SUMMARY

Background
Spontaneous bacterial peritonitis (SBP) is a severe and often fatal infection in patients with cirrhosis and ascites.

Aim
To review the known and changing bacteriology, risk factors, ascitic fluid interpretation, steps in performing paracentesis, treatment, prophylaxis and evolving perspectives related to SBP.

Methods

Results
Gram-positive cocci (GPC) such as Staphylococcus, Enterococcus as well as multi-resistant bacteria have become common pathogens and have changed the conventional approach to treatment of SBP. Health care-associated and nosocomial SBP infections should prompt greater vigilance and consideration for alternative antibiotic coverage. Acid suppressive and beta-adrenergic antagonist therapies are strongly associated with SBP in at-risk individuals.

Conclusions
Third-generation, broad-spectrum cephalosporins remain a good initial choice for SBP treatment. Levoﬂoxacin is an acceptable alternative for patients not receiving long-term ﬂuoroquinolone prophylaxis or for those with a penicillin allergy. For uncomplicated SBP, early oral switch therapy is reasonable. Alternative antibiotics such as piperacillin–tazobactam should be considered for patients with nosocomial SBP or for patients who fail to improve on traditional antibiotic regimens. Selective albumin supplementation remains an important adjunct in SBP treatment. Withholding acid suppressive medication deserves strong consideration, and discontinuing beta-adrenergic antagonist therapy in patients with end-stage liver disease and resistant ascites is standard care. Liver transplant evaluation should be undertaken for patients who develop SBP barring contraindications.
INTRODUCTION
Spontaneous bacterial peritonitis (SBP) is a common and frequently fatal bacterial infection of ascites occurring in patients with cirrhosis who have diverse symptomatology. The diagnosis is distinct from secondary peritonitis and hence is made in the absence of an intra-abdominal source of infection or inflammatory process. SBP was first described in 1907 by Krencker followed by Caroli in 1958 and Kerr and colleagues in 1963.1–3 Conn coined the term ‘spontaneous bacterial peritonitis’ in 1964 to depict a syndrome of peritonitis and bacteremia in Lannec’s cirrhosis without an apparent cause of infection.4 SBP occurs in cirrhotic patients with varied aetiologies, not just alcohol, and further research has uncovered causal factors such as translocation of gut bacteria to lymph nodes making the aetiology less elusive.

Portal hypertension, splanchnic vasodilation and activation of the renin–angiotensin cascade leads to sodium and water retention and fluid overflow into the peritoneal cavity.5 Ascites is primarily a transudative fluid with poor opsonic activity which provides a favourable environment for growth of bacteria. SBP rarely occurs without cirrhosis, but cardiac,6 renal,7 malignancy,8, 9 portal vein thrombosis10 and autoimmune11,12–related infection of ascites has been reported.

Ascitic fluid infection is classified into five types based on polymorphonuclear cell count, ascitic fluid culture results and clinical circumstances: classic culture-positive SBP, culture-negative SBP also known as culture-negative neutrocytic ascites (CNNA), monomicrobial and polymicrobial bacterascites, and secondary peritonitis (Table 1).

Intestinal Gram-negative flora are the major cause of SBP. A variety of factors are associated with the development of SBP including the pathophysiological hallmark: bacterial translocation in an immunocompromised host. The incidence of SBP ranges from 10% to 30%, and mortality from 10% to 46%14,15 in hospitalised patients. Clinical acumen, prompt diagnosis and appropriate treatment remain the most important tools for physicians when caring for patients who acquire SBP in various clinical settings.

METHODS

Literature review
This article is intended for clinicians and other health care professionals for review, study and assistance with management of patients with SBP. The goal is to demonstrate changing bacterial isolates from ascitic fluid culture and to provide an up-to-date synopsis of diagnostic and treatment strategies for SBP. Literature in PubMed and Ovid MED-LINE (1966–2014) databases were reviewed. Emphasis was given to landmark studies and new research from the last 5–10 years. Data from 14 articles published in 2014 and 58 sources published since 2009 were included herein. No language restrictions were applied to the search. Key terms including MeSH headings were SBP, bacterial peritonitis, antibiotics, antibiotic resistance, ascites, paracentesis, microbiology, treatment and prophylaxis. Randomised controlled trials conducted for treatment of SBP were identified. Abstracts were not reviewed.

BACTERIOLOGY
In a healthy individual, the variety and density of bacteria increases exponentially from the stomach to the colon with up to a 1000 or more different species and a trillion bacteria per gram of faecal material in the

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ascitic fluid analysis</th>
<th>Clinical pearls</th>
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<tbody>
<tr>
<td>Variants of SBP</td>
<td></td>
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</tr>
<tr>
<td>SBP (culture-positive)</td>
<td>PMNs ≥250 cells/mm³ Positive culture</td>
<td>Patients with cirrhosis and ascites in the presence or absence of symptoms and signs</td>
</tr>
<tr>
<td>CNNA (culture-negative neutrocytic ascites; culture-negative SBP)</td>
<td>PMNs ≥250 cells/mm³ Negative culture</td>
<td>Poor culture technique, prior antibiotics or low opsonic activity in ascitic fluid. Commonly encountered phenotype and requires antibiotic therapy</td>
</tr>
<tr>
<td>Monomicrobial bacterascites</td>
<td>PMNs &lt; 250 cells/mm³ Positive culture</td>
<td>Ascitic fluid infection which may resolve spontaneously or progress to SBP. Similar mortality to SBP and should be treated the same</td>
</tr>
<tr>
<td>Polymicrobial bacterascites</td>
<td>PMNs &lt; 250 cells/mm³ Positive culture</td>
<td>Needle perforation</td>
</tr>
<tr>
<td>Secondary peritonitis</td>
<td>PMNs ≥250 cells/mm³ Positive culture</td>
<td>Intraperitoneal source of infection, e.g. diverticulitis</td>
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</table>
caecum. A symbiotic relationship usually exists. However, in advanced liver disease, normal intestinal flora can cause deleterious effects to the host through a variety of mechanisms leading to SBP including bacterial overgrowth, increased intestinal permeability so-called leaky gut and pathological bacterial translocation – all in the setting of immune dysregulation pervasive in patients with cirrhosis.

