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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (K CLAEYS AND A VEGA, SECTION EDITORS)

Multidrug Resistant *Acinetobacter baumannii*: Resistance by Any Other Name Would Still be Hard to Treat

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Abstract

Purpose of Review *Acinetobacter baumannii* (AB) is an infamous nosocomial pathogen with a seemingly limitless capacity for antimicrobial resistance, leading to few treatment options and poor clinical outcomes. The debatably low pathogenicity and virulence of AB are juxtaposed by its exceptionally high rate of infection-related mortality, likely due to delays in time to effective antimicrobial therapy secondary to its predilection for resistance to first-line agents. Recent studies of AB and its infections have led to a burgeoning understanding of this critical microbial threat and provided clinicians with new ammunition for which to target this elusive pathogen. This review will provide an update on the virulence, resistance, diagnosis, and treatment of multidrug resistant (MDR) AB.

Recent Findings Advances in bacterial genomics have led to a deeper understanding of the unique mechanisms of resistance often present in MDR AB and how they may be exploited by new antimicrobials or optimized combinations of existing agents. Further, improvements in rapid diagnostic tests (RDTs) and their more pervasive use in combination with antimicrobial stewardship interventions have allowed for more rapid diagnosis of AB and decreases in time to effective therapy. Unfortunately, there remains a paucity of high-quality clinical data for which to inform the optimal treatment of MDR AB infections. In fact, recently completed studies have failed to identify a combination regimen that is consistently superior to monotherapy, despite the benefits demonstrated in vitro. Encouragingly, new and updated guidelines offer strategies for the treatment of MDR AB and may help to harmonize the use of high toxicity agents such as the polymyxins. Finally, new antimicrobial agents such as eravacycline and cefiderocol have promising in vitro activity against MDR AB but their place in therapy for these infections remains to be determined.

Summary Notwithstanding available clinical trial data, polymyxin-based combination therapies with either a carbapenem, minocycline, or eravacycline remain the treatment of choice for MDR, particularly carbapenem-resistant, AB. Incorporating antimicrobial stewardship intervention with RDTs relevant to MDR AB can help avoid potentially toxic combination therapies and catalyze the most important modifiable risk factor for mortality—time to effective therapy. Further research efforts into pharmacokinetic/pharmacodynamic-based dose optimization and clinical outcomes data for MDR AB continue to be desperately needed.

Keywords *Acinetobacter baumannii* · Resistance · Rapid diagnostics · Combination therapy · Polymyxins · Tetracyclines

Introduction

Despite the current renaissance in antimicrobial research and development, *Acinetobacter baumannii* (AB) remains the most important unmet medical need among resistant Gram-negative pathogens. The inability to optimally diagnose and manage AB infections in a timely manner, particularly those due to resistant phenotypes, stems from its complex genus, the repertoire of unique intrinsic and acquired resistance mechanisms, the lack of routine use of appropriate rapid diagnostic tests (RDTs), a limited number of effective treatment options, and the longstanding debate regarding its true virulence and pathogenicity [1]. For years, there has been significant challenge in differentiating the species within the *A. baumannii-calcoaceticus* (ABC) complex, which includes AB, *A. calcoaceticus*, *A. nosocomialis*, and *A. pittii*, with AB being the most clinically relevant and virulent species. Additionally, owing to the many possible resistant phenotypes of AB, the

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nomenclature for referring to AB is often inconsistent and clinically confusing. For example, multidrug resistant (MDR) AB [2] may or may not qualify as difficult-to-treat (DTR) [3•], and the most commonly encountered phenotype—carbapenem-resistant AB (CRAB) —may qualify as both or neither. Although these inconsistencies in naming conventions throughout research and clinical practice likely further complicate the understanding of this challenging pathogen, antimicrobial resistant AB (MDR, DTR, and/or CRAB) poses a significant public health threat and is responsible for excess morbidity, mortality, and healthcare costs regardless of how it is named. Fortunately, advances in our understanding of its mechanisms of resistance, progresses in antimicrobial pharmacokinetics/pharmacodynamics (PK/PD), improvements in identification of AB and its resistance mechanisms, the development of novel antimicrobial agents, and new clinical data informing the optimal therapy for AB will continue to help turn the tide against this enigmatic pathogen.

Mechanisms of Resistance

The management of AB infections is particularly complicated due to this pathogen's multiple intrinsic and acquired mechanisms of resistance including β-lactamases, aminoglycoside-modifying enzymes, efflux pumps, permeability defects, and target site modifications. AB often simultaneously co-harbor many resistance mechanisms, which may eliminate the activity of multiple, and sometimes all, antibiotic classes. Thus, it is critical that empiric and definitive antimicrobial therapy for AB infections is guided by an understanding of potential resistance mechanisms and susceptibility trends. The susceptibility rates of various agents against ABC complex are displayed in Table 1.

β-Lactams

β-Lactam resistance in AB is primarily mediated by the presence of β-lactamases, decreased permeability due to modifications in the outer membrane, alterations in penicillin-binding proteins (PBP), and efflux pumps [6]. Carbapenems are an important therapeutic option for AB due to widespread resistance to penicillins and cephalosporins. However, (CRAB) have emerged as a major problem in the USA and worldwide [10–12]. From 2009–2013, 2915/6507 (44.8%) AB isolates originating from 206 acute care hospitals across the USA were carbapenem-resistant [13]. AB is capable of possessing typical Ambler class A β-lactamases capable of hydrolyzing penicillins and cephalosporins (TEM, SHV, CTX-M, SCO, PER, and VEB) and also less commonly encountered carbapenemases such as GES-5, GES-14, and various KPC-type enzymes [14–17]. Although relatively rare at this time, AB isolates producing Ambler class B metallo-β-lactamases (MBLs) (i.e., IMP, VIM, and NDM) have also been reported [18] and are particularly worrisome due to their ability to hydrolyze all β-lactams except for aztreonam [19]. Finally, the most problematic groups of β-lactamases among resistant AB are the chromosomally encoded Ambler class C and acquired class D enzymes. *Acinetobacter*-derived cephalosporinase (ADC), an Ambler class C AmpC-type cephalosporinase, contributes to the resistance of penicillins, cephalosporins, and aztreonam, but not carbapenems [20]. The Ambler class D β-lactamases are composed of various oxacillinases (OXA), including subgroups of plasmid-mediated OXAs with carbapenemase activity such as OXA-23, OXA-24, OXA-40, OXA-51, and OXA-58 [20, 21]. Specifically, OXA-23 is a globally disseminated carbapenemase; this is highly prevalent among CRAB [22] and can be used to predict carbapenem susceptibility via genotypic rapid diagnostic tests, as discussed below [23]. Additionally, although sulbactam has intrinsic activity against *Acinetobacter* spp. and may retain activity against some CRAB isolates, resistance is widespread globally as it is susceptible to hydrolysis by many of the intrinsic and acquired β-lactamases carried in clinical AB strains, such as TEM, ADC, and OXA-23 [24–26•, 24–29].

