Spontaneous bacterial peritonitis due to methicillin-resistant *Staphylococcus aureus* in a patient with cirrhosis: the potential role for daptomycin and review of the literature

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Abstract

Gram-positive cocci are emerging causes of spontaneous bacterial peritonitis (SBP), especially in patients with healthcare-associated infections. We report the case of a 68-year-old man with hepatitis C virus and alcohol-related cirrhosis who developed SBP due to methicillin-resistant *Staphylococcus aureus* treated with daptomycin. We discuss the potential role of daptomycin in this setting with a review of the literature about the use of daptomycin in primary or secondary bacterial peritonitis.

Introduction

Spontaneous bacterial peritonitis (SBP) is a common bacterial infection in patients with cirrhosis and ascites. Its mortality is still high, accounting for 20-25% with early diagnosis and treatment.[1] In recent years, a change in epidemiology of bacteria causing SBP has been observed in patients with long-term norfloxacin prophylaxis consisting in the emergence of quinolone-resistant bacteria as well as Gram-positive cocci, and further studies have documented an increasing frequency of Gram-positive cocci in patients with culture-positive SBP.[2]

Antibiotic options for multi-drug resistant (MDR) Gram-positive cocci are limited, and may lead to undesired toxic effects especially in cirrhotic patients with thrombocytopenia, renal failure, or hepato-renal syndrome. Herein we describe a case of methicillin-resistant *Staphylococcus aureus* (MRSA) SBP that was successfully treated with daptomycin and discuss the potential role of this antibiotic in intra-abdominal infections in patients with cirrhosis.

Case Report

A 68-year-old man with a history of HCV and alcohol-related cirrhosis (Child-Pugh stage C) was admitted for confused mental state, increased abdominal volume, edema of the lower limbs, and deterioration of general conditions lasting for several days. The patient had been hospitalized the previous month for ascites and decompensated cirrhosis, and had undergone paracentesis. Up to two weeks prior to the last hospitalization he was on ciprofloxacin 500 mg BID. Allergy to tetracycline was documented.

Upon admission the patient was in poor clinical conditions: blood pressure 100/50 mmHg, heart rate 100 beats per minute, respiratory rate 20 breaths per minute, with stupor, flapping tremor, significant bilateral ankle edema with positive fovea sign, and jaundice. There was abdominal distension, pain on deep palpation on the lower and lateral quadrants, and negative Blumberg's sign. Blood gas analysis revealed respiratory and metabolic alkalosis; laboratory analysis showed total leukocytes of 11.7×10^9/L with neutrophilia, and thrombocytopenia (platelet count of 39×10^9/L); creatinine was 1.8 mg/dL (estimated creatinine clearance of 48 mL/min), hyperbilirubinemia (total 5.2 mg/dL, direct 2.9 mg/dL), increased INR (1.7), and hyperammonemia. The patient was treated with diuretics and ceftriaxone (2 g IV OD), and admitted to the internal medicine department.

After admission the patient's conditions worsened with deterioration of encephalopathy, fever of 38°C, and an increase in creatinine (2.5 mg/dL) and C-reactive protein (120 mg/L; normal value <5 g/L). Blood and urine cultures were initiated. Explorative paracentesis detected the presence of polymorphonuclear neutrophils (910/mm^3). Ceftriaxone therapy was replaced with meropenem (1 g IV BID; dose adjusted for creatinine clearance). Despite antibiotic therapy, fever persisted with hypotension and signs of sepsis. On day 4 after admission microbiological results of ascites fluid showed MRSA. The complete antibiogram of the isolate is shown in Table 1. After infectious disease consultation, daptomycin 6 mg/kg/day was initiated, considering the high MIC of vancomycin and the concomitant presence of renal insufficiency and thrombocytopenia. The informed consent was obtained from the patient.

After initiation of anti-MRSA therapy there was progressive clinical improvement with defervescence, reduction of ammonemia, improvement of encephalopathy, and a decrease in abdominal volume and peripheral edema. The patient was treated with daptomycin for 12 days with progressive normalization of C-reactive protein; an increase of CPK and/or impairment of renal function were not recorded during the treatment. The patient was then discharged and referred to an ambulatory clinic.

