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

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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...
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.

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**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*<sub>OXA-23</sub>, which is present in more than 60% of all CRAB isolates in the USA. On balance, *bla*<sub>OXA-24</sub> 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*<sub>OXA-51</sub> that carries a strong outward facing gene promoter that enhances expression [1]. The resulting IS*Aba1-bla*<sub>OXA-51</sub> 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.

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

| Drug Class     | Drug(s)                                                                 | Description                                                                 | Reference(s) |
|----------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------|
| **Carbapenem** | Imipenem/cilastin 1g IV q6h*                                            | For isolates with intermediate susceptibility                               | [15]         |
|                | Meropenem 2 g IV q8h*                                                   | Consider prolonging infusion for increased \(fT/MIC\)                        | [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                                            |                                                                             |              |
| **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**   | 300 mg IV load; 360 mg divided q12h thereafter*                          | For colistin MIC ≤ 2                                                        | [148]        |
|                |                                                                          | Dosed in colistin base activity (CBA)                                       |              |
| **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 \(fT/MIC\)                        | [149]        |
|                | Ceftazidime 2 g IV q8h*                                                 | Consider prolonging infusion for increased \(fT/MIC\)                        | [12]         |
|                | Cefiderocol 2 g IV q8h over 3 h*                                        |                                                                             | [150]        |
| **Penicillins** | Piperacillin/tazobactam 4.5 g IV q6h*                                   | Consider prolonging infusion for increased \(fT/MIC\)                        | [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].
| Mechanism of resistance | Antibiotics conferred resistant | Microbiological factors | Clinical indicators and implications |
|-------------------------|--------------------------------|-------------------------|-------------------------------------|
| Amber class A β-lactamases | Penicillins | Acquired resistance: TEM, SHV, CTX-M, KPC* | Penicillin-resistant phenotype |
|                         | Cephalosporins | | Cephalosporin-resistant phenotype |
|                         | Carbapenems | | Carbapenem-resistant phenotype |
| Amber class B β-lactamases | Penicillins | Acquired resistance: NDM, IMP*, VIM* | Carbapenem-resistant phenotype |
|                         | Cephalosporins | | Ampicillin/sulbactam-resistant phenotype |
|                         | Carbapenems | | BL/BLI-resistant phenotype |
|                         | BL/BLI combinations | | |
| Amber 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) |
| Amber class D β-lactamases | Penicillins | Acquired resistance: OXA-23*, OXA-24*, OXA-40*, OXA-58*, OXA-50* groups | Carbenamem-resistant phenotype |
|                         | Carbapenems | | Ampicillin/sulbactam-resistant phenotype |
| Efflux pumps (Ade-type, TetA, TetB) | Tetracyclines | Acquired resistance: TetA and Tetb efflux pumps | Tetracycline-resistant phenotype |
| Amino acid substitution to the DNA gyrase of topoisomerase IV | Fluoroquinolones | Acquired resistance: gyrA gene, parC gene | Ciprofloxacin-resistant phenotype |
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

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**Table 2 continued**

| Mechanism of resistance | Antibiotics conferred resistant | Microbiological factors | Clinical indicators and implications |
|-------------------------|--------------------------------|------------------------|-------------------------------------|
| Aminoglycoside-modifying enzymes | Aminoglycosides | Acquired resistance, amikacin and tobramycin: AAC(6')-Ib, AAC(6')-Ih | Amikacin-resistant phenotype |
|                         |                                | Acquired resistance, gentamicin: AAC(3)-Ia, ANT(2')-Ia | Gentamicin-resistant phenotype |
|                         |                                | APH(3')-Ia, ArmA | Tobramycin-resistant phenotype |
| Porin channel mutations (OmpA) | Carbapenems Cephalosporins | Acquired resistance: OmpAβ | |
| PBP reduced expression | Sulbactam | Acquired resistance: PBP2 | Ampicillin/sulbactam-resistant phenotype |
|                         | Cefiderocol | Acquired resistance: PBP3 | 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
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. 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 \(\beta\)-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 \(\beta\)-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, eravacycline, 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 OmpAAb, 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 ≤ 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 ceferodrol and meropenem [69]. Synergy can be attributed to the binding of ceferodrol 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 blaOXA-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: ceferodocol, 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                     | Phase 1                |
| 5153 + zidebactam (WCK 5107) | Phase 1                |
| β-Lactam                |                        |
| AIC499                  | Phase 1                |
| Polymyxin B derivative (enhancer agent) | Phase 1                |
| SPR741                  | Phase 1                |
| Aminoglycoside          |                        |
| Apramycin               | In vitro studies       |
| Tetracycline            |                        |
| TP-6076                 | Development stopped to focus on eravacycline |

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Eravacycline

Eravacycline is a tetracycline analogue and a novel fluoroacycline 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 eravacycline 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 durmlobactam–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 durmlobactam–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 durblobactam–sulbactam and in time with cefideroxicol 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.

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**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.

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