporins and monobactams and, in addition, frequently also carry genes encoding resistance even to other antibiotics including quinolones, tetracyclines and antifolates.[116] ESBL resistance genes/plasmids rapidly spread around the world, with foreign travel being associated with intestinal colonisation rates as high as 32% in Asia (and 88% specifically in India).[117 118] Moreover, colonisation of these resistant organisms persists in a large proportion of patients for many months[117] and any antibiotic treatment causes selective pressure, accelerating the clinical relevance of these bacteria.[119] For SBP, ESBL-positive strains are not yet as frequent as in Asia but have been reported to cause up to 22% of nosocomial infections in Spain (J Fernandez, personal communication, 2010). However, among European countries and even among institutions in the same country, there are wide differences in resistance rates. For instance, for *E coli* isolates, susceptibility rates of ciprofloxacin or ampicillin/sulbactam are 90% and 65%, respectively, in Estonia but are 52% and 32% in Turkey.[114]

The clinical relevance of these numbers is reflected in the associated morbidity, healthcare-associated costs and mortality. In a number of independent investigations, in-hospital mortality and/or 30-day mortality have been shown to be increased in nosocomial SBP caused by multiresistant bacteria compared with common bacteria (J G Acevedo, personal communication, 2009).[75 102 106 111] In some series, most patients with SBP due to multiresistant bacteria died within the first 5 days after the diagnosis of SBP was made and, indeed, none of the patients with persistent infection survived.[29] A meta-analysis of recently published data found a four times increased risk of mortality associated with bacterial resistance in SBP (figure 2). Nosocomial SBP due to ESBL strains or to multiresistant bacteria is often associated with a failure of first-line empirical antibiotic treatment.[29 102 109] Indeed, the need for escalation of treatment associated with poor survival is predictive of in-hospital mortality[24 29] and therefore must be avoided. The use of carbapenems and glycopeptides would be safest and easiest since no resistance has so far been reported in cases of SBP, but this is not practical and the choice of antibiotics needs to be stratified for parameters defining the risk of resistant bacteria. This includes host factors as well as validated knowledge of the resistance profile of bacteria acting in the setting in which the patient is diagnosed and treated. Reported independent risk factors for bacterial multiresistance are previous hospitalisation (particularly within 3 months and intensive care treatment) and prior prophylactic or therapeutic antibiotic treatment (figure 3).[24 29 120 121] It is

Table 1 Data on bacterial resistance in SBP and associated mortality in last decade

Reference	Country	Number of patients/number SBP episodes (year where stated)	Resistance rates for antibiotics (in culturable bacteria)	ESBL (% of cultured bacteria)	MRSA (% of cultured bacteria)	*Candida* spp	Mortality with vs without multiresistant bacteria (or resistance*/failure first-line therapy†) RR (95% CI)
Singh *et al*, 2002[108]	USA	42/61 25 (1991–1995) 17 (1996–2001)	Multiresistant: 19% (overall) 8.3% (1991–1995) 38.5% (1996–2001)	8.1%	5.4%	12%	30-day mortality: 4/7 vs 5/30, RR 3.43 (1.23 to 9.56)
Park *et al*, 2003[109]	Korea	75/87 (1995) 195/222 (1998) 207/271 (1999)	Cefotaxime‡: 7% (1995) and 28% (1999) Ciprofloxacin‡: 10% (1995) and 32% (1999) Ampicillin‡: 83% (1995) and 76% (1999)	7.9% (1995) 9.7% (1998) 19.8% (1999)	Not stated	Not stated	In-hospital mortality: ESBL 94% vs others not stated
Angeloni *et al*, 2008[106]	Italy	32/38	Cefotaxime: 44%	33%	0	0	Not stated
Heo *et al*, 2009[110]	Korea	145/157	Cefotaxime: 15.6%‡ Ciprofloxacin: 20.4%‡ Ampicillin: 61.1%‡	11.1%	0	1.9%	In-hospital mortality: 20/23 vs 13/132, RR 8.83 (5.15 to 15.15)† 4/6 for ESBL vs 29/151 for others, RR 3.47 (1.81 to 6.67)
Cheong *et al*, 2009[24]	Korea	236/236	Third-generation cephalosporin: 16.3%‡	4.7%	0	Not stated	30-day mortality: 46/61 vs 69/175, RR 1.91 (1.52 to 2.41)†
Umgelter *et al*, 2009[29]	Germany	101/101	Cefotaxime: 33% Ciprofloxacin: 45.2%Amoxicillin/clavulanic acid: 38.6% Multiresistant: 26.8%	0	0	4.9%	8/17 vs 1/12, RR 5.65 (0.81 to 39.42)* (88.9% with multiresistant bacteria; personal communication)
Fernandez *et al*, 2011[111]	Spain	100/126	Multiresistant bacteria: 22% (nosocomial); 3% (community-acquired)	16%/2%	0	0	In-hospital mortality: 17/116 vs 5/10, RR 3.41 (1.60 to 7.29) Pooled§ RR 3.87 (1.76 to 8.52)

