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REVIEW ARTICLE

Treatment Approaches for Carbapenem-Resistant *Acinetobacter baumannii* Infections

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Abstract
Carbapenem-resistant *Acinetobacter baumannii* has been associated with over three hundred thousand annual deaths globally. It is resistant to most available antibiotics and associated with high morbidity and mortality. No global consensus currently exists for treatment strategies that balance safety and efficacy because of heterogeneity of treatment regimens in current clinical practice and scarcity of large-scale controlled studies arising from difficulties in establishing robust clinical outcomes. This review outlines the epidemiology and resistance mechanisms of carbapenem-resistant *A. baumannii*, then summarizes available clinical data on each approved agent with activity against this pathogen. Emerging treatment options such as cefiderocol and sulbactam-durlobactam show promise, but their success hinges on comprehensive clinical validation and access in regions most impacted by this pathogen. New therapeutic modalities that are in various stages of clinical development are also discussed.

1 Introduction

Antimicrobial resistance is estimated to have directly caused 1.27 million deaths (i.e., deaths from infection) and indirectly contributed to 4.95 million deaths (i.e., deaths with infection) worldwide in 2019 [1]. Given the immense negative impact on human health, antimicrobial resistance has been identified as one of the top ten health challenges by the WHO [2]. Of the six leading antimicrobial-resistant pathogens associated with deaths, four are gram-negative pathogens (*Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*) [1]. Together, they account for over 600,000 annual deaths directly attributable to antimicrobial resistance globally. Carbapenem-resistant *A. baumannii* is particularly

Key Points

Carbapenem-resistant *Acinetobacter baumannii* represents a significant global health challenge as it exhibits resistance to most available antibiotics and is associated with substantial morbidity and mortality.

There is currently no global consensus on the most effective treatment strategy for *A. baumannii* infections, largely due to the limited effectiveness of available antibiotics, the heterogeneity of treatment regimens, and the scarcity of large-scale, controlled studies.

The role of new agents with activity against carbapenem-resistant *A. baumannii*, including cefiderocol and sulbactam-durlobactam, is being explored in certain high-income settings, but access remains limited in low and middle-income regions that bear most of the disease burden.

New agents with conventional as well as novel mechanisms of action are in various stages of clinical development.

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problematic in terms of lack of treatment options and has been associated with an estimated 326,000 global deaths in 2019. Many of the newer, safer treatment alternatives for carbapenem-resistant *A. baumannii* are inaccessible to the low- and middle-income regions that bear the highest burden of these infections [3]. Consequently, carbapenem-resistant *A. baumannii* continues to be designated a priority pathogen by both the Center for Disease Control and Prevention and the WHO [4, 5].

Recent approvals of new agents with activity against *A. baumannii*, in particular cefiderocol and sulbactam-durlobactam, have renewed interest in ways to optimize treatment of carbapenem-resistant *A. baumannii* infections, and the latest Infectious Diseases Society of America (IDSA) guidance on the treatment of antimicrobial-resistant gram-negative infections recommends the latter agent as the preferred option where it is available [6]. In this context, this review aims to present the latest insights into the epidemiology, mechanisms of resistance, and current treatment approaches for carbapenem-resistant *A. baumannii*, while also exploring promising emerging therapies and potential future avenues for management.

2 Epidemiology and Identification

Acinetobacter spp. are ubiquitous gram-negative bacteria that are strictly aerobic, nonfermenting, non-fastidious, nonmotile, catalase-positive, and oxidase-negative. They are widely distributed in nature, including soil and water, while they are also known to colonize human skin and mucous membranes [7]. The first member of the genus, at the time known as *Micrococcus calcoaceticus*, was first described in 1911 [8]. The genus *Acinetobacter* has since grown to contain at least 80 confirmed species, with more still under investigation [9]. Among them, *Acinetobacter baumannii,* a member of the *A. calcoaceticus–A. baumannii* complex, has emerged as a major multidrug-resistant nosocomial pathogen. It is difficult to eradicate the organism once established in the health care environment due to its resistance to disinfection and desiccation [10]. *Acinetobacter calcoaceticus–A. baumannii* complex also includes several other *Acinetobacter* species such as *A. calcoaceticus*, *Acinetobacter pittii*, and *Acinetobacter nosocomialis*. These species are grouped together because they are challenging to differentiate solely based on biochemical testing. Species within the complex other than *A. baumannii* are less likely to cause invasive disease or exhibit multidrug resistance [11, 12]. More recently, the availability of affordable whole genome sequencing and matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-ToF MS) has enabled differentiation of species within the *A. calcoaceticus–A. baumannii* complex [13, 14]. However, MALDI-ToF MS is not yet available in all clinical microbiology laboratories. Therefore, in interpreting identification results from clinical microbiology laboratories, the term "*A. baumannii*" might refer either to *A. baumannii sensu stricto* or to the *A. calcoaceticus–A. baumannii* complex, which encompasses all four main species within the complex, depending on the method used.

The success of *A. baumannii* as a human pathogen can be attributed in part to the spread of several dominant clonal lineages, each harboring a wide array of antimicrobial resistance genes. Historically, the most prevalent global lineages have been identified as Clonal Group 1 (CG1), Clonal Group 2 (CG2), and Clonal Group 3 (CG3), corresponding to sequence types (ST) ST1, ST2, and ST3, respectively, as per the Pasteur Institute classification system. However, recently CG406 and CG499 in the USA, and CG15, CG25, and CG79 in South America, have emerged as significant new lineages [15]. The complex composition of resistance and virulence genes in these diverse lineages could potentially affect the severity of illness and selection of treatment options.

3 Clinical Impact

Mortality from *A. baumannii* infections is highest in nosocomial pneumonia and bloodstream infections, with short-term mortality rates of 23% and 42%, respectively [16]. However, there is ongoing uncertainty over how much of the unfavorable outcome of these infections is attributable to the pathogen's virulence as opposed to the underlying health conditions of the host [16]. Other common infection types, such as wound and urinary tract infections, carry much lower mortality rates [16]. Health-care–associated meningitis and intra-abdominal infections can also occur. Common risk factors for *A. baumannii* infection include prior antimicrobial exposure, admission to intensive care units (ICUs), mechanical ventilation, and presence of vascular access [17]. Burn patients are especially prone to developing infections with carbapenem-resistant *A. baumannii* due to multiple risk factors including impairment of host immunity, loss of skin barrier function, and prolonged hospitalization and instrumentation [18, 19]. Colonization with *A. baumannii* is increasingly associated with health care facilities outside of the traditional hospital setting, including skilled nursing facilities, long-term acute care hospitals (LTACHs) [20] and wound clinics [21]. For example, a recent state-wide study of long-term care facilities in Maryland showed that the proportion of colonized patients was much higher in long-term care facilities (63%) than in acute care hospitals (8%) [22].

Another important clinical scenario in which *A. baumannii* is frequently identified is with war-related injuries. In the early 2000s, there was a significant rise in

carbapenem-resistant *A. baumannii* infections among US service members wounded in military operations in Iraq, Kuwait, and Afghanistan [23]. Acquisition of these pathogens have been linked to nosocomial transmission in the field hospitals and subsequent introduction into the US military health system, highlighting the challenges of maintaining sterile environments in combat zones [24]. More recently, war-related injury infections with *A. baumannii* are seen among those injured in the wars in Syria and Ukraine, likely due in part to disruption in hospital and public health infrastructure within these regions [25–28]. The movement of affected individuals, whether they are returning home or becoming displaced, contributes to the global spread of this pathogen, underlining its status as a significant global health threat.

