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Update Review Article: Spontaneous Bacterial Peritonitis

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ABSTRACT

Spontaneous bacterial peritonitis (SBP) is a frequent and severe complication in cirrhotic patients with ascites. To describe spontaneous bacterial peritonitis (SBP) in the context of currently accepted criteria for diagnosis, treatment and prevention. A review of SBP and its associated etiopathogenic factors is presented. Numerous studies on mechanisms of disease, bacteriology, epidemiology, diagnostic markers, and current guidelines for its diagnosis, treatment and prevention are discussed. Peritonitis in patients with ascites in the absence of secondary causes, such as perforation of a viscus, occurs primarily in patients with end-stage liver disease. Enteric organisms, mainly gram-negative bacilli, probably translocate to regional lymph nodes to produce bacteremia and seeding of ascitic fluid. Signs and symptoms of peritonitis are usually subtle. The ascitic fluid polymorphonuclear leukocyte count is the best determinant for early diagnosis and treatment of SBP. Third-generation cephalosporins such as cefotaxime are considered the drugs of choice for treatment, whereas quinolones such as norfloxacin are used to decrease recurrence. Despite increased awareness, early diagnosis, and prompt and effective antimicrobial therapy, SBP recurs frequently and is associated with a high mortality rate. Patients with SBP should be assessed for candidacy for liver transplantation.

Keyword: Spontaneous bacterial peritonitis, Bacteriology, Epidemiology, Diagnostic markers, Cephalosporins

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INTRODUCTION

Bacterial infections are a well-known cause of morbidity and mortality in cirrhotic patients, being a leading aetiology of progression in liver failure[1]. Subjects suffering from liver cirrhosis can be considered as immunocompromised[2] and as such, are more prone to infections, whose incidence and severity is greater than in non-cirrhotic individuals. Spontaneous bacterial peritonitis (SBP) and urinary tract infections are the most frequent infections in this setting[3]. Advanced liver disease is a concern in developed countries, representing the 14th most frequent cause of death globally and even the fourth in regions such central Europe[4]. One of the most important reasons of hepatic decompensation in cirrhotic patients is bacterial infections, which currently are deemed as a distinct prognostic stage of liver disease, worsening the outcome regardless of illness severity[5].Unfortunately; in cirrhotic patients the diagnosis of bacterial infections is often very difficult. At any rate, they are the main inciting factor of the so-called acute-on-chronic liver failure, a clinical entity associated with organ failures and notable short-term mortality[6]. Spontaneous Bacterial Peritonitis had been reported earlier, SBP was first defined by Dr. Harold O. Connen in 1964 that identified it as an infection of the peritoneal fluid with no obvious source within the abdomen that is liable to surgical treatment[7-9]. SPB is diagnosed when a culture is positive for ascites and there is a high count of polymorphonuclear leukocytes (PMN). SBP is one of the most frequent and life-threatening complications of patients with cirrhosis. Mortality rates have stayed constant in spite of the development of new antibiotic treatments and early diagnosis of SBP infection[10]. In their study, Singh and colleagues described the mortality rate of SBP in two different cohorts over a ten-year period and did not find any difference between the cohorts[11]. The in-hospital mortality rate can reach 30% in spite of infection control measures; mortality being generally due to complications such as acute variceal bleeding, development of thehepato-renal syndrome, or progressive liver failure[10,12-16]. The incidence of SBP has been estimated in 10% to 30% of unselected patients admitted to hospital[10,11,13,15-17] Nevertheless, recent studies tend to demonstrate that SBP incidence seems to be decreasing[12]. A recent multicenter study carried out in 70 different centers observed an incidence of SPB of 5.5%[18]. We studied prospectively 200 samples of ascitic fluid of 106 cirrhotic patients and detected SBP in 11% of the studied population in both inpatient and outpatient settings. In asymptomatic outpatients that were submitted to therapeutic paracenteses the incidence of SBP seems to be lower and is estimated at 0.57% to 3.5%[19,20].The outcome of SBP in this group of patient has been demonstrated to be better than in hospitalized cirrhotic patients. The probability of development of the first episode of SBP over a one-year

