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REVIEW

New antimicrobial options for the management of complicated intra-abdominal infections

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Abstract

Complicated intra-abdominal infections (cIAIs) are a common cause of morbidity and mortality in surgical patients. Optimal management of cIAI requires early source control in combination with adequate antimicrobial treatment and aggressive fluid resuscitation. cIAIs are mainly caused by Gram-negative bacilli and anaerobes. Broad-spectrum single-agent or combination drug regimens against these microorganisms are the mainstay of therapy. However, development of antimicrobial resistance has become an increasingly large concern: multidrug-resistant organisms are associated with a higher rate of inadequate antimicrobial therapy, which in turn is associated with higher mortality rate, longer hospital stay, and increased cost compared to adequate antimicrobial therapy. In this mini-review, we discuss the effectiveness of several new antimicrobial agents, recently approved or in advanced phases of clinical development, for the treatment of cIAIs, including the new beta-lactam and beta-lactamase inhibitor combinations (ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, aztreonam/avibactam), siderophore cephalosporins (cefiderocol), aminoglycosides (plazomicin), and tetracyclines (eravacycline).

Keywords Intra-abdominal infections · Antimicrobial resistance · Antimicrobial therapy · New antimicrobial agents

Introduction

Complicated intra-abdominal infections (cIAIs), defined as infections of the peritoneal space that are associated with either peritonitis or abscess formation, are a common cause of morbidity and mortality in surgical patients [1, 2]. Optimal management of cIAI requires early source control in combination with adequate antimicrobial treatment and aggressive fluid resuscitation [3–5]. cIAIs are caused by a wide variety of microorganisms, including both aerobes and anaerobes (Table 1) [4, 6]. *Enterobacteriaceae*, in combination with anaerobes, are the most common microorganisms observed in community-acquired cIAIs (CA-cIAIs), whereas other difficult-to-treat microorganisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus* spp., and *Candida* spp. can play a crucial role in healthcare-acquired cIAIs (HA-cIAIs) [7–10]. In a French multicenter study, Montravers et al. found increased numbers of *E. faecalis* and *P. aeruginosa* isolates in HA-IAIs compared to CA-cIAIs (33% vs. 19% [$P < 0.05$] and 13% vs. 5% [$P < 0.01$], respectively), whereas in CA-cIAIs, the most commonly isolated microorganisms were *Escherichia coli*, *Streptococcus* spp.,

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Table 1 Microbiology of complicated intra-abdominal infections. Adapted from [4]

Gram-negative bacteria	Percent
Escherichia coli	71
Klebsiella spp.	14
Pseudomonas aeruginosa	14
Proteus mirabilis	5
Enterobacter spp.	5
Anaerobic bacteria	
Bacteroides fragilis	35
Other *Bacteroides* spp.	71
Clostridium spp.	29
Prevotella spp.	12
Peptostreptococcus spp.	17
Fusobacterium spp.	9
Eubacterium spp.	17
Gram-positive bacteria	
Streptococcus spp.	38
Enterococcus faecalis	12
Enterococcus faecium	3
Enterococcus spp.	8
Staphylococcus aureus	4

and *Bacteroides fragilis* [11]. However, in recent years, increasing numbers of CA-cIAIs have been found to be caused by multidrug-resistant (MDR) *Enterobacteriaceae* [7, 8, 12–14]. Overall, MDR microorganisms are associated with a higher rate of inadequate antimicrobial treatment, which is associated with higher mortality rate, longer hospital stay, and increased cost compared to adequate antimicrobial treatment [15, 16]. The aim of this mini-review is to summarize the current evidence of therapeutic benefit for newer antibiotics, recently approved by US Food and Drug Administration (FDA) and/or by European Medicines Agency (EMA), or in advanced phases of clinical development, for the management of cIAIs due to MDR microorganisms.

