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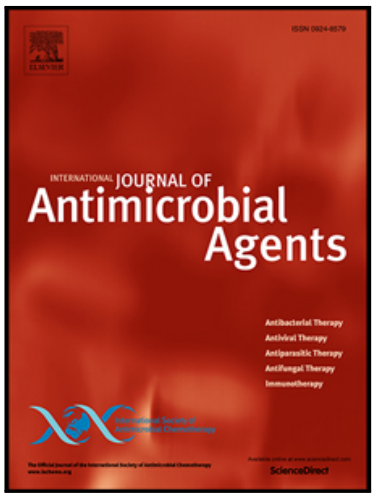

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Highlights

- *In vitro* synergy was seen in only a portion of MDR *A. baumannii* strains tested.
- Majority of observational studies did not show added benefits of combination therapy.
- No strong RCT data to support combination therapy.
- Some novel agents are promising options for the treatment of MDR *A. baumannii*.
- PK/PD optimized therapy is likely required to ensure a successful treatment.

Multidrug-resistant *Acinetobacter baumannii* infections: current evidence on treatment options and role of PK/PD in dose optimization

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Abstract

Acinetobacter baumannii remains a difficult-to-treat pathogen that poses a significant challenge to clinicians and cost to the healthcare system. There is a lack of clinical efficacy data to aid in the selection of optimal treatment for multi-drug resistant (MDR) *A. baumannii* infections. This paper aims to review recent literature on the treatment of MDR *A. baumannii* and novel agents in the pipeline and 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, due to a lack of definitive evidence from randomized controlled trials. 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 infection pathologies caused by MDR *A. baumannii*, but these have yet to be evaluated in randomized controlled trials. A better understanding of the pharmacokinetics (PK)/pharmacodynamics (PD) of the "old" antibiotics is required to optimize their dosing regimens to maximize bacterial killing, minimize toxicities and improve clinical outcomes.

Keywords

Acinetobacter baumannii; MDR; multidrug resistant; treatment; therapy

1 Introduction

There are increasing reports of nosocomial infections caused by *Acinetobacter baumannii*, a pathogen frequently identified as an etiologic agent in catheter-related bacteraemia, hospital-acquired or ventilator-associated pneumonia (VAP), urinary tract infections, surgical site and other types of wound infections [1]. *A. 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]. The risk factors for acquiring MDR *A. baumannii* include recent exposure to antibiotics, especially third-generation cephalosporins, carbapenems and fluoroquinolones, presence of central lines or urinary catheters, severe disease, recent surgery, larger hospital size, prolonged ventilation, long intensive care unit (ICU) or hospital stay, exposure to infected or colonized patients and multiple medical procedures [4-6].

MDR *A. baumannii* frequently harbour multiple resistance mechanisms, [7] which leaves us with 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 like our 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 ten years up to 1 August 2018. The main search terms were 'multidrug-resistant', 'Acinetobacter', 'treatment' AND 'combination'. Also, the reference lists of reports identified by this search strategy were searched to select relevant articles. Only articles published in English were included. We Included (1) *in vitro* and *in vivo* studies on antibiotic synergy against MDR *A. baumannii*, (2) clinical studies, both retrospective and prospective, describing the treatment of *A. baumannii* infections, and (3) studies on novel antibiotics for *A. baumannii* infections. One hundred sixty-one relevant articles were identified from our literature search and included in this review.

3. Monotherapy vs. combination therapy – the current evidence

3.1 *In vitro* and pre-clinical animal studies

There are limited therapeutic options that exist for treating 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 antimicrobials in combinations. Many *in vitro* and *in vivo* animal studies have explored the possible synergy of antibiotics to overcome *Acinetobacter spp.* resistance. During this review, we found 50 *in vitro* and 15 *in vivo* animal studies, describing the effects of various antibiotic combinations against MDR *A. baumannii*. Their characteristics are presented in Supplementary Table 1[13-62] and Supplementary Table 2 [15, 35, 45, 55, 64-74].

Most of these studies showed potential antibiotic combinations that could improve the 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 about 20% of the *in vitro* studies, and combinations that displayed antagonistic effect include various tigecycline-based combinations, [24, 33, 39, 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 is the recommended method of testing 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, which employs MIC testing methods other than broth microdilution.

3.2 Observational clinical studies

Our search identified 25 observational studies (23 retrospective and two prospective studies) that described treatment outcome for MDR *Acinetobacter spp.* infections. The characteristics of these studies are presented in Table 1.

Of the observational studies (Table 1), 12 studies compared monotherapy to combination therapy, [76-87] nine studies compared different combination treatment regimens [83, 87-94] and six 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 are differences in the study design such as case definitions and inclusion/exclusion criteria. There were also differences in the dose of antibiotics prescribed, and most of these studies were carried out before 2012, which was when the recommendation for colistin loading dose first came.

