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REVIEW

Anticipating the Unpredictable: A Review of Antimicrobial Stewardship and *Acinetobacter* Infections

Eric Wenzler · Debra A. Goff · Romney Humphries · Ellie J. C. Goldstein

ABSTRACT

Acinetobacter remains one of the most challenging pathogens in the field of infectious diseases owing primarily to the uniqueness and multiplicity of its resistance mechanisms. This resistance often leads to devastatingly long delays in time to appropriate therapy and increased mortality for patients afflicted with *Acinetobacter* infections. Selecting appropriate empiric and definitive antibacterial therapy for *Acinetobacter* is further complicated by the lack of reliability in commercial antimicrobial susceptibility testing devices and limited breakpoint interpretations for available agents. Existing treatment options for infections due to *Acinetobacter* are limited by a lack of robust efficacy and safety data along with concerns regarding appropriate dosing, pharmacokinetic/pharmacodynamic targets, and toxicity. Antimicrobial stewardship programs are essential to combat this unpredictable pathogen through use of infection prevention, rapid diagnostics, antibiogram-optimized treatment regimens, and avoidance of overuse of antimicrobials. The drug development pipeline includes several agents with encouraging in vitro activity against *Acinetobacter*, but their place in therapy and contribution to the armamentarium against this pathogen remain to be defined. The objective of this review is to highlight the unique challenge of treating infections due to *Acinetobacter* and summarize recent literature regarding optimal antimicrobial treatment for this pathogen. The drug development pipeline is also explored for future potentially effective treatment options.

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E. Wenzler (✉)
College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA
e-mail: wenzler@uic.edu

D. A. Goff
Department of Pharmacy, The Ohio State University Wexner Medical Center, Columbus, OH, USA

R. Humphries
Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, USA

E. J. C. Goldstein
Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

E. J. C. Goldstein
R M Alden Research Laboratory, Santa Monica, CA, USA

INTRODUCTION

Infections due to antibiotic-resistant bacteria are responsible for significant morbidity, mortality, and excess healthcare costs [1]. Of these resistant organisms, *Acinetobacter* remains one of the most formidable opponents, as its unique and eclectic resistance mechanisms allow it to escape the activity of the majority of our currently available antimicrobials. This pathogen is a member of the ESKAPE [*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* (AB), *Pseudomonas aeruginosa*, and *Enterobacter spp.*] group which have been highlighted for their resistance and association with negative clinical outcomes [2]. The mortality rate due to multidrug-resistant (MDR; i.e. non-susceptibility to at least one agent in three or more antimicrobial categories) [3] healthcare-associated AB alone is approximately 10.6%, with an estimated cost per infection ranging from US$33,510 to $129,917 [4]. So-called "superbugs" like MDR *Acinetobacter* undermine decades of advances made in medicine, surgery, and transplantation. The acquisition of resistance mechanisms is increasing in frequency among this pathogen [5], leading to extensively (XDR; i.e. non-susceptibility to at least one agent in all but two or fewer antimicrobial categories) [3] resistant isolates and threatening the effectiveness of our remaining antibiotics, including those used as last-resort therapeutic options. This resistance poses significant challenges when selecting empiric antibiotic therapy and often leads to devastatingly long delays in time to appropriate therapy. While these delays undoubtedly lead to increases in mortality [6, 7], knowledge of local susceptibilities and application of antimicrobial stewardship practices can work to improve outcomes.

Few currently available and pipeline agents have reliable activity against *Acinetobacter*. As a result, clinicians are forced to resort to older agents with more narrow therapeutic windows and a paucity of modern efficacy data to support their use, including the polymyxins, tetracyclines, and the aminoglycosides. This review will discuss the challenge of treating infections due to *Acinetobacter* and summarize recent literature regarding optimal antimicrobial treatment. We will also explore the horizon for antimicrobials in the development pipeline with activity against this pathogen. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

MICROBIOLOGY AND PATHOGENICITY

Bacteria within the genus *Acinetobacter* are ubiquitous, encapsulated, non-lactose fermentative, oxidase-negative Gram-negative coccobacilli. The vast majority of infections are caused by the *Acinetobacter calcoaceticus–baumannii* complex, which is comprised of *A. calcoaceticus*, *A. baumannii*, *A. nosocomialis*, and *A. pittii*, with *A. baumannnii* (AB) being the most clinically important species responsible for the highest incidence of MDR and mortality compared to other *Acinetobacter* species [8]. AB may survive on wet or dry inanimate surfaces for up to 4 months [9], and can colonize patients for up to 42 months, which may contribute to its endemicity and proclivity for outbreaks [10]. Acquisition and spread of AB has been noted particularly in long-term care and skilled nursing facilities.

The exact reason for the success of the *Acinetobacter spp.* is largely unknown. Although its name is loosely derived from the Greek word akineto, meaning "non-motile", AB actually possesses several core motility genes which can assemble pilli and produce motility under certain conditions, and may contribute to its ability to spread on fomites and form biofilms [11]. AB specifically possesses several features that may enhance its survival, including simple growth requirements and resistance to the natural bactericidal activity of human complement [12]. *Acinetobacter* has the ability to acquire and rearrange genetic material, leading to new and enhanced virulence and antimicrobial resistance. Its virulence mechanisms are not well understood, but include its outer membrane porins, surface capsules and lipopolysaccharide,

iron acquisition systems, and regulatory proteins. The implication of these mechanisms in disease transmission and pathogenicity have been reviewed in detail elsewhere [8].

AB primarily causes nosocomial infections, although community-acquired infections have been reported [13] and are increasing nationally and internationally [14–16]. Globally, the incidence of MDR AB exceeds 75% in Africa, Asia, and Latin America and 90% in parts of Europe and the Middle East [17]. In the U.S., carbapenem-resistant AB (CRAB) increased from 9% in 1995 to 40% in 2004 [18]. A 2011 survey of 11 Latin American countries found that more than 50% of AB were carbapenem-resistant [19] compared to rates as high as 85% in Turkey, Greece, Italy, Spain, and England [20]. Pneumonia is the most common AB infection, and the majority (57.6%) of AB isolates in the U.S. are cultured from the respiratory tract, followed by the bloodstream (23.9%), and skin and soft tissue (9.1%) [21]. AB is the fifth leading cause of ventilator-associated pneumonia (VAP) and 13th of central line-associated bloodstream infections [22]. Risk factors for AB infection include prolonged hospital/ICU stay, immunosuppression, invasive devices and procedures, mechanical ventilation, and broad-spectrum antibiotic exposure [18]. AB infections tend to occur in vulnerable, debilitated patients including those in ICUs and residents of long-term care facilities, especially those who are ventilator-dependent. The mortality rate for these serious infections due to AB varies by geography and type of infection, but is roughly 30–75%.