Ceftolozane/tazobactam

Ceftolozane/tazobactam (CFT/TAZ) has activity against many Gram-negative bacteria, including extended-spectrum-beta-lactamase (ESBL)-producing *Enterobacteriaceae* and some AmpC-derepressed *Enterobacteriaceae* (Fig. 1). Moreover, CFT/TAZ is stable against many *P. aeruginosa* resistance mechanisms [17, 18]. The CFT/TAZ mechanism of action is shown in Fig. 2; it is currently approved for the treatment of cIAIs and complicated urinary tract infections (cUTIs). The recommended dose of CFT/TAZ, in patients without renal impairment, is 1.5 g (1 g ceftolozane and 500 mg tazobactam) administered every 8 h by intravenous infusion over 60 min. In a phase 2, multicenter, prospective, double-blind, randomized trial (ClinicalTrials.gov identifier: NCT01147640) comparing intravenous CFT/TAZ (1.5 g every 8 h) *plus* metronidazole (500 mg every 8 h) to meropenem (1 g every 8 h) in a cohort of hospitalized adults with cIAI (82 patients received CFT/TAZ [90.2% with metronidazole] and 39 received meropenem), the primary endpoint was clinical response at the test-of-cure visit in the microbiologically modified intent-to-treat and microbiologically evaluable populations. Clinical cure in the microbiologically modified intent-to-treat population (86 patients) was observed in 83.6% (51 out of 61) of patients who received CFT/TAZ and 96.0% (24 out of 25) of patients who received meropenem (difference −12.4% [95%CI −34.9% to 11.1%]). Clinical cure in the microbiologically evaluable population (77 patients) was found in 88.7% (47 out of 53) and 95.8% (23 out of 24) of patients (difference −7.1% [95%CI −30.7% to 16.9%]) who received CFT/TAZ and meropenem, respectively [19]. The ASPECT-cIAI studies were two identical phase 3, multicenter, prospective, randomized, double-blind, placebo-controlled trials that evaluated intravenous CFT/TAZ plus metronidazole vs. meropenem for the treatment of hospitalized adult patients with cIAI (ClinicalTrials.gov identifiers: NCT01445665 and NCT01445678); CFT/TAZ was administered at a dosage of 1.5 g every 8 h, metronidazole was administered at a dosage of 500 mg every 8 h, and meropenem was administered at a dosage of 1 g every 8 h. The primary endpoint was clinical cure rate in the microbiological intent-to-treat population (806 patients) at the test-of-cure visit. Clinical cure in the microbiological intent-to-treat population was observed in 83% (323 out of 389) of patients who received CFT/TAZ plus metronidazole and 87.3% (364 out of 417) of patients who received meropenem (difference −4.2% [95%CI −8.91% to 0.54%]. Clinical cure in the microbiologically evaluable population (596 patients; secondary endpoint) was found in 94.2% (259 out of 275) and 94.7% (304 out of 321) of patients who received CFT/TAZ plus metronidazole and meropenem, respectively (difference −1.0% [95%CI −4.52% to 2.59%]). Per-pathogen clinical cure rates were similar between groups. In patients with *Enterobacteriaceae*-producing ESBL, clinical cure rates were 95.8% (23 out of 24) and 88.5% (23 out of 26) in the CFT/TAZ *plus* metronidazole and meropenem groups, respectively. The incidence of adverse events was similar in experimental and control groups (44.0% and 42.7%, respectively). Overall, adverse events were mainly mild to moderate in severity: the most common adverse events in either group were nausea and diarrhea [20]. Table 2 shows the most common adverse events of CFT/TAZ. Recently, Popejoy et al., in a pooled analysis of phase 3 trials, showed that at US FDA and EUCAST breakpoints of ≤2/≤1 mg/L, 81.8%/72.3% of *Enterobacteriaceae*-producing ESBL (*E. coli*, 95%/88.1% and *Klebsiella pneumoniae*, 56.7%/36.7%, respectively) were susceptible to CFT/TAZ. Overall, CFT/TAZ clinical cure

