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Review

Multidrug-resistant *Acinetobacter baumannii* infections: Current evidence on treatment options and the role of pharmacokinetics/pharmacodynamics in dose optimisation

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ABSTRACT

Acinetobacter baumannii remains a difficult-to-treat pathogen that poses a significant challenge to clinicians and costs to the healthcare system. There is a lack of clinical efficacy data to aid in the selection of optimal treatment for multidrug-resistant (MDR) *A. baumannii* infections. This paper aimed to review recent literature on the treatment of MDR *A. baumannii* infections and novel agents in the pipeline and to discuss the clinical data supporting their use. Colistin has been widely studied as monotherapy or as part of combination therapy, but its use is limited due to nephrotoxicity. The clinical benefit of combination therapy, whether empirical or targeted, has yet to be demonstrated owing to a lack of definitive evidence from randomised controlled trials (RCTs). Most available clinical studies are retrospective and lack control groups, which offers low-grade evidence. Novel agents such as cefiderocol, plazomicin, eravacycline and sulbactam/ETX2514 combination are promising options for the treatment of different infectious pathologies caused by MDR *A. baumannii*, but these have yet to be evaluated in RCTs. A better understanding of the pharmacokinetics/pharmacodynamics of the 'old' antibiotics is required to optimise their dosing regimens in order to maximise bacterial killing, minimise toxicities and improve clinical outcomes.

1. Introduction

There are increasing reports of nosocomial infections caused by *Acinetobacter baumannii*, a pathogen frequently identified as an aetiological agent in catheter-related bacteraemia, hospital-acquired or ventilator-associated pneumonia, urinary tract infection, and surgical site and other types of wound infection [1]. *Acinetobacter baumannii* is intrinsically resistant to many antibiotics and readily acquires resistance to others. It can survive on dry surfaces and inanimate objects for months. These characteristics have contributed to the spread of multidrug-resistant (MDR) *A. baumannii* strains [2,3]. Risk factors for acquiring MDR *A. baumannii* include recent exposure to antibiotics (especially third-generation cephalosporins, carbapenems and fluoroquinolones), the presence of central lines or urinary catheters, severe disease, recent surgery, larger hospital size, prolonged ventilation, long intensive care unit or hospital stay, exposure to infected or colonised patients, and multiple medical procedures [4–6].

MDR *A. baumannii* frequently harbours multiple resistance mechanisms [7], leaving few available treatment options. *A. baumannii* used to be susceptible to antibiotics such as ampicillin and nalidixic acid [8], however the number of treatment options has reduced drastically with increasing resistance. For example, epidemiological studies from various parts of the world reported that 70–90% of *A. baumannii* isolates were resistant to three or more antibiotics of different classes, including carbapenems, penicillins, cephalosporins, aminoglycosides, polymyxins and fluoroquinolones (i.e. MDR) [9,10].There has also been an increase in reports of MDR *A. baumannii* isolates that are resistant to colistin, which is mostly considered the last line of defence against these organisms [11,12].

This review examines existing treatment options and new antibiotics with promising activity against MDR *A. baumannii* that have been recently approved or are in clinical development.

2. Methods

The PubMed, Embase and Cochrane Library databases were searched for articles published in the last 10 years up to 1 August 2018. The main search terms were 'multidrug-resistant', '*Acineto-*

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bacter', 'treatment' AND 'combination'. The reference lists of reports identified by this search strategy were also searched to select relevant articles. Only articles published in English were included. The following articles were included: (i) in vitro and in vivo studies on antibiotic synergy against MDR *A. baumannii*; (ii) clinical studies, both retrospective and prospective, describing the treatment of *A. baumannii* infections; and (iii) studies on novel antibiotics for *A. baumannii* infections. A total of 161 relevant articles were identified from the literature search and were included in this review.

3. Monotherapy versus combination therapy: the current evidence

3.1. In vitro and pre-clinical animal studies

Limited therapeutic options exist to treat MDR *A. baumannii*. Combination therapy may be used by some clinicians to manage these infections despite little laboratory guidance as to the microbiological effectiveness of this approach. Synergy testing methods have been used to assess the interaction of antibiotic combinations in vitro. These may provide predictive information regarding the use of antimicrobial combinations. Many in vitro and in vivo animal studies have explored the possible synergy of antibiotics to overcome *Acinetobacter* spp. resistance. In this review, 50 in vitro and 15 in vivo animal studies were found describing the effects of various antibiotic combinations against MDR *A. baumannii*. Their characteristics are presented in Supplementary Table S1 [13–62] and Supplementary Table S2 [15,35,45,55,64–74].

Most of these studies showed potential antibiotic combinations that could improve treatment outcomes of MDR *A. baumannii* infections. However, the studies also show that in vitro synergy is observed only for a portion of strains tested. Antagonism was observed in approximately 20% of the in vitro studies, and combinations that displayed antagonistic effects included various tigecycline-based combinations [24,33,39,52,59], imipenem-based combinations [28], tobramycin-based combinations [30] and certain sulbactam-based combinations [53,56,59]. Unfortunately, there is limited understanding to date as to what type of strains are more susceptible to combination therapy. Indeed, this may be an important factor contributing to the lack of reproducibility of results from in vitro and animal model studies. It is also worth noting that broth microdilution (BMD) is the recommended method of determining the minimum inhibitory concentration (MIC) of colistin [75]. This has obvious implications when interpreting the results of any in vitro or in vivo studies involving colistin that employ MIC testing methods other than BMD.

3.2. Observational clinical studies

The search identified 25 observational studies (22 retrospective and 3 prospective) that described treatment outcomes for MDR *Acinetobacter* spp. infections. The characteristics of these studies are presented in Table 1 [76–100].

Of the observational studies (Table 1), 12 studies compared monotherapy with combination therapy [76–87], 9 studies compared different combination treatment regimens [83,87–94] and 6 studies looked at different routes of administration of colistin, either inhaled or intrathecal/intraventricular [95–100]. More than 90% of these observational studies looked at patients with pneumonia, either as the sole site of infection or as a large majority from various sites of infection. Sample sizes range from 27 to 386. More than 50% of these studies explored the efficacy of polymyxin-based therapy and 25% looked at the efficacy of tigecycline-based therapy. There were differences in study design, such as case definitions and inclusion/exclusion criteria. There were also differences in the dose of antibiotics prescribed, and most of the studies were carried out before 2012, which was when the recommendation for a colistin loading dose was proposed.

Of the 12 studies that compared the efficacy of combination versus monotherapy, only 1 study showed a significant difference in 30-day mortality [82]. This retrospective study included 101 patients with various sites of infection, mainly pneumonia. Patients received either intravenous (IV) polymyxin B alone at a dose of 1.5–3.0 mg/kg/day in two divided doses or in combination with other antibiotics (mainly meropenem, 69.7%). The mortality rate was 42.4% in the combination therapy group and 67.7% in the monotherapy group ($P = 0.030$). The rate of microbiological eradication was not mentioned in the study.

Another study showed a significant difference in the rate of microbiological eradication in the combination therapy group compared with the monotherapy group (79.9% vs. 55.6%; $P = 0.001$) [83]. In that study, the authors compared colistin combination therapy combined with either a carbapenem, sulbactam or other antibiotics as well as with colistin monotherapy. Colistin was given at a dose of 5 mg/kg/day colistin base activity (CBA) in two to three divided doses, with renal adjustment. No loading dose was given. However, no difference was seen in the clinical response and 14-day mortality between the two groups. Other studies, however, did not demonstrate improved clinical or microbiological outcomes [77–81,84–87].

Two studies explored the clinical efficacy of colistin–glycopeptide combination therapy compared with colistin monotherapy [76,81]. One study did not observe a statistically significant difference in the mortality rate when comparing the two treatment arms [81], whereas the other showed that giving colistin with a glycopeptide for ≥5 days was protective against 30-day mortality [76].

Of the nine studies that compared different antibiotic combinations, three studies found a significant difference in their clinical outcome [88,91,93]. The first study compared tigecycline-based therapy [IV tigecycline 50 mg every 12 h (q12h) following a loading dose of 100 mg ± other antibiotics] with non-tigecycline-based combination therapy [IV imipenem/cilastatin 500 mg and sulbactam 1 g every 6 h (q6h)] in 386 patients with hospital-acquired infection [88]. Favourable clinical outcome was considerably higher in the tigecycline-based therapy group (69.2% vs. 50%; $P < 0.001$). However, the microbiological eradication rate was better in the non-tigecycline-based combination therapy group (11.7% vs. 1.1%; $P = < 0.001$). The second study compared tigecycline-based therapy (IV tigecycline 50 mg q12h following after a loading dose of 100 mg ± other antibiotics) with colistin-based therapy (IV colistin 2.5–5 mg/kg/day CBA in two to three divided doses ± other antibiotics) in 168 patients with MDR *A. baumannii* pneumonia [91]. Mortality was significantly lower in the colistin-based therapy group (44% vs. 60.7%; $P = 0.040$). The third study compared tigecycline–imipenem combination therapy with sulbactam–imipenem combination therapy in 84 patients with MDR *A. baumannii* ventilator-associated pneumonia (VAP) [93]. A standard dose of antibiotics was used but the exact dosing was not specified. The study found that the 30-day survival rate was significantly better in the tigecycline–imipenem combination therapy group compared with the sulbactam–imipenem combination therapy group (85.7% vs. 35.7%; $P = 0.007$). However, it is important to note that in the tigecycline group patients were switched from sulbactam-based therapy to tigecycline-based therapy after failure to respond to 3 days of sulbactam–imipenem/cilastatin therapy. Another study comparing tigecycline-based therapy (IV tigecycline 50 mg q12h following a loading dose of 100 mg ± other antibiotics) with sulbactam-based therapy [IV sulbactam 1 g or ampicillin/sulbactam 3 g (at a rate of 2:1) every 6–8 h ± other antibiotics] found that microbiological eradication was much higher in the sulbactam-based therapy group (63.5% vs. 33.3%; $P < 0.001$)

Table 1
Characteristics and outcomes of observational clinical studies reporting on the treatment of multidrug-resistant *Acinetobacter* spp. infections

Reference	Study period	Study design	No. of patients	Study objective	Site of infection	Treatment given	Dose of antimicrobials	Clinical outcome	*P*-value	Microbiological outcome	*P*-value
Petrosillo (2014) [76]	2010–2011	Retrospective, cohort	103	Compare monotherapy and combination therapy	Mainly VAP	Colistin alone[a]	IV colistimethate sodium 4–8 MU/day, with or without loading dose of 4.5–9 MU	30-day mortality 27.9%	0.900	–	–
						Colistin + vancomycin or teicoplanin[a]	IV colistin + IV vancomycin 2 g/day, with or without loading dose of 15 mg/kg or IV teicoplanin 400 mg/day	30-day mortality 33.3%			
However, Cox regression analysis of risk factors for 30-day mortality showed that a colistin–glycopeptide combination was protective of 30-day mortality if administered for ≥5 days (HR = 0.42; 95% CI 0.19–0.93; *P* = 0.03)											
Kalin (2014) [77]	2011	Retrospective, cohort	89	Compare monotherapy and combination therapy	VAP	Colistin alone[a]	IV colistimethate sodium 2.5 mg/kg q12h, with renal adjustment	Clinical cure 29.8%, mortality 51.9%	0.500, 0.530	Bacteriological clearance 72.3%	0.28
						Colistin + sulbactam[a]	IV sulbactam 3 g q8h	Clinical cure 40%, mortality 73%		Bacteriological clearance 85.7%	
López-Cortéz (2014) [78]	2010	Prospective, observational cohort	101	Compare monotherapy and combination therapy	Mainly pneumonia	Combination therapy	Colistin + tigecycline (27.3%) and carbapenem + tigecycline (12.1%)	30-day mortality 24.2%	0.940	–	–
						Monotherapy	Colistin (67.6%) and carbapenems (14.7%)	30-day mortality 23.5%			
Balkan (2015) [79]	2009–2012	Retrospective, cohort	107	Compare monotherapy and combination therapy	Bacteraemia	Colistin monotherapy	IV colistin 2.5–5.0 mg/kg/day, no loading dose	Clinical cure 31.4%, 14-day mortality 52.8%	0.450, 0.360	Microbiological eradication 69%	0.13
						Non-colistin-based combination therapy	Most common combination: cefoperazone/sulbactam + aminoglycoside, carbapenem + aminoglycoside, carbapenem + tigecycline and tigecycline + aminoglycoside, dose not specified	Clinical cure 42.9%, 14-day mortality 47.2%		Microbiological eradication 83%	
Yilmaz (2015) [80]	2011–2013	Retrospective, cohort	70	Compare monotherapy and combination therapy	VAP	Colistin monotherapy[a]	IV colistin 2.25 MU q8h or 4.5 MU q12h, with renal adjustment	Clinical response 76.5%, 28-day mortality 41.2%	0.350, 0.530	Microbiological response 52.9%	0.23
						Colistin–carbapenem combination therapy[a]	IV imipenem 500 mg q6h or IV meropenem 1 g q8h (prolonged infusion), with renal adjustment	Clinical response 63.6%, 28-day mortality 48.5%	0.530, 0.210	Microbiological response 63.6%	0.16
						Colistin–sulbactam combination therapy[a]	IV sulbactam 1 g q8h, with renal adjustment	Clinical response 55.0%, 28-day mortality 70%		Microbiological response 60.0%	

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Table 1 (*continued*)

Reference	Study period	Study design	No. of patients	Study objective	Site of infection	Treatment given	Dose of antimicrobials	Clinical outcome	*P*-value	Microbiological outcome	*P*-value
Garnacho-Montero (2013) [81]	2008–2011	Retrospective, cohort	57	Compare monotherapy and combination therapy	VAP/bacteraemia	Colistin–vancomycin combination therapy[a]	IV colistin 3 MU q8h, adjusted by BW and renal function + IV vancomycin 2 g/day by 1-h infusion, adjusted by renal function	Clinical cure 55.2%, 28-day mortality 48.3%	0.320, 0.890	Microbiological eradication 54.2%	0.440
						Colistin monotherapy[a]	IV colistin 3 MU q8h, adjusted by BW and renal function	Clinical cure 67.9%. 28-day mortality 50%		Microbiological eradication 65.2%	
Rigatto (2015) [82]	2013–2014	Retrospective, cohort	101	Compare monotherapy and combination therapy	Mainly pneumonia	Polymyxin B-based combination therapy	IV polymyxin B 1.5–3.0 mg/kg/day in two divided doses ± other antibiotics	30-day mortality 42.4%	0.030	–	–
						Polymyxin B monotherapy		30-day mortality 67.7%			
Batirel (2014) [83]	2009–2012	Retrospective, cohort	250	Compare monotherapy and combination therapy	Bacteraemia	Colistin combination therapy[a]	IV colistin 5 mg/kg/day CBA in two to three divided doses, with renal adjustment + carbapenems or sulbactam or other antibiotics	Complete response 46.3%, 14-day survival 68.2%	0.190, 0.140	Microbiological eradication 79.9%	0.001
						Colistin monotherapy[a]	IV colistin 5 mg/kg/day CBA in two to three divided doses, with renal adjustment	Complete response 30.6%, 14-day survival 55.5%		Microbiological eradication 55.6%	
				Compare different antibiotic combinations		Colistin–carbapenem combination therapy[a]	IV colistin 5 mg/kg/day CBA in two to three divided doses, with renal adjustment + imipenem 500 mg q6h or meropenem 1 g q8h or doripenem 500 mg q8h	Complete response 49%, 14-day survival 70.6%	0.970, 0.790	Microbiological eradication 81%	0.920
						Colistin–sulbactam combination therapy[a]	IV colistin 5 mg/kg/day CBA in two to three divided doses, with renal adjustment + ampicillin/sulbactam 3 g q6h or sulbactam 1.5 g q6h	Complete response 46.4%, 14-day survival 68.1%		Microbiological eradication 79%	
						Colistin–other antibiotic combination therapy[a]	IV colistin 5 mg/kg/day CBA in two to three divided doses, with renal adjustment + other antibiotics	Complete response 39.5%, 14-day survival 62.8%		Microbiological eradication 82%	