Gram-negative bacilli (GNB) are the major cause of SBP (Table 2). The three most common isolates from 263 ascitic fluid cultures, compiled in 1994 from various studies published between 1971 and 1991, included *E. coli* (46%), *Streptococcus* (30%) and *Klebsiella* (9%).

Similar results were demonstrated in 1992 from numerous studies encompassing 746 cases of SBP: *E. coli* (47%), *Streptococcus* (19%) and *Klebsiella* (13%). *E. coli* was found in the majority of patients with SBP as reported by Conn *et al.* (66%) and Kerr *et al.* (72%) and consistently remains most common isolate in recent literature albeit with lower prevalence. *E. coli* was the predominant strain to cause of SBP reported by Fernandez *et al.* from data obtained between 1998 and 2000 accounting for 34 of 138 cases (25%) of SBP. Likewise, *E. coli* represented 31 of 140 cases (22%) as reported by Novovic *et al.* from data gathered between 2000 and 2006.

Gram-positive cocci (GPC) have generally accounted for less than 25% of cases of SBP. Infections with GPC including pneumonia and urinary tract infections have markedly increased in patients with cirrhosis in recent years and have been linked to therapeutic interventions and chronic antibiotic usage. The increasing trend of GPC-related SBP has also been demonstrated and represents a changing paradigm in the known bacteriology of SBP. Notably, 229 GPC were identified on ascitic fluid culture compared to 151 GNB out of 411 strains from 325 subjects. The most frequently encountered bacteria were coagulase-negative staphylococci (*n* = 85), *E. coli* (*n* = 75), enterococci (*n* = 54), streptococci (*n* = 50), *Klebsiella* (*n* = 33), *Enterobacter* (*n* = 33), *Serratia* (*n* = 33) and *S. aureus* (*n* = 33). An observational French study from the same affiliate acquired 268 positive culture results from patients with cirrhosis, and GPC-related SBP was the predominate group representing 65% (coagulase-negative *Staphylococcus* 27%, *Enterococcus* 24%) of SBP cases validating prior findings. The spectrum of bacteria causing SBP in inpatients from nine studies with ascitic fluid samples collected since 1998 has demonstrated comparable results in an original table herein. However, GNB and foremost *E. coli* remain the most common class of bacteria and isolate respectively.

The prevalence of SBP generally remains low in the out-patient setting especially in asymptomatic patients. Culture results from 427 out-patients demonstrated 1% prevalence of SBP which was predominately GPC *Staphylococcus aureus* (*n* = 1), *Streptococcus viridans* (*n* = 3) and *Staphylococcus saccharolyticus* (*n* = 1). The emergence of extended spectrum β-lactamase-producing (ESβL) GNB, methicillin-resistant *Staphylococcus aureus* (MRSA), fluoroquinolone-resistant (QR) GNB, vancomycin-resistant *Enterococcus* and other resistant microorganisms have also changed prior perceptions about SBP bacteriology and its treatment. MRSA was found to cause 9 of 87 SBP cases (10%) in a prospective study. In another study, the same research group found SBP was due to GPC in 34 of 60 cases (57%) when patients received norfloxacin (Noroxin; Merck & Co., Inc., White House Station, NJ, USA) for

<table>
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<tr>
<th>Microorganisms</th>
<th>N</th>
<th>Total (%)</th>
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<tbody>
<tr>
<td>Gram-negative bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Gram-negative bacteria</td>
<td>732</td>
<td>55</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>706</td>
<td>53</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>435</td>
<td>33</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>112</td>
<td>8</td>
</tr>
<tr>
<td>Other enterobacteriaceae</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Other Gram-negative bacilli</td>
<td>86</td>
<td>6</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Gram-positive bacteria</td>
<td>575</td>
<td>43</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>537</td>
<td>40</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp.</td>
<td>198</td>
<td>15</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>179</td>
<td>13</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>124</td>
<td>9</td>
</tr>
<tr>
<td>Other Gram-positive cocci</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>Gram-positive bacilli</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>2</td>
</tr>
</tbody>
</table>

Spp., species. Other includes fungi, undisclosed spp. Other Gram-negative bacilli include *Acinetobacter* and *Aeromonas*. Other enterobacteriaceae includes *Enterobacter*, *Serratia*, undisclosed spp. Other Gram-positive cocci include *Listeria monocytogenes*, *Bacillus* spp., undisclosed spp. The values in bold add up to 100%.

more than 1 month, and MRSA was the most common isolate (77%). Extended spectrum β-lactamase-producing (ESBL) GNB (E. coli and Klebsiella) were the most common multi-drug resistant bacteria (73%), especially among nosocomial infections, followed by fluoroquinolone resistant GNB in patients who were receiving norfloxacine prophylaxis.

One bacterium (monomicrobial) is the cause in more than 90% of cases, yet the probability of identifying a pathogen is mediocre as ascitic fluid cultures are positive in 50–60% of patients with SBP. Rare isolates reported in the literature include anaerobes, Aeromonas, Listeria, Streptococcus bovis, Bordetella bronchiseptica, Candida, Pasteurella multocida, Leclercia adecarboxylata, and Salmonella paratyphi A.