‡For Gram-negative bacteria.
§Random effect meta-analyses performed in Review Manager Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011. Statistical method Mantel-Haenszel.
ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; SBP, spontanous bacterial peritonitis.

therefore suggested that, in patients with cirrhosis who develop nosocomial SBP and present with such risk factors, a more effective first-line empirical antibiotic therapy with a broader spectrum should be used, namely carbapenems. However, this regimen should be de-escalated as soon as possible if microbiological results reveal non-resistant easily treatable causative microorganisms. This minimises resistance selection pressure on the carbapenems and underlines the paramount importance of obtaining appropriate microbiological cultures. Global susceptibility statistics from intra-abdominal infections show that the susceptibilities of Gram-negative isolates to the carbapenems have remained stable over the past years, with *E coli* and *K pneumoniae* isolates, including ESBL-positive isolates, being 98–100% susceptible.[122] Implementing carbapenems as first-line treatment in patients with nosocomial SBP with risk factors for multiresistant bacteria can therefore save lives. This has also been recommended in recent guidelines on the treatment of sepsis,[123] aiming at rapid initiation of an antibiotic regimen likely to cover all expected causative microorganisms. The same should be even more true for patients with decompensated cirrhosis who have an enhanced proinflammatory response to bacterial stimuli[124] and exhibit an increased susceptibility for any vasodilatory stimulus due to the already highly hyperdynamic splanchnic circulation.[125]

Treatment of bacterascites

It is controversial whether culture-positive results in the absence of an increased PMN count in the ascitic fluid require immediate initiation of antibiotic therapy. Some guidelines recommend antibiotic treatment only in patients with signs of infection or inflammation.[4] Otherwise, a follow-up paracentesis should establish whether SBP is present (PMN count >250/mm^3) and thus whether treatment is indicated. However, this is based on a single-centre observational cohort study[126] and has not been addressed prospectively. Until then we think that considering the lack of symptoms in a large number of cirrhotic patients even in presence of severe bacterial infection antibiotic treatment should be used in case of bacterascites.

Use of albumin as adjuvant treatment

In patients with cirrhosis with SBP, a prospective randomised comparative study reported that adjuvant administration of high-dose albumin (1.5 g/kg on day 1 and 1 g/kg on day 3) with antibiotic treatment prevented worsening of renal function with a concomitant improvement in in-hospital and 3-month survival.[108] However, this regimen is mainly effective in high-risk patients characterised by serum bilirubin >4 mg/dl. In addition, in unselected patients with SBP, even low-dose albumin (10 g/day on days 1–3) has been shown to reduce tumour necrosis factor and interleukin 6 levels in serum and ascites and to prevent increases in serum NO_x induced by SBP.[110] Therefore, future trials need to determine whether other patients with