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Table 1 (*continued*)

Reference	Study period	Study design	No. of patients	Study objective	Site of infection	Treatment given	Dose of antimicrobials	Clinical outcome	*P*-value	Microbiological outcome	*P*-value
Lin (2015) [84]	2004–2007	Retrospective, cohort	173	Compare monotherapy and combination therapy	Pneumonia	Sulbactam monotherapy	IV sulbactam 1 g or ampicillin/sulbactam 3 g (at a rate of 2:1) q6–8h ± other antibiotics	Clinical resolution 63.6%, 30-day mortality 36.4%	0.906, 0.947	Airway eradication without relapse 89.5%	0.694
						Sulbactam-based combination therapy		Clinical resolution 65.1%, 30-day mortality 37.2%		Airway eradication without relapse 81.3%	
Shin (2012) [85]	2009–2010	Retrospective, cohort	27	Compare monotherapy and combination therapy	Various, mainly VAP	Tigecycline monotherapy	IV tigecycline 50 mg q12h after a loading dose of 100 mg ± other antibiotics	Clinical success 58.5%, 14-day mortality 5.9%	0.561, 0.260	Microbiological success 76.5%	0.097
						Tigecycline combination therapy		Clinical success 70%, 14-day mortality 0%		Microbiological success 100%	
Tasbakan (2011) [86]	2009–2011	Retrospective, cohort	72	Compare monotherapy and combination therapy	Pneumonia	Tigecycline monotherapy	IV tigecycline 50 mg q12h after a loading dose of 100 mg	30-day mortality 52.1%	>0.050	Microbiological eradication 60.9%	>0.050
						Tigecycline-based combination therapy	IV tigecycline 50 mg q12h after a loading dose of 100 mg + imipenem/cilastatin 500 mg q6h or amikacin 1 g q24h or netilmicin 300 mg q24h or cefoperazone/sulbactam 2 g q8h	30-day mortality 57.1%		Microbiological eradication 67.3%	
Kim (2016) [87]	2009–2010	Retrospective, cohort	70	Compare different antibiotic combinations	Pneumonia	Tigecycline-based therapy	IV tigecycline 50 mg q12h after a loading dose of 100 mg ± other antibiotics	Clinical success 47%, 30-day mortality 33%	0.950, 0.770	Microbiological success 23%	0.540
						Colistin-based therapy	IV colistin 4.5 MU q12h after a loading dose of 9 MU, with renal adjustment ± other IV antibiotics	Clinical success 48%, 30-day mortality 33%		Microbiological success 30%	
				Compare monotherapy and combination therapy		Monotherapy	Either tigecycline or colistin	Clinical success 39%, 30-day mortality 33%	0.110, 0.560	Microbiological success 22%	0.250
						Combination therapy	Either tigecycline or colistin-based therapy	Clinical success 59%, 30-day mortality 33%		Microbiological success 35%	
Lee (2013) [88]	2007–2011	Retrospective, cohort	386	Compare different antibiotic combinations	HAI	Tigecycline-based therapy[b]	IV tigecycline 50 mg q12h after a loading dose of 100 mg ± other antibiotics	Favourable outcome 69.2%, mortality 36.1%	<0.001, 0.930	Microbiological eradication 1.1%	<0.001
						Non-tigecycline-based therapy[b]	IV imipenem/cilastatin 500 mg and sulbactam 1 g q6h	Favourable outcome 50%, mortality 38.3%		Microbiological eradication 11.7%	
Lim (2011) [89]	2000–2007	Retrospective, cohort	70	Compare different antibiotic combinations	Bacteraemia	Colistin-based therapy[a]	IV colistimethate sodium 2.5–5.0 mg/kg/day in two to three divided doses, renal adjustment	30-day mortality 35.5%	0.800	–	–
						Non-colistin-based therapy[a]	Other antibiotics	30-day mortality 38.5%			

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Table 1 (*continued*)

Reference	Study period	Study design	No. of patients	Study objective	Site of infection	Treatment given	Dose of antimicrobials	Clinical outcome	*P*-value	Microbiological outcome	*P*-value
Ye (2016) [90]	2004–2010	Retrospective, cohort	168	Compare different antibiotic combinations	Pneumonia	Tigecycline-based therapy[a]	IV tigecycline 50 mg q12h after a loading dose of 100 mg ± other antibiotics	30-day mortality 33.3%	0.618	Eradication 33.3%	<0.001
						Sulbactam-based therapy[a]	IV sulbactam 1 g or ampicillin/sulbactam 3 g (at a rate of 2:1) q6–8h ± other antibiotics	30-day mortality 29.8%		Eradication 63.5%	
Chuang (2014) [91]	2009–2010	Retrospective, matched cohort	168	Compare different antibiotic combinations	Pneumonia	Tigecycline-based therapy	IV tigecycline 50 mg q12h after a loading dose of 100 mg ± other antibiotics	Mortality 60.7%	0.040	–	–
						Colistin-based therapy[a]	IV colistin 2.5–5 mg/kg/day CBA in two to three divided doses ± other antibiotics	Mortality 44%			
Cheng (2015) [92]	2010–2013	Prospective, cohort	55	Compare different antibiotic combinations	Mainly pneumonia/ bacteraemia	Colistin–carbapenem combination therapy[a]	IV colistin 5 mg/kg/day CBA in two to three divided doses, with renal adjustment + carbapenems	14-day mortality 15%, breakthrough bacteraemia 0%	0.105, 0.059	–	–
						Colistin–tigecycline combination therapy[a]	IV colistin 5mg kg/day CBA in two to three divided doses, with renal adjustment + IV tigecycline 50 mg q12h after a loading dose of 100 mg	14-day mortality 35%, breakthrough bacteraemia 18%			
						14-day mortality was associated with the use of colistin–tigecycline in the subgroup with tigecycline MIC > 2 mg/L compared with the use of colistin–carbapenem (HR = 6.93, 95% CI 1.61–29.78; $P = 0.009$)					
Jean (2016) [93]	2013	Prospective, cohort	84	Compare different antibiotic combinations	VAP	Tigecycline–imipenem combination therapy	Standard dose (not specified)	30-day survival rate 85.7%	0.007	–	–
						Sulbactam–imipenem combination therapy	Standard dose (not specified)	30-day survival rate 35.7%			
						In the tigecycline group, patients were switched from sulbactam-based therapy to tigecycline-based therapy after failure to respond to 3 days of sulbactam–imipenem/cilastatin therapy					
He (2016) [94]	2011–2013	Retrospective, cohort	44	Compare different antibiotic combinations	VAP	Tigecycline-based combination therapy	IV tigecycline 50 mg q12h after a loading dose of 100 mg + IV imipenem/meropenem 1 g q8h + IV cefoperazone/sulbactam 3 g q8h	Clinical cure 50%, all-cause mortality 50%	1.000	Microbiological eradication 15%	0.264
						Non-tigecycline-based combination therapy	IV imipenem/meropenem 1 g q8h + IV cefoperazone/sulbactam 3 g q8h	Clinical cure 45.8%, all-cause mortality 54.2%		Microbiological eradication 29.2%	

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Table 1 (*continued*)

Reference	Study period	Study design	No. of patients	Study objective	Site of infection	Treatment given	Dose of antimicrobials	Clinical outcome	*P*-value	Microbiological outcome	*P*-value
Chen (2014) [95]	2007–2011	Retrospective, cohort	135	Compare different route of administration	Pneumonia	Inhaled colistin[a]	Neb. colistin 2 MU q12h	28-day mortality 11.3%	0.167	14-day eradication 61.1%	0.001
						Other antibiotic therapies[a]	Not specified	28-day mortality 16.7%		14-day eradication 29.6%	
Kuo (2012) [96]	2009–2010	Retrospective, case–control	78	Compare different route of administration	Pneumonia	Inhaled colistin[a]	Neb. colistin 2 MU q12h	28-day mortality 12.8%	0.723	Eradication within 14 days 84.6%	<0.001
						Other antibiotic therapies[a]	Other antibiotics	28-day mortality 10.3%		Eradication within 14 days 10.3%	
Jang (2017) [97]	2013–2016	Retrospective, cohort	95	Compare different route of administration	VAP	IV colistin-based therapy	IV colistin 4.5 MU q12h after a loading dose of 9 MU, with renal adjustment ± other IV antibiotics	Clinical cure/improvement 79.6%, mortality 13.6%	0.719, 0.438	Microbiological eradication 65%	0.921
						Inhaled colistin-based therapy	Neb. colistin 4.5 MU q8h ± other IV antibiotics	Clinical cure/improvement 76.5%, mortality 19.6%		Microbiological eradication 66%	
Kofteridis (2010) [98]	2005–2008	Retrospective, case–control	86	Compare different route of administration	VAP	IV colistin only[a]	IV colistin 9 MU in three divided doses, with renal adjustment	Clinical cure 32.5%, mortality 26%	0.050, 0.289	Bacteriological eradication 50%	0.679
						Inhaled colistin + IV colistin[a]	Neb. colistin 2 MU q12h	Clinical cure 54%, mortality 16%		Bacteriological eradication 45%	
Kalin (2012) [99]	2011	Retrospective, cohort	45	Comparing different doses	VAP	High-dose IV colistin[b]	IV colistimethate sodium 2.5 mg/kg q6h	14-day clinical cure 7%, mortality 67%	0.250, 0.180	14-day bacteriological clearance 64%	0.19
						Normal-dose IV colistin[b]	IV colistimethate sodium 2.5 mg/kg q12h	14-day clinical cure 30%, mortality 45%		14-day bacteriological clearance 65%	
						Low-dose IV colistin[b]	Adjusted according to CL_{Cr}	14-day clinical cure 30%, mortality 40%		14-day bacteriological clearance 75%	
				Compare different route of administration		IV colistin only[b]	As above	14-day clinical cure 38%, mortality 44%	0.130, 0.650	14-day bacteriological clearance 69%	0.73
						IV colistin + inhaled colistin[b]	Neb. colistin 2 MU q12h	14-day clinical cure 14%, mortality 55%		14-day bacteriological clearance 76%	
Pan (2018) [100]	2013–2017	Retrospective, cohort	61	Compare different route of administration	Meningitis/ventriculitis	IT/IVT polymyxin B-based therapy	IT/IVT polymyxin B 50 000 U/day q12h + IV polymyxin B 450 000 U q12h ± other IV antibiotics	28-day mortality 8.7%, clinical efficacy 95.6%	0.010, <0.001	Microbiological clearance 91.3%	<0.001
						Other IV antibiotic therapies	Other IV antibiotics	28-day mortality 55.2%, clinical efficacy 23.7%		Microbiological clearance 18.4%	

VAP, ventilator-associated pneumonia; MIC, minimum inhibitory concentration; BMD, broth microdilution; MU, million units; IV, intravenous; HR, hazard ratio; CI, confidence interval; q12h, every 12 h; q8h, every 8 h; q6h, every 6 h; BW, body weight; CBA, colistin base activity; q24h, every 24 h; HAI, healthcare-associated infection; Neb., nebulised; CL_{Cr}, creatinine clearance; IT, intrathecal; IVT, intraventricular.
BMD is the preferred method of susceptibility testing for colistin according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations [63].

[a] Colistin MIC testing by methods other than BMD.

[b] Colistin MIC testing not done/mentioned.

[90]. Other studies, however, did not find a significant difference in clinical or microbiological outcomes for the various combination regimens investigated [83,87,89,92,94].

Of the six studies that explored different routes of polymyxin administration, five studies looked at the efficacy of inhaled colistin [95–99] and one looked at the efficacy of intrathecal/intraventricular (IT/IVT) polymyxin B [100]. Two studies observed superior microbiological eradication with inhaled colistin (nebulised colistin 2 MU q12h) compared with systemic antibiotic therapies (61.1–84.6% vs. 10.3–29.6%; $P \leq 0.001$) [95,96]. Neither study found a significant difference in 28-day mortality rate. Other studies found no significant differences in clinical or microbiological outcomes when comparing inhaled colistin with IV colistin for the treatment of MDR *A. baumannii* pneumonia [97–99].

With regard to IT/IVT polymyxin B for the treatment of MDR *A. baumannii* meningitis/ventriculitis, one study reported significant differences in clinical and microbiological outcomes [100]. This study compared IT/IVT polymyxin B-based therapy (IT/IVT polymyxin B 50 000 U/day q12h + IV polymyxin B 450 000 U q12h ± other IV antibiotics) with other IV antibiotic therapies in 61 patients. Clinical efficacy was much higher in the IT/IVT group (95.6% vs. 23.7%; $P < 0.001$) and 28-day mortality was much lower (8.7% vs. 55.2%; $P = 0.010$). Microbiological clearance was also significantly higher in the IT/IVT group (91.3% vs. 18.4%; $P < 0.001$).

A majority of these observational studies (Table 1) did not show any added benefits of combination versus monotherapy or between different treatment regimens. However, there are several limitations observed with many studies listed in Table 1 that may affect the validity of the results obtained. In general, most of the observational studies were retrospective in nature and as such may be limited by various factors such as poor quality or missing data or the absence of data on potential confounding factors. There are also limitations in the dosing regimens of antimicrobials used, such as lack of a loading dose for colistin or suboptimal dosing of other antimicrobials such as sulbactam and tigecycline. As highlighted previously regarding the issue with colistin MIC testing, we note that most studies involving colistin did not use BMD for determining the colistin MIC. Another point of relevance is that polymyxins have limited drug exposure in the lungs following parenteral administration, resulting in lower antibacterial activity and limited efficacy in the lungs relative to other sites, as shown in several studies [101,102].

3.3. Randomised controlled trial (RCT) data

Eight RCTs comparing different treatment regimens for MDR *A. baumannii* infections were found. The characteristics of these studies are presented in Table 2 [103–110].

All eight studies focused on the treatment of MDR *A. baumannii* pneumonia, mainly VAP. Seven of the eight were open-labelled trials. The majority of the studies involving colistin did not mention the method of MIC testing used. Five of eight studies compared colistin monotherapy with colistin-based combination therapy [104–108] and two studies measured the efficacy of inhaled colistin [103,109]. One study compared colistin monotherapy with ampicillin/sulbactam monotherapy [110]. Of the five studies comparing combination and monotherapy, only one study demonstrated improved clinical response with colistin-based combination therapy [108]. This recently published study compared colistin monotherapy [IV colistin 3 MU every 8 h (q8h), with renal adjustment, without loading dose] with colistin–ampicillin/sulbactam combination therapy (IV colistin + IV ampicillin/sulbactam 6 g q6h, both with renal adjustment) in 39 patients with VAP. The authors observed better clinical response in the combination group (70% vs. 15.8%; $P = 0.001$) but failed to demonstrate a difference in microbiological outcome.

