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Current Trends in the Management of Spontaneous Bacterial Peritonitis

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Abstract
Purpose of review Spontaneous bacterial peritonitis is a life-threatening infection that is a leading cause of mortality among patients with decompensated cirrhosis. In this article, we present current trends in the management of spontaneous bacterial peritonitis (SBP), highlighting treatment failure rates of traditional regimens and ways in which to address such challenges.
Recent findings Despite available management guidelines, there are data to support that these guidelines are often not adhered to, e.g., performing a diagnostic paracentesis at the time of hospital admission in a patient with ascites. Management of SBP is now further complicated by resistant organisms and an increasing prevalence of nosocomial and healthcare-associated infections.
Summary Effective treatment of SBP requires careful consideration of patient risk factors, local antibiotic resistance patterns, and clinical presentation.

Keywords Ascites · Spontaneous bacterial peritonitis · Decompensated cirrhosis · Beta-blockers · Proton pump inhibitors

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Introduction

Spontaneous bacterial peritonitis (SBP) is classically defined as a primary infection of ascites with a positive ascitic fluid culture and an absolute polymorphonuclear leukocyte (PMN) count ≥250 cells/mm^3 in the absence of an intra-abdominal source of infection [1]. SBP occurs almost exclusively in the cirrhotic patient with ascites.

The need to recognize and treat SBP in a timely fashion is paramount to the patient's clinical outcome. SBP is the most frequent bacterial infection in cirrhosis and carries a mortality rate between 31 and 93% after its first episode [2]. The in-hospital mortality rate for SBP approaches 32% [3] with a reported range between 10 and 50% [2, 4•].

A diagnosis of SBP can only be made via a diagnostic paracentesis where culture and PMN count are assessed; a clinical diagnosis of SBP is insufficient [2]. If present, classic symptoms include fever, abdominal pain, and worsening ascites; however, symptoms may be clinically silent in approximately a third of cases [5]. A diagnostic paracentesis, therefore, should be performed in all cirrhotic patients with ascites upon hospital admission or in the setting of gastrointestinal (GI) bleeding, hepatic encephalopathy, or hepatic decompensation [2, 6, 7]. Ideally, paracentesis should be performed prior to the administration of antibiotics. Once SBP is diagnosed, empiric antibiotic treatment should be promptly started as culture and sensitivity results are not immediately available.

There are defined variants of SBP based upon culture and PMN count [8]. Classic SBP is culture positive with PMN ≥250/mm^3. Culture-negative neutrocytic ascites (CNNA) refers to ascites with a PMN ≥250 cells/mm^3 without a positive bacterial culture where other causes have been ruled out (i.e., tuberculosis, pancreatitis, hemorrhagic ascites, peritoneal carcinomatosis) [9]. In monomicrobial bacterascites, the ascitic fluid bacterial culture is positive but the PMN is <250 cells/

mm^3. Both culture positive SBP and CNNA should be treated immediately, whereas monomicrobial bacterascites may represent either a precursor to SBP or simply a transient bacterial translocation without clinical sequelae [6, 8, 10]. In this setting, recent guidelines recommend treating patients with clinical signs or symptoms of infection. Those without symptoms or among those with a low degree of suspicion, presence of monomicrobial bacterascites on a diagnostic paracentesis should be followed by a repeat paracentesis and should be treated if the PMN is ≥250 cells/mm^3 [6].

Approximately 5–10% of the cirrhotic patients with ascites with peritonitis have secondary bacterial peritonitis [3]. Secondary bacterial peritonitis stems from an intra-abdominal source (e.g., intestinal perforation or abscess). As in SBP, the PMN is ≥250 cells/mm^3 but is usually polymicrobial with at least two of the following criteria: total protein >1 g/dl, LDH >upper limit of normal, and glucose <50 mg/dl [7].

Given the poor long-term survival of patients with SBP, those who recover should be referred for consideration of liver transplantation evaluation [6].

