Infect Dis Ther (2021) 10:2177–2202
https://doi.org/10.1007/s40121-021-00541-4

REVIEW

Contemporary Perspective on the Treatment of *Acinetobacter baumannii* Infections: Insights from the Society of Infectious Diseases Pharmacists

Jacinda C. Abdul-Mutakabbir · Nicole C. Griffith · Ryan K. Shields · Frank P. Tverdek · Zahra Kassamali Escobar

Received: August 9, 2021 / Accepted: September 23, 2021 / Published online: October 14, 2021

ABSTRACT

The purpose of this narrative review is to bring together the most recent epidemiologic, preclinical, and clinical findings to offer our perspective on best practices for managing patients with *A. baumannii* infections with an emphasis on carbapenem-resistant *A. baumannii* (CRAB). To date, the preferred treatment for CRAB infections has not been defined. Traditional agents with retained in vitro activity (aminoglycosides, polymyxins, and tetracyclines) are limited by suboptimal pharmacokinetic characteristics, emergence of resistance, and/or toxicity. Recently developed and US Food and Drug Administration (FDA)-approved β-lactam/β-lactamase inhibitor agents do not provide enhanced activity against CRAB. On balance, cefiderocol and eravacycline demonstrate potent in vitro activity and are well tolerated, but clinical data for patients with CRAB infections do not yet support widespread use. Given that CRAB has the capacity to infect vulnerable patients and preferred regimens have not been identified, we advocate for combination therapy. Our preferred regimen for critically ill patients infected, or considered to be at high risk for CRAB, includes meropenem, polymyxin B, and ampicillin/sulbactam. Importantly, site of infection, severity of illness, and local epidemiology are essential factors to be considered in selecting combination therapies. Molecular mechanisms of resistance may unveil preferred combinations at individual centers; however, such data are often unavailable to treating clinicians and have not been linked to improved clinical outcomes. Combination strategies may also pose an increased risk for antibiotic toxicity and *Clostridioides difficile* infection, and should therefore be balanced by understanding patient goals of care and underlying health conditions. Promising therapies that are in clinical development and/or under

J. C. Abdul-Mutakabbir (✉)
Department of Pharmacy Practice, Loma Linda University School of Pharmacy, Loma Linda, CA, USA
e-mail: jabdulmutakabbir@llu.edu

J. C. Abdul-Mutakabbir
Department of Basic Sciences, Loma Linda University School of Medicine, Loma Linda, CA, USA

N. C. Griffith
University of Illinois at Chicago College of Pharmacy, Chicago, IL, USA

R. K. Shields
Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

F. P. Tverdek
University of Washington, Seattle Cancer Care Alliance, Seattle, WA, USA

Z. K. Escobar
University of Washington Medicine, Valley Medical Center, University of Washington School of Pharmacy, Renton, WA, USA

investigation include durlobactam–sulbactam, cefiderocol combination regimens, and bacteriophage therapy, which may over time eliminate the need for the continued use of polymyxins. Future goals for CRAB management include pathogen-focused treatment paradigms that are based on molecular mechanisms of resistance, local susceptibility rates, and the availability of well-tolerated, effective treatment options.

Keywords: *Acinetobacter baumannii*; Combination therapy; Multidrug resistance; Cefiderocol; Eravacycline

Key Summary Points

The molecular characteristics of *A. baumannii* vary by region, and therefore the preferred treatment for carbapenem-resistant *A. baumannii* (CRAB) infections should be regarded as regionally specific and based on local epidemiology.

The preferred treatment for CRAB infections is unknown. Combination approaches may help to overcome multiple mechanisms of resistance and suppress further resistance; however, the clinical benefits of combination therapy remain unclear.

Among vulnerable and critically ill patients infected with CRAB, we advocate for early combination approaches, which include a carbapenem, polymyxin B, and/or ampicillin/sulbactam on the basis of site of infection and patient-specific factors (Table 4).

Host factors, source control measures, and proper infection control practices are critical determinants of patient outcomes and containment of *A. baumannii* infections.

INTRODUCTION

Acinetobacter baumannii is a ubiquitous Gram-negative (GN) bacterium and an effective human colonizer. The organism has emerged as a problematic nosocomial pathogen owing to its resilience within the hospital environment and innate ability to evade commonly employed antibiotic therapy [1]. In the current era of rapidly evolving antibiotic resistance threats, carbapenem-resistant *A. baumannii* (CRAB) has been identified as one of the highest priority pathogens for research and development of new antibiotics [2]. Indeed, CRAB infections are the most common difficult-to-treat resistance phenotype encountered in the USA, and result in disproportionately increased mortality compared to other CR pathogens [3, 4]. The preferred treatment for CRAB infections has not been defined. Clinical trials have not provided conclusive evidence for one treatment over another; therefore, treatment selection relies heavily upon interpretation of in vitro efficacy, host factors, and pharmacokinetic-pharmacodynamic (PK/PD) data. Traditional agents with retained in vitro activity (aminoglycosides, polymyxins, and tetracyclines) are limited by site-specific PK, emergence of resistance, and/or toxicity. Moreover, the recent development of novel β-lactam/β-lactamase inhibitor (BL/BLI) agents that have expanded the armamentarium against CR Enterobacterales and *Pseudomonas aeruginosa* do not provide enhanced in vitro activity against CRAB. Clinical trials of two recently approved agents, cefiderocol and eravacycline, have offered disappointing or no CRAB-specific clinical outcomes data, respectively [5]. Taken together, treatment of CRAB infections remains a major challenge for clinicians and an ongoing threat to public health. The purpose of this narrative review is to summarize recent clinical and preclinical data, interpret molecular epidemiology, and review mechanisms of resistance to offer our perspective on best practices for managing patients with *A. baumannii* infections, with an emphasis on CRAB.

MOLECULAR EPIDEMIOLOGY OF CRAB

Antibiotic susceptibility testing is used in clinical practice as a surrogate for molecular mechanisms of resistance in *A. baumannii*. Importantly, molecular characteristics of *A. baumannii* vary by region, and thus, the preferred treatment for CRAB infections should be regarded as regionally specific and based on local epidemiology. Three genetically distinct clonal lineages have accounted for the majority of *A. baumannii* globally; those are Clonal Complex (CC) 1, 2, and 3, and are defined by their Pasteur multi-locus sequence types (ST) as ST1, ST2, and ST3, respectively. CC2 is the predominant genetic lineage in the USA and accounts for more than 75% of all CRAB infections [6, 7]. Several CC2 sub-lineages have also been identified with varying antibiotic resistance genes and susceptibility phenotypes. Closely related CC2 sub-lineages are better discriminated by the Oxford multilocus sequence typing scheme, which previously identified ST122 and ST208 as the common lineages from 2008 to 2009 [8, 9]. Predominant lineages that vary by geographic region have shifted over time, underscoring the importance of prospective surveillance to guide local treatment recommendations. From 2007 to 2016, ST281 and its single locus variant ST349 replaced prior lineages at two hospitals in Cleveland [6]. Similarly, a recent genomic epidemiology study of isolates collected from 2017 to 2018 found ST281 to be highly prevalent; however, the most common lineage varied at each of the four centers contributing isolates [7]. Interestingly, a non-CC2, ST499 lineage comprised 16% of isolates in this contemporary sample. ST499 has been reported sporadically, but never as an emerging or dominant lineage in the USA [9].

Individual STs are associated with varying antibiotic resistance genes and susceptibility patterns [6, 7]. For instance, lineages ST208, ST281, and ST349 commonly harbor plasmid-acquired $bla_{\text{OXA-23}}$, which is present in more than 60% of all CRAB isolates in the USA. On balance, $bla_{\text{OXA-24}}$ was the most commonly acquired carbapenemase among ST499 isolates. It is unclear if the presence or type of plasmid-mediated carbapenemase influences the efficacy of antibiotic therapy, particularly for carbapenem-based regimens. This is due, in part, to the frequency of an insertion sequence (IS) element IS*Aba1* upstream of chromosomally encoded $bla_{\text{OXA-51}}$ that carries a strong outward facing gene promoter that enhances expression [1]. The resulting IS*Aba1*-$bla_{\text{OXA-51}}$ structure manifests in CR, and is common among isolates with and without plasmid-mediated carbapenemases. Other important clonal differences have been reported. In rank order, rates of amikacin susceptibility were increased across isolates from ST208, ST281, and ST499 lineages [7]. Meanwhile, rates of ampicillin–sulbactam non-susceptibility increased from 49% in a prior surveillance study of ST122 and ST208 isolates to more than 80% in contemporary studies predominated by ST281 [6, 7]. Finally, alarming trends in the rates of colistin non-susceptibility have been described recently. Across 115 isolates from four centers in 2017 to 2018, 22% of isolates were colistin non-susceptible, compared to a rate of 5% in 2010 [10]. Even more worrisome, 98% of colistin non-susceptible isolates were classified as ST281, the same sub-lineage emerging in Cleveland and other US regions. Increasing rates of non-susceptibility to ampicillin–sulbactam and colistin are particularly ominous given the reliance on these agents in antibiotic combination strategies to treat CRAB.

These alarming resistance trends work in concert with the relative infrequency of isolating CRAB in many centers to create an inauspicious treatment decision for clinicians. Therefore, strategies should also be aimed toward preventing the emergence of further resistance against susceptible strains. In this regard, β-lactam therapy remains first-line treatment for susceptible *A. baumannii*. Optimized doses should be employed universally, and not reserved for strains exhibiting elevated minimum inhibitory concentrations (MICs), to improve efficacy and suppress the emergence of resistance (Table 1) [11, 12]. When clinically indicated, carbapenem-sparing treatment approaches are preferred to slow the emergence of CRAB given reported associations between carbapenem consumption and resistance

Table 1 Optimized dosing strategies for treatment of *Acinetobacter* infections for select drugs

Carbapenem	Imipenem/cilastin 1g IV q6h*	For isolates with intermediate susceptibility	PI
	Meropenem 2 g IV q8h*	Consider prolonging infusion for increased *f*T/MIC	[27, 28]
	Meropenem HDCI (> 6 g per day)*	Requires TDM capability to minimize risk of neurotoxicity. Consider once MIC > 8	[29]
Sulbactam	Ampicillin/sulbactam 6 g IV q8h or 3 g IV q4h ((12/6 g per day due to the 2:1 dosing ratio))*	Up to 9 g q8h studied, though no difference in clinical outcome	[143, 144]
Tetracyclines	Minocycline 200 mg IV/PO q12h	Monitor blood urea nitrogen and signs of uremia at doses > 200 mg/day; may be ineffective when MICs are > 1 mg/L	[145]
	Tigecycline 200 mg IV × 1 dose; 100 mg IV q12h thereafter		[146]
	Eravacycline 1 mg/kg IV q12h		PI
Aminoglycosides	7–10 mg/kg TBW IV once daily (gentamicin/ tobramycin)	Target peak/MIC 8–10; AUC/MIC ratio ~ 75	[147]
	15–20 mg/kg TBW once daily (amikacin)*		
Colistin (colistimethate)	300 mg IV load; 360 mg divided q12h thereafter*	For colistin MIC ≤ 2 Dosed in colistin base activity (CBA)	[148]
Polymyxin B	2.5 mg/kg TBW IV load; 1.5 mg/kg TBW q 12 h thereafter	For colistin MIC ≤ 2	[148]
Cephalosporins	Cefepime 2 g IV q8h*	Consider prolonging infusion for increased *f*T/MIC	[149]
	Ceftazidime 2 g IV q8h*	Consider prolonging infusion for increased *f*T/MIC	[12]
	Cefiderocol 2 g IV q8h over 3 h*		[150]
Penicillins	Piperacillin/tazobactam 4.5 g IV q6h*	Consider prolonging infusion for increased *f*T/MIC	[12]
Folate pathway inhibitor	Trimethoprim/sulfamethoxazole 15 mg/kg IV divided q8h*	Dosing variable in studies, often used in combination	[151]