However, two other studies found a better microbiological response in the combination group but failed to observe any difference in clinical outcome [105,107]. The first study compared colistin monotherapy (IV colistin 2 MU q8h, with renal adjustment, without loading dose) with colistin–rifampicin combination therapy (IV colistin + IV rifampicin 600 mg q12h) in 210 patients with MDR *A. baumannii* infection, mainly VAP [105]. The authors found better microbiological eradication in the combination group compared with the monotherapy group (60.6% vs. 44.8%; $P = 0.034$) but did not observe any difference in 30-day mortality rate between the two groups (43.3% vs. 42.9%; $P = 0.950$).

The second study compared colistin monotherapy (IV colistin 5 mg/kg/day CBA, without a loading dose) with colistin–fosfomycin combination therapy (IV colistin + IV fosfomycin 4 g q12h) in 94 patients with MDR *A. baumannii* infection, mainly VAP [107]. The study showed better microbiological response in the combination group compared with the monotherapy group (100% vs. 81.2%; $P = 0.010$) but did not observe any difference in clinical response between the two groups (59.6% vs. 55.3%; $P = 0.835$).

Another recently published study, the AIDA trial, tested the hypothesis that combination therapy would reduce clinical failure from 45% with colistin monotherapy to 30% with combination therapy. This study compared colistin monotherapy (IV colistin 4.5 MU q12h after a loading dose of 9 MU, with renal adjustment) with colistin–meropenem combination therapy (IV colistin + IV meropenem 2 g q8h by 3-h infusion, both with renally adjusted doses) in 406 patients with carbapenem-resistant Gram-negative infections (mainly pneumonia and bacteraemia), mostly due to MDR *A. baumannii* (312/406; 77%) [104]. A total of 198 patients were randomised into the colistin monotherapy group and 208 into the combination therapy group. The baseline patient clinical characteristics and demographics were comparable between the two groups. This study, however, failed to observe any superiority of combination therapy. There was no statistically significant difference in the primary outcome between combination therapy versus monotherapy (clinical failure at Day 14, 73% vs. 79%; $P = 0.172$) or in the secondary outcomes, which included microbiological failure (35% vs. 31%; $P = 0.489$) in the treatment of MDR *A. baumannii* pneumonia or bacteraemia. By Day 14, 32% of patients in the monotherapy arm and 34% in the combination therapy arm had died ($P = 0.786$) and, of the surviving patients, there was no improvement or a deterioration in Sequential Organ Failure Assessment (SOFA) score occurred.

Furthermore, a subgroup analysis of the AIDA trial also noticed a similar finding when comparing colistin monotherapy with colistin–meropenem combination therapy in patients with carbapenem-resistant, colistin-resistant *A. baumannii* [111]. The authors found that colistin–meropenem combination therapy was significantly associated with higher mortality among those with colistin-resistant isolates [odds ratio (OR) = 2.956, 95% confidence interval (CI) 1.180–7.408] compared with the monotherapy arm. However, this association was not seen in colistin-susceptible strains (OR = 0.943, 95% CI 0.640–1.389).

Overall, similar limitations observed in the observational studies were also found in these RCTs. Factors such as lack of a loading dose or suboptimal dosing for colistin, or suboptimal dosing of other antimicrobials such as sulbactam, rifampicin and fosfomycin, lack of information regarding the method used for colistin MIC testing, and limited penetration of polymyxins into the lungs need to be considered when evaluating these RCTs. There appears to be no strong RCT data to support combination therapy, although some findings suggest that there might be a benefit of treating MDR *A. baumannii* pneumonia with colistin in combination with high-dose ampicillin/sulbactam, rifampicin [105] or fosfomycin [107]. In view of the fact that these RCTs mainly included patients with

Table 2
Characteristics and outcomes of randomised controlled trials (RCTs) on the treatment of multidrug-resistant *Acinetobacter* spp. infections

Reference	Study period	Study design	No. of patients	Site of infection	Treatment given	Dose of antimicrobials	Mortality prediction score[a]	Clinical outcome	*P*-value	Microbiological outcome	*P*-value
Rattanaumpawan (2010) [103]	2006–2009	Prospective RCT, open-label	100	VAP	Inhaled colistin group [b]	Neb. colistin 2 MU q12h + IV antibiotics	19.1 (5.8) [c]	Favourable clinical outcome 51.0%, 28-day mortality 39.2%	0.840, 0.800	Favourable microbiological outcome 60.9%	0.030
					Placebo group	Neb. normal saline + IV antibiotics	18.5 (4.7) [c]	Favourable clinical outcome 53.1%, 28-day mortality 36.7%		Favourable microbiological outcome 38.2%	
Paul (2018) [104]	2013–2016	Prospective RCT, open-label	406	Mainly pneumonia/ bacteraemia	Colistin monotherapy[b]	IV colistin 4.5 MU q12h after a loading dose of 9 MU, with renal adjustment	5 (3–8)[d]	Clinical failure 79%, 28-day mortality 43%	0.172, 0.781	Microbiological failure 31%	0.489
					Colistin–meropenem combination therapy[b]	IV colistin + IV meropenem 2 g q8h by 3-h infusion, both with renal adjustment	6 (4–9)[d]	Clinical failure 73%, 28-day mortality 45%		Microbiological failure 35%	
Durante-Mangoni (2013) [105]	2008–2011	Prospective RCT, open-label	210	Mainly VAP	Colistin monotherapy[b]	IV colistin 2 MU q8h, with renal adjustment	39.0 (11.1)[e]	30-day mortality 42.9%	0.950	Bacteriological eradication 44.8%	0.034
					Colistin–rifampicin combination therapy[b]	IV colistin + IV rifampicin 600 mg q12h	40.8 (10.8)[e]	30-day mortality 43.3%		Bacteriological eradication 60.6%	
Aydemir (2013) [106]	2011–2012	Prospective RCT, open-label	43	VAP	Colistin monotherapy	IV colistin 9 MU in three divided doses, with renal adjustment	18.0 (4.9)[c]	Clinical response 49%, mortality 63.6%	0.654, 0.171	Microbiological response 59.1%	0.597
					Colistin–rifampicin combination therapy	IV colistin + oral rifampicin 600 mg/day	20.1 (6.8)[c]	Clinical response 52%, mortality 38.1%		Microbiological response 71.4%	
Sirijatuphat (2014) [107]	2010–2011	Prospective RCT, open-label	94	Mainly VAP	Colistin monotherapy[b]	IV colistin 5 mg of CBA/kg BW/day	21.9 (7.9)[c]	Favourable clinical response 55.3%, 28-day mortality 23.1%	0.835, 0.578	Microbiological response 81.2%	0.010
					Colistin–fosfomycin combination therapy[b]	IV colistin + IV fosfomycin 4 g q12h	23.0 (6.4)[c]	Favourable clinical response 59.6%, 28-day mortality 16.3%		Microbiological response 100%	

(*continued on next page*)

Table 2 (*continued*)

Reference	Study period	Study design	No. of patients	Site of infection	Treatment given	Dose of antimicrobials	Mortality prediction score[a]	Clinical outcome	*P*-value	Microbiological outcome	*P*-value
Makris (2018) [108]	Not specified	Prospective RCT, open-label	39	VAP	Colistin monotherapy[b]	IV colistin 3 MU q8h, with renal adjustment	14.5 (3.1)[c]	Clinical response 15.8%, mortality 63%	0.001, NS	Microbiological eradication 1/3	0.191
					Colistin–ampicillin/sulbactam combination therapy[b]	IV colistin + IV ampicillin/sulbactam 6 g q6h, both with renal adjustment	16.5 (4.7)[c]	Clinical response 70%, mortality 50%		Microbiological eradication 10/14	
Abdellatif (2016) [109]	2013–2015	Prospective RCT, single-blind	149	VAP	Inhaled colistin–IV imipenem[b]	Neb. colistin 4 MU q8h + IV imipenem 1 g q8h	39 (13)[e]	Favourable clinical outcome 67.1%, 28-day mortality 27.4%	0.590, 0.700	Time to bacterial eradication 9.89 ± 2.7 days	0.023
					IV colistin–IV imipenem[b]	IV colistin 4.5 MU q12h after a loading dose of 9 MU, with renal adjustment + IV imipenem 1 g q8h	40 (14)[e]	Favourable clinical outcome 72.3%, 28-day mortality 23.7%		Time to bacterial eradication 11.26 ± 3 days	
Betrosian (2008) [110]	Not specified	Prospective RCT, open-label	28	VAP	Colistin monotherapy[f]	IV colistin 3 MU q8h	14 (2)[c]	Clinical success 60%, 14-day mortality 20%	NS, NS	Bacteriological eradication 46.6%	NS
					Ampicillin/sulbactam monotherapy[f]	IV ampicillin/sulbactam (2:1) 9 g q8h	14 (5)[c]	Clinical success 61.5% 14-day mortality 15.3%		Bacteriological eradication 46.1%	

VAP, ventilator-associated pneumonia; MIC, minimum inhibitory concentration; Neb., nebulised; MU, million units; q12h, every 12 h; IV, intravenous; q8h, every 8 h; CBA, colistin base activity; BW, body weight; q6h, every 6 h; NS, not significant; BMD, broth microdilution.

BMD is the preferred method of susceptibility testing for colistin according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations [63].

[a] For the mortality prediction scores, data are presented as the mean (standard deviation) or median (interquartile range).

[b] Colistin MIC testing not done/mentioned.

[c] Acute Physiology and Chronic Health Evaluation (APACHE) II score.

[d] Sequential Organ Failure Assessment (SOFA) score.

[e] Simplified Acute Physiology Score (SAPS) II.

[f] Colistin MIC testing by methods other than BMD.

pneumonia, it is unclear whether these regimens would have similar outcomes for other sites of infection.

4. Optimised dosing of antibiotics to treat multidrug-resistant *Acinetobacter baumannii*

Given the challenges of providing effective treatment for infections caused by MDR *A. baumannii*, applying pharmacokinetic/pharmacodynamic (PK/PD) concepts to optimise dosing for individual patients should be considered an essential component of care. PK/PD-optimised antibiotic doses or altered routes of administration are likely required to ensure a successful treatment outcome while minimising side effects and the emergence of resistance.

PK/PD analyses describe the antibiotic exposure associated with maximal effect for an antibiotic and are critical determinants in establishing dosing regimens [112]. Three patterns of antimicrobial activity [113,114] and three PK/PD indices have been described: $\%fT_{>MIC}$, percentage of a 24-h time period that the unbound drug concentration exceeds the MIC; fC_{max}/MIC, maximum unbound drug concentration to MIC ratio; and *f*AUC/MIC, area under the unbound drug concentration–time curve to MIC ratio. Several studies have looked at dose optimisation of currently available antibiotics for the treatment of MDR *A. baumannii* infections. The characteristics of these studies are presented in Table 3 [31,62,115–127].

As an example, based on murine thigh and lung infection models of *A. baumannii*, PK/PD analysis of sulbactam demonstrated that $\%fT_{>MIC}$ is most predictive of bacterial killing [129]. The authors concluded that sulbactam was sufficiently bactericidal when a $\%fT_{>MIC}$ of >60% against *A. baumannii* thigh infection and >40% against *A. baumannii* lung infection was achieved. This suggests that to maximise the bactericidal activity of sulbactam, blood sulbactam concentrations should be maintained above the MIC for prolonged periods. In patients with severe sepsis, a target attainment of 60% $fT_{>MIC}$ for *A. baumannii* strains with a sulbactam MIC of 4 mg/L is more likely to be achieved when sulbactam is administered by a 4-h infusion of 1 g q8h, as demonstrated by a PK/PD study [126]. The authors of this study concluded that for pathogens with MICs of >4 mg/L, sulbactam should be given at a higher dosage regimen of ≥1 g q6h by 4-h infusion. PK/PD analysis has also helped to optimise dosing of sulbactam in patients with different renal function, as shown by Yokoyama et al. [130]. The study demonstrated that in a patient with a creatinine clearance (CL_{Cr}) of 15 mL/min, a sulbactam dose of 1 g twice daily achieves a 60% $fT_{>MIC}$ when the MIC of sulbactam against *A. baumannii* is 4 mg/L. A higher dose of 2 g four times daily is needed to achieve the same PK/PD target in a patient with a CL_{Cr} of 90 mL/min [130].

The recent revival of the long-neglected antibiotic colistin is another good example showcasing the significant role of pharmacokinetics/pharmacodynamics in optimising existing and old antibiotics against MDR infections. Animal PK/PD models were used to identify *f*AUC/MIC as the best measure of colistin exposure that correlates well with bacterial killing [131]. Against *A. baumannii*, the *f*AUC/MIC values required to achieve stasis and 1-log kill were 1.57–6.52 and 8.18–42.1, respectively, in a lung infection model and 1.89–7.41 and 6.98–13.6, respectively, in a thigh infection model [131]. For a 2-log kill, the *f*AUC/MIC values ranged from 7.4 to 17.6 [101]. These PK/PD data, in combination with those from clinical PK and toxicodynamic studies, were used for the development of dosing guidelines (Table 3) [132,133].

For carbapenems, the PK/PD index that correlates with bacterial killing is $\%fT_{>MIC}$. One study suggested that the PK/PD targets for bacteriostatic and maximal bactericidal activity of carbapenems occur with a $\%fT_{>MIC}$ of ca. 20% and ca. 40%, respectively [134]. An *A. baumannii* murine thigh infection model then demonstrated that $fT_{>MIC}$ values of 23.7%, 32.8% and 47.5% resulted in stasis, 1-log reduction and 2-log reduction in bacterial density after 24 h, respectively [135]. A subsequent PK/PD analysis of meropenem then revealed that the probabilities of achieving 40% $fT_{>MIC}$ following a bolus injection of 1 g q8h, a 3-h infusion of 1 g q8h and a 3-h infusion of 2 g q8h were 87.7%, 98.8% and 99.9%, respectively. These findings suggest that prolonged infusion maximises the bactericidal activity of meropenem against *A. baumannii* with an MIC of 4 mg/L [125].

The PK/PD index associated with bacterial killing by fosfomycin has been reported to be the $\%fT_{>MIC}$, with a target of 60–70 [136]. Based on Monte Carlo simulation, Menegucci et al. found that target attainment of 70% $fT_{>MIC}$ for pathogens with an MIC of 32 mg/L is only achievable when fosfomycin is administered as a 3-h infusion at a minimum dose of 4 g q8h [31].