Polymyxins

Historically considered agents of last resort, the polymyxins, have emerged as important agents in the management of AB infections due to extensive resistance to other antimicrobial classes. Although >90% of AB in the USA are susceptible to the polymyxins, they can infrequently be impacted by various mechanisms of resistance, the most common of which are structural changes to the target site lipid A. First, spontaneous mutations occurring in the lipid A biosynthesis genes (*IpxA*, *IpxC*, and *IpxD*) lead to complete loss of lipid A, resulting in high-level polymyxin resistance [30]. Second, mutations in the *pmrCAB* operon that lead to constitutive activation of PmrAB, a two-component regulatory system responsible for sensing and responding to environmental conditions via regulation of gene expression involved in lipid A synthesis, result in induction of the PmrC transferase [31–33]. PmrC overexpression leads to the addition of phosphoethanolamine to lipid A phosphates, which in turn reduces the negative charge of the lipopolysaccharide (LPS), ultimately compromising the essential interaction between the polymyxins and LPS. Third, the addition of galactosamine to lipid A phosphates also diminishes the polymyxin-LPS interaction by reducing the negative charge of the LPS [34]. To date, the plasmid-mediated colistin resistance gene, *mcr*, has not been reported in clinical isolates of AB, although a recent report identified an AB strain isolated from pig feces in China harboring *mcr-4.3* [35]. Due to its transmissibility, it is possible that *mcr*-harboring AB strains will be clinically encountered in the near future,

Table 1 In vitro activity of select agents against clinical *A. baumannii-calcoaceticus* species complex isolates

	MIC (mg/L)			Susceptibility (%)			Ref
	MIC_{50}	MIC_{90}	Range	S	I	R	
All isolates (n = 448)							
Aminoglycosides							
Amikacin	4	>32	≤0.25 – >32	82.6	2.5	15.0	[4]
Gentamicin	1	>16	≤0.12 – >16	69.9	6.0	24.1	[4]
Plazomicin[a,b]	2	16	≤0.06 – >128	67.4	7.4	25.2	[5]
Tobramycin	1	>16	≤0.12 – >16	79.2	2.7	18.1	[4]
β-Lactams ± β-lactamase inhibitors							
Ampicillin-sulbactam	4	64	1 – >64	64.1	10.9	25.0	[4]
Cefepime	8	>16	0.25 – >16	56.7	9.2	34.1	[4]
Ceftazidime	8	>32	0.5 – >32	63.4	7.1	29.5	[4]
Imipenem	0.25	>8	≤0.12 – >8	66.5	2.0	31.5	[4]
Meropenem	1	>32	0.03 – >32	65.2	0.9	33.9	[4]
Fluoroquinolones							
Ciprofloxacin	0.5	>4	0.06 – >4	58.1	2.2	39.7	[4]
Levofloxacin	0.25	>16	0.03 – >16	62.7	1.3	59.2	[4]
Polymyxins							
Colistin	0.25	1	≤0.06 – >8	93.8	–	6.2	[4]
Tetracyclines							
Eravacycline[c]	0.5	2	≤0.015 – 16	–	–	–	[6]
Minocycline	0.25	8	0.06 – 32	87.8	4.2	8.0	[4]
Omadacycline[a,d]	4	8	0.06 – >32	71.2	22.2	6.6	[7]
Tetracycline	4	>16	0.5 – >16	54.0	7.6	38.4	[4]
Tigecycline[a]	0.5	4	≤0.06 – >8	79.2	16.3	4.5	[4]
Carbapenem-resistant isolates (n = 152)[e]							
Aminoglycosides							
Amikacin	16	>32	0.5 – 32	52.0	5.3	42.8	[4]
Gentamicin	16	>16	0.25 – > 16	25.7	13.8	60.5	[4]
Plazomicin[f]	16	16	0.5 – 64	NR	NR	NR	[8]
Tobramycin	8	>16	0.25 – > 16	44.1	5.9	50.0	[4]
β-Lactams ± β-lactamase inhibitors							
Ampicillin-sulbactam	32	>64	2 – > 64	9.2	21.1	69.7	[4]
Cefepime	>16	>16	8 – > 16	3.3	14.5	82.2	[4]
Ceftazidime	>32	>32	1 – > 32	15.1	11.8	73.0	[4]
Imipenem	>8	>8	1 – > 8	1.3	5.9	92.8	[4]

Table 1 (continued)

	MIC (mg/L)			Susceptibility (%)			Ref
	MIC_{50}	MIC_{90}	Range	S	I	R	
Meropenem	>32	>32	8 – > 32	0.0	0.0	100.0	[4]
Fluoroquinolones							
Ciprofloxacin	>4	>4	1 – >4	0.7	0.0	99.3	[4]
Levofloxacin	>16	>16	0.5 – >16	1.3	3.3	95.4	[4]
Polymyxins							
Colistin	0.25	8	0.12 – >8	85.5	–	14.5	[4]
Tetracyclines							
Eravacycline[a,g]	0.5	1	≤0.06 – 8	78.0	–	–	[9]
Minocycline[h]	2	16	0.25 – 32	70.6	8.2	21.2	[4]
Tetracycline[h]	>16	>16	4 – >16	4.7	7.1	88.2	[4]
Tigecycline[a]	4	8	0.25 – >8	45.4	42.1	12.5	[4]

