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Newer antibiotics for the treatment of peritoneal dialysis-related peritonitis

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Abstract

Peritonitis is a debilitating infectious complication of peritoneal dialysis (PD). Drug-resistant bacterial peritonitis typically has a lower response rate to antibiotics. In the past 15 years, newer antibiotics with activities against drug-resistant Gram-positive bacteria have been developed. In most circumstances, peritonitis due to methicillin-resistant staphylococci responds to vancomycin. If vancomycin cannot be used due to allergy and/or non-susceptibility, there is increasing evidence that linezolid and daptomycin are the drugs of choice. It is reasonable to start linezolid orally or intravenously, but subsequent dose reduction may be necessary in case of myelosuppression. Daptomycin can be given intravenously or intraperitoneally and has excellent anti-biofilm activity. Other treatment options for drug-resistant Gram-positive bacterial peritonitis include teicoplanin, tigecycline and quinupristin/dalfopristin. Teicoplanin is not available in some countries (e.g. the USA). Tigecycline can only be given intravenously. Quinupristin/dalfopristin is ineffective against *Enterococcus faecalis* and there is only low-quality evidence to support its efficacy in the treatment of peritonitis. Effective newer antibiotics against drug-resistant Gram-negative bacteria are lacking. Polymyxins can be considered, but evidence on its efficacy is limited. In this review, we will discuss the potential use of newer antibiotics in the treatment of drug-resistant bacterial peritonitis in PD patients.

Key words: CAPD, end-stage renal disease, peritoneal dialysis, peritonitis, sepsis

Introduction

Peritonitis is a debilitating infectious complication in patients undergoing peritoneal dialysis (PD) [1]. A low peritonitis rate is a prerequisite for a successful and sustainable PD program [2]. The International Society of Peritoneal Dialysis (ISPD) has published guidelines on the prevention and treatment of peritonitis [3–8]. Despite these well-established guidelines, data from a large national PD cohort failed to show consistent improvement in peritonitis rates and outcomes [9]. This might be partly attributed to increasing incidence of peritonitis caused by drug-resistant organisms [10].

Camargo *et al.* [11] reported that the oxacillin resistance rate of coagulase-negative *Staphylococcus* (CNS) was nearly 70% in a Brazilian center. A recent study from India showed that 28.6% of *Staphylococcus aureus* were resistant to methicillin (MRSA), 15.4% of enterococci were resistant to vancomycin (VRE) and 54.3% of Enterobacteriaceae were extended-spectrum β-lactamase (ESBL) producers [12]. Another recent study from China revealed that 35.5% of *Escherichia coli* peritonitis was due to ESBL-producing strains [13]. Peritonitis caused by carbapenem-resistant *Acinetobacter* and multidrug-resistant *Acinetobacter* is another serious problem [14].

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Table 1. Selected newer antibiotics approved by the FDA since 1999

Year of approval	Antibiotic	Route	Drug class	Indications
2015	Ceftazidime/ avibactam	IV	Cephalosporin/ β-lactamase inhibitor	Complicated intra-abdominal and urinary tract infections
2014	Dalbavancin	IV	Lipoglycopeptide	Acute bacterial skin and skin structure infections
	Oritavancin	IV	Lipoglycopeptide	Acute bacterial skin and skin structure infections
	Tedizolid	IV/PO	Oxazolidone	Acute bacterial skin and skin structure infections
	Ceftolozane/ tazobactam	IV	Cephalosporin/ β-lactamase inhibitor	Complicated intra-abdominal and urinary tract infections
2013	Telavancin	IV	Lipoglycopeptide	Hospital-acquired and ventilator-associated bacterial pneumonia
2010	Ceftaroline	IV	Cephalosporin	Acute bacterial skin and skin structure infections, bacterial pneumonia
2009	Telavancin	IV	Lipoglycopeptide	Complicated skin and skin structure infections
2007	Doripenem	IV	Carbapenem	Complicated intra-abdominal infection, complicated urinary tract infection
2005	Tigecycline	IV	Glycylcycline	Complicated skin and skin structure infections, complicated intra-abdominal infections
2003	Daptomycin	IV	Lipopeptide	Complicated skin and skin structure infections, *S. aureus* bloodstream infections, including those with right-sided infective endocarditis
2001	Ertapenem	IV	Carbapenem	Community-acquired pneumonia, intra-abdominal, skin, urinary tract, kidney and post-surgical gynecological infections
2000	Linezolid	IV/PO	Oxazolidinone	Uncomplicated and complicated skin and skin structure infections, community-acquired pneumonia, nosocomial pneumonia and VRE infections including concurrent bacteremia
1999	Moxifloxacin	IV/PO	Flouroquinolone	Sinusitis, bronchitis, pneumonia, skin structure infections
1999	Quinupristin/ dalfopristin	IV	Streptogramin	Complicated skin and skin structure infections, vancomycin-resistant *Enterococcus faecium* infection (including bacteremia)

IV, intravenous; PO, per oral.

In 2009, the Infectious Diseases Society of America highlighted the impact of the 'ESKAPE' pathogens, including *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*, as a group of particularly troublesome bacteria that can 'escape' the effects of conventional antimicrobial therapy [15, 16]. The primary response and complete cure rates are typically lower in drug-resistant bacterial peritonitis. Newer antibiotics are now available and some of them are particularly effective against drug-resistant Gram-positive bacteria. In this review, we will focus on antibiotics that have received US Food and Drug Administration (FDA) approval since 1999, as presented in Table 1. The revival of polymyxins (polymyxin B and colistin) for the treatment of multidrug-resistant Gram-negative bacteria will also be discussed. Treatment of peritonitis due to drug-resistant fungi and mycobacterium species is beyond the scope of this review.

