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Predictors of Spontaneous Bacterial Peritonitis (SBP) in Liver Cirrhosis: Current Knowledge and Future Frontiers

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Abstract

Spontaneous bacterial peritonitis (SBP) in patients with cirrhotic liver disease is a serious complication that contributes to the high morbidity and mortality rate seen in this population. Currently, there is a lack of consensus amongst the research community on the clinical predictors of SBP as well as the risks and benefits of prophylactic antibiotic therapy in these patients. Pharmacological gastric acid suppression (namely with PPIs and H2RAs) are frequently prescribed for these patients, many times without a clear indication, and may contribute to gut bacterial overflow and SBP development. However, this remains controversial as there are conflicting findings in SBP prevalence between PPI/H2RA-users and non-users. In addition, studies show recent antibiotic use, whether for SBP prophylaxis or for another infectious process, appear to be associated with higher rates of SBP and drug-resistant organisms. Other researchers have also explored the link between zinc, platelet indices (MPV), and macrophage inflammatory protein-1 β (MIP-1β) levels in liver cirrhosis, all of which appear to be promising markers for classifying SBP risk and diagnosis. This literature review was limited by the number and quality of studies available as most are retrospective in nature. Thus, more ongoing, prospective studies and trials are needed to judge the true value of the findings in the studies reviewed in hopes that they can guide appropriate prevention, diagnosis, and management of SBP.

Keywords

Spontaneous Bacterial Peritonitis (SBP), Liver Cirrhosis, PPIs, H2RA, Antibiotic Prophylaxis, Antibiotic Resistance, Zinc, Inflammatory Biomarkers, Platelet Indices (MPV), Macrophage Inflammatory Protein-1 β (MIP-1β)

1. Introduction

Spontaneous bacterial peritonitis (SBP), an infection of the ascites fluid in the peritoneum that occurs in the absence of another infectious source, is a complication seen in patients with liver cirrhosis [1]. It carries potentially significant morbidity and mortality in this population due to their altered immunocompetency and overall disease burden [2]. SBP is generally theorized to be the result of gut bacteria translocation into the surrounding ascitic peritoneal fluid secondary to dysregulated local mucosal defense mechanisms and gastrointestinal hypomotility and is a sign of decompensated liver cirrhosis [3]. Clinical manifestations, though not always present, typically include fever, chills, and abdominal pain/discomfort, and may progress to mental status alterations and sepsis [4]. SBP may be accompanied by other signs of decompensation such as jaundice, ascites, portal hypertension (with or without resultant gastrointestinal bleeding), hepatic encephalopathy, and hepatorenal syndrome [1].

The prevalence of SBP in patients with liver cirrhosis ranges anywhere from twenty to fifty percent, depending on the study reviewed, with inpatient mortality rates as high as 32% [5]. True incidence and prevalence appear to be difficult to recognize as diagnostic ascitic fluid cultures can remain negative even in the presence of SBP [6]. In addition, some patients simply are asymptomatic through the course of the infection and would have otherwise remained missed cases if it were not for having a diagnostic or therapeutic paracentesis performed. And while those who stay asymptomatic are not burdened by the clinical manifestations that threaten their physiological state at the moment, studies suggest prior episodes of SBP may predispose them to more difficult to manage subsequent episodes [2] [5] [6].

The diagnosis of SBP requires a paracentesis to obtain an ascites fluid sample and is based on a positive ascites fluid culture and polymorphonuclear (PMN) leukocyte count greater than 250/mm^3 [1] [7]. As with any invasive procedure, performing a paracentesis comes with certain risks, such as bleeding, infection, bowel perforation, and causing hemodynamically significant fluid shifts, and ultimately, the decision to proceed is that of clinical judgement and facility-based protocols, whether it is for diagnostic (*i.e.*, suspicion of SBP in high risk individuals) or therapeutic (*i.e.*, to ease work of breathing, relieve abdominal discomfort) purposes [8]. Some facilities may also routinely perform a diagnostic paracentesis for all admitted liver cirrhosis patients with ascites, regardless of SBP suspicion; however, this practice remains controversial due to the risks of the procedure [2].

Current guidelines for inpatient SBP treatment include the use of an intravenous third-generation cephalosporin (such as ceftriaxone) or a quinolone [9] [10]. Additionally, clinicians may also choose to prescribe oral ciprofloxacin or trimethoprim-sulfamethoxazole for SBP prophylaxis in high-risk patients in both inpatient and outpatient settings [2]. Norfloxacin, a quinolone previously popular for SBP prophylaxis but has since been discontinued in the United

States in 2014, had the strongest evidence for its use but simultaneously appeared to be correlated with quinolone-resistant SBP [10]. As researchers delved more into this matter, recent findings suggest there is an increasing number of drug-resistant bacteria cases that implicate not only norfloxacin but also other agents including levofloxacin, ciprofloxacin, and cephalosporins [9] [10].

