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MINIREVIEWS

Spontaneous bacterial peritonitis due to carbapenemase-producing *Enterobacteriaceae*: Etiology and antibiotic treatment

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Abstract

Carbapenem antibiotics were first introduced in the 1980s and have long been considered the most active agents for the treatment of multidrug-resistant gram-negative bacteria. Over the last decade, carbapenem-resistant *Enterobacteriaceae* (CRE) have emerged as organisms causing spontaneous bacterial peritonitis. Infections caused by CRE have shown a higher mortality rate than those caused by bacteria sensitive to carbapenem antibiotics. Current antibiotic guidelines for the treatment of spontaneous bacterial peritonitis are insufficient, and rapid de-escalation of empiric antibiotic treatment is not widely recognized. This review summarizes the molecular characteristics, epidemiology and possible treatment of spontaneous bacterial peritonitis caused by CRE.

Key Words: Spontaneous bacterial peritonitis; Carbapenem-resistant *Enterobacteriaceae*; Carbapenem-resistant *Klebsiella pneumoniae*; Cirrhosis

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Core Tip: Carbapenem antibiotics were first introduced in the 1980s and have long been considered the most active agents for the treatment of multidrug-resistant gram-negative bacteria. Over the last decade carbapenem-resistant *Enterobacteriaceae* (CRE) have emerged as organisms causing spontaneous bacterial peritonitis (SBP). Infections caused by CRE have shown a higher mortality rate than those caused by bacteria sensitive to carbapenem antibiotics. Current antibiotic guidelines for the treatment of SBP are insufficient, and rapid de-escalation of empiric antibiotic treatment is not widely recognized. This review summarizes the molecular characteristics, epidemiology and possible treatment of SBP caused by CRE.

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INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a common complication in patients with cirrhosis. It is defined as ascitic fluid infection in the absence of alternative surgically treatable sources of intra-abdominal infection[1]. SBP diagnosis relies on ascitic fluid polymorphonuclear cell count greater than or equal to 250 cells/mm^3. Microbiological culture, either from ascitic fluid or the bloodstream, enables identification of the etiological pathogen[2,3]. Approximately 2.5% of all hospitalizations of patients with cirrhosis are for SBP, and the short-term mortality is about 25%[4]. In-hospital mortality remains a significant burden to the healthcare system, especially in patients with concurrent risk factors such as older age, female gender, hepatic encephalopathy, coagulopathy, variceal hemorrhage, sepsis, pneumonia and acute kidney injury[5].

Historically, the most frequent etiological agents remain gram-negative bacteria (GNB), especially *Enterobacteriaceae* spp. Although in recent times gram-positive bacteria (GPB) appear to be on the rise[6,7]. Today, SBP due to multidrug-resistant (MDR) bacteria represents a growing and complex healthcare problem. Infections caused by MDR-bacteria carry a high mortality rate in the cirrhotic patient[8]. This is likely due to difficulty in establishing an effective antibiotic regimen along with a depressed immune system[9].

SBP due to MDR bacteria proves to be a clinical challenge[10,11], and clinicians should consider reported resistance profiles for the decision-making process in deciding empiric antibiotic regimens[12]. Third generation cephalosporins that for decades have been used as the treatment of choice for community acquired-SBP should no longer be used as first-line therapy[13]. Carbapenem antibiotics, introduced in the 1980s, have long been considered the most active agents against MDR-GNB. Unfortunately, over the last decade carbapenem-resistant *Enterobacteriaceae* (CRE) have emerged as SBP causing bacteria[14] and have shown a higher mortality rate than infections caused by bacteria sensitive to carbapenem antibiotics[15]. Current antibiotic guidelines for the treatment of SBP are insufficient[9,16], and rapid de-escalation of empiric antibiotic treatment is not widely recognized[17]. This review summarizes the molecular characteristics, epidemiology, and possible treatment of SBP caused by CRE.

THE BURDEN OF CARBAPENEMASE-PRODUCING ENTEROBACTERIACE IN SPONTANEOUS BACTERIAL PERITONITIS

The health burden caused by cirrhosis corresponds to 14-26 new cases per 100000 individuals and results in 170000 deaths per year in Europe[18]. Cirrhotic patients have a higher susceptibility to infections caused by resistant bacteria (repeat hospitalizations and antibiotic exposure for long-term prophylaxis of SBP), and the management of these patients has become a major global health concern. In addition, antimicrobial resistance has emerged as a public health crisis. In the case of SBP, gram-positive cocci (methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant

Enterococci), extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* and CRE are emerging as the causative agents[19].