Of the 12 studies that compared the efficacy of combination versus monotherapy, only one study showed a significant difference in 30-day mortality [82]. This retrospective study included 101 patients with various sites of infection, mainly pneumonia. Patients were either given IV polymyxin B alone, at a dose of 1.5 to 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 when compared to monotherapy (79.9% vs. 55.6%, $p = 0.001$) [83]. In this study, the authors compared colistin combination therapy with either carbapenem, sulbactam or other antibiotics, and colistin monotherapy. Colistin was given at a dose of 5mg/kg/day colistin base activity (CBA) in 2-3 divided doses, with renal adjustment. No loading dose was given to the patients. 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 compared to colistin monotherapy [76, 81]. One study did not observe a statistically significant difference in the mortality rate when comparing the two treatment arms [81], but the other showed that giving colistin with a glycopeptide for at least five days was protective against 30-day mortality [76].

Of the nine studies which 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 12 hourly, after a loading dose of 100 mg ± other antibiotics), with non-tigecycline based combination therapy (IV imipenem/cilastatin 500 mg and sulbactam 1 g 6 hourly) in 386 patients with hospital-acquired infections Lee, 2013 #342}. Favourable clinical outcome was considerably higher in the tigecycline-based therapy group (69.1% vs. 50%, $p = <0.001$). However, 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 12 hourly, after a loading dose of 100 mg ± other antibiotics) with colistin-based therapy (IV colistin 2.5–5

mg/kg/day CBA in 2–3 divided doses ± other antibiotics), in 168 patients with MDR *A. baumannii* pneumonia [91]. Mortality was significantly lower in the colistin-based therapy (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* VAP [93]. The standard dose of the antibiotics was used, but the exact dosing was not specified. This study found that the 30-day survival rate was significantly better in the tigecycline/imipenem combination therapy group compared to 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-day sulbactam–imipenem/cilastatin therapy. Another study [90] comparing tigecycline-based therapy (IV tigecycline 50 mg 12 hourly, after 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) 6-8 hourly ± other antibiotics) found that microbiological eradication was much higher in the sulbactam-based therapy group (63.5% vs. 33.3%, p = <0.001). 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 12 hourly) compared to systemic antibiotic therapies (61.1-84.6% vs. 10.3-29.6%, p = 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 regards 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 units/day 12 hourly + IV polymyxin B 450,000 units 12 hourly ± 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 = 0.01). 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 vs. monotherapy or between different treatment regimens. However, there are several limitations observed with many studies listed in Table 1, which may affect the validity of the results obtained. In general, most of the observational studies are retrospective in nature, and as such may be limited by various factors such as poor quality or missing data, or absence of data on potential confounding factors. There are also limitations in the dosing regimens of antimicrobials used, such as a lack of loading dose for colistin or suboptimal dosing of other antimicrobials, such as sulbactam and tigecycline. As highlighted previously concerning the issue with colistin MIC testing, we note that most studies involving colistin did not use broth microdilution for testing of 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 Randomized controlled trial data

We found eight RCTs that compared different treatment regimens for MDR *A. baumannii* infections. The characteristics of these studies are presented in Table 2.

All eight studies focused on the treatment of MDR *A. baumannii* pneumonia, mainly VAP. Seven out eight were open-labelled trials. Majority of the studies involving colistin did not mention the method of MIC testing used. Six out eight compared colistin monotherapy with colistin-based combination therapy [104-108, 110] and the remaining two measured the efficacy of inhaled colistin [103, 109]. Of the six studies which compared 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 8 hourly, with renal adjustment, without loading dose) with colistin/ampicillin-sulbactam combination therapy (IV colistin + IV ampicillin-sulbactam 6 g 6 hourly, 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 the microbiological outcome.

Two other studies, however, found a better microbiological response in the combination group but failed to see any difference in their clinical outcome [105, 107 153].The first study compared colistin monotherapy (IV colistin 2 MU 8 hourly, with renal adjustment, without loading dose) with colistin/rifampin combination therapy (IV colistin + IV rifampin 600 mg 12 hourly), in 210 patients with MDR *A. baumannii* infection, mainly VAP [105]. The authors found better microbiological eradication in the combination group,

compared to the monotherapy group (60.6% vs. 44.8%, p = 0.034), but did not see any difference in 30-day mortality rate in 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 loading dose) with colistin/fosfomycin combination therapy (IV colistin + IV fosfomycin 4 g 12 hourly) in 94 patients with MDR *A. baumannii* infections, mainly VAP [107]. The study showed a better microbiological response in the combination group, compared to the monotherapy group (100% vs. 81.2%, p = 0.010), but did not see any difference in clinical response in 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 12 hourly after a loading dose of 9 MU, with renal adjustment) with colistin/meropenem combination therapy (IV colistin + IV meropenem 2 g 8 hourly with 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]. One hundred ninety-eight patients were randomized into the colistin monotherapy group, and 208 patients were 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 the monotherapy vs. combination therapy (clinical failure at day 14, 73% vs. 79%, p = 0.172), or 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% of patients in the combination therapy arm had died (p = 0.786), and of the surviving patients, no improvement or deterioration in SOFA occurred.

