

The challenges of difficult-to-treat *Acinetobacter* infections

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SUMMARY Infections due to *Acinetobacter* spp. are among the most difficult to treat. Most are resistant to standard antibiotics, and there is difficulty in distinguishing colonizers from pathogens. This mini-review examines the available antibiotics that exhibit activity against these organisms and provides guidance as to which cultures are relevant and how to treat active infections. Antibigrams describing resistance mechanisms and the minimum inhibitory concentration (MIC) are essential to determine which agent or combination of agents should be used after confirmation of infection, utilizing clinical parameters and biomarkers such as procalcitonin. Directed therapy should be prompt as despite its reputation as a colonizer, the attributable mortality is high. However, although combination therapy is advised, no specific combination has definite evidence of superiority.

KEYWORDS *Acinetobacter calcoaceticus*, hospital infections, surveillance studies, antibiotics, antimicrobial combinations

INTRODUCTION

The *Acinetobacter calcoaceticus/baumannii* (Acb) complex (ABC), of which *A. baumannii* (AB), *Acinetobacter pittii*, *Acinetobacter nosocomialis*, and *Acinetobacter calcoaceticus*, account for about 90% of clinical infections, is one of the most important hospital-acquired (HA) pathogens. These organisms have been designated as priority 1 critical pathogens that can cause life-threatening infections that are particularly difficult-to-treat (DTR) (1–3). DTR AB is defined by intermediate or full resistance to all

Editor Graeme N. Forrest, Rush University Medical Center, Chicago, Illinois, USA

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Guy A. Richards and Adrian J. Brink contributed equally to this article. Author order was determined by who suggested and initiated the review.

The authors declare no conflict of interest.

Ed. Note: The submission of this paper was coordinated by CMR Global Advisory Board member Vindana Chibabhai. The Global Advisory Board, independent of the peer review process, provides strategic direction for the journal in covering topics of both worldwide and regional interest. For more information, see the [Editor in Chief's 2024 editorial](#).

Published 18 November 2024

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agents in the carbapenem, β -lactam, and fluoroquinolone categories, not only because of intrinsic resistance but its ability to acquire new resistance determinants to most currently used antibiotics. Susceptibility results for ≥ 1 carbapenem, ≥ 1 extended-spectrum cephalosporin, and ≥ 1 fluoroquinolone are required to determine DTR status. The global prevalence of multidrug-resistant (MDR) strains in hospital-acquired pneumonia (HAP) and ventilator-associated bacterial pneumonia (VABP) due to AB is 79.9% (4).

MECHANISMS OF RESISTANCE

Antibiotic resistance can be conferred through three main mechanisms, i.e., control of antibiotic transportation through the outer and inner lipopolysaccharide membranes (reduction of porin permeability or increased efflux), modification of antibiotic targets, and enzymatic inactivation. The latter mainly involve beta-lactamases of Ambler classes A, B, and D (5). The resistance mechanisms for beta-lactams are inclusive of the following: (6)

Carbapenemase production [Class A. serine carbapenemases (blaKPC, blaGES), Class B. metallo- β -lactamases (blaNDM, blaIMP, blaVIM, and blaSIM), and Class D. oxacillinase-type (blaOXA-23, blaOXA-24/40 cluster, blaOXA-58, blaOXA-51 cluster, blaOXA-48, and blaOXA-235)], conferring carbapenem resistance.

Extended-spectrum β -lactamase (ESBL) production: (blaTEM-92, blaSHV, blaGES-11, blaGES-14, blaPER-1, blaPER-7, and blaVEB-1) conferring β -lactam resistance.

Intrinsic resistance by the encoding gene blaADC (formerly known as blaAmpC), (class C) often accompanied by porin deletion.

Porin-mediated: (low-permeability outer membrane protein A (OmpA) deletion increases the susceptibility of *Acinetobacter* spp. and may be involved in efflux, but it does enable uptake of molecules like sulbactam and imipenem (7).

Efflux pumps (AdeABC, AdeDE, AdeFGH, and AdeIJK), (8) which predispose to β -lactam (piperacillin, cefepime, and ceftazidime) (and extend to fluoroquinolone &/or aminoglycoside) resistance. AB, while encoding for a high number of MEX genes, expresses only the adeABC pump (in more than 80% of isolates), which along with a porin-mediated decrease in permeability leads to carbapenem resistance (9).

In addition to this array of beta-lactam resistance mechanisms, AB can become resistant to polymyxins (including hetero-resistance) due to target mutations, i.e., abnormalities of lipid A and lipopolysaccharides (mutations in PmrC, PmrB, or lpx genes) (10, 11). Furthermore, AB produces biofilms on medical devices and can survive environmental desiccation for weeks with transmission through fomites (12). Another contributing factor to its success as a pathogen is its ability to form a mucoid phenotype through capsular enhancement, which influences virulence and fitness, protecting against immune recognition and increasing clinical severity (13).

SURVEILLANCE OF RESISTANT ORGANISMS

Whereas most organisms have one or two predominant resistance mechanisms, AB organisms have many due to genetic plasticity, with 64.6% of isolates extensively drug-resistant (XDR) or pan-drug-resistant (PDR) in European countries and 73.1%–80.6% in Western Asian and South American countries (14). In a large South African surveillance study conducted over 2 years, 2,000 AB isolates were selected for sensitivity testing from a total of 4,822 isolates (15). Phenotypic characterization was performed using matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS), antimicrobial susceptibility testing was evaluated using the Microscan Walkaway System with the NM44 card, and colistin susceptibility by the SensiTitre instrument using the FRCOL panel (vision instrument as automated reading), and interpretation of susceptibility breakpoints using the Clinical Laboratory Standards Institute (CLSI) guidelines. Polymerase chain reaction (PCR) was performed on all isolates for the *mcr* 1–5 plasmids, and whole-genome sequencing (WGS) was performed on 24 isolates that were resistant to colistin according to the minimum inhibitory concentration (MIC) results (15).

Seventy-five percent of all organisms were classified as XDR, sensitive only to colistin (15). Of these, 88% were resistant to the carbapenems (meropenem specifically) and 82% to third-generation cephalosporins. The *mcr* 1–5 plasmid-mediated resistance genes were however not detected, and similarly WGS on the 24 isolates did not identify known mechanisms of chromosomal resistance. The majority of these patients were aged <1 year, and the overall, all-cause mortality was 36%.

The Department of Health of South Africa has commissioned a surveillance survey that examined all of the WHO Priority and Watch organisms that have been included in a database available to the medical community. This has been created in the form of a diagrammatic system that gives a national overview for each organism as well as for individual provinces. Figure 1 gives the national data for *Acinetobacter* specifically.

COLONIZATION VERSUS INFECTION

Because AB is a frequent colonier and this organism frequently affects the sickest patients in the ICU, or debilitated patients in the general wards, the attributable mortality is difficult to quantify; however, it appears to be considerable, ranging from 8.4% to 36.5%, and as such, this decision is critical in order for those patients infected to be treated promptly (16). Prior to initiating therapy, it should be determined if the culture was from a sterile site or not. If from a nonsterile site such as lung or skin, this has a high probability of being a colonizer, and assessment for clinical features of infection, biomarker trends (specifically procalcitonin), and imaging is essential prior to initiating antibiotic therapy. This should also be performed in immunosuppressed patients,