1.1. Scope of Problem

With the up-trending prevalence of antibiotic resistant SBP cases, treatment options will only continue to dwindle. Amongst one of the catalysts for this phenomenon is the poor and inappropriate diagnosis and management of SBP. Until around four years ago, there have been little to no distinction made by clinicians in approaching and treating community-acquired and nosocomial SBP, despite the involvement of different infectious flora between the two classifications [2]. In addition, nosocomial SBP infections are also more likely to implicate multi-drug resistant organisms (MRDOs), which only further complicate treatment strategies [9] [11] [12] [13].

The disease burden of SBP in liver cirrhosis patients greatly affect and increase morbidity and mortality amongst this group. Studies show SBP predisposes patients to recurrent episodes of SBP or infection of a different source (and vice versa), with subsequent infections more likely to be associated with more dire consequences due to involvement of drug-resistant organisms (DROs) [9] [11] [12] [13]. Those with a recent infection who are then discharged from the hospital have as high as a 41% risk of death or need for liver transplantation within six months [12]. There is also a subset of patients who become disqualified from liver transplantation while on the waitlist due to sepsis and multi-organ failure secondary to SBP. Better patient outcomes require both appropriate and timely antibiotic therapy prior to onset of hypotension and sepsis [14]. As for those who do proceed to liver transplantation, history of SBP occurrence pre-transplantation may be correlated with inferior graft function and even graft failure, with increased morbidity and mortality post-liver transplantation [15].

Lastly, the medical costs related to SBP annually place tremendous strain on the healthcare system. Based on the U.S. Nationwide Inpatient Sample (NIS) data, costs associated with ICU admission and care with presumed infection in this patient population alone approximates $3 billion annually [6].

1.2. Knowledge Gap

There is a current knowledge gap in managing liver cirrhosis patients at risk for and those who have SBP. The research community lacks a consensus regarding both prevention and treatment strategies. There are conflicting findings and opinions regarding the role and use of antibiotic therapy and pharmacological gastric acid suppression and their potential associations with SBP prevalence, disease process and progression. Some researchers are attributing the rise of antibiotic resistance organisms and poorer clinical outcomes to the absence of

up-to-date standardized guidelines on SBP prevention and treatment. Lastly, the potential roles of specific trace elements and inflammatory biomarkers are growing areas of interest amongst researchers for its prospect in predicting SBP risk in hopes of avoiding unnecessary antibiotic therapy.

1.3. Aim of Literature Review

The aim of this article is to explore the current state of knowledge regarding independent predictors of SBP development in liver cirrhosis patients as well as the potential utilization of trace elements (particularly zinc) and inflammatory biomarkers to stratify SBP risk and vulnerability. This is all in efforts to better assist clinical judgment in prioritizing antibiotic prophylactic treatment and reduce the risk of SBP development.

2. Methods

The online databases resourced for articles reviewed in the paper included PubMed, The Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Institutes of Health (NIH), and Google Scholar. Database searches were conducted in September and October 2017. The keywords used to search for articles reviewed in this paper included "spontaneous bacterial peritonitis", "SBP", "liver cirrhosis", "ascites", "end-stage liver disease", "ESLD", "predictors", "PPI", "H2RA", "antibiotic prophylaxis", "antibiotic resistance", "zinc", "mean platelet volume" and "macrophage inflammatory protein". The terms "spontaneous bacterial peritonitis" and "predictors" were initially searched in combination to identify predictors of interest. The terms in various combinations were then used to compile articles, which were subsequently reviewed for relevancy to topic. Such combinations included "spontaneous bacterial peritonitis", "ascites", "liver cirrhosis" or "end-stage liver disease" with each of the studied predictors ("PPI", "H2RA", "antibiotic prophylaxis", "antibiotic resistance", "zinc", "mean platelet volume" and "macrophage inflammatory protein"). Furthermore, the reference lists of relevant studies were reviewed in attempt to seek out additional pertinent studies not found in prior searches. Only articles available in the English language were included in this review, and the literature search was limited to articles published within the last five years (2012 to present).