Oxazolidinone

Linezolid was the first available oxazolidinone antibiotic and received FDA approval in 2000. It binds to the ribosomal peptidyl transferase center and stops bacterial growth by inhibiting protein synthesis. It is effective against many drug-resistant Gram-positive bacteria, including methicillin-resistant *Staphylococcus epidermidis* (MRSE), MRSA, vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA) and VRE [17]. Linezolid is bacteriostatic against staphylococci and enterococci. The reported overall linezolid resistance rate remained low [18–20].

Linezolid has been used successfully to treat VRE peritonitis [21–28]. The optimal dosage of linezolid in PD patients, however, remains controversial. The non-renal route accounts for ~65% of total linezolid clearance. Under steady states, ~30% of linezolid appears in the urine as unchanged drug, 40% as hydroxyethyl glycine metabolite and 10% as aminoethoxyacetic acid metabolite [29]. According to the package insert, no dosage adjustment is recommended in patients with renal insufficiency. In the reported cases of VRE peritonitis, linezolid 600 mg twice daily (intravenous, IV or per oral, PO) was used [21–28]. However, the ISPD guidelines recommend linezolid 200–300 mg daily PO for the treatment of peritonitis based on the recommendation of a renal drug reference guide [8].

Previous *in vitro* study showed that the MIC_{50} and MIC_{90} (minimum inhibitory concentration required to inhibit 50 and 90% of bacterial growth, respectively) of linezolid were ≤2 mg/L for CNS, *S. aureus*, enterococci (including VRE) and *Corynebacterium* species [30]. When PD patients were given oral linezolid 375 mg twice daily, a trough level of >4 mg/L could be achieved, a level exceeding the MIC_{90} by at least 2-fold [30]. Bone marrow suppression was reported in a case series of four PD patients who received linezolid 600 mg twice daily [31, 32]. Among these patients, three were elderly (aged 66–87 years) and all had significantly elevated trough serum linezolid levels (range 22.5–30 mg/L; therapeutic target 2–7 mg/L). Linezolid was stopped in one patient and reduced to 300 mg twice daily in two patients. Linezolid was better tolerated after dose reduction. There was a fatal case in which a 57-year-old patient developed severe lactic acidosis and pancytopenia after taking linezolid 600 mg twice daily for 20 days [32]. While it is reasonable to start linezolid 600 mg twice daily in the initial phase, subsequent dose reduction may be necessary in some patients. Suffice to say, the risk of myelosuppression increases substantially when the duration of treatment goes beyond 10–14 days. However, since the typical duration of treatment for *S. aureus* peritonitis is 3 weeks, linezolid may have to be used for more than 2 weeks in patients with MRSA peritonitis. In elderly PD patients and/or those who require treatment for more than 2 weeks, therapeutic drug monitoring (TDM) of the serum linezolid level may be considered to guide dosage adjustment. A maintenance trough level of 2–7 mg/L and/or 24-h drug exposure (AUC_{24}) of 160–300 mg/L h has been suggested to maximize therapeutic

response and at the same time minimize toxicity [33]. The risk of toxicity increases substantially if the linezolid trough level exceeds 10 mg/L and/or AUC_{24} exceeds 400 mg/L h [33]. TDM of linezolid, however, is both expensive and not readily available in many centers. Alternatively, hematological parameters should be closely monitored. Thrombocytopenia is usually the first sign of myelosuppression. Linezolid concentration can be measured in PD fluid, but its role in TDM remains to be defined [34]. Linezolid is stable in 1.5 and 4.25% dextrose PD fluid (PDF) at different temperatures (4, 25 and 37°C) [35], but there are currently no data on the efficacy of intraperitoneal (IP) linezolid for the treatment of peritonitis. Other significant side effects of linezolid include serotonin syndrome, neuropathy and lactic acidosis.

Tedizolid is the second oxazolidinone antibiotic that received FDA approval in 2014 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs), including those caused by MRSA [36]. The mechanism of action of tedizolid is similar to linezolid, but it differs from linezolid by having a modified side chain at the C-5 position of the oxazolidinone nucleus [36]. Tedizolid has been shown to be effective *in vitro* against *S. aureus* and enterococci with reduced susceptibility to vancomycin, daptomycin or linezolid [37]. It is bacteriostatic against enterococci, staphylococci and streptococci. No dosage adjustment is required in patients with renal impairment and hemodialysis (HD) patients, but no data are available for PD patients [38]. In particular, tedizolid is incompatible with solutions containing divalent cations (e.g. calcium, magnesium), hence it cannot be added to PDF.

Lipopeptide

Daptomycin is a 13-amino acid, cyclic lipopeptide with bactericidal activity against Gram-positive bacteria. Daptomycin has a lipophilic decanoyl side chain, which, upon insertion into the bacterial cell membrane, causes rapid membrane depolarization and triggers a calcium-dependent rapid efflux of potassium ions. This loss of membrane potential causes inhibition of DNA, RNA and protein synthesis, leading to bacterial cell death [39]. Daptomycin was approved by the FDA in 2003 for the treatment of complicated skin and skin structure infections (cSSSI). In 2006, daptomycin was approved for the treatment of *S. aureus* (including MRSA) bloodstream infection and right-sided infective endocarditis. Daptomycin is excreted primarily by the kidney (~54%) and dosage adjustment is required in patients with renal impairment [40]. In PD patients, the recommended dose is 4–6 mg/kg every 48 h IV, depending on the indication [41]. The recommended dose is the same for PD and HD patients, although there was some evidence that the pharmacokinetics of daptomycin were different in patients on PD and HD [42, 43]. Daptomycin is highly protein-bound (90–93%) and drug elimination by PD may be increased in hypoalbuminemic patients [44]. After administration of IV daptomycin, peak concentration in the peritoneal cavity is reached in 12 h [45].