**DIAGNOSIS**

**Clinical perspective**

The diagnosis of SBP is achieved in the absence of any apparent aetiology of infection or secondary peritonitis as may be seen with gastrointestinal tract perforation, appendicitis, diverticulitis or cholecystitis. SBP is not a clinical diagnosis, and it cannot be made without ascitic fluid analysis. Interpreting ascitic fluid results namely cell count and differential to calculate the polymorphonuclear (PMN) count, which is the result of multiplying the total ascitic fluid white blood cell count by the neutrophil count, is paramount. A PMN count greater than 250 cells/mm³ provides a preliminary diagnosis, and although culture results are often negative, historically, a positive ascitic fluid culture confirms the diagnosis of SBP. Variants to this classic definition include culture-negative neutrocytic ascites (CNNA), which was originally defined as an ascitic PMN count greater than 500/mm³ in the setting of a negative culture; however, now keeps with the 250/mm³ threshold and is a commonly encountered phenotype of SBP. This phenomenon may represent resolution of infection, small amounts of bacteria or its by-products in ascites or poor culture processing. Despite sound technique with performing paracentesis, ascitic fluid culture is negative in at least 40% of cases with an elevated PMN count. CNNA is a true infection and should be treated the same as SBP.

Spontaneous bacterial peritonitis is the most common bacterial infection in hospitalised patients with cirrhosis and ascites who are not receiving antibiotic prophylaxis. Acquisition of SBP occurs in various clinical settings which have different clinical implications (Table 3). The diagnosis should be considered in any patient with cirrhosis, ascites and clinical deterioration and although rare, can be clinically silent without apparent signs or symptoms. The prevalence of SBP in 427 cirrhotic asymptomatic out-patients, as defined by neutrocytic ascites (absolute neutrophil count >250 cells/mm³), was 3.5%. Conversely, there should be a high level of suspicion for infection when evaluating patients with Child–Pugh classification C liver disease with fever, abdominal pain and/or confusion. Diagnostic paracentesis should be performed without delay, ideally within 6 hours of patient evaluation, and before the use of antibiotics. Early and judicious use of antibiotics can be life saving especially for patients with end-stage liver disease defined by one or more of the following: history of ascites, variceal haemorrhage, hepatic encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome, SBP or hepatocellular carcinoma.

**Laboratory diagnosis**

The current gold standard for cell counting as per the College of American Pathologists is by light microscopy

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**Table 3 | Clinical setting of SBP, related definitions and commentary**

<table>
<thead>
<tr>
<th>Health care-associated (HCA) SBP</th>
<th>Diagnosis within 48 h of hospital admission in patients with any prior 90-day health care contact (e.g. hospitalisation, nursing home, dialysis centres or other health care setting).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial SBP</td>
<td>Diagnosis after 48 h of hospital admission.</td>
</tr>
<tr>
<td>Community acquired (CA) SBP</td>
<td>Diagnosis within 48 h of hospital admission without any prior 90-day health care contact.</td>
</tr>
<tr>
<td>Multi-drug resistant SBP</td>
<td>Increasingly encountered because of prior antibiotic exposure. Treat accordingly and prescribe sensitive antibiotics for prophylaxis based on culture sensitivities. Many antibiotics penetrate ascitic fluid equally well. (Gerding Ann Int Med 1977) If TS and FQ resistance, second-generation cephalosporins, e.g. Cefazolin are an option if sensitive.</td>
</tr>
<tr>
<td>Recurrent SBP</td>
<td>Portends greater risk of death compared to initial episode of SBP. Provide antibiotic prophylaxis.</td>
</tr>
</tbody>
</table>

TS, trimethoprim–sulfamethoxazole; FQ, fluoroquinolone.
using a manual counting chamber, which is operator dependent and can predispose to inconsistent results among laboratory technicians with varying expertise, yet has proven to be more reliable than automated cell counting. Automated cell counting for PMNs was shown to be accurate, reliable and faster compared to manual counting; however, this is not a universal experience and current guidelines do not recommend this modality. At particularly low cell counts, around 250, automated cell counters have been prone to false-positive results. Flow cytometry is a newer form of technology and has shown to be a suitable alternative for rapid ascitic fluid cell counting with a sensitivity and specificity of 100% for detecting PMN count greater than 250 cells/mm³.

Urinary reagent strips
Urinary reagent strips were proposed as a quick method to diagnose SBP, but a large multicentre study revealed that the Multistix 8SG strip is an unacceptable test because of poor sensitivity, positive predictive value and inability to rule out infection. Ascitic fluid lactoferrin (AFLAC) has also been supported as an initial screening test. Lactoferrin is a product and marker of PMN activity and when detected in ascitic fluid has shown high sensitivity (95.5%) and specificity (97%) for SBP, however timing of quantitative measurements using an enzyme-linked immunosorbent assay have not been reported. Its diagnostic utility is questioned and manual cytological examination remains the standard method for determining PMN concentration.

Paracentesis
Ascitic fluid is obtained by transabdominal needle puncture at one of several locations, the avascular infraumbilical midline, right lower quadrant or preferably the left lower quadrant, and its analysis is one of the most important steps in the evaluation of patients suspected of having SBP. Paracentesis should be performed in all patients with cirrhosis and ascites who require emergency room care or hospitalisation, report symptoms, or demonstrate signs of clinical deterioration such as confusion or gastrointestinal bleeding. Although paracentesis is vital in the evaluation of such patients and has been associated with nonsignificant increased short-term survival, it is underutilised, performed in only 60% of hospitalised patients with cirrhosis and ascites. In patients who do undergo paracentesis, delay in procuring ascitic fluid for analysis has led to a 2.7-fold increased risk of in-hospital mortality in patients with SBP. The clinical usefulness of paracentesis is less important in the out-patient setting as the diagnostic yield for SBP or its variants is less than 4%.

