

REVIEW

Spontaneous bacterial peritonitis

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Spontaneous bacterial peritonitis (SBP) is the infection of ascitic fluid in the absence of any intra-abdominal, surgically treatable source of infection. Despite timely diagnosis and treatment its reported incidence in ascitic patients varies between 7–30%. Ascitic paracentesis remains the chief diagnostic procedure. Automated cell counters have the same diagnostic accuracy as the manual measurement of white cells. Lately, the use of leucocyte reagent strips (dipsticks) has emerged as a useful alternative. Examination of the fluid is not complete unless the sample is inoculated in blood culture bottles. Treatment is currently with third-generation cephalosporins or oral quinolones. Following a single episode of SBP patients should have long term antibiotic prophylaxis.

nodes and thereafter to the blood stream and other extra-intestinal sites.¹⁷ It is considered to be the key step in the pathogenesis of SBP.^{18–23} Both humans and animals have duplicative mechanisms for protection from bacteria; therefore, intestinal bacterial translocation represents failure of a group of elaborate defensive factors to contain bacteria within the bowel.²

Bacterial overgrowth in association with impairment of the intestinal barrier (probably a consequence of vascular stasis due to portal hypertension), alterations of local immune defences, slow motility of the bowel in patients with cirrhosis and reduced opsonic activity (hence decreased reticulo-endothelial system activity) precede the episodes of bacterial translocation.^{17, 24–26}

More recently detection of translocation of bacterial products, such as lipopolysaccharides (LPS) from Gram-negative bacteria and peptidoglycans/lipopeptides from Gram-positive bacteria together with bacterial DNA, through the intestinal wall has been associated with production of many cytokines.²⁷ High levels of tumour necrosis factor α (TNF α), interleukin-6 (IL-6) and interleukin-1 (IL-1) in patients with cirrhosis cause over-activation of the sepsis syndrome pathways, leading eventually to renal failure and shock with reduced chances for survival.²⁸

The microorganisms more commonly isolated from cases of SBP are *Escherichia coli* (~70%), *Klebsiella* species (~10%), *Proteus* species, *Enterococcus faecalis* (~4% each), *Pseudomonas* species (~2%) and others (~6%).¹⁶

The environment in which one acquires the infection (nosocomial/community) does not seem to affect either the short or long term survival.²⁹

However, patients who survive their first episode of SBP are at increased risk of developing subsequent episodes of SBP in the future; between 50–70% of patients surviving the first episode of SBP will develop further episodes within 1 year. Factors associated with greater risk for SBP recurrence are impaired liver function (higher Child-Pugh class) and low protein concentration of the ascitic fluid.¹⁶

Therefore, it seems reasonable to refer patients after their first episode of SBP for liver transplant assessment.

The term spontaneous bacterial peritonitis (SBP) was coined by Harold Conn in the early 1970s to describe the infection of ascitic fluid in the absence of any intra-abdominal, surgically treatable source of infection.^{1–3}

Runyon describes the many unnecessary and “mysterious” deaths, in the past, before this common infection gained a place in the diagnostic algorithm of the deteriorating, confused patient with ascites.² He was one of the first advocates of the more liberal use of ascitic fluid paracentesis for the early detection of the life-threatening infection.^{4–7}

Recent British Society of Gastroenterology (BSG) guidelines on the management of ascites in cirrhosis⁸ highlight the effect of early diagnosis and prompt treatment with the reduction of in-hospital mortality from 90% to less than 20%.⁹

They suggest the performance of paracentesis in all cirrhotic patients with ascites on hospital admission and also in all patients who develop other signs suggestive of peritoneal infection—namely encephalopathy, renal impairment and peripheral blood leucocytosis without a precipitating factor.⁸

INCIDENCE AND PATHOGENESIS

Despite improvement of mortality from SBP, with prompt diagnosis and treatment, the reported incidence in patients with ascites varies between 7–30% per annum.^{10–15} Cirrhotic patients with hydrothorax can develop similar (spontaneous) infection of the pleural fluid.¹⁶