Pathogenesis

The pathogenesis of SBP is multifactorial. Bacterial translocation in a cirrhotic patient whose immune defense is impaired is thought to be the inciting event [2, 11]. Changes in the cirrhotic microbiome, increased intestinal permeability, and an impaired immune system play a central role in the pathogenesis of bacterial translocation [2]. Alterations in toll-like receptor (TLR) and nucleotide-binding oligomerization domain 2 (NOD2) have also been implicated in the pathogenesis of bacterial translocation [11]. Because of portosystemic shunting in cirrhosis, fewer gut-derived bacteria traverse the portal circulation and therefore bypass clearance by the reticuloendothelial system. Decreased phagocytic activity, excessive pro-inflammatory cytokines, decreased complement, and protein C activity all contributed to immune dysfunction in the cirrhotic patient [11].

Treatment

Antibiotics

Cefotaxime, a first third-generation cephalosporin, has historically been the treatment of choice for SBP [7]. However, the increasing prevalence of nosocomial and healthcare-associated infections and drug-resistant organisms has called this recommendation into question. Given this shifting landscape, we outline management recommendations based on either community-acquired SBP or nosocomial SBP [2, 6].

Community-Acquired SBP

For community-acquired SBP, cefotaxime covers 95% of the bacterial flora [7]. The most common organisms isolated include *Escherichia coli*, *streptococci*, and *Klebsiella pneumoniae* [7]. Cefotaxime is administered 2 g intravenously every 8–12 h. Once culture susceptibility is resulted, then antibiotic therapy can be de-escalated. Antibiotics are given for a duration of 5 days; a shorter duration is equally efficacious to 10 days of therapy in uncomplicated SBP [12]. Other treatment options include other third-generation cephalosporins (ceftriaxone), amoxicillin-clavulanate, or quinolones [11]. Quinolones should be avoided in patients who are already on one for SBP prophylaxis given higher rate of quinolone-resistant gram-negative bacteria [13]. Uncomplicated SBP, defined as cases without shock, ileus, gastrointestinal bleeding, Grade 2 or greater hepatic encephalopathy, or renal impairment, can be managed with oral antibiotics such as oral quinolones [6, 11]. Switch therapy (switching from IV to PO antibiotics) is also commonly practiced and has been shown to be efficacious [6]. A repeat paracentesis 2 days after antibiotic treatment is recommended [6]. If the PMN count does not fall greater than 25% of the pretreatment value, treatment failure is suspected and the patient should be switched to another agent based on culture susceptibility results [14•], especially in patients at high risk for multidrug resistant infections (see "Nosocomial and Healthcare-Associated SBP") [7].

Nosocomial and Healthcare-Associated SBP

The increasing prevalence of multidrug resistance organisms poses a high risk of morbidity and mortality in the patients with healthcare-associated and nosocomial SBP. Treatment failure is a known risk factor for increased mortality among patients with cirrhosis [14•]. Healthcare-associated infections have been defined as those diagnosed within 48 h of hospitalization in patients who have had exposure or contact to a healthcare system, whereas nosocomial infections are those diagnosed >48 h after hospitalization [15]. Factors giving rise to this phenomena include widespread use of quinolones for SBP prophylaxis, emergence of multidrug resistant organisms, and varying degrees of exposure to healthcare settings. Approximately 30% of the gram-negative bacteria are resistant to quinolones [6], and up to 75% resistance has been shown for third-generation cephalosporins in patients with nosocomial SBP [16]. In fact, gram-positive bacteria and multidrug resistant bacteria have become more prevalent in nosocomial settings [6, 17]. The most common multiresistant bacteria include extended-spectrum beta-lactamase (ESBL) *Enterobacteriaceae*, Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-sensitive and -resistant *enterococcus* (VSE, VRE), and non-fermentable gram-negative bacilli including *Pseudomonas aeruginosa*,

Stenotrophomonas maltophilia, or *Acinetobacter baumannii* [18•].