MECHANISMS OF RESISTANCE

In the 1970s, AB was routinely susceptible to ampicillin and cephalosporins. By the 1990s, resistance to carbapenems had emerged and current reports describe strains resistant to all available antimicrobials, including colistin, polymyxin B, and tigecycline [23]. This in vitro resistance has been associated with negative clinical outcomes including increased ICU length of stay and mortality [8]. Table 1 provides a summary of commonly identified

mechanisms of resistance in AB. Compared to other Gram-negative pathogens, the ability to and ease with which AB acquires new resistance mechanisms via plasmids, transposons, and integrons is quite remarkable. AB employs a myriad of resistance mechanisms, including enzymatic hydrolysis, target site alterations, porin loss, and efflux pumps. In contrast to many other Gram-negative species, these mechanisms are often employed in combination in MDR AB isolates [24].

Ambler class A extended spectrum β-lactamase (ESBL) enzymes are becoming increasingly common in non-fermenting Gram-negative pathogens like AB. The most common are the PER-, VEB- and GES-types [24]. These enzymes have been identified throughout the world, with PER-1 being the most common in the U.S. The next most common ESBL in AB, the Vietnamese ESBL (VEB), shares only 38% amino acid identity with PER-1, speaking to the diversity and challenging nature of AB resistance mechanisms [25]. Additionally, GES-type ESBLs, which possess amplified hydrolytic activity towards aztreonam and ceftazidime, have been increasingly reported in AB since 2010 [26]. Conversely, common ESBL enzymes found in Enterobacteriaeceae, like TEM-, SHV-, and CTX-M-types, have rarely been identified in AB and may be due to limited horizontal gene transfer as a result of narrow-spectrum plasmid replication properties [24]. Unlike Enterobacteriaceae spp., KPC enzymes have rarely been identified in AB and are not a major player in its resistance armamentarium.

Class B metallo-β-lactamase enzymes have also been identified in AB with increasing frequency, including IMP-, VIM-, SIM-, and NDM-type enzymes. These zinc-based enzymes confer resistance to β-lactams and carbapenems, and are not inhibited by clinically available β-lactamase inhibitors [27]. At least 9 different IMP varieties have been identified in AB around the world [28–32], while the Seoul imipenemase (SIM-1) carbapenemase has to date been reported only in South Korea and China [33, 34]. NDM-1 and NDM-2 have also been reported in AB, primarily in China, Europe, Africa, and the Middle East [35].

One of AB's primary mechanisms of resistance to commonly utilized first-line

Table 1 Common mechanisms of resistance in *Acinetobacter baumannii*

Mechanism	Type	Conferred resistance
PER	Acquired extended-spectrum β-lactamase	Penicillins, cephalosporins, monobactams
VEB	Acquired extended-spectrum β-lactamase	Penicillins, cephalosporins, monobactams
GES	Acquired extended-spectrum β-lactamase	Penicillins, cephalosporins, monobactams
TEM	Acquired serine β-lactamase	Penicillins, cephalosporins, monobactams, sulbactam
IMP	Acquired metallo-β-lactamase	Penicillins, cephalosporins, carbapenems, β-lactamase inhibitors
SIM	Acquired metallo-β-lactamase	Penicillins, cephalosporins, carbapenems, β-lactamase inhibitors
NDM	Acquired metallo-β-lactamase	Penicillins, cephalosporins, carbapenems, β-lactamase inhibitors
ADC	Intrinsic AmpC β-lactamase	Aminopenicillins, oxyiminocephalosporins, cephamycins, β-lactamase inhibitors
-ADC-33	Intrinsic AmpC β-lactamase	Aminopenicillins, oxyiminocephalosporins, cephamycins, cefepime, β-lactamase inhibitors
-ADC-56	Intrinsic AmpC β-lactamase	Aminopenicillins, oxyiminocephalosporins, cephamycins, cefepime, β-lactamase inhibitors
OXA	Intrinsic serine carbapenemase	Oxacillin, clavulanate, sulbactam, tazobactam
AdeABC	Resistance-nodulation-cell division efflux pump	Aminoglycosides, fluoroquinolones, tetracyclines, trimethoprim
Tet	Efflux pump	Tetracyclines, tigecycline
PmrAB	Two-component regulatory system alterations	Polymyxins
LpxA, LpxC, LpxD	Loss of LPS production	Polymyxins
ArmA	16S RNA methyltransferase	Aminoglycosides
GyrA	DNA gyrase alterations	Fluoroquinolones
ParC	DNA topoisomerase IV alterations	Fluoroquinolones
RpoB	RNA polymerase alterations	Rifampin

antimicrobials are Class C β-lactamases. A wide variety of AmpC-type cephalosporinases have been identified in AB and subsequently named *Acinetobacter*-derived cephalosporinase (ADC) enzymes. Importantly, some of these ADC variants such as ADC-33 and ADC-56 have extended spectrums which allow them to

hydrolyze cefepime, whereas wild-type AmpC such as those often found in Enterobacteriaceae do not [36, 37].

Class D β-lactamase production, primarily of the OXA-type, exhibit low-level carbapenemase activity and are only weakly expressed in most AB isolates. Overexpression can occur and lead

to carbapenem nonsusceptibility when combined with other mechanisms. The OXA-23 enzyme is the most widespread and has been identified on all inhabited continents [27].

