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TOPIC HIGHLIGHT

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Spontaneous bacterial peritonitis

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Abstract

Since its initial description in 1964, research has transformed spontaneous bacterial peritonitis (SBP) from a feared disease (with reported mortality of 90%) to a treatable complication of decompensated cirrhosis, albeit with steady prevalence and a high recurrence rate. Bacterial translocation, the key mechanism in the pathogenesis of SBP, is only possible because of the concurrent failure of defensive mechanisms in cirrhosis. Variants of SBP should be treated. Leucocyte esterase reagent strips have managed to shorten the 'tap-to-shot' time, while future studies should look into their combined use with ascitic fluid pH. Third generation cephalosporins are the antibiotic of choice because they have a number of advantages. Renal dysfunction has been shown to be an independent predictor of mortality in patients with SBP. Albumin is felt to reduce the risk of renal impairment by improving effective intravascular volume, and by helping to bind pro-inflammatory molecules. Following a single episode of SBP, patients should have long-term antibiotic prophylaxis and be considered for liver transplantation.

Key words: Spontaneous bacterial peritonitis; Infection; Ascites; Leucocyte reagent strips; Portal hypertension; Ascites

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INTRODUCTION

It seems that all diseases or syndromes that comprise our routine differential diagnoses were, not so long ago, obscure clinical entities, at least until an astute clinician came across them. It was not any different for spontaneous bacterial peritonitis (SBP).

Although Laënnec's name had been connected with cirrhosis since the early 1800s, it was only much later that SBP was diagnosed as a separate entity. The papers of Kerr *et al*[1] and Conn[2], which were published within a year of each other, describe the infection of ascitic fluid in the absence of a contiguous source of infection or an intra-abdominal inflammatory focus. Although similar reports had been published in the French literature since 1893, Conn[2] was the one who eventually coined the term (SBP) in his 1964 paper.

Since then, further research has made the once-feared disease (early reported mortality of 90%)[2] a treatable complication of decompensated cirrhosis[3], albeit with a steady prevalence and high recurrence rate[4,5]. The plethora of publications has also led to national/international guidelines and recommendations over the last 10 years[5-11].

PATHOGENESIS

The importance of the liver as a bacterial filter is well established. However, it was Conn[2] who hypothesized that intestinal bacteria escaping into the blood stream cause prolonged bacteremia, and in turn, a

greater chance of ascitic fluid invasion[3]. Other early reports have emphasized the possibility of abdominal paracentesis-induced SBP[1,3], and certainly, prior to the use of stringent skin disinfection and protective clothing, the incidence of paracentesis-induced peritonitis would have been higher. The negative impact of this thinking created generations of clinicians who were hesitant and unsure about dealing with infective ascites. The persistence of researchers has helped to assuage concerns and has led to a more liberal and appropriate paracentesis protocol[12-14].

Bacterial translocation (BT), the key mechanism in the pathogenesis of SBP, is only possible because of the concurrent failure of defensive mechanisms in cirrhosis[15-19]. Since the early 1990s, on-going research has confirmed the intensity of BT in cirrhotic rats[15-18,20,21]. Investigators have also demonstrated pronounced impairment of gastrointestinal tract motility in cirrhosis[22-24]. The disturbance of gut flora microecology that follows, in association with changes in the (ultra)structure of the gastrointestinal tract[25-27] and reduced local and humoral immunity paves the way for the relatively free flow of microorganisms and/or endotoxins to the mesenteric lymph nodes[25-27].

CLINICAL MANIFESTATIONS OF SBP

The clinical manifestations of SBP are subtle and require a high index of suspicion (Table 1). Previously, there was often delay in diagnosis, which led to considerable mortality and morbidity[28].