During the COVID-19 pandemic, an increase in infections caused by carbapenem-resistant *A. baumannii* was reported by many health care institutions, including a 78% increase in the incidence of these infections in the USA [29–33]. This trend was partly due to the large increases of COVID-infected patients requiring respiratory support but was also exacerbated by lapses in infection prevention practices, shortages of staff and protective supplies, and increased use of antibiotics. In fact, *A. baumannii* was one of the most common pathogens responsible for co-infection in COVID-19 patients [34]. Once COVID-19 hospitalizations and the aforementioned issues stabilized, some sites that had experienced outbreaks during this period reported a return of carbapenem-resistant *A. baumannii* infections to pre-pandemic levels [35]. While the global impact of COVID-19 on the incidence of carbapenem-resistant or multidrug-resistant *A. baumannii* was mixed, these observations emphasize the importance of robust infection prevention and control measures in preventing the spread of these pathogens [36].

Finally, community-acquired *A. baumannii* infection is a distinct clinical entity primarily seen in tropical and subtropical regions such as Australia and Asia Pacific. It has been notably associated with the rainy season in the summer months. Infection often presents as rapid-onset, fulminant bilateral pneumonia in patients with underlying risk factors such as chronic alcohol or tobacco use, chronic pulmonary diseases, and uncontrolled diabetes. Community-acquired *A. baumannii* strains belong to genetic lineages that are distinct from those that are prevalent in the health care environment and generally exhibit less antimicrobial resistance [37, 38].

4 Antimicrobial Resistance

Initially recognized as a generally antimicrobial-susceptible pathogen, *A. baumannii* has become progressively resistant to most classes of antibiotics through both intrinsic and acquired mechanisms. Intrinsic mechanisms include production of AmpC (ADC) β-lactamase, decreased outer membrane permeability due to alterations in outer membrane proteins, and overexpression of efflux pumps with broad substrate profiles [39]. Acquired resistance mechanisms include production of plasmid-mediated OXA-type carbapenemases and metallo-β-lactamases (conferring resistance to carbapenems), aminoglycoside-modifying enzymes and 16S ribosomal RNA methyltransferases (conferring resistance to aminoglycosides), and specific mutations in DNA topoisomerases (conferring resistance to fluoroquinolones), among others [40].

Carbapenems are antibacterial agents of last resort in critically ill patients given their broad-spectrum activity against gram-negative bacteria. Carbapenem resistance in *A. baumannii* has been increasing over the years, at one point reaching 50% in the USA, and varying between < 1% to > 55% in European countries, with higher rates observed in southern and eastern Europe [41]. Similarly, the rates of carbapenem resistance vary among countries in the Asia Pacific region. Japan reports the lowest carbapenem resistance rates of below 3%, while China, India, and South Korea have experienced rates exceeding 70% [42, 43]. In Latin America, resistance rates between 30% to > 80% have been reported [44]. Importantly, carbapenem resistance often co-exists with resistance to multiple other classes of antibiotics, resulting in multidrug resistance (MDR) or even extensive drug resistance (XDR) phenotypes, leaving virtually no treatment options for patients. The coexistence of various acquired resistance mechanisms is in part due to the presence of multiple resistance genes carried by mobile genetic elements acquired through horizontal gene transfer such as plasmids [45]. In *A. baumannii*, these resistance genes may also be organized into structures known as resistance islands on the chromosome. The first such example was described in 2006 in the epidemic strain AYE with an 86 kb-long resistance island containing a cluster of 45 antimicrobial resistance genes [46]. More recent experimental evidence suggests that an entire resistance island can be transferred via natural transformation between strains [3].

Although *A. baumannii* intrinsically produces OXA-51-group carbapenemase, clinically relevant levels of carbapenem resistance are usually conferred through production of acquired OXA-type carbapenemases including OXA-23, OXA-40 and OXA-58 [47]. Other carbapenemases that are more common in Enterobacterales, such as New Delhi metallo-β-lactamase and serine carbapenemases including KPC and GES have been reported in *A. baumannii* but they remain much rarer compared with acquired OXA-type carbapenemases. Additionally, alterations or loss of outer membrane proteins such as CarO resulting in permeability defects and upregulation of the AdeABC resistance

nodulation division (RND) efflux pump can augment carbapenem resistance [40].

5 Currently Available Treatment Options

While several antibiotics with activity against carbapenem-resistant *A. baumannii* are currently approved for clinical use in the USA (Table 1), many are associated with significant limitations, and most studies available for comparison of clinical effectiveness are retrospective in nature, which is further compounded by frequent use of various combinations of these agents for variable durations. Given the multiple uncertainties surrounding the use of available antimicrobial agents, along with limited positive data on their use as monotherapy, treatment guidelines vary between Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) on which agents should be used and whether combination therapy should be considered. However, both the IDSA and ESCMID recommend the use of at least two in vitro active agents for the treatment of high-risk carbapenem-resistant *A. baumannii* infections when feasible, with the exception of sulbactam-durlobactam, which is recommended for use in combination with a carbapenem by the IDSA [6, 48]. Furthermore, many countries lack access to these agents, especially those that were approved in the last 10 years.

Table 1 Currently available treatment options for the treatment of carbapenem-resistant *Acinetobacter baumannii* infections

Drug class	Drug	Clinical use and considerations
Polymyxins	Colistin	Still the most widely used agents globally Use in combination with another active agent is recommended [6, 48] Combination with a carbapenem is discouraged [6, 48] Epithelial lining fluid concentrations are low to undetectable when administered intravenously [69] Nephrotoxicity occurs in up to 36% [52]
	Polymyxin B	Polymyxin B has a more preferable pharmacokinetic profile compared with colistin for infections other than urinary tract infection [49] Available in fewer countries than colistin
Tetracyclines	Tigecycline	Use in combination with another active agent is recommended [6, 48] High tissue penetration favors use in skin and soft tissue infections and intra-abdominal infections Not recommended for primary bacteremia or urinary tract infection due to low serum and urine concentrations [100] A high-dose regimen (200 mg loading dose then 100 mg every 12 h) improves pharmacokinetics, though clinical benefit is yet to be established [108]
	Minocycline	Can be administered both intravenously and orally Clinical data are scarce Modern pharmacokinetic analyses suggest that a majority of clinical isolates may be considered non-susceptible [115]
	Eravacycline	Demonstrates higher in vitro activity compared with tigecycline, but clinical data are very limited Available in the USA, EU and China
β-lactam and β-lactamase inhibitor-based drugs	Sulbactam	Preferred backbone for combination therapy IDSA recommends high dose (9 g/day) regardless of susceptibility [6] ESCMID recommends use only if the strains susceptible [48] Available in most countries in combination with ampicillin Resistance is increasingly prevalent
	Durlobactam	Durlobactam restores sulbactam activity in sulbactam-resistant strains [129] In the pivotal ATTACK trial, patient survival with the sulbactam-durlobactam/imipenem combination was non-inferior to the colistin/imipenem combination for hospital-acquired/ventilator-associated/ventilated pneumonia and bacteremia, with a trend towards superiority [156] Currently available in the USA and China Sulbactam-durlobactam plus a carbapenem is endorsed as a preferred regimen by IDSA [6] Real-world data are still limited
	Cefiderocol	Demonstrates robust in vitro activity; resistance may develop on therapy Though clinical response rates were comparable to best available therapy, excess mortality was observed among patients who received cefiderocol in the CREDIBLE-CR trial Other trials and real-world data have not shown higher patient mortality with cefiderocol Currently available in the USA, EU and Japan; expected to become available worldwide through a public-private partnership