For tigecycline, the PK/PD index associated with therapeutic efficacy is *f*AUC/MIC [137]. Based on exposure–response analyses of tigecycline, the *f*AUC/MIC target associated with microbiological eradication ranged from 6–18 depending on the site of infection [137–139]. The target ratios for skin and skin-structure infections (SSSIs) and intra-abdominal infections (IAIs) are >17.9 and >6.9, respectively. These target values in combination with clinical PK data can be used for appraisal of existing dosing regimens. For example, an in silico analysis of the currently recommended doses of 50 mg and 100 mg twice daily in SSSI demonstrated that the cumulative fraction response in Gram-negative bacteria isolates was only 54.67% even when given at the highest recommended dose [127]. Whereas in IAI the cumulative fraction response against Gram-negative bacteria isolates ranged from 48% to 88%. These results suggest that current dosing recommendations of tigecycline should be adjusted to ensure optimal exposure.

Table 4 summarises the PK/PD index and the optimal magnitude for the antibiotics discussed in this chapter. Table 5 summarises the recommended dosing regimens of currently available antibiotics for the treatment of MDR *A. baumannii*.

5. New antibiotics for treating multidrug-resistant infections

With limited antibiotics that are active against MDR *A. baumannii*, clinicians and researchers look to new and novel agents that could hold this promise. There are several antibiotics, either in the pipeline or already approved, for the treatment of MDR Gram-negative organisms, examples of which include ceftazidime/avibactam, aztreonam/avibactam, cefepime/zidebactam, imipenem/relebactam, meropenem/vaborbactam, ceftolozane/tazobactam, cefiderocol, plazomicin and eravacycline. However, the efficacy of these new agents against MDR *Acinetobacter* spp. remains a question and requires further exploration. Table 6 summarises the new agents and their activity against MDR *Acinetobacter* spp. Table 7 summarises the optimal PK/PD index for novel agents with in vitro activity against MDR *A. baumannii*. Of note, there is a lack of PK/PD target assessment studies against MDR *A. baumannii*. Most studies were done on *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [144–149].

5.1. Cefiderocol

Cefiderocol (S-649266) is a new siderophore cephalosporin antibiotic with an iron-chelating siderophore moiety that contributes to its potency against Gram-negative bacteria [163,183]. It is actively transported into the periplasmic space through the outer membrane, where it inhibits cell wall synthesis [184]. Cefiderocol is more stable against various β-lactamases, including classes A, B, C and D carbapenemases [185,186]. Ito-Horiyama et al. demonstrated that catalysis by various carbapenemases, including OXA-23, for S-649266 was 260-fold lower than that of meropenem [186].

Table 3
Studies evaluating dose optimisation of antibiotics used for multidrug-resistant (MDR) *Acinetobacter* spp. infections

Reference	Study design	Method(s)	Duration of study	Antibiotics tested	Outcome
Hagihara (2014) [115]	In vitro	PD model	24 h	1 mg/kg polymyxin B q12h	Combination therapy with polymyxin B plus 100 mg or 200 mg tigecycline q12h achieved a greater reduction in bacterial density than therapy with polymyxin B alone
				100 mg tigecycline q12h	
				200 mg tigecycline q12h	
				Polymyxin B + tigecycline 100 mg	
				Polymyxin B + tigecycline 200 mg	
Li (2014) [116]	In vitro	HFIM	168 h	0.5 g meropenem q8h by 0.5-h infusion	Not bactericidal
				0.5 g meropenem q8h by 3-h infusion	Not bactericidal
				1.0 g meropenem q8h by 0.5-h infusion	3-$\log_{10}$ CFU/mL bacterial killing; did not suppress the emergence of resistance
				1.0 g meropenem q8h by 3-h infusion	3-$\log_{10}$ CFU/mL bacterial killing; did not suppress the emergence of resistance
				2.0 g meropenem q8h by 0.5-h infusion	3-$\log_{10}$ CFU/mL bacterial killing; suppressed the emergence of resistance; $\%T_{>MPC} \geq 20$
				2.0 g meropenem q8h by 3-h infusion	3-$\log_{10}$ CFU/mL bacterial killing; suppressed the emergence of resistance; $\%T_{>MPC} \geq 20$
Menegucci (2016) [31]	In silico	MCS	–	4.0 g fosfomycin q8h by 1-h infusion	PTA ≥ 0.9 for $\%fT_{>MIC}$ ≥70% (MIC = 16 mg/L)
				6.0 g fosfomycin q6h by 1-h infusion	
				8.0 g fosfomycin q8h by 1-h infusion	
				4.0 g fosfomycin q8h by 3-h infusion	PTA ≥ 0.9 for $\%fT_{>MIC}$ ≥70% (MIC = 32 mg/L)
				6.0 g fosfomycin q6h by 3-h infusion	
				8.0 g fosfomycin q8h by 3-h infusion	
				1.5 g meropenem q6h by 0.5-h infusion	PTA ≥ 0.9 for $\%fT_{>MIC}$ ≥ 40% (MIC = 4 mg/L)
				1.0 g meropenem q8h by 3-h infusion	
				1.5 g meropenem q6h by 3-h infusion	
				2.0 g meropenem q8h by 3-h infusion	
Cai (2017) [117]	In vitro	PD model	24 h	5 mg/kg/day colistin in three divided doses	Combination of colistin with either regimen of tigecycline achieved a greater reduction in bacterial density and AUBC than colistin alone. A combination of tigecycline (high-dose) and colistin may be an effective therapy to prevent the emergence of resistance during treatment of MDR *A. baumannii* synergistically
				100 mg loading dose followed by 50 mg tigecycline q12h	
				200 mg loading dose followed by 100 mg tigecycline q12h	
				Colistin + 100 mg loading dose followed by 50 mg tigecycline q12h	
				Colistin + 200 mg loading dose followed by 100 mg tigecycline q12h	
Matsumoto (2017) [118]	In vivo	Murine pneumonia model	96 h	2.0 g cefiderocol q8h by 3-h infusion	2 g q8h as a 3-h infusion for 4 days produced a >3 $\log_{10}$ reduction in the number of viable cells of these carbapenem-resistant isolates in the lungs
				2.0 g cefiderocol q8h by 1-h infusion	
Lee (2013) [119]	In vitro	PD model	72 h	Colistin at 0.5 mg/L + rifampicin with a C_{max} of 5 mg/L	Combinations resulted in substantially greater killing at the low inoculum; combinations containing 2 mg/L and 5 mg/L colistin increased killing at the high inoculum. Combinations were additive or synergistic with all colistin concentrations. Emergence of colistin-resistant subpopulations was completely suppressed in the colistin-susceptible isolate with all combinations at both inocula
				Colistin at 2 mg/L + rifampicin with a C_{max} of 5 mg/L	
				Colistin at 5 mg/L + rifampicin with a C_{max} of 5 mg/L	
Housman (2013) [120]	In vitro	PD model	24 h	9.0 g ampicillin/sulbactam q8h by 3-h infusion + 2.0 g doripenem q8h by 4-h infusion	AUBC = 87.8 ± 21.0
				9.0 g ampicillin/sulbactam q8h by 3-h infusion + 200 mg tigecycline q12h by 30-min infusion	AUBC = 100.6 ± 33.0
				9.0 g ampicillin/sulbactam q8h by 3-h infusion	AUBC = 116.7 ± 31.6
				3.0 g ampicillin/sulbactam q6h by 30-min infusion + 200 mg tigecycline q12h by 30-min infusion	AUBC = 134 ± 31.5
				2.0 g doripenem q8h by 4-h infusion + 200 mg tigecycline q12h by 30-min infusion	AUBC = 142.7 ± 16.9

(*continued on next page*)

Table 3 (*continued*)

Reference	Study design	Method(s)	Duration of study	Antibiotics tested	Outcome
Rao (2016) [121]	In vitro	HFIM	48 h	Polymyxin B traditional monotherapy: fC_{ss} of 2 mg/L administered as a continuous infusion	Bacteriostatic
				Polymyxin B traditional monotherapy: as above but with an fC_{ss} of 5 mg/L administered as a continuous infusion	Initial killing up to 3 $\log_{10}$ in the first 6 h, followed by substantial re-growth
				Doripenem monotherapy: fC_{max} of 25 mg/L q8h	Bacteriostatic
				Polymyxin B traditional (fC_{ss} of 2 mg/L continuous infusion) and doripenem (fC_{max} of 25 mg/L q8h)	Synergistic with a 7.5 $\log_{10}$ CFU/mL reduction by 48 h. This combination regimen resulted in complete eradication at 72 h that was sustained until 192 h, then re-growth at 240 h. Complete suppression of resistant subpopulations
				Polymyxin B 'front-loaded' (fC_{ss} of 5 mg/L continuous infusion for 24 h followed by fC_{ss} of 2 mg/L thereafter) and doripenem (fC_{max} of 25 mg/L q8h)	Rapid and extensive initial killing (>8 $\log_{10}$ CFU/mL) with an improved time to eradication. Complete eradication of *A. baumannii* at 48 h. Complete suppression of resistant subpopulations
				Polymyxin B 'burst 2' (fC_{ss} of 2 mg/L continuous infusion for 24 h followed by no polymyxin B thereafter) and doripenem (fC_{max} of 25 mg/L q8h)	>8 $\log_{10}$ CFU/mL reduction by 72 h with ca. 6 $\log_{10}$ re-growth beyond 144 h
				Polymyxin B 'burst 5' (fC_{ss} of 5 mg/L continuous infusion for 24 h followed by no polymyxin B thereafter) and doripenem (fC_{max} of 25 mg/L q8h)	Rapid initial and sustained killing similar to the combination of polymyxin B 'front-loaded' and doripenem regimen. Complete suppression of resistant subpopulations
				Doripenem 'burst' (fC_{max} of 25 mg/L q8h × three doses followed by no doripenem thereafter) and polymyxin B traditional regimen (fC_{ss} of 2 mg/L continuous infusion).	Re-growth after the initial ca. 3 $\log_{10}$ reduction in CFU/mL between 24 h and 48 h
Lenhard (2017) [122]	In vitro	HFIM	336 h	8/4 g ampicillin/sulbactam q8h	Bacterial eradication by 144 h, albeit with killing over the first 72 h that was slower than that with the ampicillin/sulbactam double combinations
				2 g meropenem q8h by 3-h infusion	Failed to achieve a ≥1 $\log_{10}$ reduction
				3.33 mg/kg polymyxin B, then 1.43 mg/kg q12h	Failed to achieve a ≥1 $\log_{10}$ reduction
				8/4 g ampicillin/sulbactam q8h + 2 g meropenem q8h by 3-h infusion	Sustained bactericidal activity
				3.33 mg/kg polymyxin B, then 1.43 mg/kg q12h + 2 g meropenem q8h by 3-h infusion	Reduced counts by ≥2 $\log_{10}$ at 6 h, stasis ensued for 24 h, but by 48 h counts had risen above 10^8 CFU/mL
				8/4 g ampicillin/sulbactam q8h + 3.33 mg/kg polymyxin B, then 1.43 mg/kg q12h	Sustained bactericidal activity
Liu (2016) [62]	In vitro	PD model	24 h	1 g meropenem by 3-h infusion + 1 mg/L colistin	>3 $\log_{10}$ bacterial killing, better bacterial killing compared with monotherapy
				2 g meropenem by 3-h infusion + 1 mg/L colistin	
Roberts (2009) [123]	In silico	MCS	–	2 g meropenem q8h as bolus	$\%fT_{>MIC}$ 40% = 41% (MIC = 16 mg/L)
				2 g meropenem q8h by 4-h infusion	$\%fT_{>MIC}$ 40% = 69% (MIC = 16 mg/L)
				6 g meropenem q24h by continuous infusion	$\%fT_{>MIC}$ 40% = 100% (MIC = 16 mg/L)
Nicholson (2009) [124]	In vivo	Prospective, cohort	–	1 g doripenem q8h by 4-h infusion	Overall microbiological cure: 78.6%, 66.6% for MIC ≥ 16 mg/L
Jaruratanasirikul (2013) [125]	In vivo	Prospective, cohort	–	1 g meropenem q8h as bolus	$\%fT_{>MIC}$ 40% = 87.7% (MIC = 4 mg/L)
				1 g meropenem q8h by 3-h infusion	$\%fT_{>MIC}$ 40% =98.8% (MIC = 4 mg/L)
				2 g meropenem q8h by 3-h infusion	$\%fT_{>MIC}$ 40% = 99.9% (MIC = 4 mg/L)
Jaruratanasirikul (2016) [126]	In silico	MCS	–	1 g sulbactam q6h by 4-h infusion	$\%fT_{>MIC}$ 60% = 75.7% (MIC = 16 mg/L)
				2 g sulbactam q8h by 1-h infusion	$\%fT_{>MIC}$ 60% = 52.9% (MIC = 16 mg/L)
				2 g sulbactam q8h by 4-h infusion	$\%fT_{>MIC}$ 60% = 81.6% (MIC = 16 mg/L)
				2 g sulbactam q6h by 1-h infusion	$\%fT_{>MIC}$ 60% = 81.3% (MIC = 16 mg/L)
				2 g sulbactam q6h by 4-h infusion	$\%fT_{>MIC}$ 60% = 93.5% (MIC = 16 mg/L)
				3 g sulbactam q8h by 1-h infusion	$\%fT_{>MIC}$ 60% = 78.9% (MIC = 16 mg/L)
				3 g sulbactam q8h by 4-h infusion	$\%fT_{>MIC}$ 60% = 89.2% (MIC = 16 mg/L)
				3 g sulbactam q6h by 1-h infusion	$\%fT_{>MIC}$ 60% = 86.9% (MIC = 16 mg/L)
				3 g sulbactam q6h by 4-h infusion	$\%fT_{>MIC}$ 60% = 98.0% (MIC = 16 mg/L)
				4 g sulbactam q8h by 1-h infusion	$\%fT_{>MIC}$ 60% = 82.8% (MIC = 16 mg/L)
				4 g sulbactam q8h by 4-h infusion	$\%fT_{>MIC}$ 60% = 92.6% (MIC = 16 mg/L)
Xie (2014) [127]	In silico	MCS	–	100 mg tigecycline q12h	CFR 54.67% (SSTI) CFR 48% to 88% (IAI)

PD, pharmacodynamic; q12h, every 12 h; HFIM, hollow-fibre infection model; q8h, every 8 h; $\%T_{>MPC}$, percentage of time that the drug concentration exceeded the mutant prevent concentration; MCS, Monte Carlo simulation; q6h, every 6 h; PTA, probability of target attainment; $\%fT_{>MIC}$, percentage of time that the free drug concentration remains above the MIC of an offending pathogen during a dosing interval; MIC, minimum inhibitory concentration; AUBC, area under the bactericidal curve; fC_{ss}, free steady-state concentration; fC_{max}, maximum unbound drug concentration; q24h, every 24 h; CFR, cumulative fraction response (PTA for a specific drug dose, according to MIC distribution of a specific micro-organism) [128]; SSTI, skin and soft tissue infection; IAI, intra-abdominal infection.