period in patients with end-stage-liver disease and ascites is around 10%.The mainstay of SBP physiopathology seems to be the association of bacterial translocation with the decrease in host immune system defenses. It has been demonstrated, firstly in animal models with ascites and later in cirrhotic patients, that passage of intestinal bacteria from the gut to extra intestinal sites could be increased[21, 22]. Studies using oral nonabsorbable antibiotics reinforce the hypothesis that exist a causal relationship between bacterial translocation and the occurrence of SBP. The use of these antibiotics decreases the development of SBP and other spontaneous infections in cirrhotic patients[23-25].The disturbance in small intestinal motility and the presence of hypochlorydria has been demonstrated to occur in cirrhotic patients and seems to be responsible for the bacterial overgrowth commonly observed in these patients[26]. The actual role of intestinal overgrowth in the pathogenesis of SBP has not yet been settled. Chang and colleagues demonstrated that the prevalence of bacterial overgrowth was higher in patients with a history of SBP associated to disturbances in small intestinal motility[27]. On the other hand, Bauer and colleagues[26] were not able to confirm this hypothesis in their investigation. These bacteria are translocated through the intestinal wall, which has its permeability altered by the portal hypertension; in consequence they reach the mesenteric lymphnodes. After that, they move to the systemic circulation until they contact the ascitic fluid. Other sites than gut have been demonstrated to originate bacteria seeding. These could be represented by pneumococcal sepsis, cellulites, urinary tract and dental infections[19, 27]. Once the bacteria reach the ascitic fluid, the host immune defense is responsible for the occurrence or not of SBP. The macrophages are the first line of defense of the peritoneal cavity and the impairment in phagocytic activity of reticulendothelial system (RES) can cause a prolonged bacteremia. The liver is the largest organ of the RES and this dysfunction evidently imposes infectious risks. The next step of immune system defense is the activation of complement with further release of cytokines. The polymorphonuclear neutrophilic leukocytes (PMNs) try to destroy the bacteria by entering in the peritoneal cavity. The dysfunction of PMNs and the low levels of complement, both by decreasing in liver production associated to increased consumption as an acute phase response, are commonly observed in cirrhosis and seem to contribute to the conversion of ascitic fluid colonization into SBP[28-30]. For such reasons cirrhosis is considered one of the most common current forms of acquired immune deficiency. More recently, Christou and colleagues[31] indicated bacteremia/sepsis, respiratory and urinary tract infection, meningitis, endocarditis, phlegmonous colitis and hepatic abscess as other common specific infectious complications beyond SBP, in hepatic cirrhosis. Ascites is thought to arise as a result of the marked circulatory and renal abnormalities that are associated with cirrhosis[32-34] and patients who develop this complication have a 2-year survival of approximately 50%[35]. The physiological changes leading to its formation have been encompassed in the peripheral vasodilatation hypothesis of Schrier et al[36]. This proposes that initial arterial vasodilatation leads to a reduced effective arterial blood volume and subsequent activation of mediators promoting sodium and water retention[37].These include the rennin-angiotensin-aldosterone system, the sympathetic nervous system and anti-diuretic hormone. In addition, the renal circulation appears particularly sensitive to angiotensin-II-mediated vasoconstriction[38] which may lead to reduced renal perfusion and glomerular altration rate. Thus patients with cirrhosis and ascites exhibit a precarious haemodynamic imbalance. If they are exposed to an additional insult, such as a gastrointestinal bleed, nephrotoxic drugs (e.g. NSAIDs, diuretics, aminoglycosides) or systemic infection, they are at risk of developing renal impairment and the hepatorenal syndrome. The aim of this systematic review is to provide a comprehensive overview of the microbiological features risk factors, ascitic fluid interpretation, pathogenesis, treatment, prophylaxis and evolving perspectives related to SBP.

PATHOGENESIS

Initially the term spontaneous was used because the cause of the infection was not clearly identifiable. Over time it has been partially clarified. Many factors contribute to the pathogenesis of SBP. One of them is bacterial translocation that consists of passage of bacteria from the intestinal lumen to mesenteric lymph nodes. This process is favored by three main factors: bacterial overgrowth, alteration of the intestinal mucosal and impaired local and systemic immunity. Bacterial overgrowth itself is favored by the impaired motility of the small intestine and functional changes in the intestinal mucosa are explained by increased permeability. The low concentration of hydrochloric acid produced by the use of proton pump inhibitors (PPIs) in cirrhotic patients is another factor. Some studies have found that patients who have cirrhosis and who are using PPIs have three times the risk of cirrhotic patients who do not use PPIs of developing SBP. Studies have shown that bacterial translocation increases in cirrhotic patients because of reduced local immunity that prevents bacterial clearance so that the bacteria is able to infect the mesenteric lymph nodes from where they can circulate systemically causing bacteremia. More frequent and longer lasting bacteremia occurs in cirrhotic patients because of their immunosuppressed states which are principally due to hypoalbuminemia and because of portosystemic shunts with alter the functioning of the mononuclear phagocyte system[39].