ESCMID European Society of Clinical Microbiology and Infectious Diseases, *IDSA* Infectious Diseases Society of America

5.1 Polymyxins (Colistin and Polymyxin B)

Polymyxins have served as a key class of antibiotics in treating infections caused by carbapenem-resistant *A. baumannii*, either alone or in combination with other agents. Initially developed in the 1950s, two members of this class, polymyxin B and colistin (polymyxin E), are currently in clinical use, with varying availability based on countries and regions. Polymyxin B and colistin differ by only one amino acid, and the active drugs demonstrate comparable in vitro antibacterial activity [49]. Polymyxins subsequently fell out of favor due to availability of better tolerated agents including aminoglycosides and cephalosporins. However, the early 2000s saw a resurgence in their use as a last-resort treatment due to the rise of multidrug-resistant gram-negative bacteria including carbapenem-resistant *A. baumannii* [50]. In many countries, polymyxins are the only agents with in vitro activity against carbapenem-resistant *A. baumannii* available for clinical use [51]. Nevertheless, currently available clinical and pharmacokinetic/pharmacodynamic (PK/PD) data suggest that these drugs may be of diminishing utility in the future given their significant toxicity, especially nephrotoxicity, which can occur in up to 36% of the patients, uncertain clinical efficacy, and availability of alternative agents with activity against *A. baumannii* [52].

Polymyxin mechanism of action involves the disruption of the bacterial outer membrane. This is achieved by the binding of their cationic groups to the bacterial lipopolysaccharide, followed by disruption of the inner membrane by the fatty acid polymyxin tail [53]. Resistance in *A. baumannii* to polymyxins is primarily caused by lipopolysaccharide modification through the addition of phosphoethanolamine (PEtN) moieties to lipid A by the *pmrCAB* operon-encoded enzymes or overexpression of *eptA*, a *pmrC* homolog [54, 55]. Transferable polymyxin resistance mediated by plasmid-encoded *mcr-1*, which constitutively expresses PEtN transferase and is common in *E. coli* in some regions, still appears to be extremely rare in *A. baumannii*. Total loss of lipopolysaccharide through deleterious mutations in its first three lipid A biosynthetic genes (*lpxA*, *lpxC* and *lpxD*) have also been implicated in polymyxin resistance [56, 57].

Susceptibility testing of polymyxins presents significant challenges. Currently the broth microdilution method is the accepted standard by both the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [58]. However, it is labor intensive and therefore not feasible in most clinical microbiology laboratories. Compounding the issue, the antibiotic powders used for testing are often unspecified mixtures of chemically related compounds, with composition varying between lots and sources [59]. Furthermore, binding of polymyxins to currently recommended polystyrene microplates, especially at lower concentrations, introduces non-linearity and potentially errors to observed minimum inhibitory concentrations (MICs) [59, 60]. Other methods including disk diffusion and gradient strip testing, and automated susceptibility testing by systems like Vitek2 and MicroScan have also been found to underestimate polymyxin resistance [61]. Molecular detection of resistance is also challenging due to the heterogeneity of resistance mechanisms that often involve mutations. Phenotypic approaches that are being developed include detection of alterations of lipids associated with polymyxin resistance, such as the PEtN modification with MALDI-ToF MS, which is possible on instruments with positive ion modes [62].

The PK/PD data from both animal models and humans indicate that a steady-state plasma concentration of 2 μg/mL is required for killing bacteria with a colistin MIC of 2 μg/mL, and possibly higher for treating pneumonia [63, 64]. Achieving this concentration in individual patients is challenging, with studies showing significant variability in therapeutic target attainment among critically ill patients [64, 65]. Furthermore, multiple studies have shown an extremely narrow therapeutic window, where exposures over 2 μg/mL are associated with increased risk for nephrotoxicity [66, 67]. To address this issue, International Consensus Guidelines for the Optimal Use of the Polymyxins have been created as a collaboration among multiple relevant societies, including ESCMID and IDSA [68]. Due to the aforementioned challenges with susceptibility testing and the unique PK/PD, CLSI and EUCAST have jointly issued a document addressing breakpoints for polymyxins. In this document, CLSI has determined that the 'susceptible' category for polymyxins is inappropriate. Instead, an 'intermediate only' category has been established for isolates with MICs $\leq$ 2 μg/mL, signaling that clinical response to polymyxin treatment might be lower than expected even for isolates with an MIC in this range. The body also recommended the use of polymyxins in combination with other active agents, and avoiding their use in pneumonia, given negligible concentrations in epithelial lining fluid (ELF) after intravenous administration [69, 70]. Conversely, EUCAST chose not to eliminate the 'susceptible' definition for polymyxins, but rather placed the susceptibility breakpoint of 2 μg/mL in brackets, warning that clinical evidence as monotherapy is insufficient but that they may still be used with another active agent [59]. Finally, the US Food and Drug Administration (FDA) has not established breakpoints for polymyxins. This absence means that these agents are not included in automated susceptibility panels that are typically used in clinical microbiology laboratories.

While colistin and polymyxin B are considered equivalent based on their structural and in vitro activity similarities, significant PK/PD differences exist between the two compounds [49]. Colistin is commercially available in two forms: colistin sulfate for topical use, and colistin methanesulfonate (CMS), an inactive prodrug designed for parenteral

administration to reduce the toxicity associated with colistin sulfate [71]. Once administered, CMS undergoes hydrolysis in biological fluids to become active colistin. Colistin methanesulfonate may be renally cleared faster than it is converted to colistin that leads to substantial interindividual variability in serum levels, often resulting in subtherapeutic levels and making it difficult to achieve therapeutic drug concentrations [72, 73]. However, this characteristic makes it a theoretically preferred option over polymyxin B for treating urinary tract infections.

Polymyxin B, in contrast, is administered as an active drug and its effectiveness is not compromised by renal function, as it is primarily cleared through non-renal routes. This makes it easier to achieve and maintain therapeutic levels. Furthermore, polymyxin B may be associated with an incrementally lower incidence of acute kidney injury compared to colistin [74, 75]. Given its more favorable PK/PD profile, polymyxin B is the preferred agent over colistin for the treatment of critically ill patients with non-urinary infection in regions where it is available [68]. Although the few studies that have compared the clinical performance of polymyxin and colistin have failed to show differences in patient mortality, their designs have been limited by patient heterogeneity and differences in doses used amongst patients [49, 76–79].

Despite their many limitations, colistin and polymyxin B continue to serve as key agents globally for the treatment of carbapenem-resistant *A. baumannii* infections. In clinical practice, polymyxin monotherapy has typically been avoided, and the IDSA guidance also advises against this approach. The combination of a polymyxin with a carbapenem initially showed promise in in vitro and clinical case series. However, this combination did not improve clinical outcomes over colistin monotherapy in two randomized clinical trials (AIDA and OVERCOME) [80, 81]. In these trials, dose-optimized colistin monotherapy was compared with a combination therapy of dose-optimized colistin and meropenem (high dose for AIDA and standard dose for OVERCOME) for the treatment of carbapenem-resistant, colistin-susceptible gram-negative bacterial infections, most of which were due to *A. baumannii*. In the open-label AIDA trial, the 28-day mortality rates were 46% in the colistin group and 52% in the combination group, for a risk ratio of 1.11 (95% CI 0.87–1.41) among those with *A. baumannii* infection. In the placebo-controlled OVERCOME study, the 28-day mortality rates were 46% in the colistin group and 42% in the combination group, for a difference of 4.0% (95% CI − 6.7 to 14.7) among those who had *A. baumannii* infection. Thus, no difference in mortality rates was observed between the two treatment approaches in either trial. Furthermore, on examining the *A. baumannii* isolates from the AIDA trial, the presence or absence of in vitro synergism between colistin and meropenem by the checkerboard method did not correlate with the clinical failure rates in the patients [82]. Based on these results, both IDSA and ESCMID guidelines recommended against the use of this combination [6, 48].