PI package insert, *HDCI* high-dose continuous infusion, *TBW* total body weight, *MIC* minimum inhibitory concentration
*Requires renal adjustment

[3, 13, 14]. Such options would include extended-spectrum cephalosporins that are stable against chromosomally encoded *Acinetobacter*-derived cephalosporinase (ADC) hydrolysis and ampicillin–sulbactam. Indeed, among patients with *A. baumannii* bacteremia, treatment with ampicillin–sulbactam resulted in similar outcomes compared to imipenem [15]. Taken together, treatment paradigms should be constructed with knowledge of each center's

Table 2 Clinically relevant *A. baumannii* mechanisms of antibiotic resistance

Mechanism of resistance	Antibiotics conferred resistant	Microbiological factors Intrinsic/acquired Found in combination	Clinical indicators and implications
Amber class A β-lactamases	Penicillins	Acquired resistance:	Penicillin-resistant phenotype
	Cephalosporins	TEM, SHV, CTX-M, KPC*	Cephalosporin-resistant phenotype
	Carbapenems		Carbapenem-resistant phenotype
Amber class B β-lactamases	Penicillins	Acquired resistance:	Carbapenem-resistant phenotype
	Cephalosporins	NDM, IMP*, VIM*	Ampicillin/sulbactam-resistant phenotype
	Carbapenems		BL/BLI-resistant phenotype
	BL/BLI combinations		
Ambler class C β-lactamases	All cephalosporins, with the exception of cefepime	Intrinsic resistance: *Acinetobacter*-derived cephalosporinase (ADC)	Cephalosporin-resistant phenotype (with the exception of cefepime, which is not a substrate of AmpC β-lactamases)
Ambler class D β-lactamases	Penicillins	Acquired resistance:	Carbapenem-resistant phenotype
	Carbapenems	OXA-23*, OXA-24*, OXA-40*, OXA-58*, OXA-50* groups	Ampicillin/sulbactam-resistant phenotype
		Intrinsic resistance:	
		OXA-51*	
Efflux pumps (Ade-type, TetA, TetB)	Tetracyclines	Acquired resistance:	Tetracycline-resistant phenotype
		TetA and Tetb efflux pumps	Tigecycline-resistant phenotype
			Minocycline-resistant phenotype
		Ade-type efflux pumps	Eravacycline-resistant phenotype
Amino acid substitution to the DNA gyrase of topoisomerase IV	Fluoroquinolones	Acquired resistance:	Ciprofloxacin-resistant phenotype
		gyrA gene	
		parC gene	

Table 2 continued

Mechanism of resistance	Antibiotics conferred resistant	Microbiological factorsIntrinsic/acquiredFound in combination	Clinical indicators and implications
Aminoglycoside-modifying enzymes	Aminoglycosides	Acquired resistance, amikacin and tobramycin: AAC(6')-Ib, AAC(6')-Ih Acquired resistance, gentamicin: AAC(3)-Ia, ANT(2″)-Ia APH(3')-Ia ArmA	Amikacin-resistant phenotype Gentamicin-resistant phenotype Tobramycin-resistant phenotype
Porin channel mutations (OmpA)	Carbapenems Cephalosporins	Acquired resistance: Omp_{Ab}	
PBP reduced expression	Sulbactam Cefiderocol	Acquired resistance: PBP2 PBP3	Ampicillin/sulbactam-resistant phenotype Cefiderocol-resistant phenotype
Siderophore-receptor gene reduced expression	Cefiderocol	Acquired resistance: PiuA	Cefiderocol-resistant phenotype

BL/BLI β-lactam/β-lactamase inhibitor, *ADC Acinetobacter*-derived cephalosporinase, *PBP* penicillin-binding protein
*Indicates carbapenamases

local epidemiology, antimicrobial stewardship goals, most common sites of infection, and an appreciation for underlying mechanisms of resistance.

LINKING MECHANISMS OF RESISTANCE TO TREATMENT OPTIONS

Mechanisms of intrinsic and acquired antibiotic resistance against *A. baumannii* have been described previously [16, 17]. Common mechanisms include enzymatic inactivation by β-lactamases, overexpression of drug efflux pumps, and mutations in antibiotic binding targets [16, 17]. These mechanisms often work in concert among multidrug-resistant (MDR) strains that often lead to deleterious patient outcomes [16–18]. The most common mechanisms are detailed in Table 2.

β-Lactams

Mechanisms of CR in *A. baumannii* are a focal point of ongoing research [19]. Ambler class A and B carbapenemases are uncommon, thereby limiting the potential utility of novel BL/BLIs and aztreonam, respectively [20–22]. Ambler class D β-lactamases are the most widespread

carbapenem-hydrolyzing enzymes detected worldwide [17]. Knowledge of the specific oxacillinase (OXA) is clinically relevant because each variant confers varying resistance to carbapenems and other BLs (Table 2) [23]. *A. baumannii* intrinsically produces the OXA-51 carbapenamases, which may be overcome by the appropriate dosing of carbapenem antibiotics in the absence of alterations in the gene promoter [24]. Multiple plasmid-acquired OXAs, including OXA-25, 26, and 27, have been well characterized in CRAB isolates; however, OXA-23-like and OXA-24-like (renamed OXA-40) enzymes are responsible for nosocomial CRAB outbreaks [25, 26]. Ultimately high-level CR manifests through the combination of OXA-type carbapenamases with or without secondary mechanisms including decreased outer membrane permeability and increased efflux pump activity [26]. As with other BL agents, the time that the free drug concentrations remain above the MIC ($fT > MIC$) is the pharmacodynamic driver of efficacy for carbapenems. In the setting of CRAB infections, however, maintaining $fT > MIC$ is a major challenge given the high carbapenem MICs. Thus, dosing of carbapenems should be optimized through extended or continuous infusions, against CRAB isolates, whenever possible (Table 1) [27, 28]. As a means of maintaining carbapenem concentrations above the MIC, therapeutic drug monitoring has been employed successfully, and associated with clinical cure in select cases [29].

Sulbactam, a BLI co-formulated with ampicillin in the USA, has demonstrated activity against *A. baumannii* owing to its capacity to selectively bind to penicillin-binding proteins (PBPs) 1, 2, and 3 [30, 31]. Sulbactam retains activity against some, but not all, CRAB strains that harbor OXA-23 [32]. Higher doses of sulbactam may have utility against OXA-23-producing isolates (Table 1), particularly in combination with other therapeutics like carbapenems [33, 34]. Studies indicate that sulbactam doses of more than 6 g per day are effective for CRAB infections, including ventilator-associated pneumonia [35]. Nonetheless, reduced expression of PBP2 and increased expression of TEM-1 β-lactamases contribute to sulbactam resistance [36]. Higher sulbactam MICs (> 16 mg/L) require PK-PD optimization, including higher doses and more frequent dosing, to achieve 90% probability of target attainment ($fT > MIC$ for at least 60% of the interval) [37]. Ampicillin/sulbactam MICs are useful surrogates for ascertaining sulbactam activity, when within the susceptible range (≤ 8/4 mg/L) [38]; however, they are less useful when the isolates are classified as resistant.

Tetracyclines

Tetracyclines have been shown to retain in vitro activity against greater than 60% of CRAB isolates [18, 39]. In rank order, eravacycline is the most potent in vitro, followed by tigecycline, minocycline, and tetracycline [40]. Eravacycline and tigecycline demonstrate similar PKs in healthy volunteers [41, 42]; however, clinical experience against CRAB infections has only been reported for tigecycline. Minocycline may have retained activity against CRAB even when susceptibility to other tetracyclines is lost [43]. Unfortunately, the accurate determination of minocycline MICs against *A. baumannii* is challenging; disk-diffusion and E-test methods may overcall resistance [44]. The ACUMIN study, a 2021 PK/PD investigation evaluating minocycline in critically ill patients, described the lack of target attainment with minocycline dosed 200 mg IV q12 h against CRAB isolates with MICs > 1 mg/L [45]. These data emphasize the need for clinicians to consider requesting broth microdilution to confirm minocycline susceptibility if alternative agents are unavailable, and prioritize use only in cases where MICs are less than 1 mg/L.

Aminoglycosides

Aminoglycosides maintain minimal susceptibility, less than 30%, against CRAB isolates; specifically, those characterized by the presence of class D β-lactamases [46]. With the lack in CRAB susceptibility to the agents, higher doses, associated with toxicity, are required to prevent bacterial regrowth [47]. Further, different MIC testing methods (Vitek, broth microdilution) have been shown to report varying

aminoglycoside MIC values, which is a hurdle to adequate usage of these agents in CRAB infections [46].

In vitro antibiotic activity is often more promising than clinical outcomes when addressing utility of tetracyclines and aminoglycosides to treat CRAB infections given the notable PK limitations. With the tetracyclines specifically, limitations include large volumes of distribution and high protein binding resulting in low blood plasma levels. Increased doses used to achieve PD targets with eravacycline, tigecycline, and aminoglycosides can contribute to poor patient outcomes and patient adverse events. Among tetracyclines, resistance is mediated by overexpression of efflux pump systems [48]. While minocycline, eravacyline, and tigecycline have been mostly shown to evade the most common tetracycline efflux pumps, TetB and TetA, extended-spectrum tetracycline efflux pumps, such as AdeABC and AdeIJK, can confer resistance to these agents [48, 49]. Among aminoglycosides, modification to the binding site by aminoglycoside-modifying enzymes such as acetyl transferases, phosphotransferases, and adenylyl transferases disseminates class-wide *A. baumannii* resistance [50, 51]. The AdeABC efflux system may further impact aminoglycoside activity. Decreased expression of several proteins including CarO, and $OmpA_{Ab}$, influencing antibiotic permeability have been described in strains harboring AdeABC, IJK efflux pumps, aminoglycoside-modifying enzymes, and β-lactamases, including OXA-23. Thus, the contribution of porin channels towards tetracycline or aminoglycoside resistance is not well defined independent of other resistance mechanisms [52, 53].