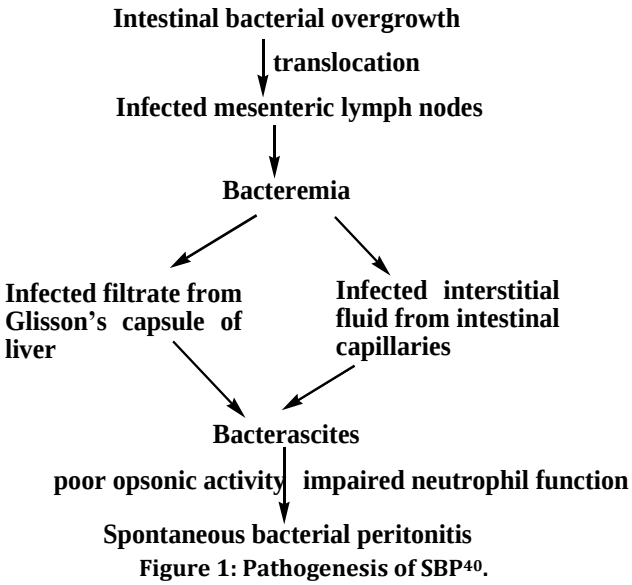

Figure 1: Pathogenesis of SBP[40].

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 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 are the major cause of SBP. 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%) [41] and Kerr et al. (72%) [42] 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 [43]. 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[44] from data gathered between 2000 and 2006. Gram-positive cocci have generally accounted for less than 25% of cases of SBP. Infections with Gram-positive cocci including pneumonia and urinary tract infections have markedly increased in patients with cirrhosis in recent years and have been linked to therapeutic intervention and chronic antibiotic usage. The increasing trend of Gram-positive cocci-related SBP has also been demonstrated and represents a changing paradigm in the known bacteriology of SBP. Notably, 229 Gram-positive cocci were identified on ascitic fluid culture compared to 151 Gram-negative bacilli 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 Gram-positive cocci 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, Gram-negative bacilli 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 Gram-positive cocci [Staphylococcus aureus (n=1), Streptococcus viridans (n=3) and Staphylococcus saccharolyticus (n=1). The emergence of extended spectrum b-lactamaseproducing (ESbL) Gram-negative bacilli, methicillin-resistant Staphylococcus aureus (MRSA), flouroquinolone-resistant (QR) Gram-negative bacilli, 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 for more than 1 month, and MRSA was the most common isolate (77%). Extended spectrum b-lactamase-producing (ESbL) Gram-negative bacilli (E. coli and Klebsiella) were the most common multi-drug resistant bacteria (73%), especially among nosocomial infections, followed by fluoroquinolone resistant Gram-negative bacilli in patients who were receiving norfloxacin 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*[45].

EPIDEMEOLOGY

SBP can occur in adults and children. In children, it most commonly occurs in neonates and those around five years of age. It is most common in patients with cirrhosis, though it can occur as a complication of any disease that results in accumulation of ascitic fluid, such as liver disease, Budd-Chiari syndrome, congestive heart failure, systemic lupus erythematosus, renal failure, or cancers, and has a poor prognosis. Approximately 10% to 25% of patients with ascites will develop SBP, and the condition is associated with a 20% in-hospital rate of mortality. Patients with a prior incidence of SBP are more likely to encounter a subsequent infection with a drug-resistant organism. Additionally, the risk of developing SBP increases with age, use of proton-pump inhibitors (PPIs), and when undergoing SBP prophylaxis such as selective intestinal decontamination[46].