Runyon suggests that we should now drop the word “spontaneous”, as the nature of the infection has been extensively studied and resolved in recent years.² Bacterial translocation is the “passage” of bacteria from the lumen to the mesenteric lymph

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Table 1 Symptoms and signs of spontaneous bacterial peritonitis and its variants

Symptoms and signs	SBP (%)	Bacterascites (%)	CNNA (%)	Secondary peritonitis (%)
Fever	68	57	50	33
Abdominal pain	49	32	72	67
Abdominal tenderness	39	32	44	59
Rebound	10	5	0	17
Encephalopathy	54	50	61	33

CNNA, culture negative neutrocytic ascites; SBP, spontaneous bacterial peritonitis.

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DIAGNOSIS

Clinical signs, ascitic fluid indices and measurement modalities

The most common symptoms and signs in patients with SBP are pyrexia, increased confusion, diffuse abdominal pain, vomiting and reduced urine output or ileus (table 1).

However, signs of sepsis in patients with SBP may be masked because patients with cirrhosis have characteristics which make recognition of sepsis difficult⁸—namely, reduced polymorphonuclear leucocyte (PMNL) count due to hypersplenism, elevated baseline heart rate due to the hyperdynamic circulation, baseline hyperventilation due to hepatic encephalopathy, and blunted elevation of body temperature.²⁸

Therefore, a high index of suspicion is necessary in order to avoid diagnostic pitfalls, especially since the mortality rate of untreated patients approaches 50%.³⁰

Fear of the complications of abdominal paracentesis, like abdominal wall haematomas and intra-abdominal bleed, had previously kept diagnostic “taps” to the minimum. Recent published articles have reduced these ungrounded fears and established the safety profile of abdominal paracentesis.^{31–33} It is now accepted that the only way to diagnose an episode of SBP is by examining a sample of ascitic fluid.¹⁶ Various diagnostic criteria (ascitic fluid pH, lactate concentration, PMNL count) were proposed and evaluated during the early 1980s.^{34–38} The use of a cut-off value of pH ≤ 7.34 or a blood–ascitic fluid gradient ≥ 0.10 in combination with a fluid PMNL count $>500/\text{mm}^3$ (μl) offered the highest accuracy in the diagnosis of SBP.³⁸

Over the same period, other investigators used a diagnostic value for PMNL count of $>75/\text{mm}^3$.³⁷ A decade later, investigators turned their interest to TNF α , IL-6 and IL-1 in the infected ascitic fluid.^{39–41} Eventually it was the time for procalcitonin (PCT), a 116-aminoacid protein with a long half-life, to come under scrutiny with a similar intent.⁴² Teleologically, elevated ascitic fluid PMNL count represents failure of the first-line defence mechanisms (namely the inhabitant peritoneal macrophages) to eliminate invading bacteria.⁴ Hence, only the PMNL count managed to pass successfully the test of time and it is now accepted that a PMNL count $>250/\text{mm}^3$, in the absence of obvious intra-abdominal source of infection, is highly indicative of SBP.¹⁶ For patients with bloodstained ascitic tap and erythrocyte counts $>10,000/\text{mm}^3$, a correction is needed in order to obtain the true number of PMNL; this is done by subtracting 1 PMNL for every 250 erythrocytes from the measured number of PMNL.

Some authorities still use the total white cell count (WCC) of the peritoneal fluid, irrespective of the differential, as the diagnostic criterion of SBP. They suggest that a WCC $>500/\text{mm}^3$ is consistent with SBP.⁵

Measurement of ascitic fluid PMNL count was until recently the “prerogative” of the on-call microbiologists.⁸ Over the last

few years, however, studies have proved the validity of automated blood cell counters for this task.⁴³

The diagnostic ascitic “tap” is usually performed by a busy junior clinician; hence, the result of the manual or automated cell count of the ascitic fluid may only be available to the resident many hours post-paracentesis.⁴⁴ This is not ideal for the diagnosis of a life-threatening condition and has resulted in a search for alternative means for diagnosis.