Furthermore, a subgroup analysis of the AIDA trial also noticed a similar finding when comparing colistin monotherapy to 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 (OR 2.956, 95%CI 1.180-7.408) when compared to 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 found in these RCTs as well. Factors such as the lack of loading dose or suboptimal dosing for colistin, or suboptimal dosing of other antimicrobials, such as sulbactam, rifampin, 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, rifampin [105] or Fosfomycin [107]. In view that these RCTs mainly included patients with pneumonia, it is unclear whether these regimens would have similar outcomes for other sites of infection.

4. Optimised dosing of antibiotics to treat MDR *A. baumannii*

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

PK/PD analyses describe the antibiotic exposure associated with maximal effect for an antibiotic and are critical determinants in establishing the 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 (maximal unbound drug concentration) and *f*AUC/MIC (area under the unbound drug concentration-time curve). Several studies have looked at dose optimization of currently available antibiotics for the treatment of MDR *A. baumannii* infections. The characteristics of these studies are presented in Table 3.

As an example, based on murine thigh and lung infection models of *A. baumannii*, PK/PD analysis of sulbactam demonstrated that the %$fT_{>MIC}$ 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 maximize the bactericidal activity of sulbactam, blood sulbactam concentrations should be maintained above MIC for prolonged periods. In patients with severe sepsis, a target attainment of 60% $fT_{>MIC}$ for *A. baumannii* strains with a MIC of sulbactam of 4 mg/L, is more likely to be achieved when sulbactam is administered by a 4-h infusion of 1 g every 8 h, 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 at least 1 g every 6 h by a 4-h infusion. PK/PD analysis has also helped to optimize dosing of sulbactam in patients with different renal functions, as shown by Yokoyama *et al.* [130]. The study demonstrated that in a patient with a creatinine clearance 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 creatinine clearance of 90 ml/min.

The recent revitalisation of the long-neglected antibiotic, colistin, is another best examples showcasing the significant role of PK/PD 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 raged 7.4 to 17.6 [101]. These PK/PD data, in combination with those from clinical pharmacokinetic 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 ~20 and ~40%, respectively [134]. An *A. baumannii* murine thigh infection model then demonstrated that the $fT_{>MIC}$ values of 23.7%, 32.8%, and 47.5% resulted in stasis, 1-log reductions, and 2-log reductions in bacterial density after 24 h, respectively [135]. A subsequent PK/PD analysis on meropenem then revealed that the

probability of achieving 40% $fT_{>MIC}$ following a bolus injection of 1 g every 8h, a 3-hour infusion of 1 g every 8h, and a 3-hour infusion of 2 g every 8h were 87.7%, 98.8%, and 99.9%. This finding suggests that prolonged infusion maximizes the bactericidal activity of meropenem against *A. baumannii* with 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 a Monte Carlo simulation, Menegucci *et al*. found that target attainment of 70% $fT_{>MIC}$ for pathogens with MIC of 32 mg/L is only achievable when fosfomycin is administered as a 3-hour infusion at a minimum dose of 4 g every 8h [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 or skin structure infections and intraabdominal infections 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 evaluation of the current recommended dose of 50 mg and 100 mg twice daily in skin and skin structure infections, demonstrated that the cumulative fraction response in the Gram-negative bacteria isolates, was only 54.67%, even when given at the highest recommended dose [127]. Whereas, in intra-abdominal infections, the cumulative fraction response against Gram-negative bacteria isolates, ranges from 48% to 88%. These results suggest that current dosing recommendation of tigecycline should be adjusted to ensure optimal exposure.

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

5. New antibiotics for treating MDR infections

With limited antibiotics that are active against MDR *A. baumannii*, clinicians and researchers look to a new and novel agent 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 summarizes the new agents and their activity against MDR *Acinetobacter* spp. Table 7 summarizes 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, which 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 beta-lactamases, including class 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].

Pharmacodynamic 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 and 1-log_{10} and 2-log_{10} reductions 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* ranges from 0.063-0.5 µg/mL. Katsube *et al*. then looked at target attainment in patients with varying renal functions using Monte Carlo simulation [143]. The simulation demonstrated that 2 g every 8h with either 1- and 3-hr infusion is likely to achieve 75% $fT_{>MIC}$ against susceptible Gram-negative bacteria including *A. baumannii.* For patients with augmented renal function (creatinine clearance ≥ 120 mL/min), 2 g every 6h with 3-hr infusion is likely to achieve 75% $fT_{>MIC}$ against susceptible organisms. The study also suggested the need of supplemental dose immediately after intermittent haemodialysis to achieve similar PK/PD target.

5.2 Plazomicin

Plazomicin (ACHN-490) is a semisynthetic aminoglycoside derived from sisomicin [189]. Its structural modifications 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].

