Review Article

New treatments of multidrug-resistant Gram-negative ventilator-associated pneumonia

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Abstract: Ventilator-associated pneumonia (VAP) remains an important clinical problem globally, being associated with significant morbidity and mortality. As management of VAP requires adequate and timely antibiotic administration, global emergence of antimicrobial resistance poses serious challenges over our ability to maintain this axiom. Development of antimicrobials against MDR Gram-negative pathogens has therefore emerged as a priority and some new antibiotics have been marketed or approach late stage of development. The aim of this review is to analyse new therapeutic options from the point view of potential treatment of VAP. Among recently developed antimicrobials presented herein, it is obvious that we will have promising therapeutic options against VAP caused by *Enterobacteriaceae* excluding those producing metallo-β-lactamases, against which only cefiderocol and aztreonam/avibactam are expected to be active. Against infections caused by carbapenem non-susceptible *Pseudomonas aeruginosa*, ceftolozane/tazobactam and to a lesser extend ceftazidime/avibactam may cover a proportion of current medical needs, but there still remain a considerable proportion of strains which harbor other resistance mechanisms. Murepavadin and cefiderocol hold promise against this particularly notorious pathogen. Finally, *Acinetobacter baummannii* remains a treatment-challenge. Eravacycline, cefiderocol and probably plazomicin seem to be the most promising agents against this difficult-to treat pathogen, but we have still a long road ahead, to see their position in clinical practice and particularly in VAP. In summary, despite persisting and increasing unmet medical needs, several newly approved and forthcoming agents hold promise for the treatment of VAP and hopefully will enrich our antimicrobial arsenal in the next few years. Targeted pharmacokinetic and clinical studies in real-life scenario of VAP are important to position these new agents in clinical practice, whereas vigilant use will ensure their longevity in our armamentarium.

Keywords: Ventilator-associated pneumonia; multidrug resistant bacteria; new antibiotics; *Acinetobacter baumannii;* *Pseudomonas aeruginosa*; Carbapenem resistant *Enterobacteriaceae*

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Introduction

Hospital-acquired pneumonia (HAP) remains one of the most important hospital-acquired infections, being associated with significant mortality, morbidity and increase in health expenditures (1,2). Gram-negative pathogens and particularly Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have progressively become predominant, the latter being more prevalent in patients

with ventilator-associated pneumonia (VAP) (3). These pathogens harbor a variety of mechanisms that confer resistance to antibiotics, rendering sometimes infections untreatable (4,5). A dry pipeline for years, led to the belief that we are approaching "the end of antibiotics" (5).

Inappropriate treatment has clearly been associated with increased mortality and healthcare costs (6,7) and MDR pathogens have been associated with inappropriate initial treatment, leading to a vicious cycle (8). In a recent meta-analysis, infections by carbapenem-resistant *Klebsiella pneumoniae* portended a 42% overall mortality versus 21% for carbapenem-susceptible counterparts (9). The World Health Organization (WHO) has listed carbapenem-resistant Enterobacteriaceae (CRE) among the highest priority pathogens in order to strive antibiotic development as a response to unmet public health threats (10). Following regulatory initiatives and social pressure, the antimicrobial pipeline has produced in the last decade a considerable number of new molecules. The aim of this article is to summarize the newly available or in late stage of development agents (phase 3 trials), expected to treat HAP and VAP caused by multi-drug resistant Gram-negative bacteria (MDR-GNB), focusing on agents with activity against CRE, MDR *P. aeruginosa*, and MDR *A. baumannii*.

Basic terms and mechanisms of resistance

After the introduction of the term MDR, a designation implying resistance to at least three different antibiotic classes, the terms extensively-drug-resistant (XDR) and pan-drug-resistant (PDR) have been introduced, implying respectively non-susceptibility in all but two or fewer antimicrobial categories and all agents in all antimicrobial categories (11). Multiple mechanisms of resistance contribute to an MDR, XDR or PDR profile in GNB (12,13). Intrinsic antimicrobial resistance mechanisms may be gradually selected by evolutional pressures; as an example, chromosomal genes that encode efflux pumps which pull antibiotics out of the bacterial cell. Acquired resistance in GNB can emerge through horizontal gene transfers, which are most commonly plasmid-mediated, or spontaneous mutations of existing genes (12). Acquired resistance mechanisms may be enzymatic (i.e., β-lactamases) or non-enzymatic (i.e., alteration of the bacterial membrane composition). Production of β-lactamases stands out as an important mechanism, hydrolysing β-lactam antibiotics which have been for decades the cornerstone of antimicrobial treatment of critically ill patients. The most relevant β-lactamases encountered in MDR pathogens causing HAP and VAP according to Ambler classification are presented in *Table 1* (12,13).

New antimicrobials

In this section we will present newly launched antibiotics and antimicrobials in late stage of development (having entered in phase 3 clinical trials). Data will be presented from the view point of their potential treatment of VAP or HAP. The main characteristics of the presented antibiotics, are shown in *Table 2*.

Combinations of cephalosporins or monobactam with β-lactamase inhibitors

Ceftazidime avibactam (Avycaz®Allergan, Inc for North America only, Zavicefta®, Pfizer)

Ceftazidime–avibactam (CAZ/AVI) combines a well-established third-generation cephalosporin, with a novel non β-lactam β-lactamase inhibitor, avibactam. The latter is active against a variety of β-lactamases, including Ambler Class A (KPC and ESBL type enzymes), Class C (AmpC) and some class D serine enzymes (such as oxacillinase OXA-48). However, it is vulnerable to metallo-β-lactamases (MBL) (*Table 2*) (14). A potent *in vitro* activity of CAZ/AVI was shown against CRE and *P. aeruginosa* excluding isolates producing MBLs (15). Avibactam is minimally active against *A. baumannii* and vulnerable to OXA-type carbapenemases carried in these species; in addition, it has poor activity against anaerobic Gram-negative bacteria and no activity against Gram-positive cocci (16). Susceptibility of *P. aeruginosa* to CAZ/AVI is improved relative to ceftazidime alone, but to a lesser extend compared to Enterobacteriaceae (17-19), with susceptibility of isolates resistant to ceftazidime and carbapenems not exceeding 50% in some studies (19-22). Isolates of *P. aeruginosa* from VAP had CAZ/AVI MIC90 at 16 whereas meropenem-non-susceptible strains had 32 mg/L, compared to 2 mg/L for Enterobacteriaceae and 8 mg/L for non-respiratory *Pseudomonas* isolates, indicating a more difficult PK/PD target (23,24).