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Discussion

Chronic liver disease and cirrhosis are among the most common causes of acquired immunodeficiency, and patients with cirrhosis are at high risk for infections. In particular, bacterial infections represent the most frequent complications and dangerous complications in cirrhotic patients, especially in advanced stages of disease. It has been estimated that 30-50% of patients with cirrhosis present with a bacterial infection upon hospital admission or will develop it during recovery, with a mortality rate of around 25%.[1]

There is evidence for a progressive change in the epidemiology of chronic infections with

an increasing prevalence of infections caused by multi-drug resistant (MDR) pathogens, and during last decades Gram-positive MDR bacteria have been becoming widespread in patients with either nosocomial or healthcare-associated (HCA) SPB. Campillo and colleagues were the first to report such increases in a prospective study on 194 consecutive episodes of SBP and 119 episodes of bacteremia: seventy percent of all infections were caused by Gram-positive bacteria, with *S. aureus* being the most prevalent pathogen (MRSA in 24.8% of cases); multivariate analysis showed that staphylococci were significantly associated with mortality [odds ratio (OR) 2.84, 95%CI 1.42-5.69, P=0.003].[3] It is interesting to note that in our case the patient developed SBP caused by MRSA after a previous treatment of few weeks earlier with ciprofloxacin, which confirms the favorable effect of fluoroquinolones in selection of MRSA and other methicillin-resistant staphylococci.

A prospective study by our group on a cohort of hospitalized cirrhotic patients revealed that 41% of HCA infections are caused by MDR bacteria, and that Gram-positive bacteria (*S. aureus* followed by CNS and enterococci) are the primary cause of nosocomial SBP. Moreover, the frequent failure of empirical therapy with 3rd generation cephalosporins such as cefotaxime or ceftriaxone was seen, along with an association between the development of nosocomial infection and the number of procedures the patient has undergone and overcrowding of hospital rooms.[4]

The predisposing mechanism of SBP is intestinal bacterial translocation, which allows bacteria present in the intestinal microflora to reach the ascites via mesenteric lymphatic vessels (or sometimes even via the bloodstream resulting in secondary bacteremia). Several factors can predispose the cirrhotic patient to bacterial translocation through increased mucosal permeability, frequent alterations in immune function especially in the advanced stages of disease, bacterial overgrowth caused by concomitant therapies, and frequent intestinal bleeding. The pathophysiology of spontaneous bacterial peritonitis is shown in Figure 1.

It is important for the clinician and gastroenterologist to consider nosocomial and HCA infections distinct from community infections: while in the latter a standard approach with 3rd generation cephalosporins seem justified, for nosocomial and HCA infections broad spectrum antibiotic therapy seems necessary that includes MRSA and Gram-negative MDR and XDR. Currently, vancomycin, which for years been the chief antibiotic for infection by MRSA, has limits in terms of *in vitro* sensitivity, toxicity, and overall management of patients. In fact, during the last decade several epidemiological studies have documented an increase in the mean MICs of vancomycin in clinical isolates of *S. aureus*, a phenomenon known as MIC creep. It has been demonstrated that the efficacy of vancomycin is directly correlated with the ability to achieve levels in blood and at the site of infection that are 10-15 × the MIC in order to obtain an adequate pharmacokinetic/pharmacodynamic target (ratio AUC/MIC). However, it is nearly impossible to reach such a target (and therefore have clinical efficacy) if the isolate has an MIC that is >1 mg/L since the concentrations of vancomycin needed to reach this level would invariably lead to renal insufficiency.[5]

A possible alternative is linezolid, which is adequately concentrated at the biliary level; however, it may be associated with myelotoxicity, and thrombocytopenia is frequent in cirrhotic patients with Child-Pugh stage C. In the clinical case described, it was problematic to use vancomycin due to the elevated MIC of the MRSA isolate (2 mg/L) and the presence of renal insufficiency. At the same time, linezolid did not seem to be indicated due to the presence of marked thrombocytopenia (39×10^9/L). Moreover, the patient was allergic to tetracycline, and thus tigecycline was contraindicated. Given the above, daptomycin was chosen. Daptomycin does not undergo hepatic metabolism, and dose adjustments are needed only in severe renal insufficiency (creatinine clearance <35 mL/min). There are some data on the use of daptomycin in intra-peritoneal infections. In an experimental mouse model of peritonitis caused by MRSA, Mortin *et al*. showed that daptomycin had greater and more rapid

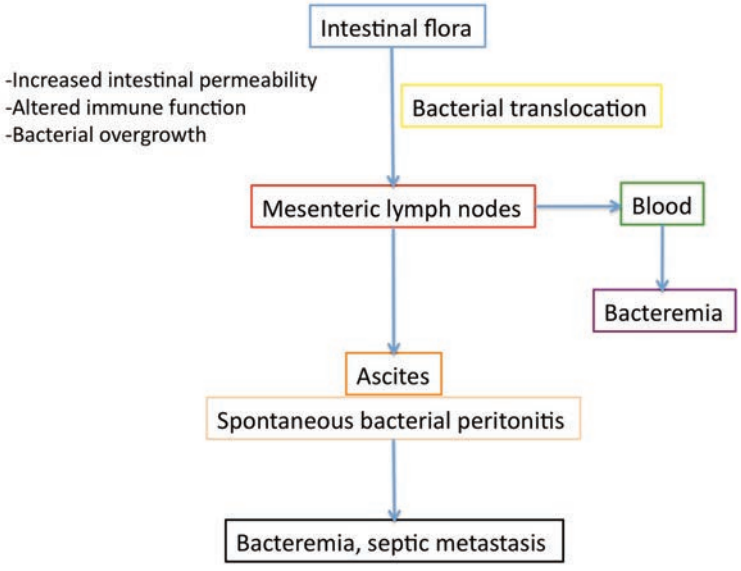

Figure 1. Pathophysiological mechanism of spontaneous bacterial peritonitis.