3. Results

3.1. Pharmacological Gastric Acid Suppression

Proton-pump inhibitors (PPIs) and histamine-2-receptor antagonists (H2RAs), the two most common classes of pharmacological gastric acid suppression, are frequently prescribed for patients for gastrointestinal prophylaxis against ulcer development (particularly within the hospital setting), for treatment of gastric or duodenal ulcers, and to relieve symptoms for those with gastroesophageal reflux disease (GERD) [16]. In liver cirrhosis patients specifically, gastric acid suppres-

sion is undoubtedly a vital part of managing this disease process and preventing complications such as gastrointestinal bleeding [16]. However, lowering the acidity level of gastric contents may also negatively affect the native gut bacterial flora, allowing for overgrowth and subsequent transmigration to the surrounding peritoneal fluid in the presence of ascites [2] [16].

A number of studies show that PPI use is associated with higher prevalence of SBP in liver cirrhosis. In a retrospective cohort study of 7299 patients with decompensated cirrhosis from the U.S. Veterans' Health Administration database between the years 2001 and 2009, PPI use appeared to increase the rate of infection by 1.75 times compared to those who were not on PPIs [17]. Around 25.9% who used PPIs developed serious infections, with the majority (75%) of infections being acid-suppression associated infections, including SBP, C. difficile, and pneumonia. Of those who developed infections while taking PPIs, the leading sources and types of infection involved were SBP (30%), pneumonia (25%), skin infections (23%), spontaneous bacteremia and septicemia (16%), C. difficile (5%), and UTI (1%). Of note, the researchers found no clinically significant difference in infection rates between patients who were on H2RA therapy and those who were not on any form of pharmacological gastric acid suppression [17].

Another study by Goel *et al.* supported the findings of Bajaj *et al.* reported above [7] [17]. In this retrospective case-control study of 130 hospitalized patients, Goel *et al.* found the SBP-positive group had a higher incidence of PPI use within 7 days of diagnosis compared to a Child-Pugh score-matched SBP-negative control (71% vs. 41% respectively) ($p < 0.001$) [7]. Those who did not use PPIs in the last 90 days were almost 70% less likely to have SBP ($p = 0.05$). And those who have used PPIs within 90 days of hospitalization were 79% less likely to have SBP than those with PPI use within 7 days of hospitalization; there was no significant difference between no PPI use within 90 days and PPI use in the last 8 - 90 days but not within 7 days.

O'Leary *et al.* examined the risk factors of recurrent bacterial infections in a prospective study of 188 hospitalized liver cirrhosis patients across 12 United States centers enrolled in North American Consortium for the Study of End-Stage Liver Disease [12]. The authors performed a six-month follow-up after discharge from the hospital and found PPI use to be an independent predictor of subsequent infections. Around 45% were readmitted for infections within this period, and a higher proportion of these patients were older in age, used PPIs, or received prophylactic therapy for SBP.

While the previous studies suggest a correlation between PPI use and SBP/infection rates, these findings do not go unopposed. In fact, Terg *et al.* report no statistically significant association with PPI use and higher SBP prevalence [18]. In their prospective study of 519 decompensated liver cirrhosis patients across 23 hospitals in Argentina between March 2011 and April 2012, 24.7% of subjects developed SBP. The authors found similar rates of PPI use between those who developed SBP and those who remained SBP-free (44.3% vs.

42.8%). In addition, the duration of PPI use and rate of SBP development were not correlated. Amongst those who developed SBP during this period, there was little difference in the microbes seen between PPI and non-PPI users.

In contrast with the PPIs, H2RAs are less commonly prescribed and appear to show mixed results with regards to its part in SBP development. Bajaj *et al.* saw no significant difference in infection rates found in subjects who used H2RAs versus no gastric acid suppression at all [17]. On the contrary, Goel *et al.* did endorse the SBP-positive group had a slightly higher incidence of H2RA use within the past 90 days compared to those in the Child-Pugh score-matched SBP-negative control group (15% versus 2%) ($p = 0.02$) [7].

3.2. Antibiotic Therapy in SBP

Another prominent area of study in examining independent predictors of SBP development is antibiotic therapy use in this group. According to Tandon *et al.*, recent antibiotic use is associated with higher rates of SBP [13]. Amongst the 115 unique bacterial infections seen in patients with cirrhosis who were admitted or developed a bacterial infection during hospitalization, 28 (24%) were SBP. Of the 70 patients with a positive ascitic fluid culture, 31 (44%) had prior exposure to one or more systemic antibiotics within 30 days of infection, 23 (33%) had no antibiotic exposure, and 16 (23%) had exposure to oral non-absorbed antibiotics alone.