Apart from MRSA, previous *in vitro* study showed that daptomycin was also effective against MRSE and VRE [46]. However, a high daptomycin non-susceptibility rate has been reported among VISA isolates [47]. Antibiotic susceptibility patterns should be known before daptomycin is used to treat VISA, VRSA or VRE infections. Daptomycin has specific anti-biofilm activity *in vitro*, which theoretically is an additional benefit for the treatment of peritonitis [48]. In PD patients, daptomycin was successfully used for the treatment of VRE peritonitis as reported by Hassoun *et al.* [49] and Huen *et al.* [50]. In Hassoun's study, two doses of IP daptomycin 15 mg/kg 10 days apart was used. In Huen's study, one patient received a loading dose of IP daptomycin 100 mg/L in a 6-h dwell, followed by a maintenance dose of IP daptomycin 20 mg/L. The other patient received IP daptomycin 20 mg/L without a loading dose. Based on the result of the Huen study, the ISPD guidelines suggested a loading dose of IP daptomycin of 100 mg/L and a maintenance dose of 20 mg/L [8]. Bahte *et al.* treated an automatic PD (APD) patient with *S. aureus* peritonitis with IP daptomycin (7 mg/kg after the end of APD and dwelled for 12 h) [51]. This resulted in significant daptomycin overdose with a peak serum daptomycin level more than 10 times the MIC_{90} for MRSA. However, the authors did not report the clinical outcome or any adverse event in this patient. There is currently no dosage recommendation on the use of IP daptomycin in APD patients.

Since the publication of the latest ISPD guidelines, daptomycin has been used successfully to treat relapsing *S. epidermidis* peritonitis [52, 53], refractory MRSA peritonitis (combined with rifampicin) [54] and polymicrobial (micrococcus and enterococcus) peritonitis [55]. Recently, Taegtmeyer *et al.* reported their experience of treating a PD patient with pacemaker infection caused by *S. epidermidis* by using IP daptomycin [56]. Daptomycin remains stable in 1.36 and 2.27% dextrose PDF, as well as amino acid PDF up to 6 h at 25 and 37°C [57, 58]. Therefore, daptomycin should be added to PDF immediately before administration to patients and the dwell time should not exceed 6 h. Due to interference of icodextrin, high-performance liquid chromatography measurements of daptomycin in icodextrin are unreliable [57]. Patients on daptomycin should be monitored for symptoms of myopathy, eosinophilic pneumonitis and peripheral neuropathy.

Glycylcycline

Tigecycline is a novel glycylcycline that was approved by the FDA in 2005 for the treatment of cSSSIs and complicated intra-abdominal infections (cIAIs) caused by various Gram-positive (including MRSA), Gram-negative and anaerobic bacteria. Tigecycline binds to bacterial 30S ribosome, blocks the entry of transfer RNA and prevents protein synthesis by halting the incorporation of amino acids into peptide chains. Similar to tetracycline and minocycline, tigecycline is generally a bacteriostatic agent, although bactericidal activity has been reported against *S. pneumoniae* and *Legionella pneumophila* [59]. Tigecycline is effective *in vitro* against MRSE, VRE, ESBL-*E. coli*, meropenem-resistant *Klebsiella*, ceftazidime-resistant *Enterobacter* and meropenem-resistant *Acinetobacter* [60]. In PD patients, IV tigecycline has been used successfully to treat MRSA peritonitis [61]. Tigecycline has a large volume of distribution, resulting in high tissue concentrations but relatively low serum concentrations. Biliary excretion is the primary route of elimination and no dosage adjustment is recommended in patients with renal impairment, including HD patients [59]. There are no data available for PD patients. Tigecycline remains stable in 1.5% dextrose and icodextrin PDF at 4, 25 and 37°C [62]. Future clinical studies on the efficacy and safety of IP tigecycline are warranted.

Lipoglycopeptide

A lipoglycopeptide antibiotic has a lipophilic side chain that is linked to a glycopeptide. Similar to vancomycin, lipoglycopeptides exert bactericidal activity by inhibition of cell wall synthesis. The lipoglycopeptides are more potent than vancomycin against Gram-positive bacteria, including MRSA, VISA and VRE [63]. There are currently three FDA-approved lipoglycopeptides, namely telavancin, dalbavancin and oritavancin. All of them disrupt both cell wall synthesis and cell membrane integrity. Both

dalbavancin and telavancin are active against VISA, but has poor activity against VRSA. Oritavancin is active against both VISA and VRSA. Dalbavancin impairs transglycosylase activity and inhibits late stages of peptidoglycan synthesis, whereas oritavancin and telavancin anchor in the bacterial membrane by the lipophilic side chain and disrupt membrane integrity, leading to bacteriolysis [64]. Telavancin was first approved by the FDA in 2009 for the treatment of Gram-positive bacterial cSSSI. It was then approved in 2013 for the treatment of hospital-acquired and ventilator-associated pneumonia due to *S. aureus*. Dalbavancin and oritavancin received FDA approval in 2014 for the treatment of ABSSSI. Dalbavancin and oritavancin have prolonged half-lives, which allow for a once-weekly or twice-weekly regimen, respectively. Telavancin is not recommended in patients with creatinine clearance (CrCl) <10 mL/min. The pharmacokinetics of oritavancin have not been evaluated in patients with CrCl <30 mL/min. Dalbavancin can be used in patients with CrCl <30 mL/min with dosage adjustment, as well as HD patients without dosage adjustment. However, currently no data are available for their use in PD patients. Previous *in vitro* study showed that telavancin exhibited significantly better bactericidal effects against MRSA than vancomycin in PDF [65]. Further clinical studies are required to assess the efficacy and safety of lipoglycopeptides in treating peritonitis.