Polymyxins

The polymyxins colistin and polymyxin B remain active against most CRAB isolates; *A. baumannii* resistance rates are reported around 5% in the USA [54, 55]. Dosing of these agents is complex, particularly for colistin (given as a prodrug colistimethate sodium, CMS) where achieving therapeutic drug concentrations is a major challenge [56]. Over time, rates of CR have forced clinicians to re-evaluate colistin as a viable therapeutic resulting in widespread use against CRAB infections. Inconsistent dosing and rampant use within endemic regions have resulted in emergence of colistin-resistance and colistin-heteroresistance. This is mediated by the mutation of lipopolysaccharide or loss of lipid A in the gram-negative outer membrane that may lead to unfavorable patient outcomes [53, 57, 58]. Colistin non-susceptible *A. baumannii* has become more prominent, especially among CRAB. Of interest, polymyxin B offers advantages over colistin such as decreased time to bacterial eradication as well as a primarily non-renal elimination; however, availability is limited globally [56]. Additionally, in disease states where CRAB isolates are prominent such as urinary tract infections, colistin reaches higher concentrations compared to polymyxin B; less than 1% of polymyxin B is recovered in the urine [59]. The inhaled formulation of colistin allows for higher pulmonary exposure without systemic toxicity. While these agents share a similar pharmacophore, the susceptibility of colistin and polymyxin B in CRAB isolates has been shown to be occasionally discordant, and different microbiological testing modalities (E-tests) have been found to be unreliable [60]. Therefore, when determining the activity of either agent against CRAB, broth microdilution tests are preferred. The Clinical and Laboratory Standards Institute has assigned only an intermediate or resistant interpretation for colistin activity, MIC $\leq$ 2 mg/L and $>$ 2 mg/L for each designation, respectively. The susceptibility breakpoint was eliminated, primarily due to a lack in scientific justification and absence of clinical efficacy data.

MECHANISTIC INSIGHTS INTO ANTIBIOTIC COMBINATIONS

A. baumannii infections with decreased susceptibility to the carbapenems, and risks for the development of resistance to last-line options, present a conundrum that points toward combination therapies as a strategy to overcome

complex mechanisms of antibiotic resistance. Combinations of antibiotics studied in vitro against CRAB include, but are not limited to, polymyxins, tigecycline, rifampin, sulbactam, and meropenem. Data demonstrate strong activity of carbapenem-based combinations measured by log-decreases in colony counts in vitro against CRAB isolates representing a range of elevated carbapenem MICs [61–63]. Among studied carbapenem combinations, the addition of colistin has resulted in noteworthy outcomes. Time-kill assays have revealed the reduction of bacterial counts greater than 2 log colony forming units (CFU)/ml with the use of carbapenem plus colistin regimens [62, 64]. This success has been attributed to the colistin-induced alteration in membrane permeability, increasing the capacity of carbapenems to reach their binding site [65]. The synergistic activity often manifests through prevention of bacterial regrowth, which occurs commonly in vitro against single agents, particularly colistin. The impact of the colistin–carbapenem combinations on the delay in the emergence of resistance remains to be elucidated given conflicting reports of both clinical successes and failures [61, 66]. Decreased susceptibility to colistin may inhibit in vitro synergy and prompt clinicians to explore alternative therapies, including three-drug combinations [62].

Combinations employing tetracycline agents (minocycline and tigecycline), aminoglycosides, and sulbactam with either carbapenems or colistin against CRAB isolates have offered mixed results [67, 68]. Alternatively, dual BL therapy against CRAB reveals strong synergistic activity and has been explored with cefiderocol and meropenem [69]. Synergy can be attributed to the binding of cefiderocol and meropenem to complementary PBPs allowing for complete saturation. Other agents intrinsically inactive against *A. baumannii*, including rifampin, glycopeptides, and fosfomycin, have been utilized in combination, most commonly with colistin, in an effort to overcome resistance [54, 70–72]. In vitro they have shown declines in bacterial burdens and restoration of colistin susceptibility among colistin non-susceptible, CRAB isolates [54, 73].

Triple-therapy regimens including colistin and a carbapenem plus sulbactam or tigecycline have been shown to further decrease the CRAB bacterial load including against isolates non-responsive to dual therapy options [33, 62]. Mechanistically, the hypotheses surrounding the increased activity of these triple combinations are similar to the basis previously described surrounding combination therapy. The increased occupancy of PBPs with sulbactam and/or the inhibition of protein synthesis with tigecycline synergizes with colistin and the carbapenem to overcome resistant genotypes (i.e., OXAs, tet efflux pumps, altered LPS) present within CRAB isolates. While pronounced effects of the triple therapies may be predicated on the colistin MIC, it is important to acknowledge that triple-therapy regimens have been shown to be more effective than dual regimens evaluated against recurrent CRAB isolates [62]. In some cases, even sub-inhibitory amounts of colistin, when used in combination, have demonstrated bactericidal activity.

Taken together, the relationship between molecular mechanisms of resistance and effective combinations against CRAB remain ill defined. While *A. baumannii* isolates responsive to combination therapy regimens are often characterized by resistance genes, such as $bla_{\text{OXA-23}}$, the *A. baumannii* clones that harbor them are typically absent from experiment reports [74]. This exposes a true gap in scientific knowledge, as uncovering the optimal combinations to utilize against specific clones and genes causative of resistant phenotypes would offer a holistic approach to selecting effective patient treatment options against CRAB.

NOVEL THERAPEUTICS NOW AND IN THE FUTURE

An improved understanding of the underlying mechanisms of resistance has facilitated the development of novel agents with in vitro activity against CRAB that have been reviewed in recent publications [75–77]. Herein, we discuss three agents with recent phase 3 trial data available or in progress: cefiderocol, eravacycline, and durlobactam–sulbactam, and explore

the utility of bacteriophage therapy [5, 78–80]. Additional agents at earlier stages of clinical development are provided in Table 3.

Cefiderocol

Cefiderocol is a novel siderophore-cephalosporin antibiotic that is FDA approved for complicated urinary tract infections (UTI) and nosocomial pneumonia [63]. Cefiderocol's siderophore catechol, iron-chelating moiety utilizes the bacterial active transport system to evade common resistance mechanisms that deactivate other β-lactam antibiotics. In vitro data demonstrate excellent activity against both colistin-resistant and CR *A. baumannii* [64]. The nuances of cefiderocol pharmacology and in vitro activity are well described in a 2020 review by Abdul-Mutakabbir and colleagues [81]. Unfortunately, clinical data among patients treated with cefiderocol for *A. baumannii* infections have not been as encouraging [5, 65]. A phase 2 study comparing cefiderocol to imipenem–cilastatin for complicated UTIs caused by GN pathogens met non-inferiority criteria, but included only one patient with infection due to *Acinetobacter* species [82].

CREDIBLE-CR, a phase 3 trial, enrolled patients with severe infections due to CR GN bacteria [5]. While clinical cure rates between best available therapy and cefiderocol were similar, participants randomized to cefiderocol treatment had a significantly higher rate of all-cause mortality. This finding was driven by the study population infected with CRAB [5]. These results should be interpreted with caution, as all-cause mortality was not the primary outcome of the study. Moreover, at the time of study enrollment, those infected with *A. baumannii* were older (≥ 65 years), with higher rates of intensive care unit admission and ongoing septic shock, although no specific factors were identified as responsible for the increased mortality [5]. During the course of the study, five cases of *A. baumannii* infection had a fourfold increase in cefiderocol MICs, three of which crossed the FDA-specified susceptibility threshold of ≤ 1 mg/L, elevating concerns for developing resistance against cefiderocol monotherapy [5]. An additional phase 3 trial, APEKS-NP, found cefiderocol was non-inferior to dose-optimized meropenem (2 g IV every 8 h, 3-h extended infusion) in patients with GN pneumonia [79]. Fourteen-day all-cause mortality, clinical cure, and microbiologic eradication were similar between treatment groups for participants infected with *A. baumannii*; however, this group only comprised 16% of the study population, of which 66% of isolates were CR. Overall, there is a need for further studies of cefiderocol against *A. baumannii*, including potential use in combination regimens. Cefiderocol has only been formally studied as monotherapy, whereas current best available therapy for *A. baumannii* infections usually includes colistin combination therapy [5]. Considering these limitations, cefiderocol's role against CRAB remains to be defined. Until further data are available, it is reasonable to consider cefiderocol as a salvage agent against CRAB with or without other in vitro active agents.

Table 3 Additional agents in the pipeline

	Status
β-Lactamase inhibitors	
LN-1-255	Outcomes studies, in vitro studies
VNRX-5113	Phase 1
β-Lactam enhancers	
WCK 5153 + zidebactam (WCK 5107)	Phase 1
β-Lactam	
AIC499	Phase 1
Polymyxin B derivative (enhancer agent)	
SPR741	Phase 1
Aminoglycoside	
Apramycin	In vitro studies
Tetracycline	
TP-6076	Development stopped to focus on eravacycline

Eravacycline

Eravacycline is a tetracycline analogue and a novel fluorocycline of the tetracycline family that is FDA approved for complicated intra-abdominal infections (cIAI) [83]. In vitro, eravacycline demonstrates lower MICs against CRAB than tigecycline and retains activity against isolates harboring tetracycline efflux pump genes; it also demonstrates reliable activity in the presence of OXA carbapenemases and colistin-resistant isolates [40, 84–91]. Eravacycline has been studied in phase 3 trials for both cIAI and cUTI [78, 92]. Phase 3 cIAI trials demonstrated non-inferiority of eravacycline to both ertapenem and meropenem; however, *A. baumannii* infections only comprised 3% and 2% of the total study infecting pathogens, respectively [78, 92]. On balance, eravacycline was inferior to levofloxacin and ertapenem for treatment of cUTI [93, 94]. The utility of eravacycline against *A. baumannii* is difficult to ascertain as clinical outcomes data have focused on infection site rather than infecting pathogen. PK data reveal an additional layer of complexity, as eravacycline has demonstrated suboptimal urinary and serum concentrations; however, the drug appears to distribute well into bone. These data provide insight regarding the potential clinical efficacy of eravacyline broadly, but the limited number of patients with *A. baumannii* infections precludes specific recommendations for *A. baumannii*. Moreover, eravacycline susceptibility interpretive criteria against *A. baumannii* have not been established.