Paracentesis has consistently been shown to be safe without using ultrasound (US) and in the setting of an elevated prothrombin time and remains the most cost-effective method of diagnosis. Major complications such as bleeding and infection have been reported to be higher in other prospective series, occurring at 1.6%, which resulted in two deaths out of 515 paracenteses. Using US during paracentesis is practised by house staff at some medical centres such as the University of California at San Francisco, and support for its use has likely derived from recent changes in standards for other procedures requiring needle puncture such as central venous line catheter placement, and case studies with poor outcomes. Evidence to recommend US for paracentesis is limited. A retrospective study supported by Sonosite, demonstrated the risk of bleeding from paracentesis was decreased from 1.25% to 0.27% with the use of US out of 70 000 paracentesis patients.

Correcting coagulopathy prior to paracentesis often using arbitrary INR thresholds of 2–3 is not based on supporting evidence but is commonly employed in clinical practice to avoid haemorrhagic complications. Liberal or unnecessary use of fresh frozen plasma may, in fact, lead to complications seen with blood product administration. Paracentesis was safe in 1100 patients with an INR as high as 8.7 and platelet count as low as 19 000. Patients with disseminated intravascular coagulation (DIC) generally pose a greater risk for complications and should be managed with greater diligence.

Paracentesis should be performed by well-trained personnel, not limited to physicians, who have completed 3–10 paracentesis under supervision by an experienced clinician. Caution is quintessential for performing procedures and should be employed especially in patients with ileus, prior abdominal surgery or bleeding diatheses. In such cases, US guidance might be particularly helpful. Ascitic fluid tests should include cell count with differential, Gram stain, culture, total protein and albumin to determine the serum-ascites albumin gradient (SAAG) if not already known.

Proper handling of ascitic fluid requires bedside inoculation of at least 10 mL into aerobic and anaerobic blood culture bottles, which increases the yield of positive culture results by 91% and speeds time of detection. For cell count, approximately 1 mL of fluid should be injected into a purple-top ethylenediaminetetraacetic acid (EDTA), which is typically used for determining serum complete blood cell count and often
included in paracentesis kits, to avoid clotting and inaccurate interpretation. Although ascitic fluid appearance such as haziness had a sensitivity of 98% in detecting SBP and clear ascitic fluid was less likely to be infected based on a retrospective review of more than 900 samples, its appearance cannot be used as a reliable surrogate marker to achieve or exclude the diagnosis of SBP. Furthermore, low clinical suspicion for SBP does not preclude the necessity for paracentesis. Obtaining a positive ascitic fluid culture result is highly variable ranging from 3.5% in the emergency room to 60% in hospitalised patients, however if performed properly prior to antibiotic administration, cultures should yield bacterial growth in more patients with SBP.

**RISK FACTORS**

**Biochemical risk factors**

Well-established risk factors for developing an initial episode of SBP are low ascitic fluid protein level (< 1 g/dL), elevated serum bilirubin level and advanced cirrhosis. The probability of developing an initial episode of SBP was substantially higher (24%) in patients with a low ascitic protein level (<1 g/dL) compared to higher levels (4%) at 3 year follow-up of 127 patients. Low levels of 25-hydroxy vitamin D have been associated with mortality in patients with cirrhosis and development of SBP independent of Child–Pugh score.

Risk factors for recurrence, based on univariate analysis, are serum bilirubin (>4 mg/dL), prothrombin (≤45%) and low ascitic fluid protein concentration (<1 g/dL). Likewise, after evaluating 86 patients who survived a first episode of SBP, a serum albumin level less than 2.85 g/dL at hospital discharge was strongly associated with SBP recurrence.

**Clinical risk factors**

Variceal haemorrhage predisposes to SBP, and randomised trials have shown reduction in infection and mortality when antibiotics are administered upon admission, now a standard of care in all patients with cirrhosis and gastrointestinal bleeding whether or not ascites is present.

**Genetic risk factors**

The Toll-like receptor 2 (TLR2) proteins are expressed in macrophages and are essential for recognition of microbial components and host cell defence. One hundred and fifty patients with cirrhosis and ascites were genotyped for TLR2, and those with specific TLR2 variants had a significant risk of developing SBP (38.5% vs. 15.3%, P = 0.002). Similarly, variants of the NOD2 (nucleotide-binding oligomerisation domain containing 2) gene were initially found to impair mucosal integrity in Crohn disease in earlier studies and have also shown to increase the risk of SBP [P = 0.008, odds ratio (OR) = 3.06] and early death (P = 0.007) compared to wildtype genotypes in patients with cirrhosis and ascites. Farnesoid X is a cellular protein and nuclear receptor and its polymorphisms have also been associated with risk of SBP in cirrhotic patients with ascites.