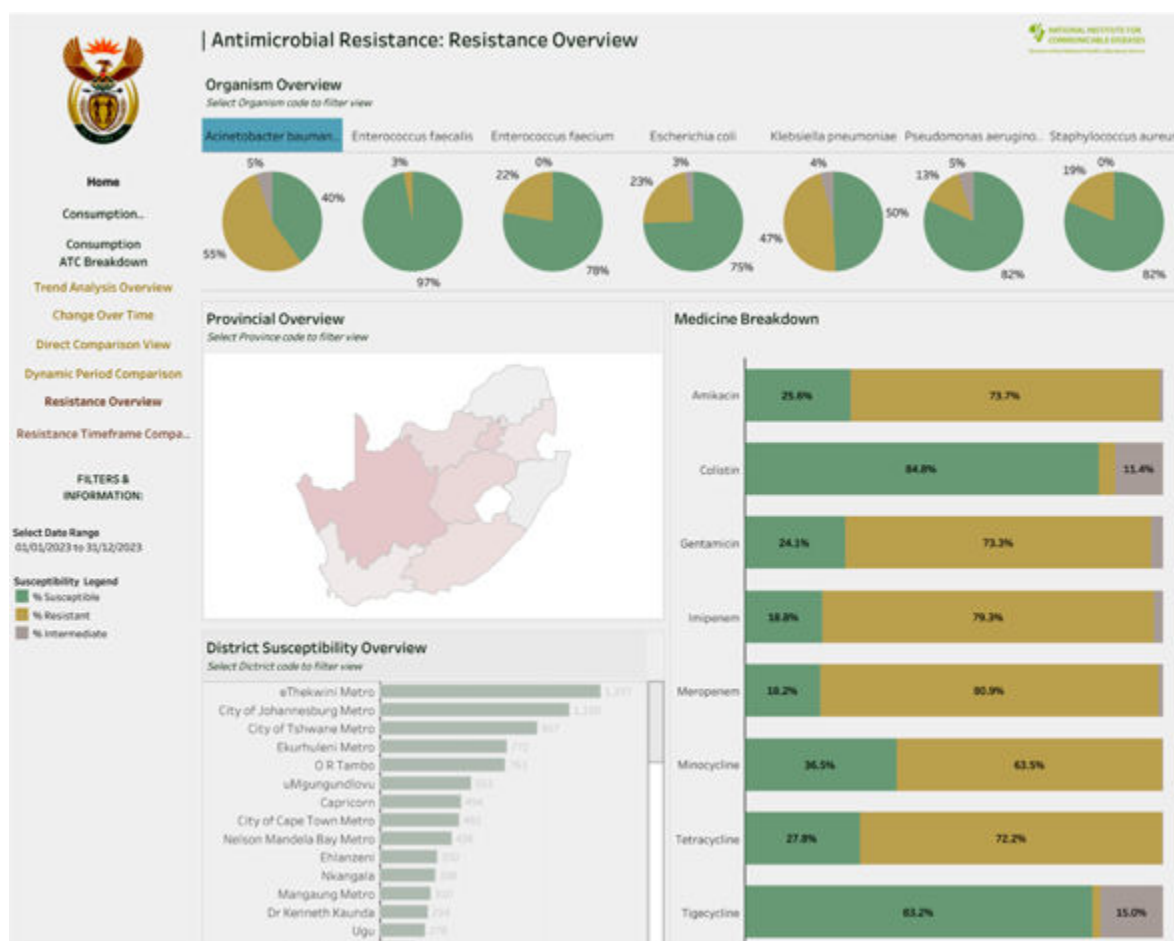


FIG 1 National Surveillance database of *Acinetobacter* Resistance in South Africa. (National Surveillance Centre, Antimicrobial Stewardship Dashboard, National Institute of Communicable Diseases, <https://www.nicd.ac.za/>, reprinted with permission from the NDOH.)

although the threshold for initiating antibiotics in this setting therapy may be lower (17). This is similar for cultures from the urinary tract, but again, trends in biomarker profiles and clinical signs of infection should be sought. Conversely, if the culture is from a sterile site such as blood, CSF, or pleura, therapy should be initiated, although if the source of a blood culture is considered to be from an indwelling device, then removal with close monitoring of the procalcitonin trend and clinical features can help determine if therapy is necessary. If these are positive, and there are signs of infection, remove the device and treat (17).

ANTIBIOTICS ACTIVE AGAINST *ACINETOBACTER* SPP.

There is no specific standard of care for the treatment of these organisms, and there are no comparative randomized controlled trials that can assist in deciding on which antibiotic or combination of antibiotics to use (Table 1). It is however recommended that combinations are used even if the organism is sensitive to a single agent (18).

Sulbactam

High-dose sulbactam is an irreversible competitive β -lactamase inhibitor that, although the precise mechanism of action is uncertain, appears to involve saturation of penicillin-binding proteins (PBP) 1 and 3 (19).

Based on meta-analyses, it has been approved by the Food and Drug Administration (FDA) and recommended by the Infectious Diseases Society of America (IDSA) as a therapy for treatment of DTR or colistin-resistant AB (CRAB) in combination with other agents. Older studies have demonstrated the efficacy and safety of ampicillin/sulbactam in MDR AB infections (18, 20), and the IDSA guideline recommends that high-dose ampicillin/sulbactam, 18–27 g total, (6–9 g of the sulbactam component) by extended or continuous infusion be included as part of the treatment regime. The (CLSI susceptibility breakpoint of 4 mg/L for sulbactam (i.e., 8/4 mg/L ampicillin/sulbactam) is appropriate

TABLE 1 Agents active against difficult-to-treat *Acinetobacter calcoaceticus* complex

Antibiotic	Dose/administration	Breakpoint $\mu\text{g/mL}$	Use
Sulbactam	6–9 g sulbactam component	≤ 4 Possibly up to 16 $\mu\text{g/mL}$ with infusion of 9 g dose (PD data only ^a)	Combinations with ampicillin, polymyxin B, minocycline, tigecycline, eravacycline, or cefiderocol.
Ampicillin/ sulbactam	18–27 g total (6–9 g sulbactam)	$\leq 8/4$ with intermittent infusion	High dose and by infusion
Sulbactam /durlobactam	2 g 6 hourly (1.0 g of each drug)	$\leq 4/4$	Monotherapy
Polymixins	Load with 300 mg colistin base activity (CBA)	< 2	Combination therapy as per the text
Colistin	(~9 million IU) over 0.5–1 hours with the first maintenance dose 12–24 hours later 300–360 mg CBA (~9–10.9 million IU) daily, in two divided doses over 0.5–1 hour at 12-hour intervals		
Polymixin B	Load with 2.0–2.5 mg/kg (20,000–25,000 IU/kg) over 1 hour; maintenance of 1.25–1.5 mg/kg (12,500–15,000 IU/kg) 12 hourly over 1 hour	< 2	Combination therapy as per the text
Tetracyclines	400 mg daily (possibly 700 mg load and then 350 mg 12 hourly	≤ 4 (possibly 1) see the text	Combination see the text
Minocycline	200 mg load then 100 mg 12 hourly	No data	Combination see the text
Tigecycline	1 mg/kg 12 hourly	No data	For situations where minocycline or tigecycline are inactive
Eravacycline			Combinations only
Cefiderocol	2 g 8 hourly	≤ 4	Only if no other options
Fosfomycin	12–24 g/day	No data	

^aReference 14, 15.

^bNo susceptibility data $\leq 2 \mu\text{g/mL}$ are considered intermediate.

for intermittent dosing, but more resistant organisms could be targeted by increasing the dose or administering the drug by continuous infusion. Infusions of 9 g every 8 hours by prolonged infusion could provide 90% or greater pharmacodynamic (PD) target attainment (PTA) for a sulbactam MIC of 16 mg/L (21). This is not a CLSI recommendation but is supported by experimental data, which provide support for the dose recommended by the IDSA guideline (18, 21).

The IDSA guideline further states that even if the organism is resistant, regimes containing high-dose sulbactam may still be effective due to its ability to saturate PBP targets (18). Additional agents that could be considered in combination with sulbactam include polymyxin B, minocycline, tigecycline, eravacycline, or cefiderocol.

Recently, sulbactam durlobactam has been shown to be an effective agent for the treatment of CRAB. In 2022, a study of 5,032 clinical isolates (96.8% CRAB) from 33 countries over 2016–2021 showed that the overall MIC₅₀ and MIC₉₀ were 1 and 2 µg/mL, respectively, for all isolates. Of interest, the durlobactam at 4 µg/mL decreased the sulbactam MIC₅₀ eightfold (from 8 to 1 µg/mL) and the MIC₉₀ 32-fold (from 64 to 2 µg/mL) for all isolates (22), and the CLSI has recently approved a breakpoint of 4/4 µg/mL (23). In the ATTACK study performed in 16 countries and 59 sites, the efficacy of SD at a dose of 2 g 6 hourly (1.0 g of each drug) or colistin (2.5 mg/kg) over 30 minutes every 12 hours for 7–14 days was evaluated for VABP, HAP, ventilated pneumonia, or blood stream infection (BSI) caused by the ABC complex. Each group received imipenem in addition as background therapy. One hundred and twenty-five of 181 had confirmed carbapenem-resistant ABC isolates, and 28-day all-cause mortality was 12 (19%) of 63 in the sulbactam durlobactam group and 20 (32%) of 62 in the colistin group, a difference of –13.2% (95% CI –30.0 to 3.5), which met the criteria for noninferiority (24). The former was however significantly less nephrotoxic. Given the limited available data, however, it should be used in combination with other agents (see below).

The polymyxins

Until recently, the polymyxins (polymyxin B and colistin (polymyxin E)) have been two of the only agents to which the organism has retained susceptibility. Due to more reliable pharmacokinetics (PK), polymyxin B has been the preferred choice for many clinicians (25). Susceptibility to colistin is defined by the CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) as an MIC of <2 mg/L, whereas resistance is defined as an MIC of >4 and >2 mg/L by the two organisations. Similar targets are recommended for polymyxin B; however, it is possible that the latter may be less toxic (26, 27).