Carbapenem

Carbapenems bind to penicillin-binding proteins and exert their bactericidal activity by inhibition of cell wall synthesis [66]. Ertapenem was approved by the FDA in 2001 for the treatment of cSSSI, community-acquired pneumonia, cIAI, complicated urinary tract infection (cUTI) and acute pelvic infections (including post-partum endomyometritis, septic abortion and post-surgical gynecologic infections). Ertapenem is stable against hydrolysis by a variety of β-lactamases (penicillinases, cephalosporinases, ESBL), but not metallo-β-lactamases. Ertapenem is inactive against *P. aeruginosa* and *A. baumannii*. Ertapenem is eliminated primarily by the kidney (~80%). The recommended dose in adult patients with CrCl <30 mL/min/1.73 m^2 is 0.5 g every 24 h. There are no data to recommend ertapenem dosage in PD patients, but 500 mg IV seemed to achieve adequate drug exposure in serum and the peritoneal cavity [67]. Ertapenem is unstable in dextrose solution, hence should not be administered intraperitoneally [68]. An excessive dose of ertapenem can cause seizure in PD patients [69]. Severe neurotoxicity has been observed in a PD patient who received just two doses of IV ertapenem 500 mg [70]. There is also some evidence that 500 mg of ertapenem daily may still be too high in Asian HD patients [71]. Given the lack of pharmacokinetic study of ertapenem in PD patients and the fact that it cannot be administered IP, ertapenem should not be used as the first-line carbapenem in the treatment of peritonitis.

Doripenem is the newest commercially available carbapenem, which was approved by the FDA in 2007 for the treatment of cIAI and cUTI [72]. Doripenem is not recommended in patients with CrCl < 10 mL/min. Although doripenem is hemodialyzable, there are insufficient data to make dosage recommendations in HD patients. There are no data in PD patients and hence doripenem cannot been recommended for the treatment of peritonitis. Imipenem/cilastin and meropenem remain the carbapenems of choice for the treatment of peritonitis.

Moxifloxacin

Moxifloxacin is a flouroquinolone that was first approved by the FDA in 1999 for IV use. Oral moxifloxacin was approved in 2001 for

Table 2. Use of newer antibiotics in the treatment of drug-resistant Gram-positive bacterial peritonitis

Antibiotic	Organisms	Route	Dose	Adverse effects	Remarks
Linezolid	MRSE, MRSA, VISA, VRSA, VRE	PO/IV	600 mg twice daily	Myelosuppression, neuropathy (optic and peripheral)	Consider therapeutic drug monitoring in elderly patients and/or prolonged therapy required (>2 weeks) Closely monitor hematological parameters and reduce to 300 mg twice daily if myelosuppression IP dosage unknown
Daptomycin	MRSE, MRSA, VRE, VISA, VRSA	IV	4–6 mg/kg Q48h	Myopathy, rhabdomyolysis, eosinophilic pneumonia, peripheral neuropathy	Monitor CPK levels and follow muscle pain or weakness Consider systemic steroid if eosinophilic pneumonia
		IP	100 mg/L loading, then 20 mg/L maintenance		Limit the dwell time to 6 h and do not mix with icodextrin
Tigecycline	MRSE, MRSA, VRE	IV	100 mg loading, then 50 mg Q12h	Liver dysfunction, pancreatitis	IP dosage unknown
Moxifloxacin	MRSE, MRSE	PO/IV	400 mg Q24h	Prolonged QT interval, CNS side effects including seizure, peripheral neuropathy, spontaneous tendon rupture	Little anti-pseudomonal activity IP dosage unknown
Quinupristin/dalfopristin	MRSE, MRSA, VRSA, VRE (*E. faecium* only)	IV + IP	IP 25 mg/L in alternate exchange given in conjunction with IV 500 mg Q12h	Infusion site pain, edema, inflammation, thrombophlebitis	Ineffective against *E. faecalis*

IV, intravenous; IP, intraperitoneal; PO, per oral; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRE, vancomycin-resistant enterococcus; VRSA, vancomycin-resistant *Staphylococcus aureus*; CNS, central nervous system; CPK, creatine phosphokinase.

the treatment of respiratory infections [73]. The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination. Moxifloxacin is unique among quinolones in that it is excreted by non-renal mechanisms and does not need dose adjustment in PD and HD patients. Oral moxifloxacin can reach adequate levels within the peritoneal cavity [74, 75]. Moxifloxacin has also been shown to have superior anti-biofilm activity against MRSE and MRSA when compared with vancomycin [76]. If quinolone is used for *Pseudomonas peritonitis*, however, ciprofloxacin should be used instead because moxifloxacin has very little anti-pseudomonal activity. Moxifloxacin remains stable in 1.36 and 3.86% dextrose PDF [77]. There is no dosage recommendation for IP use.

Streptogramin

Streptogramins consist of a mixture of two structurally unrelated chemical substances, namely the Group A streptogramins (polyunsaturated macrolactones) and the Group B streptogramins (cyclic hexadepsipeptides). Each component alone acts as a bacteriostatic agent by binding to the bacterial 50S ribosomal subunit and blocking translation, whereas the synergic combination of both substances in appropriate ratios result in a bactericidal activity [78]. Quinupristin (derived from pristinamycin I) and dalfopristin (derived from pristinamycin IIA) mixed in the ratio of 30:70 (*Q/D*) was approved by the FDA in 1999 for the treatment of cSSSI and vancomycin-resistant *E. faecium* infection including bacteremia. *Q/D* is active against MRSE, MRSA and VRSA, but not *E. faecalis* [79]. Therefore, accurate differentiation of enterococcal species is very important before using *Q/D*. *Q/D* is excreted primarily by the fecal route (~75%) and no dosage adjustment is required in patients with renal impairment and dialysis patients [80]. Previous study showed subtherapeutic drug levels in the peritoneal cavity when IV *Q/D* was given to continuous ambulatory PD (CAPD) patients [81]. Pain, inflammation and edema at the infusion site are the most common adverse reactions to IV *Q/D*. The ISPD recommendation on the use to IP *Q/D* in the treatment of peritonitis was based on a single case report [82].