SBP almost always occurs in large volume ascites, in patients with liver cirrhosis. Ascites of other causes or low volume rarely gives rise to SBP. Patients with cirrhosis usually have hypothermia; therefore, any temperature > 37.8℃ should be investigated, unless it is clearly caused by flu-like symptoms. The necessary investigations are full blood count (FBC), urinalysis, ascitic fluid cell count, and ascites, blood and urine culture. Fever caused by SBP is differentiated from that of alcoholic hepatitis, in which the ascitic fluid neutrophil count is normal[28]. Alterations in mental status may be subtle and only apparent to someone close to the patient. A connect-the-number test, e.g. Reitan trail test, is preferable to testing serum ammonia levels[29]. Abdominal pain can be continuous and is different from tense ascites. Tenderness is a common feature. Paralytic ileus, hypotension and hypothermia are seen in advanced illness, where prognosis may be dire. Thirteen percent of patients have no signs or symptoms[28]. A 'diagnostic tap' should be performed in all patients with ascites admitted to hospital. SBP in outpatients with cirrhotic ascites is less frequent, occurs in patients with less advanced liver disease, and may have a better outcome than its counterpart in hospitalized patients[30]. A retrospective review of 916 outpatient AF samples from the United States showed that abnormal AF appearance had a sensitivity of 98.1% [(95% confidence interval (CI): 95.3%-99.5%] and a specificity of 22.7% (95% CI: 19.4%-26.3%) in the detection of SBP[31]. For out- and inpatients, laboratory abnormalities such as leukocytosis, metabolic acidosis and azotemia, should prompt investigations for SBP, even in the absence of other clinical features.

Table 1 Symptoms and signs of ascitic fluid infection

Symptom or sign	Frequency (%)		
	SBP	Bacterascites	CNNA
Fever	68	57	50
Abdominal pain	49	32	72
Abdominal tenderness	39	32	44
Rebound	10	5	0
Altered mental status	54	50	61

TECHNIQUES AND LABORATORY DIAGNOSIS

The process of ascitic fluid analysis has come a long way. Inspections for color and transparency (as first evidence of infection) will probably always be carried out. Practice from this point forward, however, varies between regions and to a lesser extent, between hospitals. Over the last decade, it seems that a selective, possibly common-sense approach has started to prevail over the light-hearted dictum "send it (AF) for everything".

The diagnostic algorithm proposed by Runyon[28] (Figure 1) remains the most logical and cost-effective way to handle an abdominal paracentesis specimen, and we recommend that every gastrointestinal (GI) ward should have a laminated copy readily available in the doctors' office or protocol folder. Diagnostic paracentesis is now regarded as a safe procedure. Undoubtedly, there are complications inherent with the test, but the incidence rate of these is low[32-34]. The reported risks of diagnostic paracentesis include bleeding (hemoperitoneum or abdominal wall hematoma), visceral perforation, local infection at the site of paracentesis, or peritonitis. However, the most common complication is persistent leak. Post-procedural bleeding risk is very low, not only for diagnostic, but also for therapeutic taps[33-36]. Runyon has suggested that the practice of attempting to correct any coagulopathy prior to paracentesis is not cost-effective[28]. The use of trans-abdominal ultrasound (TUS) assists in a more accurate AF tap; therefore, it is an appealing alternative to the blind technique[37-39].

The majority of the inpatient diagnostic AF taps are performed with a blind technique. The accepted area of preference is away from the midline, at the point of maximal dullness, and ideally in the left iliac fossa, two fingerbreadths medial and two ventral to the anterior superior iliac spine ("Runyon's spot")[28]. We advise that after two dry taps, TUS should be used to mark the best insertion spot. Equipment required for the tap comprises: 10-mL syringe; 1.5-inch, 22-gauge metal (or 18-gauge) needle; pack of sterile gloves and a galipot