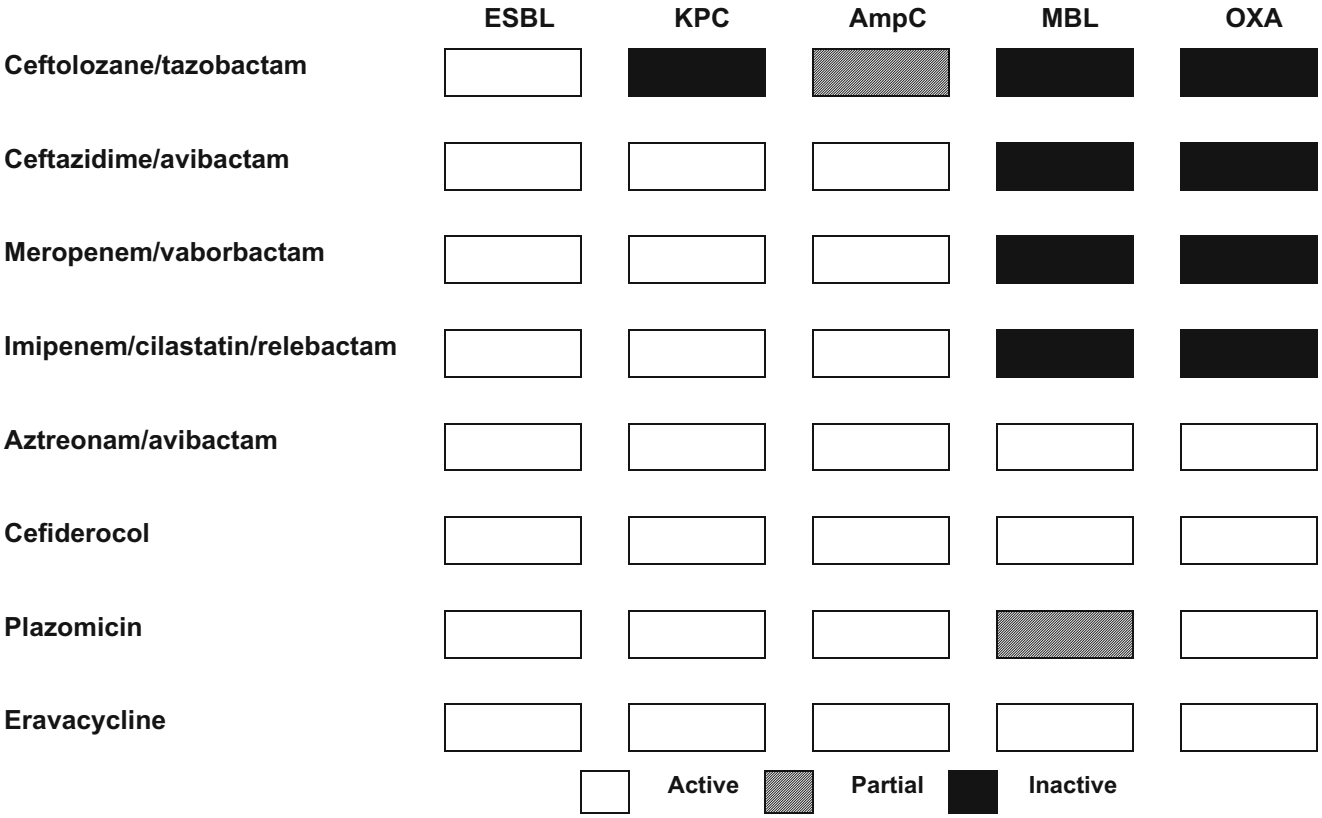

Fig. 1 Activity of new agents against Gram-negative bacteria producing beta-lactamases enzymes

rate for microbiologically evaluable patients with infections due to *Enterobacteriaceae*-producing ESBL (cIAIs and cUTIs) was 97.4% [21].