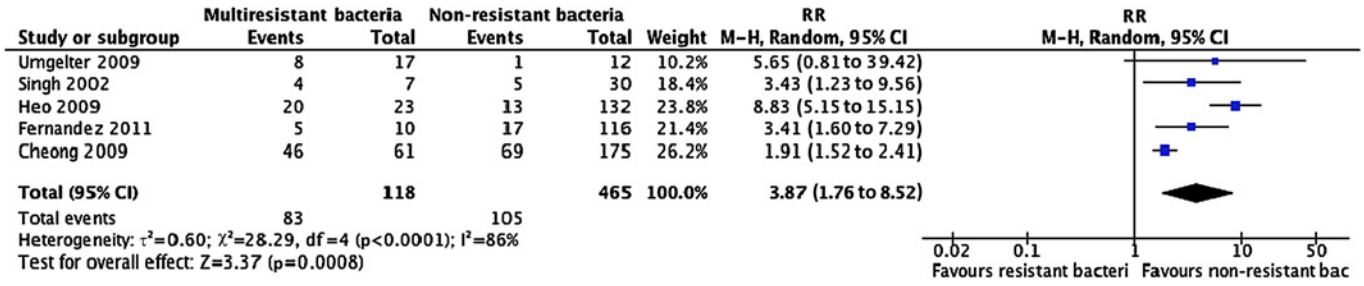

Figure 2 Meta-analysis of available data on the impact of multiresistant bacteria on mortality in cirrhosis.

cirrhosis could also benefit and to establish the dose and timing of albumin needed to give most benefit to the individual patient.

Duration of treatment and control of treatment success

Antibiotic treatment can safely be discontinued after the ascites PMN count has decreased to <250/mm^3. In a comparative study, extension of treatment duration to 10 days was not superior to treatment for 5 days,[127] and it is therefore recommended that antibiotic therapy should be given for 5 days only. Moreover, current guidelines recommend changing treatment if the PMN count does not decrease by at least 25% compared with the pretreatment level after 2 days of antibiotic treatment.[2 3] However, this has not been established in a prospective manner and/or treatment algorithm. In fact, this is based on a retrospective analysis of the half-life of PMN in ascites after initiation of antibiotic treatment[128] and the observation that the reduction in the ascites PMN count 48 h after initiation of antibiotic treatment is greater in survivors than in non-survivors (92±9% vs 66±38%).[129] There is therefore a clear need to establish the best time point and degree of reduction in PMN count to exclude accurately the chance of treatment failure in patients with SBP.

Box 2

Key messages established unequivocally

- Empirical antibiotic therapy must be initiated immediately after the diagnosis of SBP is made.
- Uncomplicated community-acquired first SBP can be treated orally with quinolones in countries with low level quinolone resistance rates, otherwise third-generation cephalosporins should be used.

Controversial but proposed

- The choice of antibiotic regimen strongly needs to consider (a) the site of acquisition (community-acquired vs nosocomial), (b) prior antibiotic treatment and (c) local resistance profile. In cases of nosocomial SBP and either prior hospitalisation with antibiotic treatement or long-term antibiotic prophylaxis, the use of carbapenems is recommended.
- Albumin should be used as adjuvant treatment in patients with SBP and a high risk of worsening renal function.

Questions to be addressed in the future

- What are the individual risk factors for SBP due to multiresistant bacteria?
- Can asymptomatic bacterascites be left untreated?
- In which patients and with what schedule (dose and timing) should albumin be used as adjuvant treatment to optimise benefit?
- What change in PMN count in the ascitic fluid during antibiotic treatment defines best treatment failure and therefore the need to alter antibiotic treatment?

PREVENTION OF SBP

Secondary and primary prophylaxis

The efficacy and role of prophylactic antibiotics is indisputable in the setting of gastrointestinal bleeding and in patients who recover from an episode of SBP.[1–4] For secondary prophylaxis, the evidence is strongest for norfloxacin.[130] Some guidelines recommend the use of oral ciprofloxacin (750 mg once weekly)[1] or trimethoprim/sulfamethoxazole as an alternative.[1 3] However, the use of intermittent ciprofloxacin has been associated with

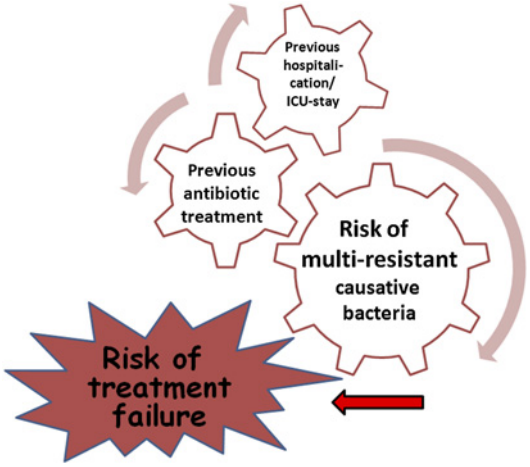

Figure 3 Key elements driving development of bacterial resistance and risk of treatment failure.