*f*AUC/MIC ratio was identified as the PK/PD index associated with 1- to 2-$\log_{10}$ colony forming unit (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 which 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 the 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 pHs which improved 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 *et. al.*, 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 *et al*. was tested against extended-spectrum beta-lactamase-producing *K. pneumoniae* isolates.

ETX2514 is a diazabicyclooctanone beta-lactamase inhibitor, which has an extended spectrum of activity that covers of a wide array of class D enzymes, and improved potency against class A and C beta-lactamases [174]. It works by binding to the penicillin-binding proteins, which are the same targets as for beta-lactams. Durand-Réville *et al*. demonstrated that ETX2514 could fully restore beta-lactam activity against class 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 6-fold. For sulbactam/ETX2514, the PK/PD index associated with bacterial killing is the % $fT_{>MIC}$ (sulbactam) and %T>C_T (time above the critical threshold) (ETX2514), with a target value of 50 for both sulbactam and ETX2514 [145]. Subsequent PK/PD analysis then revealed that 1 gm of sulbactam: 0.5 gm of ETX2514 via a 3 hr infusion every 6h is likely to achieve the PK/PD target when tested against *A. baumannii* with MICs of ≤4 mg/L [145].

6. Conclusion

A. 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 PK/PD of the "old" antibiotics is required to optimize 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 randomized controlled trials.

Declarations

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Table 1: Characteristics and outcomes of the studies reporting on the treatment of MDR *Acinetobacter spp*. infections

Reference	Study period	Study design	Number 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**	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/teicoplanin **	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 to 0.93; *p* 0.03).											
Kalin (2014) [77]	2011	Retrospective, cohort	89	Compare monotherapy and combination therapy	VAP	Colistin alone**	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**	IV sulbactam 3 g q8h	Clinical cure 40%, mortality 73%		Bacteriological clearance 85.7%	
Lopez-Cortez (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 +	Clinical cure 42.9%, 14-day mortality 47.2%		Microbiological eradication 83%	

							tigecycline and tigecycline + aminoglycoside, dose not specified				
Yilmaz (2015)[80]	2011-2013	Retrospective, cohort	70	Compare monotherapy and combination therapy	VAP	Colistin monotherapy**	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**	IV imipenem 500 mg IV 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**	IV sulbactam 1 g q8h, with renal adjustment	Clinical response 55.0%, 28-day mortality 70%		Microbiological response 60.0%	
Garnacho-Montero (2013)[81]	2008-2011	Retrospective, cohort	57	Compare monotherapy and combination therapy	VAP/ bacteraemia	Colistin/vancomycin combination therapy**	IV colistin 3 MU q8h, adjusted by BW and renal function + IV vancomycin 2 g/day with 1-h infusion, adjusted by the renal function	Clinical cure 55.2%, 28-day mortality 48.3%	0.320, 0.890	Microbiological eradication 54.2%	0.440
						Colistin monotherapy**	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 to 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**	IV colistin 5mg/kg/day CBA in 2-3 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**	IV colistin 5mg/kg/day CBA in 2-3 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**	IV colistin 5mg/kg/day CBA in 2-3 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**	IV colistin 5mg/kg/day CBA in 2-3 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**	IV colistin 5mg/kg/day CBA in 2-3 divided doses, with renal adjustment + other antibiotics	Complete response 39.5%, 14-day survival 62.8%		Microbiological eradication 82%	
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 500mg 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		Monotherapy	Either tigecycline or colistin	Clinical success 39%, 30-day mortality 33%	0.110, 0.560	Microbiological success 22%	0.250

				therapy		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#	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#	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**	IV colistimethate sodium 2.5-5.0 mg/kg per day in 2-3 divided doses, renal adjusted	30-day mortality 35.5%	0.800	-	-	
						Non-colistin based therapy**	Other antibiotics	30-day mortality 38.5%				
Ye (2016) [90]	2004-2010	Retrospective, cohort	168	Compare different antibiotic combinations	Pneumonia	Tigecycline-based therapy**	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**	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**	IV colistin 2.5–5 mg/kg/day CBA in 2–3 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**	IV colistin 5mg/kg/day CBA in 2-3 divided doses, with renal adjustment + carbapenems	14-day mortality 15%, breakthrough bacteraemia 0%	0.105, 0.059	-	-	
						Colistin/tigecycline combination therapy**	IV colistin 5mg/kg/day CBA in 2-3 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 (hazard ratio, 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-day 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%	
Chen (2014)[95]	2007-2011	Retrospective, cohort	135	Compare different route of administration	Pneumonia	Inhaled colistin**	Neb colistin 2 MU q12h	28-day mortality 11.3%	0.167	14-day eradication 61.1%	0.001
						Other antibiotic therapies**	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**	Neb colistin 2 MU q12h	28-day mortality 12.8%	0.723	Eradication within 14 days 84.6%	<0.001
						Other antibiotic therapies**	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**	IV colistin 9 MU divided in 3 divided doses, with renal adjustment	Clinical cure 32.5%, mortality 26%	0.050, 0.289	Bacteriological eradication 50%	0.679