Table 4
Pharmacokinetic/pharmacodynamic (PK/PD) index and the optimal magnitude for antibiotics against multidrug-resistant *Acinetobacter baumannii*

Antibiotic	Study model	PK/PD index	PK/PD index magnitude for optimal antimicrobial activity	Reference
Sulbactam	Neutropenic murine thigh infection model	$\%fT_{>MIC}$	>60[a]	[129]
	Neutropenic murine lung infection model		>40[a]	
Colistin	Neutropenic murine lung infection model	*f*AUC/MIC	8.18–42.1[b]	[131]
	Neutropenic murine thigh infection model		6.98–13.6[b]	
	Neutropenic murine thigh infection model		7.4–17.6[c]	[101]
Carbapenem	Neutropenic murine thigh infection model	$\%fT_{>MIC}$	47.5[c]	[135]
Fosfomycin	In vivo prospective cohort study	$\%fT_{>MIC}$	60–70	[136]
Tigecycline	In silico population PK model (for cSSSI)	*f*AUC/MIC	17.9	[137]
	In silico population PK model (for cSSSI)		6.96	[138]

$\%fT_{>MIC}$, percentage of time that the free drug concentration remains above the MIC of an offending pathogen during a dosing interval; MIC, minimum inhibitory concentration; *f*AUC/MIC, ratio of the area under the concentration–time curve during a 24-h period to the MIC; PK/PD, pharmacokinetic/pharmacodynamics; cSSSI, complicated skin and skin-structure infection.
[a] 3-log kill.
[b] 1-log kill.
[c] 2-log kill.

Table 5
Microbiological susceptibility, recommended doses and administration of antibiotics for the treatment of multidrug-resistant *Acinetobacter baumannii*

Antibiotic	Dose	Administration (IV)	MIC_{90} of agent against *A. baumannii* (mg/L)	CL_{Cr} (mL/min)	References
Sulbactam	2 g every 6 h	4-h infusion	4	90	[130]
Tigecycline	200 mg loading dose then 100 mg q12h	–	0.25	–	[137,138]
Minocycline	100 mg q12h	–	–	–	[140–142]
Rifampicin	600 mg q12h	–	≤4 to ≥512	–	[106]
Meropenem	2 g q8h	3-h infusion	8	Normal renal function	[31,123]
Fosfomycin	8 g q8h	3-h infusion	32	Normal renal function	[31]
Cefiderocol	2 g q8h	3-h infusion	≤4	Normal renal function	[118,143]
Colistin	Loading dose: 9 million IU loading dose	1–2		[132]	
	Daily dose*: in two divided doses 12 h apart according to CL_{Cr}. *Daily dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × $10^{(0.0048\ CLCr + 1.825)}$, to target a plasma colistin $C_{ss,avg}$ of 2 mg/L, depending on the patient's CL_{Cr}				

IV, intravenous; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of the bacteria; CL_{Cr}, creatinine clearance; q12h, every 12 h; q8h, every 8 h; CBA, colistin base activity; $C_{ss,avg}$, average steady-state plasma concentration.

Table 6
Microbiological susceptibility of multidrug-resistant (MDR) *Acinetobacter baumannii* to new antibiotics

Antibiotic	Antimicrobial class	MIC_{90} against MDR *Acinetobacter* spp. (mg/L)	References
Ceftazidime/avibactam	Cephalosporin/β-lactamase inhibitor	>32	[150,151]
Cefepime/zidebactam	combination	>32	[152,153]
Imipenem/relebactam	Carbapenem/β-lactamase inhibitor	>32	[154,155]
	combination	>32	[156]
Meropenem/vaborbactam			
Aztreonam/avibactam	Monobactam/β-lactamase inhibitor combination	≥64	[157–160]
Cefiderocol	Siderophore cephalosporin	≤8	[161–166]
Plazomicin	Aminoglycoside	16	[49,167]
Apramycin	Aminoglycoside	32	[168]
Eravacycline	Fluorocycline	1	[169–171]
Imipenem/LN-1-255	Carbapenem/penicillin sulfone inhibitor	≤8	[172]
Meropenem/LN-1-255	combination	≤8	[172]
Imipenem/WCK 4234	Carbapenem/β-lactamase inhibitor	≤2	[173]
Meropenem/WCK 4234		≤2	
Sulbactam/ETX2514	β-Lactam/β-lactamase inhibitor combination	4	[174]
Delafloxacin	Fluoroquinolone	≤16	[175,176]
WFQ-228	Fluoroquinolone	1	[177]
TP-6076	Fluoroquinolone	0.008 -0.5	[178]
SPR741/rifampicin	Polymyxin-B-derived molecule	0.5	[179,180]

MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of the bacteria.

Table 7
Pharmacokinetic/pharmacodynamic (PK/PD) index and the optimal magnitude for novel agents with in vitro activity against multidrug-resistant *Acinetobacter baumannii*

Antibiotic	Study model	PK/PD index	PK/PD index magnitude for optimal antimicrobial activity	Reference
Cefiderocol	*Pseudomonas aeruginosa* neutropenic murine thigh infection model	$\%fT_{>MIC}$	>62[a]	[148]
Plazomicin	Carbapenem-resistant *Klebsiella pneumoniae* neutropenic murine lung infection model	*f*AUC/MIC	39[a,b] 32[a,c]	[181]
	Carbapenem-resistant *K. pneumoniae* neutropenic murine thigh infection model		95[d]	[144]
Eravacycline	*Escherichia coli* neutropenic murine thigh infection model	*f*AUC/MIC	32.60 ± 10.85[d]	[149]
	Immunocompetent murine thigh infection model	*f*AUC/MIC	5.6 ± 5.0[d]	[182]
Imipenem/LN-1-255 Meropenem/LN-1-255	N/A			
Sulbactam/ETX2514	*A. baumannii* neutropenic murine thigh infection model	$\%fT_{>MIC}$ (sulbactam) $\%T>C_T$ (ETX2514)	50[a]XX50[a]	[145]
Delafloxacin	*K. pneumoniae* neutropenic murine lung infection model	*f*AUC/MIC	80–200[d]	[146,147]

$\%fT_{>MIC}$, percentage of time that the free drug concentration remains above the MIC of an offending pathogen during a dosing interval; MIC, minimum inhibitory concentration; *f*AUC/MIC, ratio of the area under the concentration–time curve during a 24-h period to the MIC; $\%T>C_T$, time above the critical threshold; N/A, not available.
[a] 2-log kill.
[b] Plasma *f*AUC/MIC target.
[c] Epithelial lining fluid *f*AUC/MIC target.
[d] 1-log kill.

PD assessments of cefiderocol demonstrated that $\%fT_{>MIC}$ was the PK/PD index that best predicted the bacteriostatic or bactericidal activity of this agent [187,188]. Subsequently, based on a *P. aeruginosa* neutropenic murine thigh model, the PK/PD targets for stasis, 1-$\log_{10}$ reduction and 2-$\log_{10}$ reduction were found to be 44.4–94.7%, 50.2–97.5% and 62.1–100%, respectively [148]. In this PD study, the MIC of *P. aeruginosa* ranged from 0.063–0.5 mg/L. Katsube et al. then looked at target attainment in patients with varying renal function using Monte Carlo simulation [143]. The simulation demonstrated that 2 g q8h by either 1-h and 3-h infusion is likely to achieve 75% $fT_{>MIC}$ against susceptible Gram-negative bacteria including *A. baumannii*. For patients with augmented renal function ($CL_{Cr} \geq 120$ mL/min), 2 g q6h by 3-h infusion is likely to achieve 75% $fT_{>MIC}$ against susceptible organisms. The study also suggested the need for a supplemental dose immediately after intermittent haemodialysis to achieve a similar PK/PD target.

5.2. Plazomicin

Plazomicin (ACHN-490) is a semisynthetic aminoglycoside derived from sisomicin [189]. Its structural modifications have made this molecule stable in the presence of most aminoglycoside-modifying enzymes (AMEs). Plazomicin was shown to be more potent than sisomicin, amikacin and gentamicin against various Gram-negative bacilli carrying one or more AMEs, including *A. baumannii* and other *Acinetobacter* spp. (MIC_{90}, 32 mg/L) [189].

The *f*AUC/MIC ratio was identified as the PK/PD index associated with 1- to 2-$\log_{10}$ CFU reduction for plazomicin based on a carbapenem-resistant *K. pneumoniae* neutropenic murine lung and thigh infection model [144,181]. The *f*AUC/MIC ratio target values associated with a 2-$\log_{10}$ reduction are 32–39 for lung infection [181]. For thigh infection, the *f*AUC/MIC ratio target value associated with a 1-$\log_{10}$ reduction is 95 [144].

5.3. Other novel agents

Eravacycline is a novel fluorocycline antibiotic that can overcome resistance to tetracycline-specific efflux and ribosomal protection mechanisms [190]. Its bacteriostatic or bactericidal activity was found to best correlate with *f*AUC/MIC [149,191]. The target ratios associated with net stasis and 1-$\log_{10}$ reduction were 27.97 ± 8.29 and 32.60 ± 10.85, respectively, based on an *Escherichia coli* neutropenic murine thigh infection model [149]. However, Thabit et al. found that the *f*AUC/MIC magnitude associated with 1-log reduction is 5.6 ± 5 when tested against MDR Enterobacteriaceae in an immunocompetent murine thigh infection model [182].

Delafloxacin is a novel fluoroquinolone with chemical properties that allow it to exist largely deprotonated at acidic pH, which improves its potency in the lower pH infective environments. As with other fluoroquinolones, the PK/PD index associated with bacterial killing of delafloxacin is the *f*AUC/MIC [146,147]. Based on a *K. pneumoniae* neutropenic murine lung infection model by Thabit et al. [147], the PK/PD ratio magnitude required to achieve 1-log reduction is 9.6, which is significantly lower than the value observed by Lepak and Andes, which was 80–200 [146]. However, there was a difference in the susceptibility of the *K. pneumoniae* isolates used in both studies, whereby the infection model by Lepak and Andes was tested against extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* isolates.

ETX2514 is a diazabicyclooctanone β-lactamase inhibitor that has an extended spectrum of activity covering of a wide array of class D enzymes as well as improved potency against class A and C β-lactamases [174]. It works by binding to penicillin-binding proteins, which are the same targets as for β-lactams. Durand-Réville et al. demonstrated that ETX2514 could fully restore β-lactam activity against classes A, C and D-expressing strains of *A. baumannii* when combined with piperacillin, meropenem or sulbactam [174]. The study showed that the most potent combination against *A. baumannii* was sulbactam/ETX2514, whereby ETX2514 can reduce the MIC of sulbactam by up to six-fold. For sulbactam/ETX2514, the PK/PD index associated with bacterial killing is $\%fT_{>MIC}$ (sulbactam) and $\%T>C_T$ (time above the critical threshold) (ETX2514), with a target value of 50 both for sulbactam and ETX2514 [145]. Subsequent PK/PD analysis then revealed that 1 g of sulbactam/0.5 g of ETX2514 via a 3-h infusion q6h is likely to achieve the PK/PD target when tested against *A. baumannii* with MICs of ≤4 mg/L [145].

6. Conclusion

Acinetobacter baumannii infections are exceedingly difficult to treat. The prevalence of MDR strains is increasing and knowledge of optimal treatment is limited. Colistin has been widely studied as monotherapy or as part of combination therapy, but its use is limited due to nephrotoxicity. The clinical benefit of combination therapy, whether empirical or targeted, has yet to be demonstrated, although in vitro studies have reported synergistic effects between various antibiotics against MDR *A. baumannii*. Available clinical studies are unfortunately retrospective and lack control groups, which offers low-grade evidence. A better understanding of the pharmacokinetics/pharmacodynamics of the 'old' antibiotics is required to optimise their dosing regimens for maximal bacterial killing. Novel agents such as cefiderocol, plazomicin, eravacycline and sulbactam/ETX2514 combination are promising options for the treatment of MDR *A. baumannii*, but these have yet to be evaluated in RCTs.

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Competing interests

None declared.

Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.02.016.