KPC-3 displayed significantly higher MICs of CAZ/AVI, compared to KPC-2 variants, attributed to a compilation of resistance mechanisms, including *de novo* mutations in the blaKPC-3 gene, production of multiple carbapenemases, reduced porin expression and overexpression of efflux pumps (25,26). Emergence of resistance to CAZ/AVI

Table 1 Common β-lactamases encountered in Gram-negative bacteria causing hospital-acquired and ventilator-associated pneumonia, according to Ambler Classification [adapted from (12,13)]

Ambler class	Enzyme type	Common bacterial species	Examples	Substrate
A	Narrow-spectrum	*Escherichia coli, Klebsiella spp.*	Staphylococcal penicillinase, TEM-1, TEM-2, SHV-1	
A	Extended-spectrum Or ESBLs	*Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp., Kluyvera spp.*	SHV-like, CTX-like, KLUG-like	Penicillins, cephalosporins (except cefamycins), aztreonam
A	Serine carbapenemases	*Klebsiella spp.*	KPC-like, IMI-like	Penicillins, cephalosporins, aztreonam, carbapenems
B	Metallo-β-lactamases, carbapenemases	*Stenotrophomonas maltophilia, P. aeruginosa, Bacteroides fragilis, Acinetobacter baumannii*	VIM-like, IMP-like, NDM-like, GIM, SPM, SIM	Penicillins, cephalosporins, and carbapenems. Monobactams are stable
C	Extended-spectrum, cephalosporinases	*Enterobacter spp., Klebsiella spp., Proteus spp., Citrobacter spp., E. coli*	AmpC, P99, ACT-like, CMY-like, MIR-like	
D	Carbapenemases	*A. baumannii, P. aeruginosa, E. coli*	OXA-like	Penicillin, aztreonam, and carbapenems

CTX, cefotaximase; KPC, *Klebsiella pneumoniae* carbapenemase; IMP, imipenemase; VIM, Verona Integron metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.

reported after a relative short course of therapy and particularly after monotherapy, for infections caused by *K. pneumoniae*, prompts vigilance in clinical practice (4,27). Structural derangements of the omega-loop of KPC-2 were identified, resulting in a new active site of the enzyme, which however can no longer hydrolyze aztreonam or imipenem (28,29). As a consequence, carbapenems and aztreonam could overcome this new mechanism of resistance.

Ceftazidime exerts a time-dependent bactericidal effect, possesses linear pharmacokinetics and is excreted with glomerular filtration (30). Avibactam is eliminated primarily unchanged in the urine (31). Its half-life increases by 2–3 fold, 4 fold, and 12 fold with creatinine clearance (CrCL) values of 30–79 mL/min, <30 mL/min (non-hemodialysis), and <30 mL/min (hemodialysis) respectively (32). The recommended dosage and frequency of administration of CAZ/AVI in patients with normal renal function is 2.5 g every 8 h. Dosage adjustment is required in patients with moderately or severely impaired renal function (33,34). The avibactam pharmacokinetic/pharmacodynamic (PK/PD) target related with efficacy is the percent of time that the free drug levels exceed threshold concentration (%fT>CT). Area under curve (AUC) and maximum plasma concentration (Cmax) seem to play an important role in its pharmacodynamics and particularly against KPC producers (35,36). Early PK/PD studies in humans have demonstrated that both ceftazidime and avibactam penetrate into human epithelial lining fluid (ELF) with concentrations proportionally (25–30%) lower compared to plasma (37). In a recent study, pooled PK/PD data from preclinical pneumonia mice models and phase 1 and phase 2 studies in humans verified plasma levels as a surrogate for lung penetration in patients with HAP and VAP (38). Monte Carlo simulation verified PK/PD target attainment in patients with HAP with the approved CAZ/AVI dose (35,39).

CAZ/AVI has been approved by FDA and EMA for the treatment of complicated Urinary Tract Infections (cUTIs), complicated Intraabdominal Infections (cIAIs), HAP/VAP and for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (EMA only) (33,34). CAZ-AVI with metronidazole in registrational phase 3 trials (RECLAIM 1 and 2) showed non-inferiority to meropenem in the treatment of cIAIs (40). However, patients with moderate renal impairment (creatinine clearance/CrCl >30–50 mL/min) receiving CAZ/AVI had lower response rates compared to those receiving meropenem (40). In the REPRISE registrational phase 3 trial, CAZ/AVI established non-inferiority to doripenem in cUTIs (41). In an open-label trial comparing CAZ/AVI with "best available therapy"

Table 2 Spectrum of activity, administration route, dose, current clinical indication and development phase for the use in ventilator-associated pneumonia of new anti-bacterial

Antibiotic	Manufacturer and/or clinical trial sponsor	Spectrum of *in vitro* activity								Administration route/Dose	Current clinical indications	Development phase for the use in VAP (ongoing clinical trials)[¶]
		MRSA	Ps. aeruginosa		Enterobacteriacae				A. *baumannii*			
			MBL	Porin OprD	CRE ESBL	CRE KPC	CRE Oxa48	CRE MBL				
Cephalosporins	Cefiderocol (Shionogi Inc)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	IV/2 g q8h	cUTI. EMA and FDA authorization planned for 2018	Phase 3 for HAP, VAP, HCAP (NCT03032380)—*APEKS-NP*; Phase 3 for HAP, VAP, HCAP, BSI/Sepsis, cUTI (NCT02714595)—*CREDIBLE-CR*
Cephalosporin plus b-lactamase inhibitor	Ceftaroline/ avibactam (Pfizer)	Yes	No	Unknown	Yes	Yes	Yes	No	No	IV/combination of ceftaroline fosamil [600 mg] plus avibactam [600 mg] infused over 60 (± 5) minutes in phase 1 study	No application filed yet	Population Pharmacokinetic (PK) Study of Zinforo (Ceftaroline) in Critical Care Patients With Early-onset Pneumonia and Augmented Renal Clearance (NCT03025841)—*CEFTAREA*; Note: ceftaroline alone study
	Ceftolozane/ tazobactam (Merck & Co., Inc)	No	No	Yes	Yes	No	No	No	No	IV/1.5 g q8h 3 g q8h (VAP)	FDA and EMA approved for cUTI and cIAI	Phase 3 for VAP due to Ps. Aeruginosa (NCT03581370)—*CEFTOREA*
	Ceftazidime/ avibactam (Pfizer/ Allergan Inc)	No	No	Yes	Yes	Yes	Yes	No	No[†]	IV/2.5 g q8h	FDA and EMA approved for cIAI and cITU, HAP and VAP, and (in EMA only) for the treatment Gram-negative infections in patients with limited treatment options	Phase 1 for ICU patients with various infections, including VAP (NCT02822950)

Table 2 (*continued*)