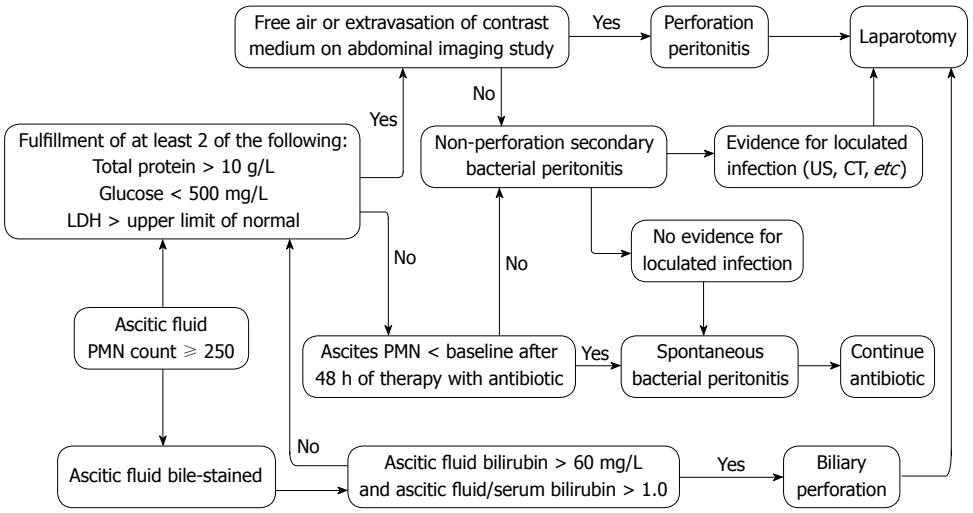

Figure 1 Algorithm for differentiating spontaneous from secondary bacterial peritonitis in patients with neutrocytic ascites (i.e. neutrophil count of 250 cells/mm^3 or greater) in the absence of hemorrhage into ascitic fluid, tuberculosis, peritoneal carcinomatosis, or pancreatitis. CT: Computed tomography; LDH: Lactate dehydrogenase; PMN: Polymorphonuclear neutrophil; US: Ultrasound (Reproduced with permission from Akriviadis EA, Runyon BA: The value of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. Gastroenterology 98: 127, 1990. Copyright 1990 by the American Gastroenterological Association).

with skin disinfectant[34,40]. Thirty milliliters of ascitic fluid should be aspirated and distributed between two blood culture bottles (aerobic and anaerobic, ideally 5-10 mL in each after replacement of the paracentesis green needle by a sterile one), a purple top tube and a brown top one for the necessary biochemistry.

The biochemical tests required for every ascitic fluid sample are for protein, albumin, glucose and lactate dehydrogenase, while other tests are graded between optional and unnecessary. Further expansion on AF biochemistry is beyond the scope of this review and the reader is advised to consult relevant textbooks/reviews[28]. Reference will only be made to AF tests used for the diagnosis of SBP.

A review of the laboratory diagnosis of SBP would not be complete without alluding to the most recent and practical change in protocol. Following aspiration of the AF sample, after inoculating the culture bottles and prior to splitting the rest of the sample into the purple- and brown-topped tubes, a small amount should be poured over a leukocyte esterase reagent strip (LERS) (any urine dipstick has the relevant reagent square), in order to detect any color change in the respective square. The colorimetric scale reference chart can be viewed on the side of the storage container. Results are obtained by direct optical comparison of the LERS with the scale, or, when available, by spectrophotometric analysis. Hepatologists, gastroenterologists and internists have developed an interest in this new addition (at least for AF analysis), especially as satisfactory sensitivity and specificity for SBP detection have been reported in small French and Spanish studies[41-43]. Further studies have been conducted worldwide[44-48]. However, initial enthusiasm and suggestions that LERSs may be used as the sole method of detection of AF infection have been tempered by the latest reports and two systematic reviews[49-51]. It appears that enthusiasm alone replaced structured, evidence-based approaches for LERSs in the presumptive diagnosis of SBP[50,51].

In rural, remote and smaller hospitals and in developing countries, LERSs shrink the 'tap-to-shot' time i.e. the time between paracentesis and first antibiotic dose, to only a few minutes. LERSs bear no resemblance to pH, lactate, lactoferrin or other difficult-to-measure infection indices. However, they are cheap and readily available. Moreover, no diagnosis is made in a clinical vacuum and in the right clinical context, the use of a single 'stat' dose prompted by a positive LERS can potentially lessen the burden of infection[51-53].

Eventually, the AF sample will find its way to the bench of a busy clinical laboratory. It is known that in SBP, the number of polymorphonuclear neutrophils (PMNs) in the ascitic fluid is ⩾ 250/mL[6,28]. Despite numerous publications emphasizing the contrary[13,28,54,55], many AF samples are prioritized inappropriately by clinical laboratories, giving rise to a significant delay in results. The manual count (performed by the traditional hematological method utilizing a microscope and Bucker chamber) is laborious and, in many instances, subjective. Angeloni *et al*[56] have produced clinical evidence that manual and automated PMN counting is equally efficient[57]. Cereto *et al*[58] have confirmed these results. Two years later, Link and colleagues (prompted by the statement of the International Ascites Club consensus document) examined the use of automated counters in detecting the total leucocyte count in ascitic fluid and diagnosing SBP[59]. It is surprising that such a crucial issue in expediting the diagnosis of SBP remained unaddressed for so long by many laboratories, which, despite the above evidence, continued to employ the old-fashioned manual technique over the automated one. At this point, it is necessary to highlight an important caveat when determining AF PMN count: an accurate PMN count may only be determined after non-traumatic paracentesis. If the tap is traumatic or the fluid is a priori hemorrhagic (red cells ⩾ 10 000/mL), the PMN count should be corrected as follows: subtract (from the measured PMN count) 1 PMN for every 250 red cells[7].