Colistin has been investigated in several randomized trials in combination with agents typically inactive as monotherapy against *A. baumannii*. Despite in vitro synergy, small-scale randomized clinical trials conducted with rifampicin and fosfomycin did not reveal significant differences in short-term mortality rates compared to colistin alone, although both combinations exhibited higher microbiological cure rates [83–85]. Colistin also shows in vitro synergy with glycopeptides (vancomycin and teicoplanin) but retrospective studies assessing this combination have failed to show a difference in mortality [86, 87]. Hence, none of these regimens are recommended by IDSA and ESCMID [6, 48].

Nebulized dosing might improve efficacy and limit toxicity over intravenous polymyxins in the treatment of *A. baumannii* respiratory tract infections through achieving very high concentrations in the epithelial lining fluid (ELF) while limiting systemic concentrations [88]. Nebulization has been studied as a substitution to intravenous polymyxins, as well as an adjunct. However, it has failed to show improved clinical outcome beyond decreasing bacterial load in limited studies [89, 90]. The studies were heterogenous in nature, and drug delivery apparently varied based on the dose and concentration of the drug used, ventilator settings, ventilator circuit, and choice of device, with mesh nebulizers performing better than jet nebulizers [91, 92]. Neither IDSA nor ESCMID recommend the use of nebulized polymyxins for the treatment of *A. baumannii*, whereas the optimal polymyxin use guidelines continue to do so [6, 48, 68].

Overall, polymyxins alone or in combination with another agent are still the only available and reasonable options in many countries despite their numerous limitations, highlighting the need to improve access to newer and safer agents.

5.2 Tigecycline

Tigecycline belongs to the glycylcycline class of semisynthetic tetracycline agents. It is an analog of minocycline and inhibits protein synthesis through binding to the 30S ribosomal subunit. It was designed to overcome major tetracycline resistance mechanisms including drug efflux and ribosomal protection [93, 94]. Tigecycline has potent and broad-spectrum in vitro activity against gram-positive, gram-negative, anaerobic, and atypical bacteria. Since its initial approval in 2005, it has been approved for the treatment of skin and soft tissue infections as well as complicated intra-abdominal and community-acquired lower respiratory tract infections in the USA [95]. Given its in vitro activity against *A.*

baumannii, it is occasionally used off label for the treatment of *A. baumannii* infections including pneumonia. However, like polymyxins it has its drawbacks and uncertainties, as discussed below.

Tigecycline resistance in *A. baumannii* is primarily associated with upregulation of a number of intrinsic resistance-nodulation-division (RND)-type efflux pumps (AdeABC, AdeFGH, AdeIJK, AbeM, and AdeDE). Additionally, the presence of acquired Tet-type efflux pumps have been reported to reduce susceptibility of *A. baumannii* to tetracyclines, including tigecycline [39, 96].

Tigecycline susceptibility testing is not straightforward. Currently, the broth microdilution and disk diffusion methods are used, with the stipulation that the media should be no older than 12 h at the time of use. Gradient diffusion tests, as well as automated testing systems like Vitek2 and MicroScan have been shown to overcall tigecycline resistance [97]. MIC breakpoints for *Acinetobacter* spp. have not been assigned by CLSI, EUCAST, or FDA (Table 2). The FDA's *Enterobacterales* breakpoints (≤ 2 µg/mL as susceptible, 4 µg/mL as intermediate, ≥ 8 µg/mL as resistant) have been extrapolated for *Acinetobacter* spp. in some clinical studies [98]. However, PK studies in critically ill patients suggest that the standard doses of tigecycline (100 mg loading dose, followed by 50 mg every 12 h) are sufficient to achieve therapeutic concentrations only for isolates with tigecycline MICs of 0.5 to 1 µg/mL. As a result, high-dose tigecycline may be considered as a treatment option for infections caused by *Acinetobacter* spp. with a MIC of 2 µg/mL [99] (see Table 2).

Tigecycline is typically regarded as an unsuitable agent for the treatment of primary bacteremia due to its large volume of distribution, which results in low serum concentration and extensive tissue distribution. By contrast, these same features of tigecycline are thought to favor its use in bone and skin and soft tissue infections [100, 101]. Additionally, it has insufficient lung penetration and low concentration in the urine [102]. While approved for treatment of community-acquired pneumonia, it was not approved for treatment of health care- or ventilator-associated pneumonia after a failed Phase 3 trial that compared the standard dose tigecycline with imipenem-based regimens [103]. In 2010, the FDA issued an alert that use of tigecycline in the treatment of severe infections and sepsis was significantly associated with an increased risk for all-cause mortality, particularly in ventilator-associated pneumonia [104]. Consequently, tigecycline's role in the treatment of pneumonia involving *A. baumannii* has been controversial. Several studies have shown increased mortality in *A. baumannii* pneumonia when used at a standard dose and as monotherapy when compared with colistin or sulbactam-based regimens [105]. Subsequent clinical studies evaluating high-dose tigecycline (200 mg loading dose, followed by 100 mg every 12 h) compared to standard dose have suggested improved patient outcomes without increase in adverse events [106, 107]. This approach is supported by an intrapulmonary PK analysis of patients receiving the high dose [108]. In a majority of the cases tigecycline was used in combination with other in vitro active agents; however, results of these observational studies should be interpreted with caution, and high-dose tigecycline should not be used as monotherapy.

In summary, tigecycline is still frequently used as part of combination therapy, but the benefit of this practice has not been definitively demonstrated. This uncertainty has also precluded establishment of *Acinetobacter*-specific clinical breakpoints, which in turn makes it difficult to define the potential role of tigecycline in this context. High-dose tigecycline improves probability of attaining pharmacodynamic targets for pneumonia and appears to be tolerated in most patients, but controlled studies that demonstrate clinical benefits are needed before its use can be broadly recommended.