Polymyxin-resistant AB strains currently represent a significant public health threat. As with other antibiotics, resistance to the polymyxins has also increased, with global rates as high as 11.2% in Southeast Asia, and with even higher rates in the Eastern Mediterranean (28). According to a recent systematic review and meta-analysis, the global prevalence of resistance to colistin among AB was 4% (95% CI 3–5%), which has increased significantly from 2% before 2011 (11).

Given the fact that the polymyxins were re-introduced relatively recently because no other agents were available to treat DTR Gram-negatives, knowledge of their PK and pharmacodynamic (PD) properties is incomplete (29). There is also confusion regarding the units used to define the dose which are either international units, milligrams of colistimethate (CMS), (the inactive prodrug), or as colistin base activity (CBA) in milligrams (30–32). As such, the dose has been difficult to determine, but guidelines recommend a loading dose of 300 mg CBA (approximately 9 million IU) infused over 0.5–1 hours with the first maintenance dose 12–24 hours later. Maintenance with normal renal function should be 300–360 mg CBA (9–10.9 million IU) daily, divided into two and infused over 0.5–1 hour at 12-hour intervals (25). The recommended dose for polymyxin B is a loading dose of 2.0–2.5 mg/kg (which is equivalent to 20,000–25,000 IU/kg) over 1 hour and maintenance of 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg) 12

hourly infused over 1 hour (25). The doses for both for patients with renal dysfunction should be guideline-directed (25).

A recent study determined that no dose regimen was able to achieve the therapeutic target if the MIC was >1 for VABP and HAP, but also that a loading dose was critical to achieve targets at other MICs (33, 34). This might be particularly so for pulmonary infections because absorption of polymyxin B to the lung and extracellular lining fluid is poor (35).

Overall, the efficacy of colistin in MDR organisms (MDRO) is reasonable despite the difficulty in achieving PK targets. In a small study, microbiological eradication was achieved in only 42.9%, but despite this, a favorable clinical response was achieved in 75%, the former possibly because of persistent colonization by AB and *Pseudomonas aeruginosa* (36). It is possible that for VABP with organisms that have an MIC >2 mg/L, that nebulized colistin may be of benefit, although no study has conclusively proven this (37).

Tetracycline derivatives: minocycline, tigecycline, and eravacycline

Minocycline is a semisynthetic tetracycline derivative, which has activity against AB and which has FDA approval for treatment of susceptible strains (38). Susceptibility ranges from 67.3 to 72.7%; however, at the recommended dose of 400 mg daily, the actual breakpoints are uncertain (39, 40). The CLSI breakpoint is stated to be 4 mg/L; however, recently a new breakpoint of 1 mg/L for the same dose has been estimated using PK/PD data (41). Similarly, when a 1-log kill PK/PD target was assessed, more than 90% target attainment was only achieved for isolates with minocycline MICs ≤ 0.5 mg/L (25, 28), which is problematic when one considers that ABC isolates, relative to other AB, have MICs eightfold higher (39, 42). If the breakpoints of ≤ 1 were applied, only in the region of 40% would they be sensitive (10). As such, this drug is seldom used as monotherapy but rather as a second or third agent. According to PD data, it is probable that higher doses (700 mg loading dose followed by 350 mg every 12 hours), in combination with other agents such as high-dose ampicillin/sulbactam and polymyxin B, would be more effective, given the sensitivity data (43).

Tigecycline is a third-generation tetracycline with modifications that increase its affinity for ribosomes, decrease its enzymatic degradation and its affinity for efflux pumps, and overcome other resistance mechanisms such as target modification and DNA gyrase mutations (44). Given its lipid solubility, it does not have recognized CLSI or EUCAST breakpoints, but it is likely that if MIC values of 1–2 mg/L are achievable, that this could indicate susceptibility. In an evaluation of the activity of 18 agents against AB, most had high-level resistance, whereas it was moderate for tigecycline at 12% and low for colistin at 3% (45).

Doses should generally exceed those recommended in the package insert for Gram-negative infections, and Cunha *et al.* recommended a 200–400 mg load and then 200 mg daily, given that the half-life is in the region of 42 hours (46). Alternatively, a 200 mg load followed by 100 mg 12 hourly is recommended (18).

This agent has been used in combination for treatment of CRAB infections, based on *in vitro* studies. Caution should be exercised when used for VABP as a randomized trial indicated a possible increase in mortality, although the lower package-insert-dose was utilized (47, 48). It is however effective as monotherapy for intra-abdominal infections for CRAB if the organism is determined to be sensitive (49).

Eravacycline is also a tetracycline derivative that is two to fourfold more potent than tigecycline for AB. It has been FDA-approved since 2018 for complicated intra-abdominal infection, and among others, is active against *Acinetobacter* spp. at a dose of 1 mg/kg IV, 12 hourly for a total duration of 4 to 14 days, with an MIC 50 and 90 of 0.06 and 0.5 μ g/mL, respectively (50). There are few studies documenting its efficacy against AB specifically, but if sensitive, promises to be a useful agent.

Cefiderocol

Cefiderocol is the first of the siderophore antibiotics with a wide range of efficacy against Gram-negative organisms. In the SIDERO-WT surveillance study from 2014 to 2019, the activity against CRAB was moderate to good, depending on the resistance mechanism. Sixty percent of metallo-beta-lactamase-, 95.6% of blaOXA-23-, 89.5% of blaOXA-24-, 100% of blaOXA-58-producing isolates, and 95.5% of carbapenemase-negative, meropenem-non-susceptible isolates, were susceptible at an MIC $\leq$ 4 mg/L. It was inactive, however, against ABC, PER, or VEB β -lactamases (51). Despite this, there is some concern that for an undefined reason, mortality was higher with this agent than best available therapy (34% for cefiderocol vs 18%) in the CREDIBLE-CR study published in 2021 (52). In this study, the increased mortality was specifically driven by *Acinetobacter* infection. Mortality for *Acinetobacter* spp. overall, was 21/42 (50%) versus 3/17 (18%) and for *Acinetobacter baumannii* specifically, 19/39 (49%) versus 3/17 (18%) for cefiderocol and best available therapy, respectively. A mortality difference was also noted for polymicrobial infections of *P. aeruginosa* and *Acinetobacter* spp., whereas there was no difference when patients had no *Acinetobacter* spp. co-infections at baseline. It should be noted however that of the 150 patients who received treatment, 85 of 101 (85%) received cefiderocol monotherapy and 30 of 49 (61%) of those that received best available therapy received combination therapy.

Nevertheless, a study of 300 critically ill patients with HAP, VABP, or healthcare-associated Gram-negative pneumonia of which 47 (16%) were caused by AB, and in which patients received 3-hour infusions of cefiderocol 2 g or meropenem 2 g every 8 hours for 7–14 days (148 to cefiderocol and 152 to meropenem), showed non-inferiority of the former. All-cause mortality at day 14 was 12.4% (cefiderocol) and 11.6% (meropenem) (53). The meropenem comparator in this study, however, has been shown to be relatively ineffective against resistant AB. In another study of 74 consecutive patients hospitalized with VABP and BSI due to CRAB in a single center from a COVID intensive care unit, 54 (74%) received a colistin-containing regimen and 19 (26%) a cefiderocol-containing regimen. The latter arm, which included cefiderocol and fosfomycin in combination, was independently, positively associated with 30-day survival, as confirmed by propensity score analysis (54). In a systematic review and meta-analysis in which 530 articles were screened, and in which six studies [one randomized controlled trial (RCT) (52) and five observational studies comprising 561 patients and including 247 cefiderocol-based and 314 non-cefiderocol-based regimens], cefiderocol did not significantly reduce in-hospital mortality relative to the colistin-based regimens, but the confidence intervals around the effect estimate did include clinically important benefit ($N = 5$; OR 0.64; 95% CI 0.40–1.04; $I^2 = 57.5\%$) (55). If only the observational studies, which provided adjustment for confounders, were considered, a lower risk of mortality was found ($N = 4$; OR 0.53; 95% CI 0.39–0.71; $I^2 = 0.0\%$). Additionally in a recent prospective, observational study of 90 patients utilizing propensity score analysis, in which there was an overall mortality of 34 (38%) patients, clinical failure was lower in the cefiderocol group, compared to the colistin group (25% vs 48%, respectively), and on multivariate analysis, along with other factors, cefiderocol-based first-line regimens (aHR = 0.38, 95% CI = 0.17–0.85, $P = 0.02$) strongly reduced failure risk ($I^2 = 0.0\%$) (56). Finally, in a systematic review with meta-analysis comprising six observational studies and 251 and 372 patients in the cefiderocol and colistin groups, respectively, the former had lower all-cause (RR = 0.71, 95% CI: 0.54–0.92, $P = 0.01$) and 30-day mortality (RR = 0.64, 95% CI: 0.43–0.95, $P = 0.03$) but not at 14 days or 28 days (57). The benefit seemed, on subgroup analysis, to be due to an increased effect with blood stream infection, but not with VAP.