						Inhaled colistin + IV colistin**	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#	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#	IV colistimethate sodium 2.5 mg/kg q12h	14-day clinical cure 30%, mortality 45%		14-day bacteriological clearance 65%	
						Low dose IV colistin#	Adjusted according to the creatinine clearance	14-day clinical cure 30%, mortality 40%		14-day bacteriological clearance 75%	
				Compare different route of administration		IV colistin only#	As above	14-day clinical cure 38%, mortality 44%	0.130, 0.650	14-day bacteriological clearance 69%	0.73
						IV colistin + inhaled colistin#	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	Intrathecal/intraventricular polymyxin B-based therapy	IT/IVT polymyxin B 50,000 units/day q12h + IV polymyxin B 450,000 units q12h ± other IV antibiotics	28-day mortality 8.70%; clinical efficacy 95.6%	0.010; <0.001	Microbiological clearance 91.3%	<0.001
						Other IV antibiotic therapies	Other IV antibiotics	28-day mortality 55.26%, clinical efficacy 23.7%		Microbiological clearance 18.4%	

VAP, ventilator-associated pneumonia; IV, intravenous; Neb, nebulized; MU, million units; CBA, colistin-based activity; IT, intrathecal; IVT, intraventricular; BW, body weight; q8h, every 8 hours; q12h, every 12 hours.

** Colistin MIC (minimum inhibitory concentration) testing by methods other than broth microdilution. # Colistin MIC testing not done/mentioned.

*Broth microdilution is the preferred method of susceptibility testing for colistin, as per European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendation [63].

Table 2: Characteristics and outcomes of RCTs on the treatment of MDR *Acinetobacter spp*. infections

Reference	Study period	Study design	Number of patients	Site of infection	Treatment given	Dose of antimicrobials	Mortality prediction score	Clinical outcome	*p*-value	Microbiological outcome	*p*-value
Rattanaumpawan (2010)[103]	2006-2009	Prospective, RCT, open-labelled	100	VAP	Inhaled colistin group[#]	Neb colistin 2 MU q12h + IV antibiotics	19.1(5.8)[†]	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) [†]	Favourable clinical outcome 53.1%, 28-day mortality 36.7%		Favourable microbiological outcome 38.2%	
Paul (2018)[104]	2013-2016	Prospective, RCT, open-labelled	406	Mainly pneumonia/ bacteraemia	Colistin monotherapy[#]	IV colistin 4.5 MU q12h after a loading dose of 9 MU, with renal adjustment	5 (3–8)[‡]	Clinical failure 79%, 28-day mortality 43%	0.172, 0.781	Microbiological failure 31%	0.489
					Colistin/meropenem combination therapy[#]	IV colistin + IV meropenem 2 g q8h with 3-h infusion, both with renal adjustment	6 (4–9)[‡]	Clinical failure 73%, 28-day mortality 45%		Microbiological failure 35%	
Durante-Mangoni (2013)[105]	2008-2011	Prospective, RCT, open-labelled	210	Mainly VAP	Colistin monotherapy[#]	IV colistin 2 MU q8h, with renal adjustment	39.0 (11.1)[¶]	30-day mortality 42.9%	0.950	Bacteriological eradication 44.8%	0.034
					Colistin/rifampin combination therapy[#]	IV colistin + IV rifampin 600 mg q12h	40.8 (10.8)[¶]	30-day mortality 43.3%		Bacteriological eradication 60.6%	
Aydemir (2013)[106]	2011-2012	Prospective, RCT, open-labelled	43	VAP	Colistin monotherapy	IV colistin 9 MU divided into 3 divided doses, with renal adjustment	18.0 (4.9)[†]	Clinical response 49%, mortality 63.6%	0.654, 0.171	Microbiological response 59.1%	0.597
					Colistin/rifampin combination therapy	IV colistin + PO rifampin 600 mg/day	20.1 (6.8)[†]	Clinical response 52%, mortality 38.1%		Microbiological response 71.4%	
Sirijatuphat (2014)[107]	2010-2011	Prospective, RCT, open-labelled	94	Mainly VAP	Colistin monotherapy[#]	IV colistin 5 mg of CBA/kg BW/day	21.9 (7.9)[†]	Favourable clinical response 55.3%, 28-day mortality 23.1%	0.835, 0.578	Microbiological response 81.2%	0.010
					Colistin/fosfomycin combination	IV colistin + IV fosfomycin 4 g q12h	23.0 (6.4)[†]	Favourable clinical response		Microbiological response 100%	