While resistant GPB can be common, the classes of resistant *Enterobacteriaceae* are much rarer and more devastating[20]. The spread of these pathogens is difficult to control because of a potential huge intestinal reservoir[21]. A recent single-center Italian study reported that the prevalence of extensively resistant (XDR) organisms increased from 16% between 2008-2009 to 36% between 2012-2013[22]. In patients with decompensated cirrhosis the major determinants of prognosis are bacterial infections, especially if caused by resistant pathogens. This can be shown to increase mortality rate four-fold[23]. The likely cause of resistant pathogens in cirrhotic patients is the inadequate long-term empirical prophylactic antibiotic treatment that they are prescribed. This results in antimicrobial resistance with life-threatening consequences. Between 11% and 45% of patients with SBP and spontaneous bacteremia are infected with organisms resistant to tigecycline, which is an antibiotic that seems to be effective in the majority of healthcare-associated and nosocomial infections[10]. The overall proportion of MDR bacteria in patients with nosocomial SBP was 22% to 73% of cases across multiple studies[24].

The high prevalence of MDR or XDR pathogens causing SBP are directly linked to high mortality rates. It is therefore not a surprise that we have been forced to incorporate empiric use of carbapenems. The rising global empiric administration of carbapenems has now created a selection pressure promoting the emergence of CRE[25]. It has furthermore been proven that the efficacy of empirical antibiotic therapy in nosocomial SBP is very low, ranging from 26% to 67.6%[26].

Piano *et al*[14] reported that even targeted therapy proved difficult for infection resolution. They described a case of SBP due to carbapenemase-producing *Klebsiella pneumoniae* (KPC) in a 57-year-old patient that was treated with meropenem for an extended period. The KPC found *via* nasal swab was susceptible to colistin and tigecycline but did not respond to treatment and ultimately led to death within 10 d. In 2015, Li *et al*[27] studied 31 patients affected by SBP both nosocomial and non-nosocomial acquired. Among these patients, four presented with KPC and two with *Escherichia coli* (*E. coli*) resistant to meropenem. While the *E. coli* cases were nosocomial-SBP, half of the KPC patients were found to be non-nosocomial, demonstrating spread of infection outside the nosocomial setting, which is where empiric treatment is more common.

Similar difficulties of treatment have been reported by Alexopoulou *et al*[28] in 2016. In this study the authors analyzed data from 130 patients affected by SBP. Meropenem showed a drug resistance rate of 30.7%. The 77% of pathogens resistant to meropenem were susceptible to colistin, while the 86% of GNB were susceptible to tigecycline. Only 54% of the pathogens resistant to meropenem were susceptible to tigecycline. All but one XDR bacteria were susceptible to a possible combination of colistin and tigecycline.

That same year, Lutz *et al*[29] described ninety-two SBP cases, three of which were *Enterococcus faecium* resistant to carbapenems. Tudorascu *et al*[30] found cases of carbapenem-resistant *E. coli*, KPC and carbapenem-resistant *Enterobacter* spp. In Italy, Salerno *et al*[31] reported one case of carbapenem-resistant *E. coli* and seven cases due to KPC. Béjar-Serrano *et al*[32] in 2019 reported a case of SBP caused by carbapenemase-producing *Enterobacter cloacae* (*E. cloacae*). Table 1 summarizes the findings of the studies mentioned above describing the total number of patients affected by SBP and the number of SBP caused by CRE. Furthermore, it describes the type of pathogen involved and if the SBP was nosocomial or non-nosocomial acquired.

MOLECULAR CHARACTERISTICS OF CARBAPENEMASE-PRODUCING *ENTEROBACTERIACEAE* CAUSING SPONTANEOUS BACTERIAL PERITONITIS

Enterobacteriaceae show two major types of antibiotic resistance. One mechanism involves the expression of ESBL, which render bacteria resistant to cephalosporins and monobactams. The other mechanism of resistance, which is even more troubling, is the expression of carbapenemases, which render bacteria resistant to almost all available β-lactams including the carbapenems[33]. These bacteria are called carbapenemase-producing CRE. Carbapenemases represent the most versatile family of β-lactamases, with a breadth of activity unrivaled by other β-lactam-hydrolyzing enzymes. Although known as "carbapenemases," many of these enzymes recognize almost all