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		MRSA	Ps. aeruginosa		Enterobacteriacae				A. *baumannii*			
			MBL	Porin OprD	CRE ESBL	CRE KPC	CRE Oxa48	CRE MBL				
Carbapenem plus novel b-lactamase inhibitor	Meropenem/ vaborbactam (Developer:Melinta Pharmaceutics, Trial sponsor: The Medicines Company)	No	No[†]	No[†]	Yes	Yes	No	No	No[†]	IV/2 g/2 g q8h	FDA, EMA approval pending cUTI	Phase 3b for HAP and VAP (NCT03006679)—*TANGOIII*; not yet recruiting
	Imipenem-cilastatin/ relebactam (Merck Sharp & Dohme Corp.)	No	No[†]	No[†]	Yes	Yes	No	No	No[†]	IV/500 mg/ 250–125 mg q6h	Imminent FDA Application	Phase 3 for HAP and VAP (NCT02493764)—*RESTORE-IMI 2*; Phase 3 for HAP and VAP (NCT03583333) to be launched
Aminoglycosides	Plazomicin (Achaogen)	Yes	Yes	Yes	Yes	Yes	Yes	Yes‡	Variable	IV/15 mg/kg q24h	FDA approval cUTI, EMA pending	No active trial related to VAP/HAP
Monobactams plus b-lactamase inhibitor	Aztreonam/ avibactam (Pfizer/ Allergan Inc)	No	Yes	Yes	Yes	Yes	Yes	Yes	No		Not reported status	Phase 3 for HAP and VAP and other Serious Infections (NCT03329092)—*REVISIT*; Phase 3 for cIAI, HAP and VAP (NCT03580044) to be launched
Tetracyclines	Eravacycline (Tetraphase Pharmaceuticals, Inc.)	Yes	No	No	Yes	Yes	Yes	Yes	Yes		FDA approval cIAI	No active trial related to VAP/HAP
Peptidomimetic	Murepavadin (Polyphor LTD)	No	Yes	Yes	No	No	No	No	No			Phase 3 for VAP (NCT03409679)—*PRISM-MDR*; (NCT03582007)—*PRISM-UDR* to be launched

[†], active against no MDR-resistant strains; [‡], not active against many NDMs; [¶], data compiled from www.clinicaltrials.gov. BSI, bloodstream Infections; cUTI, complicated Urinary Tract Infections; cIAI, complicated Intra-Abdominal Infection; ESBL, Extended-Spectrum beta-Lactamase; CRE, carbapenem-resistant Enterobacteriacae; EMA, European Medical Agency; FDA, Food and Drugs Administration; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; IV, intravenous; KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-b-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; NDM, New Delhi metallo-beta-lactamase; OprD, Outer membrane porin D; Oxa48, oxacillinase; VAP, ventilator-associated pneumonia.

in infections caused by ceftazidime-resistant isolates—mostly cUTIs—response rates were 90.9% and 91.2% respectively (42).

In a randomized prospective study, CAZ/AVI was tested versus with meropenem for the treatment of nosocomial pneumonia (NP), including VAP (REPROVE study, Clinical-Trials.gov Identifier NCT01808092) (43). Adults with NP (N=879), were randomized (1:1) to CAZ/AVI or meropenem for 7–14 days. Predominant Gram-negative baseline pathogens were *K. pneumoniae* (36.6%) and *P. aeruginosa* (29.6%), with 28.2% being ceftazidime-non-susceptible. Non-inferiority of ceftazidime-avibactam to meropenem was demonstrated in both co-primary analysis populations, with clinical cure rates at test-of-cure 68.8% for CAZ/AVI *vs.* 73% for meropenem [difference (95% CI), –4.2 (–10.76, 2.46), P=0.007] in the modified intent-to -treat population and 77.4% and 78.1%, respectively [difference (95% CI), –0.7 (–7.86, 6.39), P<0.001] in the clinically evaluable population. Secondary analysis produced similar results, including patients with VAP *vs.* non-VAP, renal function status (augmented renal clearance, normal renal function/mild impairment or moderate to severe impairment) and concomitant medication with aminoglycosides (43). Based on the results of the RECLAIM1 and 2 studies, the REPROVE protocol was amended to increase the CAZ/AVI dose for patients with moderate/severe renal impairment reflecting PK/PD data and amendments in the Summary of Product Characteristics (SPC) (33,34,40,44). Bacterial persistence with increasing MIC (≥4-fold MIC increase) at end of treatment and/or test of cure was observed in 2/125 (1.6%) patients in the CAZ/AVI group and 11/131 (8.4%) patients in the meropenem group. Overall, CAZ/AVI was well tolerated as in phase 2 and previous phase 3 trials with no similar to the comparators adverse event rates in all published studies (40-43).

In real life, CAZ/AVI is primarily used against CRE infections (not enrolled in registrational trials) displaying clinical response rates between 45% and 76% and relapse rates of 23% (4,26,45,46). A single-center observational study showed higher rates of clinical success and lower mortality with CAZ/AVI compared with other regimens employed for carbapenem-resistant *K. pneumoniae* (KPC-3 or -2) bacteraemia (47). Development of resistance to CAZ/AVI (MIC ≥16 mg/L) following relatively short courses of therapy generated questions as to whether combination treatment could avert this event (47). A recently published meta-analysis of 4,951 patients deriving from nine Randomized-controlled trials (RCTs) and three observational studies, reported comparable clinical response rate with CAZ-AVI *vs.* carbapenems and non-inferior bacterial eradication, with no significant difference in mortality rates and adverse events. However, in patients infected by CRE, CAZ/AVI produced improved clinical response (RR =1.61; 95% CI, 1.13–2.29) with reduced mortality (RR =0.29; 95% CI, 0.13–0.63) than comparator regimens. Improved clinical response with CAZ/AVI was also shown in bloodstream infections (48).

Summarizing, CAZ/AVI represents an important addition to our armamentarium against MDR Gram-negative pathogens, being the first marketed treatment option against KPC producers. Treatment as monotherapy is however questionable with existing data, particularly in the context of life-threatening infections. Expert-driven recommendations argue for combination treatment (an aminoglycoside, fosfomycin, tigecycline or colistin and hopefully plazomicin in the near future), based on the antibiogram and the required PK/PD parameters in the infectious focus (4). Its expanded spectrum, covering a considerable proportion of Enterobacteriaceae harboring ESBLs and variable proportions of P. *aeruginosa* strains, makes CAZ/AVI an appealing treatment option in the empiric treatment of severe infections by MDR pathogens and low probability of metallo-β-lactamases and *A. baumannii*. Empiric use of CAZ/AVI should be reserved for patients with strong risk factors for infections by KPC- or OXA-48-producers. Monitoring of prescriptions by antibiotic-expert teams is highly advisable. The need of combination treatment should be balanced, considering microbiology data and severity of infection. *Figure 1* summarizes potential indications for use of ceftazidime avibactam (4).

