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REVIEW ARTICLE

Developments for the treatment of invasive infections due to multidrug-resistant *Acinetobacter baumannii*

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Abstract

Acinetobacter baumannii is a significant pathogen in healthcare settings (specifically prominent in healthcare- and ventilator-associated pneumonia) due primarily to its virulence and resistance to a wide variety of antimicrobial drug classes, including carbapenems (CRAB). Existing therapies (notably polymyxins, minocycline, tigecycline, amikacin, and sulbactam) often result in suboptimal tissue concentrations, high rates of toxicity, and increasing rates of resistance. Although utilizing combinations of antibiotics (specifically those containing colistin) have been employed, results have been mixed, and control trials are lacking. Eravacycline is a novel tetracycline with an improved pharmacokinetic profile and more potent activity against *A. baumannii* relative to tigecycline. Cefiderocol has a unique mechanism of action that has performed well in vitro against multidrug-resistant (MDR) and CRAB isolates. Limited clinical data exists with each of these agents. Other novel antimicrobials are still in early phase clinical trials (ETX2514/sulbactam, TP-271, TP-6076, VNRX-5133/cefepime, cefepime/zidebactam, AIC-499, GSK3342830, and SPR741) while further research is underway for non-antibiotic approaches, specifically monoclonal antibodies and bacteriophage therapies.

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Introduction

Acinetobacter baumannii is a non-motile, aerobic, Gram-negative opportunistic pathogen often causing serious, life-threatening infections found most frequently in healthcare-associated infections (HAI), including ventilator-associated pneumonia (VAP) [1]. Effective treatments for the management of invasive *A. baumannii* infections are significantly limited due to high rates of resistance to fluoroquinolones, tigecycline, aminoglycosides, and β-lactams including carbapenems [2]. This is particularly notable in isolates associated with HAI (up to 63% in one report) [3]. For these reasons, *A. baumannii* has been identified together with other notable nosocomial multi-drug resistant (MDR) organisms as an ESKAPE pathogen (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pnemoniae, Acinetobacter baumannii, Pseduomonas aeruginosa, and Enterobacter* species) [4]. Due to the continued global rise in *A. baumannii* resistance, in 2013 the Centers for Disease Control and Prevention (CDC) declared MDR *A. baumannii* a serious threat [3]. Carbapenem resistance in *A. baumannii* is independently associated with increased hospital mortality and prolonged ICU and hospital stays [6,7]. In 2017, the World Health Organization (WHO) placed carbapenem-resistant *A. baumannii* (CRAB) on its global priority list as a critical threat to promote and encourage the research and development of new antibiotics [5,8].

Currently, there are a limited number of effective therapies targeting this highly resistant pathogen [9]. The polymyxins, minocycline, tigecycline, amikacin, and sulbactam-containing agents are potential antimicrobial treatment options, yet significant limitations exist for each agent. These include increasing rates of resistance, inadequate *in vitro* susceptibility testing methods, suboptimal tissue concentrations, and toxicity profiles. Emerging treatment options include the combination of "older" agents, new antibiotics, and novel (non-antibiotic) therapies. It is the objective of this review to describe the mechanisms, epidemiology, and the current and developing management strategies of invasive infections due to MDR *A.baumannii*.

Mechanisms of Antimicrobial Resistance

While definitions vary between sources, the term MDR most often refers to *in vitro* resistance to 3 or more antimicrobial classes, while extensively drug-resistant (XDR) is generally used to describe resistance that excludes most standard antimicrobial classes [10]. While MDR isolates may be susceptible to a carbapenem *in vitro*, XDR *A. baumannii* is most often carbapenem-resistant. For *A. baumannii*, pan-resistance

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(PDR) describe isolates with *in vitro* resistance to all β-lactams (including carbapenems), aminoglycosides, fluoroquinolones, and polymyxins [10].

While not the most common of the ESKAPE pathogens, *A. baumannii* is considered one of the most serious threats to healthcare due to its extraordinary ability to quickly adapt to selective environmental pressures (notably antibiotics) [4,11,12]. Mechanisms of drug resistance are diverse and include β-lactamase production, multidrug efflux pumps, aminoglycoside-modifying enzymes, permeability defects, and alteration in target binding sites [13,14]. These mechanisms often work in tandem to convey resistance to multiple antibiotic classes. Resistance may be a result of both vertical transfer and its natural ability to integrate exogenous DNA into its own genome [11].

Production of β-lactamases is generally considered to be the most prevalent mechanism of antibiotic resistance in *A. baumannii*. Each of the Ambler classes of β-lactamases (Class A-D) have been isolated from *A. baumannii*, conferring resistance to many commonly used β-lactam antibiotics [11]. In addition to the intrinsic Class C β-lactamases, other serine-dependent β-lactamases include Class A β-lactamases (TEM, SHV, CTX-M, KPC, and others) that hydrolyze penicillin and cephalosporins and Class D β-lactamases, oxacillinases (OXA). Class D β-lactamases are the most prominent β-lactamase conferring resistance to carbapenems via enzymatic degradation with MDR isolates often containing more than one oxacillinase. Class B β-lactamases, or metallo-β-lactamases (MBL), are the broadest spectrum β-lactamase that hydrolyze almost all β-lactams, including carbapenems. A number of MBL enzymes have been recognized in *A. baumannii* including IMP, VIM, and NDM [13,15].