S susceptible, *I* intermediate, *R* resistant, *NR* not reported

[a] Susceptibility interpretations based on approved FDA breakpoints for Enterobacteriaceae

[b] *n* = 95 *Acinetobacter* spp. isolates collected from US hospitals during 2014–2015

[c] *n* = 717 *A. baumannii* isolates collected from US hospitals during 2013–2016

[d] *n* = 441 *A. baumannii* isolated collected from US and European medical centers during 2016

[e] Defined as isolates resistant to imipenem and/or meropenem based 2019 CLSI criteria unless otherwise noted

[f] *n* = 69 imipenem-resistant *A. baumannii* isolates collected from a single medical center in Spain

[g] *n* = 286 carbapenem-resistant *A. baumannii* isolates collected from eight European countries and Singapore during 2005–2015

[h] *n* = 85

although the fitness cost associated with *mcr-1* expression may limit its pathogenicity [36].

Tetracyclines

Similar to the polymyxins, there has been a renewed interest in the clinical use and development of tetracyclines due to their potent activity against AB, especially MDR strains like CRAB. Importantly, activity varies between individual agents within the tetracycline class. Generally speaking, the potency against AB is as follows: tetracycline < doxycycline < omadacycline < tigecycline < minocycline < eravacycline [37, 38]. Resistance to tetracyclines may be attributed to four general mechanisms: efflux, ribosomal protection, target modification, and enzymatic inactivation [39]. In AB, tetracycline efflux may be mediated by the presence of acquired and/or intrinsically produced tetracycline-specific pumps. Tet(A) and Tet(B) are the most common tetracycline-specific efflux pumps encountered in AB and both pumps confer resistance to tetracycline and doxycycline whereas only Tet(B) influences minocycline resistance [40]. The newer generation tetracycline analogues (i.e., tigecycline, eravacycline, and omadacycline) are largely unaffected by the presence of Tet(A) or Tet(B) [9, 41]. Further, all tetracyclines are substrates for the AdeABC efflux pump, although the pump is more specific for tetracycline, tigecycline, and eravacycline than doxycycline or minocycline [42–44]. Additionally, minocycline and tigecycline are each substrates for both the AdeFGH and AdeIJK efflux pumps [42].

Ribosomal protection proteins, or RPPs, facilitate the dissociation of tetracyclines from their ribosomal binding site. The two most well-described RPPs are Tet(M) and Tet(O), which confer resistance to tetracycline, doxycycline, and minocycline, but spare tigecycline, eravacycline, and omadacycline due to the presence of side chains at the C9 position of the D-ring [45]. The activity of tigecycline, and its predecessors, may be diminished in AB due to modifications at the ribosomal binding site such as those caused by mutations in *rpsJ* or *trm* [46, 47]. The effect of these mutations on the activities of eravacycline and omadacycline is largely unknown at this time, although previous data demonstrate elevated eravacycline MICs in *Klebsiella pneumoniae* isolates harboring *rpsJ* mutations [48]. Finally, all currently available tetracyclines are prone to enzymatic inactivation by the presence of Tet(X), which causes covalent inactivation by adding a hydroxyl group at position C-11a [49].

Aminoglycosides

Aminoglycosides remain one of the most active antimicrobial classes in vitro against AB, with approximately 80% of isolates retaining susceptibility against at least one agent (Table 1). Among aminoglycoside-resistant isolates, the major determinant of aminoglycoside resistance is the presence of aminoglycoside-modifying enzymes (AMEs), which can be further classified into acetyltransferases, adenyltransferases, and phosphotransferases [50]. These AMEs are often co-harbored on plasmids carrying carbapenemases, making aminoglycoside resistance more common among CRAB. Additionally, the aminoglycosides are impacted to a different degree by CRAB isolates harboring AMEs. In a study of CRAB isolates collected from 8 US metropolitan areas from 2012–2015, susceptibility rates to amikacin, gentamicin, and tobramycin were 61.1%, 30.7%, and 59.9%, respectively [51]. The neoglycoside agent plazomicin retains activity against pathogens harboring AMEs, but has limited activity against AB (~ 65% susceptible) [52] given the frequent presence of other mechanisms of aminoglycoside resistance including efflux pumps (AdeABC and AdeDE) [7, 53] and ribosomal methylation (rMTs) [10].

Fluoroquinolones

Widespread resistance has considerably compromised the place in therapy of fluoroquinolones for treatment of AB infections (Table 1). Phenotypic changes in the fluoroquinolone targets topoisomerase II (DNA gyrase) and topoisomerase IV, due to mutations in the *gyrA*, *gyrB*, and *parC* genes, are the primary mechanism of fluoroquinolone resistance among AB isolates [11, 54]. The binding affinity of fluoroquinolones to DNA gyrase and topoisomerase IV may also be compromised by the presence of plasmid-encoded determinants *qnrA*, *qnrB*, and *qnrS* [55–57]. Efflux-mediated resistance by AdeABC and AdeFGH may also play a role in fluoroquinolone-resistance [58].

Rapid Diagnostics

Accurate and rapid diagnosis of AB infections is critical to the timely selection of effective antibiotic therapy. *Acinetobacter* spp. are strictly aerobic, non-fermenting, Gram-negative coccobacilli [59]. Historically, the identification of *Acinetobacter* spp. has been difficult via conventional microbiology techniques given their unique morphology, the fact that they are often Gram-variable on Gram stain, there is no single metabolic test to distinguish the genus from other non-fermenting Gram-negative bacteria, and phenotypic/DNA-DNA hybridization assays do not distinguish between the species within the ABC species complex [59–61]. Fortunately, the past decade has brought cutting-edge technologies in the form of RDTs to the clinical microbiology lab that provide more accurate and rapid results compared to conventional microbiology methods [62, 63]. These RDTs have significantly improved the ability to identify AB down to the species level, which is crucial given the propensity for the

ABC complex to cause disease in humans and possess an MDR phenotype [1, 13, 51, 64–66].