Cephalosporin

Ceftolozane is a novel cephalosporin. It differs from ceftazidime by having a modified side chain at the 3-position of the cephem nucleus, which confers potent anti-pseudomonal activity [83]. Ceftolozane/tazobactam received FDA approval in 2014. Avibactam is a novel β-lactamase inhibitor that expands the spectrum of activity of ceftazidime to include ceftazidime- and carbapenem-resistant Enterobacteriaceae, *K. pneumoniae* carbapenemase-producing organisms and *P. aeruginosa*. Ceftazidime/avibactam was approved by the FDA in 2015 [84]. Both drugs have been approved for the treatment of cIAI (with metronidazole) and cUTI [85]. Ceftaroline received FDA approval in 2010 and is particularly effective against methicillin-resistant staphylococci. It also has activity against VISA, VRSA and daptomycin non-susceptible *S. aureus*. Ceftaroline has limited activity against enterococci, anaerobes and ESBL-producing Gram-negative bacilli [86]. All three drugs can be used in patients with renal impairment, including HD patients. Nevertheless, no data are available for PD patients.

Polymyxins

Polymyxins are cyclic cationic polypeptide detergents that consist of five different compounds (polymyxins A–E). Only polymyxin B and polymyxin E (colistin) have been used in clinical practice. They increase the permeability of the bacterial cell membrane by binding to lipid A and cause bacteriolysis. They are only active on Gram-negative bacteria. Clinical use of polymyxins has previously been restricted due to the risk of nephrotoxicity and neurotoxicity. However, the emergence of multidrug-resistant Gram-negative bacteria and lack of newer effective antibiotics have led to the revival of polymyxins as a valid therapeutic option [87, 88].

Colistin is available commercially in two forms. Colistin sulfate is used topically and orally, whereas colistimethate sodium (CMS) is designed for parenteral and inhalational use. CMS is an inactive prodrug that is hydrolyzed *in vivo* into colistin. Polymyxin B and colistin differ in their amino acid components. They are both effective against some multidrug-resistant Gram-negative bacteria, including *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*. However, increasing use of colistin for the treatment of infections caused by these organisms has led to the emergence of colistin resistance in several countries worldwide [89]. Parenteral CMS is eliminated by renal excretion and dosage adjustment is required in patients with renal impairment. Previous study showed that clearance of colistin by CAPD was low. Using Monte Carlo simulations, a loading dose of 300 mg colistin base activity (CBA) on Day 1 and a maintenance dose of either 150 or 200 mg CBA daily have been suggested to achieve a target average steady-state plasma colistin concentration of 2.5 mg/L [90]. The clinical experience of using colistin [91, 92] and polymyxin B [93, 94] to treat peritonitis in PD patients is limited.

Conclusion

Treatment of drug-resistant bacterial peritonitis is challenging. Newer antibiotics with activities against drug-resistant Gram-positive bacteria have been developed. However, many of them have not been formally tested in PD patients. Future studies are required to obtain pharmacokinetic data and evaluate the efficacy and safety of these newer antibiotics in PD patients. In most circumstances, methicillin-resistant staphylococci peritonitis responds to vancomycin. If vancomycin cannot be used due to allergy and/or non-susceptibility, linezolid and daptomycin are the drugs of choice. Daptomycin, in particular, has excellent anti-biofilm activity. Other options include *Q/D*, teicoplanin and tigecycline, but teicoplanin is not available in some countries (e.g. the USA). The recommended dose, route of administration, major side effects and precautions when using these antibiotics are summarized in Table 2. Effective treatment options of multidrug-resistant Gram-negative bacteria are limited. Polymyxins can be considered, but evidence on dosage adjustment in PD patients is lacking.

Conflict of interest statement

None declared.

References

1. Li PK, Chow KM. Infectious complications in dialysis–epidemiology and outcomes. *Nat Rev Nephrol* 2011; 8: 77–88
2. Li PK, Chow KM. Peritoneal dialysis-first policy made successful: perspectives and actions. *Am J Kidney Dis* 2013; 62: 993–1005
3. Piraino B, Bernardini J, Brown E *et al.* ISPD position statement on reducing the risks of peritoneal dialysis-related infections. *Perit Dial Int* 2011; 31: 614–630