AB has also demonstrated the ability to confer resistance to aminoglycosides, fluoroquinolones, tetracyclines, and trimethoprim through complex efflux systems such as the resistance-nodulation-cell division system [38, 39]. Tigecycline maintains in vitro activity against AB, and the mechanisms of resistance in cases of resistant isolates is likely due to efflux pumps. Resistance to colistin has been described and is commonly due to either alterations of the lipid A component of the lipopolysaccharide (LPS) [40] or complete loss of LPS production [41], although diversity among polymyxin resistance mechanisms is beginning to be described [42].

Worldwide, less than 30% of AB are fluoroquinolone-susceptible [17], due to mutations in the quinolone resistance determining regions of *gyrA* and *parC* genes and/or overexpression of efflux pumps [12]. Resistance to aminoglycosides exceeds 60% in most countries and is due primarily to production of aminoglycoside-modifying enzymes like ArmA, or efflux pumps. The major mechanism underlying rifampin resistance is substitution of amino acids in the target protein, commonly occurring through a single mutation to the *rpoB* gene.

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Laboratories in the U.S. have reached a critical juncture in their ability to perform antimicrobial susceptibility testing (AST) as a result of regulatory changes that limit test menus of commercial AST devices (cASTs). These changes drastically limit the ability to test *Acinetobacter* spp., a genus for which antibiotic susceptibility is rarely predictable. As such, timely and accurate AST of *Acinetobacter* isolates is critical to the management of patients. In the U.S., two organizations establish breakpoints—the Clinical and Laboratory Standards Institute (CLSI) and the U.S. Food and Drug Administration (FDA). The vast majority of U.S. laboratories perform susceptibility testing using cASTs, which are

regulated by the FDA; by U.S. law, cASTs must use FDA breakpoints. This presents a major challenge for *Acinetobacter* spp., as FDA only grants breakpoints for those organisms against which a given antibiotic has proven activity, both in vitro and in clinical infections (i.e., organisms listed in the drug monograph under clinical indications for use) [43]. Only 9 antibiotics have an FDA-approved clinical indication for use for *Acinetobacter* spp. (Table 2). Given the complexity of clinical trial design and relative infrequency of infections caused by *Acinetobacter* spp., it is unlikely that new antimicrobials will achieve indications for treatment of *Acinetobacter*. As of November 2017, Language in the 21st Century Cures Act allows the FDA to designate breakpoints set by standard setting organizations, like CLSI, for use with cASTS. CLSI can establish breakpoints independent of a pharmaceutical sponsor, as occurred for colistin in 2015 [44]. However, even if CLSI *Acinetobacter* breakpoints are recognized by the FDA, it may be years before a test is cleared for those antibiotics on the automated cASTs that are used by most laboratories (e.g., Vitek 2, Microscan) [43], as development and marketing of new cASTS typically takes 3–7 years. There is a lack of prioritization for development of such cASTs by the manufacturers [43].

It should be noted that tests are available for *Acinetobacter* spp. outside the U.S, in countries where manufacturers of cASTs are not subject to FDA oversight. Furthermore, many laboratories are able to perform susceptibility testing of *Acinetobacter* spp. using CLSI breakpoints for some drugs using FDA-cleared cASTs (Table 2). This is because these devices were cleared prior to 2007, the year FDA started enforcing regulations requiring use of FDA breakpoints on cASTs. However, the ability of these systems to detect resistance mechanisms that have emerged or become more common since 2007 is unknown [43]. To further complicate matters, several differences exist between CLSI and FDA *Acinetobacter* breakpoints for the carbapenems (Table 2). CLSI updated *Acinetobacter* carbapenems breakpoints in 2012, in light of updated PK/PD and clinical outcome data, but FDA has yet to make adjustments. This is a critical issue, as CLSI updates to breakpoints are designed to

Table 2 CLSI and FDA breakpoints for *Acinetobacter* spp

Antibiotic	Susceptible breakpoints (µg/mL)		FDA cleared cAST
	CLSI	**FDA**	
Ampicillin-sulbactam	≤8/4	≤8[a]	All automated systems, Etest and disk
Piperacillin-tazobactam	≤16/4	≤16/4[b]	All automated systems, Etest and disk
Ceftazidime	≤8	None	
Cefepime	≤8	None	
Cefotaxime	≤8	≤8	
Ceftriaxone	≤8	None	
Doripenem	≤2	≤1	
Imipenem	≤2	≤4	All automated systems, Etest and disk
Meropenem	≤2	None	
Polymyxin B	≤2	None	None
Colistin	≤2	None	None
Gentamicin	≤4	None	
Tobramycin	≤4	None	
Amikacin	≤16	≤16	
Doxycycline	≤4	≤4	
Minocycline	≤4	≤4	Etest and disk
Tetracycline	≤4	≤4	
Ciprofloxacin	≤1	None	
Levofloxacin	≤2	None	
Trimethoprim-sulfamethoxazole	≤2/38	None	
Tigecycline[c]	None	None	None

[a] For *Acinetobacter calcoaceticus* only

[b] For *A. baumannii* only

[c] Many use a functional breakpoint of ≤2 ug/mL, but this has not been clinically validated

detect clinically relevant resistance that might be missed by historical (FDA) breakpoints.

PRACTICAL APPROACHES TO AST OF *ACINETOBACTER* SPP.

The performance of available cASTs for detecting resistance in *Acinetobacter* spp. is unknown as almost no studies performed in the past 10 years utilized current breakpoints and contemporary isolates. Only one recent, systematic evaluation of Vitek 2 as compared to CLSI reference MICs has been performed, including a small sample of 26 isolates of *A. baumannii*. In this study, only 1 very major error (i.e., false susceptibility) was noted, for tobramycin, among 364 overall readings. In

contrast, between 11.5% and 30.7% minor errors (i.e., intermediate MIC by Vitek2 and susceptible by the reference method) were noted for the β-lactam/β-lactamase inhibitor combinations and cephems. This high incidence of minor errors could potentially reduce use of these drugs for treatment of AB, as many clinicians view the intermediate and resistant interpretations to be synonymous [45]. Two additional studies evaluated the performance of various methods for testing activity of tetracyclines against CRAB [46, 47]. From these studies, it is apparent that Etest (bioMerieux, Durham, NC, USA) yields elevated MICs for minocycline, tigecycline and doxycycline, again resulting in rates of false non-susceptibility ranging from 15 to 37%. This observation varied by manufacturer of the Mueller–Hinton agar used, highlighting the critical importance of cation content in testing media for the tetracyclines, and in particular tigecycline [46]. In contrast, broth-based MIC methods, including Vitek 2 and Sensititre panels, performed well.

