Chapter 31
Spontaneous Bacterial Peritonitis (SBP)

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1. How do I know I have SBP?

   Patient-Level Answer: In order to get SBP, you have to have ascites or fluid in the abdomen as a result of your liver disease. Once this fluid is present it runs the risk of becoming infected. The most common signs of infection include abdominal pain, fevers, or confusion. The only way to diagnose SBP is with a paracentesis where a sample of fluid is removed from the abdomen and analyzed to see if an infection is present.
2. How is it treated?

   Patient-Level Answer: SBP is a serious infection and can lead to death if not treated promptly and aggressively. Typically once the diagnosis is suggested based on preliminary findings from a paracentesis, antibiotics should be started. The length of treatment depends on how well a patient is responding to the treatment but is typically between 5 and 10 days.
3. What can be done to prevent me from getting SBP again?

   Patient-Level Answer: The most effective way to prevent SBP is to prevent the development of ascites or fluid in the abdomen from accumulating in the first place. Once fluid is present, there are certain patients who may benefit from taking antibiotics regularly to prevent an infection from developing including those who have had prior episodes of SBP.

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Pathogenesis and Risk Factors

Spontaneous bacterial peritonitis (SBP) is defined as an intraperitoneal infection of ascitic fluid without underlying anatomic or pathologic cause. The term was initially described by Conn in 1964 who postulated that translocation of enteric pathogens in decompensated cirrhotic patients could lead to peritonitis and bacteremia, a vastly underreported syndrome at the time [1]. Initial reports suggested an exceedingly high mortality rate of greater than 90 % associated with SBP. Despite advances in management and more widespread use of antimicrobial prophylaxis, mortality continues to range from 10 to 30 % making it a significant cause of death in patients with end-stage liver disease [2].

At least 90 % of cases of SBP are monomicrobial with the most common causative organisms including gram negative enteric flora such as *Escherichia coli* and *Klebsiella pneumoniae*, as well as various Streptococcal species [3]. Studies seem to suggest a role for bacterial overgrowth and delayed intestinal motility as predisposing factors for the development of SBP. A study by Chang, et al. from 2003 compared cirrhotic patients with and without a history of SBP and found significantly higher rates of bacterial overgrowth and small intestinal dysmotility as assessed by hydrogen breath testing and small bowel manometry respectively among patients with a history of SBP [4]. The study was limited by significantly higher Child-Pugh score in the group with a history of SBP. A subsequent analysis using jejunal aspirates from cirrhotic patients found an association between bacterial overgrowth and acid-suppressive therapy, but no association with the development of SBP [5]. Independent of bacterial overgrowth concerns, the phenomena of bacterial translocation of enteric pathogens in patients with cirrhosis has been well documented. For example, analysis of mesenteric lymph node sampling has revealed increased levels of bacteria in cirrhotic compared to noncirrhotic patients [6].

SBP typically develops in patients with advanced liver disease, and risk is directly proportional to Child-Pugh score which has been shown to be an independent risk factor for bacterial infections in general including SBP [7]. An elevated Model for End-Stage Liver Disease (MELD) score has also been implicated. A retrospective case–control analysis found that for every 1-point increase in MELD score there is an associated 11 % increased risk of developing SBP [8].

There has also been considerable interest in the role of acid-suppressive therapy in the development of SBP. A retrospective case–control analysis of cirrhotic patients admitted with SBP compared to matched control cirrhotic patients admitted for other reasons found on multivariate analysis that PPI use was associated with an increased risk of SBP (odds ratio 4.31, 95 % CI 1.34–11.7) [9]. A more recent large, multicenter prospective analysis found no increase in risk of SBP among patients taking proton-pump inhibitors [10].

Additional known risk factors predisposing to the development of SBP include: low ascitic fluid total protein concentrationcoagulopathy, hyperbilirubinemia, gastrointestinal hemorrhage, and prior episode of SBP [11–14]. Several randomized trials were analyzed and based on results showing mortality benefit and reduced rate

of infection, primary prophylaxis with antibiotics to prevent SBP is recommended in patients with cirrhosis and ascites whose ascitic total protein level is less than 1.0 g/dL, in addition to evidence of either impaired renal function (serum creatinine ≥1.2 mg/dL, blood urea nitrogen ≥25 mg/dL, or serum sodium ≤130 mEq/L) or hepatic failure (Child-Pugh score ≥9 or total bilirubin ≥3 mg/dL) [14, 15]. Genetic variability in terms of inflammatory signaling may play a role in terms of SBP risk as well. A recent genotypic analysis showed that specific variants of a Toll-Like Receptor 4 gene were associated with lower serum levels of tumor necrosis factor-alpha (TNF-α) and a significantly decreased risk of severe bacterial infections among patients awaiting liver transplant. Zero deaths as a result of severe bacterial infections were observed while awaiting transplant in this group [16].