**Pharmacological risk factors**

**Acid suppressive therapy.** Proton pump inhibitors (PPI) increase gastric pH, impair natural host defence against ingested bacteria and predispose to an altered intestinal milieu. PPIs have been associated with pneumonia and implicated in other infections such as SBP. In fact, PPI therapy has been associated with and identified as an independent risk factor for SBP in patients with advanced cirrhosis in retrospective series as well as prospective series, and its use should be curtailed or at least re-examined in this population as 50% of patients who develop SBP have no documented indication for PPI therapy. In a meta-analysis, PPI therapy was found to increase the risk of SBP by three-fold in hospitalised patients with cirrhosis compared to those not receiving acid suppressive medication. In another meta-analysis including four studies with 772 patients, there was a significant association between PPI use and SBP (OR 2.77, 95% CI 1.82–4.23). Moreover, in a large multi-centre prospective study examining 188 hospitalised patients with cirrhosis and infections, PPI therapy imposed the highest risk for re-infection including SBP (OR 2.94, 95% CI, 1.39–6.20) within 6 months. Cause and effect of PPI-related SBP has not been proven. However, PPI therapy and its association with other infections is widely familiar and applying these concepts is at the discretion of the clinician on a case-by-case basis until there is surmounting evidence to restrict its use in patients with ascites.

**Beta-adrenergic antagonist therapy.** Beta-adrenergic antagonists namely nonselective beta-blocker (NSBB) therapy was found to be protective for SBP as reported in a meta-analysis examining three retrospective and three randomised controlled trials, which demonstrated a statistically significant difference (12.1%, P < 0.001) in favour of propranolol for SBP prevention in patients with predominantly Child class A and B cirrhosis.
However, evidence and expert opinion herald caution with NSBB use in patients with end-stage liver disease and discontinuation of such therapy in the setting of refractory ascites due to poor cardiac compensatory reserve in these patients.93 Survival was significantly decreased in patients with cirrhosis and refractory ascites who were receiving NSBBs as opposed to patients not receiving NSBBs who lived nearly 2 years longer.94 NSBB therapy also reduced transplant-free survival in patients with cirrhosis after a first episode of SBP and conferred greater risk for complications requiring hospitalisation such as haemodynamic instability and renal insufficiency.95

PROGNOSIS
Mortality from SBP has remained unchanged in recent times39 and after reviewing records of 350 patients with SBP admitted to Maryland Hospitals during a 10-year period, SBP was found to be the second leading cause of bacterial-related death in hospitalised patients with a mortality rate of 33%.96 Survivors of SBP have a poor prognosis as well. After an initial diagnosis of SBP, 1-month, 6-month and 1-year mortality rates are 33%, 50% and 58% respectively.97

Renal injury develops in 30–40% of patients with SBP and is the best biochemical predictor for mortality.98, 99 Child–Pugh and MELD scores have also been found to be reliable measures for outcome in these patients.39, 99

LIVER TRANSPLANTATION
Spontaneous bacterial peritonitis is not a contraindication for liver transplantation, rather it should be considered after a first episode of SBP or sooner unless predisposing factors make patients unsuitable candidates.100 A 5-day course of antibiotics is adequate to effectively treat patients with SBP who undergo liver transplantation in the acute period.101 Post-treatment paracentesis is prudent to ensure pathogen eradication. Furthermore, patients with or without a history of SBP have similar 4-year outcomes after liver transplantation including morbidity and mortality.102

TREATMENT

Intravenous antibiotics
If suspicion for SBP arises (i.e. fever, abdominal pain or tenderness, altered mental status, or otherwise unexplained decompenstation in patients with cirrhosis and ascites), then antibiotics should be started immediately to reduce complications and improve survival. Third-generation, broad-spectrum cephalosporins are the agents of choice for SBP treatment because of their superiority in randomised controlled trials and rare side effect profile with minimal risk of nephrotoxicity compared to other antibiotics.103–105 Cefotaxime covers most culprit pathogens, has excellent ascitic fluid penetration and achieves sterilisation in 94% of cases after initial antibiotic dosing.106 Treatment efficacy and clinical resolution with cefotaxime 4 g/day has ranged from 77% to 98%. Higher dosing, i.e. 8 g/day has not provided a therapeutic advantage.107 However, cefotaxime 2 g every 8 h (6 g/day) is considered the standard regimen and current guideline recommendation put forth by the American Association for the Study of Liver Diseases.57 A 5-day course of cefotaxime 2 g every 8 h is as effective as 10 days of treatment. No differences were seen with infection cure, SBP recurrence and hospital mortality rates.104

Alternative intravenous antibiotic regimens for SBP include amoxicillin–clavulanic acid, which has comparable results to cefotaxime,108 ampicillin and gentamicin,103 and fluoroquinolones. Antibiotics other than third-generation cephalosporins have an increased risk for adverse events, and there is less evidence supporting their role in primary treatment. A second-line choice of third-generation cephalosporins is ceftriaxone, a strongly protein bound antibiotic, and because of poor protein synthesis in cirrhotic patients, is theoretically less effective for SBP treatment. Nevertheless, ceftriaxone has been well studied for primary treatment of SBP,109, 110 and although considered inferior to cefotaxime, ceftriaxone is effective therapy particularly at doses of 2 g/day for 5 days.111, 112 Aminoglycosides cause renal impairment in 5% of patients and should be avoided in patients with cirrhosis who have considerable risk for renal injury.113 Fluoroquinolones have comparable ascitic fluid penetration to cephalosporins.114 Levofloxacin has shown similar efficacy compared to (cefotaxime and cefepime) at providing E. coli coverage [71% vs. (82%)] and coagulase-negative Staphylococcus coverage [90% vs. (44%)] in patients with SBP not receiving fluoroquinolone prophylaxis.26 In patients with penicillin allergy who are not receiving long-term fluoroquinolone therapy, levofloxacin is a reasonable and safe alternative treatment for SBP.115