Table 2 Published randomised controlled trials including primary prophylaxis of SBP treatment

Reference	Intervention, controls, comparison	Patients	Follow-up	Previous SBP	GI bleed	Ascites protein (g/dl)	Child class (A/B/C/score)	Exclusion criteria	Incidence of SBP	Survival	As	Ac	B	O	I	S	C/D
Soriano *et al*, 1991[136]	Norfloxacin 400 mg/day vs no treatment	32/31	No data	6%	4/61 (6.6%)	All <1.5 TP: 0.71±0.3 Con: 0.67±0.3	TP: 2/3/17 Con: 1/14/16	Recent infection GI bleed	TP: 0/32 (0%) Con: 7/31 (22.5%) p<0.05	TP: 30/32 (93.7%) Con: 26/31 (83.9%)NS	?	?	–	+	+	–	
Rolachon *et al*, 1995[137]	Ciprofloxacin 750 mg/week vs placebo	28/32	6 months	11%	No	All <1.5 TP: 0.94±0.3 Con: 1.03±0.3	TP: 0/17/11 Con: 1/18/13	HCC GI bleed HE	TP: 1/28 (3.6%) Con: 7/32(22%) p<0.05	TP:24/28 (85.7%) Con: 26/32 (81.2%) NS	?	?	+	+	+	+	Non-compliant (n=3), withdrawal or lost to follow-up (n=5), overall 13%
Singh *et al*, 1995[134]	Trimethoprim-sulfamethoxazole double-strength 1×/day (5 days/week) vs no treatment	30/30	90 days (7–682)	22%	13%	No data	No data	No data	TP: 1/30 (3%) Con: 7/30 (23.3%) (8/30 (27%) for end point* p<0.05	TP:28/30 (93%) Con: 24/30 (80%) NS	?	?	–	?	+	–	
Novella *et al*, 1997[51]	Norfloxacin 400 mg/day continuous vs norfloxacin 400 mg/day in-hospital	56/53	43+3 week	No	23/109 (>21%)	TP: 1.0±0.2 Con: 0.9±0.1	TP: 0/29/27 Con: 0/24/29	HCC Bilirubin >15 mg/dl	TP: 1/56 (1.8%) Con: 9/53 (16.9%) p<0.01	TP: 75% Con: 62% NS	?	+	–	?	?	–	Drop-out: >10%
Grange *et al*, 1998[138]	Norfloxacin 400 mg/day vs placebo	53/54	6 months	No	No	All <1.5 TP: 0.93±0.29 Con: 1.04±0.0.3	No data	GI bleed HCC	SBP or bacteraemia† TP: 1/53 (1.9%) Con: 9/54 (16.7%) p<0.05	TP:45/53 (84.9%) Con: 44/54 (81.5%) NS	?	?	?	+	+	+	Lost to follow-up (4/53 and 4/54) Drop-out: 7.5% non-compliant (3/53 and 2/54), withdrawal (2/53), overall 14%
Alvarez *et al*, 2005[139]	Norfloxacin 400 mg/day vs trimethoprim-sulfamethoxazole 160/800 mg 5 days/week	32/25	3–547 days	39%	No	Also pts with >1.5 Norfloxacin: 0.96±0.55 SMT: 1.37±0.84 p<0.05	Norfloxacin: 1/10/21 SMT: 0/8/17	Antibiotic within 2 weeks GI bleed within 1 week HCC/malignancy	Norfloxacin: 3/32 (9.4%) SMT: 4/25 (16%) NS	Norfloxacin: 25/32 (78.1%) SMT: 20/25 (75%) NS	+	+	–	?	?	–	No data
Fernandez *et al*, 2007[140]	Norfloxacin 400 mg/day vs placebo	35/33	12 months	No	3/68 (4.4%)	All <1.5 TP: 0.93±0.29 Con: 1.04±0.3	TP: 9.9±1.5 Con: 10.4±1.5	HCC, HIV organic renal disease	TP: 2/35 (5.7%) Con: 10/33 (30.3%) p<0.05	TP: 25/35 (71.4%) Con: 20/33 (60.6%) NS	+	+	+	+	+	?	Lost to follow-up (3/35 and 2/33), one protocol violation, non-compliant (3/35 and 3/33)
Terg *et al*, 2008[141]	Ciprofloxacin 500 mg/day vs placebo	50/50	12 months	No	No data	All <1.5 TP: 0.84±0.01 Con: 0.85+0.4	TP: 8.3±1.3 Con: 8.5±1.5	HE, HCC/ malignancy creatinine >3 mg/dl platelets <98 000	TP: 2/50 (4%) Con: 7/50 (14%) NS	TP: 44/50 (80%) Con: 36/50 (72%) p<0.05							