In addition to β-lactamase production, other well-described mechanisms contributing to MDR isolates include efflux pumps, decreased permeability of the cell wall, and alterations in target sites. Two efflux pumps, tet(A) and tet(B), are tetracycline specific efflux pumps that confer resistance to most tetracyclines, with the exception of tigecycline [16]. Tet(A) confers resistance to tetracycline, while tet(B) is highly suggestive for minocycline resistance [11,17,18]. Multidrug efflux pumps, such as AdeFGH and AdeABC, increase resistance to many antibiotics, including carbapenems, tetracyclines, and even tigecycline [11,15]. Interestingly, subinhibitory concentrations of antibiotics due to low-dose treatment can induce upregulation of the AdeFGH efflux pump, thereby increasing biofilm formation [19]. The AdeABC efflux pump is the most well-described multidrug efflux pump in *A. baumannii* and effects β-lactams, aminoglycosides, tetracyclines, fluoroquinolones, and others [11]. The AdeABC efflux pump can also be upregulated when exposed to subinhibitory concentrations. This mechanism may be most notable when exposing *A. baumannii* to subinhibitory concentrations of tigecycline, such as for treatment of bacteremia, as increased minimum inhibitory concentrations (MICs) have been found *in vitro* and likely contribute to poor clinical outcomes [20]. A reduction in porin channels affecting membrane permeability of many antibiotics have also been reported, while a downregulation or alteration in lipopolysaccharides found on the outer membrane of *A. baumannii* increases resistance to colistin [21]. Finally, overexpression or alteration of target sites via penicillin-binding protein (PBP) result in decreased susceptibility of carbapenems, while the presence of GyrA or aminoglycoside-modifying enzymes are key contributors to quinolone and aminoglycoside resistance, respectively [15].

Epidemology of MDR and XDR *A. baumannii* Infections

With the capabilities of forming biofilm and its propensity to survive harsh, dry conditions, *A. baumannii* is a significant hospital-acquired pathogen, particularly found in the intensive care units (ICU) [22]. Risk factors for *Acinetobacter* spp acquisition include receipt of broad-spectrum antibiotics (specifically later generation cephalosporins), receipt and duration of mechanical ventilation, ICU admission and duration of stay, invasive procedures or devices, total parenteral nutrition, and exposure to contaminated sources [1]. While most notable for causing respiratory tract infections (including VAP), it has also been reported to cause bloodstream infections (BSI), wound or acute bacterial skin and skin structure infections (ABSSSI), complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), and meningitis [1]. *A. baumannii* has the propensity for biofilm formation, making it particularly difficult to eradicate in certain conditions (notably on blood and urinary catheters and endotracheal tubes) [23]. According to the National Healthcare Safety Network (NHSN), *A. baumannii* is the fifth most common VAP pathogen, accounting for 6.1% to 7.5% of all cases [24,25]. Despite only 2% of HAIs are caused by *Acinetobacter* spp., crude mortality in patients with *A. baumannii* infections can be as high as 75% [3,26].

Antimicrobial resistance in *A. baumannii* has demonstrated notable increases in the last several years. For example, the Meropenem Yearly Susceptibility Test Information Collection Program demonstrated a 61% increase in meropenem resistance over a 10-year period (1999-2008). Tobramycin maintained the highest susceptibility rate over this period (59.1%) followed by meropenem (45.7%), levofloxacin (33.9%) and ceftazidime (31.5%) [2]. In a more recent global pooled prevalence study assessing resistance in *A. baumannii* infections from countries participating in the Organization for Economic Cooperation and Development, a 55.7% meropenem resistance rate was reported from 2006-2016. Meropenem resistance increased dramatically from 25.7% in the years 2000 to 2005 compared to 55.6% from 2006 to 2010 and increased further to 70.1% from 2011 to 2016. Amikacin resistance increased from 38.2% to 43.6% to 66.6% over the same period, respectively [27].

Limitations of Established Monotherapy Treatments for MDR *A. baumannii*

Polymyxins

Discovered over 70 years ago, use of the polymyxins (polymyxin B and colistin) have reemerged due to the rise in MDR Gram-negative pathogens, including (but not limited to) CRAB. Use of polymyxins is generally limited by a narrow therapeutic window, with the most significant (often treatment-limiting) adverse effects of nephrotoxicity and neurotoxicity (occurring in 6% to 55% and 7% to 27% of patients, respectively) [28,29]. Polymyxins are further restricted from widespread use in invasive infections due to lack of optimal exposure targets in critically ill patients and lack of reliable *in vitro* colistin testing [30].

Since colistin is administered as the inactive prodrug formulation, colistin methanesulfonate (CMS), some hypothesize that the delayed conversion to the active form may result in reduced bacterial killing and promote the development of treatment-emergent resistance or in subsequent *A. baumannii* isolates [31-33]. When colistin MICs to *A. baumannii* approach the susceptible breakpoint (≤ 2 μg/mL, see **Table 2**), attaining adequate serum concentrations in subjects with normal renal function is reported in only 30-40% of patients receiving loading doses and at the maximum recommended maintenance dose (capped due to increased toxicity risks) [30,34]. Likewise, at the highest recommended doses, polymyxin B is not consistently effective at achieving optimal respiratory tract concentrations [30]. Furthermore, rates of colistin resistance in respiratory isolates are increasing [12,35]. The most concerning report of colistin resistance is from a collection of VAP isolates from Europe. These isolates demonstrated a 47.7% resistance rate with an MIC50/90 of 2 μg/mL and 256 μg/mL, respectively [12]. Previous treatment with colistin is regarded as a significant risk factor for the development of colistin heteroresistance, with colistin resistance being associated with poor clinical outcomes [36-38]. This is most evident in a report of 19 patients infected with a colistin-susceptible isolate and treated with intravenous CMS, inhaled CMS, or both [37]. Colistin resistance was isolated in all 19 patients after a median interval of 20 days. Of note, the authors do not comment on the dosing of CMS. Retrospective evaluations of colistin monotherapy versus a monotherapy comparator agent (ampicillin/sulbactam) in the treatment of mixed CRAB infections demonstrated increased 30-day mortality and mortality during therapy in the colistin cohorts [39,40]. In a prospective evaluation of 28 MDR *A. baumannii* VAP patients treated with colistin or imipenem-cilastatin, clinical efficacy was similar among cohorts (60.0% vs 61.5%) [41]. Efficacy data for the use of monotherapy polymyxins for MDR *A. baumannii* remain scarce with contrasting outcomes. Irrespective of the preceding limitations, polymyxins remain as a primary treatment option for MDR *A. baumannii* with the majority of clinical data surrounding polymyxins as combination therapy.