Durlobactam–Sulbactam

Durlobactam is a diazabicyclooctanone (DBO) β-lactamase inhibitor that has been studied in combination with sulbactam in multiple phase 1 trials [95–97], one phase 2 trial [98], and in an ongoing phase 3 trial against *A. baumannii–calcoaceticus* complex infections [80]. At the time of publication, this agent has not been FDA approved. This BL/BLI combination demonstrates activity against Ambler class A, C, and D β-lactamases with potential utility for CRAB. The current phase 3 trial addresses many limitations that have been faced in evaluating agents for efficacy against *A. baumannii*. Although the BL/BLI combination was evaluated as a stand-alone agent in vitro, clinical studies have combined it with other BLs to extend the empiric spectrum to include other GN pathogens. The phase 3 trial designed to study infections caused by *A. baumannii–calcoaceticus* complex infections compares durlobactam–sulbactam, dosed 1 g/1 g infused over 3 h and administered every 6 h with imipenem/cilastin 1 g/1 g infused over 1 h every 6 h versus colistin 2.5 mg/kg infused over 30 min every 12 h after an initial loading dose with imipenem/cilastin [80]. It is worth noting that the sulbactam dose used in this investigation, 4 g daily, is less than the 6 g threshold discussed previously. This therapy regimen is more reflective of real-world practice with CRAB than monotherapy regimens employed in the CREDIBLE-CR trial. However, this will lead to difficulty in interpreting the stand-alone efficacy of the novel BL/BLI. In addition to focusing on CR, the phase 3 study includes a planned subgroup analysis of colistin-resistant isolates [80].

Bacteriophage Therapy

Phage therapy refers to the use of viruses (bacteriophages) that parasitize specific bacterial species or strains as a means of treating bacterial infections. Although first discovered in the early 1900s, clinical research on the use of phage therapy was largely abandoned in favor of effective and easily mass-produced therapies, such as antibiotics [99, 100]. Increased antimicrobial resistance worldwide has renewed the interest in phage therapy. Although identification of bacteriophages targeting *A. baumannii* was introduced in 2010, phage therapy presents many unique challenges [101]. Typical clinical trial standardization can be difficult when studying phage therapy as the same therapeutic is not always administered to each participant. Even in cases where a standardized phage cocktail is utilized for all patients, the cocktail may necessitate alterations throughout the treatment course in order to target evolving

susceptibility of the organisms [102]. New regulatory practices that create a pathway for bacteriophage clinical research and approval are needed to aid development efforts and promote the availability of this alternative therapeutic approach. There are many bacteriophage clinical trials underway, including a phase 1/2 trial evaluating the use of a personalized bacteriophage therapy for patients with UTIs due to *Klebsiella pneumoniae* or *E. coli* [103], and an expanded access program for patients with COVID-19 and pneumonia or bacteremia/septicemia infected with *A. baumannii, Pseudomonas aeruginosa*, or *Staphylococcus aureus* [104].

These clinical trials will begin to address important knowledge gaps for use of bacteriophages against *A. baumannii*. More robust data is needed to determine the optimal route, dosage form, dose, or duration of therapy for phage therapy. In the USA, the current practice for obtaining bacteriophages for patient treatment requires contacting and being evaluated by one of the few organizations with bacteriophage libraries and, if deemed appropriate by the contacted organization, submitting an emergency investigational drug application (eIND) to the FDA [105, 106].

Two available case reports highlight the use of the eIND process in patients infected with CRAB, both treated with phage therapy in conjunction with antimicrobials as a last resort after failure of sole antimicrobial therapy. The first was a 68-year-old man with sepsis, diabetes, and an MDR *A. baumannii* infected pseudocyst secondary to necrotizing gallstone pancreatitis [102]. A phage cocktail was initially administered locally into the pseudocyst, biliary, and intrabdominal cavities and then intravenously. With the addition of phage therapy, the patient clinically improved from a comatose, intubated state, requiring vasopressor support, to clinical success and subsequent discharge. Drug resistance to the individual phages developed during therapy, but the phage therapy was also found to make the *A. baumannii* more sensitive to antibiotic therapy [102]. The second case was a 77-year-old man with traumatic brain injury requiring craniectomy and intraoperative cultures positive for MDR *A. baumannii* [107]. Phage therapy was administered intravenously; local administration via the patient's subdural or lumbar drains was not possible. The patient's craniectomy site improved; however, the patient subsequently died [102, 107]. To date, phage therapy has been employed in a limited number of clinical trials with varying success [108, 109]; however, additional trials are underway and likely to provide further insights into the role of bacteriophages in conjunction with antibiotic therapy.

While phage therapy presents promising results as described, the development of phage resistance and the need for multiple phages to provide adequate patient treatment is a concern [102]. Further, obtaining and administering phages that are isolate-specific is a substantial barrier to the use of phage therapy, both for individual patients and for designating their place within CRAB infection treatment algorithms.

HOST FACTORS

A critical factor in treatment of *A. baumannii* infections is antimicrobial choice; however, when choosing a regimen for a specific patient, host factors that influence drug choice and prognosis must be considered. Risk factors that have been associated with *A. baumannii* infection are numerous [14, 110]. The general tenet is that the organism is recovered from patients with previous healthcare exposure, recent and extensive antimicrobial exposure, and chronic comorbid conditions. These risk factors and their intertwined nature are highlighted by solid organ transplant and oncology patients who inevitably receive more healthcare and antimicrobial exposure than the general population given their immunocompromised state [14, 110–112]. Furthermore, increased expression of certain epithelial cell receptors, often during inflammatory processes, can increase risk of *A. baumannii* infection through adhesion to those receptors [113]. Another notable risk factor for *A. baumannii* infection is diabetes or glucose intolerance during critical illness [110, 114].

Risk of the various *A. baumannii* resistance phenotypes is either a matter of previous antimicrobial exposure (likely the selection of a resistant phenotype within a patient) or patient exposure to an environment where an outbreak-type pathogen is lurking [14, 115, 116]. Clinicians are encouraged to review their local antibiogram to understand the current *A. baumannii* phenotypes most likely to be present in their patients. In the case of a local outbreak, it may be prudent to target the outbreak phenotype empirically as opposed to the more generalized antibiogram-driven phenotypes as the antibiogram often covers a longer time period and varied patient population [117].

In choosing a suitable pharmacologic agent, site of infection must play into the decision-making. Most MDR infections with *A. baumannii* are in the respiratory tract. This may be in part due to its ability to interact with respiratory epithelial cell surface receptors as a means of adhering to and even invading the cell [113]. Antimicrobials targeting pneumonia are typically dosed more aggressively than the doses utilized for UTIs, given that epithelial lining fluid concentrations are generally diminished as compared to urine/serum levels [118]. Further compounding the source of infection is the likelihood with which critically ill patients with altered volumes of distribution and augmented renal clearance may require dose adjustment. Therapeutic drug monitoring would be ideal; however, it is typically scarce outside of aminoglycosides. Therefore, optimized dosing for BL antimicrobials should be considered (Table 1). Aminoglycosides can be effective in pneumonia—the caveat is that doses should target recommended area under the curve (AUC) and/or peak with respect to MIC ratios [119]. Current dosing breakpoints are too liberal to be appropriate for these types of infections and generally tobramycin and amikacin MICs above 4 and 8 μg/ml, respectively, will require doses exceeding those that can be safely administered to patients. For minocycline and tigecycline, the site of infection and relatively higher MICs are important to take into account when considering their use. Poor target attainment in the blood by the tetracyclines, tigecycline especially, should discourage use as monotherapy for *A. baumannii* bacteremia. Higher than standard dosing has been investigated to somewhat overcome these limitations (Table 1) [120].

Lastly, source control is the cornerstone of optimal management against CRAB infections given its persistence on foreign devices and ability to form biofilms [121, 122]. Biofilm formation is also a hallmark of the more resistant phenotypes, further enhancing their virulence and tenacity [123]. When *A. baumannii* bacteremia is associated with an intravenous catheter (or other foreign devices) it is recommended to remove the device in conjunction with antimicrobial therapy, as it is associated with improved outcomes [124]. When foreign material is retained, it may be prudent to utilize antimicrobials that penetrate and impair biofilm production, such as rifampin or the tetracyclines [125]. The importance of source control is also a common dilemma in the transplant and surgical populations, as those patients may be difficult to take back to surgery for proper source control. It is controversial in these cases as to what role antimicrobials play to create a stalemate rather than intention to cure the infection. Surgical intervention should be prioritized when possible. An antimicrobial regimen aimed at suppressing infection progression until clinical recovery may be a reasonable strategy. However, the risk of promoting selection of resistance increases over time with such a strategy. In cases where source management is not feasible, it is important to determine patient wishes and be clear about the futility of antimicrobials alone to cure some of these difficult-to-treat infections.

CLINICAL CONSIDERATIONS

Adequate treatment of *A. baumannii* remains more gray than black and white. The biggest questions remain unanswered: which empiric therapy to select first, combination therapy or monotherapy? Once susceptibilities are known, questions still persist: does clinical susceptibility testing provide enough insight into harbored, but not phenotypically expressed mechanisms of resistance? Do antibiotics selected prevent

Table 4 Preferred and alternate treatments for CRAB by infection site

Infection site	Preferred[b]	Alternatives, including colistin/polymyxin-sparing regimens	Therapies to avoid when alternatives exist
Bacteremia, primary or line-related	Meropenem + polymyxin B ± ampicillin–sulbactam[c]	Meropenem + Minocycline ± Ampicillin–sulbactam[c] OR Cefiderocol in combination[d]	Tigecycline, eravacycline
Pneumonia[a]	Meropenem + polymyxin B ± ampicillin–sulbactam[c]	Meropenem + minocycline OR Cefiderocol in combination[d]	Monotherapy with any agent
Intra-abdominal infection	Tigecycline ± meropenem	Eravacycline ± meropenem	Aminoglycosides
Osteomyelitis	Minocycline ± meropenem	Eravacycline ± meropenem	
UTI—pyelonephritis	Amikacin OR colistin	Gentamicin Tobramycin Cefiderocol	Tigecycline, eravacycline
UTI—cystitis	Amikacin OR colistin	Gentamicin Tobramycin Cefiderocol	Tigecycline, eravacycline
Central nervous system[b]	Meropenem + polymyxin B + ampicillin–sulbactam	Meropenem + tigecycline + ampicillin–sulbactam	Aminoglycosides

[a] Evidence does not support or refute local delivery of antibiotics (intrathecal, inhaled) and may be considered on a case-by-case basis

[b] Combination therapy merited where source control is unachieved and/or for secondary bacteremia

[c] We prefer adding a third agent in the setting of septic shock or clinical instability while acknowledging there are no clinical data to support this approach

[d] At this time we recommend cefiderocol as an alternative treatment on the basis of the available evidence. When indicated, we recommend using in combination with an in vitro active agent

emerging resistance? The newest FDA-approved antimicrobial therapies with activity against *A. baumannii* are promising because they are much less toxic compared to polymyxins. However, worse outcomes versus treatment with colistin among subjects with CRAB raise major concerns [5].

Selecting appropriate antibiotic therapies therefore falls into three guiding principles:

- Patient-specific factors: severity of illness, medical history, and organ function
- Infection characteristics: site and extent of source control, biofilms
- Mechanisms of resistance: local epidemiology and prior antibiotic exposures

Given the high propensity of *A. baumannii* to colonize patients, particularly those in the intensive care unit, the first decision is to adjudicate whether it is the source of an infection or a colonizing organism [126]. Regardless of infection or colonization, clear and consistent infection control practices should be maintained to limit the spread of this pathogen, particularly in the setting of nosocomial outbreaks and/or high risk for healthcare transmission [22, 25, 117].