DIAGNOSTIC MARKERS OF SBP

The gold standard for a diagnosis of SBP is the PMN count in the ascetic fluid, but paracentesis is not always possible. Laboratory markers are useful for early diagnosis of SBP and early prediction of the response to initial treatment because a lack of response is a predictor of SBP mortality. TNF-α and interleukin-6 are significantly higher in the ascitic fluid of patients with SBP than in those with sterile ascites and increases of those proinflammatory cytokines have been associated with renal impairment complicated by SBP and with mortality. The lactoferrin concentration is also higher in patients with SBP than in those with sterile ascites and the lactoferrin level in ascitic fluid has shown high sensitivity and specificity for the diagnosis of SBP. The optimal timing of lactoferrin assays is not yet clear and diagnostic assay kits are not commercially available Procalcitonin, a prohormone of calcitonin synthesized in the C cells of the thyroid gland, is an acute-phase reactant protein that has been studied in patients with SBP. Seven studies assayed serum procalcitonin; three assayed procalcitonin in ascitic fluid. Serum procalcitonin was significantly higher in SBP than in sterile ascites in six of the seven which supports use of serum procalcitonin as an SBP marker. In a review by Yang et al[47] of the available data from 339 patients with LC accompanied by SBP, it was concluded that serum procalcitonin was a relatively sensitive and specific marker for the diagnosis of SBP. It has been reported that serum procalcitonin was significantly higher in cirrhotic patients with culture-positive SBP than in those with CNNA. Two of the three evaluations of procalcitonin in ascitic fluid found no significant differences in procalcitonin levels in patients with SBP and those with sterile ascites. The usefulness of ascitic fluid procalcitonin to distinguish between SBP and sterile ascites has not been demonstrated. Calprotectin is a calcium- and zinc-binding protein with antimicrobial and antiproliferative functions. It is almost exclusively expressed in neutrophils and its level in body fluids is proportional to the influx of neutrophils. Burri et al[48] reported that ascitic fluid calprotectin level was correlated with the PMN count and that it reliably predicted a count of ≥ 250 cells/mm3, which is the standard for a diagnosis of SBP. Subsequent studies found that ascites calprotectin is significantly higher in cirrhotic patients with SBP than in those without SBP. Lutz et al[49] have shown that the ratio of calprotectin to total protein in ascitic fluid was a better diagnostic marker of SBP than calprotectin alone and that a high ratio was independently associated with 30-d mortality Leukocyte esterase activity, which can be assayed with commercially available reagent strips, may have diagnostic value.

Castellote et al[50] reported that the use of reagent strips is a rapid and inexpensive tool for the diagnosis of ascitic fluid infection and it had a high negative predictive value (99%), indicating that a negative result may be useful as screening to exclude SBP. Oey et al[51] reviewed 23 studies of leukocyte esterase in patients with SBP published between 2002 and 2015 and concluded that it had poor sensitivity and positive predictive value for the diagnosis of SBP. They found that the sensitivity of the reagent strips for diagnosing SBP was variable, and a negative test result strongly suggested the absence of SBP. In another review of 26 studies published from 2002 to 2010, Koulaouzidis[52] confirmed the poor sensitivity and poor positive predictive value of leukocyte esterase activity as well as the high 93%-100% negative predictive value. A negative test result may thus indicate a high probability of the absence of SBP. There is evidence for the diagnostic value of other markers including monocyte chemotactic protein-1 in serum and ascitic fluid, lipopolysaccharide-binding protein in serum and ascitic fluid, macrophage inflammatory protein type-1 beta in ascitic fluid, interferon-γ-induced protein-10 in serum and ascitic fluid, triggering receptor expressed on myeloid cells-1 in ascitic fluid, high-sensitivity CRP in serum and ascitic fluid and neutrophil gelatinase-associated lipocalin in ascitic fluid. Further study is needed to validate the diagnostic usefulness of these candidate markers[53].

The possible serum or ascitic fluid markers of spontaneous bacterial peritonitis reported in previous studies[54]. Are as follows: **Serum-** Tumor necrosis factor-α, Interleukin-6, Procalcitonin, Interferon-induced protein 10 kDa, High-sensitivity CRP, **Ascitic fluid-**Tumor necrosis factor-α, Interleukin-6, Lactoferrin, Calprotectin, Leukocyte esterase reagent strips, Macrophage inflammatory protein type 1 β, Interferon-γ-induced protein 10 kDa, Triggering receptor expressed on myeloid cells 1, High-sensitivity CRP.

HISTORY AND PHYSICAL

One should have a high index of suspicion for SBP in all patients presenting with ascites, and this is especially true if the patient has an acute history of clinical deterioration. The majority of patients with SBP will present with fever, chills, nausea, vomiting and abdominal pain, although some patients may be asymptomatic and SBP is an incidental finding. Fever is the most common symptom encountered in patients with SBP, which is a particularly useful clinical symptom as patients with cirrhosis are typically hypothermic. Additional signs and symptoms include diarrhea, paralytic ileus, new-onset or worsening encephalopathy (e.g., altered mental status) without any other identifiable cause, new-onset or worsening renal failure, or presence of ascites that does not improve with use of diuretic medications. On physical examination, most patients will have a tender abdomen, although patient response can vary from mild discomfort to the presence of guarding and rebound tenderness. In cases of acute or chronic liver failure SBP is one of the main triggers for hepatic encephalopathy, and where there is no other clear causal indication for this, SBP may be suspected. These symptoms can also be the same for a spontaneous fungal peritonitis (SFP) and therefore make a differentiation difficult. Delay of diagnosis can delay antifungal treatment and lead to a higher mortality rate[54-56].