Minocycline

Minocycline is yet another agent with a recent resurgence due to carbapenem- resistant Gram-negative infections, most notably CRAB. Following a brief hiatus, intravenous minocycline was re-introduced to the market in 2009 and is accompanied with an FDA-approved indication for infections caused by *Acinetobacter* spp. *In vitro* data suggests minocycline may play a role in the treatment of infections involving prosthetic material. In one study, minocycline prevented biofilm formation in 96% of biofilm-forming *A. baumannii* isolates [42]. *In vitro* susceptibility of *A. baumannii* to minocycline ranges from 70.3% to 79.1% in highly carbapenem-resistant isolates (meropenem susceptibilities ranging from 8.7% to 36.4%) [16,43,44]. In contrast, only 37.8% of 200 carbapenem-resistant isolates were minocycline susceptible in one report [45]. The majority of minocycline resistance (71.1%) in *A. baumannii* was due to the presence of the tet(B) clinical strains, whereas when this efflux pump was absent, only 6.7% of isolates were resistant [18]. Clinical success rates in CRAB VAP patients treated with minocycline are high (> 80%), yet clinical data are extremely limited and generally associated with combination therapy [46].

Tigecycline

Tigecycline, a glycylcycline, is a semisynthetic derivative of minocycline that is able to overcome most tetracycline resistance mechanisms. Pharmacokinetic limitations, risk of treatment-emergent failure, and higher mortality (compared to imipenem-cilastatin) in HAP/VAP treated patients limit its widespread use [11,47]. Currently, no Clinical Laboratory Standards Institute (CLSI)-approved breakpoints for tigecycline against *A. baumannii* exist, and (as expected) variability in testing methods have produced inconsistent *in vitro* susceptibility results [48,49]. Although worldwide surveillance studies show that the MIC90 against MDR *A. baumannii* isolates has remained at 2 μg/mL, treatment-emergent resistance has occurred in various case reports at standard dosing [44,50] . This is thought to be a result of suboptimal concentrations of tigecycline (notably in the treatment of bacteremia) combined with overexpression of efflux pumps [20,32,50]. Clinical data concerning tigecycline treatment, often in combination, are not promising as higher rates of in-hospital mortality were observed [51]. Due to these limitations, tigecycline's current role is generally restricted to the treatment of colistin-resistant isolates or as part of combination therapy to prevent the emergence of colistin resistance or heteroresistance.

Amikacin

The emergence of resistance to all aminoglycosides is due to the production of aminoglycoside-modifying enzymes or efflux pumps mechanisms in MDR *A. baumannii* strains [11]. Amikacin is an aminoglycoside used in the treatment of *A. baumannii* infections since it often retains *in vitro* susceptibility to CRAB isolates. However, resistance rates to amikacin have been on the rise [27]. In one report, less than 20% of CRAB isolates maintained susceptibility to amikacin [52]. Treatment-emergent resistance to amikacin has also been shown to develop [53]. Clinical studies evaluating amikacin monotherapy against *A. baumannii* infections are lacking.

Sulbactam-containing regimens

Sulbactam, a class A β-lactamase inhibitor, has intrinsic *in vitro* activity against *A. baumannii* and exhibits high-affinity for penicillin-binding proteins (notably types 1a and 2) [54]. However, resistance to sulbactam-containing combinations (such as ampicillin or cefoperazone) has dramatically increased with MICs often ≥ 16 μg/mL. One study reports ampicillin-sulbactam resistance rates at 72.3% in the years 2011-2016 [27]. In another report, rates of ampicillin/sulbactam susceptibility to carbapenem-susceptible strains was 94.1%, yet when tested against the carbapenem-resistant phenotype, only 19.4% remained susceptible [45].

For these reasons, the majority of sulbactam-containing studies in the treatment of *A. baumannii* have been in combination with other therapies. In a pooled analysis of 13 studies, including one prospective study, sulbactam-containing combination regimens were similar in terms of clinical response, bacteriological response and in-hospital mortality compared to the control group. When analyzing for dose, the high-dose regimen (sulbactam ≥ 9 g/day) was found to be more effective and was well tolerated without serious adverse effects [55]. High-dose sulbactam- containing regimens may be a suitable treatment option for CRAB at an MIC ≤ 4 μg/mL to preserve other therapies and better safety profile.

Combination Therapies

The vast majority of data surrounding combination therapies

Table 1. *In vitro* activity of select therapies against carbapenem-resistant *A. baumannii* isolates

Novel Therapy	Number of CRAB isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)	Reference
Eravacycline	286	0.5	1	≤ 0.06 to ≥ 64	[82]
	707	1	2	0.06 to 8	[158]
	52	0.5	2	≤ 0.016 to 4	[159]
	193	1	2	0.12 to 8	[119]
Cefiderocol	595 (EU)	0.12	1	0.004 to 64	[101]
	173 (NA)	0.25	1	≤ 0.002 to 8	[101]
	562	0.5	2	≤ 0.002 to > 256	[102]
	100	0.5	8	0.06 to > 64	[103]
	768	0.12	1	≤ 0.002 to 64	[104]
	107	0.06	0.5	≤ 0.03 to 2	[105]
	44	0.12	1	0.012 to 4	[160]
ETX2514SUL	731	1	4	≤ 0.06 to 32	[54]
	72	1	2	N/A	[109]
TP-6076	121	0.03	0.06	≤ 0.002 to 0.12	[117]
	326	0.06	0.125	0.008 to 0.5	[119]
	41	0.008	0.063	0.002 to 0.25	[108]

EU: Europe; NA: North America; MIC_{50}: minimum inhibitory concentration at which 50% of isolates are inhibited; MIC_{90}: minimum inhibitory concentration at which 90% of isolates are inhibited; CRAB: carbapenem-resistant *Acinetobacter baumannii*

Table 2. *In vitro* susceptibility testing of select therapies for *A. baumannii* isolates [34].