Management of Non-CR *A. baumannii*

Although discussion of *A. baumannii* treatment focuses on resistance, anticipated or confirmed, antibiotic susceptible strains are more common at some centers. Evidence is lacking to support combination therapy to prevent emergence of resistance in pan-susceptible *A. baumannii* infections. In the absence of compelling data, dose-optimized therapy to maximize antibacterial activity and use of the shortest duration possible to minimize development of resistance among other antibiotic toxicities should be considered.

For infections limited to the urinary tract, selecting a renal-specific antibiotic, like an aminoglycoside or trimethoprim/sulfamethoxazole, combines targeted exposure and efficacy. Doses of 3–5 mg/kg/day for gentamicin and tobramycin or 7–10 mg/kg/day for amikacin is a reasonable approach given high urinary concentrations [127]. Higher doses should be considered for patients who are critically ill or whose external devices cannot be removed (Table 1).

In general, for any non-urinary tract infection, including respiratory tract, skin and soft tissue, and central nervous system infections, BLs are an ideal first choice on the basis of their antimicrobial activity and their favorable toxicity profile at optimized doses (Table 1). Decisions among 3rd or 4th generation cephalosporins or BL/BLI combinations should be guided by a local antibiogram. However, patients should be monitored closely for clinical response. Cephalosporin resistance due to the chromosomally mediated cephalosporinase, ADC, may not always be identified when susceptibility testing is performed and several variants have been reported [128]. Carbapenems are a reasonable empiric therapy for critically ill patients in the absence of recent history of CRAB infection, individually or institutionally (e.g. an outbreak). Combination therapies should be considered empirically in critically ill patients, particularly in the case of local empiric susceptibilities below 90% for individual agents and infections outside the urinary tract [129].

Management of CRAB

Once susceptibilities are known and if BLs, specifically carbapenems, are rendered ineffective, the most optimal option is less clear. Table 4 details our preferred approach to therapy based on the limited clinical data available. Duration of therapy depends on clinical response and source management. A drug-resistant phenotype alone does not merit prolonged treatment; however, the factors such as an immunocompromised host or uncontrolled source of infection may necessitate durations exceeding the typical 7- to 14-day course for many infection types. Importantly, many patients are not started on initial empiric therapy covering CRAB, and accordingly the total antibiotic therapy should be counted from the start of antibiotic therapy with in vitro activity [130].

Intravenously administered colistin and polymyxin B may have a therapeutic role for CRAB infections, including pneumonia [5, 131]. Because of the challenges in dosing to achieve therapeutic concentrations without causing renal failure, especially with colistin, as well as the emergence of heteroresistance, use in combination is reasonable despite the apparent lack of clinical benefit in clinical trials. Indeed, colistin combination therapy has been evaluated in two randomized controlled trials comparing meropenem plus colistin versus colistin alone that demonstrated no statistically significant differences in rates of clinical failure among patients with CRAB infections [131, 132]. In the AIDA study, a total of 312 patients with CRAB infections were randomized, but no differences in overall mortality or clinical failure rates were identified [131]. More recently, preliminary results of the OVERCOME trial have been presented which largely corroborate the initial findings of AIDA among 283 patients with CRAB infections [132]. Interestingly, the OVERCOME study found the absolute difference in rate of clinical failure to be 5.4% lower among patients who received combination therapy (69.5% vs 64.1%; $P = 0.33$); however, the study was not powered to detect this difference statistically [131, 132]. This combination is still one to be considered as an infectious diseases equivalent of an onside kick in American football, unlikely to succeed but worth a try. Notably, there was no difference in 14 or 28-day mortality, supporting the importance of host factors in overall improvement or lack of improvement among patients with CRAB infections [131]. The trade-off with toxicity is substantial including both nephro- and neurotoxicity, manifested by myalgias and perioral paresthesias. The decision to use polymyxins should be patient-specific; for some, polymyxin-alternative regimens may be preferable (Table 4).

Among the tetracyclines, eravacycline demonstrates the greatest susceptibility in vitro against CRAB whereas tigecycline and to some extent minocycline have the most clinical data [40, 133]. Much of these data are limited; for central nervous system infections related to CRAB for example, we found no published data with either minocycline or eravacycline and a few case reports with tigecycline [134]. The 2010 FDA warning of increased risk of death with tigecycline versus comparator therapy indicates that use of an alternate therapy is prudent, if one is available, particularly for ventilator-associated pneumonia [135]. Favorable PK/PD parameters and clinical data in the intraabdominal space make this a reasonable therapeutic for IAIs [92, 136, 137]. However, given high bacterial burden and in cases of indwelling mesh or other foreign materials, it would be reasonable to use tetracyclines in combination with another agent, like a carbapenem. Clinical data are limited and in the absence of source control, success may be uncommon.

Mechanisms of antibiotic resistance in *A. baumannii* are numerous and may not be identified by traditional clinical laboratory susceptibility testing [138]. Some agents used for *A. baumannii* are not routinely tested in many clinical microbiology labs, e.g. colistin, tigecycline, eravacycline which can delay targeted treatment. Nuances around accurate testing with minocycline and polymyxins are also hurdles to targeted treatment. Future management of this organism will likely involve enhanced resistance detection measures including genotypic analysis in addition to phenotypic measurements [138]. Knowledge of harbored and/or expressed resistance will guide better therapeutic regimens. The direction of *A. baumannii* treatment will likely follow CR Enterobacterales, for which antibiotic decisions are made depending on which carbapenemase an organism harbors: KPC, VIM, etc. [130]. For now, the rationale for combination empiric therapy is to increase odds of initial active therapy, particularly in the setting of increased resistance to colistin and sulbactam in the USA [129]. Increased odds of initial active therapy are most important among critically ill or otherwise clinically unstable patients. Conversely, among patients who are hemodynamically stable, empiric monotherapy is reasonable to minimize toxicity and future antibiotic resistance [139]. In locations where *A. baumannii* carbapenem susceptibilities are particularly low (< 75%), or if patient factors limit dose optimization like with polymyxin B or colistin,

combination therapy may include three agents, a carbapenem, polymyxin, and ampicillin/sulbactam. This combination is supported by in vitro data, limited clinical data, and is generally affordable in most US hospitals [55, 62]. This would be a reasonable upfront strategy in a patient presenting with shock or otherwise clinically unstable for whom there is a high suspicion of or confirmed CRAB. At this time, agents like eravacycline and cefiderocol are less likely to be maintained in stock because of their high cost and niche use, as globally most bacterial infections remain carbapenem-susceptible. While other agents could be justified in place of polymyxin or ampicillin/sulbactam, a carbapenem backbone is supported most consistently among clinical and in vitro data. Once susceptibilities have returned and source control is achieved, it is reasonable to adjust antibiotics according to the identified susceptibility pattern. Continued combination therapy may be considered in CRAB isolates for which multiple mechanisms of resistance are suspected, and/or in patients unexpected to mount a sufficient immune response.

Cefiderocol has demonstrated activity against CRAB in both the lab and in clinical practice, and appears well tolerated [140]. However, as aforementioned, patients randomized to cefiderocol monotherapy had higher overall mortality versus best available therapy, which was primarily polymyxin-based combinations. This raises concern over cefiderocol's place in therapy and the once optimistic view that the agent could eventually replace polymyxins for treatment of CRAB infections [5]. Despite inferior performance of cefiderocol monotherapy in the CREDIBLE-CR study, this drug merits consideration if host factors limit polymyxin use: obesity, augmented renal clearance with colistin, neurotoxicity, and nephrotoxicity. Combination treatment with cefiderocol remains our preferred approach until further clinical data are available [69]. Studies of durlobactam–sulbactam coming through the pipeline may be better positioned for management of CRAB because of their combination strategy [80].

Among patients with pneumonia, inhaled antibiotics like tobramycin and colistin may bring down organism burden in the lungs, but they have not consistently demonstrated benefit with regard to clinical outcomes and mortality [141]. Their use may be appropriate in clinical scenarios for which reducing colonization reduces incidence of disease exacerbation, among patients with cystic fibrosis for example. This principle might be extended to patients with structural lung diseases, both pre and post lung transplant, but like most therapeutic recommendations for resistant *A. baumannii* infections, is not well supported by clinical data [142].

CONCLUSIONS

Acinetobacter baumannii, and in particular CRAB, remains a formidable foe given extensive drug resistance and propensity to colonize patients with high healthcare exposures. Colonization is particularly challenging in critically ill or immunocompromised patients for whom an incorrect assessment of colonization versus infection may be more impactful regarding clinical outcome. At this point, the number of clinical questions vastly outnumbers the clinical certainties when it comes to treating infections related to this pathogen. Because of its broad capacity for antibiotic resistance and its tendency to impact our most vulnerable patients, we advocate for combination therapy empirically even though this clinical decision has not been supported by well-designed clinical studies [131]. In most cases, we would combine meropenem, a polymyxin, and ampicillin/sulbactam initially. However, site of infection and severity of illness impact this decision (Table 4). There are a few important points regarding combination therapy data. First, it cannot be overemphasized that poor overall outcomes in clinical studies may mask potential benefits of combination therapy. Secondly, the variation among mechanisms of resistance may favor certain combinations over others, but so far this is a hypothesis unevaluated clinically. The tide is turning with clinical trials like CREDIBLE-CR and durlobactam–sulbactam utilizing a pathogen-focused rather than an infection-site-focused approach,

despite significantly more challenging design, costs, and execution [140]. Lastly, the decision of combination versus monotherapy is dynamic, and certainly not an all or nothing approach. Empiric combination therapy is reasonable to increase the chance of achieving initial appropriate antibiotic therapy, manage resistance that may be undetected by clinical susceptibility testing methods, and reduce bacterial burdens. Thereafter, once susceptibilities are known and depending on source control as well as the patient's immune status, one could consider a de-escalation strategy. A combination strategy is not without risk and collateral damage, including antibiotic toxicity and *Clostridioides difficile* infection. Therefore, understanding a patient's goals and underlying health conditions are key prior to exposing them to toxic therapies. Personalized therapy informed by resistance mechanisms could identify the best combination for a patient; individualized phage therapies may complement small molecular therapeutics with less collateral damage. Data forthcoming with durlobactam–sulbactam and in time with cefiderocol combination regimens will hopefully eliminate clinical need for polymyxin therapies. In the meantime, all of these agents remain part of the armamentarium, contributing to the dynamic decision-process of how to best treat this pathogen.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the study concept and design. Data collection and analysis were performed by Jacinda Abdul-Mutakabbir, Nicole Griffith, Frank Tverdek, Ryan Shields, and Zahra Kassamali Escobar. The first draft of the manuscript was written by Jacinda Abdul-Mutakabbir and all authors commented on previous versions of the manuscript. All authors read and approve the final manuscript. The SIDP Publications and Podcasts Committee developed the concept for this manuscript, identified expert authors, provided peer review throughout its composition, and approved its final form. The SIDP Board of Directors also reviewed and approved the manuscript at each stage in its development, including its final form.