Ceftazidime/avibactam

Ceftazidime/avibactam (CAZ/AVI) has activity against several Gram-negative bacteria, including ceftazidime-resistant strains. It is active against Gram-negative bacteria strains producing Ambler class A (ESBL and *K. pneumoniae* carbapenemase [KPC]), class C (AmpC), and some class D (OXA-48) enzymes, whereas it is inactive against metallo-beta-lactamases (MBL) and *Acinetobacter* OXA-type carbapenemases (Fig. 1) [17, 22]. Figure 2 shows the mechanism of action of CAZ/AVI. It is currently approved for the treatment of cIAIs, cUTIs, hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP). The recommended dose of CAZ/AVI in patients without renal impairment is 2.5 g (2 g ceftazidime and 500 mg avibactam) administered every 8 h by intravenous infusion over 120 min. A phase 2 multicenter, prospective, double-blind, randomized trial (ClinicalTrials.gov identifier: NCT00752219) compared CAZ/AVI (2.5 g every 8 h) plus metronidazole (500 mg every 8 h) to meropenem (1 g every 8 h) in a cohort of hospitalized adults with cIAI (101 patients received CAZ/AVI plus metronidazole and 102 received meropenem). The primary endpoint was clinical response at the test-of-cure visit in the microbiologically evaluable population. Clinical cure in the microbiologically evaluable population was observed in 91.2% (62 out of 68) of patients who received CAZ/AVI plus metronidazole and 93.4% (71 out of 76) of patients who received meropenem (difference − 2.2% [95%CI − 20.4% to 12.2%]). At the test-of-cure visit, a favorable microbiological response was similar in experimental and control groups (91.2% and 93.4%, respectively) [23]. The RECLAIM 1 and 2 studies were two identical phase 3, multicenter, prospective, randomized, double-blind, placebo-controlled trials that evaluated intravenous CAZ/AVI plus metronidazole vs. meropenem for the treatment of hospitalized adult patients with cIAI (ClinicalTrials.gov identifiers: NCT01499290 and NCT01500239). CAZ/AVI was administered at a dosage of 2.5 g every 8 h, metronidazole was administered at a dosage of 500 mg every 8 h, and meropenem was administered at a dosage of 1 g every 8 h. The primary endpoint was the clinical response rate in the microbiologically modified intent-to-treat population at the test-of-cure visit and clinical response rate in the modified intent-to-treat and clinically evaluable populations at the test-of-cure visit. Clinical cure in the microbiologically modified intent-to-treat population (823 patients) was observed in 81.6% (337 out of 413) of patients who received CAZ/AVI *plus* metronidazole and 85.1% (349 out of 410) of