Table 2 MIC breakpoints of key anti-*Acinetobacter* agents for *A. baumannii* (µg/mL)

Agent	CLSI			EUCAST			FDA		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Colistin	–	≤ 2	≥ 4	≤ 2	–	≥ 4	–	–	–
Polymyxin B	–	≤ 2	≥ 4	–	–	–	–	–	–
Tigecycline	–	–	–	–	–	–	–	–	–
Minocycline	≤ 4	8	≥ 16	–	–	–	≤ 4	8	≥ 16
Eravacycline	–	–	–	–	–	–	–	–	–
Ampicillin-sulbactam	≤ 8/4	16/8	≥ 32/16	–	–	–	≤ 8/4	16/8	≥ 32/16
Sulbactam-durlobactam	≤ 4/4	8/4	≥ 16/4	–	–	–	≤ 4/4	8/4	≥ 16/4
Cefiderocol	≤ 4	8	≥ 16	–	–	–	≤ 1	2	≥ 4

CLSI Clinical and Laboratory Standards Institute (M100-ED34), *EUCAST* European Committee on antimicrobial Susceptibility Testing (v.14.0), *FDA* (US) Food and Drug Administration

Table 3 Agents with activity against *Acinetobacter baumannii* in clinical development

Classes	Agents	Characteristics	Anticipated indications	NCT IDs of efficacy trials
BLBLI	Cefepime-zidebactam (WCK5222)	Zidebactam is a bicyclic-acyl hydrazide BLI	Complicated UTI including pyelonephritis	NCT04979806
	Imipenem-cilastatin-funobactam (XNW4107)	Funobactam is a diazabicyclooctane BLI	Complicated UTI including pyelonephritis Hospital-acquired or ventilator-associated bacterial pneumonia	NCT05204368 NCT05204563
	Meropenem-xeruborbactam	Xeruborbactam is a bicyclic boronate BLI	–	–
	Meropenem-ANT3310	ANT3310 is a diazabicyclooctane BLI	–	–
	Meropenem-KSP-1007	KSP-1007 is a bicyclic boronate BLI	–	–
Peptide	SPR206	Polymyxin derivative with improved safety profile	–	–
	MRX-8	Polymyxin derivative with improved safety profile	–	–
	BRII-693	Lipopeptide with improved safety over existing polymyxins	–	–
	PLG0206	Engineered antibiotic peptide	Prosthetic joint infection	–
	OMN6	Engineered antibiotic peptide	Hospital-acquired or ventilator-associated bacterial pneumonia	–
Tetracycline	Zifanocycline (KBP-7072)	Aminomethylcycline	–	–
Aminoglycoside	Apramycin (EBL-1003)	Reformulation of existing veterinary aminoglycoside	–	–
Rifamycin	BV100	Reformulation of rifabutin	Hospital-acquired or ventilator-associated bacterial pneumonia Bloodstream infections	–
Bacteriophage	TP-102	Bacteriophage cocktail	Diabetic foot infection	NCT05948592
Antibody	CMTX-101	Biofilm-binding monoclonal antibody	–	–
	F598	PNAG-binding monoclonal antibody	Prevention of ICU infections	–
New mechanisms	Zosurabalpin (RG6006)	Lipopolysaccharide transport inhibitor	–	–
	BWC0977	Non-quinolone topoisomerase inhibitor	–	–
	APL-2301	Outer membrane permeabilizer	–	–

BLBLI β-lactam-β-lactamase inhibitors, *ICU* intensive care unit, *NCT ID* ClinicalTrials.gov Identifier, *PNAG* Poly-β-(1–6)-*N*-acetylglucosamine

5.3 Minocycline

Minocycline, a synthetic tetracycline derivative, was originally introduced in the 1960s. Due to limited use, the intravenous formulation was taken off the US market and was re-introduced in 2009 given the rising clinical need for the treatment of carbapenem-resistant *A. baumannii* infections. A new intravenous formulation was subsequently approved in 2015, which included an indication for the treatment of *A. baumannii* infections [109]. Similar to tigecycline, it acts through inhibition of protein synthesis by binding to the ribosomal 30S subunit and has a broad-spectrum activity against various bacterial pathogens [110]. Minocycline is less prone than other tetracyclines to efflux by *A. baumannii* RND efflux pumps and Tet(A), an acquired efflux pump belonging to major facilitator superfamily (MFS), but it remains vulnerable to efflux by Tet(B), which is a major resistance mechanisms for this drug [111].

Minocycline has high tissue penetration and may be suitable for the treatment of skin and soft-tissue infection

and osteoarticular infections [112]. Another advantage of minocycline is the excellent oral bioavailability that allows for conversion from intravenous to oral dosing. However, clinical data on minocycline use for *A. baumannii* infections are limited to case series and observational data, primarily used in combination with other agents, leaving its clinical effectiveness uncertain [111, 113]. Furthermore, these data were collected under the CLSI breakpoints of ≤ 4 µg/mL for susceptibility and ≥ 16 µg/mL for resistance, which were assigned in the 1970s (Table 2). A more stringent susceptibility breakpoint of ≤ 1 µg/mL has been proposed for daily doses of 400 mg in order to reliably meet the pharmacodynamic target based on more recent PK/PD studies [114–116]. If this revision is implemented, it would significantly reduce the susceptibility rates of multidrug-resistant *A. baumannii* isolates from approximately 70% to 40%, as extrapolated from the susceptibility data reported through a US surveillance program [117]. This concern, along with the dearth of clinical data either as monotherapy or combination therapy, makes it unlikely that minocycline will be considered as part of the treatment strategy moving forward.

5.4 Eravacycline

Eravacycline, approved in the USA in 2018, is a synthetic fluorocycline that is structurally similar to tigecycline. Surveillance studies have demonstrated that eravacycline has a 2- to 4-fold lower MIC_{90} against *A. baumannii* compared to tigecycline, indicating enhanced intrinsic activity [118, 119]. Although it has a smaller volume of distribution than tigecycline, it is still significant, leading to extensive tissue distribution and low plasma levels. Consequently, the theoretical PK/PD concerns similar to those with tigecycline may apply in the treatment of primary bacteremia. Furthermore, a comparative study reported significantly higher 30-day mortality rates in patients with *A. baumannii* pneumonia and treated with eravacycline-containing regimens compared with other regimens [120]. The difference was entirely driven by outcome of patients with secondary bacteremia, where all four patients in the eravacycline group died whereas the two patients in the comparator group both survived. Despite its promising intrinsic activity, in the absence of supportive clinical data it is unlikely that eravacycline will become a key component of the treatment strategies against carbapenem-resistant *A. baumannii* infections.

5.5 Conventional Sulbactam Combinations

Sulbactam is a semi-synthetic β-lactamase inhibitor primarily targeting class A β-lactamases such as TEM-1. As a penicillanic sulfone, sulbactam also has intrinsic activity against *Acinetobacter* spp. through direct inhibition of penicillin-binding proteins PBP1a, PBP1b and PBP3 [121]. Resistance of *A. baumannii* to sulbactam has been linked to specific PBP3 mutations that reduce its binding affinity. Additionally, over-expression of β-lactamases TEM-1 and ADC, the intrinsic class C (AmpC) enzyme of *A. baumannii*, has been associated with resistance [121, 122]. Sulbactam penetrates well into multiple body sites, including the lower respiratory tract, making it one of the preferred agents for the treatment of *A. baumannii* pneumonia [123–125]. There are three sulbactam combinations currently in clinical use: ampicillin-sulbactam, cefoperazone-sulbactam (not available in the USA), and sulbactam-durlobactam. This section will focus on the conventional ampicillin and cefoperazone combinations.

5.5.1 Ampicillin-Sulbactam

Sulbactam is partnered with ampicillin as a fixed 2:1 ratio of ampicillin to sulbactam and is approved at doses of up to 3 g (2 g ampicillin and 1 g sulbactam) every 6 h for treatment of skin and skin structure infections, intra-abdominal infections, and gynecological infections. However, it is used for treatment of *A. baumannii* infections as it is the only formulation available in the USA containing sulbactam. The CLSI breakpoints of ampicillin-sulbactam for *A. baumannii* are defined as susceptible for MICs ≤ 8/4 µg/mL, intermediate for the MIC of 16/8 µg/mL, and resistant for MICs ≥ 32/16 µg/mL (Table 2). The values following the slash (/) represent the actual MIC for sulbactam, since ampicillin on its own is not active against *A. baumannii* [126].