Antimicrobial Agent	Interpretive Categories and MIC breakpoints (µg/mL)			Comments
	S	I	R	
Colistin	≤ 2		≥ 4	• BMD is only approved MIC testing method; disk diffusion and gradient diffusion methods should not be performed • Predicts MIC to polymyxin B
Minocycline	≤ 4	8	≥ 16	• *A. baumannii* that are susceptible to tetracycline predicts susceptibility to minocycline. If intermediate/resistant to tetracycline, susceptibility to minocycline cannot be assured
Tigecycline	-	-	-	
Amikacin	≤ 16	32	≥ 64	
Ampicillin/sulbactam	≤ 8/4	16/8	≥ 32/16	
Meropenem	≤ 2	4	≥ 8	• Breakpoints are based on a dosage regimen of 1 g administered every 8 h or 500 mg administered every 6 h
Eravacycline	-	-	-	
Omadacycline	-	-	-	
Cefiderocol	≤ 4	8	≥ 16	• Breakpoints based on a dosage regimen of2 g every 8 h administered over 3 h • Testing cefiderocol required iron-depleted cation-adjusted Mueller-Hinton broth (CAMHB). Chelation is used for iron depletion, which removes other cations (calcium, magnesium, and zinc). Following this process, cations are added back to concentrations of calcium 20-25 mg/L, magnesium 10-12.5 mg/L, and zinc 0.5-1.0 mg/L

MIC: minimum inhibitory concentration; S: susceptible; I: intermediate; R: resistant; BMD: broth microdilution

of *A. baumannii* treatment are in patients with pneumonia or mixed infections. Polymyxin-based therapies were most commonly studied (> 50%), while tigecycline-based therapies were the next most frequent (25%) [34].

Several *in vitro* studies have shown synergistic effects of colistin in combination with sulbactam, tigecycline, carbapenems, glycopeptides, and others [56]. In addition, combination regimens may improve microbiological cure rates (when compared to monotherapy), yet has rarely translated to improved clinical outcomes, specifically reductions in mortality [57]. To date, five prospective trials have evaluated colistin-based regimens combined with rifampin, fosfomycin (twice), ampicillin- sulbactam, and meropenem for MDR Gram-negative bacteria, primarily *A. baumannii* [58-62]. When these data are combined, colistin combination therapy showed no difference for in-hospital morality and clinical response. Only the combination with ampicillin/sulbactam (n=39) was associated with a favorable clinical response compared to colistin monotherapy, whereas the remaining studies showed no difference for in-hospital mortality and clinical response [60,63]. While polymyxin-based therapies appear to offer no additional benefit over monotherapy groups, significant limitations to the available data remain. These include high mortality or treatment failure regardless of treatment, documentation of time to appropriate therapy, use of colistin rather than polymyxin B in invasive infections, and suboptimal reporting of MICs, dosing regimens, and use of concomitant antibiotics [30].

The majority of data for tigecycline-based combination therapies are limited to retrospective data in pneumonia treated patients, mainly VAP, and clinical outcomes are not promising. In two retrospective studies evaluating tigecycline monotherapy (100 mg IV loading dose, then 50 mg IV q12h) versus tigecycline-based combination therapy (multiple agents), there was no difference in clinical success, mortality, or microbiological outcomes [64,65]. Similarly, when evaluating tigecycline-based combination therapy versus non-tigecycline-based combination therapy, clinical cure and mortality outcomes were similar [66-69], while microbiological eradication with tigecycline-based therapy was significantly lower in one trial [67]. In a more recent evaluation of 238 adult ICU patients with CRAB pneumonia, those treated with tigecycline-based combination therapies had higher ICU mortality than non-tigecycline therapy (adjusted odds ratio 2.30, 95% confidence interval 1.19-4.46) [70]. When the data are combined, treatment with tigecycline for MDR *A. baumannii* is associated with higher in-hospital mortality and trended towards a longer hospital stay; however, monotherapy versus combination therapies did not show the same difference [51]. While the data for tigecycline-combination therapies has obvious limitations, there seems to be no additional benefit of combination therapy with tigecycline.

Data regarding use of minocycline combination are also sparse. A retrospective review of 36 VAP patients with CRAB isolates and treated with minocycline/doxycycline found a clinical response rate of 81.8% (n=11) for the monotherapy group and 80.0% (n=25) in those receiving minocycline-combination therapy [46]. Another retrospective review demonstrated a clinical success rate of 40/55 (73%) in patients treated with minocycline for MDR *A. baumannii* infection of various types. Of those 55 patients, only three received treatment with minocycline monotherapy while 52 received combination with another active agent [71]. While doses utilized in these studies ranged from 200-400 mg daily, one study suggests utilizing high dose minocycline (e.g. 700 mg daily) or as combination therapy to prevent rapid emergence of resistance [5]. However, the safety and tolerability of such regimens has not been established.

Pharmacokinetic / Pharmacodynamic (PK/PD)-Based Dosing

With the rising of resistance rates of *A. baumannii* and the lack of new antimicrobials to the marketplace in recent years, clinicians have pursued optimizing the dosing of existing agents based on their PK/PD properties. This includes utilizing higher doses, shortening the dosing interval and prolonging infusion times. Each of these principles may be applied to β-lactams (eg, carbapenems, ampicillin/sulbactam) as they demonstrate a time-dependent antibacterial activity with maximal bactericidal effects occurring at serum concentrations approximately four times the MIC of the pathogen for at least 40% of the dosing interval [72]. Additionally, greater clinical cure and bacteriological eradication is achieved if the free drug concentration remains above the MIC of the pathogen for 100% of the dosing interval in critically ill patients [73].