References

[1] Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538–82.
[2] Neidell MJ, Cohen B, Furuya Y, Hill J, Jeon CY, Glied S, et al. Costs of healthcare- and community-associated infections with antimicrobial-resistant versus antimicrobial-susceptible organisms. Clin Infect Dis 2012;55:807–15.
[3] Lautenbach E, Synnestvedt M, Weiner MG, Bilker WB, Vo L, Schein J, et al. Epidemiology and impact of imipenem resistance in *Acinetobacter baumannii*. Infect Control Hosp Epidemiol 2009;30:1186–92.
[4] Karageorgopoulos DE, Falagas ME. Current control and treatment of multidrug-resistant *Acinetobacter baumannii* infections. Lancet Infect Dis 2008;8:751–62.
[5] Ng TM, Teng CB, Lye DC, Apisarnthanarak A. A multicenter case–case control study for risk factors and outcomes of extensively drug-resistant *Acinetobacter baumannii* bacteremia. Infect Control Hosp Epidemiol 2014;35:49–55.
[6] Cisneros J, Rodríguez-Baño J, Fernández-Cuenca F, Ribera A, Vila J, Pascual A, et al. Risk-factors for the acquisition of imipenem-resistant *Acinetobacter baumannii* in Spain: a nationwide study. Clin Microbiol Infect 2005;11:874–9.
[7] Lee C-R, Lee JH, Park M, Park KS, Bae IK, Kim YB, et al. Biology of *Acinetobacter baumannii*: pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. Front Cell Infect Microbiol 2017;7:55.
[8] Bergogne-Bérézin E, Towner KJ. *Acinetobacter* spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. Clin Microbiol Rev 1996;9:148–65.
[9] Bialvaei AZ, Kouhsari E, Salehi-Abargouei A, Amirmozafari N, Ramazanzadeh R, Ghadimi-Daresajini A, et al. Epidemiology of multidrug-resistant *Acinetobacter baumannii* strains in Iran: a systematic review and meta-analysis. J Chemother 2017;29:327–37.
[10] Labarca JA, Salles MJC, Seas C, Guzmán-Blanco M. Carbapenem resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in the nosocomial setting in Latin America. Crit Rev Microbiol 2016;42:276–92.
[11] Cai Y, Chai D, Wang R, Liang B, Bai N. Colistin resistance of *Acinetobacter baumannii*: clinical reports, mechanisms and antimicrobial strategies. J Antimicrob Chemother 2012;67:1607–15.
[12] Liu Y-Y, Wang Y, Walsh TR, Yi L-X, Zhang R, Spencer J, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 2016;16:161–8.
[13] Ni W, Cui J, Liang B, Cai Y, Bai N, Cai X, et al. In vitro effects of tigecycline in combination with colistin (polymyxin E) and sulbactam against multidrug-resistant *Acinetobacter baumannii*. J Antibiot (Tokyo) 2013;66:705–8.
[14] Principe L, Capone A, Mazzarelli A, D'Arezzo S, Bordi E, Di Caro A, et al. In vitro activity of doripenem in combination with various antimicrobials against multidrug-resistant *Acinetobacter baumannii*: possible options for the treatment of complicated infection. Microb Drug Resist 2013;19:407–14.
[15] Sun Y, Wang L, Li J, Zhao C, Zhao J, Liu M, et al. Synergistic efficacy of meropenem and rifampicin in a murine model of sepsis caused by multidrug-resistant *Acinetobacter baumannii*. Eur J Pharmacol 2014;729:116–22.
[16] Phee LM, Betts JW, Bharathan B, Wareham DW. Colistin and fusidic acid: a novel potent synergistic combination for the treatment of multidrug-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2015;59:4544–50.
[17] Majewski P, Wieczorek P, Ojdana D, Sacha PT, Wieczorek A, Tryniszewska EA. In vitro activity of rifampicin alone and in combination with imipenem against multidrug-resistant *Acinetobacter baumannii* harboring the bla_{OXA-72} resistance gene. Scand J Infect Dis 2014;46:260–4.
[18] Liu B, Bai Y, Liu Y, Di X, Zhang X, Wang R, et al. In vitro activity of tigecycline in combination with cefoperazone–sulbactam against multidrug-resistant *Acinetobacter baumannii*. J Chemother 2015;27:271–6.
[19] Galani I, Orlandou K, Moraitou H, Petrikkos G, Souli M. Colistin/daptomycin: an unconventional antimicrobial combination synergistic in vitro against multidrug-resistant *Acinetobacter baumannii*. Int J Antimicrob Agents 2014;43:370–4.
[20] Liu B, Liu Y, Di X, Zhang X, Wang R, Bai Y, et al. Colistin and anti-Gram-positive bacterial agents against *Acinetobacter baumannii*. Rev Soc Bras Med Trop 2014;47:451–6.
[21] Wareham D, Gordon N, Hornsey M. In vitro activity of teicoplanin combined with colistin versus multidrug-resistant strains of *Acinetobacter baumannii*. J Antimicrob Chemother 2011;66:1047–51.
[22] Safarika A, Galani I, Pistiki A, Giamarellos-Bourboulis E. Time–kill effect of levofloxacin on multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: synergism with imipenem and colistin. Eur J Clin Microbiol Infect Dis 2015;34:317–23.
[23] Kiratisin P, Apisarnthanarak A, Kaewdaeng S. Synergistic activities between carbapenems and other antimicrobial agents against *Acinetobacter baumannii* including multidrug-resistant and extensively drug-resistant isolates. Int J Antimicrob Agents 2010;36:243–6.
[24] Park GC, Choi J, Jang SJ, Jeong SH, Kim C-M, Choi IS, et al. In vitro interactions of antibiotic combinations of colistin, tigecycline, and doripenem against extensively drug-resistant and multidrug-resistant *Acinetobacter baumannii*. Ann Lab Med 2016;36:124–30.
[25] Bai Y, Liu B, Wang T, Cai Y, Liang B, Wang R, et al. In vitro activities of combinations of rifampin with other antimicrobials against multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2015;59:1466–71.
[26] Rodríguez CH, Nastro M, Vay C, Famiglietti A. In vitro activity of minocycline alone or in combination in multidrug-resistant *Acinetobacter baumannii* isolates. J Med Microbiol 2015;64:1196–200.
[27] Lim T-P, Tan T-Y, Lee W, Sasikala S, Tan T-T, Hsu L-Y, et al. In-vitro activity of polymyxin B, rifampicin, tigecycline alone and in combination against carbapenem-resistant *Acinetobacter baumannii* in Singapore. PLoS One 2011;6:e18485.
[28] Rodriguez CH, De Ambrosio A, Bajuk M, Spinozzi M, Nastro M, Bombicino K, et al. In vitro antimicrobials activity against endemic *Acinetobacter baumannii* multiresistant clones. J Infect Dev Ctries 2010;4:164–7.
[29] Pongpech P, Amornnopparattanakul S, Panapakdee S, Fungwithaya S, Nannha P, Dhiraputra C, et al. Antibacterial activity of carbapenem-based combinations against multidrug-resistant *Acinetobacter baumannii*. J Med Assoc Thai 2011;93:161–71.
[30] Nageeb W, Metwally L, Kamel M, Zakaria S. In vitro antimicrobial synergy studies of carbapenem-resistant *Acinetobacter baumannii* isolated from intensive care units of a tertiary care hospital in Egypt. J Infect Public Health 2015;8:593–602.
[31] Menegucci TC, Albiero J, Migliorini LB, Alves JLB, Viana GF, Mazucheli J, et al. Strategies for the treatment of polymyxin B-resistant *Acinetobacter baumannii* infections. Int J Antimicrob Agents 2016;47:380–5.
[32] Lee C-H, Tang Y-F, Su L-H, Chien C-C, Liu J-W. Antimicrobial effects of varied combinations of meropenem, sulbactam, and colistin on a multidrug-resistant *Acinetobacter baumannii* isolate that caused meningitis and bacteremia. Microb Drug Resist 2008;14:233–7.
[33] Principe L, D'Arezzo S, Capone A, Petrosillo N, Visca P. In vitro activity of tigecycline in combination with various antimicrobials against multidrug resistant *Acinetobacter baumannii*. Ann Clin Microbiol Antimicrob 2009;8:18.

[34] Lim T-P, Tan T-Y, Lee W, Sasikala S, Tan T-T, Hsu L-Y, et al. In vitro activity of various combinations of antimicrobials against carbapenem-resistant *Acinetobacter* species in Singapore. J Antibiot (Tokyo) 2009;62:675–9.
[35] Wei W, Yang H, Hu L, Ye Y, Li J. Activity of levofloxacin in combination with colistin against *Acinetobacter baumannii*: in vitro and in a *Galleria mellonella* model. J Microbiol Immunol Infect 2017;50:821–30.
[36] Gordon N, Png K, Wareham D. Potent synergy and sustained bactericidal activity of a vancomycin–colistin combination versus multidrug-resistant strains of *Acinetobacter baumannii*. Antimicrob Agents Chemother 2010;54:5316–22.
[37] Marie MAM, Krishnappa LG, Alzahrani AJ, Mubaraki MA, Alyousef AA. A prospective evaluation of synergistic effect of sulbactam and tazobactam combination with meropenem or colistin against multidrug resistant *Acinetobacter baumannii*. Bosn J Basic Med Sci 2015;15:24–9.
[38] Deveci A, Coban AY, Acicbe O, Tanyel E, Yaman G, Durupinar B. In vitro effects of sulbactam combinations with different antibiotic groups against clinical *Acinetobacter baumannii* isolates. J Chemother 2012;24:247–52.
[39] Kaya İA, Guner MD, Akca G, Tuncbilek S, Alhan A, Tekeli E. Evaluation of the synergistic effect of a combination of colistin and tigecycline against multidrug-resistant *Acinetobacter baumannii*. Pak J Med Sci 2017;33:393–7.
[40] Phee L, Hornsey M, Wareham D. In vitro activity of daptomycin in combination with low-dose colistin against a diverse collection of Gram-negative bacterial pathogens. Eur J Clin Microbiol Infect Dis 2013;32:1291–4.
[41] Arroyo LA, Mateos I, González V, Aznar J. In vitro activities of tigecycline, minocycline, and colistin–tigecycline combination against multi- and pan-drug-resistant clinical isolates of *Acinetobacter baumannii* group. Antimicrob Agents Chemother 2009;53:1295–6.
[42] Sheng W-H, Wang J-T, Li S-Y, Lin Y-C, Cheng A, Chen Y-C, et al. Comparative in vitro antimicrobial susceptibilities and synergistic activities of antimicrobial combinations against carbapenem-resistant *Acinetobacter* species: *Acinetobacter baumannii* versus *Acinetobacter* genospecies 3 and 13TU. Diagn Microbiol Infect Dis 2011;70:380–6.
[43] Le Minh V, Nhu NTK, Phat VV, Thompson C, Lan NPH, Nga TVT, et al. In vitro activity of colistin in antimicrobial combination against carbapenem-resistant *Acinetobacter baumannii* isolated from patients with ventilator-associated pneumonia in Vietnam. J Med Microbiol 2015;64:1162–9.
[44] Santimaleeworagun W, Wongpoowarak P, Chayakul P, Pattharachayakul S, Tansakul P, Garey KW. In vitro activity of colistin or sulbactam in combination with fosfomycin or imipenem against clinical isolates of carbapenem-resistant *Acinetobacter baumannii* producing OXA-23 carbapenemases. Southeast Asian J Trop Med Public Health 2011;42:890–900.
[45] O'Hara JA, Ambe LA, Casella LG, Townsend BM, Pelletier MR, Ernst RK, et al. Activity of vancomycin-containing regimens against colistin-resistant *Acinetobacter baumannii* clinical strains. Antimicrob Agents Chemother 2013;57:2103–8.
[46] Karaoglan I, Zer Y, Bosnak VK, Mete AO, Namıduru M. In vitro synergistic activity of colistin with tigecycline or β-lactam antibiotic/β-lactamase inhibitor combinations against carbapenem-resistant *Acinetobacter baumannii*. J Int Med Res 2013;41:1830–7.
[47] Liang W, Liu X-f, Huang J, Zhu D-m, Li J, Zhang J. Activities of colistin- and minocycline-based combinations against extensive drug resistant *Acinetobacter baumannii* isolates from intensive care unit patients. BMC Infect Dis 2011;11:109.
[48] Dizbay M, Tozlu DK, Cirak MY, Isik Y, Ozdemir K, Arman D. In vitro synergistic activity of tigecycline and colistin against XDR-*Acinetobacter baumannii*. J Antibiot (Tokyo) 2010;63:51–2.
[49] García-Salguero C, Rodríguez-Avial I, Picazo JJ, Culebras E. Can plazomicin alone or in combination be a therapeutic option against carbapenem-resistant *Acinetobacter baumannii*? Antimicrob Agents Chemother 2015;59:5959–66.
[50] Pei G, Mao Y, Sun Y. In vitro activity of minocycline alone and in combination with cefoperazone–sulbactam against carbapenem-resistant *Acinetobacter baumannii*. Microb Drug Resist 2012;18:574–7.
[51] Zhu W, Wang Y, Cao W, Cao S, Zhang J. In vitro evaluation of antimicrobial combinations against imipenem-resistant *Acinetobacter baumannii* of different MICs. J Infect Public Health 2018;11:856–60.
[52] Cikman A, Gulhan B, Aydin M, Ceylan MR, Parlak M, Karakecili F, et al. In vitro activity of colistin in combination with tigecycline against carbapenem-resistant *Acinetobacter baumannii* strains isolated from patients with ventilator-associated pneumonia. Int J Med Sci 2015;12:695–700.
[53] Temocin F, Erdinc FS, Tulek N, Demirelli M, Ertem G, Kinikli S, et al. Synergistic effects of sulbactam in multi-drug-resistant *Acinetobacter baumannii*. Braz J Microbiol 2015;46:1119–24.
[54] Hong DJ, Kim JO, Lee H, Yoon E-J, Jeong SH, Yong D, et al. In vitro antimicrobial synergy of colistin with rifampicin and carbapenems against colistin-resistant *Acinetobacter baumannii* clinical isolates. Diagn Microbiol Infect Dis 2016;86:184–9.
[55] Yang Y-S, Lee Y, Tseng K-C, Huang W-C, Chuang M-F, Kuo S-C, et al. In vivo and in vitro efficacy of minocycline-based combination therapy for minocycline-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2016;60:4047–54.
[56] Wei W, Yang H, Liu Y, Ye Y, Li J. In vitro synergy of colistin combinations against extensively drug-resistant *Acinetobacter baumannii* producing OXA-23 carbapenemase. J Chemother 2016;28:159–63.
[57] Lee H, Roh KH, Hong SG, Shin HB, Jeong SH, Song W, et al. In vitro synergistic effects of antimicrobial combinations on extensively drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates. Ann Lab Med 2016;36:138–44.
[58] Zhang Y, Chen F, Sun E, Ma R, Qu C, Ma L. In vitro antibacterial activity of combinations of fosfomycin, minocycline and polymyxin B on pan-drug-resistant *Acinetobacter baumannii*. Exp Ther Med 2013;5:1737–9.
[59] Madadi-Goli N, Moniri R, Bagheri-Josheghani S, Dasteh-Goli N. Sensitivity of levofloxacin in combination with ampicillin–sulbactam and tigecycline against multidrug-resistant *Acinetobacter baumannii*. Iran J Microbiol 2017;9:19–25.
[60] Wei W-j, Yang H-f. Synergy against extensively drug-resistant *Acinetobacter baumannii* in vitro by two old antibiotics: colistin and chloramphenicol. Int J Antimicrob Agents 2017;49:321–6.
[61] Li T, Sheng M, Gu T, Zhang Y, Yirepanjiang A, Li Y. In vitro assessment of cefoperazone–sulbactam based combination therapy for multidrug-resistant *Acinetobacter baumannii* isolates in China. J Thorac Dis 2018;10:1370–6.
[62] Liu X, Zhao M, Chen Y, Bian X, Li Y, Shi J, et al. Synergistic killing by meropenem and colistin combination of carbapenem-resistant *Acinetobacter baumannii* isolates from Chinese patients in an in vitro pharmacokinetic/pharmacodynamic model. Int J Antimicrob Agents 2016;48:559–63.
[63] Matuschek E, Åhman J, Webster C, Kahlmeter G. Antimicrobial susceptibility testing of colistin—evaluation of seven commercial MIC products against standard broth microdilution for *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter* spp. Clin Microbiol Infect 2018;24:865–70.
[64] Dinc G, Demiraslan H, Elmali F, Ahmed SS, Metan G, Alp E, et al. Efficacy of sulbactam and its combination with imipenem, colistin and tigecycline in an experimental model of carbapenem-resistant *Acinetobacter baumannii* sepsis. Chemotherapy 2013;59:325–9.
[65] Monogue ML, Sakoulas G, Nizet V, Nicolau DP. Humanized exposures of a β-lactam–β-lactamase inhibitor, tazobactam, versus non-β-lactam–β-lactamase inhibitor, avibactam, with or without colistin, against *Acinetobacter baumannii* in murine thigh and lung infection models. Pharmacology 2018;101:255–61.
[66] Song JY, Cheong HJ, Lee J, Sung AK, Kim WJ. Efficacy of monotherapy and combined antibiotic therapy for carbapenem-resistant *Acinetobacter baumannii* pneumonia in an immunosuppressed mouse model. Int J Antimicrob Agents 2009;33:33–9.
[67] Pachón-Ibáñez ME, Docobo-Pérez F, López-Rojas R, Domínguez-Herrera J, Jiménez-Mejias ME, García-Curiel A, et al. Efficacy of rifampin and its combinations with imipenem, sulbactam, and colistin in experimental models of infection caused by imipenem-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2010;54:1165–72.
[68] Bowers DR, Cao H, Zhou J, Ledesma KR, Sun D, Lomovskaya O, et al. Assessment of minocycline and polymyxin B combination against *Acinetobacter baumannii*. Antimicrob Agents Chemother 2015;59:2720–5.
[69] Yilmaz EM, Sunbul M, Aksoy A, Yilmaz H, Guney AK, Guvenc T. Efficacy of tigecycline/colistin combination in a pneumonia model caused by extensively drug-resistant *Acinetobacter baumannii*. Int J Antimicrob Agents 2012;40:332–6.
[70] Queenan AM, Davies TA, He W, Lynch AS. Assessment of the combination of doripenem plus a fluoroquinolone against non-susceptible *Acinetobacter baumannii* isolates from nosocomial pneumonia patients. J Chemother 2013;25:141–7.
[71] Fan B, Guan J, Wang X, Cong Y. Activity of colistin in combination with meropenem, tigecycline, fosfomycin, fusidic acid, rifampin or sulbactam against extensively drug-resistant *Acinetobacter baumannii* in a murine thigh--infection model. PLoS One 2016;11:e0157757.
[72] Yang H, Chen G, Hu L, Liu Y, Cheng J, Li H, et al. In vivo activity of daptomycin/colistin combination therapy in a *Galleria mellonella* model of *Acinetobacter baumannii* infection. Int J Antimicrob Agents 2015;45:188–91.
[73] Yang H, Lv N, Hu L, Liu Y, Cheng J, Ye Y, et al. In vivo activity of vancomycin combined with colistin against multidrug-resistant strains of *Acinetobacter baumannii* in a *Galleria mellonella* model. Infect Dis (Lond) 2016;48:189–94.
[74] Hornsey M, Wareham D. In vivo efficacy of glycopeptide/colistin combination therapies in a *Galleria mellonella* model of *Acinetobacter baumannii* infection. Antimicrob Agents Chemother 2011;55:3534–7.
[75] European Committee on Antimicrobial Susceptibility Testing (EUCAST). Recommendations for MIC determination of colistin (polymyxin E) as recommended by the joint CLSI-EUCAST Polymyxin Breakpoints Working Group. Växjö, Sweden: EUCAST; 2016 http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/General_documents/Recommendations_for_MIC_determination_of_colistin_March_2016.pdf [accessed 19 April 2019].
[76] Petrosillo N, Giannella M, Antonelli M, Antonini M, Barsic B, Belancic L, et al. Clinical experience of colistin–glycopeptide combination in critically ill patients infected with Gram-negative bacteria. Antimicrob Agents Chemother 2014;58:851–8.
[77] Kalin G, Alp E, Akin A, Coskun R, Doganay M. Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Infection 2014;42:37–42.
[78] López-Cortés L, Cisneros J, Fernández-Cuenca F, Bou G, Tomás M, Garnacho-Montero J, et al. Monotherapy versus combination therapy for sepsis due to multidrug-resistant *Acinetobacter baumannii*: analysis of a multicentre prospective cohort. J Antimicrob Chemother 2014;69:3119–26.
[79] Balkan II, Batirel A, Karabay O, Agalar C, Akalin S, Alici O, et al. Comparison of colistin monotherapy and non-colistin combinations in the treatment of multi-drug resistant *Acinetobacter* spp. bloodstream infections: a multicenter retrospective analysis. Indian J Pharmacol 2015;47:95–100.