There are currently several genotypic and phenotypic RDTs that support the species identification, resistance determinant detection, and/or susceptibilities of AB isolates (Table 2). Of these platforms, the ePlex BCID-GN panel and the Verigene BC-GN assay are the most comprehensive for bloodstream infections due to AB. The primary difference between these platforms is that the ePlex BCID-GN is able to identify AB to the species level, while the Verigene BC-GN assay is limited to genus identification [22, 67–69]. The detection of genotypic markers of resistance in AB (i.e., bla_{OXA}) has been shown to correlate well with subsequent phenotypic susceptibilities. In a multicenter study by Pogue et al., the absence of bla_{OXA} detection in AB by Verigene BC-GN was highly predictive of phenotypic meropenem susceptibility (93% negative predictive value), and vice versa [23]. Although limited by isolate count and the absence of detecting other mechanisms of resistance, this genotypic and phenotypic correlation allows for rapid escalation or de-escalation of antimicrobial therapy and dramatically improves time to effective therapy, which allows for the implementation of genotypic-phenotypic antibiograms and care pathways.

It is essential that RDTs are employed in conjunction with active antimicrobial stewardship (AMS) intervention in order to improve patients' clinical outcomes, particularly mortality. The combination of RDT + AMS intervention decreases mortality primarily by improving the time to effective antimicrobial therapy. Patients with infections due to MDR AB often experience long delays in time to effective therapy given the baseline resistance present in the majority of isolates negating the typical first-line antimicrobial agents. This has been demonstrated in a study by Wenzler et al. in which identification of AB by MALDI-TOF MS in patients with pneumonia and/or bacteremia along with AMS intervention resulted in decreased time to effective therapy compared to conventional identification methods and was associated with an increase in clinical cure [70]. Future RDT advances that will impact treatment of AB infections include utilizing non-blood RDTs to diagnose AB pneumonia. Accordingly, Entasis Therapeutics has incorporated the BioFire® FilmArray Pneumonia Panel to provide earlier organism identification in order to optimize enrollment into their phase 3 study of ETX2514SUL for the treatment of serious infections due to ABC complex (NCT03894046) [71].

Treatment

There have been several recent advances toward improving the safety and efficacy of current therapeutic options for AB including additional pre-clinical and clinical data regarding optimal treatment of AB infections, new guidelines (Table 3), and the availability of new antibiotics.

β-Lactams

β-Lactams are the drugs of choice against susceptible AB infections [1, 81]. However, just 26% of MDR AB in the USA remains susceptible to one or more first line agents, including carbapenems or sulbactam [2, 3•, 82•]. Despite low rates of in vitro susceptibility, the β-lactams, typically carbapenems, may be effectively utilized as part of a treatment regimen for MDR AB via optimization of PK/PD parameters (high dose, extended infusion) and combining with another agent that improves its bactericidal activity (polymyxins). In vitro, carbapenem-polymyxin combinations frequently

Table 2 Commercially available rapid diagnostic tests relevant to *Acinetobacter spp.*

Test	Technology	Identification	Resistance markers detected	Source	FDA approved
Verigene BC-GN	Nucleic acid test	*Acinetobacter* spp.	$bla_{\text{CTX-M}}$, bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, $bla_{\text{OXA-48}}$, $bla_{\text{OXA-23}}$, $bla_{\text{OXA-40}}$, $bla_{\text{OXA-58}}$	Positive blood culture	Yes
Accelerate Pheno	Morphokinetic cellular analysis	*A. baumannii*	Susceptibilities to piperacillin-tazobactam and amikacin	Positive blood culture	Yes
Unyvero	Multiplex PCR	*Acinetobacter* spp.	$bla_{\text{CTX-M}}$, bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{TEM}, $bla_{\text{OXA-48}}$, $bla_{\text{OXA-23}}$, $bla_{\text{OXA-24}}$, $bla_{\text{OXA-58}}$	Endotracheal aspirate	Yes
Biofire FilmArray Blood Culture ID 2 Panel	Multiplex PCR	*Acinetobacter calcoaceticus-baumannii* complex	bla_{KPC}, bla_{NDM}*, bla_{VIM}*, bla_{IMP}*, $bla_{\text{OXA-48-like}}$*	Positive blood culture	No[a]
Biofire FilmArray Pneumonia Panel			None	BAL, sputum	Yes

PCR polymerase chain reaction, *BAL* bronchoalveolar lavage

*New resistance targets that will be added to the current FDA-approved FilmArray BCID Panel

[a] The Blood Culture ID 2 Panel is currently research use only, while the FilmArray BCID Panel is FDA-approved

Table 3 Guideline updates and recommendations relevant to the management of MDR *Acinetobacter baumannii*[a]