Concerns exist for ampicillin-sulbactam with regards to the accuracy of susceptibility testing using gradient diffusion tests, as well as automated systems like Vitek2, Phoenix, and MicroScan [127]. Pharmacokinetic studies suggest that, at the approved dose, only isolates with MIC of ≤ 4 µg/mL can be adequately treated, while in multidrug-resistant *A. baumannii* MIC_{50}/MIC_{90} values are 16 µg/mL and 64 µg/mL, respectively, making the approved dosing regimen not adequate for most isolates [128–130]. An alternative dosing strategy has been proposed based on available population PK and animal data, where 6 to 9 g of sulbactam per day is administered as extended or continuous infusion, with the theoretical goal to saturate the PBP targets [131–134]. The use of high-dose ampicillin-sulbactam for highly sulbactam-resistant isolates has also been proposed in combination with other agents [131, 134]. Clinical data on the use of ampicillin-sulbactam for *A. baumannii* infections are highly heterogeneous, with different doses and combinations with other drugs used. Nonetheless, ampicillin-sulbactam–based therapy has emerged superior to other treatments in several clinical studies and meta-analyses [90, 135]. However, due to the absence of definitive, controlled studies to support the benefit of this approach, there is a divergence in guideline recommendations regarding the use of ampicillin-sulbactam. While IDSA advocates the use of

high-dose ampicillin-sulbactam as part of combination therapy regardless of susceptibility when sulbactam-durlobactam is not available, ESCMID recommends ampicillin-sulbactam only when the strain is susceptible to sulbactam and advises use of polymyxin or tigecycline if the strain is resistant to sulbactam. The ESCMID is also more selective in recommending combination therapy, reserving it for patients with severe and high-risk infections. In countries without access to sulbactam-durlobactam, high-dose ampicillin-sulbactam will likely remain an important backbone in formulating active combinations for individual patients.

5.5.2 Cefoperazone-Sulbactam

Cefoperazone is a third-generation cephalosporin with antibacterial activity against gram-positive and gram-negative bacteria and is combined with sulbactam in a ratio of 2:1 or 1:1. Although not as widely available as ampicillin-sulbactam, it is utilized in some countries against gram-negative bacterial infections resistant to multiple antibiotics. While MICs for *Acinetobacter* spp. tend to be relatively high compared to other gram-negative pathogens, potential benefit beyond the sole effect of sulbactam has been suggested [136]. Cefoperazone is not marketed in the USA, thus breakpoints have not been established by the CLSI. Likewise, there are no established EUCAST breakpoints. Compared to ampicillin-sulbactam, there is a notable scarcity of PK/PD data, dosage recommendations, and clinical effectiveness data concerning this drug combination [137, 138]. Consequently, it is not included in either the IDSA or ESCMID guidelines.

6 Recently Approved Agents

In the last 5 years, two new agents with robust in vitro activity against carbapenem-resistant *A. baumannii* have been approved in the USA: cefiderocol and sulbactam-durlobactam.

6.1 Cefiderocol

Cefiderocol is a synthetic cephalosporin conjugate consisting of a cephalosporin moiety and a catechol-type siderophore [139]. Approved initially in November 2019 for complicated urinary tract infections in the USA, the indication was expanded to include hospital- and ventilator-associated pneumonia. In contrast, the European Medicine Agency (EMA) therapeutic indication is for infections due to aerobic gram-negative organisms in adults with limited treatment options. It has subsequently been approved in Japan for infections caused by carbapenem-resistant and cefiderocol-susceptible gram-negative bacteria.

As a siderophore, it achieves high periplasmic concentrations by actively entering the gram-negative bacterial cells through iron transporters and exerts its activity by inhibiting penicillin-binding protein 3 (PBP3), a major component of the gram-negative cell wall. Cefiderocol is also resistant to hydrolysis by most β-lactamases, a unique feature that contributes to its broad spectrum of activity across gram-negative bacterial pathogens [140]. In the case of carbapenem-resistant *A. baumannii*, the agent is stable against intrinsically produced OXA-51-group carbapenemase, ADC cephalosporinase and acquired OXA carbapenemases including OXA-23/40/58, resulting in robust in vitro activity against this pathogen. However, despite pre-approval studies suggesting high barrier to resistance, resistance emergence on therapy is reported with increasing clinical use [18]. The mechanisms of resistance include loss of function mutations in siderophore receptors, PirA and PiuA, as well as mutations in ADC β-lactamases that alter substrate specificity in favor of cefiderocol hydrolysis [141]. Presence of metallo-β-lactamases and PER-like β-lactamases have also been associated with elevated cefiderocol MICs [142].

Susceptibility testing of cefiderocol has proven to be a major challenge. The broth microdilution method requires the use of special iron-depleted cation-adjusted Mueller-Hinton broth to provide MICs [143]. Interpretation of the results is especially complicated by trailing endpoints, in which diminishing growth can be observed across multiple wells in up to 30% of *A. baumannii* strains. When trailing is observed, the MIC should be determined from the first well in which there is a significant reduction in growth compared to the positive growth control well. Another way to test for cefiderocol susceptibility is disk diffusion testing, which can be performed on standard Mueller-Hinton agar plates. The accuracy and reproducibility of cefiderocol susceptibility testing, whether by disk diffusion or broth microdilution, are significantly influenced by factors such as iron concentration and inoculum preparation, with potential variations arising from different disk and media manufacturers, resulting in difficulty obtaining reproducible MICs [144, 145]. The challenge is highlighted by a recent recall of a Sensititre product due to concerns over reporting of falsely low cefiderocol MICs. Currently, there are no gradient diffusion or automated tests approved for cefiderocol susceptibility testing, further limiting testing options [145]. Cefiderocol breakpoints are yet to be harmonized (Table 2). Notably, EUCAST has established non-species–specific PK/PD breakpoints as MICs of ≤ 2 µg/mL for susceptibility and > 2 µg/mL for resistance, specifically noting the lack of sufficient evidence for the effectiveness of treating *Acinetobacter* spp. with this agent. These variations in breakpoints in part stem from outcomes observed in the CREDIBLE-CR trial [146].

The CREDIBLE-CR trial was a pathogen-specific trial of various infections caused by carbapenem-resistant

gram-negative bacteria that compared clinical cure rates of cefiderocol-based therapy and best available therapy as the primary endpoint. Although cefiderocol showed similar clinical and microbiological efficacy to best available therapy for infections caused by carbapenem-resistant gram-negative pathogens, the subgroup of patients infected with carbapenem-resistant *A. baumannii* and assigned to receive cefiderocol-based therapy had a higher mortality rate compared with those who received best available therapy. These patients were more likely to be in the ICU with ongoing septic shock at the time of randomization, possibly explaining the mortality imbalance [146]. While this was a highly anticipated drug for carbapenem-resistant *A. baumannii* infections, these unexpected results lead the IDSA guidance document to recommend the use of cefiderocol for the treatment of refractory *A. baumannii* infections and only in combination with other active agents, while ESCMID recommends against using cefiderocol altogether [6, 48]. However, post-approval, several observational studies from Italy have reported clinical outcomes of cefiderocol-based versus colistin-based treatments for *A. baumannii* infections, with results ranging from comparable to improved patient outcomes, suggesting that there may be opportunities for cefiderocol use in *A. baumannii* infections [147–152].