Table 1 Synthesis of a selection of the studies published on spontaneous bacterial peritonitis due to carbapenem-resistant *Enterobacteriaceae* producing pathogens

Ref.	Total number SBP/CRE SBP	CRE	CRE N-SBP/Total SBP	Not-N-SBP/Total SBP
Piano *et al*[14], 2012	1/1	*K. pneumoniae*	1/1	0/1
Li *et al*[27], 2015	31/6	*K. pneumoniae, E. coli*	2/4, 2/2	2/4, 0/2
Alexopoulou *et al*[28], 2016	130/6	*K. pneumoniae, E. coli*	5/5, 1/1	0/5, 0/1
Lutz *et al*[29], 2016	92/3	*E. faecium*	3/3	0/3
Tudorascu *et al*[30], 2016	64/3	*K. pneumoniae, E. coli, Enterobacter*	1/1, 1/1, 1/1	0/1, 0/1, 0/1
Salerno *et al*[31], 2016	56/8	*K. pneumoniae, E. coli*	5/7, 0/1	7/2, 1/1
Béjar-Serrano *et al*[32], 2019	22/1	*E. cloacae*	1/1	0/1

CRE: Carbapenem-resistant *Enterobacteriaceae*; N: Nosocomial; SBP: Spontaneous bacterial peritonitis; CRE SBP: Spontaneous bacterial peritonitis due to carbapenem-resistant *Enterobacteriaceae*; CRE N-SBP: Nosocomial spontaneous bacterial peritonitis due to carbapenem-resistant *Enterobacteriaceae*; Not-N-SBP: Not nosocomial spontaneous bacterial peritonitis; *K. pneumoniae: Klebsiella pneumoniae; E. coli: Escherichia coli; E. cloacae: Enterobacter cloacae; E. faecium: Enterococcus faecium*.

hydrolyzable-lactams and are resilient against inhibition by all commercially viable β-lactamase inhibitors.

Carbapenemases are classified according to the degree of homology of the respective polypeptide chains. According to Ambler classification, four classes of enzymes are recognized. Classes A, C and D include the β-lactamases with serine at their active site, whereas molecular class B β-lactamases (MβLs) are all metalloenzymes with zinc at their active-site[34]. Currently, among the four classes of β-lactamases defined by the Ambler classification system, three have been identified to give resistance to carbapenems: (1) The class A of β-lactamases in which KPC is included; (2) The class B of metal-β-lactamases to which the imipenemase (IMP) and the Verona integron-encoded metal-β-lactamase [Verona imipenemase (VIM)] belong; and (3) The class D to which β-lactamases, such as oxicillinase oxacillin-hydrolyzing (OXA)-48, belong[35].

These enzymes are coded starting from specific genes that can be acquired in two ways: By transfer through plasmid or by clonal bacterial strain expansion[36]. Class A carbapenemases have a serine in the active state in position 70 and can hydrolyze carbapenemics, cephalosporins, penicillins and aztreonam while being inhibited by clavulanic acid and tazobactam. The enzymes KPC-1, KPC-2, KPC-3, *Guiana-Extended-Spectrum* (GES)-4, GES-5 and GES-6 have been found mainly in *Klebsiella pneumoniae*. *Serratia marcescens (S. marcescens)* enzyme (SME)-1, SME-2 and SME-3 have been found in *S. marcescens*; NMC-A and KPC-3 have been found in *E. cloacae,* and GES-5 has been found in *E. coli*[34]. These enzymes are summarized in Table 2.

KPC and GES are associated with mobile elements. None have been reported yet for the SME genes[37,38]. Figure 1 illustrates the different kind of genes and mobile elements related to each class of carbapenemase with the site of action, the inhibitor substances and the antimicrobials hydrolyzed for each class of enzymes.