	Organization (reference)	Guideline recommendation	Guideline comment	Authors' recommendation
Empiric				
General treatment	BSAC [72] ERS [73] ESICM [74] IDSA [75] SIS [76]	Consult local epidemiologic data and antibiograms for assistance in selecting empiric antimicrobial therapy in patients at risk for *A. baumannii*	Consider combination therapy for empiric MDR AB/CRAB coverage	Agree with Guideline Recommendation
General treatment	BSAC [72] ERS [106] ESICM [74] IDSA [75] SIS [76]	Recommend against/do not recommend empiric tigecycline, at least in monotherapy	Recommend against tigecycline in HAP/VAP caused by AB [75] May be considered as part of combination therapy for suspected MDR isolates; suggest 100 mg q12h dose [72, 74]	Do not recommend empiric tigecycline; Consider as part of combination therapy for soft tissue and intra-abdominal infections; If used, recommend 200 mg load then 100 mg q12 h
General treatment	BSAC [106] ESICM [74] IDSA [75] SIS [76, 77]	Suggest avoiding polymyxins/aminoglycosides if alternative agents with adequate activity are available	May be considered as part of combination therapy for suspected MDR isolates	Agree with Guideline Recommendation
Low risk of MDR AB/CRAB	ESICM [74] AST-IDCOP [78]	Carbapenems (β-lactams) are the drugs of choice		Suggest meropenem 2 g q8 h via 3 h infusion[b,c]
High risk of MDR AB/CRAB	ESICM [74] SIS [76]	Suggest broad-spectrum carbapenem plus an aminoglycoside, polymyxin, or tigecycline	Suggest against carbapenem monotherapy [74]	Unless local susceptibility data suggests β-lactam susceptibility, recommend empiric therapy with minocycline and polymyxin B combination for severe infections
Definitive				
General	ERS [73] IDSA [75] SCCM/ESICM [158] SIS [76]	Suggest tailoring/de-escalating antibiotic therapy based on final susceptibility data		Agree with Guideline Recommendation
Monotherapy				
Carbapenem-susceptible AB	BSAC [72] ESICM [77] IDSA [75, 79] SIS [76]	Recommend a carbapenem	Meropenem recommended in CNS infection [74, 79]; no specific agent recommendation outside CNS infection, β-lactam monotherapy is recommended in susceptible strains	Suggest meropenem 2 g q8 h via 3 h infusion[b,c]
Sulbactam-susceptible AB	BSAC [72] ESICM [74] IDSA [75] SIS [76]	Suggest sulbactam as a potential option for susceptible isolates	Ampicillin/sulbactam if susceptible based on improved safety profile and to preserve polymyxins; Sulbactam dose 9-12 g[b,c] daily in divided doses recommended [74, 78]	Ampicillin/sulbactam monotherapy not generally recommended in critical illness due to difficulty achieving PK/PD targets; If used, suggest ampicillin/sulbactam 4 g/2 g q6 h via 4 h infusion[b,c]
Polymyxin-only susceptible AB	IDSA [75] Polymyxin [80]	If second active agent is unavailable, use polymyxin B or colistin alone as monotherapy	Polymyxin panel voted 8–7 in favor of monotherapy [80]; suggest against adjunctive rifampicin [75]	Recommend polymyxin-based combination therapy; if possible, use in vitro synergy analysis to guide combination therapy selection
Combination therapy				

Table 3 (continued)

	Organization (reference)	Guideline recommendation	Guideline comment	Authors' recommendation
CRAB with carbapenem MIC < 8 mg/L	AST-IDCOP [78] SIS [76]	Carbapenem plus an aminoglycoside, polymyxin, or tigecycline	Carbapenem and polymyxin combination therapy is associated with microbiologic eradication of CRAB and can be used to treat CRAB infections [78]	Polymyxin B in combination with minocycline
CRAB with carbapenem MIC ≥ 8 mg/L	BSAC [72]	Suggest polymyxins with aminoglycosides or tigecycline in combination when isolate is susceptible		Polymyxin B in combination with minocycline
Special populations				
CRAB HAP/VAP	BSAC [72] ESICM [74] IDSA [75] Polymyxin [80]	Consider adjunctive therapy with inhaled polymyxin/aminoglycoside agent in patients requiring systemic polymyxin/aminoglycoside therapy	Some division among guidelines regarding the strength of recommendation owing to low quality clinical evidence to support use.	Recommend inhaled colistin (CMS) for patients requiring systemic polymyxin therapy, administered as described in [105] Suggested dose 150 mg colistin base activity every 12 h
CRAB CNS infection	BSAC [72] ESICM [74] IDSA [79] Polymyxin [80]	Recommend systemic and intraventricular or intrathecal therapy with a polymyxin/aminoglycoside agent	IDSA [79], ESCIM [74], and polymyxin guidelines [80] also include dosing and administration recommendations	Recommend adjunctive therapy with intraventricular or intrathecal polymyxin

CMS colistimethate sodium, *CNS* central nervous system, *CRAB* carbapenem resistant *A. baumannii*, *BSAC* British Society of Antimicrobial Chemotherapy, *ERS* European Respiratory Society, *ESICM* European Society of Intensive Care Medicine, *HAP/VAP* hospital-acquired pneumonia/ventilator-associated pneumonia, *PK/PD* pharmacokinetic/pharmacodynamic, *MDR* multidrug resistant, *SCCM* Society of Critical Care Medicine, *SIS* Surgical Infection Society

[a] This summary of diverse guideline recommendations does not necessarily represent the complexity of recommendations from each. Please refer to individual guidelines for more detailed information

[b] Adjusted for renal function

[c] For additional PK/PD information, see reference [80]

demonstrate synergy and improved bactericidal activity compared to either agent alone, especially against AB [83]. Previous data have suggested that the efficacy of this combination is maximized when the meropenem MIC is ≤ 8 mg/L and it is administered as a high dose, extended infusion regimen in combination with a polymyxin [84, 85]. These findings were confirmed in the recent AIDA study, a prospective, multicenter, open-label randomized clinical trial [86]. AIDA sought to answer whether colistin plus high dose extended infusion meropenem (2 g every 8 h infused over 3 h) improved clinical success and mortality compared to colistin monotherapy in patients with severe infections (hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), bacteremia, or urosepsis) caused by carbapenem non-susceptible bacteria. The majority of subjects had pneumonia or bacteremia (87%, 355/406) with AB being the most common pathogen (77%, 312/406). Unfortunately, 97% of AB isolates had meropenem MICs > 8 mg/L, likely obfuscating the true benefit, if any, of carbapenem-polymyxin combination therapy. There was a trend toward reduced clinical failure with combination therapy in the most severe infection types (73% vs. 82% $p = 0.059$), but nearly every clinical endpoint including 14- and 28-day mortality showed a lack of benefit for adding meropenem to colistin for CRAB infections. Moreover, among patients with isolates later confirmed to be colistin-resistant by the central laboratory, combination therapy with meropenem and colistin was associated with increased mortality compared to colistin monotherapy [87••].