Ceftolozane/Tazobactam (Zerbaxa®, Merck & Co., Inc)

Ceftolozane/tazobactam (C/T) combines a well-established β-lactamase inhibitor with ceftolozane, a novel oxyimino-cephalosporin structurally related to ceftazidime. The latter has higher affinity than ceftazidime for the penicillin-binding proteins PBP1b, PBP1c, PBP2 and PBP3, which are essential in *Pseudomonas aeruginosa* (49,50). Ceftolozane remains active in AmpC overproduction, overexpression of efflux pumps, and loss of the OprD outer membrane porin, which are common in *P. aeruginosa* (51). The development of mutational resistance to C/T in *P. aeruginosa* requires several mutations leading to AmpC overexpression and structural modification (52).

Tazobactam provides stability against most extended-

Figure 1 Summary of potential indications of ceftazidime-avibactam, as empiric or targeted treatment.

spectrum β-lactamases (ESBLs) which hydrolyze ceftolozane alone (49), but the combination of C/T is vulnerable in the presence of carbapenemases (e.g., KPC, VIM, NDM, GES), except for OXA-48 (51). Large surveillance studies show that C/T has the most potent *in vitro* activity among β-lactams against *P. aeruginosa* and excellent activity against Enterobacteriaceae. *Haemophilus influenzae* and *Moraxella catarrhalis* are susceptible to C/T whereas some of the *Burkholderia* spp. and *Stenotrophomonas maltophilia* isolates have relatively low MICs to C/T. *A. baumannii* displays no substantial susceptibility (51-53). Among Gram-positive bacteria, C/T shows considerable *in vitro* activity against *Streptococcus viridans* and β-hemolytic streptococci (*Streptococcus pyogenes* and *S. agalactiae*), but has uncertain activity against *S. pneumoniae*. While it is not active against staphylococci and enterococci and has minimal anaerobic activity (49,51,53). Time-kill studies have also shown a greater bactericidal activity against *P. aeruginosa* compared with other cephalosporins whereas carbapenems appear to be more potent against Enterobacteriaceae (54). Pharmacodynamic studies have shown that the time of free drug concentration above the MIC required to induce the same magnitude of bactericidal activity or to prevent the emergence of resistance is lower for C/T compared with other cephalosporins against Gram-negative bacteria (55).

C/T is currently approved for clinical use in the United States and Europe for the indications of cIAIs and cUTIs, based on phase 3, non-inferiority clinical trials that compared C/T in combination with metronidazole versus meropenem and C/T versus levofloxacin, respectively (56,57). Another phase 3 clinical trial (ASPECT-NP) comparing C/T with meropenem in patients with HAP

requiring mechanical ventilation or VAP has been completed in June 2018. Up to this writing, the results have not been announced.

The dosage of C/T used in the nosocomial pneumonia trial was double (3 g every 8 h for normal renal function) the dosage used in the previous trials (1.5 g every 8 h). This was based on a phase 1 pharmacokinetic study in healthy volunteers that showed the area under the concentration (AUC)—time curve for ceftolozane in the ELF was approximately half than that in plasma (12,58). A population pharmacokinetic model verified that doubling of the ceftolozane dosage is required for a higher than 90% probability of pharmacodynamic target attainment for 1-log killing of pathogens with an MIC ≤8 mg/L (13,59). Of note, the breakpoint of susceptibility for C/T against *P. aeruginosa* is 4 mg/L according to both CLSI and EUCAST. The 3 g every 8 h dosage for C/T has been further evaluated in healthy volunteers for a duration of 10 days. No safety concerns were raised (60). A study using an experimental rabbit *P. aeruginosa* pneumonia model showed that C/T was equally effective to ceftazidime, piperacillin/tazobactam, and imipenem, if a dosage of C/T of 1.5 g every 8 h used, but more effective than the comparators with doubling of the dosage (61).

Pending the announcement of the results of the ASPECT-NP trial, data on the clinical effectiveness of C/T for respiratory infections and VAP in particular, are currently based on small case series and case-reports relating to off-label use. Variable dosage regimens were used and C/T was often administered in combination with other antibiotics. The published relevant case-series up to this writing overall show that C/T resulted in clinical success in 61.4% of patients with *P. aeruginosa* pneumonia (62-69). Based on the available data, failure of C/T therapy in serious *P. aeruginosa* infections is associated with an MIC higher than 4 mg/L (70) and the use of the lower dosage regimen (71). Development of C/T resistance during therapy of *P. aeruginosa* infections has also been described (64,67,70).

Regarding the effectiveness of C/T for infections caused by ESBL-producing Enterobacteriaceae, in a secondary analysis of the cases included in the clinical trials of cIAIs and cUTIs C/T achieved clinical cure rates (97.4%) among patients with *E. coli* or *K. pneumoniae* infections compared with 82.6% for levofloxacin and 88.5% for meropenem (72).

Both ceftolozane and tazobactam are excreted mainly through kidneys. Substantial reductions in the dosage of C/T should be made with decreasing creatinine clearance according the approved label of the drug. Monte Carlo simulations have shown the currently approved dosage of C/T for various degrees of renal impairment have a probability of pharmacodynamic target attainment more than 90% for an MIC up to 8 mg/L (73). This figure decreases to an MIC of 4 mg/L for patients with normal renal function or augmented renal clearance (73). Moderate renal impairment has not shown to affect the outcomes of C/T therapy in the clinical trials of cIAIs and cUTIs (71). Higher than the currently approved dosage may be required though to treat serious respiratory infections due to MDR *P. aeruginosa* (74). Case-reports have proposed a dosage up to 1.5 g three times daily for continuous venovenous hemofiltration (75) and of 1.5–3 g three times daily for continuous venovenous hemodiafiltration (76,77). The labelled duration of the infusion is 1 hour. However, a 4- to 5-hour extended infusion regimen has been shown to maximise the probability of pharmacodynamic target attainment for infections with pathogens with elevated MICs, according to Monte Carlo simulations (75,78).

As part of combination empiric regimens, C/T can provide adequate coverage of *P. aeruginosa* isolates in settings where carbapenemase-production is low (79). In conclusion, C/T appears to be a valuable addition to the antimicrobial armamentarium for the treatment of VAP. The main place in therapy of C/T in this setting is for empirical or targeted coverage of infections caused by *P. aeruginosa*. It has been recommended for this indication in a reiteration of the current international guidelines for ventilator-associated pneumonia (80). C/T may be the treatment of choice for *P. aeruginosa* strains with resistance to carbapenems attributed to mechanisms other than the production of carbapenemases. Against ESBL-producing Enterobacteriaceae C/T may be considered as a carbapenem-sparing option. The results of a recently completed phase 3 clinical trial are awaited to establish the role of C/T in HAP/VAP.