Disclosures. Ryan K. Shields has served on advisory boards for Shionogi, Merck, Entasis, Utility, Venatorx, Allergan, Accelerate and Summit; and has received grants from Shionogi, Merck, Venatorx, Allergan, Melinta and Tetraphase. Jacinda C. Abdul Mutakabbir, Nicole C. Griffith, Frank Tverdek, and Zahra Kassamali Escobar declare that they have no conflict of interest.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother. 2007;10:3471–84.
2. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;3:318–27.
3. Babiker A, Clarke LG, Saul M, et al. Changing epidemiology and decreased mortality associated with Carbapenem-resistant Gram-negative bacteria from 2000–2017. Clin Infect Dis. 2020;2:2.
4. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-treat resistance in gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. Clin Infect Dis. 2018;12:1803–14.
5. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis. 2021;2:226–40.
6. Adams MD, Wright MS, Karichu JK, et al. Rapid replacement of Acinetobacter baumannii strains accompanied by changes in lipooligosaccharide loci and resistance gene repertoire. MBio. 2019;2:2.
7. Iovleva A, Mustapha MM, Cober E, et al. 636. Genome Epidemiology of Carbapenem-Resistant Acinetobacter baumannii (CRAb) in the United States. Open Forum Infect Dis. 2019;6(Suppl 2): S295. https://doi.org/10.1093/ofid/ofz360.704.
8. Adams-Haduch JM, Onuoha EO, Bogdanovich T, et al. Molecular epidemiology of carbapenem-nonsusceptible Acinetobacter baumannii in the United States. J Clin Microbiol. 2011;11:3849–54.
9. Wallace L, Daugherty SC, Nagaraj S, Johnson JK, Harris AD, Rasko DA. Use of comparative genomics to characterize the diversity of Acinetobacter baumannii surveillance isolates in a health care institution. Antimicrob Agents Chemother. 2016;10: 5933–41.
10. Queenan AM, Pillar CM, Deane J, et al. Multidrug resistance among Acinetobacter spp. in the USA and activity profile of key agents: results from CAPITAL Surveillance 2010. Diagn Microbiol Infect Dis. 2012;3:267–70.
11. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis. 2018;1:108–20.
12. Abdul-Aziz MH, Portunato F, Roberts JA. Prolonged infusion of beta-lactam antibiotics for Gram-negative infections: rationale and evidence base. Curr Opin Infect Dis. 2020;6:501–10.
13. Cao J, Song W, Gu B, et al. Correlation between carbapenem consumption and antimicrobial resistance rates of Acinetobacter baumannii in a university-affiliated hospital in China. J Clin Pharmacol. 2013;1:96–102.
14. Huang L, Chen TL, Lee YT, et al. Risk factors for imipenem-nonsusceptible Acinetobacter nosocomialis bloodstream infection. J Microbiol Immunol Infect. 2014;4:311–7.
15. Jellison TK, McKinnon PS, Rybak MJ. Epidemiology, resistance, and outcomes of Acinetobacter baumannii bacteremia treated with imipenem-cilastatin or ampicillin-sulbactam. Pharmacotherapy. 2001;2:142–8.
16. Vrancianu CO, Gheorghe I, Czobor IB, Chifiriuc MC. Antibiotic resistance profiles, molecular mechanisms and innovative treatment strategies of Acinetobacter baumannii. Microorganisms. 2020;6: 2.
17. Asif M, Alvi IA, Rehman SU. Insight into Acinetobacter baumannii: pathogenesis, global resistance, mechanisms of resistance, treatment options, and alternative modalities. Infect Drug Resist. 2018;2: 1249–60.
18. Viehman JA, Nguyen MH, Doi Y. Treatment options for carbapenem-resistant and extensively drug-resistant Acinetobacter baumannii infections. Drugs. 2014;12:1315–33.
19. Rumbo C, Gato E, Lopez M, et al. Contribution of efflux pumps, porins, and beta-lactamases to multidrug resistance in clinical isolates of Acinetobacter baumannii. Antimicrob Agents Chemother. 2013;11:5247–57.
20. Higgins PG, Wisplinghoff H, Stefanik D, Seifert H. In vitro activities of the beta-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam alone or in combination with beta-lactams against

epidemiologically characterized multidrug-resistant Acinetobacter baumannii strains. Antimicrob Agents Chemother. 2004;5:1586–92.

21. Tsakris A, Ikonomidis A, Pournaras S, et al. VIM-1 metallo-beta-lactamase in Acinetobacter baumannii. Emerg Infect Dis. 2006;6:981–3.

22. Decousser JW, Jansen C, Nordmann P, et al. Outbreak of NDM-1-producing Acinetobacter baumannii in France, January to May 2013. Euro Surveill. 2013;31:2.

23. Thomson JM, Bonomo RA. The threat of antibiotic resistance in Gram-negative pathogenic bacteria: beta-lactams in peril! Curr Opin Microbiol. 2005;5: 518–24.

24. Brown S, Young HK, Amyes SG. Characterisation of OXA-51, a novel class D carbapenemase found in genetically unrelated clinical strains of Acinetobacter baumannii from Argentina. Clin Microbiol Infect. 2005;1:15–23.

25. Mugnier PD, Poirel L, Naas T, Nordmann P. Worldwide dissemination of the blaOXA-23 carbapenemase gene of Acinetobacter baumannii. Emerg Infect Dis. 2010;1:35–40.

26. Evans BA, Amyes SG. OXA beta-lactamases. Clin Microbiol Rev. 2014;2:241–63.

27. Song X, Wu Y, Cao L, Yao D, Long M. Is meropenem as a monotherapy truly incompetent for meropenem-nonsusceptible bacterial strains? A pharmacokinetic/pharmacodynamic modeling with monte carlo simulation. Front Microbiol. 2019;2777:2.

28. Kim A, Kuti JL, Nicolau DP. Probability of pharmacodynamic target attainment with standard and prolonged-infusion antibiotic regimens for empiric therapy in adults with hospital-acquired pneumonia. Clin Ther. 2009;11:2765–78.

29. Liebchen U, Paal M, Jung J, et al. Therapeutic drug monitoring-guided high dose meropenem therapy of a multidrug resistant Acinetobacter baumannii - a case report. Respir Med Case Rep. 2020;2:100966.

30. Pasteran F, Cedano J, Baez M, et al. A new twist: the combination of sulbactam/avibactam enhances sulbactam activity against carbapenem-resistant Acinetobacter baumannii (CRAB) isolates. Antibiotics (Basel). 2021;5:2.

31. Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in Acinetobacter baumannii. Antimicrob Agents Chemother. 2015;3:1680–9.

32. Yang Y, Xu Q, Li T, et al. OXA-23 is a prevalent mechanism contributing to sulbactam resistance in diverse Acinetobacter baumannii clinical strains. Antimicrob Agents Chemother. 2019;1:2.

33. Housman ST, Hagihara M, Nicolau DP, Kuti JL. In vitro pharmacodynamics of human-simulated exposures of ampicillin/sulbactam, doripenem and tigecycline alone and in combination against multidrug-resistant Acinetobacter baumannii. J Antimicrob Chemother. 2013;10:2296–304.

34. Hiraki Y, Yoshida M, Masuda Y, et al. Successful treatment of skin and soft tissue infection due to carbapenem-resistant Acinetobacter baumannii by ampicillin-sulbactam and meropenem combination therapy. Int J Infect Dis. 2013;12:e1234–6.

35. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs colistin as monotherapy for the treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia. J Infection. 2008;2:432–6.

36. Krizova L, Poirel L, Nordmann P, Nemec A. TEM-1 β-lactamase as a source of resistance to sulbactam in clinical strains of Acinetobacter baumannii. J Antimicrob Chemother. 2013;12:2786–91.

37. Chen H, Liu Q, Chen Z, Li C. Efficacy of sulbactam for the treatment of Acinetobacter baumannii complex infection: a systematic review and meta-analysis. J Infect Chemother. 2017;5:278–85.

38. Ferencz JR, Assia EI, Diamantstein L, Rubinstein E. Vancomycin concentration in the vitreous after intravenous and intravitreal administration for postoperative endophthalmitis. Arch Opthal. 1999;2:1023–7.

39. Falagas ME, Vardakas KZ, Kapaskelis A, Triarides NA, Roussos NS. Tetracyclines for multidrug-resistant Acinetobacter baumannii infections. Int J Antimicrob Agents. 2015;5:455–60.

40. Livermore DM, Mushtaq S, Warner M, Woodford N. In vitro activity of eravacycline against carbapenem-resistant enterobacteriaceae and Acinetobacter baumannii. Antimicrob Agents Chemother. 2016;6:3840–4.

41. Connors KP, Housman ST, Pope JS, et al. Phase I, open-label, safety and pharmacokinetic study to assess bronchopulmonary disposition of intravenous eravacycline in healthy men and women. Antimicrob Agents Chemother. 2014;4:2113–8.

42. Rubino CM, Bhavnani SM, Forrest A, et al. Pharmacokinetics-pharmacodynamics of tigecycline in patients with community-acquired pneumonia. Antimicrob Agents Chemother. 2012;1:130–6.

43. Castanheira M, Mendes RE, Jones RN. Update on Acinetobacter species: mechanisms of antimicrobial resistance and contemporary in vitro activity of minocycline and other treatment options. Clin Infect Dis. 2014;2:S367–73.

44. Akers KS, Mende K, Yun HC, et al. Tetracycline susceptibility testing and resistance genes in isolates of Acinetobacter baumannii-Acinetobacter calcoaceticus complex from a US military hospital. Antimicrob Agents Chemother. 2009;6:2693–5.

45. Lodise TP, Van Wart S, Sund ZM, et al. Pharmacokinetic and pharmacodynamic profiling of minocycline for injection following a single infusion in critically ill adults in a phase IV open-label multicenter study (ACUMIN). Antimicrob Agents Chemother. 2021;3:2.

46. Akers KS, Chaney C, Barsoumian A, et al. Aminoglycoside resistance and susceptibility testing errors in Acinetobacter baumannii-calcoaceticus complex. J Clin Microbiol. 2010;4:1132–8.

47. Adams-Haduch JM, Paterson DL, Sidjabat HE, et al. Genetic basis of multidrug resistance in Acinetobacter baumannii clinical isolates at a tertiary medical center in Pennsylvania. Antimicrob Agents Chemother. 2008;11:3837–43.

48. Testa RT, Petersen PJ, Jacobus NV, Sum PE, Lee VJ, Tally FP. In vitro and in vivo antibacterial activities of the glycylcyclines, a new class of semisynthetic tetracyclines. Antimicrob Agents Chemother. 1993;11:2270–7.

49. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother. 2006;2:256–65.

50. Landman D, Kelly P, Bäcker M, et al. Antimicrobial activity of a novel aminoglycoside, ACHN-490, against Acinetobacter baumannii and Pseudomonas aeruginosa from New York City. J Antimicrob Chemother. 2010;2:332–4.