[80] Yilmaz GR, Guven T, Guner R, Tufan ZK, Izdes S, Tasyaran MA, et al. Colistin alone or combined with sulbactam or carbapenem against *A. baumannii* in ventilator-associated pneumonia. J Infect Dev Ctries 2015;9:476–85.

[81] Garnacho-Montero J, Amaya-Villar R, Gutiérrez-Pizarraya A, de Tena EE-G, Artero-González ML, Corcia-Palomo Y, et al. Clinical efficacy and safety of the combination of colistin plus vancomycin for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. Chemotherapy 2013;59:225–31.

[82] Rigatto MH, Vieira FJ, Antochevis LC, Behle TF, Lopes NT, Zavascki AP. Polymyxin B in combination with antimicrobials lacking in vitro activity versus polymyxin B in monotherapy in critically ill patients with *Acinetobacter baumannii* or *Pseudomonas aeruginosa* infections. Antimicrob Agents Chemother 2015;59:6575–80.

[83] Batirel A, Balkan I, Karabay O, Agalar C, Akalin S, Alici O, et al. Comparison of colistin–carbapenem, colistin–sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections. Eur J Clin Microbiol Infect Dis 2014;33:1311–22.

[84] Lin H-S, Lee M-H, Cheng C-W, Hsu P-C, Leu H-S, Huang C-T, et al. Sulbactam treatment for pneumonia involving multidrug-resistant *Acinetobacter calcoaceticus–Acinetobacter baumannii* complex. Infect Dis (Lond) 2015;47:370–8.

[85] Shin JA, Chang YS, Kim HJ, Kim SK, Chang J, Ahn CM, et al. Clinical outcomes of tigecycline in the treatment of multidrug-resistant *Acinetobacter baumannii* infection. Yonsei Med J 2012;53:974–84.

[86] Tasbakan M, Pullukcu H, Sipahf O, Tasbakan M, Aydemir S, Bacakoglu F. Is tigecycline a good choice in the treatment of multidrug-resistant *Acinetobacter baumannii* pneumonia? J Chemother 2011;23:345–9.

[87] Kim W-Y, Moon J-Y, Huh JW, Choi S-H, Lim C-M, Koh Y, et al. Comparable efficacy of tigecycline versus colistin therapy for multidrug-resistant and extensively drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients. PLoS One 2016;11:e0150642.

[88] Lee Y-T, Tsao S-M, Hsueh P-R. Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant *Acinetobacter baumannii* infections. Eur J Clin Microbiol Infect Dis 2013;32:1211–20.

[89] Lim S-K, Lee S-O, Choi S-H, Choi J-P, Kim S-H, Jeong J-Y, et al. The outcomes of using colistin for treating multidrug resistant *Acinetobacter* species bloodstream infections. J Korean Med Sci 2011;26:325–31.

[90] Ye J-J, Lin H-S, Yeh C-F, Wu Y-M, Huang P-Y, Yang C-C, et al. Tigecycline-based versus sulbactam-based treatment for pneumonia involving multidrug-resistant *Acinetobacter calcoaceticus–Acinetobacter baumannii* complex. BMC Infect Dis 2016;16:374.

[91] Chuang Y-C, Cheng C-Y, Sheng W-H, Sun H-Y, Wang J-T, Chen Y-C, et al. Effectiveness of tigecycline-based versus colistin-based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis. BMC Infect Dis 2014;14:102.

[92] Cheng A, Chuang Y-C, Sun H-Y, Sheng W-H, Yang C-J, Liao C-H, et al. Excess mortality associated with colistin–tigecycline compared with colistin—carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii* bacteremia: a multicenter prospective observational study. Crit Care Med 2015;43:1194–204.

[93] Jean S-S, Hsieh T-C, Hsu C-W, Lee W-S, Bai K-J, Lam C. Comparison of the clinical efficacy between tigecycline plus extended-infusion imipenem and sulbactam plus imipenem against ventilator-associated pneumonia with pneumonic extensively drug-resistant *Acinetobacter baumannii* bacteremia, and correlation of clinical efficacy with in vitro synergy tests. J Microbiol Immunol Infect 2016;49:924–33.

[94] He H, Zheng Y, Sun B, Tang X, Wang R, Tong Z. Tigecycline combination for ventilator-associated pneumonia caused by extensive drug-resistant *Acinetobacter baumannii*. J Thorac Dis 2016;8:2784–92.

[95] Chen Y-M, Fang W-F, Kao HC, Chen H-C, Tsai Y-C, Shen L-S, et al. Influencing factors of successful eradication of multidrug-resistant *Acinetobacter baumannii* in the respiratory tract with aerosolized colistin. Biomed J 2014;37:314–20.

[96] Kuo S-C, Lee Y-T, Yang S-P, Chen C-P, Chen T-L, Hsieh S-L, et al. Eradication of multidrug-resistant *Acinetobacter baumannii* from the respiratory tract with inhaled colistin methanesulfonate: a matched case–control study. Clin Microbiol Infect 2012;18:870–6.

[97] Jang JY, Kwon HY, Choi EH, Lee W-Y, Shim H, Bae KS. Efficacy and toxicity of high-dose nebulized colistin for critically ill surgical patients with ventilator-associated pneumonia caused by multidrug-resistant *Acinetobacter baumannii*. J Crit Care 2017;40:251–6.

[98] Kofteridis DP, Alexopoulou C, Valachis A, Maraki S, Dimopoulou D, Georgopoulos D, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case–control study. Clin Infect Dis 2010;51:1238–44.

[99] Kalin G, Alp E, Coskun R, Demiraslan H, Gündogan K, Doganay M. Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia: do we really need this treatment? J Infect Chemother 2012;18:872–7.

[100] Pan S, Huang X, Wang Y, Li L, Zhao C, Yao Z, et al. Efficacy of intravenous plus intrathecal/intracerebral ventricle injection of polymyxin B for post-neurosurgical intracranial infections due to MDR/XDR *Acinetobacter baumannii*: a retrospective cohort study. Antimicrob Resist Infect Control 2018;7:8.

[101] Cheah S-E, Wang J, Nguyen VTT, Turnidge JD, Li J, Nation RL. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection. J Antimicrob Chemother 2015;70:3291–7.

[102] Yapa SW, Li J, Patel K, Wilson JW, Dooley MJ, George J, et al. Pulmonary and systemic pharmacokinetics of inhaled and intravenous colistin methanesulfonate in cystic fibrosis patients: targeting advantage of inhalational administration. Antimicrob Agents Chemother 2014;58:2570–9.

[103] Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwinai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria. J Antimicrob Chemother 2010;65:2645–9.

[104] Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis 2018;18:391–400.

[105] Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. Clin Infect Dis 2013;57:349–58.

[106] Aydemir H, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Epidemiol Infect 2013;141:1214–22.

[107] Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2014;58:5598–601.

[108] Makris D, Petinaki E, Tsolaki V, Manoulakas E, Mantzarlis K, Apostolopoulou O, et al. Colistin versus colistin combined with ampicillin–sulbactam for multiresistant *Acinetobacter baumannii* ventilator-associated pneumonia treatment: an open-label prospective study. Indian J Crit Care Med 2018;22:67–77.

[109] Abdellatif S, Trifi A, Daly F, Mahjoub K, Nasri R, Lakhal SB. Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial. Ann Intensive Care 2016;6:26.

[110] Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Infect 2008;56:432–6.

[111] Dickstein Y, Lellouche J, Dalak Amar MB, Schwartz D, Nutman A, Daitch V, et al. Treatment outcomes of colistin and carbapenem-resistant *Acinetobacter baumannii* infections: an exploratory subgroup analysis of a randomized clinical trial. Clin Infect Dis 2018 Nov 20 [Epub ahead of print]. doi:10.1093/cid/ciy988.

[112] Preston SL. The importance of appropriate antimicrobial dosing: pharmacokinetic and pharmacodynamic considerations. Ann Pharmacother 2004;38(9 Suppl):S14–18.

[113] Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am 2009;23:791–815.

[114] Craig WA. Pharmacodynamics of antimicrobials: general concepts and applications. In: Nightingale CH, Murakawa T, Ambrose PG, editors. Antimicrobial pharmacodynamics in theory and clinical practice. Boca Raton, FL: CRC Press; 2001. p. 1–22.

[115] Hagihara M, Housman ST, Nicolau DP, Kuti JL. In vitro pharmacodynamics of polymyxin B and tigecycline alone and in combination against carbapenem-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2014;58:874–9.

[116] Li X, Wang L, Zhang X-J, Yang Y, Gong W-T, Xu B, et al. Evaluation of meropenem regimens suppressing emergence of resistance in *Acinetobacter baumannii* with human simulated exposure in an in vitro intravenous-infusion hollow-fiber infection model. Antimicrob Agents Chemother 2014;58:6776–81.

[117] Cai X, Yang Z, Dai J, Chen K, Zhang L, Ni W, et al. Pharmacodynamics of tigecycline alone and in combination with colistin against clinical isolates of multidrug-resistant *Acinetobacter baumannii* in an in vitro pharmacodynamic model. Int J Antimicrob Agents 2017;49:609–16.

[118] Matsumoto S, Singley CM, Hoover J, Nakamura R, Echols R, Rittenhouse S, et al. Efficacy of cefiderocol against carbapenem-resistant Gram-negative bacilli in immunocompetent-rat respiratory tract infection models recreating human plasma pharmacokinetics. Antimicrob Agents Chemother 2017;64 pii: 00700-17.

[119] Lee HJ, Bergen PJ, Bulitta JB, Tsuji B, Forrest A, Nation RL, et al. Synergistic activity of colistin and rifampicin combination against multidrug-resistant *Acinetobacter baumannii* in an in vitro pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother 2013;57:3738–45.

[120] Housman ST, Hagihara M, Nicolau DP, Kuti JL. In vitro pharmacodynamics of human-simulated exposures of ampicillin/sulbactam, doripenem and tigecycline alone and in combination against multidrug-resistant *Acinetobacter baumannii*. J Antimicrob Chemother 2013;68:2296–304.

[121] Rao GG, Ly NS, Bulitta JB, Soon RL, San Roman MD, Holden PN, et al. Polymyxin B in combination with doripenem against heteroresistant *Acinetobacter baumannii*: pharmacodynamics of new dosing strategies. J Antimicrob Chemother 2016;71:3148–56.

[122] Lenhard JR, Smith NM, Bulman ZP, Tao X, Thamlikitkul V, Shin BS, et al. High-dose ampicillin–sulbactam combinations combat polymyxin-resistant *Acinetobacter baumannii* in a hollow-fiber infection model. Antimicrob Agents Chemother 2017;61 e01268-16.