DIAGNOSIS OF SBP

Diagnostic paracentesis

Paracentesis is extremely important, as the PMN count in the ascitic fluid plays an essential role in obtaining a diagnosis of SBP. Diagnostic paracentesis should be performed in all patients who present with

(1) Compatible signs or symptoms.

(2) Impairment of the hepatic or renal function

(3) Unexplained hepatic encephalopathy

(4) Gastrointestinal bleeding.

Although all cirrhotic patients with ascites are at risk of SBP, the prevalence of SBP among hospitalized patients (10%) is higher than that observed in outpatients (1.5–3.5%). It is therefore recommended that diagnostic paracentesis be performed in all cirrhotic patients with ascites who require hospital admission, regardless of whether they exhibit clinical symptom(s) of SBP.

Ascitic fluid cell analysis

Despite the use of a sensitive method ascites cultures often show negative results, even in patients with an increased ascitic PMN count and clinical symptoms suggestive of SBP. Therefore, the diagnosis of SBP is confirmed based on a PMN count in the ascites of >250 cells/mm^3 in the absence of an intra-abdominal and surgically treatable source of infection. The cutoff value of 250 PMN cells/mm^3 has the greatest sensitivity, whereas 500 PMN cells/mm^3 exhibits the greatest specificity. However, the most sensitive cutoff value should be used for diagnosis, as it is important not to miss cases of SBP. Physicians should subtract one PMN for every 250 red blood cells in patients with hemorrhagic ascites with a fluid red blood cell count of >10,000/mm^3 (due to the effects of concomitant malignancy or traumatic tap) in order to adjust for the presence of blood in the ascites. The PMN count in the ascitic fluid may be determined according to a hematological method using either a light microscope and manual counting chamber or an automated cell counter. The ascitic fluid is centrifuged in order to manual count the number of ascitic cells, after which a smear of the collected cells is stained with Giemsa and the total and differential cell counts are determined using a light microscope. The microscopic cell counting method requires several hours and carries a risk at inter- and/or intra observer discrepancy. On the other hand, automated cell counters provide reproducible results within a few minutes; however, coulter counter findings of the neutrophil count have been shown to be inaccurate for relatively low levels of neutrophils in the ascitic fluid. Therefore, the manual PMN counting method is conventionally preferred. However, a recent study demonstrated that automated cell counts have sufficient sensitivity for diagnosing SBP, thus suggesting that this simple method may be used in place of traditional manual counting.

Ascitic fluid culture

Conventional bacterial culture methods, such as laboratory analyses of fluid collected in syringes or tubes, effectively detect bacteria in less than 50% of ascites samples with an elevated PMN count (>250/mm^3). Therefore, it is recommended to inoculate the ascitic fluid into blood culture bottles at the patient's bedside in order to increase the sensitivity of the bacterial culture. The culture-positive rate of SBP ascites is approximately 80%, namely, between 72% and 90% of cases assessed using the culture-bottle method. However, several recent studies have reported lower culture-positive rates for SBP ascites, ranging from approximately 40% to 60%. In addition, even with the sensitive culture-bottle method, positive results for ascitic cultures are estimated to be approximately 40–70%, according to various recent guidelines[57-60]. Since patients

with an increased PMN count in the ascitic fluid (>250 cells/mm^3) and negative cultures exhibit a clinical presentation similar to that of bacteriologically confirmed SBP, these patients are categorized as having culture negative SBP and should be treated in the same manner as those with culture-positive SBP.

DIFFERENTIATION FROM SECONDARY BACTERIAL PERITONITIS

Differentiating SBP from secondary peritonitis due to perforation or inflammation of intra-abdominal organs is clinically very important. Secondary bacterial peritonitis should be suspected in patients with relevant abdominal signs or symptoms, multiple organisms in ascitic cultures and a very high PMN count and/or high protein concentration in the ascites, as well as those who display an inadequate response to therapy. However, accurately diagnosing secondary peritonitis based on these criteria generally takes a long time and patients with perforated secondary peritonitis require surgical treatment in a timely fashion. Therefore, performing abdominal CT to detect perforation is recommended in patients with suspected secondary bacterial peritonitis. Various parameters available at the time of paracentesis have been proposed to assist in rapidly detecting secondary peritonitis. Parameters in the ascitic fluid in patients with secondary peritonitis, as proposed by Runyon and Hoefs[61], are as follows:

(1) An elevated PMN count in the ascitic fluid (>250/mm^3: usually many thousands)

(2) at least two of the following: a total protein level of >1 g/dL, a serum lactate dehydrogenase level above the upper limit of normal and a glucose level of 240 U/l and carcinoembryonic antigen level of >5 ng/mL in the ascitic fluid have been reported to exhibit good diagnostic performance for detecting gut perforation into the ascitic fluid with a sensitivity of 92% and specificity of 88%. However, it is not easy to differentiate SBP from secondary peritonitis based only on biochemical parameters of ascitic samples, and abdominal CT is essential in the clinical setting[72].