51. Yu Y-S, Zhou H, Yang Q, Chen Y-G, Li L-J. Widespread occurrence of aminoglycoside resistance due to ArmA methylase in imipenem-resistant Acinetobacter baumannii isolates in China. J Antimicrob Chemotherapy. 2007;2:454–5.

52. Smani Y, Fabrega A, Roca I, Sanchez-Encinales V, Vila J, Pachon J. Role of OmpA in the multidrug resistance phenotype of Acinetobacter baumannii. Antimicrob Agents Chemother. 2014;3:1806–8.

53. Kwon HI, Kim S, Oh MH, et al. Outer membrane protein A contributes to antimicrobial resistance of Acinetobacter baumannii through the OmpA-like domain. J Antimicrob Chemother. 2017;11:3012–5.

54. Santimaleeworagun W, Wongpoowarak P, Chayakul P, Pattharachayakul S, Tansakul P, Garey KW. In vitro activity of colistin or sulbactam in combination with fosfomycin or imipenem against clinical isolates of carbapenem-resistant Acinetobacter baumannii producing OXA-23 carbapenemases. Southeast Asian J Trop Med Public Health. 2011;4:890–900.

55. Qureshi ZA, Hittle LE, O'Hara JA, et al. Colistin-resistant Acinetobacter baumannii: beyond carbapenem resistance. Clin Infect Dis. 2015;9:1295–303.

56. Kassamali Z, Jain R, Danziger LH. An update on the arsenal for multidrug-resistant Acinetobacter infections: polymyxin antibiotics. Int J Infect Dis. 2015;2:125–32.

57. Elham B, Fawzia A. Colistin resistance in Acinetobacter baumannii isolated from critically ill patients: clinical characteristics, antimicrobial susceptibility and outcome. Afr Health Sci. 2019;3:2400–6.

58. Pelletier MR, Casella LG, Jones JW, et al. Unique structural modifications are present in the lipopolysaccharide from colistin-resistant strains of Acinetobacter baumannii. Antimicrob Agents Chemother. 2013;10:4831–40.

59. Zavascki AP, Goldani LZ, Cao G, et al. Pharmacokinetics of intravenous polymyxin B in critically ill patients. Clin Infect Dis. 2008;10:1298–304.

60. Simar S, Sibley D, Ashcraft D, Pankey G. Colistin and polymyxin B minimal inhibitory concentrations determined by etest found unreliable for gram-negative bacilli. Ochsner J. 2017;3:239–42.

61. Soudeiha MAH, Dahdouh EA, Azar E, Sarkis DK, Daoud Z. In vitro evaluation of the colistin-carbapenem combination in clinical isolates of A. baumannii using the checkerboard, etest, and time-kill curve techniques. Front Cell Infect Microbiol. 2017;2:209.

62. Oleksiuk LM, Nguyen MH, Press EG, et al. In vitro responses of Acinetobacter baumannii to two- and three-drug combinations following exposure to colistin and doripenem. Antimicrob Agents Chemother. 2014;2:1195–9.

63. Lim TP, Tan TY, Lee W, et al. In vitro activity of various combinations of antimicrobials against carbapenem-resistant Acinetobacter species in Singapore. J Antibiot (Tokyo). 2009;12:675–9.

64. Park GC, Choi JA, Jang SJ, et al. In vitro interactions of antibiotic combinations of colistin, tigecycline, and doripenem against extensively drug-resistant

and multidrug-resistant Acinetobacter baumannii. Ann Lab Med. 2016;2:124–30.

65. Armengol E, Domenech O, Fuste E, et al. Efficacy of combinations of colistin with other antimicrobials involves membrane fluidity and efflux machinery. Infect Drug Resist. 2019;2:2031–8.

66. Dickstein Y, Lellouche J, Schwartz D, et al. Colistin resistance development following colistin-meropenem combination therapy vs colistin monotherapy in patients with infections caused by carbapenem-resistant organisms. Clin Infect Dis. 2019;2:2.

67. Song JY, Kee SY, Hwang IS, et al. In vitro activities of carbapenem/sulbactam combination, colistin, colistin/rifampicin combination and tigecycline against carbapenem-resistant Acinetobacter baumannii. J Antimicrob Chemother. 2007;2:317–22.

68. Kempf M, Djouhri-Bouktab L, Brunel JM, Raoult D, Rolain JM. Synergistic activity of sulbactam combined with colistin against colistin-resistant Acinetobacter baumannii. Int J Antimicrob Agents. 2012;2:180–1.

69. Abdul-Mutakabbir JC, Nguyen L, Maassen P, et al. In-vitro antibacterial activities of cefiderocol (S-649266) alone and with the addition of beta-lactamase inhibitors against multidrug-resistant Acinetobacter baumannii (Abstract 1297). Open Forum Infect Dis. 2020;2:S663.

70. Lee HJ, Bergen PJ, Bulitta JB, et al. Synergistic activity of colistin and rifampin combination against multidrug-resistant Acinetobacter baumannii in an in vitro pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother. 2013;8:3738–45.

71. Gordon NC, Png K, Wareham DW. Potent synergy and sustained bactericidal activity of a vancomycin-colistin combination versus multidrug-resistant strains of Acinetobacter baumannii. Antimicrob Agents Chemother. 2010;12:5316–22.

72. Petrosillo N, Giannella M, Antonelli M, et al. Clinical experience of colistin-glycopeptide combination in critically ill patients infected with Gram-negative bacteria. Antimicrob Agents Chemother. 2014;2:851–8.

73. Mohammadi M, Khayat H, Sayehmiri K, et al. Synergistic effect of colistin and rifampin against multidrug resistant Acinetobacter baumannii: a systematic review and meta-analysis. Open Microbiol J. 2017;2:63–71.

74. Ramadan RA, Gebriel MG, Kadry HM, Mosallem A. Carbapenem-resistant Acinetobacter baumannii and Pseudomonas aeruginosa: characterization of carbapenemase genes and E-test evaluation of colistin-based combinations. Infect Drug Resist. 2018;2:1261–9.

75. Butler DA, Biagi M, Tan X, Qasmieh S, Bulman ZP, Wenzler E. Multidrug resistant Acinetobacter baumannii: resistance by any other name would still be hard to treat. Curr Infect Dis Rep. 2019;12:46.

76. Mohd Lim S, Sime FB, Roberts JA. Multidrug-resistant Acinetobacter baumannii infections: current evidence on treatment options and the role of pharmacokinetics/pharmacodynamics in dose optimisation. Int J Antimicrob Agents. 2019;6:726–45.

77. Isler B, Doi Y, Bonomo RA, Paterson DL. New treatment options against carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother. 2019;1:2.

78. Solomkin JS, Gardovskis J, Lawrence K, et al. IGNITE4: results of a phase 3, randomized, multicenter, prospective trial of eravacycline vs meropenem in the treatment of complicated intraabdominal infections. Clin Infect Dis. 2019;6:921–9.

79. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2021;2:213–25.

80. Entasis Therapeutics. A randomized, active-controlled study to evaluate the efficacy and safety of intravenous sulbactam-ETX2514 in the treatment of patients with infections caused by Acinetobacter baumannii-calcoaceticus compl ex. Accession no. NCT03894046. ClinicalTrials.gov, NIH. https://clinicaltrials.gov/ct2/show/NCT03894046. 2019.

81. Abdul-Mutakabbir JC, Alosaimy S, Morrisette T, Kebriaei R, Rybak MJ. Cefiderocol: a novel siderophore cephalosporin against multidrug-resistant gram-negative pathogens. Pharmacotherapy. 2020;12:1228–47.

82. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2018;12:1319–28.

83. Xerava (eravacycline) Prescribing Information. Tetraphase Pharmaceuticals, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211109lbl.pdf. 2020.

84. Xu Y, Jin L, Liu N, et al. Evaluation of the ratio of the estimated area under the concentration-time curve to minimum inhibitory concentration (estimated AUIC) as a predictor of the outcome for tigecycline treatment for pneumonia due to multidrug-resistant bacteria in an intensive care unit. Int J Infect Dis. 2019;2:79–85.

85. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible Acinetobacter baumannii. Int J Antimicrob Agents. 2018;1:62–4.

86. Seifert H, Stefanik D, Olesky M, Higgins PG. In vitro activity of the novel fluorocycline TP-6076 against carbapenem-resistant Acinetobacter baumannii. Int J Antimicrob Agents. 2020;1:105829.

87. Morrissey I, Olesky M, Hawser S, et al. In vitro activity of eravacycline against gram-negative bacilli isolated in clinical laboratories worldwide from 2013 to 2017. Antimicrob Agents Chemother. 2020;3:2.

88. Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J. Activity of eravacycline against Enterobacteriaceae and Acinetobacter baumannii, including multidrug-resistant isolates, from New York City. Antimicrob Agents Chemother. 2015;3:1802–5.

89. Bassetti M, Corey R, Doi Y, et al. In vitro global surveillance of eravacycline and comparators against Enterobacteriaceae, Acinetobacter baumannii, Stenotrophomonas maltophilia, including multidrug-resistant (MDR) isolates, over a three-year period (2013–2015). IDWeek abstract #1825. IDWeek 2016, New Orleans, LA. 2016.

90. Fyfe C, Barry R, Close B, Kerstein K, Nordmann P, Newman J. Eravacycline is active against bacterial isolates carrying emergent resistance types. ECCMID 2018 Abstract #1156. Madrid, Spain. 2018.

91. El-Bouseary MM, Tyrrell JM, Walsh TR, Olesky M. Eravacycline, a novel fluorocycline, has antibacterial activity against carbapenem-resistant Enterobacteriaceae (CRE) and Acinetobacter spp. (CRA). ECCMID 2017. Abstract #2588. Vienna, Austria. 2017.

92. Solomkin J, Evans D, Slepavicius A, et al. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the investigating gram-negative infections treated with eravacycline (IGNITE 1) trial: a randomized clinical trial. JAMA Surg. 2017;3:224–32.

93. Tetraphase Pharmaceuticals. Efficacy and safety of eravacycline compared with levofloxacin in complicated urinary tract infections. Accession No. NCT01978938. ClinicalTrials.gov, NIH. https://clinicaltrials.gov/ct2/NCT01978938. 2019.

94. Tetraphase Pharmaceuticals. Efficacy and safety of eravacycline compared with ertapenem in participants with complicated urinary tract infections (IGNITE3). Accession No. NCT03032510. ClinicalTrials.gov, NIH. https://clinicaltrials.gov/ct2/show/NCT03032510. 2019.

95. Entasis Therapeutics. Evaluation of the pharmacokinetics, safety, and tolerability of intravenous ETX2514 and sulbactam administered concurrently to subjects with various degrees of renal impairment and healthy matched control subjects. Accession No. NCT03310463. ClinicalTrials.gov, NIH. https://clinicaltrials.gov/ct2/show/NCT03310463. 2018.

96. Entasis Therapeutics. Evaluation of the safety, tolerability, and pharmacokinetics of intravenous ETX2514 adminstered to healthy subjects. Accession No. NCT02971423 ClinicalTrials.gov, NIH. https://clinicaltrials.gov/ct2/show/NCT02971423. 2017.