Table 1. Antibiogram of *Staphylococcus aureus* isolate.

Antibiotic	Min. inhibitory concentration	Resistant/sensitive
Amoxicillin/clavulanic acid	≥32	R
Ampicillin/sulbactam	32	R
Fusidic acid	≥32	R
Cefoxitin screening	Positive	+
Quinupristin/dalfopristin	0.25	S
Gentamycin	0.25	S
Linezolid	1	S
Imipenem	1	S
Oxacillin	≥4	R
Rifampicin	<0.25	S
Teicoplanin	4	S
Trimethoprim/sulfamethoxazole	<10	S
Vancomycin	2	S
Tigecycline	1	S

Table 2. Review of literature about use of daptomycin in primary or secondary bacterial peritonitis.

First author	Type of article	N° of patients	Type of infection	Etiology	Dosage of daptomycin	Outcome
Burklein[10]	Case report	1	Secondary peritonitis	*Enterococcus faecium*	4 mg/kg/day	Cure
Huen[11]	Case report	2	Peritonitis associated with peritoneal dyalisis	VR-*Enterococcus faecium*; VR-*Enterococcus faecium*	IP infusion with a loading dose of 100 mg/L, continued to 20 mg/L: IP infusion of 4 mg/L	Cure
Khadzhynov[12]	Case report	1	Peritonitis associated with peritoneal dyalisis	*Staphylococcus capitis*	5 mg/Kg every 48 hours	Cure
Hassoun[13]	Case report	1	Peritonitis associated with peritoneal dyalisis	VR-*Enterococcus faecium*	IP 15 mg/kg once weekly	Cure
Bahte[14]	Case report	1	Peritonitis associated with peritoneal dyalisis	Probably *Staphylococcus aureus*	7 mg/kg intraperitoneally	Cure
Lin[15]	Case report	1	Peritonitis associated with peritoneal dyalisis	MRSA	IP infusion with a loading dose of 100 mg/L, continued to 20 mg/L plus rifampin	Cure
Gilmore[16]	Case report	1	Peritonitis associated with peritoneal dyalisis	*Micrococcus* spp + *Enterococcus* spp	IP infusion of 40 mg/ in 2 L	Cure
Piano[9]	Randomized clinical trial	16	Nosocomial SBP	Enterococcal species	6 mg/Kg/day plus meropenem	Cure:13 patients Failure: 3 patients
Current case	Case report	1	SBP	MRSA	6 mg/kg/day	Cure

VR, vancomycin-resistant; IP, intraperitoneal; MRSA, methicillin-resistant Staphylococcus aureus; SBP, spontaneous bacterial peritonitis.

anti-bacterial activity than vancomycin or linezolid.[6] Daptomycin has also been studied in patients undergoing peritoneal dialysis and pharmacokinetic data showed a good activity of daptomycin and optimal levels of the drug in peritoneal fluid.[7] Moreover, Tascini *et al.* reported the drug to be effective at a dose of 8 mg/kg/day in the treatment of biliary-tract infections, and the drug reached significant concentrations both in bile and serum.[8] In Table 2 is reported the review of literature about use of daptomycin in primary or secondary bacterial peritonitis.[9-16] Recently, Piano *et al.* reported as the empiric use of daptomycin in association with meropenem was more effective than ceftazidime in the antibiotic treatment of nosocomial SBP due to *Enterococcus* spp.[9]

The approved dose of daptomycin is 6 mg/kg/day for bacteremia, although there is convincing evidence that higher doses are needed in critical patients with sepsis.[17,18] In fact, patients with severe sepsis or in septic shock have several dysfunctions in the acute phase that can significantly reduce the serum levels of daptomycin. It may thus be necessary to increase the dose to 10 mg/kg/day or use a fixed dose such as 750 mg/day (doses should be reduced as soon as the patient achieves hemodynamic compensation).[17] However, in the presence of reduced glomerular filtration the dose of daptomycin in cirrhotic patients should be carefully monitored, dosing the levels of the drug if possible, and reserving high doses only for critical cases.

Conclusions

We describe a case of SBP caused by MRSA in a cirrhotic patient with Child-Pugh stage C that was successfully treated with daptomycin. Additional clinical and pharmacokinetic data is needed regarding the available treatment options, including daptomycin. Considering its spectrum of activity of activity, tolerability, and preliminary results on concentrations at the sites of infection, daptomycin may be an option of interest in this setting.

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