Two small studies suggest the use of broad-spectrum antibiotics as a first line drug in this patient population until culture results return [14•, 17]. Piano et al. performed a randomized study of 32 patients comparing ceftazidime vs. meropenem/daptomycin (MER/DAPTO). Patients who did not respond to ceftazidime (based on repeat paracentesis) were switched to MER/DAPTO. While there was no difference in 30- or 90-day transplant-free survival, patients in the MER/DAPTO group had a significantly higher rate of treatment success (86.7 vs. 25%, $p < 0.001$). Similarly another trial that randomized cirrhotic patients with healthcare-associated infections (including SBP) to imipenem vs. cefepime showed a lower rate of treatment failure (18 vs. 51%; $p = 0.001$), shorter length of stay (12.3 ± 7 vs. 18 ± 15 days; $p = 0.03$), and a reduction in mortality with the former regimen (6 vs. 25%; $p = 0.01$) [17]. These two studies suggest that starting with broad-spectrum antibiotics may improve treatment outcome, including patient survival. Inadequate treatment of this high-risk patient population confers a poor prognosis. Of significant concern is the exacerbation of multidrug resistance. While there has not been any documented resistance to carbapenems, controversy exists on how best to approach this problem.

A recent single center study found that 22% of the patients did not respond to initial antibiotic treatment [4•]. Furthermore, 21% of those with culture positive SBP grew out gram-positive organisms with third-generation cephalosporin resistance. Even in patients thought to have low risk or "easiest to treat" SBP, treatment failure rates were 23% (similar to the overall cohort) [4•]. Low-risk patients in the study met the following inclusion criteria: no recent beta-lactam exposure, typical organism culture (if culture positive), community-acquired SBP, and clinical improvement or stability 72 h after SBP diagnosis [4•].

Given the high prevalence of treatment failure in real-world settings and the ongoing challenges of treating nosocomial SBP, a repeat paracentesis may be advisable in most patients [4•] and is supported by European guidelines [6]. The AASLD guidelines recommend repeat paracentesis in the following patient population: recent B-lactam exposure, culture with an atypical organism, an atypical response to treatment, or ascites in a nosocomial setting [7]. We present a SBP checklist in Table 1.

Table 1 SBP checklist

- □ Perform diagnostic paracentesis in patients with ascites from cirrhosis who have been hospitalized
- □ Empiric antibiotic treatment until culture and sensitivity results return
  - □ Ceftriaxone 2 g/day or cefotaxime 2 g Q8 hours IV
- □ Continue treatment for 5 days if diagnosis of SBP, either
  - □ PMN ≥250 cells/mm^3 (culture negative neutrocytic ascites)
  - □ PMN ≥250 cells/mm^{3}and culture positive
- □Give albumin 1.5 g/kg on Day 1 and 1.0 g/kg on Day 3
- □Consider repeat paracentesis in 48 h for all patients to document treatment efficacy
- □Strongly recommend repeat paracentesis in 48 h if patient is not clinically improving or for any of the following criteria: escalate antibiotics to broader coverage or based on hospital resistance profiles
  - □ Recent beta-lactam exposure
  - □ Culture with an atypical organism
  - □ Atypical response to treatment
  - □ Ascites in a nosocomial setting

Albumin and the Prevention of Hepatorenal Syndrome

In addition to antibiotic therapy, albumin infusion is recommended to prevent renal impairment, namely hepatorenal syndrome [8, 19]. Renal failure is a major cause of death among cirrhotic patients and develops in 30–40% of the patients with SBP [20] Patients who received albumin infusion (1.5 g/kg albumin was infused on Day 1 and 1 g/kg was given on Day 3) in addition to cefotaxime (vs. cefotaxime alone) had a decreased risk of developing renal impairment (10 to 33%) and had a lower risk of morality (10 to 29%) as compared to antibiotics alone [21]. Albumin is recommended in patients with Cr >1 mg/dl, BUN >30 mg/dl, or if the total bilirubin is >4 mg/dl. This recommendation is further supported by a meta-analysis of four randomized controlled trials examining the effect of albumin on renal impairment and mortality in patients with SBP. The pooled odds ratio for the decrease in mortality after receiving albumin was 0.34 (95% CI: 0.19–0.60) [22]. Albumin provides benefit not only by volume expansion but also by improving cardiac function as well as by mitigating arterial vasoconstriction [19]. Albumin is also known to have anti-oxidant and anti-inflammatory properties [23]. While hypoalbuminemia is a known feature of cirrhosis, our understanding of albumin dysfunction in cirrhosis is still not completely understood [23].