Antibiotic resistance has been in the forefront of discussion in the recent decade across the field of medicine, and SBP in liver cirrhosis is certainly no exception. Multiple studies show a higher prevalence of drug-resistant organisms in SBP cases with recent antibiotic use, whether intended for SBP treatment, SBP prophylaxis, or treatment of non-SBP infections. DROs were found at higher rates in those with SBP as a subsequent infection rather than SBP as a primary/index infection (42 versus 7%, $p = 0.02$) [12]. In Ariza *et al.*'s study, 21.5% of the positive ascitic fluid cultures were found to have global resistance to third-generation cephalosporins, an antibiotic traditionally used for treatment, with resistance rates higher in nosocomial SBP cases [9]. Further analyses show that previous use of cephalosporins, history of diabetes, history of upper GI bleed, and low PMN in ascitic fluid were other positive risk factors and predictors for DRO involvement [9]. Fernández *et al.* reported similar findings in their 2012 study, attributing recent beta-lactam use, long-term SBP prophylaxis with norfloxacin, and history of MDROs as risk factors for development of MDRO-related infections [11].

Tandon *et al.* also shed light on this topic in their 17-month study of 115 participants admitted to the liver unit of Yale New Haven Hospital [13]. They not only saw a higher prevalence of antibiotic resistance in those with recent systemic antibiotic use as the previous studies showed but also discovered 35% of these resistant infections were spontaneous infections (including SBP, spontaneous bacterial empyema, and spontaneous bacteremia). Of the 13 culture-positive SBP infections, 6 (46%) were resistant to both third-generation cephalosporins,

the first-line empiric antibiotic used in SBP treatment, and ciprofloxacin, a quinolone commonly used for SBP prophylaxis. Further analysis of culture sensitivities showed there was no significant difference in the presence and rate of antibiotic resistant SBP between the specific systemic antibiotics the patients took or were taking, whether it was used for SBP prophylaxis (typically fluoroquinolones or trimethoprim-sulfamethoxazole) or for another infection.

Other researchers shifted their attention to rifaximin, an antibiotic commonly prescribed for acute hepatic encephalopathy in those with liver disease for its role in eliminating ammonia-producing bacteria in the intestinal tract [2] [19]. It is a poorly absorbed oral agent and thus has a relatively low risk of acquiring resistance [19]. Two recent studies support its use, stating rifaximin alone may be sufficiently effective in serving as a SBP prophylactic agent. In a retrospective study published by Hanouneh *et al.* including 404 patients, 89% of the liver cirrhotic ascites patients who received rifaximin remained free of SBP compared to 68% of those not on rifaximin; the rifaximin test group saw a 72% reduction in SBP development [19]. The study by Tandon *et al.* showed no significant correlation for antibiotic resistant infections with prior use of oral non-absorbed antibiotics (like rifaximin) when compared to traditional systemic antibiotics stated previously [13].

The implication of DROs in SBP-positive ascitic fluid is associated with poorer outcomes and survival, primarily due to limited treatment options. Those with ESBL-E and other MDROs involved have higher incidence of septic shock, rapid clinical deterioration and mortality [11]. Ariza *et al.* supported these findings, revealing that the presence of DROs in ascites fluid is linked to increased mortality rate, especially in the setting of hepatorenal syndrome [9].

3.3. Zinc

Zinc, a physiological trace element with known functions in the immune system, has recently received some attention for its potential role in SBP development. Zinc deficiency is a frequent finding in decompensated cirrhosis [20]. In a 2015 study performed by Mohammad *et al.*, low zinc levels (defined as less than 60 μg/dL) were correlated with SBP development [21]. In this study, 35 of 54 (64.8%) SBP-positive subjects had a serum zinc level < 60 μg/dL, whereas only 45 of 122 (36.9%) SBP-negative subjects were found to have low serum zinc ($p = 0.001$). Sengupta *et al.* concluded in their 2015 study that serum zinc concentrations were inversely correlated with infection and ascites [20]. In addition, Sengupta *et al.* and Kar *et al.* examined and reported that zinc deficiency was linked to poorer clinical outcomes and shorter transplant-free survival [20] [22]. These latest findings indicate zinc may be an independent predictor of SBP in liver cirrhosis and have the potential to serve as a useful diagnostic and prognostic marker.

3.4. Platelet Indices and Inflammatory Biomarkers

Some researchers have turned to platelet activation and other inflammatory

biomarkers as indicators for identifying the underlying inflammatory process involved in SBP. Higher mean platelet volume (MPV) levels are seen in those with ascitic fluid infections compared to liver cirrhosis patients without SBP and healthy controls alike, with no statistically significant difference between the latter two [1] [23]. The authors for both studies endorse MPV as an accurate diagnostic test and marker in predicting the presence of ascitic fluid infection in the liver cirrhosis population.