POTENTIAL DIAGNOSTIC METHODS FOR SBP

Leukocyte esterase reagent strips (LERS)

It takes several hours to obtain the results of an ascitic fluid cell count. Therefore, the use of leukocyte reagent strips has been proposed as a fast and inexpensive method for diagnosing SBP. These reagent strips, which were originally developed to diagnose urinary tract infections, detect leukocytes based on their esterase activity according to a colorimetric method. However, a large, multicenter prospective study recently showed that the Multistix 8 SG has a low level of diagnostic accuracy for diagnosing SBP, with a high false-negative rate (55%). In addition, a systemic review of 19 studies of several strips (including Multistix, Aution, Combur, Nephur, and UriScan) demonstrated that these LERS have both low sensitivity and a high risk of false-negative results [62]. According to a recent review of 26 studies regarding the validity of LERS for SBP diagnosis[63], LERS display low sensitivity for diagnosing SBP, with significant interstudy variability among brands of LERS. However, LERS have consistently shown high negative predictive value (>95% in the majority of studies) and may therefore be used as a preliminary screening tool to diagnose SBP. However, the utility of LERS for diagnosing SBP has not been confirmed. Most of the above strips were developed for use in urine with a threshold of >50 PMN cells/mm^3 ; however, the diagnostic performance of a reagent strip test calibrated for ascitic fluid with a cutoff of 250 PMN cells/mm^3 has recently been reported [64]. That study showed excellent results, with a sensitivity of 100% and a negative predictive value of 100%. Although these conclusions have yet to be confirmed in large multicenter trials, this method may provide a new and useful diagnostic tool for detecting SBP[72].

Measurement of leukocyte-derived proteins

The levels of proteins, such as granulocyte elastase and lactoferrin , released by activated PMNs are elevated in patients with SBP. Lactoferrin shows notable sensitivity (95.5%) and specificity (97%) for diagnosing SBP, with a cutoff value of 242 ng/ml. Nevertheless, the diagnostic performance of this parameter must be further evaluated in other studies with a larger number of patients due to the small number of SBP cases in that study. In addition to the proteins described above, the levels of several inflammatory cytokines and chemokines in the ascitic fluid are reported to be associated with the severity of SBP. However, these potential diagnostic biomarkers are generated by host reactions against inflammatory stimulation and fail to provide any direct evidence of bacterial infection in SBP ascites[72].

Detection of bacterial DNA using polymerase chain reaction (PCR)

Bacterial cultures require several days to obtain results. Hence, bacterial DNA detection and sequencing is increasingly being used to diagnose various infectious diseases. Some PCR-based methods for detecting bacterial DNA have also been applied to the microbiological diagnosis of SBP. However, these methods have received several major criticisms regarding the detection of bacterial DNA. First, most previous studies enrolled a limited number of patients and a recent report including a large number of patients showed poor results for diagnosis. Furthermore, previous studies have revealed serious concerns regarding contamination of bacterial DNA in the PCR system. Commercially available Taq-polymerases may be contaminated with bacterial DNA[65,66]. Moreover, the reagents used for DNA extraction procedures carry a risk of exposing the clinical samples to exogenous bacterial DNA[67,68]. Although PCR is a very sensitive method for detecting DNA, PCR-based methods display discrepant and controversial findings with respect to diagnostic performance in detecting the causative pathogen(s) in SBP patients with ascites, perhaps, or at least in part, due to the problems described above. Therefore, no definitive PCR based method for providing an accurate diagnosis of SBP has been established[72].