Opinion is still divided on the issue of automated *vs* manual testing, but utilization of culture bottles in SBP diagnosis is now the well-established gold standard. SBP is a low-colony-count, monomicrobial infection of the

AF and, in this context, is very similar to bacteremia. The use of blood culture bottles can increase the yield of AF culture from 40% to > 80%[7].

Although initially attractive[60], pH testing of the AF, has now fallen into obscurity[28,34]. This is partly attributable to limited clinical accessibility and partly to increased investigator interest in newer measurements, i.e. procalcitonin and lactoferrin[4,60]. pH was last used in a clinical study in 1995[34]. In their systematic review, Wong *et al*[34] have found that ascitic fluid pH $\leqslant$ 7.35 and blood-ascitic fluid odds ratio (OR) $\geqslant$ 0.10 had the highest diagnostic OR for SBP, and it may be reasonable to suggest a return to pH testing combined with LERSs as an appropriate means to diagnose SBP. The majority of urine dipsticks include a pH reagent square and the latest study on the subject has demonstrated that combination of LERSs with nitrite offers no additional benefit in SBP detection[48]. As far as we are aware, no study has investigated the combination of pH squares with LERSs. We can, however, envisage similar problems to those experienced by investigators in LERS studies occurring in this instance, namely, the lack of specificity of the reagents used for the usual pH values of AF (urine pH reference range is 6.75-7.5).

The use of procalcitonin should also be mentioned. Procalcitonin is the pro-hormone of calcitonin. It is synthesized in many different tissues of infected organs and has been hailed as a novel index of inflammation. Initial interest in its use in SBP[61] was eventually dampened by another study a year later[62]. Lactoferrin seems far more promising to serve as a rapid and reliable screening tool for SBP in patients with cirrhosis, and a recent study has suggested the need to develop an AF-specific dipstick[63].

SBP VARIANTS

Bacterascites (monomicrobial non-neutrocytic bacterascites) is the term used to describe the colonization of ascitic fluid by bacteria, in the absence of an inflammatory reaction in the bacterial fluid. By definition, the PMN count is < 250/mm^3 and bacterial culture is positive, while the patient may present with symptoms and signs of infection. The natural course of bacterascites, if untreated, is variable. Diagnosis of bacterascites can only be made 2-3 d after initial paracentesis (the time necessary for culture growth), and a repeat ascitic tap is recommended on day 3. If the second sample has a PMN count > 250/mm^3, the current recommendation is to treat as for SBP. If the PMN count is < 250/mm^3, but the second set of cultures is positive, treat again as for SBP. If the PMN count is < 250/mm^3 and the second set of cultures is negative, no further action is recommended[7,28].

Culture-negative neutrocytic ascites is the term used to describe the clinical situation in which the ascitic PMN count is > 250/mm^3 but fluid cultures fail to grow any bacteria. It is considered to represent the expected 20% failure rate of culture to isolate microorganisms, and it requires antibiotic treatment as if it were SBP. However, the term is now considered obsolete[28,55].

Table 2 Pathogens in ascitic fluid infection

Micro-organism	Frequency (%)	
	SBP	Bacterascites
Escherichia coli	37	27
Klebsiella pneumoniae	17	11
Pneumococci	12	9
Streptococcus viridans	9	2
Staphylococcus aureus	0	7
Miscellaneous gram-negative	10	14
Miscellaneous gram-positive	14	30

Table 3 Costs of antibiotics used for spontaneous bacterial peritonitis

Route of administration	Antibiotic	Costs (£)[1] 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[2] 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]£1 approximately €1.45 and US$2.00; [2]Amoxicillin-clavulanic acid.

MANAGEMENT

Appropriate antibiotic therapy should achieve resolution of infection in most cases of SBP[64]. However, the management of SBP is complex and not just a matter of empirical therapy. Important issues include: (1) identification of the underlying organism; (2) choice of safe and appropriate antibiotics; (3) preservation of renal function and treatment of renal dysfunction; (4) duration of antibiotic therapy; and (5) subsequent antibiotic prophylaxis.