Class B enzymes are characterized by resistance to beta-lactamase inhibitors. They share hydrolytic activity with Class A carbapenemases but are not effective against aztreonam. The hydrolysis mechanism depends on the activation of the active site by zinc ions. This feature makes them highly sensitive to inhibition by ethylene diamine tetraacetic acid, which is capable of chelating zinc and other cations. Although the amino acid homology of these proteases is poor (about 23%), all the class B carbapenemases show excellent zinc binding capacity and a well-preserved active site[39]. The B carbapenemases have been found, as described in Table 3, mainly in *Klebsiella pneumoniae* (IMP-1, IMP-1-like, IMP-4, VIM-1, VIM-2-like, VIM-4), *E. coli* (VIM-1, IMP-4, IMP-1-like), *S. marcescens* (IMP-1-like, VIM-2, VIM-2-like), *E. cloacae* (VIM-1, VIM-2, VIM-2-like, VIM-5, VIM-4, IMP-1-like, IMP-4, IMP-8) and *Citrobacter freundii* (IMP-1, IMP-1-like, VIM-2)[34]. Shown in Figure 1, these enzymes are associated with respective genes such as VIM, NMD and IMP. Furthermore, they are associated with several mobile elements (*i.e.* IncN, IncI1, multiple types; class I integrons, IncL/M, IncA/C)[37].

Class D enzymes include oxacillin-hydrolyzing–β-lactamases identified mainly in

Table 2 Class A carbapenemase asset found in each pathogen

Pathogens	Class A carbapenemase									
	KPC-1	KPC-2	KPC-3	GES-4	GES-5	GES-6	SME-1	SME-2	SME-3	NMC-A
K. pneumoniae	+	+	+	+	+	+				
S. marcescens							+	+	+	
E. coli					+					
E. cloacae			+							+

KPC: *Klebsiella pneumoniae*; GES: *Guiana-Extended-Spectrum*; SME: *Serratia marcescens* enzyme; *K. pneumoniae: Klebsiella pneumoniae; E. coli: Escherichia coli; E. cloacae: Enterobacter cloacae; S. marcescens: Serratia marcescens*.

Table 3 Class B carbapenemase asset found in each pathogen

Pathogens	Class B carbapenemase									
	IMP-1	IMP-1-like	IMP-4	IMP-8	VIM-1	VIM-1-like	VIM-2	VIM-2-like	VIM-4	VIM-5
K. pneumoniae	+	+	+		+		+		+	+
S. marcescens		+				+	+	+		
E. coli		+	+			+				
E. cloacae		+	+	+	+		+	+	+	+
C. freundii	+	+					+			

IMP: Imipenemase; VIM: Verona imipenemase; *K. pneumoniae: Klebsiella pneumoniae; E. coli: Escherichia coli; E. cloacae: Enterobacter cloacae; S. marcescens: Serratia marcescens*; *C. freundii: Citrobacter freundii*.

Enterobacteriaceae and *Pseudomonas aeruginosa*[40]. Functionally they are penicillinases capable of hydrolyzing both oxacillin and cloxacillin. These enzymes are characterized by extreme variability in the amino acid sequence producing many enzyme variants that are only weakly inhibited by ethylene diamine tetraacetic acid and clavulanate[41]. The molecular structure was analyzed by detecting a homology with class A enzymes with serine in the active site in positions varying between 70 and 73 in the S-T-F-K tetrad[34]. The active site of the D carbapenemases is very efficient due to its small size and increased hydrophobicity due to the tyrosine and methionine residues present in position 112 and 223, respectively. The OXA carbapenemases have highly conserved structures in position 144-146 with sequence Y-G-N and in position 216-218 with sequence K-T-G. At present, 102 distinct OXA enzymes have been identified, of which at least 37 (9 broad spectrum enzymes) are to be considered carbapenemases. These 37 were then divided into 9 main subgroups based on an amino acid homology exceeding 92.5%[42]. Subgroups 1 and 2 share the substitution F with Y in the sequence Y-G-N that does not seem to improve the hydrolyzation of the imipenem compared to the other carbapenemases.

The mechanism of action is similar to other serine-carbapenemases but carbon dioxide seems to influence the kinetics of OXA-carbapenemases. In cases of high carbon dioxide concentrations, the carboxylation of lysine occurs in position 73 activating the serine at the catalytic site[43]. OXA carbapenemases act on penicillin, cephalosporin and imipenem with faster hydrolysis of imipenem than meropenem[44]. These enzymes, as described in Table 4, have been found mainly in *Klebsiella pneumoniae* (OXA-48, OXA-181, OXA-163), *S. marcescens* (OXA-48), *E. coli* (OXA-48, OXA-244, OXA-181) and *E. cloacae* (OXA-48). They are associated with *OXA* genes and several mobile elements (*i.e.* IncL/M, Tn1999, IS1999)[37], as reported extensively in Figure 1.