In addition to traditional β-lactams, the β-lactamase inhibitor sulbactam has in vitro activity against *Acinetobacter* species and recent studies have continued to explore its utility in patients. Two meta-analyses assessed the use of sulbactam in patients with severe infections due to MDR AB and XDR AB and concluded that sulbactam-based regimens had comparable effectiveness to alternative antimicrobial regimens [88, 89]. Another meta-analysis found that sulbactam-based therapies were comparable to carbapenem and polymyxin therapies but that clinical response was higher with doses of sulbactam ≥ 9 grams/day [90]. Population PK and Monte Carlo simulations have demonstrated that in patients with severe sepsis due to AB, high dose extended infusion sulbactam (2 g every 6 h infused over 4 h) may achieve 90% probability of target attainment (PTA) at 60% time above the MIC (60%$fT_{>MIC}$) for AB isolates with sulbactam MICs ≤ 16 mg/L [91, 92]. However, sulbactam doses > 12 g/day would be necessary to achieve 90% PTA against most MDR AB isolates encountered outside North America (MIC_{50} > 16 mg/L) [74, 82, 91]. These high dose sulbactam regimens (12 g/day) have also demonstrated promise as part of dual or triple combination regimens in in vitro hollow fiber infection models and may warrant additional investigation [75, 79].

For the treatment of β-lactam susceptible AB, guidelines generally recommend a carbapenem administered as a prolonged infusion [76–78, 93]. The American Society of Transplantation Infectious Diseases Community of Practice (AST IDCOP), which is among the few guidelines that have been updated since the publication of the AIDA trial, continues to recommend carbapenem and polymyxin combination therapy for CRAB infections in transplant patients on the basis of improved microbiologic eradication [93]. For sulbactam, conditional recommendations are given for use as pathogen-directed therapy among susceptible isolates, including CRAB [77, 93–95]. When used, 9–12 g of daily sulbactam in divided doses infused over 4 h has been recommended for severe infections [78, 93]. Finally, guidelines for the optimization of treatment with β-lactams by the French Society of Pharmacology and Therapeutics (SFPT) recommend prolonged or continuous infusions β-lactams for isolates with high MICs (e.g., near the susceptibility breakpoint) and in patients who are critically ill [96].

Although several new β-lactam/β-lactamase inhibitor agents have been approved for the treatment of MDR Gram-negative pathogens like carbapenem-resistant *Enterobacteriaceae*, none of them (ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam) have any appreciable activity against CRAB. Fortunately, novel β-lactam-based agents are currently in the developmental pipeline with activity against MDR AB including cefiderocol and ETX2514. Cefiderocol is a siderophore cephalosporin with activity against CRAB including isolates producing serine carbapenemases and metallo-β-lactamases. Currently proposed dosing provides > 90% PTA with a PK/PD target of 75–85% $fT_{>MIC}$ for MICs ≤ 4 mg/L [92, 97, 98]. Cefiderocol demonstrated non-inferiority to imipenem in a Phase 2 clinical trial for complicated urinary tract infection (cUTI) involving *Enterobacteriaceae* and *Pseudomonas aeruginosa* and Phase 3 trials for HAP/VAP and carbapenem-resistant Gram-negative pathogens have recently completed but results are not yet available [98–101]. ETX2514 is a diazabicyclooctenone β-lactamase inhibitor currently in development in combination with sulbactam specifically for the treatment of AB. ETX2514 has potent activity against Ambler class A, C, and D β-lactamases, and also enhances the bactericidal activity of sulbactam against AB by binding PBP2 [102]. Having recently completed a Phase 2 clinical trial for cUTI, a Phase 3 trial is currently recruiting to evaluate the efficacy and safety of sulbactam-ETX2514 in the treatment of patients with infections due to ABC complex (NCT03894046) [72, 73, 80, 103]. Ultimately, although these new β-lactam-based agents may have promising activity against AB, carbapenems remain an important treatment option for infections caused by AB with low MICs (e.g., meropenem MICs ≤ 8 mg/L). While some data support the use of sulbactam for AB infections, large scale clinical trials are absent and PK/PD analyses do not favor its routine use as

monotherapy for a majority of the AB isolates outside North America [74, 82•, 91].

Polymyxins

Over the last two decades, polymyxins became the backbone of therapy for MDR AB, and specifically CRAB infections. Among available studies, the reported mortality rates of severe MDR AB infections treated with polymyxins cluster between 30 and 60%, in part reflecting frequent limitations of many polymyxin clinical trials, such as a lack of standardized polymyxin susceptibility testing and dosing [81]. The recent AIDA trial used standardized intravenous colistin dosing, including a loading dose, for severe infections due to colistin-susceptible, carbapenem-resistant Gram-negative bacteria, yet the 28-day mortality rate was still 49% (154/312) among patients with severe CRAB infections [86]. Secondary analyses of CRAB infections showed that active empiric therapy with colistin was not associated with improved survival compared to inactive therapy ($p = 0.504$), nor was subsequent colistin-resistance confirmed by broth microdilution (19% (52/266) of available CRAB isolates) associated with lower survival [87••, 104]. In fact, both secondary analyses showed a trend toward reduced mortality when either inactive empirical treatment was prescribed or the CRAB isolate was colistin resistant. In part due to limitations of the trial itself, a trend toward reduced mortality in colistin-resistant isolates also hints at the tradeoff between colistin-resistance and virulence as previously noted.