Leucocyte esterase reagent strips (commonly used as urine dipsticks) have high sensitivity and specificity in the detection of an elevated PMNL in ascitic fluid.⁴⁵ A few peer reviewed studies have been already published and support their routine use in clinical practice.^{14 15 45–52}

While the diagnostic parameters of ascitic fluid—and their measurement modalities—have been extensively studied, the location of needle insertion was until recently a “fleeting” X-mark.⁵³ Infra-umbilical midline sites are certainly out of fashion; the left lower quadrant emerges as the scientifically-confirmed “safe” area (thinner abdominal wall with greater ascites pool) at a spot located two-finger breadths medially and two-finger breadths cephalad to the anterior superior iliac spine.⁵

Ascitic fluid culture has an important role in the diagnosis and management of SBP. SBP, like its blood stream counterpart, is an infection of low microbial concentration (only one bacterium per ml of fluid).^{16 54–57} Inoculation of ascitic fluid (at least 10 ml) in both aerobic and anaerobic blood culture bottles, at the bedside immediately post-paracentesis increases the yield of the culture technique from 40–50% to more than 80%.¹¹

SBP variants and secondary bacterial peritonitis

- Bacterascites (monomicrobial non-neutrocytic bacterascites) is the term used to describe the colonisation of ascitic fluid by bacteria, in the absence of inflammatory reaction in the bacterial fluid.¹¹ By definition, the PMNL count is $<250/\text{mm}^3$ and the culture positive while the patient may present with symptoms and signs of infection. The natural course of bacterascites, if untreated, is variable. As the diagnosis of bacterascites is made 2–3 days after initial paracentesis (the time necessary for culture growth), a repeat “tap” is recommended on day 3. If the second sample has a PMNL count $>250/\text{mm}^3$, treat as for SBP. If the PMNL count is $<250/\text{mm}^3$ and a second set of cultures is positive, treat as for SBP. If the PMNL count is $<250/\text{mm}^3$ and the second set of cultures is negative, no further action is recommended.¹¹
- Culture negative neutrocytic ascites (CNNA) is the term used to describe the clinical situation when the ascitic PMNL count is $>250/\text{mm}^3$ but cultures fail to grow any bacteria. It is considered to represent the expected 20% fail rate of culture to isolate the microorganism and it requires antibiotic treatment as if it were SBP. However, the term is now considered obsolete.
- Secondary peritonitis. The vast majority of patients with ascites present with SBP and not with the secondary bacterial variant. It is useful to differentiate the two conditions, especially when one is faced with non-responders to antibiotic treatment, as secondary peritonitis rarely resolves without surgical treatment.⁵⁸ It seems reasonable to think of the secondary form of peritonitis in the presence of a very high PMNL count when^{11 28}:

- there is a lack of response to antibiotic treatment
- cultures grow two or more microorganisms
- two of the following three findings of ascitic fluid are present: glucose <50 mg/dl (2.78 mmol/l), protein >10 g/l

Table 2 Causative microorganisms of spontaneous bacterial peritonitis, bacterascites and secondary peritonitis

Microorganisms	SBP (%)	Bacterascites (%)	Secondary peritonitis (%)
Monomicrobial			
<i>Escherichia coli</i>	37	27	20
<i>Klebsiella pneumoniae</i>	17	11	7
<i>Pneumococcus</i>	12	9	0
<i>Streptococcus viridans</i>	9	2	0
<i>Staphylococcus aureus</i>	0	7	11
Miscellaneous Gram-negative	10	14	7
Miscellaneous Gram-positive	14	10	0
Polymicrobial	1	0	53

SBP, spontaneous bacterial peritonitis.
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and lactate dehydrogenase values exceed normal serum levels.

Once suspected, the next step should be to add antibiotics against anaerobic organisms and seek surgical input.