Oral antibiotics
Oral fluoroquinolones are generally acceptable for uncomplicated SBP (i.e. absence of sepsis and patients at risk for aspiration). Fluoroquinolones have excellent oral bioavailability ranging from 70% for ciprofloxacin to 95% for levofloxacin.116 In a randomised controlled trial,
oral ofloxacin and IV cefotaxime resolved SBP at the same rate (84% vs. 85%) respectively.\textsuperscript{105}

**Switch therapy**

In a randomised study in 2000, Terg \textit{et al.} showed that patients with SBP can be adequately treated with oral ciprofloxacin after a short course of IV cefotaxim.\textsuperscript{117} Switch therapy with oral ciprofloxacin was as effective as IV cefotaxim at infection resolution in a randomised study involving 116 patients with SBP and was more cost effective.\textsuperscript{118}

**Antibiotics for multi-resistant bacteria**

Emergence of antibiotic resistance and changing profile to SBP-causing-bacteria have made standard treatment less reliable in some instances. In fact, 8–22% of Enterobacteriaceae have cephalosporin resistance.\textsuperscript{33, 119} A 5-year retrospective study of 8 SBP-causing-bacteria have made standard treatment less reliable in some instances. In fact, 8–22% of Enterobacteriaceae have cephalosporin resistance.\textsuperscript{33, 119} A 5-year retrospective study of 67 patients with SBP revealed that long-term prophylactic norfloxacin treatment reduced the risk of Gram-negative infections but increased the risk of severe hospital-acquired staphylococcal infections, whereby 77% were methicillin-resistant.\textsuperscript{120}

**Albumin**

Albumin is a single chain peptide protein, made in the liver, with a half-life of approximately 21 days. It regulates plasma oncotic pressure, buffers plasma, scavenges free radicals, and transports hormones, fatty acids, unconjugated bilirubin, metals, ions, and drugs. The structure and function of albumin is abnormal in advanced liver disease thereby impairing many key physiological processes.\textsuperscript{121} Hypoalbuminemia has myriad causes and is associated with increased morbidity and mortality regardless of aetiology.\textsuperscript{122, 123}

Albumin is cornerstone therapy for select patients with SBP in addition to antibiotics. A randomised, controlled trial involving patients with SBP treated with cefotaxime alone compared to cefotaxime and albumin (1.5 g/kg within 6 h of diagnosis, followed by 1 g/kg on day 3) demonstrated that by adding albumin patients avoided irreversible renal impairment (10 vs. 33%, \(P = 0.002\)) and had lower mortality both during hospitalisation (10 vs. 29%, \(P = 0.01\)) and at 3-month follow-up after discharge (22 vs. 41%, \(P = 0.03\)).\textsuperscript{124} Renal impairment occurs in one-third of patients with SBP, and albumin is not indicated for all patients. Patients should be carefully screened to receive albumin infusion, because those at risk for renal impairment (i.e. serum creatinine \(> 1\) mg/dL = 88.4 \(\mu\)mol/L), bilirubin \(> 4\) mg/dL = 68.4 \(\mu\)mol/L), BUN \(> 30\) mg/dL] have clearly shown benefit.\textsuperscript{125} Patients with chronic kidney disease with or without dialysis dependency who develop SBP should receive albumin therapy.

**PREVENTION**

**Primary prophylaxis**

\textbf{Norfloxacin.} Spontaneous bacterial peritonitis naïve patients with cirrhosis and low ascitic fluid protein (<1 g/dL) with additional risk factors are candidates to receive long-term norfloxacin therapy for survival benefit\textsuperscript{125, 126} and to reduce risk of SBP as well as extraperitoneal infections.\textsuperscript{127} Norfloxacin has been the most widely studied antibiotic for SBP prevention in a variety of settings including gastrointestinal bleeding,\textsuperscript{128} primary SBP prophylaxis\textsuperscript{47, 127, 129, 130} and secondary SBP prophylaxis and remains the first-line choice for selective intestinal decontamination. In a double-blind, placebo-controlled trial, patients with low ascitic protein (<1.5 g/dL) and one additional risk factor including advanced cirrhosis (Child score \(\geq 9\)), serum creatinine \(\geq 1.2\) mg/dL, blood urea nitrogen \(\geq 25\) mg/dL or serum sodium \(\leq 130\) mEq/L who were receiving norfloxacin 400 mg/day had significant survival advantage at 3-month (94% vs. 62%, \(P = 0.003\)) and 1-year (60% vs. 48%, \(P = 0.05\)) follow-up, as well as decreased risk of hepatorenal syndrome (28% vs. 41%, \(P = 0.02\)) and SBP (7% vs. 61%, \(P < 0.001\)) at 1-year follow-up.\textsuperscript{47}

\textbf{Ciprofloxacin.} The risk of developing an initial episode of community acquired SBP within 1 year is substantially higher (55%) in patients with low ascitic fluid protein (\(\leq 1\) g/dL) and a bilirubin level greater than 3.2 mg/dL and/or platelet count less than 98 000/mm\(^3\) compared to patients without these bilirubin and platelet cut-offs whose risk is approximately 24%.\textsuperscript{15} There is one randomised, placebo-controlled trial that examined the role of ciprofloxacin in primary prophylaxis and found that patients with ascitic protein <1.5 g/dL who were receiving oral ciprofloxacin 500 mg/day had a significantly greater chance of survival in 1 year than patients receiving placebo (86% vs. 66%, \(P < 0.04\)).\textsuperscript{131}