4. Keane WF, Everett ED, Golper TA *et al*. Peritoneal dialysis-related peritonitis treatment recommendations. 1993 update. The Ad Hoc Advisory Committee on Peritonitis Management. International Society for Peritoneal Dialysis. *Perit Dial Int* 1993; 13: 14–28
5. Keane WF, Alexander SR, Bailie GR *et al*. Peritoneal dialysis-related peritonitis treatment recommendations: 1996 update. *Perit Dial Int* 1996; 16: 557–573
6. Keane WF, Bailie GR, Boeschoten E *et al*. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. *Perit Dial Int* 2000; 20: 396–411
7. Piraino B, Bailie GR, Bernardini J *et al*. Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int* 2005; 25: 107–131
8. Li PK, Szeto CC, Piraino B *et al*. Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* 2010; 30: 393–423
9. Brown MC, Simpson K, Kerssens JJ *et al*. Peritoneal dialysis-associated peritonitis rates and outcomes in a national cohort are not improving in the post-millennium (2000–2007). *Perit Dial Int* 2011; 31: 639–650
10. Kitterer D, Latus J, Pöhlmann C *et al*. Microbiological surveillance of peritoneal dialysis associated peritonitis: antimicrobial susceptibility profiles of a referral center in GERMANY over 32 years. *PLoS One* 2015; 10: e0135969
11. Camargo CH, Cunha Mde L, Caramori JC *et al*. Peritoneal dialysis-related peritonitis due to coagulase-negative *Staphylococcus*: a review of 115 cases in a Brazilian center. *Clin J Am Soc Nephrol* 2014; 9: 1074–1081
12. Prasad KN, Singh K, Rizwan A *et al*. Microbiology and outcomes of peritonitis in northern India. *Perit Dial Int* 2014; 34: 188–194
13. Feng X, Yang X, Yi C *et al*. Escherichia coli Peritonitis in peritoneal dialysis: the prevalence, antibiotic resistance and clinical outcomes in a South China dialysis center. *Perit Dial Int* 2014; 34: 308–316
14. Zhang W, Wu YG, Qi XM *et al*. Peritoneal dialysis-related peritonitis with *Acinetobacter baumannii*: a review of seven cases. *Perit Dial Int* 2014; 34: 317–321
15. Boucher HW, Talbot GH, Bradley JS *et al*. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48: 1–12
16. Peterson LR. Bad bugs, no drugs: no ESCAPE revisited. *Clin Infect Dis* 2009; 49: 992–993
17. Fung HB, Kirschenbaum HL, Ojofeitimi BO. Linezolid: an oxazolidinone antimicrobial agent. *Clin Ther* 2001; 23: 356–391
18. Flamm RK, Mendes RE, Hogan PA *et al*. Linezolid surveillance results for the United States (LEADER Surveillance Program 2014). *Antimicrob Agents Chemother* 2016; 60: 2273–2280
19. Mendes RE, Deshpande LM, Jones RN. Linezolid update: stable *in vitro* activity following more than a decade of clinical use and summary of associated resistance mechanisms. *Drug Resist Updat* 2014; 17: 1–12
20. Gu B, Kelesidis T, Tsiodras S *et al*. The emerging problem of linezolid-resistant *Staphylococcus*. *J Antimicrob Chemother* 2013; 68: 4–11
21. DePestel DD, Peloquin CA, Carver PL. Peritoneal dialysis fluid concentrations of linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* peritonitis. *Pharmacotherapy* 2003; 23: 1322–1326
22. Allcock NM, Krueger TS, Manley HJ *et al*. Linezolid disposition during peritonitis: a case report. *Perit Dial Int* 2004; 24: 68–70
23. Tedla FM, Salifu M, Friedman EA. Successful treatment of vancomycin-resistant enterococcal peritonitis with linezolid in a kidney transplant patient: a case report and review of the literature. *Perit Dial Int* 2004; 24: 70–72
24. Unal A, Agkus C, Kocyigit I *et al*. Peritoneal dialysis-related peritonitis caused by vancomycin-resistant Enterococcus faecium. *Ther Apher Dial* 2011; 15: 115–116
25. Yang JW, Kim YS, Choi SO *et al*. Successful use of intravenous linezolid in CAPD patient with vancomycin-resistant enterococcal peritonitis. *Perit Dial Int* 2011; 31: 209–210
26. Song IJ, Seo JW, Kwon YE *et al*. Successful treatment of vancomycin-resistant enterococcus peritonitis using linezolid without catheter removal in a peritoneal dialysis patient. *Perit Dial Int* 2014; 34: 235–239
27. Nepal HP, Khanal B, Sharma SK *et al*. Peritonitis in a continuous ambulatory peritoneal dialysis patient by two different species of enterococci: a rare finding. *Indian J Nephrol* 2014; 24: 324–326
28. Bailey EM, Faber MD, Nafziger DA. Linezolid for treatment of vancomycin-resistant enterococcal peritonitis. *Am J Kidney Dis* 2001; 38: E20
29. Dryden MS. Linezolid pharmacokinetics and pharmacodynamics in clinical treatment. *J Antimicrob Chemother* 2011; 66 Suppl 4: iv7–iv15
30. Bowker KE, Wootton M, Holt HA *et al*. *In vitro* activity of linezolid against Gram-positive isolates causing infection in continuous ambulatory peritoneal dialysis patients. *J Antimicrob Chemother* 2002; 49: 578–580
31. Gervasoni C, Terzi R, Heidempergher M *et al*. Linezolid-related haematological toxicity in a peritoneal dialysis patient: the role of therapeutic drug monitoring. *Eur J Clin Pharmacol* 2015; 71: 383–385
32. Gervasoni C, Bergia R, Cozzi V *et al*. Is it time to revise linezolid doses in peritoneal dialysis patients? A case series. *J Antimicrob Chemother* 2015; 70: 2918–2920
33. Pea F, Viale P, Cojutti P *et al*. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. *J Antimicrob Chemother* 2012; 67: 2034–2042
34. Tobin CM, Sunderland J, Lovering AM *et al*. A high performance liquid chromatography (HPLC) assay for linezolid in continuous ambulatory peritoneal dialysis fluid (CAPDF). *J Antimicrob Chemother* 2003; 51: 1041–1042
35. Manley HJ, McClaran ML, Bedenbaugh A *et al*. Linezolid stability in peritoneal dialysis solutions. *Perit Dial Int* 2002; 22: 419–422
36. Zhanel GG, Love R, Adam H *et al*. Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant gram-positive pathogens. *Drugs* 2015; 75: 253–270
37. Barber KE, Smith JR, Raut A *et al*. Evaluation of tedizolid against *Staphylococcus aureus* and enterococci with reduced susceptibility to vancomycin, daptomycin or linezolid. *J Antimicrob Chemother* 2016; 71: 152–155
38. Flanagan S, Minassian SL, Morris D *et al*. Pharmacokinetics of tedizolid in subjects with renal or hepatic impairment. *Antimicrob Agents Chemother* 2014; 58: 6471–6476
39. Jeu L, Fung HB. Daptomycin: a cyclic lipopeptide antimicrobial agent. *Clin Ther* 2004; 26: 1728–1757
40. Humphries RM, Pollett S, Sakoulas G. A current perspective on daptomycin for the clinical microbiologist. *Clin Microbiol Rev* 2013; 26: 759–780
41. Cardone KE, Lodise TP, Patel N *et al*. Pharmacokinetics and pharmacodynamics of intravenous daptomycin during continuous ambulatory peritoneal dialysis. *Clin J Am Soc Nephrol* 2011; 6: 1081–1088