Aztreonam/avibactam (Pfizer)

Aztreonam, a well-established monobactam antibiotic since 1986, with clinically useful activity against aerobic MBL-producing bacteria, is currently being re-examined due to its potential to treat MDR Gram negative bacteria. Its activity in current clinical practice against MBL-producers is hampered by the frequent co-production of additional β-lactamases including ESBLs, AmpC enzymes, and serine carbapenemases on the same isolate, which hydrolyse and inactivate aztreonam (81-84). Its combination with

avibactam expands the *in vitro* spectrum to include strains producing Ambler class A and class C, and some class D β-lactamases, including ESBLs, and serine carbapenemases (KPC and OXA-48-type) (85). The combination of aztreonam-avibactam achieved a significant reduction in MIC values for Enterobacteriaceae isolates producing β-lactamases, ESBL and AmpC enzymes, including OXA-48 (86). The addition of avibactam to aztreonam failed to restore susceptibility in MDR strains of *P. aeruginosa* and *A. baumannii*, suggesting that resistance to aztreonam in these species is primarily driven by other mechanisms (82,83,87-89).

At present, a phase 3 clinical trial is recruiting patients with serious infections due to Gram- negative bacteria and limited or no treatment options, in order to determine efficacy, safety and tolerability of aztreonam/avibactam ± metronidazole versus meropenem ± colimycin (NCT03329092). In addition, a randomized phase 3 clinical trial is estimated to start in September 2018, with aim to evaluate the clinical use of aztreonam/avibactam compared to best available therapy (BAT) in hospitalized patients with infections due to metallo-β-lactamase (MBL)- producing Gram-negative bacteria, including HAP and VAP.

In this regard, aztreonam/avibactam represents one of the most promising treatment options for serious infections, including HAP and VAP, caused by resistant bacteria, and particularly those expressing metallo-b-lactamases, for which currently very few agents are coming from the pipeline.

Ceftaroline/Avibactam (Zinforo™, Pfizer)

Ceftaroline is a novel, fifth generation cephalosporin, which has been approved by the FDA and EMA for acute bacterial skin and skin structure infections caused by MRSA and community-acquired pneumonia (CAP) including that caused by *S. pneumoniae* (90-92). This novel cephalosporin possesses both Gram-positive and Gram-negative coverage, including methicillin susceptible *Staphylococcus aureus* (MSSA), MRSA and Enterobacteriaceae, although demonstrates limited anaerobic activity and no activity against abdominal anaerobes as well as ESBL and AmpC expressing species, *A. baumannii* and *P. aeruginosa* (90,93). The prodrug, ceftaroline fosamil, is converted to active ceftaroline in the plasma, which binds to the plasma proteins in approximately 20% and it is mainly excreted by the kidneys. The recommended dose is 600 mg iv over one-hour infusion twice daily and adjustment for moderate and severe renal impairment is needed (36,90,94).

Although the ceftaroline/avibactam combination is not yet thoroughly tested, the addition of avibactam seems promising with view to overcoming the above-mentioned limitations in terms of spectrum and extending activity against many multidrug-resistant (MDR) pathogens, while preserving its potent anti-staphylococcal spectrum (including MRSA strains) (95). This combination could prove to be extremely useful as a single-agent empirical coverage for Gram-positive/Gram-negative pathogens with multiple mechanisms of resistance. Although further pharmacokinetic studies are required in critically ill and mechanically ventilated populations, this antibiotic, due to its relative antimicrobial spectrum covering both Gram-negative and Gram-positive strains, seems quite promising coupled with avibactam in VAP/HAP.

New cephalosporins

Cefiderocol (Shionogi Inc)

Cefiderocol, formerly S-649266, is a siderophore cephalosporin for parenteral use with a novel mechanism of bacterial cell entry. Siderophores are small, high-affinity iron-chelating compounds that are produced by a variety of bacteria and fungi (96). Microorganisms recognize only certain siderophores, therefore, such conjugates exhibit a selective antimicrobial activity (97). For years, use of the iron transport abilities of siderophores to carry antimicrobials into cells has been a great challenge (98). Cefiderocol possesses a catechol moiety functioning as a siderophore to form a chelating complex with iron; it utilizes the bacterial iron transport system to penetrate susceptible microorganisms (99).

Cefiderocol demonstrated *in vitro* activity against ESBL-producers and CRE. Organisms producing Ambler Class A, D and B enzymes (metallo-β-lactamases) including NDM-1 enzymes were susceptible to cefiderocol (100). In vitro study of a large international collection of clinical strains showed for cefiderocol MIC90s of 0.5 and 1 μg/mL respectively, including a variety of MDR-bacterial pathogens such as *P. aeruginosa*, *A. baumannii*, *S. maltophilia* and *Burkholderia cepacia* (101). In an *in vitro* study of cefiderocol against 282 meropenem-nonsusceptible isolates of *P. aeruginosa*, *A. baumannii*, *K. pneumoniae*, and *Providencia stuartii* collected from Greek hospitals, cefiderocol displayed the lowest MIC values among 10 comparators (102). In the neutropenic murine thigh infection model, cefiderocol achieved bacterial stasis 85%) *P. aeruginosa* isolates, 88% *A. baumannii* isolates, and 77% of Enterobacteriaceae isolates with cefiderocol MIC ≤4 μg/mL. Furthermore, it was efficacious against two

tested isolates of NDM-producing *K. pneumoniae* (103).

Cefiderocol is currently in phase 3 of clinical development. Data from one Phase 3 trial known as APEKS-cUTI has been reported by Shionogi (104). Cefiderocol in hospitalized patients at risk for MDR cUTI, demonstrated non-inferiority over treatment with imipenem/cilastatin. Cefiderocol non-inferiority was consistent across patient clinical and microbiologic subgroups demonstrating a treatment difference of 15–20% *vs.* comparator arm, while being generally well tolerated, with no unexpected safety concerns identified (104).

Two phase 3 clinical trials are currently ongoing for various infections, including VAP. The APEKS-NP trial is a clinical study on adults with nosocomial pneumonia [HAP, VAP and healthcare-associated pneumonia (HCAP)] caused by Gram-negative pathogens versus meropenem (NCT03032380). A second multicenter Phase 3 trial comparing cefiderocol to best available therapy in infections caused by carbapenem-resistant pathogens (CREDIBLE) is also underway (NCT02714595).

Cefiderocol stands out as one of the most promising new antimicrobials against MDR Gram negative pathogens, with possible indication nosocomial pneumonia. Some of the most appealing characteristics of this molecule are the unique mechanism of entry into the bacterial cell and the expanded antimicrobial spectrum including metallo-β-lactamase producers and *A. baumannii*, against which very few forthcoming therapeutic options will be active.