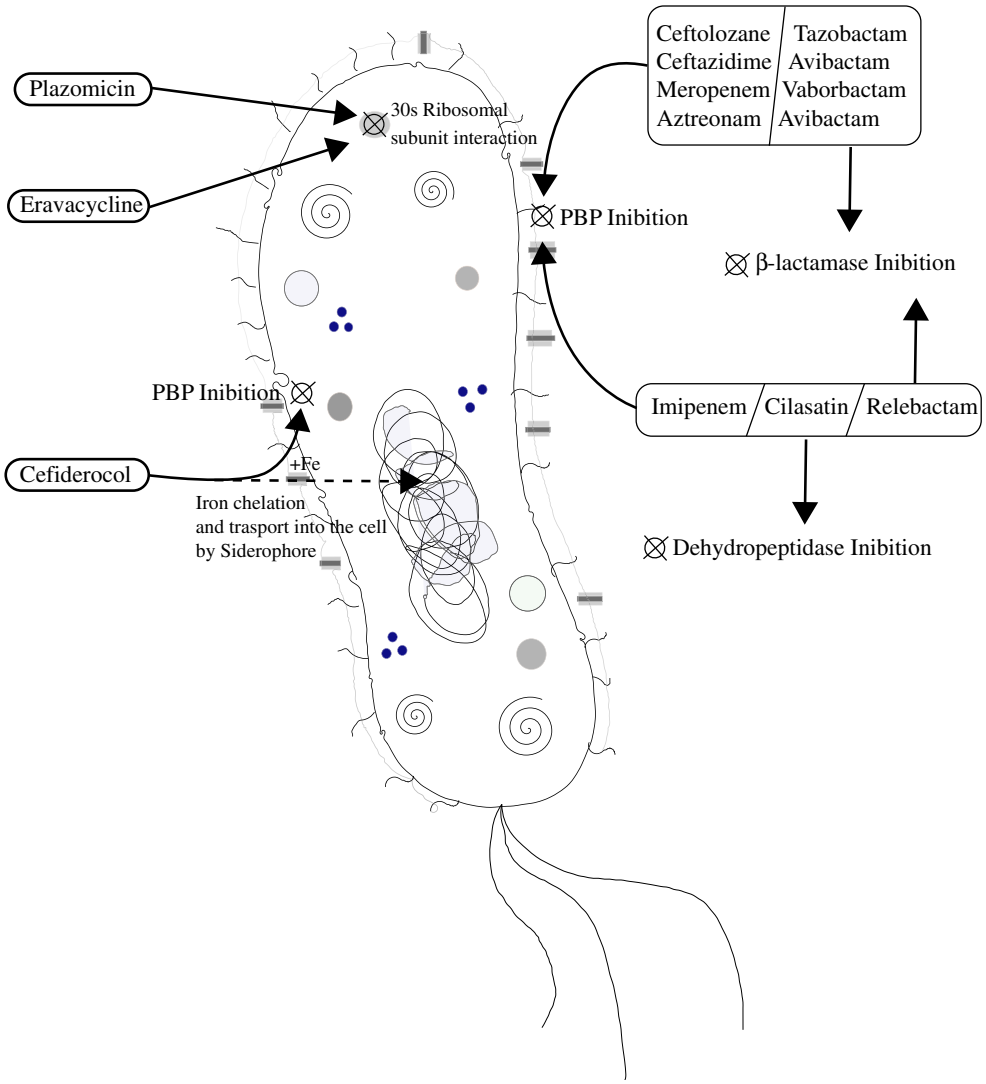

Fig. 2 Mechanism of action of new antibiotics for the treatment of complicated intra-abdominal infections

patients who received meropenem (difference − 3.5% [95%CI − 8.64% to 1.58%]). Moreover, clinical cure in the modified intent-to-treat (1043 patients) and clinically evaluable (826 patients) populations was found in 82.5% (429 out of 520) and 91.7% (376 out of 410) of patients who received CAZ/AVI *plus* metronidazole and 84.9% (444 out of 523) and 92.5% (385 out of 416) of the patients who received meropenem, respectively (difference − 2.4% [95%CI − 6.90% to 2.10%] and difference − 0.8% [95%CI − 4.61% to 2.89%], respectively). No difference in adverse event rate was observed between groups [24]. Table 2 shows the most common adverse events of CAZ/AVI. The RECLAIM 3 study (ClinicalTrials.gov identifier: NCT01726023) was another phase 3, randomized, multicentre, double-blind trial that assessed efficacy and safety of CAZ/AVI *plus* metronidazole compared to meropenem in patients with cIAI in Asian countries. Overall, the study demonstrated non-inferiority of CAZ/AVI plus metronidazole compared to meropenem [25]. Finally, Stone et al., in a pooled analysis of phase 3 clinical trials, observed that 78.4% and 57.1% of all MDR *Enterobacteriaceae* and *MDR P. aeruginosa* had a favorable microbiological response when treated with CAZ/AVI [26].

Meropenem/vaborbactam

Meropenem/vaborbactam (MER/VAB) has activity against Gram-negative bacteria producing Ambler class A (ESBL and KPC) and class C β-lactamases (AmpC), but it is inactive against class B (MBL) and D (OXA) enzymes (Fig. 1) [17, 27, 28]. Figure 2 shows the mechanism of action of MER/VAB. It is currently approved for the treatment of cUTIs. The recommended dose of MER/VAB in patients without renal impairment is 4 g (2 g meropenem and 2 g vaborbactam) administered every 8 h by intravenous infusion over 180 min. A phase 3, multicenter, prospective, randomized, open-label trial (TANGO II; ClinicalTrials.gov identifier: NCT02168946) evaluated the effectiveness of MER/VAB (4 g every 8 h)