One option for testing antibiotics is off-line testing using manual, research-use-only (RUO) MIC tests (such as Sensititre panels made by ThermoFisher, or in some cases Etest). This approach allows interpretation of MICs by CLSI breakpoints, or reporting of MICs without interpretation if no breakpoint exists (for example, for tigecycline). Laboratories that take the RUO MIC approach should perform a verification study to ensure the RUO test yields results that are accurate as compared to CLSI reference broth microdilution method, and include a disclaimer on patient reports indicating testing was performed using a device that is not cleared by the FDA [43]. Performing a verification study for RUO products is critical, as not all RUO tests perform acceptably for detecting resistance, and may not yield reproducible results. For example, RUO colistin disk and Etest have been shown in several studies to yield unacceptably high rates of false susceptibility and false resistance, when compared to CLSI broth microdilution [48], the only method endorsed by CLSI and EUCAST for testing the polymyxins [49].

ANTIBIOGRAM DATA

Cumulative institution-level antibiogram data can be of significant value when evaluating empiric treatment options prior to receipt of antimicrobial susceptibility data. However, the integrity of data used to generate the antibiogram is crucial. The vast majority of laboratories produce antibiograms from data generated by cAST, which may be associated with bias towards overcalling resistance. Additionally, the number of isolates tested per antibiotic is important. If a laboratory performs off-line testing for a given agent (for example, minocycline or colistin), it is likely that only more resistant isolates would be tested against these drugs. For example, the data presented in Table 3 from one of our laboratories documents 54.4% of AB isolates were susceptible to meropenem in 2015 ($n = 119$ patients tested). In this same year, only 4.3% of isolates were susceptible to doripenem ($n = 65$ patients tested), because doripenem was tested using an off-line panel and only for isolates that were not susceptible to one or more carbapenems. This being said, knowledge of cumulative susceptibility for more resistant isolates alone may be of use—for example, when waiting for the laboratory to perform off-line testing for agents like minocycline, tigecycline or colistin for the patient with a carbapenem-resistant *A. baumannii* infection (Table 3).

Generally speaking, if <30 isolates were tested in a given year, that species should not be included in the cumulative antibiogram as it makes the data less generalizable to future isolates. For instance, in Table 3, we have calculated the antibiogram for all isolates of *A. baumannii* recovered from all hospital inpatients in our institution ($n = 119$ patients/isolates) versus only those recovered from patients in the ICU ($n = 21$ patients/isolates). While the percent of isolates susceptible to colistin is very similar (93.6% and 90.0%, respectively), the 95% confidence interval surrounding these data is very broad—at the low end 74.9% versus 45.9% susceptible. While these data may still be useful, it is important to report the number of isolates included in antibiogram calculations.

Table 3 Demonstration of the impact of number of isolates on confidence for data and effect of inclusion of duplicate isolates in the antibiogram

Antibiotic	All isolates, all patients ($n = 125$)		1 isolate per patient, ICU only ($n = 22$)		Meropenem resistant isolates ($n = 30$)
	%S	95% CI	%S	95% CI	%S
Ampicillin–sulbactam	53.6	42.9–64.3	50	25.5–74.5	0
Piperacillin–tazobactam	36	28.8–43.2	31.8	16.2–47.4	0
Ceftazidime	45.6	36.5–54.7	45.5	23.2–67.8	0
Cefepime	48.8	39.0–58.6	36.4	18.6–54.2	0
Imipenem	57.6	46.1–69.1	63.6	32.4–94.8	0
Meropenem	54.4	43.5–65.2	63.6	32.4–94.8	0
Amikacin	65.5	52.4–78.6	68.2	34.7–100	33.3
Gentamicin	53.6	42.9–64.3	54.5	27.8–81.2	11.5
Tobramycin	57.6	46.1–69.1	59.1	30.1–88.1	11.5
Ciprofloxacin	45.6	36.5–54.7	50	25.5–74.5	0
Trimethoprim–sulfamethoxazole	56	44.8–67.2	59.1	30.1–88.1	17.2
Colistin	93.6	74.9–100	90	45.9–100	92.8
Minocycline	60.9	48.7–73.1	57.1	29.1–85.1	50.0

Table 4 Example combination antibiogram for 89 isolates of AB isolated in 2015

	Amikacin (67.4)	Ciprofloxacin (50.6)	Colistin [89]
Ampicillin–sulbactam (56.2)	67.4	59.5[a]	95.5[a]
Ceftazidime (50.6)	71.9[a]	55.1[a]	96.6[a]
Cefepime (52.8)	78.6[a]	57.3[a]	95.5[a]
Meropenem (59.6)	74.2[a]	59.5	95.5[a]

Data in parentheses indicate % of isolates susceptible to antimicrobial on their own, whereas other figures indicate % of isolates that are susceptible to one or both of the antimicrobials

[a] Isolates for which a higher % is susceptible to the combination that either agent alone

Alternatively, use of >1 year's data can be considered, in particular if year-to-year susceptibility remains fairly stable. Finally, a combination antibiogram can be constructed, which presents data on the percent of isolates that are susceptible to one or both agents in combination (Table 4). This data can be very useful for determining empirical treatment for patients with, or suspected to have, infections caused by *Acinetobacter* spp.

TREATMENT OF AB INFECTIONS

The most important facet of treatment for patients infected with AB is early appropriate antimicrobial therapy. Delays in administration

of antimicrobial therapy have been associated with increased mortality, and time to appropriate therapy is the strongest modifiable risk factor for poor outcomes of AB infections [7, 50–52]. Randomized controlled trials are lacking and the optimal antimicrobial treatment for serious AB infections has not been established. B-lactam antibiotics are the preferred antibiotics of choice for susceptible AB infections [53]. Carbapenems have been regarded as the treatment of choice for more resistant isolates, although the incidence of CRAB is increasing. Carbapenem resistance in AB has been associated with three–fourfold higher mortality during bacteremia and pneumonia, primarily due to delays in time to effective therapy and forcing the use of suboptimal agents for definitive therapy [54–56]. Combination therapy is often recommended for these infections on the premise that it may ensure at least one agent is active in vitro, achieve cidality, improve clinical outcomes, and potentially prevent the emergence of resistance.