					therapy[#]			59.6%, 28-day mortality 16.3%		
Makris (2018)[108]	Not specified	Prospective, RCT, open-labelled	39	VAP	Colistin monotherapy[#]	IV colistin 3 MU q8h, with renal adjustment	14.5 (3.1)[†]	Clinical response 15.8%, mortality 63%	0.001, NS	Microbiological eradication 1/3 vs Microbiological eradication 10/14: 0.191
					Colistin/ampicillin-sulbactam combination therapy[#]	IV colistin + IV ampicillin-sulbactam 6 g q6h, both with renal adjustment	16.5 (4.7)[†]	Clinical response 70%, mortality 50%		
Abdellatif (2016)[109]	2013-2015	Prospective, RCT, single-blind	149	VAP	Inhaled colistin/IV imipenem[#]	Neb colistin 4 MU q8h + IV imipenem 1 g q8h	39 (13)[¶]	Favourable clinical outcome 67.1%, 28-day mortality 27.4%	0.590, 0.700	Time to bacterial eradication 9.89 ± 2.7 days vs Time to bacterial eradication 11.26 ± 3 days: 0.023
					IV colistin/IV imipenem[#]	IV Colistin 4.5 MU q12h after a loading dose of 9 MU, with renal adjustment + IV imipenem 1 g q8h	40 (14)[¶]	Favourable clinical outcome 72.3%, 28-day mortality 23.7%		
Betrosian (2008)[110]	Not specified	Prospective, RCT, open-labelled	28	VAP	Colistin monotherapy**	IV colistin 3 MU q8h	14 (2)[†]	Clinical success 60%, 14-day mortality 20%	NS, NS	Bacteriological eradication 46.6% vs Bacteriological eradication 46.1%: NS
					Ampicillin-sulbactam monotherapy**	IV ampicillin-sulbactam (2:1) 9 g q8h	14 (5)[†]	Clinical success 61.5% 14-day mortality 15.3%		

RCT, randomized controlled trial; CRAB, carbapenem-resistant *Acinetobacter baumannii*; VAP, ventilator-associated pneumonia; UTI, urinary tract infection; IV, intravenous; Neb, nebulized; MU, million units; CBA, colistin-based activity; BW, body weight; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours; NS, not significant; SD, standard deviation; IQR, inter quartile range; † APACHE (Acute Physiology And Chronic Health Evaluation) II score; ǂ SOFA (Sequential Organ Failure Assessment) score; ¶ SAPS (Simplified Acute Physiology) II score. For the mortality prediction scores, data are presented as mean (SD) or median (IQR).

** Colistin MIC (minimum inhibitory concentration) testing by methods other than broth microdilution. [#]Colistin MIC testing not done/mentioned.

*Broth microdilution is the preferred method of susceptibility testing for colistin, as per European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendation [63].

Table 3: Studies evaluating dose optimization of antibiotics used for MDR *Acinetobacter spp.* infections

Reference	Study design	Method(s)	Duration of study	Antibiotics tested	Outcome
Hagihara (2014)[115]	*In vitro*	PD model	24h	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 did 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	168h	0.5 g given q8h with a 0.5-h infusion	Not bactericidal
				0.5 g meropenem q8h with a 3-h infusion	Not bactericidal
				1.0 g given q8h with a 0.5-h infusion	3-$\log_{10}$ CFU/ml bacterial killing; did not suppress the emergence of resistance
				1.0 g meropenem q8h with a 3-h infusion	3-$\log_{10}$ CFU/ml bacterial killing; did not suppress the emergence of resistance
				2.0 g given q8h with a 0.5-h infusion	3-$\log_{10}$ CFU/ml bacterial killing; suppressed emergence of resistance; %*T*>MPC ≥ 20
				2.0 g meropenem q8h with a 3-h infusion	3-$\log_{10}$ CFU/ml bacterial killing; suppressed emergence of resistance; %T>MPC ≥ 20
Menegucci (2016)[31]	*In silico*	MCS		4.0 g fosfomycin q8h with 1-h infusion	PTA ≥ 0.9 for %$fT_{>MIC}$ ≥ 70% (MIC 16 mg/L)
				6.0 g fosfomycin q6h with a 1-h infusion	
				8.0 g fosfomycin q8h with a 1-h infusion	
				4.0 g fosfomycin q8h with 3-h infusion	PTA ≥ 0.9 for %$fT_{>MIC}$ ≥ 70% (MIC 32 mg/L)