Table 2 Adverse events in new anti-bacterial agents

	Adverse events
Ceftolozane/tazobactam	Systemic: dizziness, hypertension, insomnia, nausea, pyrexia, vomiting; Gastrointestinal: constipation, diarrhea; Musculoskeletal: arthralgia, myalgia; Others: headache, upper abdominal pain, urinary tract infection; Laboratory alterations: increased alanine aminotransferase and aspartate aminotransferase concentration.
Ceftazidime/avibactam	Systemic: fatigue, feeling hot or jittery, insomnia, nausea, pyrexia; Gastrointestinal: diarrhea, dyspepsia, vomiting; Mucocutaneous: administration site bruising, dry mouth, dysgeusia, hyperhidrosis, venipuncture site bruising, vulvovaginal candidiasis; Musculoskeletal: arthralgia; Others: abdominal pain, chest discomfort, cough, headache, nasal congestion, edema peripheral, phlebitis, upper respiratory tract infection.
Meropenem/vaborbactam	Systemic: nausea, pyrexia; Gastrointestinal: diarrhea; Mucocutaneous: vaginal infection; Others: catheter site phlebitis, headache, urinary tract infection; Laboratory alterations: asymptomatic bacteriuria, hypokalemia, increased alanine aminotransferase and aspartate aminotransferase concentration, anemia.
Imipenem/cilastatin/relebactam	Not reported
Aztreonam/avibactam	Not reported
Cefiderocol	Systemic: pyrexia; Gastrointestinal: diarrhea; Mucocutaneous: rash; Others: abdominal pain; headache, oropharyngeal pain; Laboratory alterations: decreased TSH level, increased alanine aminotransferase and aspartate aminotransferase concentration, increased creatine phosphokinase level, increased urea level, increased white blood cell count, red cells in urine.
Plazomicin	Systemic: dizziness, somnolence; Others: blurred vision, headache, tinnitus; Laboratory alterations: mild transient increased serum creatinine.
Eravacycline	Systemic: nausea, pyrexia; Gastrointestinal: diarrhea, vomiting; Others: phlebitis; Laboratory alterations: anemia.

compared to best available therapy for the management of infections due to carbapenem-resistant *Enterobacteriaceae* (CRE). In the microbiologic-CRE-modified intent-to-treat population, MER/VAB compared to best available therapy resulted in a higher rate of clinical cure at the end of therapy (65.6% [21 out of 32] vs. 33.3% [5 out of 15], respectively; difference 32.3% [95%CI 3.3% to 61.3%]) and at the test-of-cure visit (59.4% [19 out of 32] vs. 26.7% [4 out of 15], respectively; difference 30.5% [95%CI 1.6% to 59.4%]). In a sensitivity analysis (only patients without previous antibiotic failure at randomization were included in this analysis), MER/VAB was associated with a higher clinical cure rate at the test-of-cure visit (69.6% [16 out of 23] vs. 26.7% [4 out of 15)]; difference 42.9 [95%CI 13.7 to 72.1%]) and at day-28 all-cause mortality (4.3% [1 out of 23] vs. 33.3% [5 out of 15]; difference − 29.0 [95%CI − 54.3% to − 3.7%]) compared to the control group [29]. Table 2 shows the most common adverse events of MER/VAB.

Imipenem/cilastatin/relebactam

Imipenem/cilastatin/relebactam (IMI/CIL/REL) is a carbapenem-beta-lactamase inhibitor combination in late phase of development. It has activity against Gram-negative bacteria producing ESBL, KPC, and AmpC enzymes (Fig. 1) [17, 27]. Figure 2 shows the mechanism of action of IMI/CIL/REL. A phase 2, multicenter, double-blind, randomized trial (ClinicalTrials.gov identifier: NCT01506271) compared IMI/CIL alone (500 mg every 6 h) to IMI/CIL plus REL (500 mg IMI/CIL plus 125 mg or 250 mg REL every 6 h) in a cohort of hospitalized adults with cIAI. The primary endpoint was clinical response at discontinuation of intravenous therapy (DCIV) in the microbiologically evaluable population. Clinical cure rates were similar in patients who received IMI/CIL plus REL 250 mg (96.3%; 78 out of 81 patients), IMI/CIL plus REL 125 mg (98.8%; 85 out of 86 patients), or IMI/CIL alone (95.2%; 79 out of 83 patients). Overall, both IMI/CIL/REL regimens were non-inferior to IMI/CIL alone (both at $P < 0.001$). Similarly, per-pathogen clinical cure rate was similar between groups [30]. Finally, a phase 3, multicenter, prospective, randomized, double-blind study (RESTORE-IMI 1; ClinicalTrials.gov identifier: NCT02452047) evaluated the effectiveness of IMI/CIL plus REL compared to IMI/CIL plus colistin for the treatment of serious infections (cIAI, cUTI, HAP, VAP) due to IMI/CIL-resistant strains. Overall, in the microbiologically modified intent-to-treat population, a

favorable overall response was demonstrated in experimental and control group (71.4% vs. 70.0%, respectively) [31].

