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].
remains controversial. The non-renal route accounts for total linezolid clearance. Under steady states, reported overall linezolid resistance rate remained low [18]. Linezolid is bacteriostatic against staphylococci and enterococci. The glycine metabolite and 10% as aminoethoxyacetic acid appears in the urine as unchanged drug, 40% as hydroxyethyl 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].

**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 aminoethoxycetic 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\textsubscript{50} and MIC\textsubscript{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\textsubscript{50} 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 22.5–50 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\textsubscript{24}) of 160–300 mg/L.h has been suggested to maximize therapeutic...

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

<table>
<thead>
<tr>
<th>Year of approval</th>
<th>Antibiotic</th>
<th>Route</th>
<th>Drug class</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Ceftazidime/ avibactam</td>
<td>IV</td>
<td>Cephalosporin/ β-lactamase inhibitor</td>
<td>Complicated intra-abdominal and urinary tract infections</td>
</tr>
<tr>
<td>2014</td>
<td>Dalbavancin</td>
<td>IV</td>
<td>Lipoglycopeptide</td>
<td>Acute bacterial skin and skin structure infections</td>
</tr>
<tr>
<td>2014</td>
<td>Oritavancin</td>
<td>IV</td>
<td>Lipoglycopeptide</td>
<td>Acute bacterial skin and skin structure infections</td>
</tr>
<tr>
<td>2014</td>
<td>Tedizolid</td>
<td>IV/PO</td>
<td>Oxazolidinone</td>
<td>Acute bacterial skin and skin structure infections</td>
</tr>
<tr>
<td>2013</td>
<td>Telavancin</td>
<td>IV</td>
<td>Lipoglycopeptide</td>
<td>Complicated intra-abdominal and urinary tract infections</td>
</tr>
<tr>
<td>2010</td>
<td>Ceftaroline</td>
<td>IV</td>
<td>Cephalosporin</td>
<td>Complicated skin and skin structure infections</td>
</tr>
<tr>
<td>2009</td>
<td>Telavancin</td>
<td>IV</td>
<td>Lipoglycopeptide</td>
<td>Community-acquired pneumonia, intra-abdominal, skin, urinary tract, kidney and post-surgical gynecological infections</td>
</tr>
<tr>
<td>2007</td>
<td>Doripenem</td>
<td>IV</td>
<td>Carbapenem</td>
<td>Community-acquired pneumonia, intra-abdominal, skin, urinary tract, kidney and post-surgical gynecological infections</td>
</tr>
<tr>
<td>2005</td>
<td>Tigecycline</td>
<td>IV</td>
<td>Glycylcycline</td>
<td>Community-acquired pneumonia, intra-abdominal, skin, urinary tract, kidney and post-surgical gynecological infections</td>
</tr>
<tr>
<td>2003</td>
<td>Daptomycin</td>
<td>IV</td>
<td>Lipopeptide</td>
<td>Community-acquired pneumonia, intra-abdominal, skin, urinary tract, kidney and post-surgical gynecological infections</td>
</tr>
<tr>
<td>2001</td>
<td>Ertapenem</td>
<td>IV</td>
<td>Carbapenem</td>
<td>Community-acquired pneumonia, intra-abdominal, skin, urinary tract, kidney and post-surgical gynecological infections</td>
</tr>
<tr>
<td>2000</td>
<td>Linezolid</td>
<td>IV/PO</td>
<td>Oxazolidinone</td>
<td>Community-acquired pneumonia, intra-abdominal, skin, urinary tract, kidney and post-surgical gynecological infections</td>
</tr>
<tr>
<td>1999</td>
<td>Moxifloxacin</td>
<td>IV/PO</td>
<td>Fluoroquinolone</td>
<td>Sinusitis, bronchitis, pneumonia, skin structure infections</td>
</tr>
<tr>
<td>1999</td>
<td>Quinupristin/ dalfopristin</td>
<td>IV</td>
<td>Streptogramin</td>
<td>Sinusitis, bronchitis, pneumonia, skin structure infections</td>
</tr>
</tbody>
</table>

IV, intravenous; PO, per oral.
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 AUC0-t 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 MIC90 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 lipoglycopeptidase in treating peritonitis.

**Carbapenems**

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 Gram-positive bacterial 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 m² 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 fluoroquinolone 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

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

IV, intravenous; IP, intraperitoneal; PO, per oral; M RSA, 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 synergistic combination of both substances in appropriate ratios result in a bactericidal action [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 ammatory 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 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.

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