Polymyxins

The efficacy of colistin (polymyxin E) in severe infections due to AB has been demonstrated in published reports [57–60], while data on polymyxin B are limited. In a prospective study of 35 episodes of VAP due to MDR AB, 21 patients were treated with intravenous colistin monotherapy as this was the only active agent in vitro [57]. These patients were compared to 14 who received imipenem–cilistatin. The cure rate was identical for both groups at 57% and VAP-related mortality rates were also similar at 38% and 35.7% between colistin and imipenem, respectively. Despite the scarcity of published PK, PD, and clinical outcomes literature on polymyxin B compared to colistin, polymyxin B possesses superior PK properties and may be less nephrotoxic than colistin [61]. Regardless of which polymyxin is used, the optimal dosing remains an enigma [62].

Recent in vitro pharmacodynamic evaluations have suggested aggressive, "front-loaded" polymyxin B dosing regimens in combination with carbapenems to combat MDR AB strains

and suppress the emergence of resistance [63]. A retrospective study evaluated the safety and efficacy of a colistin loading dose, high-dose maintenance regimen in critically ill patients with MDR Gram-negative pneumonia (68% of whom had AB) and found no increase in clinical cure or nephrotoxicity overall when compared to cohort of patients receiving a lower dose regimen without a loading dose [64]. Patients in the high-dosing regimen group did have a significantly higher rate of renal injury as assessed by the risk, injury, failure, Loss of kidney function, and end-stage kidney disease criteria (10% vs. 37%, $P = 0.03$). A recent review of the published PK and clinical data regarding the utility of a loading dose of colistin found that, despite the theoretical PK benefit, data from randomized controlled trials are lacking while data from observational studies do not support the use of loading doses. To add to the confusion, the latest in vitro hollow fiber infection model work has demonstrated a paradoxical effect in which higher polymyin B exposures dramatically increased the isolation of resistant subpopulations of AB that grew on plates containing 10 mg/L of polymyxin B [65]. These high exposures also proliferated polymyxin-dependent growth of AB. These experiments were carried out under high bacterial inoculums and without the benefit of the mammalian immune system, so the clinical impact of these findings remains to be determined, although this work contributes to the notion that the polymyxins should preferentially be given as part of a combination therapy against AB.

Tetracyclines

Minocycline was first introduced in the 1960s and maintains excellent in vitro activity against AB, including isolates that are MDR, and has been used successfully clinically in several small case series. Minocycline is FDA approved for infections due to *Acinetobacter*, both an intravenous and oral formulation are available for use, and toxicity after short-term use remains minimal. The parenteral minocycline product was also reformulated and FDA approved under the Qualified Infectious Disease Product by The

Medicines Company in April 2015 [66]. This reformulated product (previously RPX-602) incorporates magnesium sulfate which allows intravenous minocycline to be administered in smaller volumes of fluid and may improve tolerability. Minocycline often retains antimicrobial activity even against AB strains resistant to other tetracyclines and glycyclines, although cross-resistance exists. It is important that doxycycline not be used as a surrogate for minocycline susceptibilities, as resistance rates are significantly higher for doxycycline. In a recent study of 107 CRAB isolates, minocycline susceptibility rates were approximately 49% higher than for doxycycline [67]. Several studies have demonstrated the efficacy and safety of minocycline for serious infections due to AB. Minocycline has been used successfully in the literature to treat VAP due to AB [68] and CRAB [69]. The details of these studies have been summarized by Ritchie et al. [70]. Doxycycline retains some in vitro activity against AB but less than that of minocycline and has been rarely used for AB infections. Falagas et al. recently reviewed the use of doxycycline and minocycline for infections due to AB [71]. They included 10 retrospective studies comprising 156 patients, 65.4% of which had respiratory infections and 13% bacteremia. Clinical success was achieved in 76.9% of patients with microbiological eradication in 71.3%. Adverse events were reported in only 1 of 88 cases. The utility of intravenous minocycline in the modern era of widespread bacterial resistance has also been reviewed in detail by Colton et al. [72] and Greig and Scott [73].

Tigecycline, a semisynthetic glycylcyline derivative of minocycline, also maintains excellent in vitro activity and has been used successfully both alone and in combination with colistin for AB infections [74]. Worldwide, over 90% of AB isolates are susceptible to tigecycline [75, 76], although the data demonstrating the clinical efficacy of tigecycline for the treatment of AB infections are plagued by high mortality rates, emergence of resistance while on therapy, and frequent adverse events [77–80]. A large, retrospective study examined 266 patients with XDR AB treated with tigecycline alone or in combination and compared them to 120 patients treated with imipenem–cilastatin and sulbactam [81]. Thirty-day mortality rates were high but similar between the groups (44.7% vs. 46.7%). One prospective multicenter Phase III trial compared tigecycline to imipenem-cilastatin for patients with VAP due to AB and found lower cure rates in the tigecycline group (68% vs. 78%) [82]. Another retrospective study in ICU patients with pneumonia due to MDR AB matched 84 patients receiving tigecycline to 84 receiving colistin [83]. In this study, mortality was significantly higher among patients receiving tigecycline with a tigecycline MIC of >2 mg/L (44% vs. 60.7%, $P = 0.04$). Several studies have confirmed the relevance of the in vitro breakpoint of ≥ 2 mg/L for tigecycline, demonstrating higher mortality when tigecycline MICs were ≥ 2 mg/L, even when tigecycline was used as part of a combination regimen [83, 84]. Some retrospective studies have demonstrated adequate clinical and microbiologic outcomes with tigecycline, although it was given as part of a combination therapy in almost all cases [85–87].