Other inflammatory biomarkers have been examined in its reliability in diagnosis and correlation with SBP. Specifically, macrophage inflammatory protein-1 beta (MIP-1β) have been examined in two studies by Khorshed *et al.* and Lesińska *et al.*, both showing ascitic fluid MIP-1β to be significantly increased in the presence of SBP ($p < 0.001$ and $p = 0.01$ for the respective studies), with sensitivity and specificity for SBP diagnosis to be 80% and 76.1%; and 72.7 and 100% respectively [1] [24]. Perhaps of more value, a combined measurement of serum and ascitic fluid MIP-1β levels was found to have 100% sensitivity and specificity for SBP diagnosis [1]. Lesińska *et al.* also looked at procalcitonin levels but concluded it was not useful as a diagnostic marker [24].

4. Discussion

While ongoing further research is still necessary, the current state of knowledge regarding pharmacological gastric acid suppression therapy suggests there is stronger evidence relating PPI use with increased SBP incidence and overall poorer clinical outcomes in decompensated liver cirrhosis. Oftentimes, these agents are seen as fairly benign medications and can arguably be described as something clinicians prescribe out of habit or tradition rather than for a true indication [10] [25]. In fact, Ladato *et al.* argue there may be little efficacy of PPI use in the presence of hypertensive gastropathy, such as seen in liver cirrhosis patients [25]. By bringing more awareness to the potential adverse effects of pharmacologic gastric acid suppression particularly in this patient population, clinicians can better assess the risk-benefit ratio of its use prior to starting therapy, ensuring benefits outweigh the potential morbidity of SBP.

Based on the literature, recent antibiotic use is associated with higher rates of SBP infections and prevalence of DROs, presenting either through SBP or other infections. With the emergence of multi-drug resistant "superbugs", healthcare providers must be more conscientious about the risks related to inappropriate antibiotic prescription, particularly in caring for vulnerable groups such as in decompensated liver cirrhosis. Providers must also avoid indiscriminate antibiotic use and escalation in otherwise low-risk patients. The rise in antibiotic resistance has led to increased treatment failure with traditional methods and will continue to exhaust the availability of effective antibiotics, such as third-generation cephalosporins and ciprofloxacin in SBP treatment and prophylaxis respectively. It will then only be a matter of time before they and other agents are rendered useless, leaving these patients completely defenseless against infections.

In order to improve clinical management and establish updated guidelines for SBP diagnosis and treatment, further exploration of the role of zinc would increase the knowledge base of SBP pathophysiology. Zinc has known functions in immunocompetency and serves as an enzyme cofactor in a number of metabolic and cellular processes, plays a role in oxidative stress, and may also have anti-inflammatory effects [21] [26]. With the rise of antibiotic resistance, it is becoming more difficult for clinicians to determine the risk-benefit ratio in prophylactically treating SBP. If further studies determine and support that zinc is indeed a significant independent predictor of SBP, perhaps zinc replacement can alter infection risk and/or overall outcomes. In essence, can zinc replacement delay or prevent decompensation, and if so, to what extent? With a greater understanding of such questions, providers can take a more proactive rather than reactive approach in hopes of significantly reducing morbidity and mortality in those with chronic liver disease and failure.

On a similar note, inflammatory biomarkers like MPV and MIP-1β appear to be promising indicators that can be utilized for SBP diagnosis. Use of inflammatory biomarkers to determine the need to initiate empiric antibiotic therapy in the absence of elevated PMN and/or while pending fluid culture reports is a topic worth exploring more. And if future research supports the utility of these biomarkers to assess for presence of ascitic fluid infections, a practice guideline change reflective of such may allow for earlier and proper diagnosis and treatment of SBP, with hopes of improving patient outcomes, reduce patient risk of need for more invasive diagnostic measures (*i.e.*, paracentesis), and lower overall healthcare spending.

5. Conclusion

While this paper is limited by the relatively small number of studies available on this topic as well as the quality and type of studies (most are retrospective in nature), it sheds light on how much is still unknown regarding this disease process and how there is a need to change certain aspects of SBP clinical management in liver cirrhosis based on the high rates of morbidity and complications. In performing a literature search, it is clear more prospective, randomized controlled trials are required to better assess the risk versus protective factors for SBP development in liver cirrhosis. This is vital in judging the true value of the findings presented in the studies reviewed in this paper and will be a major milestone for the research community before updated evidence-based practice guidelines can be put forth.

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