Given the conflicting results of available studies, cefiderocol should only be used in combination with other agents active against the specific organism or when there has been no response to other agents (18).

Fosfomycin

AB is intrinsically resistant to fosfomycin through a recently described efflux mechanism (58) and as such is not recommended for use with CRAB. However, this is primarily due to a lack of data regarding its efficacy. Despite this, there have been few studies indicating that combinations do exert synergy in the treatment of AB infections, particularly because of increasing colistin resistance, as described above. *In vitro* synergy studies have demonstrated a synergistic effect of cefiderocol in combination with fosfomycin or ceftazidime–avibactam for some strains of cefiderocol-resistant CRAB (59). Lim et al., have, in addition, demonstrated that in a hollow fiber model, at least fosfomycin /sulbactam combinations could be effective for treatment of CRAB (60). In the clinical studies, the dose has varied from 12 to 24 g /day in two to three divided doses according to the severity of infection, but it is uncertain as to how much is required when used for its synergistic properties. This agent might become an important component of combination therapy in an era of increasing resistance; however, there are not enough data to endorse using this drug for treatment of life-threatening infections, unless there are no other options.

Carbapenems

Carbapenems should not be used as monotherapy, and in fact, the era of polymixin–carbapenem combinations as the gold standard is over, as recent studies indicate that addition of the carbapenem to colistin makes no difference to the outcome (10, 61, 62). If these agents are used at all, it should be in the form of triple therapy, inclusive of agents known to be active against AB.

Aminoglycosides

These agents may be of value in select situations in combination with other agents if the organism is susceptible, but because of very high resistance rates, including in South Africa, where in 2023, the resistance to gentamicin was 73% overall (Fig. 1). They also penetrate the lungs poorly and have a range of side effects that limit their use to a few cases only (63, 64).

Rifampicin/rifampin

As with the carbapenems, it was hoped that rifamycin compounds would exert synergy with colistin against AB infections. This has not however been the case, and there is probably no role for these agents (18).

COMBINATION THERAPIES

Given the paucity of agents active against this organism, various combinations have been tried in a search for a synergistic clinical effect (Table 2). Most of the studies have been small and have not conclusively shown benefit. As mentioned above, the IDSA has recommended that ampicillin–sulbactam (itself a combination) be used as a backbone for therapy to which additional agents could be added. In a small study of 39 patients with VAP caused by colistin-sensitive CRAB, 19 received colistin only and the others colistin plus ampicillin sulbactam, with early cure rates of 15.8% and 70%, respectively ($P = 0.001$) (65). On multiple regression, the combination (odds ratio [OR]: 43.6, 95% CI: 3.594–530.9) was independently associated with a favorable clinical response, and this was associated with survival benefit and discharge from the ICU (OR: 244.4, 95% CI: 2.151–27,850.9) (65).

In a very detailed systematic review and network meta-analysis consisting of 18 studies and 1,835 patients (seven RCTs and 11 retrospective studies), Liu et al. (66), demonstrated that ≥ 6 g daily of sulbactam, combined with another agent (levofloxacin or tigecycline), was significantly more effective in terms of clinical improvement than colistin and rifampicin (RR 2.33, 95% CI 0.70–7.77), colistin and fosfomycin (RR

TABLE 2 Combination therapies^a

Combination	References
Ampicillin/sulbactam + levofloxacin	(18, 66, 67)
+tigecycline	(66, 68)
+colistin	(65, 68)
+cefiderocol	(56)
Colistin/polymyxin + tigecycline	(68, 69)
Sulbactam durlobactam +imipenem	(17, 18, 24, 70)
+tigecycline	(71)
Tigecycline +sulbactam	(71)
Cefiderocol +tigecycline	(55, 56, 69, 72)
+colistin	(53, 68)
+ampicillin sulbactam	(56)
+meropenem	(56)
+fosfomycin	(54, 56)

^aPlease note that none of these combinations have been proven to be superior, and certain agents such as fosfomycin are not recommended by the IDSA unless as a third agent where nothing else is available (18).

2.77, 95% CI 0.95–8.11), colistin plus high-dose sulbactam (RR 2.92, 95% CI 1.06–8.07), colistin monotherapy (RR 2.99, 95% CI 1.08–8.24), colistin plus levofloxacin, tigecycline or others, (RR 3.06, 95% CI 1.13–8.29), or high-dose sulbactam with a carbapenem (RR 3.37, 95% CI 1.15–9.85). In terms of clinical cure, the high-dose sulbactam plus levofloxacin or tigecycline were the highest ranked when compared with colistin and carbapenems (RR 2.19, 95% CI 0.76–6.34), colistin and high-dose sulbactam (RR 2.30, 95% CI 0.79–6.66), colistin monotherapy (RR 2.95, 95% CI 1.03–8.40), and colistin with one additional antibacterial agent (levofloxacin, tigecycline, or others; RR 3.06, 95% CI 1.13–8.29). There were however no significant differences in mortality with the various drug regimens, and no drug regimen actually reduced mortality. The quality of the studies also varied with none of the RCTs reporting randomization methods, and two were single-blinded and three open-label. The observational studies were all evaluated to be of medium quality, and of the RCTs, three were considered to be at low risk and two, high risk of bias.

Another network meta-analysis and systematic review, comprising 23 studies and 2,118 patients, showed reduced mortality with sulbactam monotherapy or in combination with another agent, relative to polymyxin- or tetracycline-based regimens (67). Other studies have not demonstrated superiority over colistin alone or in combination; however, they were small and difficult to interpret (18).

In the ATTACK trial, sulbactam durlobactam was used in combination with imipenem, and whereas microbiological studies cast doubt on the contribution of the latter (24), another study of 109 CRAB isolates did indicate that carbapenem lowers the MIC of the sulbactam durlobactam (70). It is possible that combinations with other agents such as tigecycline may be a better option (71). At this time, additional studies are necessary to determine whether sulbactam durlobactam should be used in combination or not, but until then combinations are recommended (18, 63).

Combinations with tigecycline are potentially useful, but only if the MIC to tigecycline is <2 mg/L. If higher, the mortality may actually be increased (73). However, this latter study utilized the standard dose of tigecycline of 100 mg load and 50 mg twice daily, and there is evidence that this is insufficient for resistant Gram-negatives (74).

In a recent propensity study, tigecycline was shown to be of benefit when added to colistin, sulbactam (ampicillin–sulbactam or cefoperazone–sulbactam), aminoglycoside, or carbapenem, in which sensitivity to tigecycline was taken to be an MIC ≤ 2 mg/L, intermediate at 4 mg/L, and resistant at ≥ 8 mg/L (68). In this study, few patients received high-dose tigecycline. Of 395 patients with Gram-negative HABP (80% with CRAB), 148 received tigecycline and 247 did not. There was a trend to decreased mortality with tigecycline, but in the propensity-matched cohort (102 patient pairs) at 28 days, patients with tigecycline had significantly lower clinical failure (46.1% vs 62.7%, *P* = 0.017)

and mortality (28.4% vs 52.9%, $P < 0.001$). Multivariate analysis indicated a protective effect against clinical failure (propensity-matched cohort: aOR 0.52, 95% CI 0.28–0.95) and all-cause mortality (original cohort: aHR 0.69, 95% CI 0.47–0.99; propensity-matched cohort: aHR 0.47, 95% CI 0.30–0.74). Kaplan–Meier survival analysis suggested significant clinical benefits when added to a colistin (log rank P value 0.005) or carbapenem (log rank P value 0.007), but not with sulbactam.