International polymyxin guidelines have been published and may help to standardize the clinical use and investigational use of these last-line agents [105]. Most significantly, the polymyxin guidelines include dosing recommendations for colistin and polymyxin B in multiple clinical scenarios including renal replacement therapy. Overall, guideline bodies generally recommend avoiding polymyxins when possible, but consider combination therapy with aggressively dosed polymyxins to be the workhorse for CRAB infections [76–78, 92, 93, 106, 107]. Additionally, administering the polymyxins by alternative routes such as via inhalation may help to maximize their efficacy and minimize toxicity, although clinical data supporting their use in nosocomial pneumonia due to AB are conflicting [108, 109].

In addition to alternative routes of administration, several novel polymyxin derivatives are in development designed to improve efficacy and reduce toxicity. A review of these novel polymyxin agents is available elsewhere [110]. One such agent is SPR741, a low toxicity polymyxin analog with limited intrinsic activity which can potentiate the activity of many antimicrobials by permeabilizing the outer membrane of Gram-negative bacteria thereby increasing the penetration of antimicrobials to their intracellular targets [111]. The antibiotic to be paired with SPR741 has not been announced, but significant potentiation of activity against MDR AB has been noted for rifampin, macrolides, and β-lactams [111]. SPR741 was generally well tolerated in a recent Phase I clinical trial with 4 of 6 patients in the highest dosing cohort of SPR741 (600 mg every 8 h for 14 days) experiencing a reversible mild or moderate decrease in creatinine clearance [112]. As a whole, the polymyxins remain a backbone in treatment of AB infections and continued efforts into dose optimization and understanding their use in combination will be critical to their continued effectiveness.

Tetracyclines

Tetracyclines are second only to polymyxins for most reliable in vitro activity against AB and are often the drugs of choice for combination therapy against CRAB. Most recent studies were retrospective in design and nearly all featured tigecycline in combination with a variety of other agents including polymyxins, β-lactams, and aminoglycosides [113–115]. The use of tigecycline for bacteremia is still cautioned, however, as a prospective multicenter study of empiric tigecycline-based salvage therapies for persistent febrile neutropenia (> 72 h) demonstrated the risk of treatment failure in bacteremia was over 4-fold higher than non-bacteremic infections (OR 4.42; 95% CI 1.41–13.89, $p = 0.011$) [116]. Overall, systemic tigecycline-based therapies compared unfavorably to alternatives for MDR AB when assessed by both traditional and Bayesian network meta-analyses [88, 89, 117]. Though results have not been confirmed by large clinical trials, unfavorable outcomes with tigecycline may be potentially offset by using higher dosages (e.g., 200 mg loading dose, 100 mg every 12 h) [118, 119].

Eravacycline, a tetracycline analogue, is 2- to 4-fold more potent than tigecycline against CRAB [120]. The eravacycline registrational clinical trials in the treatment of complicated intra-abdominal infection (cIAI) included 13 patients with infections due to AB, all of whom achieved clinical and microbiologic cure on pooled microbiologic analysis [121]. New clinical trial data for minocycline is unavailable, but many practitioners continue to view it as a favorable alternative due to high in vitro activity and previous clinical successes against MDR AB, especially in higher doses (e.g., 400 mg loading dose, 200 mg every 12 h) [122–124].

Updated guidelines reflect the somewhat divisive clinical data regarding tetracycline agents for AB infection. There is consensus recommendation against the empiric use of tigecycline in HAP/VAP, with suggested use in combination with other agents for the treatment of MDR AB soft tissue and intra-abdominal infections [77, 78, 93, 94, 106]. When tigecycline is used, the British Society of Antimicrobial Chemotherapy recommends tigecycline dosages of 100 mg twice daily [106]. Though minocycline is largely absent from treatment guidelines, the ASTIDCOP do issue a weak

recommendation in favor of its use as an alternative treatment option for CRAB [93].

New tetracycline-derivatives for the treatment of MDR AB are also in development. One notable agent is TP-6076, a fully synthetic tetracycline with potent in vitro activity against CRAB ($MIC_{50/90}$ 0.03/0.06 mg/L) [125]. Available data shows potent *in vivo* efficacy of TP-6076 in murine infection models, but it may also have non-linear PK and dose limiting nausea similar to others of the class [126, 127]. Development of this agent was recently halted by the sponsor in order to focus on eravacycline, so it is unclear if or when TP-6076 will be clinically available [128]. Overall, although clinical data are largely lacking, tetracycline compounds such as tigecycline, minocycline, and eravacycline are likely to be the second most active agents in vitro against AB behind the polymyxins. As discussed, tigecycline should generally be avoided in favor of minocycline or eravacycline if possible, and nuanced differences in vulnerability to AB's tetracycline resistance mechanisms are important to recognize. Finally, the future of the tetracyclines in the treatment of serious AB infections will likely depend in large part on generating more robust PK/PD data for which to establishing optimal dosing regimens and accurate exposure-response relationships.

Other Agents

The aminoglycosides, fluoroquinolones, and fosfomycin are typically used in combination with other agents for the treatment of CRAB. Although new agents from these classes have been approved, plazomicin (aminoglycoside) and delafloxacin (fluoroquinolone) do not offer significant improvements against AB compared to other drugs from their respective classes [129, 130]. There have been no reports to date demonstrating efficacious use of plazomicin or delafloxacin in AB infections [130, 131]. Intravenous fosfomycin is expected to be available in the USA in the near future, but clinical data to support its use against AB is still lacking [81]. As AB possesses intrinsic resistance against fosfomycin, fosfomycin has been recommended in very high doses as an extended infusion (e.g., 8 g every 8 h infused over 3 h) and in combination with other agents on the basis of in vitro synergy and Monte Carlo Analysis [132].

Guidelines mirror the clinical data for aminoglycosides, fluoroquinolones, and fosfomycin, with a paucity of direct recommendations for MDR AB infections. When discussed, current guidelines advocate that aminoglycosides, fluoroquinolones, and/or fosfomycin may be an acceptable alternative therapy in susceptible isolates when used in combination with other agents [77, 93, 94, 105, 106].