While high-quality efficacy data are limited with this approach, β-lactam agents are generally well tolerated without an increased risk of toxicity when intermittent infusions were compared to prolonged infusion strategies. In the largest of these randomized control trials (all pathogens n=214, *Acinetobacter* spp. n=20), continuous infusion meropenem had a similar clinical cure rate when compared to intermittent dosing [74]. Higher microbiological success rates, shorter ICU lengths of stay, and shorter durations of meropenem therapy were observed with no difference in safety outcomes. In a meta-analysis comparing prolonged infusions to intermittent bolus doses of meropenem, the prolonged infusion cohort had higher rates of clinical success (OR 2.10, 95% CI 1.31-3.38) and lower mortality (RR 0.66, 95% CI, 0.50-0.88) [75]. In the single study evaluating 30 HAP patients with MDR *A. baumannii* isolates, no difference in clinical efficacy or relapse rates were observed among cohorts [76]. Of note, doripenem is the lone carbapenem that should not utilize prolonged infusions, as higher mortality rates were seen among patients with microbiologically confirmed late-onset VAP [77].

To overcome suboptimal tigecycline concentrations, a phase II study and a retrospective analysis demonstrated higher tigecycline doses (100 mg IV every 12 hr) in VAP-treated patients were associated with improved clinical cure rates compared to standard doses without increases in adverse events [78,79]. While higher doses may be warranted in severe infections (eg, pneumonia), clinical data are limited due to early termination of the phase II study due to poor recruitment.

Newly Approved Therapies

Eravacycline

Eravacycline (Xerava™) is a novel, fully synthetic fluorocycline antibiotic approved by the FDA in August 2018. Similar to other tetracycline derivatives, it inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit [80]. Eravacycline is structurally similar to tigecycline, except it has

two modifications to the D-ring core at C-7 and C-9 [80]. These modifications enhance its antibacterial spectrum of activity and its stability against tetracycline- specific resistance mechanisms (e.g. efflux pumps and ribosomal protection proteins) [81].

Eravacycline demonstrates a broad spectrum of activity *in vitro* against aerobic and anaerobic Gram-positive and Gram-negative pathogens, including MDR *A. baumannii* [80,82-84]. The MIC50/90 were 0.06/0.5 μg/mL and 0.5/1 μg/mL(respectively) against *A. baumannii* isolates from patients in 13 Canadian hospitals and 11 hospitals in New York [81,84]. Another study reported MIC50/90 values against CRAB isolates of 0.5 μg/mL and 1 μg/mL, respectively (**Table 1**) [82]. In two *in vitro* studies, 89% and 96% of CRAB isolates had eravacycline MICs of ≤ 1 μg/mL [82,83]. When compared to tigecycline, eravacycline has been shown to be two- to four-fold more potent than tigecycline against *A. baumannii* isolates, including carbapenem-resistant isolates [81-84].

The efficacy of eravacycline has been evaluated in several Phase II and III studies for the management of cIAI and cUTIs [85-88]. Despite these numerous studies, efficacy relating to infections caused by *A. baumannii* is limited. In a pooled analysis of the IGNITE 1 and 4 studies, the clinical and microbiological response rates were 100% for patients with *A. baumannii*, including MDR isolates [89]. Of note, IGNITE 1 only had 8 patients and IGNITE 4 had 5 patients with *A. baumannii* infections [85,90]. In contrast, the efficacy of eravacycline in cUTIs has not been as promising [88,91]. Eravacycline is eliminated predominately in the feces (with low urinary excretion), suggesting eravacycline may not be an effective treatment option for UTIs caused by MDR *A. baumannii*.

Eravacycline has been well-tolerated in clinical studies and most adverse events have been similar to comparator agents with a few exceptions. Notably, the reported incidences of infusion site reactions, nausea, and vomiting have been higher compared to carbapenems [80]. Despite higher incidences of nausea and vomiting compared to carbapenems, they are still significantly lower than those reported with tigecycline (6.5% vs 26% and 3.7% and 18%, respectively) [44,80]. One potential disadvantage of eravacycline compared to other therapies for MDR *A. baumannii* is the concern for drug interactions. Eravacycline is a substrate for the CYP450 enzyme system, specifically CYP3A. When administered concomitantly with a strong CYP3A inducer (e.g. rifampin), the dose of eravacycline should be increased to 1.5 mg/kg IV every 12 hours. There are no formal recommendations regarding eravacycline and strong CYP3A inhibitors at this time. Additionally, eravacycline has the potential to increase the effects of warfarin, thus dose adjustments may be warranted [80].

Omadacycline

Omadacycline (NUZYRA™) is a semisynthetic derivative of minocycline and is a novel aminomethylcycline antibiotic. Much like eravacycline, omadacycline has the ability to remain active in the presence of tetracycline efflux and ribosomal protection genes resulting in a broad spectrum of activity [92].

In vitro omadacycline data against a collection of 2101 worldwide clinical isolates of *A. baumannii* demonstrated an $MIC_{50/90}$ of 2 μg/mL and 4 μg/mL, respectively, with 91.5% of isolates inhibited at MIC values ≤ 4 μg/mL [92]. In a collection of 441 *A. baumannii* isolates from 2016, omadacycline $MIC_{50/90}$ values were slightly higher at 4 μg/mL and 8 μg/mL, respectively, while 71.2% of isolates were inhibited at an MIC of ≤ 4 μg/mL. Additionally, in the 293 tetracycline resistance strains, the $MIC_{50/90}$ values were unchanged, although only 57.3% of strains were inhibited at 4 μg/mL [93].