Table 4 Class D carbapenemase asset found in each pathogen

Pathogens	Class D carbapenemase			
	OXA-48	OXA-163	OXA-181	OXA-244
K. pneumoniae	+	+	+	
S. marcescens	+			
E. coli	+		+	+
E. cloacae	+			

OXA: Oxacillin-hydrolyzing; *K. pneumoniae: Klebsiella pneumoniae; E. coli: Escherichia coli; E. cloacae: Enterobacter cloacae; S. marcescens: Serratia marcescens.*

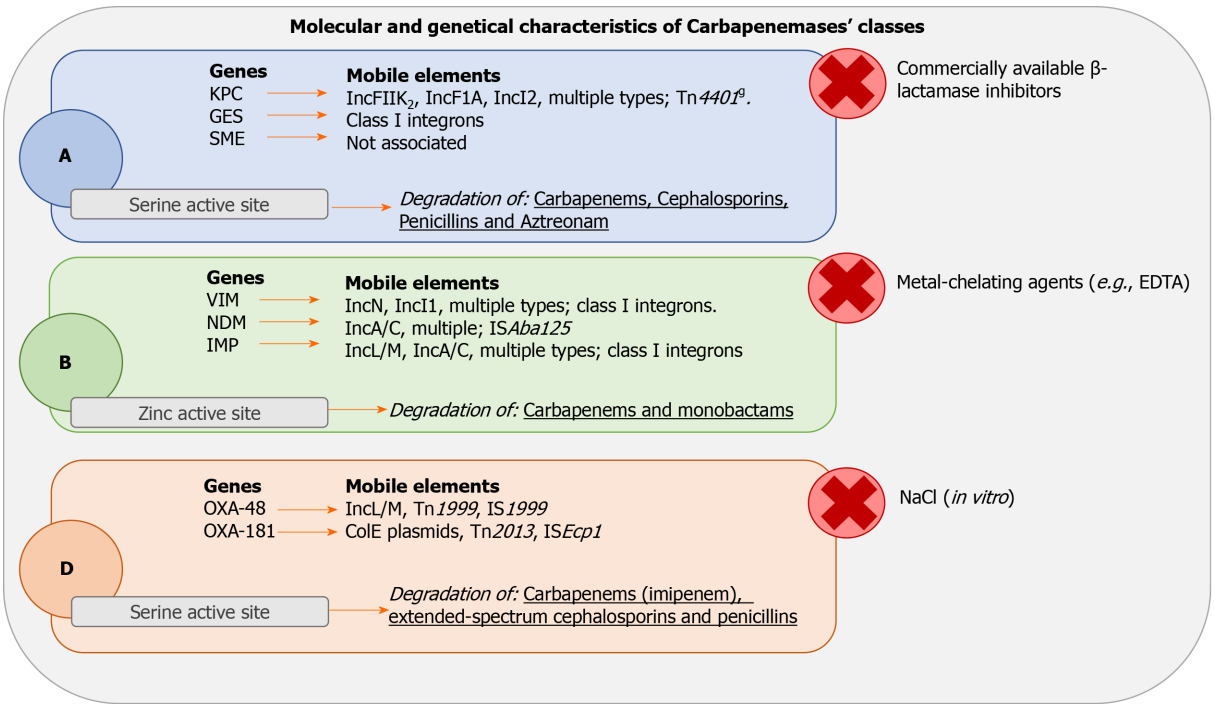

Figure 1 Molecular characteristics, genetics and activity of carbapenems classes. A: Class A carbapenemases; B: Class B carbapenemases; D: Class D carbapenemases; GES: *Guiana-Extended-Spectrum*; SME: *Serratia marcescens* enzyme; KPC: *Klebsiella pneumoniae* carbapenemase; VIM: Verona imipenemase; NDM: New Delhi carbapenemase; IMP: Imipenemase; OXA: Oxacillinase.

ANTIMICROBIAL MANAGEMENT OF SPONTANEOUS BACTERIAL PERITONITIS DUE TO CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE

Aminoglycosides, mainly amikacin and gentamicin, have been widely utilized in the era of limited treatment options for the management of CRE[45]. Overall, antimicrobial susceptibility for CRE varies[46]. These antibiotic agents require high dose daily administration with therapeutic drug monitoring to optimize their use[46-48]. Plazomicin is a newly marketed aminoglycoside. It is approved for the management of complicated urinary tract infections (cUTI) in patients with limited or no options for alternative treatment[49]. It has activity against GNB producing ESBL, KPC and AmpC[50,51]. Overall, it has poor activity against nonfermenting GNB[52,53].