Cefiderocol could potentially be an option in combination with other agents. In the prospective observational study by Dalfino et al., described above (56), cefiderocol was administered in combination in 52.5% of patients (tigecycline, ampicillin/sulbactam, meropenem, or fosfomycin), but comparison was not made between those who received combinations or monotherapy. It is possible however that the benefit shown in the Dalfino study relative to the CREDIBLE-CR study (52), in which it was administered as monotherapy, may have been due to more than half receiving the drug in combination. *In vitro* synergism between tigecycline and cefiderocol has been demonstrated in cefiderocol-resistant and -susceptible CRAB isolates (72) and tigecycline has been frequently and successfully utilized in combination with cefiderocol (55). In a study comprising 124 patients, 79 (63.7%) with bloodstream infection, 35 (28.5%) with VAP, and 10 (8.1%) with other infections, cefiderocol-based therapy (15 as monotherapy and 32 in combination, mostly with tigecycline) was compared with colistin-based therapy (13 as monotherapy and 63 in combination, also mostly with tigecycline), and 30-day mortality was 34% versus 55.8% ($P = 0.018$), respectively (69). With inverse probability of treatment weighting analysis, cefiderocol therapy was protective (hazard ratio 0.44, 95% CI 0.22–0.66, $P < 0.001$), although microbiological failure was higher (17.4% vs 6.8%), and eight cases in this group developed resistance (69). Concern has been expressed that this might indicate ineffective therapy (18).

Fosfomycin has been utilized for synergism in a number of small studies; a retrospective evaluation of 20 critically ill patients with pan-drug-resistant (PDR) AB, primary bacteremia in Greece over a 2-year period (2020–2022) found that inclusion of fosfomycin in the combination regimen was associated with significantly better survival ($P = 0.005$) as compared to non-fosfomycin-containing regimens (75). However, in three patients, fosfomycin was part of a three-drug, in two parts of a four-drug, and in two parts of a five-drug regimen, and it would be difficult to state definitively that it was fosfomycin that improved the outcome. Finally, in an observational study of 73 patients with coronavirus disease and hospital-acquired VABP with concomitant bacteremia, regimens containing cefiderocol plus fosfomycin were independently associated with 30-day survival (54).

Early combinations that have been recommended were polymixin and rifampicin; however, RCTs of this practice have not shown benefit relative to colistin alone (76). Similarly, as mentioned above, colistin/carbapenem regimes, while having been used extensively and initially appearing to be effective, have not subsequently had this confirmed (61, 62).

THE FUTURE

Early research on the tethered macrocyclic peptide zosurabalpin, targeting the molecular complex that blocks lipopolysaccharide transport from the inner bacterial membrane to the outer membrane, has been found to have significant efficacy against CRAB and may be useful when available. It however has no activity against *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *S. aureus*, but the CRAB MIC ranged from 0.12 to 1.0 mg/L (77). Of interest, rifabutin hyperactivity against CRAB has been noted following culture in nutrient-limited media, in which this enhanced efficacy occurs via a Trojan horse mechanism. This may have relevance in future in the development of new agents (78). New B-lactam–B-lactamase inhibitor combinations with activity may be found, as with sulbactam durlobactam, which has been mentioned above, and cefepime–zidebactam. Other ultra broad-spectrum B-lactamase inhibitors could also be useful (79, 80). Next-generation polymyxins with activity against CRAB, and hopefully less toxicity, are

in development and may offer effective therapies in future (81). Other potential novel advances include the use of bacteriophage therapy and peptides (82). Bacteriophages have been used for many years as an option for refractory or highly resistant infections, with one of the first candidates for therapy of CRAB reported in 2010 (83). Thereafter, many studies have investigated the mechanism of lysis *in vitro*, and multiple case reports have been published, which have demonstrated efficacy in refractory infections. Bacteriophages have been used singly, as cocktails, or in combination with antibiotics (82). There are still many problems associated with their use however, primarily an absence of RCTs, that specific bacteriophages need to be developed for each organism, making empiric therapy difficult, (although cocktails do help in this regard), whether combinations with antibiotics would be the optimal approach, and whether ethical and regulatory barriers to their production can be overcome (84, 85). Antimicrobial microbicidal peptides that are produced by all organisms can be modified to eradicate resistant organisms. These studies are still at the experimental stages but do hold out hope for the future (86).

Eight international lineages (IC I–VIII) of AB have been described, and it is known that the spread of most antibiotic-resistant organisms has been shown to be associated with distinct epidemic clones that belong to these lineages. In this regard, in the future, whole-genome sequencing may provide insight into the transmission and evolutionary dynamics of AB (9). This may allow use of the clustered regularly interspaced short palindromic repeats/CRISPR-associated protein (CRISPR-Cas) system, which is a mechanism in bacteria that protects against viral and bacteriophage attacks, by its manipulation through precise genome editing (87). This has recently been explored in AB to alter its genetic profile by targeting and disrupting antimicrobial resistance genes in order to reduce virulence, pathogenicity, and biofilm formation and even to kill the bacterium (87). CRISPR can also be utilized to modify or introduce new genes into the genome of AB to reduce its ability to resist antibiotics or increase its sensitivity (87).

CONCLUSION

Surveillance is an important tool to obtain information about capsulated and hypervirulent AB strains circulating in each healthcare environment to identify and prevent outbreaks and streamline clinical care. The treatment of AB infections is becoming increasingly difficult, and new agents are urgently required to combat this scourge. In the interim, strict stewardship principles are required, concentrating on infection control and discrimination of colonizers from pathogens. The optimal regimen is uncertain but should consist of combinations, inclusive of sulbactam plus cefiderocol, polymyxin B, or tigecycline in appropriate dosing and according to the site of the infection. The doses used should be according to PK/PD principles where possible.

ACKNOWLEDGMENTS

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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REFERENCES