Efficacy of cefiderocol for health-care–associated and hospital-acquired gram-negative bloodstream infection has been compared with the standard of care in the GAMECHANGER trial. In this > 500-patient, international, investigator-initiated clinical trial, the all-cause 14-day mortality rates were 8.0% for cefiderocol and 6.7% for the standard of care, fulfilling the predefined noninferiority criteria. The all-cause 14-day mortality rates among those with carbapenem-resistant *A. baumannii* were numerically lower at 9% for cefiderocol compared with 21% for the standard of care, though the numbers of patients were likely too small to draw a definitive conclusion on the efficacy of cefiderocol in this setting (Abstract O0810, ESCMID Global 2024). Full results of the trial are yet to be reported.

Shionogi & Co., Ltd., the manufacturer of cefiderocol and the Global Antibiotic Research and Development Partnership (GARDP) have agreed to manufacture and commercialize cefiderocol through sub-licensees in a large number of low- and middle-income countries with otherwise limited access to new antibiotics, an arrangement which is expected to make the agent available to patients in countries with a high burden of carbapenem-resistant gram-negative pathogens including *A. baumannii* [153]. Additionally, a combination of cefiderocol and a new investigational β-lactamase inhibitor, xeruborbactam, is in early development with hopes of addressing some of the current limitations of cefiderocol [154].

In summary, due to the gap in the patient outcomes observed between the CREDIBLE-CR trial and real-world studies, the potential role of cefiderocol in the treatment of carbapenem-resistant *A. baumannii* infections is yet to be fully defined, but there is emerging consensus that this, if any, will be in the context of combination therapy. Cefiderocol will likely become available in a much larger number of countries than sulbactam-durlobactam; thus, more comparative effectiveness data are needed, especially in identifying cefiderocol-containing combinations that balance safety and effectiveness.

6.2 Sulbactam-Durlobactam

Durlobactam, a novel β-lactamase inhibitor of the diazabicyclooctane (DBO) class, was specifically designed to inhibit acquired OXA-type carbapenemases produced by carbapenem-resistant *A. baumannii* in addition to Ambler class A and class C β-lactamases, including ADC enzymes produced by *A. baumannii* [21, 22]. The addition of durlobactam to sulbactam has been shown to restore the activity of sulbactam and lower its MIC_{90} of carbapenem-resistant *A. baumannii* strains from 64 µg/mL to 2 µg/mL as durlobactam protects hydrolysis of sulbactam by various β-lactamases produced by *A. baumannii* [23]. Limited information has linked resistance to the sulbactam-durlobactam combination to PBP3 mutations that confer high-level sulbactam resistance as well as production of metallo-β-lactamases such as NDM, which are not inhibited by durlobactam. Fortunately, the production of metallo-β-lactamases still appears to be relatively uncommon in carbapenem-resistant *A. baumannii* [155].

A Phase 3, multicenter, randomized controlled study (ATTACK) investigated the safety and efficacy of sulbactam-durlobactam in comparison to colistin, both used in conjunction with imipenem, for the treatment of pneumonia or bloodstream infections caused by *A. baumannii*. In the primary efficacy analysis that included 125 patients with laboratory-confirmed carbapenem-resistant *A. baumannii* strains, sulbactam-durlobactam plus imipenem demonstrated non-inferiority to colistin plus imipenem for the primary endpoint of 28-day all-cause mortality (12 [19%] of 63 in the sulbactam–durlobactam group and 20 [32%] of 62 in the colistin group, a difference of −13.2% [95% confidence interval, −30.0 to 3.5]). Additionally, sulbactam-durlobactam plus imipenem was associated with a significantly lower incidence of nephrotoxicity compared to colistin plus imipenem [156]. These safety and efficacy data led to the approval by the FDA in 2023 of sulbactam-durlobactam for hospital-acquired and ventilator-associated pneumonia caused by susceptible isolates of *A. baumannii-calcoaceticus* complex, positioning it as a preferred treatment option for carbapenem-resistant *A. baumannii* infections in the 2024 IDSA guidance document in combination with a carbapenem

[6]. Sulbactam-durlobactam has also subsequently been approved for clinical use in China.

The FDA breakpoints for sulbactam-durlobactam are MICs of (i) ≤ 4/4 µg/mL for susceptible, (ii) an MIC of 8 µg/mL for intermediate, and (iii) MICs of ≥ 16 µg/mL for resistant (Table 2) [157]. The FDA has cleared several susceptibility testing options, including disk diffusion, gradient diffusion, and MIC testing (Sensititre). As they are just entering clinical use, it remains to be seen how these tests perform in the real world.

While sulbactam-durlobactam shows great promise, further investigations are warranted to determine its optimal role in the treatment of carbapenem-resistant *A. baumannii*. It is still uncertain whether it should be used routinely in conjunction with a carbapenem, specifically imipenem (which sulbactam-durlobactam was combined with in the pivotal trial), with another therapeutic agent, or administered as monotherapy. The rationale of adding imipenem in the clinical trial was to provide coverage for potential co-infecting pathogens other than *A. baumannii*, to which sulbactam-durlobactam would not be active. In terms of specific activity against *A. baumannii*, the addition of imipenem typically shows a two-fold reduction in the MIC of sulbactam-durlobactam [158, 159]. While the numerical difference may be modest, we support the recommendation of the IDSA guidance to use sulbactam-durlobactam in combination with a carbapenem (either imipenem or meropenem) at least until more real-world experience is accumulated and shared on this issue, given that (i) mixed infection is common for *A. baumannii* infection, especially pneumonia, (ii) the pivotal trial demonstrated clinical efficacy with this combination, and (iii) complementary inhibition of PBPs (primarily PBP2 by carbapenems and PBP3 by sulbactam) may have contributed to the efficacy observed in the pivotal trial from a mechanistic viewpoint.

Sulbactam-durlobactam is a new agent with the most robust clinical data supporting its use in the treatment of severe carbapenem-resistant *A. baumannii* infections. The major challenge moving forward will be access, which is now limited to the USA and China. The cost of the product is also a barrier to broader uptake in countries where it is available. An innovative distribution model, as has been envisioned for cefiderocol, will likely be needed for the sulbactam-durlobactam to realize its full clinical potential.

7 New Agents in Clinical Development

Since 2017 when the WHO performed the initial analysis of the clinical antibacterial pipeline [160], only two agents with activity against *A. baumannii* received approval by FDA and EMA: cefiderocol and sulbactam-durlobactam. There remains a noticeable shortage of novel antibiotics with activity against *A. baumannii* currently in development. Furthermore, the majority of these new compounds represent iterations of existing drug classes, focusing on enhancing bioavailability and tolerability. There is a notable dearth of compounds with novel mechanisms of action, which are crucial in overcoming pre-existing resistance mechanisms [161]. In this section we will discuss new agents with anti-*A. baumannii* activity currently in clinical development (Table 3).

7.1 β-lactam and β-lactamase Inhibitor Combinations

β-lactams, often in combination with various β-lactamase inhibitors, are the most widely used class of antibiotics due to their preferable pharmacokinetics, low toxicity, and potent activity. Some of the β-lactamase inhibitors currently in clinical trials show in vitro activity against *A. baumannii* when paired with their corresponding β-lactam partners including zidebactam, funobactam, xeruborbactam, ANT3310, and KSP-1007. These combinations are in development as broad-spectrum gram-negative agents and there are currently no ongoing *A. baumannii*-specific clinical trials [162–167].