Combinations of carbapenems with novel β-lactamase inhibitors

Meropenem/vaborbactam (Vabomere™, Melinta Therapeutics)

This combination includes an existing β-lactam antibiotic (meropenem) with a novel inhibitor (vaborbactam) which is a cyclic boronate non-β-lactam β-lactamase inhibitor. Vaborbactam (formerly RPX7009) possesses high affinity for serine proteases therefore inhibits KPC enzymes, as well as other Ambler class A and C enzymes but not members of Amber class B (metallo-β-lactamases/MBLs). It has not antibacterial activity itself (105). In a concentration of 8 μg/mL, vaborbactam augments *in vitro* the activity of meropenem against carbapenemase-producing Enterobacteriaceae isolates by least 64-fold but has no effect on meropenem non-susceptible *A. baumannii* spp producing OXA-type carbapenemases or on *P. aeruginosa* (106,107). The half-life of vaborbactam is 1.23 h and the steady state volume of distribution 21.0 L mimicking PK properties of β-lactams (108). The used combination dose of meropenem–vaborbactam in clinical studies is 2 g—2 g iv every 8 h. With this dose the achieved concentrations in plasma and ELF display a similar time-course and magnitude, with a penetration of 65% and 79% for meropenem and vaborbactam respectively (108).

In a phase 3, multi-center, 1:1 randomized, double-blind study comparing meropenem-vaborbactam to piperacillin-tazobactam in the treatment of cUTI in adults (TANGO-1) non-inferiority was achieved for the FDA and the EMA endpoints (109). According to the TANGO-1 study data, the US FDA approved recently meropenem–vaborbactam for the treatment of cUTIs including pyelonephritis (110). The TANGO-2 study (ClinicalTrials.gov Identifier: NCT02168946) was a randomized 2:1 study comparing meropenem-vaborbactam to best-available therapy (BAT) for the treatment of a variety of infections including cUTI, hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), cIAI and bacteremia by suspected carbapenem-resistant *Enterobacteriaceae* (111). TANGO-2 recruitment was prematurely terminated following interim analysis by the independent Data and Safety Monitoring Board (DSMB) based on 72 patients. Preliminary results showed statistically significant efficacy over BAT (57.1% *vs.* 33.3%), decreased nephrotoxicity and fewer treatment-related adverse events across all groups (111,112). In the cohort of patients with HABP/VABP and bacteremia, a lower day-28 all-cause mortality rate was demonstrated versus BAT (25.0% *vs.* 44.4%, respectively) (112). TANGO-3 (ClinicalTrials.gov identifier: NCT03006679, not yet recruiting at the writing of this review) will compare meropenem-vaborbactam *vs.* piperacillin-tazobactam in patients with HABP/VABP. Furthermore, a new phase 1 trial is currently underway in pediatric patients (ClinicalTrials.gov Identifier: NCT02687906).

Imipenem-relebactam (Merck Sharp & Dohme Corp.)

This combination includes an existing β-lactam antibiotic, imipenem-cilastatin, with the novel non β-lactam β-lactamase inhibitor relebactam (formerly MK-7655) which is a bridged bicyclic urea molecule (113). Relebactam, is a serine-based molecule with a diazabicyclooctane core and a piperidine ring has a mechanism of action similar to that of avibactam, resulting in a potent inhibition of both class A and C β-lactamases including KPC enzymes but is not active against metallo-beta-lactamases (MBLs)

and class D carbapenemases (113). The combination of relebactam with imipenem broadens the spectrum to include imipenem-resistant Enterobacteriaceae and *P. aeruginosa* strains without however providing any benefit against *A. baumannii*. At a concentration of 4 mg/L it relebactam reduced the imipenem MIC for KPC-producing Enterobacteriaceae from 16–64 mg/L to 0.12–1 mg/L, but is not clear if there is an activity against OXA-48 producing isolates (114,115).

The PK index correlating to efficacy of relebactam is AUC while the optimal dosing has not been determined yet. However, phase 1 studies suggested that relebactam doses at or above 125 mg every 6 h achieve an adequate PK/PD target (116). Imipenem and relebactam are associated with a promising intrapulmonary penetration (ELF 53% of plasma) reflecting a good therapeutic profile against nosocomial respiratory infections (117). Clinical but not published yet data from phase 1 trials showed a favorable tolerability and the most common observed adverse events (incidence >5%) are diarrhea, nausea, and vomiting (117). In phase 2 clinical studies in patients with cIAI and cUTI the administration of imipenem (500 mg every 6 h) with relebactam in different dosages (125 and 250 mg) *vs.* imipenem-cilastatin alone was associated with high clinical response (>97%) in both infections and similar rates of microbiological response, confirming non-inferiority of both imipenem/cilastatin + relebactam doses to imipenem/cilastatin alone (118). All 23 patients with imipenem non-susceptible pathogens had favorable microbiological responses (100% in each group). A phase 3, randomized, double-blind, controlled trial (including HAP and VAP) in adult patients with infections due to imipenem-resistant strains (imipenem-relebactam versus colistimethate sodium plus imipenem/cilastatin was used) has been completed without announced results yet (ClinicalTrials.gov Identifier: NCT02452047). Currently a phase 3 study is ongoing, aiming to assess the non-inferiority of imipenem-relebactam against piperacillin/tazobactam in patients with HAP or VAP (ClinicalTrials.gov Identifier: NCT02493764).

New tetracyclines

Eravacycline (Xerava™, Tetraphase Pharmaceuticals, Inc.)

Eravacycline is a novel, synthetic fluorocycline, with *in vitro* broad-spectrum activity against aerobic bacteria, both Gram-positive cocci and Gram-negative bacilli, including difficult-to-treat resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), GNB producing ESBL and KPC enzymes and MDR *A. baumannii* except for *P. aeruginosa* (119,120). Eravacycline, compared to commonly used antibiotics showed a potent *in vitro* activity against the majority of MDR pathogens with an MIC90 of 0.5 mg/L against *E. coli* isolates that were non-susceptible to third-generation cephalosporins and fluoroquinolones (120,121). In a PK/PD study of eravacycline in a murine model of infection by Enterobacteriaceae, fAUC/MIC index was confirmed, as the parameter which is associated with efficacy of the tetracyclines class (122). Eravacycline, has similar structure, mechanism of action and antibacterial spectrum with tigecycline, retaining activity against most tetracycline resistance mechanisms (efflux pumps and ribosomal protection proteins) (123). However, eravacycline is more potent *in vitro*, 2- to 4-fold versus Gram-positive cocci and 2- to 8-fold versus Gram-negative bacilli (119,124). In addition, eravacycline has excellent oral bioavailability, high metabolic stability and low potential for drug to drug interactions while its activity in biofilm cultures appeared more effective than tigecycline (119). Against clinical isolates of *A. baumannii*, eravacycline displayed greater susceptibility than tigecycline and demonstrated improved *in vitro* activity against CRE isolates, higher serum levels, and better tolerability (120,125). PK/PD studies support once-daily administration. The availability of both oral and intravenous formulations is an advantage, whereas good lung penetration and activity on bacterial biofilm provide promising features for the treatment of ICU infections and particularly VAP and VAT (119,125,126). PK/PD studies in murine thigh infection have shown maximum plasma concentration (C_{max}) values of 0.34 to 2.58 mg/L, area under the concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) values of 2.44 to 57.6 mg·h/L, and elimination half-lives of 3.9 to 17.6 h (127).