Aztreonam/avibactam

Aztreonam/avibactam (ATM/AVI) is a new investigational beta-lactam and beta-lactamase inhibitor combination in late phase of development. It has activity against Gram-negative bacteria producing Ambler class A (ESBL and KPC), B (MBL), C (AmpC), and some class D enzymes (OXA-48 producers) (Fig. 1) [17, 27]. ATM/AVI exhibited limited activity against *P. aeruginosa* and *A. baumannii* [32]. Figure 2 shows the mechanism of action of ATM/AVI. A phase 3 study (ClinicalTrials.gov identifier: NCT03329092) comparing ATM/AVI with or without metronidazole versus meropenem with or without colistin for the treatment of severe infections due to Gram-negative bacteria is ongoing [33].

Cefiderocol

Cefiderocol is a first-in-class siderophore cephalosporin antibiotic. It has a broad spectrum of activity against Gram-negative bacteria, including *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* [17, 27]. In a large microbiological study, o*ver 95%* of isolates, including clinical isolates of carbapenem-non-susceptible *Enterobacteriaceae*, MDR *A. baumannii*, MDR *P. aeruginosa*, *S. maltophilia*, and *B. cepacia*, had minimum inhibitory concentrations of ≤ 4 μg/ml [34]. Figure 2 shows the mechanism of action of cefiderocol. A phase III trial (ClinicalTrials.gov Identifier: NCT02714595) designed to provide evidence of efficacy of cefiderocol in the treatment of serious infections due to carbapenem-resistant Gram-negative bacteria is currently recruiting [35]. Table 2 shows the most common adverse events of cefiderocol.

Plazomicin

Plazomicin (PLZ) is a new aminoglycoside developed to be active against microorganisms containing aminoglycoside-modifying enzymes [36]. Like other agents of the same class, PLZ inhibits protein biosynthesis by irreversibly binding the bacterial 30S ribosomal subunit (Fig. 2). PLZ has activity against Gram-positive bacteria, including both methicillin-sensitive and resistant *S. aureus*, and MDR Gram-negative bacteria, namely CRE (Fig. 1). However, PLZ has poor activity against non-fermenting Gram-negative bacteria [17, 27]. In a European multicenter study, Castanheira et al. showed that PLZ inhibited 96% of *Enterobacteriaceae*, including CRE, but has limited activity against MBL producers [37]. Moreover, combination of PLZ with some beta-lactams (piperacillin/tazobactam or ceftazidime) shows synergistic activity against MDR *Enterobacteriaceae* [38]. The recommended dose of PLZ in patients without renal impairment is 15 mg/kg body weight administered every 24 h by intravenous infusion over 30 min. It is currently approved for the treatment of *Enterobacteriaceae* cUTIs, including pyelonephritis, in patients who have limited or no alternative treatment options. PLZ has also shown promise in treating bloodstream infections: in the CARE study, a phase 3, multicenter, open-label, randomized trial (ClinicalTrials.gov Identifier: NCT01970371), PLZ improved the outcomes of patients with CRE bloodstream infections. In the microbiologically modified intent-to-treat population (29 patients), PLZ (plus meropenem or tigecycline) was associated with lower 28-day all-cause mortality rate compared to control (colistin plus meropenem or tigecycline) (7.1% [1 out 14 patients] vs. 40.0% [6 out 17 patients], respectively; difference − 32.9% [95% CI -60.1% to − 4.0%]). Moreover, PLZ was associated with an over 80% relative increase in CRE bacteremia clearance by day 5 compared to colistin-based therapy [39]. Table 2 shows the most common adverse events of PLZ.