Colistin is an old polymyxin widely utilized for the management of serious infections due to CRE[47,48,54,55]. Colistin resistance remains low among nonfermenting GNB but is increasing in *Klebsiella* spp. producing KPC enzymes[56]. Its role as monotherapy or within a combination regimen is still under discussion due to the absence of reliable data[48,57,58]. Fosfomycin is another old antibiotic utilized in the treatment of infections due to CRE in critically ill patients[59]. It has activity against GPB and GNB, including MDR strains such as CRE. However, during monotherapy rapid emergence of antibiotic resistance has been described[17,60,61]. High doses of tigecycline

have been widely utilized as a last-resort option for the treatment of serious infections due to CRE. It is a glycylcycline with activity against a broad range of GPB and GNB including MDR strains but not *Pseudomonas* spp. or *Proteus* spp.[62].

Eravacycline is a synthetic fluorocycline antibiotic recently approved for the treatment of complicated intra-abdominal infections (cIAI). It has broad spectrum activity including MDR and XDR isolates with the exception of *Pseudomonas* spp. and *Burkholderia* spp. Overall, it has activity against GNB producing ESBL, KPC, AmpC, MβL and OXA enzymes[6,7,20,50]. Moreover, eravacycline is active against the most common tetracycline-resistance mechanisms such as efflux and ribosomal protection[63]. In IGNITE 1 and 4 clinical trials, it showed a high clinical and microbiological response with a favorable safety and tolerability profile in patients with cIAIs[64,65]. Eravacycline also has a high oral bioavailability that can facilitate a sequential antibiotic regimen (from intravenous to oral formulation) with patients being discharged home[66].

Among β-lactam antibiotics, ceftazidime/avibactam is a novel cephalosporin/β-lactamase inhibitor combination with activity against several GNB including strains producing ESBL, KPC, AmpC and some OXA enzymes (OXA-48)[50]. In phase 2 and 3 clinical trials, ceftazidime/avibactam demonstrated efficacy and safety in patients with cIAIs[67-69]. It was successfully used as salvage therapy in patients with severe infections due to CRE[70,71]. Of note, emergence of resistance during therapy has already been described[30]. The appropriate use of ceftazidime/avibactam in the management of CRE infections as monotherapy or part of combination regimen is still an open debate[72].

Meropenem/vaborbactam is a novel carbapenem/β-lactamase inhibitor combination with activity against GNB producing ESBL, KPC and AmpC but not MβL and OXA enzymes[50-52,73]. Meropenem/vaborbactam was approved for the treatment of bacteremic cUTI, cIAIs, hospital-acquired pneumonia including those associated to mechanical ventilators (hospital-acquired pneumonia and ventilator associated pneumonia) and for the treatment of all infections due to GNB where treatment options were limited. In TANGO 1 and 2 clinical trials, meropenem/vaborbactam was associated with high clinical and microbiological success[74,75]. In a sensitivity analysis of the TANGO 2 clinical trial among patients without prior antibiotic failure, meropenem/vaborbactam showed a significant higher clinical cure rate at the test-of-cure visit and a lower day-28 all-cause mortality than the best available therapy[75].

In a multicenter retrospective cohort study, meropenem/vaborbactam was found to have similar clinical success to ceftazidime/avibactam (69% *vs* 62%; $P = 0.49$)[76]. Although the propensity of meropenem/vaborbactam for development of resistance is lower than ceftazidime/avibactam, mechanisms of antibiotic resistance are described (porin mutations and increase in the blaKPC expression)[77,78]. Interestingly, an *in vitro* study showed a synergistic effect of meropenem/vaborbactam plus a ceftazidime/avibactam combination against susceptible KPC strains but also against both meropenem/vaborbactam and ceftazidime/avibactam-resistant KPC isolates[79].

Imipenem/cilastatin/relebactam is another novel carbapenem/β-lactamase inhibitor combination with activity against GNB producing ESBL, KPC and AmpC enzymes[50-52]. Imipenem/cilastatin/relebactam was approved for the management of cUTIs and cIAIs in adult patients with limited or no available treatment options. In a phase 3 clinical trial (RESTORE-IMI 1), imipenem/cilastatin/relebactam was found as an effective and well-tolerated treatment agent for CRE infections[80].