1. Rapid risk assessment: carbapenem-resistant *Acinetobacter baumannii* in healthcare settings – 8 December 2016. 2016. Available from: <https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-carbapenem-resistant-acinetobacter-baumannii-healthcare>. Retrieved 25 Jan 2024.
2. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M, Outtersen K, Patel J, Cavaleri M, Cox EM, Houchens CR, Grayson ML, Hansen P, Singh N, Theuretzbacher U, Magrini N, WHO Pathogens Priority List Working Group. 2018. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 18:318–327. [https://doi.org/10.1016/S1473-3099\(17\)30753-3](https://doi.org/10.1016/S1473-3099(17)30753-3)
3. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, Palmore TN, Rhee C, Klompas M, Dekker JP, Powers JH 3rd, Suffredini AF, Hooper DC, Fridkin S, Danner RL, National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH–ARORI). 2018. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. *Clin Infect Dis* 67:1803–1814. <https://doi.org/10.1093/cid/ciy378>
4. Mohd Szally Lim S, Zainal Abidin A, Liew SM, Roberts JA, Sime FB. 2019. The global prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia and its associated mortality: a systematic review and meta-analysis. *J Infect* 79:593–600. <https://doi.org/10.1016/j.jinf.2019.09.012>
5. Ruppé É, Woerther P-L, Barbier F. 2015. Mechanisms of antimicrobial resistance in Gram-negative bacilli. *Ann Intensive Care* 5:61. <https://doi.org/10.1186/s13613-015-0061-0>
6. Kyriakidis I, Vasileiou E, Pana ZD, Tragiannidis A. 2021. *Acinetobacter baumannii* antibiotic resistance mechanisms. *Pathogens* 10:373. <https://doi.org/10.3390/pathogens10030373>
7. Sugawara E, Nikaido H. 2012. OmpA is the principal nonspecific slow porin of *Acinetobacter baumannii*. *J Bacteriol* 194:4089–4096. <https://doi.org/10.1128/JB.00435-12>
8. Kornelsen V, Kumar A. 2021. Update on multidrug resistance efflux pumps in *Acinetobacter* spp. *Antimicrob Agents Chemother* 65:e0051421. <https://doi.org/10.1128/AAC.00514-21>
9. Brink AJ. 2019. Epidemiology of carbapenem-resistant Gram-negative infections globally. *Curr Opin Infect Dis* 32:609–616. <https://doi.org/10.1097/QCO.0000000000000608>
10. Shields RK, Paterson DL, Tamma PD. 2023. Navigating available treatment options for carbapenem-resistant *Acinetobacter baumannii*-calcoaceticus complex infections. *Clin Infect Dis* 76:S179–S193. <https://doi.org/10.1093/cid/ciad094>
11. Bostanghadiri N, Narimisa N, Mirshekar M, Dadgar-Zankbar L, Taki E, Navidifar T, Darban-Sarokhalil D. 2024. Prevalence of colistin resistance in clinical isolates of *Acinetobacter baumannii*: a systematic review and meta-analysis. *Antimicrob Resist Infect Control* 13:24. <https://doi.org/10.1186/s13756-024-01376-7>
12. Farrow JM, Wells G, Pesci EC. 2018. Desiccation tolerance in *Acinetobacter baumannii* is mediated by the two-component response regulator BfmR. *PLOS ONE* 13:e0205638. <https://doi.org/10.1371/journal.pone.0205638>
13. Kon H, Schwartz D, Temkin E, Carmeli Y, Lellouche J. 2020. Rapid identification of capsulated *Acinetobacter baumannii* using a density-dependent gradient test. *BMC Microbiol* 20:285. <https://doi.org/10.1186/s12866-020-01971-9>
14. Zheng Y, Xu N, Pang J, Han H, Yang H, Qin W, Zhang H, Li W, Wang H, Chen Y. 2021. Colonization with extensively drug-resistant *Acinetobacter baumannii* and prognosis in critically ill patients: an observational cohort study. *Front Med* 8. <https://doi.org/10.3389/fmed.2021.667776>
15. Perovic O, Duse A, Chibabhai V, Black M, Said M, Prentice E, Wadula J, Mahabeer Y, Han KSS, Mogokotleng R, Strasheim W, Lowe M, Jallow S, Ismail H, Germs-Sa F. 2022. *Acinetobacter baumannii* complex, national laboratory-based surveillance in South Africa, 2017 to 2019. *PLOS ONE* 17:e0271355. <https://doi.org/10.1371/journal.pone.0271355>
16. Falagas ME, Rafailidis PI. 2007. Attributable mortality of *Acinetobacter baumannii*: no longer a controversial issue. *Crit Care* 11:134. <https://doi.org/10.1186/cc5911>
17. Bartal C, Rolston KVI, Nesher L. 2022. Carbapenem-resistant *Acinetobacter baumannii*: colonization, infection and current treatment options. *Infect Dis Ther* 11:683–694. <https://doi.org/10.1007/s40121-022-00597-w>
18. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. 2023. Infectious diseases society of America 2023 guidance on the treatment of antimicrobial resistant Gram-negative infections. *Clin Infect Dis* ciad428:ciad428. <https://doi.org/10.1093/cid/ciad428>
19. Penwell WF, Shapiro AB, Giacobbe RA, Gu R-F, Gao N, Thresher J, McLaughlin RE, Huband MD, DeJonge BLM, Ehmann DE, Miller AA. 2015. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 59:1680–1689. <https://doi.org/10.1128/AAC.04808-14>
20. Jellison TK, McKinnon PS, Rybak MJ. 2001. Epidemiology, resistance, and outcomes of *Acinetobacter baumannii* bacteremia treated with imipenem-cilastatin or ampicillin-sulbactam. *Pharmacotherapy* 21:142–148. <https://doi.org/10.1592/phco.21.2.142.34114>
21. Wangchinda W, Pogue J. 2023. Sulbactam for treatment of carbapenem-resistant *Acinetobacter baumannii* 08
22. Karlosky JA, Hackel MA, McLeod SM, Miller AA. 2022. *In vitro* activity of sulbactam-durlobactam against global isolates of *Acinetobacter baumannii*-calcoaceticus complex collected from 2016 to 2021. *Antimicrob Agents Chemother* 66:e0078122. <https://doi.org/10.1128/aac.00781-22>
23. Humphries R. 2024. AST News Update January 2024: Sulbactam-Durlobactam: The “double beta-lactamase inhibitor” drug. CLSI.
24. Kaye KS, Shorr AF, Wunderink RG, Du B, Poirier GE, Rana K, Miller A, Lewis D, O'Donnell J, Chen L, Reinhart H, Srinivasan S, Isaacs R, Altarac D. 2023. Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii*–calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). *Lancet Infect Dis* 23:1072–1084. [https://doi.org/10.1016/S1473-3099\(23\)00184-6](https://doi.org/10.1016/S1473-3099(23)00184-6)
25. Tsuji BT, Pogue JM, Zavaski AP, Paul M, Daikos GL, Forrest A, Giacobbe DR, Viscoli C, Giamarelou H, Karaikos I, Kaye D, Mouton JW, Tam VH, Thamlikitkul V, Wunderink RG, Li J, Nation RL, Kaye KS. 2019. International consensus guidelines for the optimal use of the polymyxins: endorsed by the American college of clinical pharmacy (ACCP), European society of clinical microbiology and infectious diseases (ESCMID), infectious diseases society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), society of critical care