Ampicillin/Sulbactam

Sulbactam is a penicillanic acid sulfone β-lactamase inhibitor with intrinsic in vitro activity against AB, although MICs have shown a steady increase over the last decade [76]. Ampicillin–sulbactam has demonstrated similar results to imipenem–cilastatin when treating severe AB infections, including VAP, in small case series, and was more effective than the polymyxins in treating CRAB infections [88–90]. It has demonstrated similar clinical and microbiologic outcomes to colisin for MDR AB VAP with less nephrotoxicity [91]. A recent retrospective study from Taiwan reviewed patients who received sulbactam alone or ampicillin–sulbactam for the treatment of pneumonia due to MDR AB [92]. Forty-five patients received sulbactam compared to 125 who received ampicillin-sulbactam, although 79.8% of patients received combination therapy primarily with a carbapenem (86.2%). Clinical resolution of pneumonia occurred in 67.6% of

patients with 69% demonstrating microbiological eradication of AB from the airways. The 30-day mortality rate was 31.2%, and independent predictors of clinical failure on multivariate analysis included malignancy, bilateral pneumonia, and shorter duration of therapy. The latest retrospective observational study examined patients with infections due to AB treated with ampicillin–sulbactam or an alternative β-lactam for at least 72 h [93]. Of the 69 patients included, 33 received ampicillin–sulbactam and 36 received an alternative β-lactam (primarily cefepime), and most had a respiratory source of infection. Approximately 20% of patients received combination therapy with colistin or tigeycline in the amnpicillin–sulbactam group. There were no significant differences in baseline demographics between the groups including source of infection and severity of illness. Clinical cure was similar between the groups (78.8% ampicillin–sulbactam vs 72.2% β-lactam, $P = $ NS), along with length of stay and mortality. Finally, a retrospective study of 168 patients comparing tigecycline-based versus sulbactam-based antimicrobial regimens for the treatment of MDR AB pneumonia found identical rates of clinical resolution (66.7%), similar mortality, but a lower rate of microbiological eradication in the tigecycline-based group (26.2% vs. 63.5%, $P < 0.05$) [94].

Similar to the polymyxins, ampicillin–sulbactam is likely most effective as part of a combination regimen against AB, and optimal dosing remains unclear. Case series and observational studies have demonstrated the efficacy of the combination of ampicillin and sulbactam against AB infections, including bacteremia [88, 89, 95–97]. When the AB isolate is susceptible to ampicillin–sulbactam, the efficacy appears to be comparable to other agents including carbapenems and polymyxins [90, 98]. Population PK studies with Monte Carlo simulations have demonstrated that, at typical ampicillin–sulbactam doses of 3 g every 8 h, a probability of target attainment (PTA) of 90 of 40% time above the MIC can only be achieved using a 4-h infusion and only for pathogens with an MIC ≤2 mg/L [99]. Even at 12 g every 8 h as a 4-h infusion, a PTA of 90% could only be achieved for pathogens with an MIC ≤8 mg/L. Both of these doses are likely inadequate, as in one study evaluating 121 isolates of AB, the MIC_{50} and MIC_{90} for ampicillin sulbactam were 16/8 and 64/32 mg/L, respectively [100]. In a clinical study, Betrosian et al. randomized 27 patients with MDR AB VAP to receive a total daily dose of either 27 or 36 g of ampicillin–sulbactam divided every 8 h and demonstrated no significant differences in clinical improvement or bacteriologic success [101]. Importantly, there were no major adverse events reported with this high-dosing scheme.

Aminoglycosides

Amikacin and tobramycin remain the most active in vitro agents against AB among the aminoglycosides. It is important to be mindful of susceptibility differences based on the methods used for testing against aminoglycosides against AB [102], as significant discordance has been reported. Aminoglycosides are falling out of favor for the treatment of MDR Gram-negative infections in general due to their high toxicity, lack of efficacy, low tissue penetration, ambiguous synergy, and the availability of more active, less toxic agents [103, 104]. As a general rule, aminoglycosides should not be used as monotherapy for AB, as they demonstrate rapid regrowth and persistence in vitro and poor clinical outcomes [103, 105, 106], although one small study from South Africa demonstrated similar toxicity and clinical outcomes of tobramycin compared to colistin when treating 32 patients with AB infections [107].

Rifampin

Rifampin has demonstrated activity against MDR AB in vitro and in in vivo animal models, although two randomized controlled trials failed to show improved outcomes with the addition of rifampin to colistin versus colistin alone for infections due to AB [108, 109].

COMBINATION THERAPY

The wealth of in vitro data suggests that combination therapy should be beneficial for the

treatment of serious infections due to AB [110, 111]. This includes utilizing carbapenems in combination for CRAB, although clinical reports have not always upheld the in vitro data [112, 113]. The published results are not conclusive and may be disease state-dependent, as combination therapy has demonstrated improved rates of 14 day survival and microbiological eradication for AB bacteremia [114], but failed to show a benefit in patients with AB sepsis [115]. The combination of colistin plus rifampin for serious infections due to AB has failed to demonstrate improved outcomes in two clinical trials and a systematic review [108, 109, 116]. A meta-analysis also concluded that there was no clear benefit to combination therapy for MDR, XDR, or PDR AB infections [71].

The heterogeneity of combination therapies used in the literature for AB infections is broad but often includes colistin a part of the combination approach. Unfortunately, the vast majority of the literature on combination therapies with colistin is in vitro in nature [23]. Colistin combination therapy has shown improved outcomes over colistin monotherapy for patients with AB bacteremia, although no specific combination proved better than another [114]. A study of 101 patients in Spain with MDR AB infections contrasts these results and found no significant difference in 30-day mortality between combination and monotherapy [115]. A contemporary study found no advantage of colistin combination therapy for AB VAP in critically ill patients [117]. The combination of colistin and glycopeptides has demonstrated synergy in vitro, although two clinical studies are conflicting in terms of clinical outcomes [118, 119]. A recently published review examined the in vitro and in vivo data regarding synergy of polymyxin combinations and concluded that limitations in current clinical studies (retrospective design, small sample sizes) preclude the translation of even well-executed in vitro experiments [120]. Two clinical trials are underway in the US and Europe (NCT01732250, NCT01597973) comparing colistin monotherapy to colistin plus meropenem, which may provide insight into

some of the ambiguity surrounding combination therapy for AB.