Whilst clarifying the diagnosis of SBP with paracentesis, an attempt should be made at identification of the underlying organism with inoculation of ascitic fluid into blood culture bottles. This vastly improves the identification of the responsible organism and, therefore, allows improved treatment of atypical or resistant organisms. Inoculation into blood culture bottles improves diagnostic yield from 40% to around 80%[65]. Simultaneous blood cultures should be taken as 50% of cases of SBP are associated with bacteremia[66].

The common causative organisms of SBP are Gram-negative bacteria such as Escherichia coli and other coliforms such as Klebsiella spp. These account for at

least 50% of cases. Other causative organisms include pneumococci, streptococci and miscellaneous Gram-positive and -negative organisms[28,55,65,66] (Table 2).

Empirical therapy should not be delayed (beyond the first few minutes needed for LERS reading) while awaiting identification of the exact organism. Third generation cephalosporins are the antibiotic of choice as they have a number of advantages: (1) relatively safe and well tolerated; (2) broad spectrum activity; and (3) effectiveness, with many studies confirming high levels of SBP resolution.

Cefotaxime 2 g every 12 h is often used intravenously for at least 5 d[67-69]. A 5-d course of treatment has been shown to be equally effective as 10 d[70]. Other third generation cephalosporins (e.g. ceftriaxone) are felt to be equally effective[3,71-73]. Alternative antibiotic regimens include amoxycillin/clavulanic acid, fluoroquinolones or piperacillin/tazobactam[74-77] (Table 3). Regional resistance patterns should be accounted for with early communication with a microbiologist if necessary[11,77]. According to the International Ascites Club, it is important to perform a second tap 48 h after the start of therapy. If there is a less than a 25% drop in PMN count from baseline, a change of antibiotic should be considered[4,5].

Renal function

One third of patients with SBP will develop renal failure. The renal dysfunction is thought to occur as a result of a reduced effective circulating volume[7,78]. Renal dysfunction has been shown to be an independent predictor of mortality in patients with SBP[79]. Therefore, close attention to renal function and the avoidance of nephrotoxic medication is paramount. On the other hand, diuretic therapy and large-volume paracentesis should not be necessarily withheld (they potentially exacerbate the reduction in effective circulating volume and contribute to renal deterioration) if albumin is administered[80,81]. The benefit of human albumin solution for treating renal dysfunction has been studied in randomized controlled trials[82,83]. Albumin is thought to reduce the risk of renal impairment by improving effective intravascular volume and by helping to bind pro-inflammatory molecules[7,8,11]. Studies have shown an improvement in short-term survival and a reduction in renal impairment in patients with SBP treated with albumin. Although these studies have been subject to criticism[84,85], most authors agree that infusion of 1.5 g/kg on day 1 and 1 g/kg on day 3 is beneficial in patients that have developed, or are developing renal dysfunction[7,61]. Patients with normal renal function are unlikely to benefit from albumin therapy.

PROPHYLAXIS

Unfortunately, the long-term prognosis of patients with cirrhosis who have had a prior episode of SBP is poor. Mortality rates of 50%-70% have been reported at 1 year follow-up[7,11]. This is largely a result of the advanced stage of liver cirrhosis in these patients, along with the associated complications[86]. The recurrence rate of SBP following a first episode is up to 70% at 1 year[7,86]. Given the high recurrence rate, it seems sensible to recommend prophylaxis to this group of patients and referral for transplant assessment. This therapy is backed up by evidence showing a reduction in recurrence of SBP from 68% to 20% in one study[87].

Norfloxacin 400 mg/d or ciprofloxacin 500 mg/d orally appear to be the most studied and commonly recommended regimes[87-92]. Levofloxacin or antibiotic cycling may be used as an alternative[93-95]. There is debate over the use of antibiotics as primary prophylaxis against SBP. Some studies have shown reduced rates of SBP in selected patients deemed at high risk of developing SBP (those with low ascitic total protein)[79,91,96]. However, there are various criticisms of these studies, and at present, primary prophylaxis is not recommended. Further studies may help clarify this issue.

The last group of patients that are felt to benefit from antibiotic prophylaxis are those with known cirrhosis admitted with GI bleeding. Infection rates are high in this group regardless of whether they have ascites. The infection rates are also higher than those in patient with cirrhosis admitted for other reasons[61]. Several studies have shown a clear benefit from initiating antibiotic prophylaxis in this group[97-100]. Reductions in infection rate and mortality have been noted. Once again, the choice of antibiotic should be broad spectrum and guided by local policy; either oral norfloxacin or ciprofloxacin have been suggested[7,61].

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