				6.0 g fosfomycin q6h with a 3-h infusion	
				8.0 g fosfomycin q8h with a 3-h infusion	
				1.5 g meropenem q6h with 0.5-h infusion	PTA ≥ 0.9 for $\%fT_{>MIC} \geq 40\%$ (MIC 4 mg/L)
				1.0 g meropenem q8h with a 3-h infusion	
				1.5 g meropenem q6h with a 3-h infusion	
				2.0 g meropenem q8h with a 3-h infusion	
Cai (2017)[117]	*In vitro*	PD model	24h	5 mg/kg/day colistin in 3 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-AB synergistically.
				100 mg loading followed by 50 mg tigecycline q12h	
				200 mg loading followed by 100 mg tigecycline q12h	
				Colistin + 100 mg loading followed by 50 mg tigecycline q12h	
				Colistin + 200 mg loading followed by 100 mg tigecycline q12h	
Matsumoto (2017)[118]	*In vivo*	Murine pneumonia model	96h	2.0 g cefiderocol q8h with a 3-h infusion	2 g every 8 h 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 with a 1-h infusion	
Lee (2013)[119]	*In vitro*	PD model	72h	Colistin at 0.5 mg/L + rifampin with a Cmax of 5 mg/L	Combinations resulted in substantially greater killing at the low inoculum; combinations containing 2 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 + rifampin with a Cmax of 5 mg/L	
				Colistin at 5 mg/L + rifampin with a Cmax of 5 mg/L	
Housman (2013)[120]	*In vitro*	PD model	24h	9.0 g ampicillin/sulbactam q8h with 3-h infusion + 2.0 g doripenem q8h with 4-h infusion	AUBC 87.8+21.0
				9.0 g ampicillin/sulbactam q8h with 3-h infusion	AUBC 100.6+33.0

				+200 mg tigecycline q12h with 30-min infusion	
				9.0 g ampicillin/sulbactam q8h with a 3-h infusion	AUBC 116.7+31.6
				3.0 g ampicillin/sulbactam q6h with 30-min infusion + 200 mg tigecycline q12h with 30-min infusion	AUBC 134+31.5
				2.0 g doripenem q8h with 4-h infusion + 200 mg tigecycline q12h with a 30-min infusion	AUBC 142.7+16.9
Rao (2016)[121]	*In vitro*	HFIM	48h	Polymyxin B traditional monotherapy: free steady-state concentration (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 regrowth
				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 regrowth 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 ~6 $\log_{10}$ regrowth 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 every 8 h × 3 doses followed by no doripenem thereafter) and polymyxin B traditional regimen (fC_{ss} of 2 mg/L continuous infusion).	Regrowth after the initial ~3 $\log_{10}$ reductions in CFU/mL between 24 and 48 h.
Lenhard	*In vitro*	HFIM	336h	8/4 g ampicillin-sulbactam q8h	Bacterial eradication by 144 h, albeit with killing over the first 72 h that was slower

(2017)[122]					than that with the ampicillin-sulbactam double combinations.
				2 h meropenem q8h, with a 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 h meropenem q8h, with a 3-h infusion	Sustained bactericidal activity
				3.33 mg/kg polymyxin B, then 1.43 mg/kg q12h + 2 h meropenem q8h with 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	24h	1 g meropenem with 3-h infusion + 1 mg/L colistin	> 3 log_{10} bacterial killing, better bacterial killing compared to monotherapy
				2 g meropenem with a 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, with a 4-h infusion	$\%fT_{>MIC}$ 40% = 69% (MIC 16 mg/L)
				2 g meropenem q8h, with a 4-h infusion	$\%fT_{>MIC}$ 40% = 100% (MIC 16 mg/L)
Nicholson (2009)[124]	*In vivo*	Prospective, cohort	-	1 g doripenem q8h, with 4-hr infusion	Overall microbiologic 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, with a 3-hour infusion	$\%fT_{>MIC}$ 40% =98.8% (MIC 4 mg/L)
				2 g meropenem q8h, with a 3-hour infusion	$\%fT_{>MIC}$ 40% = 99.9% (MIC 4 mg/L)
Jaruratanasirikul (2016)[126]	*In silico*	MCS	-	1g sulbactam q6h, with a 4-hour infusion	$\%fT_{>MIC}$ 60% = 75.7% (MIC 16 mg/L)
				2g sulbactam q8h, with a 1-hour infusion	$\%fT_{>MIC}$ 60% = 52.9% (MIC 16 mg/L)
				2g sulbactam q8h, with a 4-hour infusion	$\%fT_{>MIC}$ 60% = 81.6% (MIC 16 mg/L)
				2g sulbactam q6h, with a 1-hour infusion	$\%fT_{>MIC}$ 60% = 81.3% (MIC 16 mg/L)
				2g sulbactam q6h, with a 4-hour infusion	$\%fT_{>MIC}$ 60% = 93.5% (MIC 16 mg/L)
				3g sulbactam q8h, with a 1-hour infusion	$\%fT_{>MIC}$ 60% = 78.9% (MIC 16 mg/L)