TREATMENT OF SBP

Antibiotics

As *E coli* and other coliforms such as *Klebsiella* and other streptococcal and enterococcal species are the most common causative microorganisms, empirical therapy should use appropriate antibiotics (table 2). Therefore, third generation cephalosporins are the antibiotics of choice due to their broad antibacterial spectrum (98% of causative organisms are susceptible to cefotaxime) and extremely good safety profile.¹⁶ The most commonly used agent of this class of antibiotics is cefotaxime, although other agents like ceftriaxone and ceftazidime have similar efficacy. On the other hand, the use of oral fluoroquinolones seems a reasonable therapeutic step for conscious patients who are not vomiting. A recent Cochrane review concluded that there is no evidence that cephalosporins are more effective, or associated with less mortality and adverse events, than other antibiotics in the treatment of SBP. With cephalosporins both short-term (5 days) and long-term (10 days) treatment offer similar rates of cure. The short-term course is therefore recommended.¹⁶

Other antibiotics which have been used in the past include amoxicillin-clavulanic acid, tobramycin, combination of ampicillin and gentamicin, trimethoprim-sulfamethoxazole, and

Table 3 Costs of antibiotics used for spontaneous bacterial peritonitis

Route of administration	Antibiotic	Costs (£)* including VAT
Intravenous	Ciprofloxacin vial 400 mg	29.60 (per vial)
	Ciprofloxacin vial 200 mg	19.50 (per vial)
	Ofloxacin vial 200 mg	22.63 (per vial)
	Cefotaxime vial 1 g	0.94 (per vial)
	Ceftriaxone vial 1 g	0.91 (per vial)
	Augmentin† vial 1.2 g	1.35 (per vial)
Oral	Ciprofloxacin tabl 500 mg (10 tablets pack)	0.40 (4 p per tablet)
	Ciprofloxacin tabl 250 mg (20 tablets pack)	0.36 (1.8 p per tablet)
	Norfloxacin 400 mg (6 tablets pack)	2.30 (40 p per tablet)

VAT, value added tax.

*£1 approximately €1.45 and US\$2.00.

†Amoxicillin-clavulanic acid.

aztreonam (table 3). Duration of treatment varies between five and seven days.

Cephalosporins offer a reported 75–90% resolution of SBP.¹⁶ More specifically, 2 g of intravenous cefotaxime has been shown to offer 20-fold killing power after only one dose.⁵ Cephalosporins are less likely to cause nephrotoxicity, compared to the aminoglycosides which have an unpredictable volume of distribution in patients with ascites,⁵ and they do not lead to microbial resistance development either (the main concern with the use of quinolones and penicillins).

The use of repeat paracentesis to check sterility of ascitic fluid, after 48 h of antibiotic treatment, is recommended by some authors and certainly has a place when no clinical improvement occurs; however, it is unnecessary in routine clinical practice.

Albumin

Patients with SBP are prone to develop hepatorenal syndrome (HRS). The translocation of bacteria and their endotoxins trigger the production of cytokines and vasodilators (nitric oxide) from inflammatory pathways.^{12–59} The incurred haemodynamic changes are exaggerated. Vasodilation in association with reduced effective blood volume poses a significant burden for an already impaired (for most patients) renal function.⁶⁰ The development of renal impairment in patients with SBP is an indicator of poor prognosis and volume expansion seems a reasonable adjunct to antibiotic administration.⁶¹ Albumin can bind toxins and help delivery to removal sites, improve opsonic activity of ascitic fluid and expand the intravascular volume. Sort and colleagues established its use in patients with SBP in 1999.⁶¹ In addition, albumin was found to decrease renin activity and improve the mortality rate of SBP from 29% to 10%. However, the study was criticised for the lack of volume expansion in the “control” arm (patients only on cefotaxime with no crystalloid or colloid support). The current regimen dictates co-administration of albumin (1.5 mg/kg of body weight) within 6 h of the first dose of cefotaxime and a repeat dose of 1 mg/kg body weight on day 3. In summary, the use of albumin offers “scavenger” (for free oxygen radicals) action, a stabilising effect on vascular endothelium and repletion of intravascular volume.