Immune dysfunction is thought to play a significant role in cirrhotic patients by predisposing them to the development of infections including SBP. For example, complement deficiency has been well documented in the cirrhotic population and has been demonstrated to correlate with elevated rates of SBP [17]. A variety of other host factors play a role as well including malnutrition, decreased phagocyte activity, neutrophil dysfunction, and altered inflammatory cytokine levels [18].

True SBP in patients with ascites due to noncirrhotic causes, or elevated ascitic protein levels >2.5 g/dL is very uncommon and limited in the literature to case reports and small series [19]. Typically when there is an infection in this setting, an underlying predisposing anatomic defect leading to secondary bacterial peritonitis should be sought.

Clinical Manifestations

SBP tends to develop only in cases of clinically apparent and preexisting ascites. Its most common presenting features include abdominal pain, fevers, encephalopathy, diarrhea or ileus, and hemodynamic instability or sepsis, and it should be strongly considered in any patient with cirrhosis and clinically apparent ascites who presents with these complaints. Common laboratory findings include peripheral leukocytosis with or without left shift, acidosis, and renal failure. A significant number of patients present without symptoms, and more routine use of paracentesis for hospitalized cirrhotic patients with ascites has led to increased recognition of this clinical entity. Despite this, mortality rates related to SBP have remained high [20].

Diagnosis

SBP is associated with high mortality and early identification and initiation of appropriate antibiotics is critical to mitigating this risk. Based on AASLD guidelines it is recommended that all hospitalized patients with cirrhosis and ascites receive a diagnostic paracentesis during their admission, and paracentesis should also be obtained

any time a patient shows clinical signs or laboratory evidence suggestive of possible SBP. Despite these recommendations a recent large retrospective database analysis found that paracentesis remains underutilized, being performed in 61 % of the 17,711 cirrhosis-related hospitalizations included in the study. Patients who received a paracentesis had a 24 % reduction of in-hospital mortality, though their length of stay and cost of hospitalization were slightly higher [21]. Paracentesis should ideally be performed prior to the administration of antibiotics if clinically feasible to prevent false negative results from partially treated sample specimens. Procedural delay should be avoided, and in general, an elevated prothrombin time or international normalized ratio is not a contraindication to diagnostic paracentesis as it has been shown to be safe despite presence of abnormal coagulation factors [22]. Patients with SBP who had paracentesis performed >12 h after admission had a 2.7-fold higher mortality compared to those who received early paracentesis [23].

It is important to utilize sterile technique to prevent contamination from skin flora. Direct bedside inoculation of the sample into culture media has been shown to be superior to conventional inoculation of sample sent to a clinical laboratory with increased sensitivity for diagnosing SBP [24]. Fluid sample should be sent for aerobic and anaerobic culture, cell count with differential, gram stain, and if the initial sampling albumin and total protein levels, in addition to other values relevant on a case by case basis (i.e. cytology for cases of suspected metastatic malignancy, etc.).

The diagnosis of SBP is made by the finding of ≥250 polymorphonuclear (PMN) cells per mm^3 with positive culture results and potential causes of secondary peritonitis excluded. Patients meeting criteria based on cell count alone should be presumed to have SBP and treatment with antibiotics should be initiated empirically while awaiting culture results. Correction for grossly blood specimens as occurs during a traumatic paracentesis can be performed by subtracting one PMN from the total count for every 250 red blood cells per mm^3 present in the specimen. Additional ascitic fluid chemistries can also be helpful in confirming or excluding the presence of SBP. For example, the serum-ascites albumin gradient (SAAG) is calculated by subtracting the ascitic fluid albumin level from the serum level. A value of >1.1 g/dL indicates the presence of portal hypertension with 97 % certainty. As SBP rarely develops in patients without portal hypertension, a SAAG of <1.1 g/dL makes the diagnosis of SBP unlikely [25]. Additionally, the total protein concentration of ascitic fluid has been shown to inversely correlate with the risk of development of SBP [11].