Bacterial DNA in SBP ascites using in situ hybridization

A new strategy using an ISH method for detecting the genomic DNA of bacteria phagocytized in neutrophils and macrophages was recently developed to identify causal bacteria in cases of sepsis[69-71]. The utility of this ISH method for detecting bacterial genomic DNA phagocytized in the leukocytes of patients with sepsis has been demonstrated, providing evidence for the presence of bacterial infection in such cases. Notably, the ISH method is almost four times more sensitive than blood cultures in detecting the causal bacteria of sepsis[70]. In addition, the results of ISH tests can be acquired within one day, whereas it takes several days, at least, to obtain the results of cultures. Based on the rapid and sensitive detection of bacterial DNA provided by the ISH method, we investigated whether this method can be used to obtain direct evidence of bacterial infection in SBP patients with ascites. In addition to the low amount of bacteria present in the ascitic fluid of SBP patients, phagocytosis and

the digestion of bacteria by leukocytes may reduce the amount of proliferative, suspended bacteria in the ascitic fluid, thus making it difficult to identify the pathogen using standard methods. Phagocytosis is thought be responsible for the low rate of detectable causative bacteria. Therefore, we attempted to detect ingested bacterial DNA using the ISH method. Since all bacteria have the 23S ribosomal RNA gene, a novel cDNA probe for this gene was generated to detect the genomic DNA of the causative bacteria[72].

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 admis-sion, now a standard of care in all patients with cir-rhosis 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 hun-dred 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 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 asci-tes.[84] Farnesoid X is a cellular protein and nuclear recep-tor and its polymorphisms have also been associated with risk of SBP in cirrhotic patients with ascites.

PHARMACOLOGICAL RISK FACTORS

Acid suppressive therapy

Proton pumps 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 sig-nificant 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 sur-mounting 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. 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. 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.

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. A 5-day course of antibiotics is adequate to effectively treat patients with SBP who undergo liver transplantation in the acute period. 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[45].

TREATMENT

Intravenous antibiotics

If suspicion for SBP arises 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. Cefotaxime covers most culprit pathogens, has excellent ascitic fluid penetration and achieves sterilisation in 94% of cases after initial antibiotic dosing. 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. 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[73]. 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. Alternative intravenous antibiotic regimens for SBP include amoxicillin–clavulanic acid, which has comparable results to cefotaxime, ampicillin and gentamicin, 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 and although considered inferior to cefotaxime, ceftriaxone is effective therapy particularly at doses of 2 g/day for 5 days. Aminoglycosides cause renal impairment in 5% of patients and should be avoided in patients with cirrhosis who have considerable risk for renal injury. Fluoroquinolones have comparable ascitic fluid penetration to cephalosporins. Levofloxacin has shown similar efficacy compared to (cefotaxime and cefepime) at providing E. coli coverage [71% vs. (82%)] and coagulasenegative Staphylococcus coverage [90% vs. (44%)] in patients with SBP not receiving fluoroquinolone prophylaxis. In patients with penicillin allergy who are not receiving long-term fluoroquinolone therapy, levofloxacin is a reasonable and safe alternative treatment for SBP[45].

Oral antibiotics

Oral fluoroquinolones are generally acceptable for uncomplicated SBP. Fluoroquinolones have excellent oral bioavailability ranging from 70% for ciprofloxacin to 95% for levofloxacin. In a randomised controlled trial, oral ofloxacin and IV cefotaxime resolved SBP at the same rate (84% vs. 85%) respectively[74].

Switch therapy

In a randomised study in 2000 Terg et al[75] showed that patients with SBP can be adequately treated with oral ciprofloxacin after a short course of IV ciprofloxacin. Switch therapy with oral ciprofloxacin was as effective as IV ciprofloxacin at infection resolution in a randomised study involving patients with SBP and was more cost effective.

Antibiotics for multi-resistant bacteria

Emergence of antibiotic resistance and changing profile to SBP-causing-bacteria has made standard treatment less reliable in some instances. In fact, 8–22% of Enterobacteriaceae have cephalosporin resistance. 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[76].

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. Hypoalbuminemia has myriad causes and is associated with increased morbidity and mortality regardless of aetiology. 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). 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 have clearly shown benefit. Patients with chronic kidney disease with or without dialysis dependency that develops SBP should receive albumin therapy[77,78].

PREVENTION

Primary prophylaxis

Norfloxacin

Spontaneous bacterial peritonitis native 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 and to reduce risk of SBP as well as extraperitoneal infections. Norfloxacin has been the most widely studied antibiotic for SBP prevention in a variety of settings including gastrointestinal bleeding, primary SBP prophylaxis and secondary SBP prophylaxis and remains the first-line choice for selective intestinal decontamination.

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 (≤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%. 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) [45].

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 at 90-day follow-up[79].

Rifaximin

There is limited and inconsistent data for rifaximin a non-absorbable antibiotic with broad-spectrum coverage, in primary or secondary SBP prophylaxis[80].