Primary Prophylaxis

Primary prophylaxis is recommended in patients without prior SBP who have low protein ascites (<1.5 g/dl) alongside impaired renal and liver dysfunction [2]. Norfloxacin (400 mg/day) in patients with advanced liver disease (ascitic total protein <1.5 mg/dl, creatinine ≥1.2 mg/dl, BUN ≥25 mg/dl, Na ≤130 mEq/l, Child-Pugh score ≥9, and bilirubin ≥3 mg/dl) was associated with a reduction in the 1-year probability of SBP (7 vs. 61%, $p < 0.001$), hepatorenal syndrome (28 vs.

41%, $p = 0.02$), and 1 year mortality (60 vs. 48%, $p = 0.05$) [24].

A more recent randomized trial using the same inclusion criteria for renal and liver dysfunction compared alternating rifaximin with norfloxacin vs. either rifaximin or norfloxacin alone for a 6-month period. Patients alternated taking rifaximin with norfloxacin on a monthly basis for 6 months. Rates of prophylaxis were superior in those who alternated vs. either norfloxacin or rifaximin alone (74.7 vs. 56.4 vs. 68.3%, $p < 0.048$) [25]. Rifaximin as primary prophylaxis in retrospective studies may confer a transplant-free survival benefit in cirrhotic patients with ascites [26]. Resistance to rifaximin has not been found in patients with cirrhosis and ascites followed for up to 5 years [27]. Rifaximin may offer many potential advantages including low resistance profile, broader range of antimicrobial activity, and mechanism of action in the small intestine, the site of bacterial translocation occurrence [2]. Further studies are needed prior to broad use of rifaximin in patients with SBP. Of note, antibiotic cycling has also been proposed as another solution to avoid continuously using the same antibiotic [2]. However, there have been a lack of studies in this regard.

Gastrointestinal Bleeding Patients with cirrhosis and gastrointestinal bleeding are at high risk for infections [3]. Norfloxacin has also been studied in this setting; however, one study demonstrated that ceftriaxone is more effective than oral norfloxacin in the prevention of infections [28]. For this reason, Ceftriaxone 1 g IV daily × 7 days is often given to hospitalized cirrhotic patients (Child-Pugh Class B or C) with GI bleeding. Once the patient has stabilized and resumed oral intake, IV antibiotics are often switched to PO [7].

Secondary Prophylaxis

Prior Episode of SBP All patients with a previous episode of SBP should receive secondary prophylaxis. Patients who have had an episode of SBP are at high risk for recurrence and reduced survival. The risk of recurrence is up to 70% in the first year with a survival rate of 30–50% in the first year [3]. These patients should be considered for suppressive antibiotic therapy as well as be considered for LT evaluation given the increased mortality rate. Norfloxacin (400 mg/day) has been shown to reduce the risk of recurrence to approximately 20% in the first year [29]. Trimethoprim-sulfamethoxazole (one double-strength tablet daily) or ciprofloxacin (400 mg/day) are often used in the USA. Rifaximin has also been studied in secondary prophylaxis, but further data are needed before it is widely used in this regard. In a randomized controlled trial of 262 cirrhotic patients, patients received either 1200 mg rifaximin or 400 mg norfloxacin. SBP recurrence (3.9 vs. 14.1%) and mortality (13.7 vs. 24.4%) were significantly lower in the rifaximin group [30]. The rifaximin group also experienced decreased side effects and fewer encephalopathy-related deaths [30]. While long-term prophylaxis has shown to be beneficial in reducing SBP recurrence and mortality, one significant consequence has been the emergence of gram-negative bacteria resistant to both quinolones and trimethoprim-sulfamethoxazole and increased risk of gram-positive infection in this population as previously outlined [6].

Role of Non-Selective Beta-Blockers in SBP

Non-selective beta-blockers have been used primarily in cirrhotics to prevent against variceal bleeding [31, 32]; however, the role of beta-blockers in the patient with cirrhosis has been a subject of debate in recent years. Within the last decade, a few studies have suggested that beta-blockers may cause potential harm for patients with advanced liver disease [33–35]. One current hypothesis, known as the "window hypothesis," posits that beta-blockade is only useful within a certain clinical window [36]. Beta-blockers are thought at one end of the spectrum to be ineffective in early cirrhosis [37] and at the other end of the spectrum harmful in patients with end-stage liver disease complicated by refractory ascites. Such patients have poor cardiac reserve, and beta-blockade may lead to decreased organ perfusion and even hepatorenal syndrome [35, 38]. There is only a brief window, during a period of decompensated cirrhosis when a patient's cardiac reserve is still intact where beta-blockers have been shown to improve survival, primarily in the context of secondary prophylaxis of gastrointestinal bleeding [33]. This poses a dilemma for the patient with SBP who already has decompensated liver disease with risk of progression to acute on chronic liver failure or refractory ascites.