Management

It is imperative that intravenous antibiotics be initiated promptly following diagnostic paracentesis in cases of suspected SBP due to the high mortality associated with this disease, especially in patients with fevers, abdominal pain, or altered mental status. Patients who are asymptomatic but are found to have bacterascites (defined as the presence of bacteria on culture or gram stain in the setting of PMN count less

than 250 cells per mm^3) should have a repeat paracentesis performed within 48 h and antibiotics should be initiated if symptoms develop or the PMN count rises above 250 cells per mm^3. Initial therapy regimen should consist of broad antimicrobial coverage such as a third generation cephalosporin or floroquinolone, though local resistance patterns should be taken into account when selecting an agent. Choice of antibiotic should be rapidly narrowed when culture results and sensitivities become available to prevent the development of bacterial resistance.

There is a relative dearth of large, prospective, randomized controlled trials available to guide initial antibiotic selection, and a 2009 Cochrane review was unable to provide clear evidence in favor of any specific regimen [26]. One small prospective trial found improved efficacy with IV cefotaxime as compared to ampicillin-tobramycin (clinical cure in 85 % as compared to 56 %, $p < 0.02$) as well as fewer superinfections and lower rates of renal failure [27]. In general, aminoglycosides are avoided due to their accumulation in the ascitic fluid and thus difficulty in measuring true levels with the potential development of renal failure.

Duration of Treatment

SBP typically responds rapidly to appropriate antibiotic administration, and clinical resolution is typically readily apparent. Typical treatment regimens consist of 5 days of therapy based on findings from a prospective, randomized trial which found equivalent outcomes among patients with SBP who were treated with either 5 or 10 days of antibiotics. Clinical cure was obtained in 93.1 % with 5 days of therapy versus 91.2 % with 10 days of therapy. The groups had similar rates of recurrence (11.6 % and 12.8 % respectively) as well as hospital mortality (32.6 % and 42.5 % respectively), neither of which were statistically significant [28]. Short treatment duration has the added benefit of reduced costs as well as minimizing the development of antimicrobial resistance. After completion of therapy, repeat clinical assessment should be performed and if persistent symptoms or signs of ongoing infection are present (abdominal pain, fevers, leukocytosis, altered mental status) then repeat paracentesis should be performed. Antibiotics should be continued if the polymorphonuclear cell count remains elevated above 250 cells per mm^3. For the majority of patients who respond promptly to treatment and have clinical resolution of symptoms, a repeat paracentesis is not typically needed despite previous recommendations of follow-up paracentesis to guide therapy.

Renal failure is common among patient with SBP, occurring in approximately one-third of patients [29]. A recent meta-analysis found that the development of renal failure was the highest independent predictor of mortality among patients with SBP, followed by MELD score. Mortality among those with renal dysfunction in the analysis was 67 % compared to 11 % in patients without renal impairment [30]. Altered renal hemodynamics that occur during infection are thought to play a role, including activation of the renin-angiotensin system as well as release of norepinephrine, effectively reducing renal perfusion [31]. Volume expansion using

IV albumin has been shows to improve outcomes among sub-groups of patients with SBP who develop renal failure. A randomized controlled analysis assessed administration of intra-venous albumin concomitantly with antibiotics in patients with SBP who also have evidence of elevated serum creatinine >1.0 mg/dL, blood urea nitrogen >30 mg/dL, or serum bilirubin >4 mg/dL. The treatment arm who received albumin had lower risk of progression to renal failure as well as lower overall mortality [32]. These findings have been corroborated in other randomized trials including a meta-analysis as well [33]. Thus, albumin at a dose of 1.5 g/kg IV within 6 h of diagnosis followed by 1 g/kg IV on day 3 should be administered.

Nonselective beta-blockers are commonly used for prophylaxis of esophageal varices in certain scenarios. This class of medications has myriad influences on systemic hemodynamics and on circulatory reserve. The role of nonselective beta-blocker usage in outcomes among patients with SBP has been investigated. A retrospective analysis of 607 consecutive patients with cirrhosis undergoing paracentesis found that nonselective beta-blocker usage in patients without SBP was associated with increased survival (HR 0.75, 95 % CI 0.581–0.968). Conversely, among patients who were diagnosed with SBP, beta-blocker use reduced survival (HR 1.58, 95 % CI 1.098–2.274), led to more prolonged length of hospitalization (mean 29.6 days per person year versus 23.7 days per person year) and increased incidence of hepatorenal syndrome (24 % versus 11 %) [34]. Therefore, patients who are taking nonselective beta-blockers for prophylaxis of esophageal varices should have this medication discontinued at the time that SBP is first suspected.