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.

Ciprofloxacin

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

Trimethoprim–sulfamethoxazole

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

SUPPORTIVE THERAPY

Diet

Patients with advanced cirrhosis have continued protein catabolism, also referred to as hypermetabolism and the majority suffer from malnutrition. 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. 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 and generally should consume 4–6 small frequent meals throughout the day including a bedtime carbohydrate-rich snack[45].

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 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 and Lactobacillus combined with antioxidants (vitamin C and glutamate) have been shown to decrease endotoxemia compared to water lavage in rats with induced cirrhosis. 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. 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 followup. 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[45].

FUTURE PERSPECTIVES

Host response-based serum biomarkers such as procalcitonin (PCT) and c-reactive protein are the most frequently used serum markers for the early detection (as well as to test the severity) of bacterial infection, to complement direct pathogen detection. Unfortunately, their sensitivity and specificity in cirrhotic patients is impaired by a wide array of factors, among them the stimulus represented by the bacterial translocation through the gut, which, irrespective of real infection, stands out. Recently, new markers have been proposed for the early diagnosis of peritonitis, including lactoferrin, expression of CD64 on neutrophils (CD64 index), serum PCT and ascitic calprotectin. Lactoferrin may be useful to diagnose SBP in ESLD patients; the limit of this method is that elevated ascitic fluid lactoferrin level may also be related to hepatocellular carcinoma in ESLD patients without SBP. Another potential marker of SBP in cirrhotic patients is the CD64 index and this could be used as a more effective marker of PMN counts to modulate antimicrobial therapy.The aforementioned PCT is a valid test to diagnose SBP but as shown by a recent meta-analysis, it cannot serve as a standalone examination and needs further clinical or laboratory findings. Ascitic calprotectin is an accurate marker for SP especially when it is combined with serum procalcitonin and the combined use of these two markers is very promising. Notwithstanding, these tools present an important limitation: they do not permit the etiological diagnosis of SP. On the other hand, methods able to detect a few bacteria per milliliter might potentially serve as a game-changer in the microbiological field: for instance, label-free bimodal waveguide immunosensor demonstrates this property and in the future could possibly become a very user-friendly tool for clinical microbiologists. Meanwhile, the objective of rapid diagnostic platforms is to provide a (near) point-of-care system to yield microbiological results within 1–2 hours: potential pitfalls could be the clinical significance of detected bacteria in the context of massive gut bacterial translocation (when no clear signs and/or symptoms of infection are present) and the limited number of the pathogens identified by the panels.The 20th century has been characterized by the dramatic effect of the large-scale use of antibiotics after their discovery, saving millions of lives. Unfortunately, natural selection and misuse of antibiotics, both in human beings and in animals, have led to the development of difficult to treat infections by multi-drug resistant bacteria, also known as superbugs, the nightmare of the new century. Research efforts by pharmaceutical companies are not keeping pace with the worldwide spread of superbugs and this has prompted new strategies to optimize existing resources, such as the reviving of old antibiotics, the implementation of antimicrobial stewardship programs and the judicious use of new anti-infective agents. However, the epidemiology of bacterial infections has a huge intercentre variability and the therapeutic approach should be inspired by the principle of one size does not fit all which obviously also applies to SBP. In other words, the current challenge is to accurately identify patients with SBP for whom empirical broad-spectrum therapy would be appropriate, with special attention to MDR-GPB in contexts where their prevalence is relevant. Risk factors could be integrated into predictive models of mortality in individuals with SBP so as to further help identify patients in need of more aggressive therapeutic strategies from the very start of the infective process[81,82].

CONCLUSION

SBP has a high mortality rate and early diagnosis and antimicrobial therapy are essential for improving patient outcomes. SBP is a clinical entity noted primarily in patients with end stage liver disease. Aerobic gram-negative bacilli are the predominant organisms involved. Primary bacteremia which occurs as a consequence of impaired function of the reticuloendothelial system along with an increase in bacterial translocation from the bowel, is probably followed by secondary seeding of the ascitic fluid. Although fever and abdominal pain are the most frequent clinical manifestations, the signs and symptoms may be subtle, or the patient may be asymptomatic. The ascitic fluid PMN count is the best determinant for the diagnosis of SBP; however, its clinical variants should be closely monitored for appropriate management of patients with SBP. Currently, cefotaxime is considered the drug of choice for treatment, whereas nonabsorbable antibiotics such as norfloxacin are used to decrease the recurrence of SBP.

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