On the other hand, beta-blockers play a potential role in decreasing bacterial translocation, a key step in the pathogenesis of SBP [39]. One animal study showed that propranolol in cirrhotic rats compared to those without propranolol resulted in lower portal pressure, faster intestinal transit, and lower rates of bacterial overgrowth and translocation [40]. One clinical study with 50 patients with cirrhosis demonstrated a correlation between increased portal pressure (HVPG measurements were performed) and increased intestinal permeability. Patients given a non-selective beta-blocker (NSBB) had decreased intestinal permeability and a decrease in bacterial translocation [41]. Further studies should be performed to further investigate the role of portal hypertension, NSBB, and bacterial translocation.

While beta-blockers can ameliorate a key step in the pathogenesis of bacterial translocation, controversy regarding safety of beta-blockers in decompensated cirrhotics remains. One meta-analysis published in 2009 looking at three randomized controlled trials and three retrospective studies showed

that beta-blockers may play a role in protecting against spontaneous bacterial peritonitis in cirrhotic patients [42] (Table 2(a)). Subsequently, Mandorfer et al. found in a retrospective study that beta-blockers were associated with an increased risk of HRS and death in patients with cirrhosis and SBP [43]. However, multiple recent studies demonstrated that beta-blockers were not associated with increased mortality and in fact had a reduced mortality compared to those not on beta-blockade [44–48]. Mookerjee et al. demonstrated benefit from beta-blockade even in patients thought to have the most advanced liver disease, acute on chronic liver failure [49••]. The patient sample included patients enrolled in the CANONIC study, a prospective observational investigation of patients with acute decompensation. They found a relative risk reduction for death of 0.596 in the beta-blocker group [49••]. Given the controversy with beta-blocker use, one

Table 2 Studies on the (a) association between beta-blockers and mortality risk among cirrhotic patients and (b) association between PPI use and SBP

Reference	Design	Number	Results
(a)			
Serste et al.	Single-center, observational, case-only, prospective study	151	Beta-blocker was an independent predictor of mortality. 1-year survival was significantly lower in patients who received propranolol for those who did not (19 vs. 64%, $p < 0.0001$)
Senzolo et al.	Meta-analysis	3 RCT and 3 retrospective	A 12.1% statistically significant difference was found in support of beta-blockers protecting against SBP
Mandorfer et al.	Retrospective study	182	Among patients with SBP, NSBB reduced transplant-free survival (HR 1.58, 95% CI 1.0908–2.264)
Leithead et al.	Retrospective study	322	Among patients with refractory ascites, NSBB was associated with reduced risk of death (HR 0.35; 95% CI0.14–0.86)
Bossen et al.	Post hoc analysis of 3 RCTs	1188	NSBB did not increase mortality in patients with refractory ascites HR 1.02 (95% CI 0.74–1.10)
Mookerjee et al.	Data from CANONIC study	349	Fewer patients in NSBB group died compared to those not on NSBB (risk reduction 0.596 95%CI0.3631–0.985)
Onali et al.	Retrospective study	316	Multivariate analysis NSBB use was associated with reduced mortality (HR 0.55, 95% CI 1.06–1.14)
Sinha et al.	Retrospective study	325	HR 0.59 (95% CI 0.29–0.77), 41% reduction in mortality risk with BB
Bang et al.	Retrospective study	3719	Propranolol HR 0.4 (95% CI 0.2–0.9) for developing SBP among patients with decompensated cirrhosis
(b)			
Bajaj et al.	Retrospective case control	70 cases, 70 controls	Patients with SBP had a higher rate of prehospital PPI use compared to those without. PPI use found to be independently associated with SBP (OR 4.31, 95% CI 1.34–11.7)
Goel et al.	Retrospective case control	65 cases, 65 controls	Subjects who took PPIs within 8–90 days before hospitalization were 79% less likely to develop SBP than those who took PPIs within 7 days prior to hospitalization (OR 0.21, 95% CI 0.06–0.66)
Dam et al.	Data from 3 trials	865 patients	Adjusted HR of SBP for PPI users vs. non-users was 1.72 (95% CI 1.10–2.69)
Khan et al.	Systematic review and meta-analysis	6 case-control, 8 cohort studies	Pooled OR (association between PPI and SBP) of 2.32 (95% CI: 1.57–3.42). Sensitivity analysis for high-quality studies → pooled OR of 1.49 (95% CI 1.19–1.88)
Yu et al.	Meta-analysis	10 case-control, 6 cohort (8145 patients)	Overall analysis OR 2.11 (association between PPI and SBP), 95% CI, 1.46–3.06. No association, however, in cohort studies
O'Leary et al.	Prospective cohort study	188 patients	PPI use OR 2.94, 95% CI 1.39–6.20 increased risk of a second infection after hospital discharge
Terg et al.	Prospective cohort study	519 patients	No difference in PPI consumption between patients with ascites and SBP vs. patients with ascites (no SBP) (46 vs. 42%)
Miozzo et al.	Prospective cohort study	582 patients	No difference in development of SBP in cirrhotics using PPIs vs. cirrhotics not using PPIs (22.5 vs. 21.5%; $p = 0.176$)