Prophylaxis

Patients who are considered to be at high risk for the development of SBP have been shown to benefit from antimicrobial prophylaxis to prevent infections and reduce mortality. High risk groups include patients with a history of prior episode of SBP, patients with GI bleeding, and patients with a low ascitic fluid total protein concentration.

Patients with a history of prior episode of SBP are at particularly high risk of developing recurrent infection. One study of consecutive cirrhotic patients who survived and recovered from an initial episode of SBP found a 43 % incidence of recurrent SBP at 6 months and 69 % incidence at 1 year with overall 1 year survival of only 38 % [12]. Similar risk of SBP recurrence at 1 year was found in a randomized, controlled trial assessing prophylactic norfloxacin versus placebo in patients with a history of prior episode of SBP. Risk of development of SBP at 1 year in the placebo arm was 68 % compared to 20 % in the arm receiving prophylactic norfloxacin 400 mg daily [35].

Patients with low ascitic fluid total protein concentration have a significantly increased risk of development of SBP and have been demonstrated to benefit from prophylactic antibiotic administration as well. A prospective trial assessing use of norfloxacin versus placebo in patients with low protein ascites found rates of SBP

in the placebo group to be 22.7 % as compared to 0.0 % in the group receiving antimicrobial prophylaxis. There was a trend toward improved mortality as well in the treatment group; however, this did not reach statistical significance [36].

Advanced cirrhosis and renal dysfunction are additional patient subsets that have been suggested to benefit from prophylaxis against SBP. A randomized controlled trial including patients with advanced cirrhosis (Child-Pugh score ≥9, with serum bilirubin ≥3 mg/dL) or impaired renal function (serum creatinine ≥1.2 mg/dL, blood urea nitrogen ≥25 mg/dL, or serum sodium level of ≤130 mEq/L) compared prophylactic treatment with norfloxacin to placebo in the prevention of SBP [15]. Primary endpoints were 3-month and 1-year survival, and secondary endpoints included the probability of development of SBP or hepatorenal syndrome at 1-year. The risk of developing SBP at 1-year was 7 % in the treatment group compared to 61 % with placebo ($p<0.001$), and overall survival was significantly improved at 3-months (94 % versus 62 %, $p=0.003$) and at 1-year (60 % and 48 %, $p=0.05$). The trial served for the basis of the AASLD guideline statement suggesting antimicrobial prophylaxis for patients meeting the clinical criteria required for inclusion into the study.

In general, regimens with coverage against gram negative organisms have been preferred for use as prophylactic agents including quinolones and trimethoprim-sulfamethoxazole. A randomized trial assessing the use of trimethoprim-sulfamethoxazole five times per week (Monday–Friday) for prophylaxis in patients at high risk for SBP (low ascitic protein level, renal dysfunction, hyperbilirubinemia, etc.) found that treatment reduced the risk of development of SBP from 27 % in the placebo group to 3 % in the treatment group. There was a trend toward improved mortality as well, though this was not statistically significant [37]. Another trial looking at once-weekly ciprofloxacin among cirrhotic patients with low protein ascites found similar reduction in risk of development of SBP from 22 % in the placebo group to 3.6 % in the treatment group [38].

Gastrointestinal bleeding and variceal hemorrhage predispose patients to the development of SBP and prophylactic antibiotics have been shown to improve outcomes in these patients. A meta-analysis consisting of a total of five trials and 534 patients with cirrhosis and gastrointestinal bleeding found that short course antibiotic prophylaxis administration reduces rates of infections including SBP and improves overall survival [14]. A Cochrane systematic review from 2010 confirmed these findings. A total of 12 trials and 1241 patients were included in this analysis. Overall mortality was improved with use of antibiotics among patients with cirrhosis and gastrointestinal bleeding (RR 0.79, 95 % CI 0.63–0.98), as well as improvements in infection-related morality (RR 0.43, 95 % CI 0.19–0.97) and risk of SBP (RR 0.29, 95 % CI 0.15–0.57). Length of hospitalization and rebleeding risks were also improved among patients receiving prophylactic antibiotics [39]. As practice habits have changed and antimicrobial prophylaxis in the setting of gastrointestinal bleeding in cirrhotic patients has become more routine, improved outcomes over the years have been observed among these patients. In-hospital mortality from variceal hemorrhage in 1980 at a single center in Europe was 42.6 %, and had improved by year 2000 to 14.5 % [40]. Although direct causality has not been proven, prophylactic antibiotics are postulated to play a role in this observed improvement.