Omadacycline was granted FDA approval in October 2018 for the treatment of community-acquired bacterial pneumonia (CABP) and ABSSSI [73]. In two randomized controlled trials, OPTIC and OASIS-1, treatment with omadacycline was noninferior for early clinical response when compared to moxifloxacin and linezolid, respectively [94,95]. However, both trials failed to include MDR Gram-negative pathogens, including *A. baumannii*. While studies are nearing completion for cystitis and pyelonephritis, it is unlikely that these will provide any useful data to its clinical utility in the treatment of *A. baumannii*.

Agents Undergoing Phase I-III Clinical Trials in the US

Cefiderocol

Cefiderocol (previously S-649266) is a parenteral siderophore cephalosporin currently in phase III clinical trials for the treatment of nosocomial pneumonia and other severe infections caused by Gram-negative pathogens [96,97]. Cefiderocol has a unique catechol moiety at the C-3 position contributing to its mechanism of action, ability to chelate with ferric iron, and ultimately bacterial cell entry. Termed a "Trojan horse" antibiotic through a strategy of exploiting the iron transport mechanism of bacteria, the siderophore-drug complex selectively interacts with the siderophore receptors on the bacterial cell surface to be actively transported across the outer membrane. Due to this mechanism, this novel antimicrobial is able to circumvent permeability-mediated drug resistance [98,99]. The halogenated catechol group along with the quaternary amine at the C-3 position produces increased *in vitro* activity when certain MBLs, KPC and OXA producing strains are present [100].

Cefiderocol demonstrates potent *in vitro* activity in isolates tested against a broad range of ESBL-producing Gram-negative organisms, including MDR and XDR *P. aeruginosa* and *A. baumannii* (susceptible breakpoint of 4 μg/mL, **see Table 2**), with negligible activity against Gram-positive aerobic and anaerobic bacteria [98]. When tested against 1148 *A. baumannii* isolates from North America and Europe, the MIC_{90} value for cefiderocol was 1 μg/mL. When evaluated against CRAB, cefiderocol retained an MIC_{90} of 1 μg/mL and 96.9% (744/768) of meropenem-nonsusceptible isolates had MICs of ≤ 4 μg/mL [101]. Other studies confirmed this potent activity against CRAB isolates ranging from 88% to 96.9% with MICs of ≤ 4 μg/mL [102-104]. With regard to colistin-nonsusceptible strains of *A. baumannii* (n=121), cefiderocol's MIC range was ≤ 0.002 to 8 μg/mL with an MIC_{90} of 2 μg/mL [101]. In another study comparing colistin-resistant strains versus colistin non-resistant strains, the MIC range of cefiderocol did not differ [105]. When evaluating specific carbapenemase enzymes, there does not appear to be a correlation of carbapenemase production and cefiderocol resistance [104]. Of note, the mechanisms conferring elevated MICs are currently being evaluated [104].

Cefiderocol has been well tolerated in phase I and II studies with its safety profile being similar to that of other cephalosporins [106,107]. Most adverse events have been gastrointestinal

related (diarrhea, constipation, nausea, vomiting) while occurring less frequently than the comparator agent (12% vs 18%, respectively) [107]. Cefiderocol is a β-lactam with a chemical structure most closely related to cefepime. Allergic reactions are possible, however, only one patient discontinued treatment due to urticaria during the infusion. This adverse event was deemed not to be an antibody-mediated reaction [106].

To date, the efficacy of cefiderocol has been evaluated in one completed Phase II trial. This study included 452 patients for the treatment of cUTI at risk for MDR Gram-negative uropathogens, primarily *E. c*oli and *K. pneumoniae (*no *A. baumannii* isolates noted), compared to high-dose imipenem-cilastatin. Cefiderocol met the noninferiority primary endpoint of the composite of clinical and microbiological outcomes at the test-of-cure (73% vs 55%, p=0.0004) and achieved superiority in the post-hoc analysis [107].

Two phase III clinical trials focusing on the treatment of invasive MDR pathogens are currently enrolling patients [96,97]. The CREDIBLE-CR trial (NCT02714595) is estimated to enroll 150 patients to compare cefiderocol to best available therapy (a polymyxin-based or non-polymyxin based regimen) for the treatment of severe infections (BSI, HAP/VAP, cUTI, sepsis) caused by CR Gram-negative pathogens [96]. The APEKS-NP trial (NCT03032380), is estimated to enroll approximately 300 patients to compare 14-day all-cause mortality with cefiderocol versus meropenem (both in association with linezolid) in adults for the treatment of nosocomial pneumonia caused by Gram-negative pathogens [97].

ETX2514 + sulbactam (ETX2514SUL)

ETX2514, a novel diazabicyclooctane β-lactamase inhibitor, also has intrinsic activity to *Enterobacteriaceae* and also has the ability to fully restore sulbactam's activity against *A. baumannii* while protecting against all serine-dependent β- lactamases (Class A, C, and D) [108]. In a globally diverse collection of *A. baumannii* isolates (n=1131), the *in vitro* activity of ETX2514SUL was 16-fold more active than sulbactam alone (MIC_{90} 4 μg/mL vs 64 μg/mL, respectively) [54]. Additionally, ETX2514SUL retained the same activity when subsets of meropenem-resistant (**Table 1**), colistin-resistant, and MDR isolates were evaluated, while there was reduced activity against one isolate containing an MBL [54]. Similarly, a study of 72 *A. baumannii* isolates with the majority being MDR isolates, had an MIC_{90} of 2 μg/mL [109]. Spontaneous resistance has not been observed and the use of this agent has not resulted in the generation of resistant β-lactamases to ETX2514SUL [110].