Apart from the previously mentioned intravenous fosfomycin, the only agent from these classes undergoing clinical development is apramycin, a veterinary aminoglycoside that is not subject to resistance due to RNA methylation [133]. With increased in vitro activity against AB and purportedly reduced toxicity compared to traditional aminoglycosides, apramycin will make a welcome addition to potential combination therapies.

Non-Antibiotic Therapies

Some of the most forward-thinking strategies in the treatment of MDR AB are non-small molecule therapies. One such example is the use of bacteriophages which are viruses that parasitize bacteria, and have bacterial host-specificity which is often species or even strain-specific [134, 135]. Though in their infancy, bacteriophages have been effectively used in the prevention of MDR AB infection through environmental aerosolization [136], and the treatment of MDR AB infection through systemic and local administration [137–140].

Also under investigation are monoclonal antibodies for the treatment of MDR AB infections which target capsular polysaccharides with the intent to opsonize bacteria and improve clearance by macrophages [141]. Nielsen et al. evaluated a monoclonal antibody able to abolish mortality in lethal murine models of MDR AB bacteremia, and having synergistic effect with colistin [142]. Conversely, a recent investigation into another anticapsular monoclonal antibody resulted in substantially *increased* bacterial burden and mortality in an AB pneumonia model [143]. This discordance highlights the complexity of AB infections and the disparity of effect that may be elicited by an immune response toward enhancing or hindering the clearance of infection.

Approach to Antimicrobial Selection

Empiric Therapy

As with all infections, patient risk factors and local antibiogram data should be utilized to inform and select optimal therapeutic options. If the isolate is strongly suspected to be susceptible to a β-lactam, or if RDTs do not detect a carbapenemase (e.g., OXA-negative by Verigene BC-GN), monotherapy with a carbapenem in sufficiently high doses to achieve effective concentrations at the site of infection is recommended. Preference is generally given to meropenem over other group 2 carbapenems as meropenem is less susceptible to OXA β-lactamases [144] and more clinical and translational evidence is available. Although many MDR AB isolates retain susceptibility to sulbactam, empiric therapy with carbapenems is preferred over sulbactam for several reasons: {1} carbapenems have broader spectrum of activity for empiric coverage of critically ill patients, {2} PK/PD targets of carbapenems are more easily achieved than sulbactam (> $40\%fT_{>\ MIC}$ vs. > 40–$60\%fT_{>\ MIC}$, respectively), and {3} the increased incidence of acquired β-lactamases that

hydrolyze sulbactam in MDR AB (e.g., TEM, ADC, OXA) presents a concern for its efficacy in monotherapy [22, 25, 26, 29, 81].

When β-lactam resistance is suspected or MICs preclude the use of carbapenems, polymyxin-based combination therapies are recommended. Polymyxin B is the preferred agent over colistin due to its more predictable PK profile and decreased risk of nephrotoxicity [105]. Polymyxins should be used in combination with other agents for serious AB infections in order to achieve synergy and prevent the development of resistance. For empiric coverage of presumed CRAB in severe infections, the combination of polymyxin B (2.0–2.5 mg/kg loading dose, 1.25–1.5 mg/kg every 12 h; see polymyxin guidelines [105]) and minocycline (400 mg loading dose, 200 mg every 12 h) is suggested given their reliable in vitro susceptibility.

Definitive Therapy

For severe infections due to AB with meropenem MIC ≤ 8 mg/L, meropenem is recommended as monotherapy given as high dose extended infusion [76, 78, 93, 94, 106]. High dose extended infusion ampicillin-sulbactam with or without additional agents may also be an alternative for susceptible isolates [77, 78, 93, 106]. In cases of CRAB where combination therapy was used empirically, therapy should be consolidated to two or fewer agents from different classes with known in vitro activity [77, 94, 107, 145]. Generally, this will be a combination of a polymyxin plus a secondary agent to which the CRAB is susceptible, if available. When polymyxins or aminoglycosides are used systemically in pneumonia or meningitis/ventriculitis, adjunctive inhaled or intrathecal/intraventricular administration is recommended, respectively [76–78, 105, 106].

Polymyxin monotherapy may be an option in cases where it is the only susceptible agent or there are no other active agents available; however, a second agent (e.g., minocycline or ampicillin/sulbactam) should still be utilized if possible for the goal of achieving synergy [81]. Synergy is often strain-specific and selection of agents to use in combination with a polymyxin should consider patient-specific factors such as the source of the infection and potential toxicities of the combination [94, 105]. If possible, isolates should be tested for in vitro synergy in the clinical microbiology laboratory to inform the clinical management of the patient. When tested in vitro against MDR AB, meropenem, sulbactam, and minocycline have all shown synergistic effect when combined with polymyxins [81]. Triple combination therapy has also shown significant promise in the ability to eradicate AB that is resistant to all three agents, such as with the combination of polymyxin B, meropenem, and ampicillin/sulbactam [79].

Finally, in patients for whom oral therapy is considered to complete a treatment course, monotherapy with minocycline or ciprofloxacin/levofloxacin may be an acceptable option in susceptible isolates following clinical improvement after intravenous therapy.

Conclusion

The management of MDR AB infections has continued to be exceptionally challenging owing to a limited understanding of the pathogen's virulence, its near limitless ability to possess and acquire resistance, a paucity of adequate pre-clinical and clinical data, and a dearth of novel treatment options. At present, employing RDTs and aggressive antimicrobial combination therapy up front with de-escalation based on genotypic/phenotypic susceptibilities is optimal for managing serious MDR AB infections. Importantly, several guidelines are now available that may help to standardize the treatment of AB and guide the use of agents with narrow therapeutic windows such as the polymyxins. Finally, continued advances in both the antimicrobial and non-antimicrobial treatment pipelines for AB will be essential for combating this difficult to treat pathogen.

Compliance with Ethical Standards

Conflict of Interest Eric Wenzler serves on the speaker's bureau for Melinta Therapeutics and Astellas Pharma and on the advisory board for Shionogi and Genmark Diagnostics. All other authors certify no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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