Current updated practice guidelines from the AASLD in 2012 recommend prophylactic antibiotics be given to all patients with cirrhosis who present with gastrointestinal bleeding, whether or not they have ascites, with a recommended duration of therapy of 7 days. These recommendations are also endorsed by the ASGE as reflected in the recent guideline statement regarding use of antibiotics for GI endoscopy [41].

Current guidelines do not comment on the routine use of antibiotic prophylaxis to prevent SBP in the setting of patients awaiting liver transplant who do not already have an indication. A small trial that assessed the effect of daily administration of ciprofloxacin in patients with advanced liver disease awaiting transplant found that, compared to placebo, treatment with ciprofloxacin was not associated with improvements in hepatic function, though rates of hospitalization were improved (5 % in Ciprofloxacin group versus 32 % in placebo group, $p = 0.02$) [42]. The trial did not look at perioperative or posttransplant outcomes, and at this time there is a lack of data to support routine use of antibiotics in this setting. Another area where routine antibiotic prophylaxis is not routinely recommended is among patient receiving treatment with sclerotherapy. A trial comparing use of antibiotics to prevent post-sclerotherapy bacteremia found no significant difference among patients receiving prophylactic imipenem/cilastatin. A higher risk of infection was observed in patients who underwent emergent as compared to elective sclerotherapy, which was likely reflective of increased risk of infection among cirrhotic patients with active gastrointestinal bleeding [43].

Future Trends

Evolving research and active investigation is underway involving several areas of SBP. One particular area of interest involves the use of enhanced diagnostic tools for the detection and diagnosis of patients with SBP, as early identification and implementation of appropriate therapy has consistently been shown to improve outcomes as previously discussed. Serum procalcitonin concentration has been identified as an important tool in the early identification of patients with sepsis from a bacterial infection, and has been increasingly integrated into sepsis protocols among emergency rooms and intensive care units [44]. Research has suggested a role for this biomarker in the diagnosis of patients with SBP as well. The identification of a diagnostic marker easily obtained from the serum would potentially be of benefit given the challenges sometimes associated with obtaining a prompt diagnostic paracentesis specimen. A recent meta-analysis identified three relevant trials and found pooled sensitivity and specificity values for use of this marker in the diagnosis of SBP of 86 % and 80 % respectively [45]. This finding suggests a high diagnostic accuracy and the authors note that further larger trials are warranted.

Additional investigation has suggested a role for ascitic fluid markers as well, citing the possibility of false negatives obtained from a manual cell count if lysis of PMN's has occurred during prolonged transport or specimen processing. One trial assessed the use of ascitic lactoferrin concentration among consecutive ascitic fluid

samples [46]. Among the 22 samples meeting diagnostic criteria for SBP, an ascitic lactoferrin level of ≥242 ng/mL had a sensitivity and specificity of 95 % and 97 % respectively with an area under the receiver operating characteristic curve of 0.98.

For even more rapid identification of SBP, investigation into the use of dipsticks for ascitic fluid analysis is also underway. One such product is designed to detect leukocyte esterase from ascitic fluid, and calibrated to a PMN count of 250 cells per mL. An analysis of 1089 ascitic fluid samples found a sensitivity and specificity of 100 % and 59 % respectively for the detection of samples positive for SBP [47]. At this point the product remains investigational and further investigation is underway.

Identification of additional antimicrobial agents given ongoing concerns for resistance, side-effect profiles, and cost, is an area of interest as well. A commonly used agent among patients with cirrhosis and hepatic encephalopathy is rifaximin. Recent literature has suggested that this agent may reduce incidence of SBP and may impact the bacterial flora as well. In one retrospective study, consecutive patients with cirrhosis and large-volume ascites were analyzed, excluding patients with a history of SBP or patients already receiving prophylactic antibiotics. The authors identified 49 patients who received rifaximin and after mean follow-up of 4.2 months, 89 % remained SBP-free compared to 68 % of those not on rifaximin ($p = 0.002$) [48]. Another study prospectively assessed patients undergoing diagnostic paracentesis and found that treatment with rifaximin did not reduce incidence of SBP compared to no antibiotics [49]. The predominate species isolated among patients not receiving antibiotics were *Escherichia coli* and enterococci whereas those on rifaximin tended to grow Klebsiella species, suggesting that rifaximin plays a role in modulating the bacterial flora and impacting pathogenesis. Further studies are needed to better delineate the role of rifaximin in patients with or at risk for SBP.

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