\textbf{Trimethoprim–sulfamethoxazole.} A randomised controlled trial involving 66 consecutive patients with cirrhosis and ascites at a University-affiliated VA medical centre demonstrated decreased risk of SBP (27% vs. 3%, \(P = 0.025\)) and other infections with daily double strength trimethoprim–sulfamethoxazole (Bactrim; Mutual Pharmaceutical Company, Inc., Philadelphia, PA, USA) at 90-day follow-up.\textsuperscript{132}
**Rifaximin.** There is limited and inconsistent data for rifaximin (Xifaxan; Salix Pharmaceuticals, Inc., Raleigh, NC, USA), a non-absorbable antibiotic with broad-spectrum coverage, in primary or secondary SBP prophylaxis. 133, 134

Secondary prophylaxis

**Norfloxacin.** Patients with a prior history of SBP are also candidates to receive indefinite antibiotic prophylaxis that is until liver transplantation, resolution of ascites or death. Recurrence of SBP ranges from 43% at 6 months to 74% at 2 years after initial diagnosis. 76 In a double-blind, placebo-controlled study, patients receiving norfloxacin 400 mg/day were less likely to have SBP recurrence at 1-year follow-up (20% vs. 68%, \( P = 0.0063 \)) compared to patients receiving placebo. 135

**Ciprofloxacin.** A meta-analysis reported short-term survival and reduced overall risk of infections with antibiotic prophylaxis when compared to untreated control groups. 126

**Trimethoprim–sulfamethoxazole.** Trimethoprim–sulfamethoxazole demonstrated similar efficacy and adverse effect profile compared to norfloxacin for prevention of SBP recurrence in a retrospective series. 136 Trimethoprim–sulfamethoxazole and norfloxacin for primary and secondary SBP prophylaxis also demonstrated similar and significant cost savings per patient per year. 137

**SUPPORTIVE THERAPY**

**Diet**

Patients with advanced cirrhosis have continued protein catabolism, also referred to as hypermetabolism, and the majority suffer from malnutrition. 138 There are no studies assessing the role of diet in prevention or treatment of SBP; however, malnutrition predisposes to bacterial translocation and SBP as demonstrated in experiments with rats. 139 Simple evidence-based dietary measures should not be overlooked when providing patient recommendations. Referral for dietician consultation is at the discretion of clinicians and will at least imprint the importance of diet in health. Patients with cirrhosis should avoid raw food due to the risk of consuming harmful bacteria, limit dietary sodium intake, aim for 1.2–1.5 g of daily protein intake 140 and generally should consume 4–6 small frequent meals throughout the day including a bedtime carbohydrate-rich snack. 141

**Probiotics**

Anaerobic bacteria species such as *Lactobacillus* and *Bifidobacterium* are normal inhabitants of the gastrointestinal lumen, are less likely to translocate compared to Gram-negative aerobic bacteria, 142 and have been hypothesised to play a role in the prevention of SBP. In fact, VSL#3 (Lactobacillus spp., Bifidobacterium spp., Streptococcus salivarius spp. and Thermophilus spp.) has been shown to improve hepatic function and decrease liver enzymes in patients with cirrhosis, 143 and *Lactobacillus* combined with antioxidants (vitamin C and glutamate) have been shown to decrease endotoxemia compared to water lavage in rats with induced cirrhosis. 144 Subsequent studies involving a similar rat model have used *Lactobacillus* alone, which has succeeded in changing the intestinal milieu of the host but not SBP occurrence. 145, 146 The addition of probiotics to a daily norfloxacin regimen did not improve outcomes with regard to primary or secondary SBP prophylaxis nor did it demonstrate a survival benefit in a randomised, double-blind, placebo-controlled trial with 6-month follow-up. 147 The health benefits of probiotic therapy for a variety of gastrointestinal illnesses are well known although no evidence supports their use in the prevention or management of SBP.

**CONCLUSION**

Spontaneous bacterial peritonitis is a severe infection with high mortality occurring in 7–31% of hospitalised patients with cirrhosis and ascites, 148 and its prevalence, among other infections, is increasing in such patients across the United States. 149 Patients susceptible to SBP require stringent evaluation and comprehensive care with pertinent focus on evidence-based strategies such as optimising nutrition and avoidance of unnecessary medications (Figure 1). Strong associations with SBP have recently been identified including beta-blocker therapy, PPI therapy and vitamin D deficiency, which should prompt caution and heightened awareness. Removal of these possible offending agents needs adequate consideration especially for patients at risk for SBP, and vitamin D supplementation should be provided to all patients with deficiency. PPI therapy should have clear and necessary indications for all patients foremost those with decompensated cirrhosis who are at greater risk for complications including infection.

Asitic fluid and blood culture analyses are often not performed in patients with cirrhosis and ascites who are hospitalised for gastrointestinal and nongastrointestinal illness but remain an essential step in the management.
PATIENTS WITH CIRRHOSIS and DETERIORATION or HOSPITALIZATION

IS THERE ASCITES?
- History: Increased abdominal girth LR (95% CI) 4.1 (2.3-4.7)
  Recent weight gain LR (95% CI) 3.2 (1.7-6.2)
  Ankle swelling LR (95% CI) 2.8 (1.8-4.3)
- Exam: Fluid wave LR (95% CI) 5.3 (2.9-9.5)
  Shifting dullness LR (95% CI) 2.1 (1.6-2.9)
  Simel D. The Rational Clinical Examination JAMA Evidence 2009

PARACENTESIS
- Consider US guidance for novices and obtain ascitic fluid before antibiotic use, within 6 hours
  Sekiguchi H. Chest 2013;143:1136-1139
- No evidence that LVP improves outcomes in SBP, in fact, may pose risk, worsen hemodynamics
- Injecting 10 mL into BC tubes at bedside improves culture yield, speeds time to detection
  Runyon BA. Arch Intern Med 1987;147:73-75