The clinical efficacy of eravacycline was demonstrated in community-acquired cIAIs and cUTIs (128-130). At the time of the writing of this review, several studies have been completed, including a phase 2 clinical trial for the treatment of cIAIs and four phase 3 clinical trials known as IGNITE trials (Investigating Gram-negative Infections Treated with Eravacycline). IGNITE1 and IGNITE4 were randomized, double-blind, double-dummy, multi-center studies assessing the efficacy and safety of intravenous (IV) eravacycline (1 mg/kg iv q12h) compared to ertapenem and meropenem, respectively, in patients with cIAI. Both IGNITE1 (541 enrolled patients) and IGNITE 4 (500 enrolled patients)

met the primary endpoints of clinical cure (128,129). In a pooled analysis of IGNITE1 and IGNITE 4 studies announced as congress presentation, favorable clinical and microbiological responses were observed for eravacycline against *Enterobacteriaceae* and *Acinetobacter baumannii*, including those demonstrating resistant phenotypes and genotypes (130). In patients with cIAIs caused by *A. baumannii*, of which most strains were MDR, eravacycline-treated patients achieved a 100% clinical and microbiological response rate. Both IGNITE 2 and 3 phase 3 randomized, multi-center, double-blind, clinical trials evaluating the efficacy and safety of once-daily iv eravacycline (1.5 mg/kg every 24 h) compared to levofloxacin (750 mg every 24 h) and ertapenem (1 g every 24 h) respectively for the treatment of cUTI failed to meet non-inferiority criteria. Full data analysis is not yet available however the selected lower dose compared to that administered in the cIAI trials may have contributed to this. The manufacturing company applied in US and European regulatory agencies only for the cIAI indication. Approval was granted at the time of writing for US market (131).

A phase 1 study in healthy volunteers showed an excellent penetration profile in lung tissue (concentrations greater than plasma by six-fold in the ELF and 50-fold in the alveolar macrophages), highlighting eravacycline as a perfect candidate for treatment against MDR bacteria causing pneumonia in critically ill patients (126). Summarizing, eravacycline allows good coverage of the vast majority of difficult-to-treat bacteria except *P. aeruginosa*. It is the only antibiotic under development with potential activity against MDR *A. baumannii* and it may play a role in reducing the use of cephalosporins and carbapenems. However, considering the discordance of pharmacokinetics encountered in healthy volunteers compared to critically ill patients with tigecycline, and the surprising failure of eravacycline pivotal trials in cUTIs, further PK/PD studies of eravacycline in critically ill patients with HAP/VAP are warranted in order to establish adequate lung tissue penetration in mechanically ventilated patients and inflamed lung tissue (132,133).

New aminoglycosides

Plazomicin (Zemdri™, Achaogen)

Plazomicin is a next-generation semisynthetic aminoglycoside which acts by inhibiting bacterial protein synthesis and was developed to target MDR Enterobacteriaceae and specifically strains that express aminoglycoside-modifying enzymes (134,135). However, before its entry into clinical practice, ribosomal ribonucleic acid (rRNA) methyltransferase enzymes were already identified in *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii*, conferring broad-spectrum resistance to all aminoglycosides, including plazomicin (136-139). Plazomicin exhibits dose-dependent bactericidal activity and is active *in vitro* against Gram-negative bacteria, such as Enterobacteriaceae, including CRE, ESBL and MDR isolates resistant to currently available aminoglycosides (136,138,140). In vitro activity with MIC90 ≤2 mg/L or 4 mg/L was demonstrated against KPC-producers exhibiting resistance to other aminoglycosides (137,140). In vitro activity of plazomicin against nonfermenters is less potent compared to Enterobacteriaceae. MDR *P. aeruginosa* had plazomicin MICs similar to those of other aminoglycosides (138). However, OXA-producing *A. baumannii* resistant to other aminoglycosides may be susceptible to plazomicin (139). Tested against 82 isolates of CRE, plazomicin showed 79% *in vitro* susceptibility with MICs ≤2 mg/L, including isolates producing metallo-β-lactamases type VIM or IMP but not NDM-1. Ribosomal methyltransferases are commonly co-produced by NDM-1-positive Enterobacteriaceae, therefore, plazomicin is not anticipated to be active against these isolates (136). In addition, plazomicin has shown potent activity against Gram-positive bacteria such as MRSA, including isolates with resistance to previous generation aminoglycosides (138).

The PK/PD properties of plazomicin revealed a linear and dose-proportional profile, with an elimination half time (t1/2) estimated at 4 h and lack of accumulation supportive of once daily therapy, whereas the dosage of plazomicin 15 mg/kg should be considered as therapeutic (141,142). With 15 mg/kg once daily dose, steady state volume of distribution was 0.19±0.02 L/kg, clearance 1.04±0.11 mL/min/kg, urinary excretion 89%±6% of the dosage after a single dose, Cmax at 144±45 mg/L for the first dose and 142±32 mg/L following repeated administration, whereas the trough levels were 0.21±0.06 mg/L after multiple dose.

Plazomicin showed promising clinical characteristics and safety in the phase 2 trial (ClinicalTrials.gov under identifier NCT01096849) (143). EPIC (Evaluating Plazomicin in cUTI), was the first phase 3 registration trial (NCT02486627), in which plazomicin met the non-inferiority endpoint when compared with meropenem (144). The second phase 3, CARE descriptive trial (ClinicalTrials.gov Identifier NCT01970371), evaluated the efficacy and

safety of plazomicin versus colistin as part of a definitive combination regimen for the treatment of serious infections due to CRE excluding NDM-producers. CARE enrolled 39 patients with a variety of infections including 29 bloodstream infections (BSI), and 8 HAP/VAP. Patients received plazomicin 15 mg/kg every 24 h or colistin, in both arms combined with a second agent (tigecycline or meropenem). The plazomicin group was associated with a lower rate of mortality (23.5% *vs.* 50.0%, respectively; 90% confidence interval: 0.7–51.2%). Serious disease-related complications were observed in 5.6% *vs.* 19% in plazomicin and colistin groups respectively (145,146). Plazomicin exhibited a favorable safety profile including renal function and no reported ototoxicity.