Clinical Kidney Journal
ckj

42. Goedecke VA, Clajus C, Burkhardt O *et al*. Pharmacokinetics and dialysate levels of daptomycin given intravenously in a peritoneal dialysis patient. *Scand J Infect Dis* 2009; 41: 155–157
43. Benziger DP, Pertel PE, Donovan J *et al*. Pharmacokinetics and safety of multiple doses of daptomycin 6 mg/kg in noninfected adults undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Clin Nephrol* 2011; 75: 63–69
44. Khadzhynov D, Joukhadar C, Peters H. Plasma and peritoneal dialysate levels during daptomycin therapy for peritonitis. *Am J Kidney Dis* 2009; 53: 911–912
45. Gika HG, Michopoulos F, Divanis D *et al*. Daptomycin determination by liquid chromatography-mass spectrometry in peritoneal fluid, blood plasma, and urine of clinical patients receiving peritoneal dialysis treatment. *Anal Bioanal Chem* 2010; 397: 2191–2197
46. Hermsen ED, Hovde LB, Hotchkiss JR *et al*. Increased killing of staphylococci and streptococci by daptomycin compared with cefazolin and vancomycin in an *in vitro* peritoneal dialysate model. *Antimicrob Agents Chemother* 2003; 47: 3764–3767
47. Kelley PG, Gao W, Ward PB *et al*. Daptomycin non-susceptibility in vancomycin-intermediate *Staphylococcus aureus* (VISA) and heterogeneous-VISA (hVISA): implications for therapy after vancomycin treatment failure. *J Antimicrob Chemother* 2011; 66: 1057–1060
48. Roveta S, Marchese A, Schito GC. Activity of daptomycin on biofilms produced on a plastic support by *Staphylococcus* spp. *Int J Antimicrob Agents* 2008; 31: 321–328
49. Hassoun AA, Coomer RW, Mendez-Vigo L. Intraperitoneal daptomycin used to successfully treat ancomycin-resistant enterococcus peritonitis. *Perit Dial Int* 2009; 29: 671–673
50. Huen SC, Hall I, Topal J *et al*. Successful use of intraperitoneal daptomycin in the treatment of vancomycin-resistant enterococcus peritonitis. *Am J Kidney Dis* 2009; 54: 538–541
51. Bahte SK, Bertram A, Burkhardt O *et al*. Therapeutic serum concentrations of daptomycin after intraperitoneal administration in a patient with peritoneal dialysis-associated peritonitis. *J Antimicrob Chemother* 2010; 65: 1312–1314
52. Levy F, Camarero Temiño V, Blasco Mollá A *et al*. Treatment with intravenous daptomycin for a peritonitis relapse caused by *Staphylococcus epidermidis*. *Nefrologia* 2011; 31: 374–375
53. García-López L, Gómez Sayago L, Fernández-Reyes Luis MJ. Intraperitoneal daptomycin. *Nefrologia* 2011; 31: 375–376
54. Lin SY, Ho MW, Liu JH *et al*. Successful salvage of peritoneal catheter in unresolved methicillin-resistant *staphylococcus aureus* peritonitis by combination treatment with daptomycin and rifampin. *Blood Purif* 2011; 32: 249–252
55. Gilmore JF, Kim M, LaSalvia MT *et al*. Treatment of enterococcal peritonitis with intraperitoneal daptomycin in a vancomycin-allergic patient and a review of the literature. *Perit Dial Int* 2013; 33: 353–357
56. Taegtmeyer AB, Kononowa N, Fasel D *et al*. Successful treatment of a pacemaker infection with intraperitoneal daptomycin. *Perit Dial Int* 2016; 36: 114–117
57. Peyro Saint Paul L, Albessard F, Gaillard C *et al*. Daptomycin compatibility in peritoneal dialysis solutions. *Perit Dial Int* 2011; 31: 492–495
58. Parra MA, Campanero MA, Sádaba B *et al*. Effect of glucose concentration on the stability of daptomycin in peritoneal solutions. *Perit Dial Int* 2013; 33: 458–461.
59. Zhanel GG, Karlowsky JA, Rubinstein E *et al*. Tigecycline: a novel glycylcycline antibiotic. *Expert Rev Anti Infect Ther* 2006; 4: 9–25
60. Sader HS, Flamm RK, Jones RN. Tigecycline activity tested against antimicrobial resistant surveillance subsets of clinical bacteria collected worldwide (2011). *Diagn Microbiol Infect Dis* 2013; 76: 217–221
61. Antony S, Dominguez DC. Use of a novel antibiotic (tigecycline) in the treatment of peritoneal dialysis-associated MRSA peritonitis. *Dial Transplant* 2008; 37: 30
62. Robiyanto R, Zaidi ST, Shastri MD *et al*. Stability of tigecycline in different types of peritoneal dialysis solutions. *Perit Dial Int* 2015; in press
63. Klinker KP, Borgert SJ. Beyond vancomycin: the tail of the lipoglycopeptides. *Clin Ther* 2015; 37: 2619–2636
64. Van Bambeke F. Lipoglycopeptide antibacterial agents in gram-positive infections: a comparative review. *Drugs* 2015; 75: 2073–2095
65. Clouse FL, Hovde LB, Rotschafer JC. *In vitro* evaluation of the activities of telavancin, cefazolin, and vancomycin against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* in peritoneal dialysate. *Antimicrob Agents Chemother* 2007; 51: 4521–4524
66. Breilh D, Texier-Maugein J, Allaouchiche B *et al*. Carbapenems. *J Chemother* 2013; 25: 1–17
67. Cardone KE, Grabe DW, Kulawy RW *et al*. Ertapenem pharmacokinetics and pharmacodynamics during continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother* 2012; 56: 725–730
68. McQuade MS, Van Nostrand V, Schariter J *et al*. Stability and compatibility of reconstituted ertapenem with commonly used i.v. infusion and coinfusion solutions. *Am J Health Syst Pharm* 2004; 61: 38–45
69. Yılmaz F, Uslu H, Ersoy F. Ertapenem associated with seizures in treatment of pyelonephritis in a chronic peritoneal dialysis patient. *Ther Apher Dial* 2016; 20: 89–90
70. Seto AH, Song JC, Guest SS. Ertapenem-associated seizures in a peritoneal dialysis patient. *Ann Pharmacother* 2005; 39: 352–356
71. Lee KH, Ueng YF, Wu CW *et al*. The recommended dose of ertapenem poses a potential risk for central nervous system toxicity in haemodialysis patients – case reports and literature reviews. *J Clin Pharm Ther* 2015; 40: 240–244
72. Paterson DL, Depestel DD. Doripenem. *Clin Infect Dis* 2009; 49: 291–298
73. Miravitlles M, Anzueto A. Moxifloxacin: a respiratory fluoroquinolone. *Expert Opin Pharmacother* 2008; 9: 1755–1772
74. Stass H, Rink AD, Delesen H *et al*. Pharmacokinetics and peritoneal penetration of moxifloxacin in peritonitis. *J Antimicrob Chemother* 2006; 58: 693–696
75. Skalioti C, Tsaganos T, Stamatiadis D *et al*. Pharmacokinetics of moxifloxacin in patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2009; 29: 575–579
76. Salem AH, Elkhatib WF, Ahmed GF *et al*. Pharmacodynamics of moxifloxacin versus vancomycin against biofilms of methicillin-resistant *Staphylococcus aureus* and *epidermidis* in an *in vitro* model. *J Chemother* 2010; 22: 238–242
77. Fernández-Varón E, Marín P, Espuny A *et al*. Stability of moxifloxacin injection in peritoneal dialysis solution bags (Dianeal PD1 1.36% and Dianeal PD1 3.86%). *J Clin Pharm Ther* 2006; 31: 641–643
78. Mast Y, Wohlleben W. Streptogramins - two are better than one! *Int J Med Microbiol* 2014; 304: 44–50
79. Bearden DT. Clinical pharmacokinetics of quinupristin/dalfopristin. *Clin Pharmacokinet* 2004; 43: 239–252
80. Jevitt LA, Smith AJ, Williams PP *et al*. *In vitro* activities of daptomycin, linezolid, and quinupristin-dalfopristin