Eravacycline

Eravacycline (EVC) is a new, broad-spectrum, synthetic fluorocycline antibiotic. EVC has activity against MDR Gram-positive and Gram-negative bacteria, including CRE; however, this agent lacks activity against *P. aeruginosa* [17, 27]. Overall, in the CANWARD surveillance study, EVC shows in vitro activity that is equivalent to or 2- to 4-fold greater than tigecycline against *Enterobacteriaceae* and Gram-positive bacteria [40]. Figure 2 shows the mechanism of action of EVC. It is currently approved for the treatment of cIAIs. Moreover, although EVC has higher serum level compared to tigecycline, further studies are needed to clarify its role in the treatment of bacteremic infections [41]. The recommended dose of EVC in patients without hepatic impairment is 1 mg/kg body weight administered every 12 h by intravenous infusion over 60 min. A phase 2, multicenter, double-blind, randomized trial (ClinicalTrials.gov identifier: NCT01265784) that compared EVC (1.5 mg/kg every 24 h or 1.0 mg/kg every 12 h) to ertapenem (1 g every 24 h) was performed in a cohort of hospitalized adults with cIAI. The primary outcome was clinical response at the test-of-cure visit in the microbiologically evaluable population. Clinical response in the microbiologically evaluable population (109 patients) was observed in 92.9% (39 out of 42) of patients who received EVC at 1.5 mg/kg, 100% (41 out of 41) of patients who received EVC at 1 mg/kg, and 92.3% (24 out of 26) of patients who received ertapenem. The estimated difference in clinical success rates between EVC at 1.0 mg/kg

and ertapenem was 7.7% (95%CI − 6.7% to 40.9%) [42]. IGNITE 1 is a phase 3, multicenter, double-blind, randomized trial that evaluated the efficacy of EVC versus ertapenem for the treatment of hospitalized adult patients with cIAI (Clinicaltrials.gov identifier: NCT01844856). The primary endpoint was the clinical response at the test-of-cure visit in the microbiological intent-to-treat population and in the modified intent-to-treat and clinically evaluable populations. Clinical cure in the microbiological intent-to-treat population (446 patients) was observed in 86.8% (191 out of 220) of patients who received EVC and 87.6% (198 out of 226) of patients who received ertapenem (difference − 0.80% [95%CI − 7.1% to 5.54%]). Moreover, clinical cure in the modified intent-to-treat (538 patients) and clinically evaluable (477 patients) populations was found in 87.0% (235 out of 270) and 92.9% (222 out of 239) of patients who received EVC and 88.8% (238 out of 268) and 94.5% (225 out of 238) of patients who received ertapenem, respectively (difference − 1.80% [95%CI − 7.4% to 3.8%] and difference − 1.70 [95%CI − 6.3% to 2.8%). Overall, there were more treatment-related adverse events in the EVC group (113 out of 270) than the control group (75 out of 268). Rates of nausea and phlebitis were higher among patients who received EVC than patients who received ertapenem [43]. Table 2 shows the most common adverse events of EVC. Finally, IGNITE 4, another phase 3, multicenter, double-blind, randomized trial, demonstrated the non-inferiority of EVC compared to meropenem for the treatment of hospitalized adult patients with cIAI (Clinicaltrials.gov identifier: NCT02784704) [44].

Conclusions

Antimicrobial therapy plays a crucial role, in combination with the source control, in the management of cIAIs. Moreover, early adequate antimicrobial therapy is essential to improve prognosis and outcome of surgical patients with cIAI. In recent years, several newer antimicrobial agents have become available for the management of these infections. Adequate knowledge of the microbiological and pharmacological characteristics of these new antimicrobial options is essential for selecting an appropriate drug regimen to treat cIAI. Overall, we believe that these new agents should be used as first-line option for the management of severe cIAIs in critically ill patients according to the local epidemiology and in patients at high risk for MDR microorganisms, especially ESBL- and KPC-producing bacteria. Moreover, new antimicrobial options can be a mainstay of carbapenem-sparing strategies, especially in setting with high prevalence of MDR microorganisms, minimizing the microbiological damage due to antibiotic pressure selection that is a main risk factor for the development of antibiotic-resistant bacteria. At the same time, both implementation of effective infection control practices to minimize or prevent the transmission of antibiotic-resistant bacteria and careful antimicrobial and diagnostic stewardship programs to ensure the appropriateness of antimicrobial therapies play a crucial role to preserve antibiotic effectiveness. Finally, a multidisciplinary approach including infectious diseases specialists, intensivists, microbiologists, pharmacists, and surgeons should be the milestone of the optimization of antimicrobial treatment in order to minimize inappropriate antibiotic use in an era of limited antibiotic options [45–48].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not required.

Informed consent Not required.

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