*SBP or spontaneous bacteraemia.
†Primary end point is Gram-negative infections but no information on SBP alone.
As, allocation sequence; Ac, allocation concealment; B, blinding; O, outcome data set complete?; I, intention to treat; S, sample size calculation; C/D, compliance/drop-out rate.
Con, control; GI, gastrointestinal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; NS, not significant; SBP, spontanous bacterial peritonitis; SMT, trimethoprim-sulfamethoxazole; TP, therapy.

a higher rate of quinolone-resistant organisms[131] and, in our view, should therefore be avoided. Data supporting the use of trimethoprim/sulfamethoxazole are weak,[132] while its side effects are potentially dangerous and probably under-reported.[133] Moreover, resistance to this class of antibiotics has increased to a degree that it is no longer recommended as the first-line choice for the empirical treatment of urinary tract infections in some countries.[134] In patients with cirrhosis with gastrointestinal haemorrhage, quinolones are most frequently used and have been found to decrease the incidence of severe infections (SBP and/or septicaemia) and mortality. However, in patients with bleeding necessitating invasive procedures, infections are increasingly caused by Gram-positive bacteria and intravenous delivery may be more appropriate than the oral route. In fact, the third-generation cephalosporin ceftriaxone administered intravenously has been shown to be superior to oral norfloxacin in patients with advanced cirrhosis (ie, with at least two of the following: ascites, severe malnutrition, encephalopathy or bilirubin >3 mg/dl).[135]

With regard to the use of antibiotics for primary prophylaxis in the setting of low protein ascites (<1.5 mg/dl), eight randomised controlled trials have been performed so far and are summarised in table 2. However, four trials also included patients with prior SBP[132 139 142 143] and the remaining have recently been summarised in two meta-analyses.[136 137] Surprisingly, these came to different conclusions, most likely due to erroneous data extraction.[144] The study by Novella *et al* included a large number of patients with gastrointestinal bleeding,[51] so only three trials truly focused on primary prophylaxis.[140 145 146] Here we present a meta-analysis of these three studies, which supports the efficacy of quinolones in the primary prevention of SBP (figure 4).[140 145 146] Corresponding numbers needed to treat (NNT) at 6 months to prevent one episode of SBP or death are 8.4 and 8.6, respectively. Even limiting the data to the two most recent and highest quality trials with follow-up for 12 months[140 145] demonstrates significant preventive power for both end points: SBP (NNT 6.3) and mortality (NNT 7.3). Despite this evidence, most expert panels do not recommend the routine use of antibiotics in every patient with low protein ascites unless additional risk factors are present.[1 3 4] This is based on the fear of accelerating selection of resistant bacteria by long-term use of broad-spectrum antibiotics[119] and the lack of conclusive data supporting this approach. Indeed, primary prophylaxis in patients with low protein ascites without additional risk factors failed to reach statistical significance in preventing SBP, although reducing mortality was not calculated for this end point.[140] In contrast, Fernandez *et al* further selected patients from the cohort with low protein ascites by the presence of one of the following criteria: (1) severe liver insufficiency, defined as Child score ≥9 and serum bilirubin ≥3 mg/dl; or (2) renal dysfunction defined as serum creatinine ≥1.2 mg/dl, serum BUN ≥25 mg/dl or serum sodium ≤130 mEq/l.[145] In this highly selected 'high-risk' group of patients with cirrhosis, norfloxacin reduced the 1-year probability of SBP from 61% to 7% (p<0.001) and improved the 1-year survival probability from 48% to 60% (p<0.05).