Plazomicin was FDA approved in June 2018 for patients 18 years of age or older for the intravenous treatment of cUTIs, including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae*. In the drug's SPC it is advised to be reserved for use in cUTI patients who have limited or no alternative treatment options, whereas potential nephrotoxicity, ototoxicity, neuromuscular blockade and foetal harm have been included in a boxed warning (147,148).

In summary, plazomicin is characterized by a favorable lung penetration, minor toxicity issues and a challenging antimicrobial spectrum including MDR Gram-negatives (mainly *Enterobacteriaceae* but variably *P. aeruginosa* and *A. baumannii*) and MRSA. It could be an important treatment option in patients with VAP, particularly as part of empiric regimens and also as combination treatment where monotherapy is not advised. As an aminoglycoside, its use as monotherapy particularly in VAP requires further strong clinical evidence.

Outer membrane protein targeting antibiotics (OMPTA)

Murepavadin (Polyphor Ltd)

Murepavadin (POL7080) is a 14-amino-acid macrocyclic peptide and is the first in-class pathogen-specific peptidomimetic antimicrobial. OMPTA possess a novel, non-lytic mechanism of action against Gram-negative bacteria. Murepavadin is Pseudomonas-specific and acts by binding to the lipopolysaccharide transport protein D (LptD), involved in lipopolysaccharide biogenesis (149). Disruption of the lipopolysaccharide transport causes alterations in the outer membrane of the bacterial cell and, ultimately death. Due to its selective affinity for *Pseudomonas* spp and the targeted mechanism of action, selection of resistance to other bacterial species or disruption of the colonic flora is not anticipated with murepavadin (150). *In vitro*, murepavadin exhibits potent antimicrobial activity against *P. aeruginosa* and good activity against some other tested Pseudomonas species but is not active against other Gram-negative species (i.e., *S. maltophilia*, *B. cepacia*, *Enterobacteriaceae*, *A. baumannii*) or Gram-positive cocci (151). In large *in vitro* studies of murepavadin and comparators, carbapenemase-producing, colistin-resistant, XDR and PDR isolates of *P. aeruginosa* were susceptible to murepavadine and exhibited an MIC90 of 0.12 mg/L, similar to non-MDR isolates (152,153).

Murepavadin has shown to be highly effective in several animal infection models and particularly potent in neutropenic lung infection models against XDR isolates where polymyxins were the only treatment option (151). Murepavadin has completed 6 phase 1 (POL7080-001, NP29332, NP29333, NP29334, POL7080-005 and POL7080-009 and two phase 2 trials (POL7080-002 and POL7080-003) (151,154), assessing safety and pharmacokinetics. PK studies after a single dose of murepavadin, showed a geometric mean half-life of 2.52 to 5.30 h, a total clearance of 80.1 to 114 mL/h/kg, and a volume of distribution of 415 to 724 mL/kg, consistent across dose levels, with linear and dose-proportional pharmacokinetics (155,156). Lung penetration was assessed in a multiple dose study (ClinicalTrials.gov identifier: NCT02165293); ELF concentrations measured in this and subsequent studies were comparable with free plasma concentration with a third compartment effect (157-159).

Murepavadin was well tolerated, adverse events were transient and generally mild (155). Nephrotoxicity, might be a concern in clinical practice, since systemic exposure to murepavadin (both as AUC and Cmax) increased in subjects with renal function impairment compared to subjects with normal renal function; therefore dose adjustments according to CrCl will be required (156). A phase 2 open-label study in VABP (ClinicalTrials.gov identifier: NCT02096328) enrolled 25 VABP patients who received murepavadin, twelve of which had a microbiologically documented infection due to *P. aeruginosa* (in nine cases MDR or XDR isolate). Clinical cure rate was 83% at test of cure among patients with confirmed *P. aeruginosa* with a reported 28-day all-cause mortality rate of 8%, far below the 20–40% expected mortality rate (160). No development of treatment-emergent resistance to murepavadin was detected. Small sample size calls for caution in the

interpretation of this encouraging however preliminary data in humans with VABP. Currently a phase 3 clinical study of murepavadin in HABP/VABP is underway.

In conclusion, murepavadin is a promising "concept approach to pathogen-specific treatment". Its broad *in vitro* spectrum against XDR isolates of *Pseudomonas* spp, offers therapeutic option against this notorious pathogen and could enhance initial appropriate treatment regimens in patients with strong risk factors for infections by this pathogen. The drug would also be ideal for de-escalation of initial treatment, once identification and susceptibility are available. Due to its unique mechanism of action, no cross-resistance with other antibiotics and no ecologic damage in bacterial flora seem to be additional advantages.

Conclusions

As management of VAP requires adequate and timely antibiotic administration, global emergence of antimicrobial resistance poses serious challenges over our ability to maintain this axiom. Among recently developed antimicrobials presented herein, it is obvious that we will have good therapeutic options against Enterobacteriaceae excluding those producing metallo-β-lactamases, against which only cefiderocol and aztreonam/avibactam are expected to be active. As far as carbapenem non-susceptible *P. aeruginosa* is concerned, ceftolozane/tazobactam and to a lesser extend ceftazidime/avibactam may cover a proportion of current medical needs, but there still remain a considerable proportion of strains which harbor other resistance mechanisms. Murepavadin and cefiderocol hold promise against this particularly notorious pathogen. On the other hand, *A. baummannii* remains a treatment-challenge. Eravacycline, cefiderocol and maybe plazomicin seem to be the most promising agents against this difficult-to treat pathogen, but we have still a long road ahead, to see their position in clinical practice and particularly in VAP.

In summary, despite persisting and increasing unmet medical needs, several newly approved and forthcoming agents hold promise for the treatment of VAP and hopefully will enrich our antimicrobial arsenal in the next few years. Some very optimists believe that we will be able to delete the term PDR from our medical dictionary. Recent experience with new antibiotics however, calls for studies assessing the efficacy of these novel agents in real-life, particularly considering their potential of selecting resistance. A crucial question is the potential of these agents to stand alone as monotherapy, which is questionable in an empiric regimen given their "precise" spectrum, whereas in the context of targeted therapy more real-life data are required. Companion drugs have to be carefully evaluated in terms of potential adverse events and ecologic consequences; finally, the economic component of combinations must be carefully balanced. The introduction of rapid microbiological methods of identification albeit costly and labour-demanding at this timepoint, could provide invaluable support in the rational use of new antimicrobials. Newly approved and forthcoming antibiotics with activity against MDR, XDR and currently PDR Gram negative pathogens have to be protected against unjustified use, otherwise, the joyful dawn will end and the PDR nightmare will be a global reality.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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