against a challenge panel of *Staphylococci* and *Enterococci*, including vancomycin-intermediate *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. *Microb Drug Resist* 2003; 9: 389–393
81. Johnson CA, Taylor CA III, Zimmerman SW *et al*. Pharmacokinetics of quinupristin-dalfopristin in continuous ambulatory peritoneal dialysis patients. *Antimicrob Agents Chemother* 1999; 43: 152–156
82. Lynn WA, Clutterbuck E, Want S *et al*. Treatment of CAPD-peritonitis due to glycopeptide-resistant Enterococcus faecium with quinupristin/dalfopristin. *Lancet* 1994; 344: 1025–1026
83. Zhanel GG, Chung P, Adam H *et al*. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. *Drugs* 2014; 74: 31–51
84. Zhanel GG, Lawson CD, Adam H *et al*. Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination. *Drugs* 2013; 73: 159–177
85. Liscio JL, Mahoney MV, Hirsch EB. Ceftolozane/tazobactam and ceftazidime/avibactam: two novel β-lactam/β-lactamase inhibitor combination agents for the treatment of resistant Gram-negative bacterial infections. *Int J Antimicrob Agents* 2015; 46: 266–271
86. Lodise TP, Low DE. Ceftaroline fosamil in the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections. *Drugs* 2012; 72: 1473–1493
87. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005; 40: 1333–1341
88. Dijkmans AC, Wilms EB, Kamerling IM *et al*. Colistin: revival of an old polymyxin antibiotic. *Ther Drug Monit* 2015; 37: 419–427
89. Bialvaei AZ, Samadi Kafil H. Colistin, mechanisms and prevalence of resistance. *Curr Med Res Opin* 2015; 31: 707–721
90. Koomanachai P, Landersdorfer CB, Chen G *et al*. Pharmacokinetics of colistin methanesulfonate and formed colistin in end-stage renal disease patients receiving continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother* 2014; 58: 440–446
91. Djurdjević TD, Gvozdenović L, Majstorović-Strazmester G *et al*. An experience with colistin applied in treatment of immunocompromised patients with peritonitis on peritoneal dialysis. *Vojnosanit Pregl* 2015; 72: 379–382
92. Lim K, Pak J, Moon J *et al*. A case of imipenem resistance *Acinetobacter baumannii* peritonitis successfully treated with colistin therapy. *Korean J Nephrol* 2008; 27: 402–406
93. Parchuri S, Mohan S, Cunha BA. Extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* chronic ambulatory peritoneal dialysis peritonitis treated successfully with polymyxin B. *Heart Lung* 2005; 34: 360–363
94. Fitzpatrick MA, Esterly JS, Postelnick MJ *et al*. Successful treatment of extensively drug-resistant *Acinetobacter baumannii* peritoneal dialysis peritonitis with intraperitoneal polymyxin B and ampicillin-sulbactam. *Ann Pharmacother* 2012; 46: e17

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