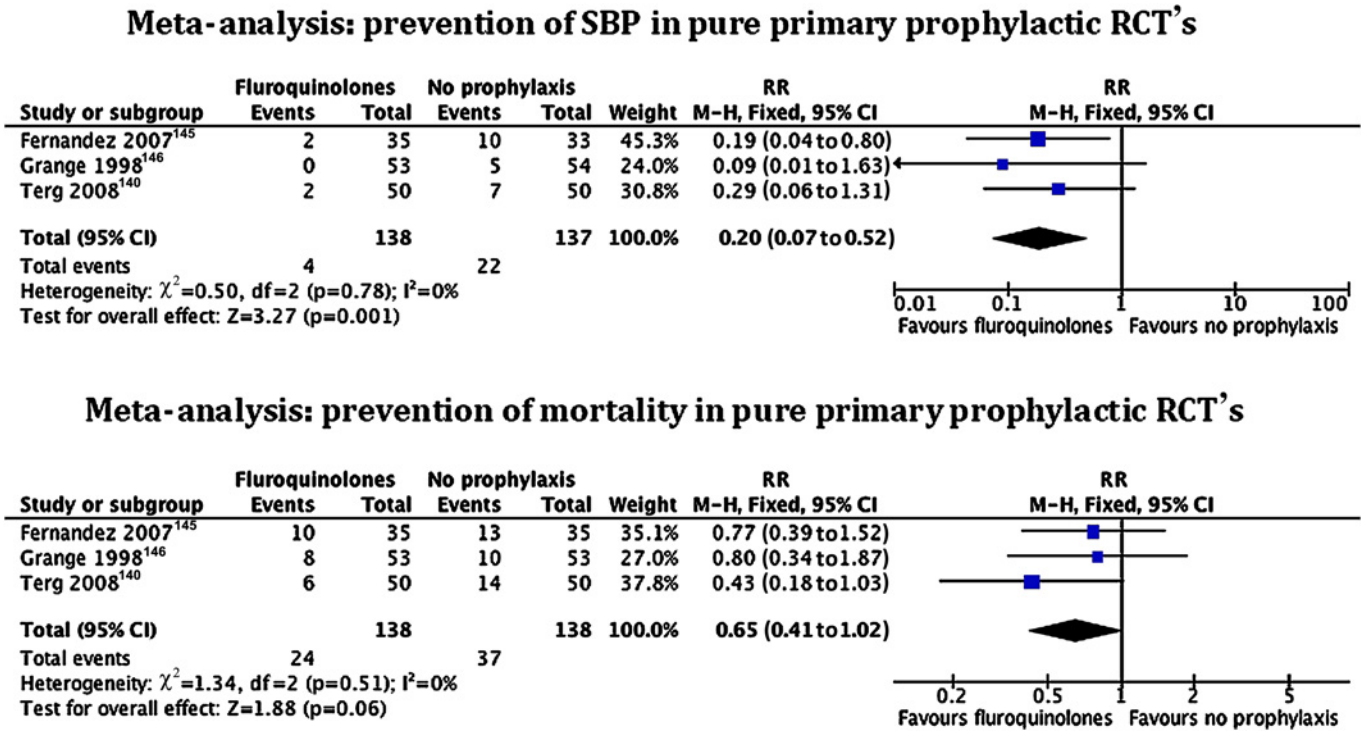

Figure 4 Meta-analysis of randomised controlled trials of primary prophylaxis for spontanous bacterial peritonitis (12 months follow-up).

Nonetheless, guidelines state very cautiously that the long-term use of norfloxacin can be justified[4] or should be considered in these selected patients.[1 3] However, since this trial fulfils the highest quality criteria (Jadad score 5) and represents a well-defined group of patients, we consider the use of norfloxacin for primary prophylaxis as a standard of care procedure.