One phase II study has been completed with positive results [111]. This phase II double-blind, placebo-controlled trial of 80 patients compared ETX2514SUL (1g/1g q6h for 7 days) plus imipenem-cilastatin to imipenem-cilastatin plus placebo in adult patients with cUTI including acute pyelonephritis. Outcomes were similar between the two groups. In an exploratory analysis, eight patients had imipenem-non-susceptible pathogen resulting in microbiological eradication in 3/3 (100%) in the ETX2514SUL plus imipenem-cilastatin cohort vs 3/5 (60%) patients in the imipenem-cilastatin plus placebo cohort. Entasis Therapeutics plans to initiate a Phase III study focused on CRAB infections in the first quarter of 2019 [111].

TP-271

TP-271 is a novel, fully-synthetic fluorocycline antibiotic under the development by Tetraphase Pharmaceuticals for treatment of CABP, pneumonic tularemia, and other serious respiratory bacterial/bio threat infections [112,113]. When the most common tetracycline-specific mechanisms are present, efflux pumps and ribosomal protection proteins, TP271 remains active *in vitro* [114]. When evaluated against four CRAB isolates in a neutropenic lung mouse model, TP271 was dose-dependent with area under the curve (AUC) to MIC ratio best correlating with efficacy. This study supported the future research in respiratory infections including *A. baumannii* infections. A phase I study of escalating doses was well tolerated with gastrointestinal symptoms being most frequently reported [112]. Additionally, there are two ongoing phase I studies assessing single and multiple ascending doses of an oral formulation [115,116].

TP-6076

Another novel, fully synthetic tetracycline is currently in phase I studies. It has a similar mechanism of action to tetracyclines in which it disrupts bacterial synthesis by binding to the 30S ribosomal subunit. *In vitro* data have shown potent activity against CRAB isolates with many containing OXA and OXA-like β-lactamases [117-120]. In the largest of these studies with 326 global isolates from the years 2005-2016, TP-6076 had MIC_{50} and MIC_{90} values of 0.06 μg/mL and 0.125 μg/mL while eravacycline had values of 0.5 μg/mL and 1 μg/mL, respectively (**Table 1**) [119]. TP-6076 did not demonstrate higher MIC values when comparing colistin-susceptible and non-susceptible isolates. However, the MIC_{90} was one dilution lower for tigecycline- and minocycline-susceptible and non-susceptible isolates [117]. In isolates overexpressing genes encoding the AdeABC multidrug efflux pump, the major contributor to tigecycline resistance, TP-6076 had an MIC range of 0.008 to 0.13 μg/mL [118]. Gastrointestinal events (nausea and vomiting) were the most frequently reported adverse event with higher rates at the higher doses [121]. A second phase I study is currently recruiting to assess the safety and bronchopulmonary PK with a dose of 30 mg daily [122]. With very little data, it seems as if TP-6076 is minimally impacted by the major resistance mechanisms of the tetracycline class with MICs mostly unaffected by serine-dependent β-lactamases.

VNRX-5133 + cefepime

Combined with cefepime, VNRX-5133 is a cyclic boronate β- lactamase inhibitor with broad-spectrum activity against serine- (classes A, C, and D) and metallo-β-lactamases (VIM/ NDM, class B). This combination agent is primarily being explored for CRE and CR *Pseudomonas aeruginosa*. *In vitro* data describes VNRX-5133/cefepime as a highly active agent against *Enterobacteriaceae* and *P. aeruginosa* that is resistant or has evolved resistance to other β-lactam/ β-lactamase inhibitors, however, its use against *A. baumannii* has not been described [123].

Zidebactam (WCK 5107), WCK 5153, cefepime/zidebactam (WCK 5222)

Zidebactam (WCK 5107) and WCK5153 are novel non-β-lactamase bicyclo-acyl hydrazide β-lactam enhancer antibiotics that are under development for MDR *Enterobacteriaceae*, *P. aeruginosa*, and CRAB [124]. These novel agents have a dual mechanism of action where they enhance β- lactams

through complementary high-affinity binding to PBP2 while strongly inhibiting class A and C β-lactamases along with modest inhibition of Class D β-lactamases. When zidebactam is combined with cefepime (WCK 5222) *in vitro* against 5946 *Enterobacteriaceae* isolates, the combination demonstrated potent activity even against CR isolates. However, the MIC range of 639 *A. baumannii* isolates was 0.06 μg/mL to > 64 μg/mL with only 44.3% of isolates having a MIC ≤ 8 μg/mL [125]. These are less than optimal *in vitro* results against *A. baumannii* isolates, yet *in vivo* activity against OXA-23 or OXA-24 isolates in a neutropenic thigh model and lung infection model showed greater than expected results [110,126].

WCK 5222 has been well tolerated in Phase I studies in subjects with both normal and impaired renal dysfunction [127,128]. Both agents are highly renally eliminated and will require dose adjustments based on the severity of dysfunction [127]. The pharmacodynamic property predicting therapeutic response for WCK 5222 is the free drug concentration in plasma exceeding the MIC over the dosing interval (T_f > MIC). In subjects with normal renal function receiving multiple doses of either 2 g/1 g or 2 g/2 g of cefepime/zidebactam, AUC and maximum serum concentration (Cmax) were dose proportional, no accumulation occurred, and no pharmacokinetic interaction was observed when co-administered [128]. Phase I studies evaluating plasma and lung tissue provided data to support the use of WCK 5222 in the treatment of pneumonia, while other organ systems have yet to be evaluated [129].

Other Antibiotics

AIC-499 (BL) + unknown BLI

AIC499 is termed as an innovative β-lactam antibiotic and is combined with a currently unspecified β-lactamase inhibitor. According to the drug developer's website, AIC499 shows potent activity against many Gram-negative pathogens including MDR *P. aeruginosa* and *A. baumannii* for use in cUTI and cIAI. Phase I studies were expecting results in 2017 with plans for future phase II studies, however, no trials are currently registered on multiple government trial registries. The phase I study was to be a single dose study in 48 healthy subjects immediately followed by a multiple ascending dose study in 36 subjects at the Medical University of Vienna, Austria. The Innovative Medicines Initiative with the COMBACTE-MAGNET project is supporting AiCuris in the clinical development of AIC499 [130].