may postulate continuing with current practice of care but consider cessation of beta-blockade if other reasons for discontinuation, such as low blood pressure, exist.

Proton Pump Inhibitors and SBP

Proton pump inhibitors (PPIs) are among the one of the most widely prescribed drugs in both the USA and abroad and have come under scrutiny given overutilization [50] and linkage to infections, including *C. difficile* and pneumonia [51, 52].

Proton pump inhibitors are often prescribed in patients with cirrhosis given bleeding complications from peptic ulcer disease [53]. Like beta-blockers, the use of proton pump inhibitors in cirrhosis has also been controversial [54]. Proton pump inhibitors may be associated with an increased risk of developing SBP [55–57] (Table 2(b)). The proposed pathogenesis is that PPIs can lead to small intestinal bacterial overgrowth which can in turn lead to bacterial translocation and infection [58••, 59]. Data from a recent multicenter trial concluded that PPIs continue to be a risk factor for SBP [59]. Cox regression analysis was used to compare rates of SBP between users and non-users of PPIs. Among PPI users, the adjusted HR of SBP was 1.72 (95% CI, 1.10–2.69). This study, however, was retrospective in nature, and the dataset used was from another trial. A small but statistically significant association between PPI use and SBP was shown in a recent meta-analysis examining 14 observational studies (6 case control, 8 cohort). The pooled odds ratio was 2.32 (95% CI, 1.57–3.42) with a lower OR (1.49; 95% CI, 1.19–1.88) when a sensitivity analysis was performed for high quality studies [60].

Two larger prospective studies, however, have offered different results. One study specifically looking at this question among hospitalized patients with decompensated cirrhosis found no association between PPI use and the incidence of SBP [58••]. In this multicenter prospective study, there was no difference in PPI use among the patients with SBP (n = 95) and patients with ascites without SBP (n = 289) (46 vs. 42%) [58••]. Another study among outpatient cirrhotics also failed to find any significant association between PPI use and SBP [61]. In multivariate analyses, Child-Pugh score was the only predictor of SBP [61].

Given the conflicting nature of reports on the association between SBP and infection, PPI use in decompensated cirrhotics needs further clarification and whether duration of PPI use and degree of decompensation may provide a tipping point beyond which PPI use should be discontinued or prescribed at a lower dose.

Conclusion

The changing landscape of organisms responsible for spontaneous bacterial peritonitis presents many treatment challenges. Increasing multidrug-resistant organisms and the shift of culprit organisms from gram-negative to gram-positive bacteria have led to suboptimal treatment success rates. Early diagnosis and prompt initiation of antibiotics and albumin remain the cornerstone of therapy; however, vigilance is necessary to identify the increasing subset of patients that do not respond to standard therapy.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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