7.2 Novel Polymyxins

In recent years, there has been development of novel polymyxins aimed at overcoming issues with nephrotoxicity, neurotoxicity and unpredictable pharmacokinetics. These novel polymyxins, similar to β-lactam/β-lactamase inhibitor combinations, are designed to target multiple carbapenem-resistant gram-negative pathogens rather than focusing on carbapenem-resistant *A. baumannii* alone. The compounds currently undergoing clinical trials include SPR206, MRX-8, and BRII-693 (formerly known as QPX9003). These compounds have demonstrated improved toxicity profiles and higher pulmonary levels than the currently available polymyxins. Among them, BRII-694 is also active against polymyxin-resistant isolates [168–171].

7.3 Tetracyclines

KBP-7072 (Zifanocycline) is a novel third-generation aminomethylcycline antibacterial belonging to the tetracycline class. It is active against both gram-positive and gram-negative pathogens and overcomes common resistance mechanisms including efflux and ribosomal protection, which negatively impact the activity of older tetracyclines. It has activity against multidrug-resistant *A. baumannii*, including those with elevated minocycline and tigecycline

MIC, but it is unclear if it can address the challenges of low pulmonary and plasma concentrations, which are typical for this antibiotic class [172].

7.4 Aminoglycosides

Aminoglycoside antibiotics inhibit protein synthesis through binding to the 30S ribosomal subunit and have been used in the treatment of *A. baumannii* infection. However, their use has declined due to increasing rates of resistance caused by production of aminoglycoside-modifying enzymes (AMEs) and 16S ribosomal RNA methyltransferases (16S-RMTases), along with concerns over nephrotoxicity, vestibular toxicity, and poor pulmonary penetration [173]. EBL-1003 (Apramycin), a crystalline-free base of apramycin formerly known as nebramycin factor 2 produced by *Streptomyces tenebrarius* and currently used in veterinary medicine, is under development for use in humans for the treatment of infections caused by various gram-negative pathogens including *A. baumannii*. The apramycin structure makes it resistant to modification by most AMEs as well as 116S-RMTases like ArmA and RmtB, which protect the ribosome from all currently available aminoglycosides that are administered parenterally, including plazomicin. It has also shown reduced ototoxicity and nephrotoxicity in animal models compared to traditional aminoglycosides [174, 175].

7.5 Topoisomerase Inhibitors

Carbapenem-resistant *A. baumannii* are mostly resistant to fluoroquinolones through mutations in bacterial topoisomerases which they target. BWC0977 is a novel bacterial topoisomerase inhibitor of both DNA gyrase and topoisomerase IV. As a member of a new class of non-quinolone inhibitors, it binds to different sites of these enzymes, thereby maintaining activity against fluoroquinolone-resistant strains. Its spectrum of activity encompasses both gram-positive and gram-negative organisms including *A. baumannii* [176, 177].

7.6 Rifamycins

BV100, an intravenous formulation of rifabutin, is being developed to specifically treat carbapenem-resistant *A. baumannii* infections. Rifabutin is an oral rifamycin antibiotic, initially approved for the prevention of *Mycobacterium avium* complex disease in patients with HIV infection and is also used in the treatment of active tuberculosis. Rifabutin inhibits RNA transcription through binding to the β-subunit (RpoB) of RNA polymerase. Rifamycin use has been limited to *Mycobacterium* spp. and gram-positive bacteria, as they generally have limited activity against gram-negative bacteria due to reduced capacity to cross the outer membrane. Despite this, rifabutin has shown robust activity against *A. baumannii,* which is mediated by increased uptake through a TonB-dependent siderophore receptor FhuE. Importantly, no cross-resistance to cefiderocol has been noted, suggesting that different iron transport systems are utilized in the uptake of these drugs. The low oral bioavailability of rifabutin, ranging from 12%–20%, makes it unsuitable as a therapeutic agent for carbapenem-resistant *A. baumannii*, therefore an intravenous formulation is currently in development [178].

7.7 Other Notable Compounds and Therapies

7.7.1 Zosurabalpin (Abx MCP, RG6006)

Zosurabalpin (Abx MCP, RG6006) is a small molecule, novel chemical class antibiotic with specific activity against *A. baumannii*. It belongs to the class of tethered macrocyclic peptides (MCPs). Macrocyclic peptides represent a class of synthetic compounds that is rapidly gaining attention as a new drug modality. The MCP class comprises various groups of molecules with a macrocyclic scaffold spanning from 5 to 14 amino acid residues, and their molecular weights are between 500–2000 [179, 180]. Their footprint on the binding surface of the target protein is generally comparable to that of a typical antibody [181]. Additionally, cyclization allows for a decrease in the polar surface area leading to an increase in cell permeability and improved tissue distribution. Zosurabalpin works by inhibiting the LptB2FGC complex, a liposaccharide transport system responsible for LPS transport from the inner to the outer membrane [182]. The compound has completed two Phase 1 clinical trials, in which the drug was shown to be safe and well tolerated in healthy subjects [183].

7.7.2 APL-2301 (ASN-1733, MET-102)

APL-2301 (ASN-1733, MET-102) is a nitroxoline derivative being developed to specifically target *A. baumannii*. It works through disruption of outer membrane integrity through detachment of lipopolysaccharide. Additionally, APL-2301 is capable of inhibiting the NDM enzyme [184, 185].

7.7.3 Phage-based Therapy

Phage-based therapy has emerged as a potential treatment option for *A. baumannii* infections. However, experience with this approach is largely confined to case reports. Procuring active phages for these treatments is often technically

challenging, with phages being sourced from various places such as biotech companies and research laboratories [186–188]. To date, no phage-based therapeutics have received regulatory approval from either the FDA or EMA. TP-102 is being developed as a topically applied bacteriophage cocktail that targets *P. aeruginosa*, *A. baumannii*, and *Staphylococcus aureus*, and it is currently in a Phase 2b trial to test its safety and efficacy in the treatment of diabetic foot infection [189].

7.7.4 Antimicrobial Peptides

Antimicrobial peptides belong to a molecular class of short, often positively charged peptides that work through lysis of bacterial membrane and occur naturally as part of the intrinsic defense mechanisms of numerous organisms [190]. Currently, two antimicrobial peptides with activity against *A. baumannii* are undergoing clinical development. PLG0206, with activity against both gram-positive and gram-negative pathogens as well asbacterial biofilm, is being studied in prosthetic joint infections for intraoperative irrigation [191, 192]. The other peptide OMN6 will be studied in a clinical trial of *A. baumannii* pneumonia in addition to conventional antibiotics [193].

7.7.5 Antibody Therapies

Vaccines and monoclonal antibodies specific against *A. baumannii* have not been successful so far, partly due to challenges in identifying highly conserved epitopes given the pathogen's characteristic heterogeneity and genome plasticity [17]. However, two broad-spectrum monoclonal antibodies are currently in trials, CMTX-101 and F598, both designed to target and disrupt biofilms formed by gram-negative and gram-positive bacteria, including *A. baumannii* [194, 195].

8 Conclusion

Carbapenem-resistant *A. baumannii* represents a significant challenge to public health, reflecting the broader crisis of antimicrobial resistance. Despite advancements in understanding its epidemiology and resistance mechanisms, clinicians continue to face obstacles treating this pathogen due to the lack of effective treatment options. The variability in treatment guidelines, compounded by the lack of definitive clinical outcomes data, highlights the urgent need for novel therapeutic approaches. Emerging treatment strategies, including new antibiotic classes and combination therapies, show promise, but their success hinges on comprehensive clinical validation and availability in regions most impacted by this pathogen. The collaboration between researchers, clinicians, pharmaceutical companies and policymakers is crucial to improving existing therapies and discovering novel antimicrobial agents that mitigate the escalating threat of multidrug-resistant infections.

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