[123] Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 2009;64:142–50.
[124] Nicholson S, Peterson J, Ambruzs M, Yektashenas B, Xiang J. Doripenem 1 g infused for 4 hours in the treatment of nosocomial pneumonia/ventilator associated pneumonia (NP/VAP) due to *Acinetobacter baumannii* (*A. baumannii*). In: Infectious Diseases Society of America (IDSA) 47th Annual Meeting; 29 October–1 November 2009, Philadelphia, PA. Arlington, VA. IDSA; 2009. [abstract 386].
[125] Jaruratanasirikul S, Kositpantawong N, Jullangkoon M, Aeinlang N, Wongpoowarak W. Pharmacodynamics of meropenem in critically ill patients with ventilator-associated pneumonia. J Med Assoc Thai 2013;96:1283–9.
[126] Jaruratanasirikul S, Wongpoowarak W, Wattanavijitkul T, Sukarnjanaset W, Samaeng M, Nawakitrangsan M, et al. Population pharmacokinetics and pharmacodynamics modeling to optimize dosage regimens of sulbactam in critically ill patients with severe sepsis caused by *Acinetobacter baumannii*. Antimicrob Agents Chemother 2016;60:7236–44.
[127] Xie J, Wang T, Sun J, Chen S, Cai J, Zhang W, et al. Optimal tigecycline dosage regimen is urgently needed: results from a pharmacokinetic/pharmacodynamic analysis of tigecycline by Monte Carlo simulation. Int J Infect Dis 2014;18:62–7.
[128] Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother 2005;55:601–7.
[129] Yokoyama Y, Matsumoto K, Ikawa K, Watanabe E, Shigemi A, Umezaki Y, et al. Pharmacokinetic/pharmacodynamic evaluation of sulbactam against *Acinetobacter baumannii* in in vitro and murine thigh and lung infection models. Int J Antimicrob Agents 2014;43:547–52.
[130] Yokoyama Y, Matsumoto K, Ikawa K, Watanabe E, Morikawa N, Takeda Y. Population pharmacokinetic–pharmacodynamic target attainment analysis of sulbactam in patients with impaired renal function: dosing considerations for *Acinetobacter baumannii* infections. J Infect Chemother 2015;21:284–9.
[131] Dudhani RV, Turnidge JD, Nation RL, Li J. *f*AUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against *Acinetobacter baumannii* in murine thigh and lung infection models. J Antimicrob Chemother 2010;65:1984–90.
[132] Nation RL, Garonzik SM, Thamlikitkul V, Giamarellos-Bourboulis EJ, Forrest A, Paterson DL, et al. Dosing guidance for intravenous colistin in critically ill patients. Clin Infect Dis 2016;64:565–71.
[133] Nation RL, Garonzik SM, Li J, Thamlikitkul V, Giamarellos-Bourboulis EJ, Paterson DL, et al. Updated US and European dose recommendations for intravenous colistin: how do they perform? Clin Infect Dis 2015;62:552–8.
[134] Maglio D, Banevicius MA, Sutherland C, Babalola C, Nightingale CH, Nicolau DP. Pharmacodynamic profile of ertapenem against *Klebsiella pneumoniae* and *Escherichia coli* in a murine thigh model. Antimicrob Agents Chemother 2005;49:276–80.
[135] MacVane SH, Crandon JL, Nicolau DP. Characterizing in vivo pharmacodynamics of carbapenems against *Acinetobacter baumannii* in a murine thigh infection model to support breakpoint determinations. Antimicrob Agents Chemother 2014;58:599–601.
[136] Joukhadar C, Klein N, Dittrich P, Zeitlinger M, Geppert A, Skhirtladze K, et al. Target site penetration of fosfomycin in critically ill patients. J Antimicrob Chemother 2003;51:1247–52.
[137] Meagher A, Passarell J, Cirincione B, Van Wart S, Liolios K, Babinchak T, et al. Exposure–response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. Antimicrob Agents Chemother 2007;51:1939–45.
[138] Passarell J, Meagher A, Liolios K, Cirincione B, Van Wart S, Babinchak T, et al. Exposure–response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. Antimicrob Agents Chemother 2008;52:204–10.
[139] Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1–10.
[140] Chan JD, Graves JA, Dellit TH. Antimicrobial treatment and clinical outcomes of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Intensive Care Med 2010;25:343–8.
[141] Wood GC, Hanes SD, Boucher BA, Croce MA, Fabian TC. Tetracyclines for treating multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Intensive Care Med 2003;29:2072–6.
[142] Bishburg E, Shah M, Chan T. Use of intravenous minocycline for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and resistant Gram-negative organisms: experience in a tertiary care hospital. Infect Dis Clin Pract 2014;22:26–31.
[143] Katsube T, Wajima T, Ishibashi T, Ferreira JCA, Echols R. Pharmacokinetic/pharmacodynamic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, for dose adjustment based on renal function. Antimicrob Agents Chemother 2017;61 e01381-16.
[144] Van Wart SA, Forrest A, Bulik CC, Ambrose PG, Kostrub CF, Louie A, et al. Pharmacokinetic/pharmacodynamic (PK/PD) assessment predicts high efficacy for plazomicin against serious infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CR Kp). In: 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 10–13 September 2013, Denver, CO. Washington, DC. ASM Pres; 2013.
[145] O'Donnell J, Miller A, Mueller J, Tommasi R, Shankaran H, Ferguson D. Human pharmacokinetics and dose projection of ETX2514/sulbactam combination for use in the treatment of infections caused by *Acinetobacter baumannii*. Open Forum Infect Dis 2016;3(Suppl 1):2445.
[146] Lepak AJ, Andes DR. In vivo pharmacodynamic target assessment of delafloxacin against *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Klebsiella pneumoniae* in a murine lung infection model. Antimicrob Agents Chemother 2016;60:4764–9.
[147] Thabit AK, Crandon JL, Nicolau DP. Pharmacodynamic and pharmacokinetic profiling of delafloxacin in a murine lung model against community-acquired respiratory tract pathogens. Int J Antimicrob Agents 2016;48:535–41.
[148] Ghazi IM, Monogue ML, Tsuji M, Nicolau DP. Pharmacodynamics of cefiderocol, a novel siderophore cephalosporin, in a *Pseudomonas aeruginosa* neutropenic murine thigh model. Int J Antimicrob Agents 2018;51:206–12.
[149] Zhao M, Lepak AJ, Marchillo K, VanHecker J, Andes DR. In vivo pharmacodynamic target assessment of eravacycline against *Escherichia coli* in a murine thigh infection model. Antimicrob Agents Chemother 2017;61 e00250-17.
[150] Flamm RK, Farrell DJ, Sader HS, Jones RN. Ceftazidime/avibactam activity tested against Gram-negative bacteria isolated from bloodstream, pneumonia, intra-abdominal and urinary tract infections in US medical centres (2012).. J Antimicrob Chemother 2014;69:1589–98.
[151] Flamm RK, Nichols WW, Sader HS, Farrell DJ, Jones RN. In vitro activity of ceftazidime/avibactam against Gram-negative pathogens isolated from pneumonia in hospitalised patients, including ventilated patients. Int J Antimicrob Agents 2016;47:235–42.
[152] Sader HS, Castanheira M, Huband M, Jones RN, Flamm RK. WCK 5222 (cefepime–zidebactam) antimicrobial activity tested against clinical isolates of Gram-negative bacteria collected worldwide in 2015. Antimicrob Agents Chemother 2017;61 pii: 00072-17.
[153] Livermore DM, Mushtaq S, Warner M, Vickers A, Woodford N. In vitro activity of cefepime/zidebactam (WCK 5222) against Gram-negative bacteria. J Antimicrob Chemother 2017;72:1373–85.
[154] Lob SH, Hackel MA, Kazmierczak KM, Young K, Motyl MR, Karlowsky JA, et al. In vitro activity of imipenem–relebactam against Gram-negative ESKAPE pathogens isolated by clinical laboratories in the United States in 2015 (results from the SMART global surveillance program). Antimicrob Agents Chemother 2017;61:e02209–16.
[155] Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, et al. Activity of imipenem with relebactam against Gram-negative pathogens from New York City. Antimicrob Agents Chemother 2015;59:5029–31.
[156] Castanheira M, Huband MD, Mendes RE, Flamm RK. Meropenem–vaborbactam tested against contemporary Gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant Enterobacteriaceae. Antimicrob Agents Chemother 2017;61 pii: 00567-17.
[157] Biedenbach DJ, Kazmierczak K, Bouchillon SK, Sahm DF, Bradford PA. In vitro activity of aztreonam–avibactam against a global collection of Gram-negative pathogens from 2012 and 2013. Antimicrob Agents Chemother 2015;59:4239–48.
[158] Testa R, Cantón R, Giani T, Morosini M-I, Nichols WW, Seifert H, et al. In vitro activity of ceftazidime, ceftaroline and aztreonam alone and in combination with avibactam against European Gram-negative and Gram-positive clinical isolates. Int J Antimicrob Agents 2015;45:641–6.
[159] Yoshizumi A, Ishii Y, Aoki K, Testa R, Nichols WW, Tateda K. In vitro susceptibility of characterized β-lactamase-producing Gram-negative bacteria isolated in Japan to ceftazidime–, ceftaroline–, and aztreonam–avibactam combinations. J Infect Chemother 2015;21:148–51.
[160] Wang X, Zhang F, Zhao C, Wang Z, Nichols WW, Testa R, et al. In vitro activities of ceftazidime–avibactam and aztreonam–avibactam against 372 Gram-negative bacilli collected in 2011 and 2012 from 11 teaching hospitals in China. Antimicrob Agents Chemother 2014;58:1774–8.
[161] Ito A, Sato T, Ota M, Takemura M, Nishikawa T, Toba S, et al. In vitro antibacterial properties of cefiderocol, a novel siderophore cephalosporin, against Gram-negative bacteria. Antimicrob Agents Chemother 2017;62 pii: e01454-17.
[162] Falagas ME, Skalidis T, Vardakas KZ, Legakis NJ. Activity of cefiderocol (S-649266) against carbapenem-resistant Gram-negative bacteria collected from inpatients in Greek hospitals. J Antimicrob Chemother 2017;72:1704–8.
[163] Ito A, Kohira N, Bouchillon SK, West J, Rittenhouse S, Sader HS, et al. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. J Antimicrob Chemother 2015;71:670–7.
[164] Dobias J, Dénervaud-Tendon V, Poirel L, Nordmann P. Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens. Eur J Clin Microbiol Infect Dis 2017;36:2319–27.
[165] Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In vitro activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant Gram-negative bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 Study). Antimicrob Agents Chemother 2017;61 pii: 00093-17.
[166] Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In vitro activity of the siderophore cephalosporin, cefiderocol, against carbapenem-nonsusceptible and multidrug-resistant isolates of Gram-negative bacilli collected worldwide in 2014 to 2016. Antimicrob Agents Chemother 2018;62 e01968-17.

[167] Landman D, Kelly P, Bäcker M, Babu E, Shah N, Bratu S, et al. Antimicrobial activity of a novel aminoglycoside, ACHN-490, against *Acinetobacter baumannii* and *Pseudomonas aeruginosa* from New York City. J Antimicrob Chemother 2010;66:332–4.
[168] Kang AD, Smith KP, Eliopoulos GM, Berg AH, McCoy C, Kirby JE. In vitro apramycin activity against multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Diagn Microbiol Infect Dis 2017;88:188–91.
[169] Livermore DM, Mushtaq S, Warner M, Woodford N. In vitro activity of eravacycline against carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii*. Antimicrob Agents Chemother 2016;60:3840–4.
[170] Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J. Activity of eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, including multidrug-resistant isolates, from New York City. Antimicrob Agents Chemother 2015;59:1802–5.
[171] Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible *Acinetobacter baumannii*. Int J Antimicrob Agents 2018;51:62–4.
[172] Vázquez-Ucha JC, Maneiro M, Martínez-Guitián M, Buynak J, Bethel CR, Bonomo RA, et al. Activity of the β-lactamase inhibitor LN-1-255 against carbapenem-hydrolyzing class D β-lactamases from *Acinetobacter baumannii*. Antimicrob Agents Chemother 2017;61 e01172-17.
[173] Mushtaq S, Vickers A, Woodford N, Livermore DM. WCK 4234, a novel diazabicyclooctane potentiating carbapenems against Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* with class A, C and D β-lactamases. J Antimicrob Chemother 2017;72:1688–95.
[174] Durand-Réville TF, Guler S, Comita-Prevoir J, Chen B, Bifulco N, Huynh H, et al. ETX2514 is a broad-spectrum β-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including *Acinetobacter baumannii*. Nat Microbiol 2017;2:17104.
[175] Almer LS, Hoffrage JB, Keller EL, Flamm RK, Shortridge VD. In vitro and bactericidal activities of ABT-492, a novel fluoroquinolone, against Gram–positive and Gram-negative organisms. Antimicrob Agents Chemother 2004;48:2771–7.
[176] Pfaller M, Sader H, Rhomberg P, Flamm R. In vitro activity of delafloxacin when tested against contemporary bacterial pathogens from the United States and Europe, 2014. Antimicrob Agents Chemother 2017;61 pii 02609-16.
[177] Hirano T, Kinoshita T, Kazamori D, Inoue S, Nishimura K, Sakurai A, et al. Discovery of a novel fluoroquinolone antibiotic candidate WFQ-228 with potent antimicrobial activity and the potential to overcome major drug resistance. Chem Pharm Bull (Tokyo) 2018;66:235–8.
[178] Seifert H, Stefanik D, Sutcliffe J, Higgins P. In vitro activity of the novel fluorocycline TP-6076 against carbapenem non-susceptible *Acinetobacter baumannii*. In: 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 22–25 April 2017, Vienna, Austria. Basel, Switzerland. ESCMID; 2017. [abstract P1364].
[179] Zurawski DV, Reinhart AA, Alamneh YA, Pucci MJ, Si Y, Abu-Taleb R, et al. SPR741, an antibiotic adjuvant, potentiates the in vitro and in vivo activity of rifampin against clinically relevant extensively drug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2017;61 e01239-17.
[180] Corbett D, Wise A, Langley T, Skinner K, Trimby E, Birchall S, et al. Potentiation of antibiotic activity by a novel cationic peptide: potency and spectrum of activity of SPR741. Antimicrob Agents Chemother 2017;61 pii: 00200-17.
[181] Van Wart SA, Forrest A, Drusano GL, Bhavnani SM, Bulik CC, Kostrub CF, et al. Pharmacokinetic–pharmacodynamic analysis predicts a high probability of efficacy for plazomicin against serious infections caused by carbapenem-resistant Enterobacteriaceae. In: 23rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 27–30 April 2013, Berlin, Germany. Basel, Switzerland. ESCMID; 2013. [poster P914].
[182] Thabit AK, Monogue ML, Newman JV, Nicolau DP. Assessment of in vivo efficacy of eravacycline against Enterobacteriaceae exhibiting various resistance mechanisms: a dose-ranging study and pharmacokinetic/pharmacodynamic analysis. Int J Antimicrob Agents 2018;51:727–32.
[183] Möllmann U, Heinisch L, Bauernfeind A, Köhler T, Ankel-Fuchs D. Siderophores as drug delivery agents: application of the 'Trojan horse' strategy. Biometals 2009;22:615–24.
[184] Ito A, Nishikawa T, Oota M, Kanazawa S, Fukuhara N, Yamaguchi T, et al. S-649266, a novel siderophore cephalosporin: binding affinity to PBP and bactericidal activity. In: 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen, Denmark. Basel, Switzerland. ESCMID; 2015. [abstract ECCMID-1871].
[185] Kohira N, West J, Ito A, Ito-Horiyama T, Nakamura R, Sato T, et al. In vitro antimicrobial activity of a siderophore cephalosporin, S-649266, against Enterobacteriaceae clinical isolates, including carbapenem-resistant strains. Antimicrob Agents Chemother 2016;60:729–34.
[186] Ito-Horiyama T, Ishii Y, Ito A, Sato T, Nakamura R, Fukuhara N, et al. Stability of novel siderophore cephalosporin S-649266 to clinically relevant carbapenemases. Antimicrob Agents Chemother 2016;60:4384–6.
[187] Horiyama T, Toba S, Nakamura R, Tsuji M, Yamano Y, Shimada J. A novel siderophore cephalosporin: VI. Magnitude of PK/PD parameter required for efficacy in murine lung infection model. In: 54th Interscience Conference on Antimicrobial Agents Chemotherapy (ICAAC); 5–9 September 2014, Washington, DC. Washington, DC. ASM Press; 2014.
[188] Tsuji M, Ito-Horiyama T, Nakamura R, Sato T, Yamano Y. S-649266, a novel siderophore cephalosporin: pharmacodynamic assessment by using MIC in iron-depleted cation-adjusted Mueller Hinton broth (ID-CAMHB). Open Forum Infect Dis 2016;3:1995.
[189] Aggen JB, Armstrong ES, Goldblum AA, Dozzo P, Linsell MS, Gliedt MJ, et al. Synthesis and spectrum of the neoglycoside ACHN-490. Antimicrob Agents Chemother 2010;54:4636–42.
[190] Grossman TH, Starosta AL, Fyfe C, O'Brien W, Rothstein DM, Mikolajka A, et al. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic. Antimicrob Agents Chemother 2012;56:2559–64.
[191] Weiss WJ, Pulse M, Renick P, Sutcliffe J. Efficacy of fluorocycline TP-434 in the neutropenic thigh infection model is predicted by AUC/MIC. In: 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 12–15 September 2010, Boston, MA. Washington, DC. ASM Press; 2010. [abstract F1-2164].