- medicine (SCCM), and society of infectious diseases pharmacists (SIDP). Pharmacotherapy 39:10–39. <https://doi.org/10.1002/phar.2209>
26. Eucast: recommendations for reference MIC-testing of colistin. Available from: https://www.eucast.org/eucast_news/news_singleview?tx_ttnews%5Btt_news%5D=171&cHash=387b192a5e9d82d2e74ae72fdb456602. Retrieved 25 Jan 2024. Accessed January 25, 2024
 27. Clinical & laboratory standards institute: CLSI guidelines. n.d. Clinical & Laboratory Standards Institute. Available from: <https://clsi.org>
 28. Pormohammad A, Mehdinejadani K, Gholizadeh P, Nasiri MJ, Mohtavinejad N, Dadashi M, Karimaei S, Safari H, Azimi T. 2020. Global prevalence of colistin resistance in clinical isolates of *Acinetobacter baumannii*: a systematic review and meta-analysis. Microb Pathog 139:103887. <https://doi.org/10.1016/j.micpath.2019.103887>
 29. Ortwin JK, Kaye KS, Li J, Pogue JM. 2015. Colistin: understanding and applying recent pharmacokinetic advances. Pharmacotherapy 35:11–16. <https://doi.org/10.1002/phar.1484>
 30. Biswas S, Brunel J-M, Dubus J-C, Reynaud-Gaubert M, Rolain J-M. 2012. Colistin: an update on the antibiotic of the 21st century. Expert Rev Anti Infect Ther 10:917–934. <https://doi.org/10.1586/eri.12.78>
 31. Pike M, Saltiel E. 2014. Colistin- and polymyxin-induced nephrotoxicity: focus on literature utilizing the RIFLE classification scheme of acute kidney injury. J Pharm Pract 27:554–561. <https://doi.org/10.1177/0897190014546116>
 32. Nation RL, Li J, Cars O, Couet W, Dudley MN, Kaye KS, Mouton JW, Paterson DL, Tam VH, Theuretzbacher U, Tsuji BT, Turnidge JD. 2015. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. Lancet Infect Dis 15:225–234. [https://doi.org/10.1016/S1473-3099\(14\)70850-3](https://doi.org/10.1016/S1473-3099(14)70850-3)
 33. Tang T, Li Y, Xu P, Zhong Y, Yang M, Ma W, Xiang D, Zhang B, Zhou Y. 2023. Optimization of polymyxin B regimens for the treatment of carbapenem-resistant organism nosocomial pneumonia: a real-world prospective study. Crit Care 27:164. <https://doi.org/10.1186/s13054-023-04448-z>
 34. Dalfino L, Puntillo F, Mosca A, Monno R, Spada ML, Coppolecchia S, Miragliotta G, Bruno F, Brienza N. 2012. High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. Clin Infect Dis 54:1720–1726. <https://doi.org/10.1093/cid/cis286>
 35. Shi R, Fu Y, Gan Y, Wu D, Zhou S, Huang M. 2023. Use of polymyxin B with different administration methods in the critically ill patients with ventilation associated pneumonia: a single-center experience. Front Pharmacol 14:1222044. <https://doi.org/10.3389/fphar.2023.1222044>
 36. Kagami K, Ishiguro N, Yamada T, Niinuma Y, Iwasaki S, Taki K, Fukumoto T, Hayasaka K, Oyama R, Watanabe T, Nishida M, Sugita J, Teshima T, Sugawara M, Takekuma Y. 2021. Efficacy and safety of colistin for the treatment of infections caused by multidrug-resistant gram-negative bacilli. J Infect Chemother 27:473–479. <https://doi.org/10.1016/j.jiac.2020.10.024>
 37. Almangour TA, Alruwaili A, Almutairi R, Alrasheed A, Alhifany AA, Eljaaly K, Alkofide H, Alhammad AM, Ghonem L, Alsharidi A. 2021. Aerosolized plus intravenous colistin vs intravenous colistin alone for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria: a retrospective cohort study. Int J Infect Dis 108:406–412. <https://doi.org/10.1016/j.ijid.2021.06.007>
 38. Yang J-L, Yang C-J, Chuang Y-C, Sheng W-H, Chen Y-C, Chang S-C. 2022. Minocycline susceptibility and *tetB* gene in carbapenem-resistant *Acinetobacter baumannii* in Taiwan. IDR Volume 15:2401–2408. <https://doi.org/10.2147/IDR.S357344>
 39. Flamm RK, Shortridge D, Castanheira M, Sader HS, Pfaller MA. 2019. *In vitro* activity of minocycline against U.S. isolates of *Acinetobacter baumannii*-*Acinetobacter calcoaceticus* species complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* complex: results from the SENTRY antimicrobial surveillance program, 2014 to 2018. Antimicrob Agents Chemother 63:e01154-19. <https://doi.org/10.1128/AAC.01154-19>
 40. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. 2019. Antimicrobial susceptibility of *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex and *Stenotrophomonas maltophilia* clinical isolates: results from the SENTRY antimicrobial surveillance program (1997-2016). Open Forum Infect Dis 6:534–546. <https://doi.org/10.1093/ofid/ofy293>
 41. Tsakris A, Koumaki V, Dokoumetzidis A. 2019. Minocycline susceptibility breakpoints for *Acinetobacter baumannii*: do we need to re-evaluate them? J Antimicrob Chemother 74:295–297. <https://doi.org/10.1093/jac/dky448>
 42. Lodise TP, Van Wart S, Sund ZM, Bressler AM, Khan A, Makley AT, Hamad Y, Salata RA, Silveira FP, Sims MD, Kabchi BA, Saad MA, Brown C, Oler RE Jr, Fowler V Jr, Wunderink RG. 2021. Pharmacokinetic and pharmacodynamic profiling of minocycline for injection following a single infusion in critically ill adults in a phase IV open-label multicenter study (ACUMIN). Antimicrob Agents Chemother 65:e01809. <https://doi.org/10.1128/AAC.01809-20>
 43. Beganovic M, Daffinee KE, Luther MK, LaPlante KL. 2021. Minocycline alone and in combination with polymyxin B, meropenem, and sulbactam against carbapenem-susceptible and -resistant *Acinetobacter baumannii* in an *in vitro* pharmacodynamic model. Antimicrob Agents Chemother 65:e01680-20. <https://doi.org/10.1128/AAC.01680-20>
 44. Sun C, Yu Y, Hua X. 2023. Resistance mechanisms of tigecycline in *Acinetobacter baumannii* Front Cell Infect Microbiol 13:1141490. <https://doi.org/10.3389/fcimb.2023.1141490>
 45. Wareth G, Linde J, Hammer P, Nguyen NH, Nguyen TNM, Splettstoesser WD, Makarewicz O, Neubauer H, Sprague LD, Pletz MW. 2020. Phenotypic and WGS-derived antimicrobial resistance profiles of clinical and non-clinical *Acinetobacter baumannii* isolates from Germany and Vietnam. Int J Antimicrob Agents 56:106127. <https://doi.org/10.1016/j.ijantimicag.2020.106127>
 46. Cunha BA, Baron J, Cunha CB. 2018. Monotherapy with high-dose once-daily tigecycline is highly effective against *Acinetobacter baumannii* and other multidrug-resistant (MDR) Gram-negative bacilli (GNB). Int J Antimicrob Agents 52:119–120. <https://doi.org/10.1016/j.ijantimicag.2018.02.011>
 47. Rao GG, Ly NS, Diep J, Forrest A, Bulitta JB, Holden PN, Nation RL, Li J, Tsuji BT. 2016. Combinatorial pharmacodynamics of polymyxin B and tigecycline against heteroresistant *Acinetobacter baumannii*. Int J Antimicrob Agents 48:331–336. <https://doi.org/10.1016/j.ijantimicag.2016.06.006>
 48. Research C for DE and. 2019. FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning. FDA.
 49. Chusri S, Singkhamanan K, Wanitsuan W, Suphasynth Y, Kositpantawong N, Panthuwong S, Doi Y. 2019. Adjunctive therapy of intravenous colistin to intravenous tigecycline for adult patients with non-bacteremic post-surgical intra-abdominal infection due to carbapenem-resistant *Acinetobacter baumannii*. J Infect Chemother 25:681–686. <https://doi.org/10.1016/j.jiac.2019.03.017>
 50. Yusuf E, Bax HI, Verkaik NJ, van Westreenen M. 2021. An update on eight “New” antibiotics against multidrug-resistant Gram-negative bacteria. J Clin Med 10:1068. <https://doi.org/10.3390/jcm10051068>
 51. Wise MG, Karlowsky JA, Hackel MA, Takemura M, Yamano Y, Echols R, Sahm DF. 2023. *In vitro* activity of cefiderocol against meropenem-nonsusceptible Gram-negative bacilli with defined β -lactamase carriage: SIDERO-WT surveillance studies, 2014-2019. Microb Drug Resist 29:360–370. <https://doi.org/10.1089/mdr.2022.0279>
 52. Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, Lodise TP, Naas T, Niki Y, Paterson DL, Portsmouth S, Torre-Cisneros J, Toyozumi K, Wunderink RG, Nagata TD. 2021. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis 21:226–240. [https://doi.org/10.1016/S1473-3099\(20\)30796-9](https://doi.org/10.1016/S1473-3099(20)30796-9)
 53. Wunderink RG, Matsunaga Y, Ariyasu M, Clevenbergh P, Echols R, Kaye KS, Kollef M, Menon A, Pogue JM, Shorr AF, Timsit J-F, Zeitlinger M, Nagata TD. 2021. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 21:213–225. [https://doi.org/10.1016/S1473-3099\(20\)30731-3](https://doi.org/10.1016/S1473-3099(20)30731-3)
 54. Russo A, Bruni A, Gulli S, Borrazzo C, Quirino A, Lionello R, Serapide F, Garofalo E, Serraino R, Romeo F, Marascio N, Matera G, Longhini F, Trecarichi EM, Torti C. 2023. Efficacy of cefiderocol- vs colistin-containing regimen for treatment of bacteraemic ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii* in patients