97. Entasis Therapeutics. Study to determine and compare plasma and intrapulmonary concentrations of ETX2514 and sulbactam in healthy subjects. Accession No. NCT03303924. ClinicalTrials.gov, NIH. https://clinicaltrials.gov/ct2/show/NCT03303924. 2017.

98. Sagan O, Yakubsevitch R, Yanev K, et al. Pharmacokinetics and tolerability of intravenous sulbactam-durlobactam with imipenem-cilastatin in hospitalized adults with complicated urinary tract infections including acute pyelonephritis. Antimicrob Agents Chemother. 2020;3:2.

99. Wittebole X, De Roock S, Opal SM. A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. Virulence. 2014;1:226–35.

100. Cisek AA, Dabrowska I, Gregorczyk KP, Wyzewski Z. Phage therapy in bacterial infections treatment: one hundred years after the discovery of bacteriophages. Curr Microbiol. 2017;2:277–83.

101. Lin NT, Chiou PY, Chang KC, Chen LK, Lai MJ. Isolation and characterization of phi AB2: a novel bacteriophage of Acinetobacter baumannii. Res Microbiol. 2010;4:308–14.

102. Schooley RT, Biswas B, Gill JJ, et al. Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant Acinetobacter baumannii infection. Antimicrob Agents Chemother. 2017;10:2.

103. Bacteriophage therapy in patients with urinary tract infections. Accession No. NCT04287478.

ClinicalTrials.gov, NIH. https://clinicaltrials.gov/ct2/show/NCT04287478. 2021.

104. Personalized phage treatment in Covid-19 patients with bacterial co-infections microbials for pneumonia or bacteremia/septicemia. Accession No. NCT04636554. ClinicalTrials.gov, NIH. https://clinicaltrials.gov/ct2/show/NCT04636554. 2021.

105. Fauconnier A. Phage therapy regulation: from night to dawn. Viruses. 2019;4:2.

106. Furfaro LL, Payne MS, Chang BJ. Bacteriophage therapy: clinical trials and regulatory hurdles. Front Cell Infect Microbiol. 2018;376:2.

107. LaVergne S, Hamilton T, Biswas B, Kumaraswamy M, Schooley RT, Wooten D. Phage therapy for a multidrug-resistant Acinetobacter baumannii craniectomy site infection. Open Forum Infect Dis. 2018;4:064.

108. Jault P, Leclerc T, Jennes S, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. Lancet Infect Dis. 2019;1:35–45.

109. Leitner L, Ujmajuridze A, Chanishvili N, et al. Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial. Lancet Infect Dis. 2021;3:427–36.

110. Ballouz T, Aridi J, Afif C, et al. Risk factors, clinical presentation, and outcome of Acinetobacter baumannii bacteremia. Front Cell Infect Microbiol. 2017;156:2.

111. Fan L, Wang Z, Wang Q, et al. Increasing rates of Acinetobacter baumannii infection and resistance in an oncology department. J Cancer Res Ther. 2018;1:68–71.

112. Serifoglu I, Er Dedekarginoglu B, Savas Bozbas S, Akcay S, Haberal M. Clinical characteristics of Acinetobacter baumannii infection in solid-organ transplant recipients. Exp Clin Transplant. 2018;1:171–5.

113. Sarshar M, Behzadi P, Scribano D, Palamara AT, Ambrosi C. Acinetobacter baumannii: an ancient commensal with weapons of a pathogen. Pathogens. 2021;4:2.

114. Furniss D, Gore S, Azadian B, Myers SR. Acinetobacter infection is associated with acquired glucose intolerance in burn patients. J Burn Care Rehabil. 2005;5:405–8.

115. Mantzarlis K, Makris D, Zakynthinos E. Risk factors for the first episode of Acinetobacter baumannii resistant to colistin infection and outcome in critically ill patients. J Med Microbiol. 2020;1:35–40.

116. Vitkauskiene A, Dambrauskiene A, Cerniauskiene K, Rimdeika R, Sakalauskas R. Risk factors and outcomes in patients with carbapenem-resistant Acinetobacter infection. Scand J Infect Dis. 2013;3:213–8.

117. Munier AL, Biard L, Legrand M, et al. Incidence, risk factors and outcome of multi-drug resistant Acinetobacter baumannii nosocomial infections during an outbreak in a burn unit. Int J Infect Dis. 2019;2:179–84.

118. Heffernan AJ, Sime FB, Lipman J, et al. Intrapulmonary pharmacokinetics of antibiotics used to treat nosocomial pneumonia caused by Gram-negative bacilli: a systematic review. Int J Antimicrob Agents. 2019;3:234–45.

119. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother. 1999;3:623–9.

120. Motos A, Kuti JL, Li Bassi G, Torres A, Nicolau DP. Is one sample enough? Beta-lactam target attainment and penetration into epithelial lining fluid based on multiple bronchoalveolar lavage sampling time points in a swine pneumonia model. Antimicrob Agents Chemother. 2019;2:2.

121. Longo F, Vuotto C, Donelli G. Biofilm formation in Acinetobacter baumannii. New Microbiol. 2014;2:119–27.

122. Pompilio A, Scribano D, Sarshar M, Di Bonaventura G, Palamara AT, Ambrosi C. Gram-negative bacteria holding together in a biofilm: the Acinetobacter baumannii way. Microorganisms. 2021;7:2.

123. Bardbari AM, Arabestani MR, Karami M, Keramat F, Alikhani MY, Bagheri KP. Correlation between ability of biofilm formation with their responsible genes and MDR patterns in clinical and environmental Acinetobacter baumannii isolates. Microb Pathog. 2017;2:122–8.

124. Burnham JP, Rojek RP, Kollef MH. Catheter removal and outcomes of multidrug-resistant central-line-associated bloodstream infection. Medicine (Baltimore). 2018;42:e12782.

125. Beganovic M, Luther MK, Daffinee KE, LaPlante KL. Biofilm prevention concentrations (BPC) of minocycline compared to polymyxin B, meropenem, and amikacin against Acinetobacter baumannii. Diagn Microbiol Infect Dis. 2019;3:223–6.

126. Martin-Aspas A, Guerrero-Sanchez FM, Garcia-Colchero F, Rodriguez-Roca S, Giron-Gonzalez JA. Differential characteristics of Acinetobacter baumannii colonization and infection: risk factors, clinical picture, and mortality. Infect Drug Resist. 2018;2:861–72.

127. Gilbert DN, Eubanks N, Jackson J. Comparison of amikacin and gentamicin in the treatment of urinary tract infections. Am J Med. 1977;6:924–9.

128. Manchanda V, Sanchaita S, Singh N. Multidrug resistant Acinetobacter. J Glob Infect Dis. 2010;3:291–304.

129. Lodise TP, Berger A, Altincatal A, et al. Antimicrobial resistance or delayed appropriate therapy-does one influence outcomes more than the other among patients with serious infections due to carbapenem-resistant versus carbapenem-susceptible Enterobacteriaceae? Open Forum Infect Dis. 2019;6:194.

130. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-P. aeruginosa). Clin Infect Dis. 2020;2:2.

131. Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018;4:391–400.

132. Kaye KS, Marchaim D, Thamlikitkul V, et al. Results from the OVERCOME trial: colistin monotherapy versus combination therapy for the treatment of pneumonoia or bloodstream infection due to extensively drug resistant Gram-negative bacilli. Abstract #04773, presented at the 31st ECCMID (virtual). 2021.

133. Alosaimy S, Molina KC, Claeys KC, et al. Early experience with eravacycline for complicated infections. Open Forum Infect Dis. 2020;5:071.

134. Kim BN, Peleg AY, Lodise TP, et al. Management of meningitis due to antibiotic-resistant Acinetobacter species. Lancet Infect Dis. 2009;4:245–55.

135. FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections. U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-increased-risk-death-tygacil-tigecycline-compared-other-antibiotics#sa. 2017.

136. Eckmann C, Montravers P, Bassetti M, et al. Efficacy of tigecycline for the treatment of complicated intra-abdominal infections in real-life clinical practice from five European observational studies. J Antimicrob Chemother. 2013;2:25–35.

137. Alosaimy S, Abdul-Mutakabbir JC, Kebriaei R, Jorgensen SCJ, Rybak MJ. Evaluation of eravacycline: a novel fluorocycline. Pharmacotherapy. 2020;3:221–38.

138. Esterly JS, Richardson CL, Eltoukhy NS, Qi C, Scheetz MH. Genetic mechanisms of antimicrobial resistance of Acinetobacter baumannii. Ann Pharmacother. 2011;2:218–28.

139. Cain SE, Kohn J, Bookstaver PB, Albrecht H, Al-Hasan MN. Stratification of the impact of inappropriate empirical antimicrobial therapy for Gram-negative bloodstream infections by predicted prognosis. Antimicrob Agents Chemother. 2015;1:245–50.

140. Bassetti M, Ariyasu M, Binkowitz B, et al. Designing a pathogen-focused study to address the high unmet medical need represented by carbapenem-resistant gram-negative pathogens - the international, multicenter, randomized, open-label, phase 3 CREDIBLE-CR study. Infect Drug Resist. 2019;2:3607–23.

141. Vardakas KZ, Voulgaris GL, Samonis G, Falagas ME. Inhaled colistin monotherapy for respiratory tract infections in adults without cystic fibrosis: a systematic review and meta-analysis. Int J Antimicrob Agents. 2018;1:1–9.

142. Kalil AC, Metersky ML, Klompas M, et al. Executive summary: management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;5:575–82.

143. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant Acinetobacter baumannii. Scand J Infect Dis. 2007;1:38–43.

144. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Infect. 2008;6:432–6.

145. Lashinsky JN, Henig O, Pogue JM, Kaye KS. Minocycline for the treatment of multidrug and extensively drug-resistant A. baumannii: a review. Infect Dis Ther. 2017;2:199–211.

146. Gong J, Su D, Shang J, et al. Efficacy and safety of high-dose tigecycline for the treatment of infectious diseases: a meta-analysis. Medicine (Baltimore). 2019;38:e17091.

147. Pai MP, Rodvold KA. Aminoglycoside dosing in patients by kidney function and area under the curve: the Sawchuk-Zaske dosing method revisited in the era of obesity. Diagn Microbiol Infect Dis. 2014;2:178–87.

148. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy. 2019;1: 10–39.

149. MacVane SH, Kuti JL, Nicolau DP. Prolonging beta-lactam infusion: a review of the rationale and evidence, and guidance for implementation. Int J Antimicrob Agents. 2014;2:105–13.

150. Fetroja (cefiderocol) Prescribing Information. Shionogi & Co., Ltd. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209445s002lbl.pdf. 2020.

151. Falagas ME, Vardakas KZ, Roussos NS. Trimethoprim/sulfamethoxazole for *Acinetobacter* spp.: a review of current microbiological and clinical evidence. Int J Antimicrob Agents. 2015;3:231–41.

Publisher's Note