Limitations in antibiotic prophylaxis and alternatives

The longer the duration of antibiotic treatment, the greater is the risk for selection of resistant strains and the lower is the chance of reducing the incidence of SBP. In fact, survival advantage using norfloxacin as primary prophylaxis in highly selected patients is most marked during the first 3 months of treatment (94% vs 62%, p=0.003) and decreases over time.[138 145] We therefore propose that the use of norfloxacin for primary prophylaxis should also be considered in unselected patients with low protein ascites if liver transplantation is a realistic option within a few months. Although there are no long-term data, the same time course of antibiotic efficacy is likely to be present as in secondary prophylaxis. Its use is recommended to be continued until liver transplantation or until the disappearance of ascites (eg, in alcoholics stopping alcohol ingestion).[2 3] In any other case, antibiotic treatment guidelines support long-term use but, in our view, improvement in liver disease should lead to interruption of treatment.

Overall, the continuous use of a single antibiotic appears not to be the optimal solution and efforts should be made to seek alternatives which could include antibiotic cycling. The basic principle of cycling antibiotics is that bacteria acquiring resistance to the first course of treatment would remain susceptible to the second regimen, and so on. In this context, future trials should test the use of rifaximin since (a) it belongs to a different antibiotic class from the antibiotics tested prospectively so far; (b) it exerts a broad range of antimicrobial activity including Gram-positive bacteria[141]; (c) it appears to cause considerably less bacterial resistance[147 148]; and (d) it acts predominantly in the small intestine,[147–149] the site of bacterial overgrowth in cirrhosis. Finally, as has been pointed out by others,[150 151] effective non-antibiotic approaches in reducing the incidence of SBP represent the Holy Grail. Interestingly, a significant decrease in the incidence of postoperative infections has been reported in a cohort study of patients with cirrhosis treated with propranolol and ciprofloxacin compared with ciprofloxacin alone after laparoscopic surgery.[152] Moreover, NSBB have been reported to ameliorate pathological BT in experimental cirrhosis.[153] Finally, recent meta-analyses of available data indicate that NSBB lower the risk of SBP in patients with cirrhosis which may occur independently of the haemodynamic response achieved.[65 66] However, the use of NSBB in patients with refractory ascites has been suggested to worsen prognosis[154 155] and to be associated with haemodynamic adverse effects after large-volume paracentesis.[156] Future prospective trials therefore need to address these questions in detail in order to establish the use of NSBB in the right patient at the right time.

Cisapride, a serotonin 5-HT4 receptor agonist and intestinal prokinetic drug, has been shown to decrease SIBO and BT in experimental cirrhosis[41 157] but was abandoned due to cardiac side effects. Nonetheless, these encouraging results should stimulate human prospective trials investigating other prokinetics such as the new highly selective 5-HT4 receptor agonist prucalopride which showed no interaction at other receptor sites.[158]

Other promising approaches reported to ameliorate BT in experimental cirrhosis include orally administered conjugated bile acids, cholylsarcosine,[159] insulin-like growth factor I)[160] and anti-tumour necrosis factor.[161] Probiotics have been reported to correct bacterial overgrowth, stabilise mucosal barrier function, improve neutrophil function and decrease BT in experimental liver failure.[162 163] In patients with cirrhosis, symbiotic treatment significantly reduced endotoxin levels and improved the Child-Pugh functional class in nearly 50% of cases.[164] Similarly, the addition of fibre to lactobacilli decreased postoperative bacterial infections after liver transplantation.[165] Probiotics may even be helpful in limiting the development of bacterial resistance, and trials are ongoing to investigate their efficacy in eradicating carbapenem-resistant bacteria as well as the decolonisation of MRSA in carrier patients (NCT00722410/NCT00941356).

Box 3

Key messages: established unequivocally

- In patients with gastrointestinal haemorrhage, antibiotic prophylaxis is mandatory using third-generation cephalosporins (eg, ceftriaxone) in severe liver disease or quinolones in less severe and uncomplicated cases.
- Secondary prophylaxis is recommended after resolution of SBP with the strongest evidence supporting use of norfloxacin.

Controversial but proposed

- Primary prophylaxis can be justified in patients with low protein ascites (<1.5 g/dl) and should be used in the presence of severe liver disease or renal impairment.
- Regimens applying antibiotics intermittently (eg, once a week) should be avoided.

Questions to be addressed in the future

- Strong efforts should focus on effective prophylactic measures with low or zero risk for development of bacterial resistance including use of: (a) antibiotic cycling; (b) rifaximin; or (c) non-antibiotic treatments (eg, NSBB, prokinetics, probiotics, bile acids).