- with COVID-19. *Int J Antimicrob Agents* 62:106825. <https://doi.org/10.1016/j.ijantimicag.2023.106825>
55. Gatti M, Cosentino F, Giannella M, Viale P, Pea F. 2024. Clinical efficacy of cefiderocol-based regimens in patients with carbapenem-resistant *Acinetobacter baumannii* infections: a systematic review with meta-analysis. *Int J Antimicrob Agents* 63:107047. <https://doi.org/10.1016/j.ijantimicag.2023.107047>
 56. Dalfino L, Stufano M, Bavaro DF, Diella L, Belati A, Stolfa S, Romanelli F, Ronga L, Di Mussi R, Murgolo F, Loconsole D, Chironna M, Mosca A, Montagna MT, Saracino A, Grasso S. 2023. Effectiveness of first-line therapy with old and novel antibiotics in ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*: a real life, prospective, observational, single-center study. *Antibiotics (Basel)* 12:1048. <https://doi.org/10.3390/antibiotics12061048>
 57. Zhan Y, Mao W, Zhao C, Lu D, Chen C, Hu W, Yang Q. 2024. Comparison of cefiderocol and colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*: a systematic review with meta-analysis and trial sequential analysis. *BMC Infect Dis* 24:967. <https://doi.org/10.1186/s12879-024-09899-5>
 58. Sharma A, Sharma R, Bhattacharyya T, Bhandu T, Pathania R. 2017. Fosfomycin resistance in *Acinetobacter baumannii* is mediated by efflux through a major facilitator superfamily (MFS) transporter-Abaf. *J Antimicrob Chemother* 72:68–74. <https://doi.org/10.1093/jac/dkw382>
 59. Palombo M, Bovo F, Amadesi S, Gaibani P. 2023. Synergistic activity of cefiderocol in combination with piperacillin-tazobactam, fosfomycin, ampicillin-sulbactam, imipenem-relebactam and ceftazidime-avibactam against carbapenem-resistant Gram-negative bacteria. *Antibiotics (Basel)* 12:858. <https://doi.org/10.3390/antibiotics12050858>
 60. Mohd Szalily Lim S, Heffernan A, Naicker S, Wallis S, Roberts JA, Sime FB. 2022. Evaluation of fosfomycin-sulbactam combination therapy against carbapenem-resistant *Acinetobacter baumannii* isolates in a hollow-fibre infection model. *Antibiotics (Basel)* 11:1578. <https://doi.org/10.3390/antibiotics11111578>
 61. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, Skiada A, Andini R, Eliakim-Raz N, Nutman A, et al. 2018. 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* 18:391–400. [https://doi.org/10.1016/S1473-3099\(18\)30099-9](https://doi.org/10.1016/S1473-3099(18)30099-9)
 62. Kaye KS, Marchaim D, Thamlikitkul V, Carmeli Y, Chiu C-H, Daikos G, Dhar S, Durante-Mangoni E, Gikas A, Kotanidou A, et al. 2023. Colistin monotherapy versus combination therapy for carbapenem-resistant organisms. *NEJM Evid* 2:EVIDo2200131. <https://doi.org/10.1056/evidoa2200131>
 63. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, de Waele J, Daikos GL, Akova M, Harbarth S, Pulcini C, Garnacho-Montero J, Seme K, Tumbarello M, Lindemann PC, Gandra S, Yu Y, Bassetti M, Mouton JW, Tacconelli E, Rodríguez-Baño J. 2022. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect* 28:521–547. <https://doi.org/10.1016/j.cmi.2021.11.025>
 64. Najmeddin F, Shahrami B, Azadbakht S, Dianatkah M, Rouini MR, Najafi A, Ahmadi A, Sharifnia H, Mojtahedzadeh M. 2020. Evaluation of epithelial lining fluid concentration of amikacin in critically ill patients with ventilator-associated pneumonia. *J Intensive Care Med* 35:400–404. <https://doi.org/10.1177/0885066618754784>
 65. Makris D, Petinaki E, Tsolaki V, Manoulakas E, Mantzaris K, Apostolopoulou O, Sfyras D, Zakyntinos E. 2018. 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* 22:67–77. https://doi.org/10.4103/ijccm.IJCCM_302_17
 66. Liu J, Shu Y, Zhu F, Feng B, Zhang Z, Liu L, Wang G. 2021. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant *Acinetobacter baumannii* infections: a systematic review and network meta-analysis. *J Glob Antimicrob Resist* 24:136–147. <https://doi.org/10.1016/j.jgar.2020.08.021>
 67. Jung SY, Lee SH, Lee SY, Yang S, Noh H, Chung EK, Lee JI. 2017. Antimicrobials for the treatment of drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients: a systemic review and Bayesian network meta-analysis. *Crit Care* 21:319. <https://doi.org/10.1186/s13054-017-1916-6>
 68. Yang K-Y, Peng C-K, Sheu C-C, Lin Y-C, Chan M-C, Wang S-H, Chen C-M, Chen C-Y, Zheng Z-R, Feng J-Y, the T-CARE (Taiwan Critical Care and Infection) Group. 2023. Clinical effectiveness of tigecycline in combination therapy against nosocomial pneumonia caused by CR-GNB in intensive care units: a retrospective multi-centre observational study. *J Intensive Care* 11:1. <https://doi.org/10.1186/s40560-022-00647-y>
 69. Falcone M, Tiseo G, Leonildi A, Della Sala L, Vecchione A, Barnini S, Farcomeni A, Menichetti F. 2022. Cefiderocol- compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 66:e0214221. <https://doi.org/10.1128/aac.02142-21>
 70. Petropoulou D, Siopi M, Vourli S, Pournaras S. 2021. Activity of sulbactam-durlobactam and comparators against a national collection of carbapenem-resistant *Acinetobacter baumannii* isolates from Greece. *Front Cell Infect Microbiol* 11:814530. <https://doi.org/10.3389/fcimb.2021.814530>
 71. Holger DJ, Kunz Coyne AJ, Zhao JJ, Sandhu A, Salimnia H, Rybak MJ. 2022. Novel combination therapy for extensively drug-resistant *Acinetobacter baumannii* necrotizing pneumonia complicated by empyema: a case report. *Open Forum Infect Dis* 9:ofac092. <https://doi.org/10.1093/ofid/ofac092>
 72. Ni W, Wang Y, Ma X, He Y, Zhao J, Guan J, Li Y, Gao Z. 2022. *In vitro* and *in vivo* efficacy of cefiderocol plus tigecycline, colistin, or meropenem against carbapenem-resistant *Acinetobacter baumannii*. *Eur J Clin Microbiol Infect Dis* 41:1451–1457. <https://doi.org/10.1007/s10096-022-04503-7>
 73. Cheng A, Chuang Y-C, Sun H-Y, Sheng W-H, Yang C-J, Liao C-H, Hsueh P-R, Yang J-L, Shen N-J, Wang J-T, Hung C-C, Chen Y-C, Chang S-C. 2015. 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* 43:1194–1204. <https://doi.org/10.1097/CCM.0000000000000933>
 74. Han H, Qin W, Zheng Y, Cao D, Lu H, Zhang L, Cui Y, Hu Y, Li W, Guo H, Wu D, Li C, Wang H, Chen Y. 2021. High-dose versus standard-dose tigecycline treatment of secondary bloodstream infections caused by extensively drug-resistant *Acinetobacter baumannii*: an observational cohort study. *Infect Drug Resist* 14:3837–3848. <https://doi.org/10.2147/IDR.S322803>
 75. Assimakopoulos SF, Karamouzou V, Eleftheriotis G, Lagadinou M, Bartzavali C, Kolonitsiou F, Paliogianni F, Fligou F, Marangos M. 2023. Efficacy of fosfomycin-containing regimens for treatment of bacteremia due to pan-drug resistant *Acinetobacter baumannii* in critically ill patients: a case series study. *Pathogens* 12:286. <https://doi.org/10.3390/pathogens12020286>
 76. Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, Bassetti M, Malacarne P, Petrosillo N, Galdieri N, Mocavero P, Corcione A, Viscoli C, Zarrilli R, Gallo C, Utili R. 2013. 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* 57:349–358. <https://doi.org/10.1093/cid/cit253>
 77. Zampaloni C, Mattei P, Bleicher K, Winther L, Thäte C, Bucher C, Adam J-M, Alanine A, Amrein KE, Baidin V, et al. 2024. A novel antibiotic class targeting the lipopolysaccharide transporter. *Nature New Biol* 625:566–571. <https://doi.org/10.1038/s41586-023-06873-0>
 78. Luna B, Trebosc V, Lee B, Bakowski M, Ulhaq A, Yan J, Lu P, Cheng J, Nielsen T, Lim J, Ketphan W, Eoh H, McNamara C, Skandalis N, She R, Kemmer C, Lociuo S, Dale GE, Spellberg B. 2020. A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant *Acinetobacter baumannii*. *Nat Microbiol* 5:1134–1143. <https://doi.org/10.1038/s41564-020-0737-6>
 79. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. 2020. New β -lactam- β -lactamase inhibitor combinations. *Clin Microbiol Rev* 34:e00115-20. <https://doi.org/10.1128/CMR.00115-20>
 80. Lomovskaya O, Tsvikovskiy R, Sun D, Reddy R, Trovot M, Hecker S, Griffith D, Loutit J, Dudley M. 2021. QPX7728, an ultra-broad-spectrum β -lactamase inhibitor for intravenous and oral therapy: overview of

- biochemical and microbiological characteristics. *Front Microbiol* 12:697180. <https://doi.org/10.3389/fmicb.2021.697180>
81. Aslan AT, Akova M, Paterson DL. 2022. Next-generation polymyxin class of antibiotics: a ray of hope illuminating a dark road. *Antibiotics (Basel)* 11:1711. <https://doi.org/10.3390/antibiotics11121711>
 82. Zhang S, Di L, Qi Y, Qian X, Wang S. 2024. Treatment of infections caused by carbapenem-resistant *Acinetobacter baumannii*. *Front Cell Infect Microbiol* 14:1395260. <https://doi.org/10.3389/fcimb.2024.1395260>
 83. Lin N-T, Chiou P-Y, Chang K-C, Chen L-K, Lai M-J. 2010. Isolation and characterization of phi AB2: a novel bacteriophage of *Acinetobacter baumannii*. *Res Microbiol* 161:308–314. <https://doi.org/10.1016/j.resmic.2010.03.007>
 84. Choi Y-J, Kim S, Shin M, Kim J. 2024. Isolation and characterization of novel bacteriophages to target carbapenem-resistant *Acinetobacter baumannii*. *Antibiotics (Basel)* 13:610. <https://doi.org/10.3390/antibiotics13070610>
 85. Samson R, Dharne M, Khairnar K. 2024. Bacteriophages: status quo and emerging trends toward one health approach. *Sci Total Environ* 908:168461. <https://doi.org/10.1016/j.scitotenv.2023.168461>
 86. Hazam PK, Cheng C-C, Hsieh C-Y, Lin W-C, Hsu P-H, Chen T-L, Lee Y-T, Chen J-Y. 2022. Development of bactericidal peptides against multidrug-resistant *Acinetobacter baumannii* with enhanced stability and low toxicity. *Int J Mol Sci* 23:2191. <https://doi.org/10.3390/ijms23042191>
 87. Junaid M, Thirapanmethee K, Khuntayaporn P, Chomnawang MT. 2023. CRISPR-based gene editing in *Acinetobacter baumannii* to combat antimicrobial resistance. *Pharmaceuticals (Basel)* 16:920. <https://doi.org/10.3390/ph16070920>

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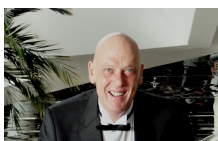
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