Aztreonam/avibactam is a monobactam and β-lactamase inhibitor combination in the late form of development. It has activity against GNB producing ESBL, KPC, AmpC, MβL and some OXA enzymes (OXA-48)[50-52]. Cefiderocol is a siderophore cephalosporin recently approved for the treatment of cUTIs in adults. It has a broad spectrum of activity against GNB, including MDR *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*[50]. The approved drugs used to treat these CRE producing pathogens causing SBP are displayed with their advantages and disadvantages in Table 5.

Many more agents are in several phases of development: Cefepime/taniborbactam (phase 3), cefepime/enmetazobactam (phase 3), sulbactam/durlobactam (phase 3), sulopenem/etzadroxil/probenecid (phase 3), tebipenem pivoxil hydrobromide (phase 3), BOS-228 (phase 2), OP0595/RG6080 (phase 1), QPX-2015/QPX-7728 (phase 1), SPR206 (phase 1), SPR741 (phase 1), TP-6076 (phase 1) and WCK 5222 (phase 1).

CONCLUSION

SPB due to CRE is a major concern for hepatologists. Overall, CRE infections are

Table 5 Advantages and disadvantages of the antimicrobials used to treat spontaneous bacterial peritonitis due to gram-negative bacteria producing carbapenem-resistant *Enterobacteriaceae*

Antimicrobial agent	Advantages	Disadvantages	Ref.
Aminoglycosides (*i.e.* Plazomicin)	Good activity against GNB producing ESβL, KPC, AmpC but not MβL enzymes	Heterogeneous susceptibility high dose (toxicity)	[49]
Polimixins (*i.e.* Colistin)	Low resistance emergence	Low efficacy for *Klebsiella* spp. producing KPC enzymes	[56]
Fosfomicyn	Moderate activity against MDR–CRE	Rapid emergence of antibiotic resistance	[59]
Glycylcycline (*i.e.* Tigecycline)	Good activity against MDR–CRE	High dose (toxicity)	[62]
Fluorocycline (*i.e.* Eravacycline)	Broad spectrum activity (even if MDR and XDR pathogens). Active against the most common tetracycline-resistance mechanisms. High oral bioavailability. Safety and tolerability	Not active on *Pseudomonas* spp. and *Burkholderia* spp.	[63-65]
β-lactams/β-lactamase inhibitors (*i.e.* ceftazidime/avibactam)	Good activity against GNB producing ESβL, KPC, AmpC, OXA-48 and MβL. Safety and tolerability	Frequent emergence of antibiotic resistance	[67]
Carbapenem/β-lactamase inhibitors (*i.e.* meropenem/vaborbactam or Imipenem/cilastatin/relebactam)	Good activity against GNB producing ESβL, KPC and AmpC. Outcome improvement	Not active on GNB producing OXA-48 and MβL	[79]
Monobactam/β-lactamase inhibitor (*i.e.* aztreonam/avibactam)	Good activity against GNB producing ESβL, KPC, AmpC and OXA-48	Recently approved	[50-52]
Siderophore cephalosporin (*i.e.* Cefidecol)	Broad spectrum of activity against GNB, including MDR *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *A. baumannii*	Recently approved	[50]

GNB: Gram-negative bacteria; ESβL: Extended-spectrum β-lactamase; CRE: Carbapenem-resistant *Enterobacteriaceae*, KPC: *Klebsiella pneumoniae*; MβL: Molecular class B β-lactamases; MDR: Multidrug resistant; XDR: Extensively resistant.

associated with an increased risk of morbidity and mortality. Current antibiotic guidelines for the treatment of SBP caused by CRE are insufficient. This review summarizes the current molecular characteristics, epidemiology and possible treatment regimens for CRE causing SBP. Many new antibiotics are being introduced into clinical practice and others are still in the preclinical and clinical phases of development. Further research of these novel agents is required for appropriate use (microbiological activity and pharmacokinetic/pharmacodynamic parameters). A multidisciplinary approach (hepatologists, infectious diseases specialists, intensivists, microbiologists, pharmacists) is essential for the adequate placement of these newer anti-infective agents in therapy. In order to optimize antimicrobial treatments and preserve the antibiotic armamentarium, a careful knowledge of local microbiological epidemiology and antibiotic-resistant rates along with detailed antimicrobial stewardship programs must be applied.

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