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Spontaneous bacterial peritonitis: recent guidelines and beyond

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in situ hybridisation, the authors found bacteria deeply infiltrating the appendix. Fusobacteria (mainly *Fusobacterium nucleatum/necrophorum*) were specific components of epithelial and submucosal infiltrates in 62% of patients and were not found in various controls. The presence of Fusobacteria correlated positively with the severity of appendicitis. Conversely, main faecal microbiota including *Faecalibacterium prausnitzii* groups were significantly decreased with an inverse relationship with the severity of the disease.[1]

Altogether, these observations point to the presence of a local appendiceal dysbiosis with more bacteria with inflammatory properties and fewer bacteria with anti-inflammatory properties associated with acute appendicitis. The genus *Fusobacterium* is characterised by high proteolytic activity and comprises different distinct species. The most frequently encountered is *F nucleatum*, which is frequent in the oral sphere and implicated in periodontitis. *F necrophorum* has a high pathogenic potential and is implicated in life-threatening infections such as Lemierre's syndrome. In cattle, it is found in footrot disease and is also frequent in liver abscesses. The third important species is *F varium*. All species are part of the normal intestinal microflora. By contrast, *F prausnitzii*, which showed decreased numbers in appendicitis, is a bacterium with anti-inflammatory properties. Its numbers are also reduced in patients with inflammatory bowel disease and it is associated with postoperative recurrence of Crohn's disease.[2]

Over 30 studies have now analysed the association between appendectomy and ulcerative colitis (UC) and the majority of the studies support a highly significant inverse relationship.[3] It is also well established that the protective effect of appendectomy depends on the inflammatory conditions (appendicitis or lymphadenitis) that were the indication for appendectomy rather than on appendectomy itself.[4] The available data regarding whether or not appendectomy performed after the onset of UC can modulate its clinical course arey still limited and conflicting and properly controlled trials are needed.[5] Despite accumulating clinical evidence, the mechanism linking appendicitis, appendectomy and UC remains elusive.

Interestingly, a link between Fusobacteria and UC has been reported in several studies. In 2002, *F varium* was reported to be present in the colonic mucosa of a high proportion (84%) of UC patients.[6] Using immunoblotting with a *F varium* antigen Minami *et al* found positive signals with sera from 45 (40.2%) of 112 UC patients versus 20 (15.6%) of 128 healthy controls ($p<0.01$). Seropositive UC patients were more likely to have clinically severe disease than seronegative UC patients and the disease location in seropositive patients was more extensive than in seronegative patients.[7] Finally, a 2-week triple antibiotic therapy to which *F varium* is susceptible (tetracycline, metronidazole and amoxicillin) produced improvement, remission and steroid withdrawal in active UC more effectively than a placebo.[8]

In conclusion, the development of an appendiceal dysbiosis may be a priming event in the occurrence of UC. The removal of the appendix may reduce the risk of further development of UC in genetically susceptible individuals. We believe that this hypothesis should be further explored in studies examining the protective role of appendicitis and appendectomy in UC.

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CORRECTION

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Unfortunately, references have been misplaced and/or omitted in this paper, and the following citations should be used:

1. **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.

2. **Garcia-Tsao G,** Lim JK. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *Am J Gastroenterol* 2009;**104**:1802–29.

3. **Gerbes AL,** Gulberg V, Sauerbruch T, *et al*. [German S 3-guideline "ascites, spontaneous bacterial peritonitis, hepatorenal syndrome"]. *Z Gastroenterol* 2011;**49**(6):749–79.

On page 302, in the last paragraph, the correct citations for references 108 and 110 (not given in the reference list) should be respectively:

108. **Sort P,** Navasa M, Arroyo V, *et al*. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;**341**:403–9.

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The citations given in table 2 are not correctly reflected in the reference list and hence, please refer to author and year to identify the corresponding investigation.

Finally, the most valuable investigation by Fernandez *et al* has meanwhile been accepted for publication (Fernandez J, *et al*. *Hepatology* 2011 Dec 20. doi:10.1002/hep.25532. [Epub ahead of print]). Therefore, this citation should be used in table 1 and at each place where a personal communication with either JG Acevedo or J Fernandez is stated in the text.