			3g sulbactam q8h, with a 4-hour infusion	%$fT_{>MIC}$ 60% = 89.2% (MIC 16 mg/L)
			3g sulbactam q6h, with a 1-hour infusion	%$fT_{>MIC}$ 60% = 86.9% (MIC 16 mg/L)
			3g sulbactam q6h, with a 4-hour infusion	%$fT_{>MIC}$ 60% = 98.0% (MIC 16 mg/L)
			4g sulbactam q8h, with a 1-hour infusion	%$fT_{>MIC}$ 60% = 82.8% (MIC 16 mg/L)
			4g sulbactam q8h, with a 4-hour infusion	%$fT_{>MIC}$ 60% = 92.6% (MIC 16 mg/L)
Xie (2014)[127]	*In silico*	MCS	100 mg tigecycline q12h	CFR 54.67% (skin and soft tissue infection)
		-		CFR 48% to 88% (intra-abdominal infection)

q8h, every 8 hours; q12h, every 12 hours, CFU, colony forming unit; PTA, probability of target attainment; HFIM, hollow-fibre infection model; PD, pharmacodynamic; MCS, Monte-Carlo simulation; %*T*>MPC, percentage of time that the drug concentrations exceeded the mutant prevent concentration; %$fT_{>MIC}$, percentage of time that the free drug concentration remains above the MIC of an offending pathogen during a dosing interval; AUBC, area under the bactericidal curve; fC_{ss}, fraction of the steady-state concentration; fC_{max}, maximal unbound drug concentration; MIC, minimum inhibitory concentration; CFR, cumulative fraction response (probability of target attainment for a specific drug dose, according to a MIC distribution of a specific microorganism).[128]

Table 4: The PK/PD index and the optimal magnitude of antibiotics against MDR *A. baumannii.*

Antibiotic	Study model	PK/PD index	PK/PD index magnitude for optimal antimicrobial activity	References
Sulbactam	Neutropenic murine thigh infection model	% $fT_{>MIC}$	>60[@]	[129]
	Neutropenic murine lung infection model		>40[@]	
Colistin	Neutropenic murine lung infection model	*f*AUC/MIC	8.18-42.1[#]	[131]
	Neutropenic murine thigh infection model		6.98-13.6[#]	
	Neutropenic murine thigh infection model		7.4-17.6[*]	[101]
Carbapenem	Neutropenic murine thigh infection model	% $fT_{>MIC}$	47.5	[135]
Fosfomycin	*In vivo*, prospective cohort study	% $fT_{>MIC}$	60-70	[136]
Tigecycline	*In silico* population PK model (for complicated skin and skin-structure infection)	*f*AUC/MIC	17.9	[137]
	In silico population PK model (for complicated skin and skin-structure infection)		6.96	[138]

Abbreviations: *f*AUC/MIC, the ratio of the area under the concentration-time curve during a 24-hour period to MIC; % $fT_{>MIC}$, percentage of time that the free drug concentration remains above the MIC of an offending pathogen during a dosing interval; PK/PD, pharmacokinetic/pharmacodynamics; [#]1-log kill; *2 -log kill [@]3-log kill.

Table 5: Microbiological susceptibility, recommended doses and administration of antibiotics for the treatment of MDR *A. baumannii.*

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

Table 6: Microbiological susceptibility of MDR *A. baumannii* to new antibiotics.

Antibiotic	Antimicrobial class	MIC_{90} against MDR *Acinetobacter* spp (mg/L)	References
Ceftazidime/avibactam	Cephalosporin/beta-lactamase inhibitor combination	>32	[150, 151]
Cefepime/zidebactam		>32	[152, 153]
Imipenem/relebactam	Carbapenem/beta-lactamase inhibitor combination	>32	[154, 155]
Meropenem/vaborbactam		>32	[156]
Aztreonam/avibactam	Monobactam/beta-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 sulphone inhibitor combination	≤8	[172]
Meropenem/LN-1-255		≤8	[172]
Imipenem/ WCK 4234	Carbapenem/ beta-lactamase inhibitor	≤2	[173]
Meropenem/ WCK 4234		≤2	
Sulbactam/ ETX2514	Beta-lactam/beta-lactamase inhibitor combination	4	[174]
Delafloxacin	Fluoroquinolone	≤16	[175, 176]
WFQ-228	Fluoroquinolone	1	[177]
TP-6076	Fluoroquinolone	0.008 -0.5	[178]
SPR741/rifampin	polymyxin-B-derived molecule	0.5	[179, 180]

MDR, multi-drug resistant; MIC_{90}, the minimum inhibitory concentration required to inhibit the growth of 90% of the bacteria.

Table 7: The PK/PD index and the optimal magnitude for novel agents with in vitro activity against MDR *A. baumannii.*

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

Abbreviations: *f*AUC/MIC, the ratio of the area under the concentration-time curve during a 24-hour period to MIC; % $fT_{>MIC}$, percentage of time that the free drug concentration remains above the MIC of an offending pathogen during a dosing interval; %$T>C_T$, time above the critical threshold; PK/PD, pharmacokinetic/pharmacodynamics; N/A, not available

[a] Plasma *f*AUC/MIC target; [b] Epithelial lining fluid (ELF) *f*AUC/MIC target; #1-log kill; *2 -log kill