A recent study examined the correlation between in vitro checkerboard and time-kill synergy and clinical outcomes in patients infected with XDR AB [121]. In this study, colistin with minocycline produced the highest rate of synergy in vitro via checkerboard assay, although only 6.6% of wells tested demonstrated synergy which was equal to that of doripenem–colistin–minocycline. Tigecycline–colistin showed a 13.2% rate of antagonism while minocycline and colistin was bactericidal against 100% of the 5 isolates tested via time-kill. Patients who received a combination that demonstrated inhibition of growth in vitro demonstrated improved microbiological outcomes.

A retrospective study among critically ill patients with MDR Gram-negative pneumonia, the majority of whom had AB isolated, demonstrated that colistin combination therapy did not improve clinical cure but did significantly improved microbiological cure (87% vs. 35.5%, $P < 0.001$) [122]. Tigeycycline was the most common combination agent (51.2%) followed by minocycline (12.2%). A post hoc analysis of only patients with AB pneumonia demonstrated no significant differences in clinical cure, even after multivariate analysis, but again demonstrated a higher rate of microbiological eradication for the 44 patients with repeat cultures available.

A particularly interesting study examined the outcomes of 101 critically ill patients with infections due to AB ($n = 83$) or *P. aeruginosa* ($n = 18$) who received either polymyxin B monotherapy or polymyxin B in combination with another agent that lacked in vitro activity [123]. Combination therapy consisted primarily of polymyxin B plus meropenem. The 30-day mortality rate in the combination therapy group was significantly lower than that of the monotherapy group (42.4% vs. 67.6%, $P = 0.03$) despite the lack of in vitro activity and combination therapy was independently associated with lower 30-day mortality upon Cox proportional hazards modeling along with normal renal function. These differences remained after

a propensity score adjustment was made to account for the likelihood of receiving combination therapy. Given that all isolates but one in this study were considered highly carbapenem-resistant (MIC >32 mg/L), it is likely that some degree of synergy was occurring in vivo and that there may be a benefit to combination therapy regardless of susceptibility profiles.

A prospective observational study of patients with sepsis due to MDR AB who received active mono- or combination therapy included 68 patients who received monotherapy and 33 who received combination therapy. A propensity score was used to account for bias in receiving combination therapy. The primary infection was pneumonia, primarily VAP, and colistin was used most often as monotherapy (67.6%) followed by carbapenems (14.7%). Colistin plus tigeycline was the most common combination therapy, although this accounted for only 27.3% of cases and the remaining combination regimens were very heterogeneous including carbapenem plus tigecycline. There was no significant difference in all-cause 30-day mortality between the groups on univariate or multivariate analyses [115].

ANTIMICROBIAL STEWARDSHIP PRINCIPLES

Controlling the morbidity and mortality associated with AB requires a multifaceted approach including early detection and identification, strategies for patient risk factor identification, infection control practices, and antimicrobial stewardship surveillance and intervention.

A robust infection prevention program is crucial to help curb the introduction and spread of AB throughout a healthcare system. The primary goals of infection prevention as they relate to AB are early recognition and containment. Identifying high-risk patients and those colonized with AB is vital, as previous colonization with CRAB has been associated with infection due to CRAB [124]. Despite the obvious advantages of identifying patients who are colonized with AB, particularly MDR AB, surveillance culturing is not often implemented due to

significant logistic and practical challenges. Surveillance cultures, especially from a single site, have demonstrated low sensitivity and require considerable labor and time commitment from hospital and microbiology staff [10]. Specific microbiology laboratory media such as CHROMagar™ can assist in this process by rapidly and accurately identifying CRAB. The CDC recommends active microbiological surveillance for patients at high risk of colonization with resistant Gram-negative organisms and contact precautions. Cohorting, improved hand hygiene, and enhanced environmental cleaning have been successful at reducing hospital infection rates and controlling outbreaks of AB [125–127].

A multinational task force on the management and prevention of AB infections in the ICU was recently established [128]. The goal of the task force was to provide clinicians with clear and practical recommendations to optimize therapy and establish infection control measures to eradicate AB. Among the processes endorsed in the document, the group recommends that AB should be routinely identified to the species level by the clinical microbiology laboratory in order to differentiate it from other *Acinetobacter* spp. outside the AB group which are only rarely known to cause human disease. Additionally, AB bacteremia has been associated with higher mortality than *A. nosocomialis* or *A. pitti* bacteremia [129] and it is important to correctly associate antibiotic resistant rates with the appropriate species for epidemiologic purposes.

Antimicrobial stewardship programs (ASPs) play an important role in the management of MDR AB infections. Among many important interventions, ASPs can assist in the selection of appropriate agents for the treatment of AB based on the institutional antibiogram along with an appropriate duration and deescalation of therapy once susceptibility reports are known. Limiting the use of broad spectrum antimicrobial therapy is vitally important, particularly in the treatment of AB, as the use of carbapenems has been linked with increased incidence of CRAB [130], while restricting carpabenem use in the ICU has demonstrated a twofold decrease in the incidence of CRAB

[131]. ASPs can also support the implementation of rapid diagnostic testing (RDT) in order to more quickly identify AB and its resistant mechanisms in order to assist in infection control and optimize patient outcomes.

In the only published RDT and ASP intervention study to incorporate non-blood isolates, Wenzler et al. evaluated the use of MALDI-TOF and ASP intervention in patients with pneumonia and/or bacteremia due to AB [132]. This study was unique in the fact that it capitalized on the weakness of MALDI-TOF. By selecting to study a specific pathogen that is inherently MDR a majority of the time, the identification of AB by MALDI-TOF allowed for a rapid change in empiric antimicrobial therapy prior to susceptibility results being available. In this quasi-experimental study, 66 patients were included in the pre-intervention group and 53 in the intervention group. The pre-intervention group consisted of traditional microbiological methods and standard existing stewardship interventions, while the intervention group utilized MALDI-TOF to identify AB and targeted stewardship interventions to provide appropriate antimicrobial therapy. Importantly, in this study, patients who were already on effective therapy (defined as any antimicrobial agent with in vitro susceptibility) at the time of MALDI-TOF identification were excluded in order to assess the true impact of ASP intervention. The combination of MALDI-TOF and ASP in patients with pneumonia and/or bacteremia due to AB significantly reduced the time to effective therapy by over 40 h and also significantly improved clinical cure at 7 days in the intervention group (34% vs. 15%, $P = 0.016$). No significant differences in mortality or costs were observed, although MALDI-TOF plus ASP decreased the median infection-related length of stay in the intervention group (13 vs 11 days).