PROPHYLAXIS OF SBP

SBP is a serious complication in patients with cirrhosis with high mortality rates (20–40%). Patients at risk of developing SBP can be categorised in three groups: (1) patients with active variceal bleeding; (2) patients with ascitic fluid protein <10 g/dl; and (3) those with a prior episode of SBP.¹¹ These patients are the target for antibiotic prophylaxis (primary or secondary) with antibiotic administration. Newer quinolones are the prophylactic antibiotics of choice because they not only eliminate aerobic Gram-negative bacteria from the intestinal flora but also appear to have immunoregulatory capabilities by stimulating bactericidal capacity of polymorphonuclear cells and decreasing bacterial adhesion to mucosal surfaces.⁶²

All patients with cirrhosis (with or without ascites) and variceal bleeding are at high risk of developing SBP. In this acute setting several trials have demonstrated the effectiveness of short-term (7–14 days) prophylactic antibiotic administration in the prevention of SBP.^{63–69} A recent meta-analysis by Bernard *et al*⁷⁰ indicates that antibiotic prophylaxis not only prevents infection of patients with cirrhosis (including SBP) but also improves survival in acute bleeding. In the same meta-analysis no difference was found between orally versus intravenously administered antibiotics. Norfloxacin, 400 mg/12 h, administered orally (or by nasogastric tube) over a minimum of 7 days is recommended as the first drug of choice by the International Ascites Club (IAC).²⁸ Ciprofloxacin and

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trimethoprim–sulfamethoxazole have also been used with similar good results.⁷¹

Several trials^{71–76} have identified a specific subgroup of cirrhotic patients with ascites who seem to benefit from primary SBP prophylaxis through administration of ciprofloxacin, norfloxacin or trimethoprim–sulfamethoxazole. These patients have low ascitic protein count (<10 g/dl) and poor hepatic function. Long-term antibiotic administration effectively prevents the first episode of SBP although overall infection and mortality rates are unchanged. Unfortunately, most studies have included a wide range of patient populations while others do not have a control arm or have small patient numbers making it difficult to formulate clear conclusions. On this basis the IAC was unable to reach a consensus¹¹ but there is enough evidence (level III D) that this specific subgroup (patients with cirrhosis with low ascitic protein count and no previous SBP) would clearly benefit from antibiotic prophylaxis.⁹

Patients with cirrhosis who survive an episode of SBP have a 40–70% risk of relapse in the following 12 months.²⁸ Secondary prophylaxis for prevention of recurrence has been investigated in studies^{72–74, 76–78} using different antibiotics (ciprofloxacin, norfloxacin, ofloxacin). Based on those results long-term antibiotic administration is advised for all patients recovering from an episode of SBP until resolution of ascites, transplantation or death.^{9–11} It must be mentioned that prophylaxis also seems to be more cost-effective compared to the “diagnosis and treat” strategy when applied to high-risk cirrhotic patients.^{78–80}

Selection of antibiotic-resistant bacteria is a worrying issue attributed to prolonged antibiotic administration. Quinolone-resistant Gram-negative bacteria have been increasingly isolated and thought to be a result of long-term treatment with norfloxacin. Crossover resistance to trimethoprim–sulfamethoxazole also seems to be a serious issue. All this together with the ongoing increase of infections from Gram-positive bacteria underlines the need to restrict the use of prophylactic antibiotics to patients with the greatest risk of SBP.^{81–83} Rotating antibiotics may be an alternative.⁸⁴

Non-antibiotic SBP prophylaxis has been tried through administration of lactobacilli (with or without antioxidants)^{85–86} prokinetic agents such cisapride^{87–88} and non-selective β -blockers (propranolol)^{89–91} with variable results. Propranolol seems to be an attractive agent and promising results have been

reported although further studies, properly designed, are needed to confirm its effectiveness for prophylaxis.

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