GSK3342830 (GSK830)

GSK3342830 or GSK830 is a catechol-cephalosporin with a spectrum of activity similar to that of the other siderophore cephalosporin, cefiderocol [131]. *In vitro* data are promising against *A. baumannii* with 94 MDR global isolates having MIC_{50} and MIC_{90} of 0.06 μg/mL and 0.6 μg/mL, respectively [131]. However, a phase I dose-escalation study was stopped early. It is important to note that 35.7% of subjects discontinued the study drug during the multi- dose arm due to fever, headache, malaise or transaminitis [132].

SPR741 (formerly NAB74)

SPR741 (formerly NAB74) is a polymyxin-B-like molecule being developed as an antibiotic adjuvant for the treatment of XDR *A. baumannii*. This molecule does not have certain structural features of the polymyxins that contribute to their nephrotoxicity, however, this agent has minimal intrinsic activity against *A. baumannii* and must be used as combination therapy [133]. When combined with rifampin in pre-clinical data of a murine pneumonia model, this combination has shown to be effective in reducing bacterial burden (suggesting utility in *A. baumannii* lung infections) [133,134]. SPR741 has a short half-life of approximately 3 hours with 50% of the drug excreted in the urine within one-hour post-dose with no evidence of accumulation with 400 mg administered intravenously every 8 hours [135]. Other phase I studies have been completed in 2017; however, no results are available [136,137].

Novel Therapies

Monoclonal antibodies

Antibacterial monoclonal antibodies (MAbs) have the ability to protect (e.g., palivizumab for prophylaxis against respiratory syncytial virus) and treat (e.g., obiltoxaximab for treatment of inhalational anthrax) against deadly infections. MAbs are highly specific and may lessen the disruption of normal gastrointestinal flora with less selective pressure for cross-resistance with antibiotics [138]. Additionally, antibacterial MAbs could have an enormous impact on controlling institutional outbreaks once the pathogen is known. However, aside from their narrow spectrum, there are concerns surrounding the use of MAb therapy in infectious diseases. Notably, these include high cost, complex administration, and barriers to MAb development [139].

Several studies have shown MAb efficacy against *A. baumannii* in mice when provided as active immunization (i.e., vaccine) and passive immunization in various models [140-143]. Most recently, a MAb, C8 in an *A. baumannii* mice pneumonia and sepsis model demonstrated enhanced bacterial clearance, prevented progression to septic shock, and had synergistic activity with colistin. An area of concern in this study was the ability of C8 to bind to only 60% of *A. baumannii* strains tested [144].

Phage therapy

As *A. baumannii* resistance continues to increase and the portfolio of antibiotics is becoming increasingly less effective, bacteriophage therapy becomes an alluring option. Termed "phage," this technology is simply a virus engineered to infect a pathogenic bacterium, replicate inside the host cell, and finally rupture the bacterial cell wall resulting in cell death [145]. Similarly to MAbs, phage are highly specific, infecting only prokaryotic cells resulting in minimal toxicities and side effects [146]. Additionally, their mechanism of action is completely independent of antibiotics so their efficacy is not altered against highly resistant bacteria [147]. Other advantages of this technology include the potential for combinations with traditional therapies [148]. However, numerous questions about this therapy remain. This therapy is not currently recognized as a drug and a clear lack of regulatory framework exists [145,149]. Because it is given in high quantities, the human body may recognize phage as foreign antigens, produce antibodies, and theoretically result in a diminished activity. Finally, the possibility of horizontal gene transfer can occur resulting in the transfer of resistance genes and virulence factors between bacterium and phage [146].

Numerous studies (n=30) with a total of 1,152 patients have been conducted to evaluate the efficacy and safety of phage therapy against ESKAPE pathogens. Of the 30 studies, 87% showed

efficacy of reducing bacterial growth with successful outcomes. Twenty-two studies reported on the safety profile with only two reporting side effects after phage treatment [147]. Regarding *A. baumannii* specific infections, several animal models have been conducted in MDR and CRAB isolates with promising results [150-155]. To date, only two human case reports of phage therapy directed against MDR *A. baumannii* have been published [156,157]. The first describes a case of a 68-year-old diabetic patient with necrotizing pancreatitis complicated by an MDR *A. baumannii* infection. In conjunction with combination antibiotics, three phage cocktails were provided intravenously and percutaneously into the abscessed cavity in repeated daily intervals for a total of 59 days. The patient's initial status was improved after commencing phage therapy with an eventual return to health. Interestingly, however, subsequent cultures were obtained with strains showing reduced susceptibility to phage therapy [157]. The second case report describes a 77-year- old traumatic brain injury patient undergoing craniectomy complicated by cerebritis and subdural and epidural empyemas. Debridement was deemed necessary and intraoperative cultures grew MDR *A. baumannii*. In addition to antibiotics, the first dose of phage therapy was administered intravenously on day 12 and continued for 8 days (98 intravenous administrations). While the site of infection healed, the patient did not clinically improve and family withdrew care on hospital day 19 [156].

Conclusion

Acinetobacter baumannii has the extraordinary adaptive ability to develop resistance to overcome all treatment options currently available. Despite the promising focus in recent years on developing novel therapies, more real-world experience in critically ill patients with invasive MDR *A. baumannii* infections is needed to solidify a place in therapy for one or more of these novel therapies. Moreover, many of these novel antimicrobials have already demonstrated vulnerability as reports of increasing MICs have been observed. Despite these challenges, novel treatment modalities for MDR *A. baumannii* are encouraging, yet further advances will be required as the era of antimicrobial resistance continues.

Declarations of Potential Conflict of Interest

The authors declare that they have no competing interests.

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