An ASP-driven study also evaluated the safety and effectiveness of minocycline for patients with infections due to MDR AB [133]. The ASP program recommended the addition of intravenous minocycline to formulary after an examination of susceptibility rates revealed that it was the third most susceptible agent behind the polymyxins and tigecycline, and was active against four of the six tigecycline-resistant strains tested. After addition to formulary, the ASP then conducted a retrospective evaluation of the use of minocycline for patients with serious MDR AB infections. A total of 55 critically ill patients (median APACHE II score 21) were evaulated and the primary site of infection was the respiratory tract in 58% of patients followed by the bloodstream (18%). The majority of infections were hospital-acquired and clinical success was achieved in 73% of patients with presumed or documented microbiological eradication in 78%. A quarter of the patients died from their infection and the median length of stay was 30 days. Only 3 patients received minocycline as monotherapy in this study, while the most common agent used in combination was colistin [19], but there were 10 other heterogeneous combination regimens used for the remaining 33 patients. There were no documented adverse events related to the use of minocycline.

PIPELINE AGENTS WITH ACTIVITY AGAINST AB

There are several agents in the drug development pipeline with promising in vitro activity and innovative mechanisms of action, although their place in therapy and effectiveness for infections due to AB remains to be established. Future non-antibacterial treatment options for AB have been recently reviewed by Wong et al. [53].

Bal30072

BAL30072 is a novel dihydroxypyridone monobactam siderophore β-lactam that permeates Gram-negative bacteria via non-pori-based routes involved in iron transport that may allow it to escape resistance mechanisms that compromise other β-lactams. BAL30072 has demonstrated activity in vitro against OXA-23-producing AB, with 73% of 200 isolates susceptible at 1 mg/L [134]. Against MDR AB, it has demonstrated an MIC_{90} of 4 mg/L to isolates with a meropenem MIC_{90} of >32 mg/L,

while its in vitro susceptibility against CRAB is comparable to tigecycline [135]. Importantly, BAL30072 also demonstrated activity against MBL-producing AB, including those strains resistant to aztreonam [136]. This molecule has also been shown to decrease meropenem MICs two–eightfold and produce synergy in in vitro time-kill assays, although in vivo efficacy was suboptimal in a rat soft tissue infection model [137]. Conversely in a murine septicemia model, in vitro synergy of BAL30072 and meropenem did translate into improved efficacy in vivo [138]. The addition of β-lactamase inhibitors does not improve the activity of BAL30072 against AB [139], but sub-MIC concentrations of colistin have been shown to decrease the MIC fourfold in 82% of AB isolates. Reduced susceptibility of AB to BAL30072 in vitro has been correlated to *adeb* expression [140].

S-649266

Another novel parenteral siderophore cephalosporin antibiotic, S-649266, has been evaluated in vitro against 104 strains of AB. This compound demonstrated MIC_{50} and MIC_{90} values of 0.125 and 2 mg/L, respectively, compared to >16 and >16 mg/L for meropenem. It also demonstrated excellent activity against carbapenemase-producing strains, including MBL-producers [141]. A multicenter, randomized, open-label clinical study comparing S-649266 to best available therapy for the treatment of severe infections caused by carbapenem-resistant Gram-negative pathogens is currently recruiting (NCT02714595).

Plazomicin

Plazomicin is a next-generation aminoglycoside ("neoglycoside") with extended activity over other aminoglycosides against some Gram-positive and -negative pathogens. Against 407 AB organisms isolated from 15 hospitals in New York, plazomicin demonstrated MIC_{50} and MIC_{90} values of 8 and 16 mg/L, respectively, compared to 32–64 and >64 mg/L for all other aminoglycosides tested [142]. Plazomicin

achieved synergy in combination with meropenem or imipenem against 69 imipenem-resistant AB isolates from Spain. MIC_{90} values were lower than the other aminoglcyosides, carbapenems, and fosfomycin against CRAB, but higher than colistin or tigecycline MICs [143]. Overall, the in vitro activity of plazomicin appears comparable to that of amikacin, and this drug will come with the same clinical downsides as traditional aminoglycosides, as discussed earlier.

Omadacycline

Omadacycline is a novel aminomethycycline antibiotic similar to the tetracycline class but with the ability to circumvent typical tetracycline resistance mechanisms. It has demonstrated MIC_{50} and MIC_{90} values of 0.025 and 4 mg/L, respectively, to AB [144] and excellent activity against 5 NDM and 39 OXA-producing isolates.

Eravacycline

Eravacycline is a novel synthetic fluorocycline similar to the tetracyclines with broad anti-Gram-positive and -negative activity [145]. Against tigecycline and carbapenem-resistant AB from the UK, eravacycline MICs were approximately twofold lower than that of tigecycline. Importantly, eravacycline retains activity against most high-level minocycline-resistant AB isolates.

SUMMARY

AB has become one of the most unpredictable and difficult to treat pathogens over the last 20 years, aided by its numerous mechanisms of resistance. Empiric antibiotic selection should be based on specific local susceptibility data when available. Specific therapy of AB infection is confounded by the lack of cAST with limited breakpoint interpretations for AB. The use of RUO testing methods can be problematic. Previously, carbapenems were regarded as the drugs of choice for AB infections,

although the incidence of CRAB is increasing. Currently, the polymyxins have become increasingly used, but concerns about dosing, PK/PD, and toxicities have limited their utilization. Among the tetracyclines, only minocycline is included in automated cAST, has FDA-cleared breakpoints, and has reliable in vitro activity against AB. Combination therapy for serious infections due to AB is reinforced by in vitro data, although supporting clinical data are inconclusive. Antimicrobial stewardship programs are essential to combat this unpredictable pathogen through use of infection prevention, rapid diagnostics, antibiogram-optimized treatment regimens, and avoidance of carbapenem overuse. The antimicrobial development pipeline includes several agents with in vitro activity against AB, but their place in therapy and contribution to the armamentarium against this pathogen remain to be defined.

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