DIAGNOSIS
- Polymorphonuclear (PMN) count ≥ 250 cells/mm³
  Jones SR. West J Med 1977;126:344-6
- Total ascites WBC x (segs% + bands%) = PMN
- Example: 2,100 WBC count x 38% neutrophils = 798 PMNs
- Correct for RBC by subtracting 1 PMN/250 RBCs
  Hoefs JC. Hepatology 1981;1:249-254

ANTIBIOTICS
- Community-acquired SBP: Rx 3rd generation cephalosporin
  1st line: Cefotaxime 2 g IV Q 8 h x 5 days
  2nd line: Ceftiraxone 1 g IV bid x 5 days
  Baskol M. J Clin Gastroenterol 2003;37:403-405
- PCN allergy: Levofoxicin 500 mg IV daily x 5 days
  Yarac T. Dig Dis Sci 2010;55:1149-54
- Nosocomial SBP: TAZ 3.75 g IV Q 6 hrs & Vancomycin 1 g IV Q 12 hrs x 5 days
  Novovic S. Scand J Gastroenterol 2012;47:212-6
- VRE SBP: Linezolid (Zyvox; Pfizer Inc., New York City, NY, USA) or [Daptomycin (Cubicin; Cubist Pharmaceuticals, Lexington, MA, USA) for bacteremia]
- ESBL Enterobacteriaceae SBP: Meropenem 1 g IV Q 8 h x 5-7 days
  Badawy AA. World J Gastroenterol 2013;19:1271-7

ALBUMIN
- Rx 20-25% IV albumin if total bilirubin >4, <30, or Cr >1
  Albumin decreases incidence of renal failure and mortality.
  1.5 g/kg on day #1 (within 6 hours of diagnosis)
  1.0 g/kg on day #3

SECONDARY PROPHYLAXIS
- Norfloxacin 400 mg PO daily or
  Ginés P. Hepatology 1990;12:716-24
- Bactrim DS PO daily or 5 days/week or
- Ciprofloxacin 500 mg PO daily
  Terg R. J Hepatol 2008;48:774-779

ADJUNCT MEASURES
- Optimize nutrition with oral BCAA in ESLD; hospitalization, improves liver tests, and prolongs survival.
  Marchesini G. Gastroenterology 2003;124:1792-801
- Arrange liver transplant evaluation after 1st SBP episode.
  Bac DJ, Scand J Gastroenterol Suppl 1996;218:38-42
- Control ascites with diuretic therapy, < 2 g/day Na+ diet.
  Runyon BA. Gastroenterology 1989;97:158-62
- Limit PPI therapy to necessary indications.
  Goel GA. Clin Gastroenterol Hepatol 2012;10 (4):422-7
  Bajaj JS. Am J Gastroenterol 2009;104:1130-4
- Correct vitamin D deficiency.
  Anty R. Clin Transl Gastroenterol 2014;5:656
- Discontinue/taper beta-blocker use in ESLD + refractory ascites or SBP. Linked to hospital-free survival (HR, 1.58) after diagnosis of SBP.
  Mandorfer M. Gastroenterology 2014;146:1680-90
  Serste T. Hepatology 2010;52:1017-22

Figure 1 | Evidence-based algorithm for evaluation of at-risk patients, diagnosis and management of SBP. LR, likelihood ratio; CI, confidence interval; US, ultrasound; LVP, large volume paracentesis; BC, blood culture; WBC, white blood cell; segs, segmented neutrophils; bands, young neutrophil; RBC, red blood cells; Rx, prescription; IV, intravenous; Q, every; x, for; PCN, penicillin; TAZ, tazobactam–pipericillin; VRE, vancomycin-resistant Enterococcus; ESBL, extended spectrum beta-lactamase; abx, antibiotics; BUN, blood urea nitrogen; Cr, creatinine; #, number; BCAA, branched-chain amino acids; ESLD, end-stage liver disease; ↓↓, decrease; Na⁺, sodium; PPI, proton pump inhibitor; HR, hazard ratio; DS, double strength; PO, per os.
for all of these patients regardless of their presenting complaint. A diagnostic paracentesis is safe, easy to perform, and should not be delayed or prevent timely administration of antibiotics primarily in unstable patients. Identifying the bacterium culprit and watchful clinical assessment are especially important because of chronic antibiotic use, emergence of multi-drug resistant bacteria, and recent changes to the bacterial profile including an increased prevalence of GPC-related SBP namely *Staphylococcus* and *Enterococcus* species, which can portend significantly higher mortality.

First-line treatment with a third-generation cephalosporin is sufficient in the majority of patients with SBP. Piperocillin–tazobactam and/or vancomycin are suitable antibiotic alternatives for patients who fail to improve or for empiric treatment of nosocomial SBP. As such, clinical acumen and close patient monitoring for deterioration are paramount to prevent poor outcomes. Administration of antibiotics for 5 days has proven effective for SBP. However, incomplete resolution of infection with a short course of antibiotics was reported in approximately 20% of patients with SBP and extending treatment to 7 days can be advocated. Antibiotics with selective albumin therapy and liver transplantation are currently the only available options to improve survival in patients with SBP.

**AUTHORSHIP**

**Guarantor of the article:** John Dever.

**Author contributions:** John Dever contributed to the design, literature search and review, creation of the tables and figure, and writing of the manuscript. Muhammad Sheikh contributed to the study inception, proofreading of the manuscript and provided expert counsel. All authors approved the final version of the manuscript.

**ACKNOWLEDGEMENT**

Declaration of personal and funding interests: None.

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