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THERAPY IN PRACTICE

Treatment Options for Carbapenem-Resistant and Extensively Drug-Resistant *Acinetobacter baumannii* Infections

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Abstract *Acinetobacter baumannii* is a leading cause of healthcare-associated infections worldwide. Because of various intrinsic and acquired mechanisms of resistance, most β-lactam agents are not effective against many strains, and carbapenems have played an important role in therapy. Recent trends show many infections are caused by carbapenem-resistant or even extensively drug-resistant (XDR) strains, for which effective therapy is not well established. Evidence to date suggests that colistin constitutes the backbone of therapy, but the unique pharmacokinetic properties of colistin have led many to suggest the use of combination antimicrobial therapy. However, the combination of agents and dosing regimens that delivers the best clinical efficacy while minimizing toxicity is yet to be defined. Carbapenems, sulbactam, rifampin and tigecycline have been the most studied in the context of combination therapy. Most data regarding therapy for invasive, resistant *A. baumannii* infections come from uncontrolled case series and retrospective analyses, though some clinical trials have been completed and others are underway. Early institution of appropriate antimicrobial therapy is shown to consistently improve survival of patients with carbapenem-resistant and XDR *A. baumannii* infection, but the choice of empiric therapy in these infections remains an open question. This review summarizes the most current knowledge regarding the epidemiology, mechanisms of resistance, and treatment considerations of carbapenem-resistant and XDR *A. baumannii*.

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Key Points

Acinetobacter baumannii exhibits multiple mechanisms of multi-class resistance and represents a clinical challenge due to extensively-resistant nosocomial infections occurring worldwide.

Polymyxins, tigecycline and sulbactam are the most commonly used therapies in carbapenem-resistant and extensively drug-resistant *A. baumannii* infections, with published results varying on efficacy of each.

Combination therapy for *A. baumannii* infections with first-line agents and also glycopeptides, rifamycins and fosfomycin has been studied and may be of benefit.

1 Introduction

Acinetobacter species have been increasingly recognized as major pathogens implicated in hospital-acquired and healthcare-associated infections worldwide. The common presentations of infections include ventilator-associated pneumonia, bloodstream infection, wound infection and urinary tract infection [1]. It is one of the most common etiologic pathogens causing ventilator-associated pneumonia in the USA [2]. The genus *Acinetobacter* comprises more than 30 genomic species which are aerobic, non-motile, catalase-positive and oxidase-negative coccobacilli. Among these genomic species, the most clinically relevant species is *Acinetobacter baumannii*, both in terms of relative virulence and the degree of multidrug resistance. In addition, *Acinetobacter nosocomialis* (genomospecies 13TU) and *Acinetobacter pittii* (genomospecies 3) are increasingly implicated in hospital-acquired and healthcare-associated infections [3]. However, the standard biochemical identification methods employed in clinical microbiology laboratories do not differentiate *A. baumannii* from *A. nosocomialis*, *A. pittii* or *Acinetobacter calcoaceticus*, the last of which is considered to be an environmental pathogen of little clinical significance. Identification of *A. baumannii* requires the use of at least one genetic method, which is usually not available in clinical laboratories. It therefore should be kept in mind when reviewing the literature that *A. baumannii*, especially in clinical studies, may refer to the actual *A. baumannii* as the genomic species or, more frequently, *A. baumannii* complex, which includes all of the four genomic species above.

The most prominent feature of *A. baumannii* is its ability to develop resistance to multiple classes of antimicrobial agents. While the term multidrug resistance (MDR) is often used to describe this phenomenon, MDR technically refers to non-susceptibility to one or more agents in three or more antimicrobial categories [4], which may apply to even relatively antimicrobial-susceptible isolates in *A. baumannii*. For example, resistance to ceftriaxone, ciprofloxacin and trimethoprim–sulfamethoxazole is sufficient to define an isolate as MDR, in which case, many treatment options are still available. In contrast, extensive drug resistance refers to non-susceptibility to one or more agents in all but two or fewer antimicrobial categories [4] and is more clinically relevant. For instance, an isolate which is susceptible to colistin and tigecycline but resistant to all other categories tested would be defined as extensively drug resistant (XDR). These XDR isolates are increasingly encountered in clinical practice [5]. Non-susceptibility to all antimicrobial agents tested defines pan-drug resistance. In addition, carbapenem resistance merits special consideration given its otherwise reliable activity against *A. baumannii*. Resistance to carbapenems poses a major challenge as the second-line treatment options are much less defined in their efficacy and often accompany toxicity. Carbapenem-resistant isolates are often but not always XDR, and vice versa. Therefore, attention should also be paid to the definitions of resistance used when surveying clinical studies addressing treatment of *A. baumannii* infections. Another key feature of *A. baumannii* is its ability to survive on dry surfaces for prolonged periods. This unique trait further facilitates its dissemination in the healthcare environment, often leading to outbreaks [6].

This review will describe the current epidemiology of antimicrobial resistance in *A. baumannii*, mechanisms underlying resistance, and treatment considerations for *A. baumannii* infections.

2 Epidemiology

Acinetobacter spp. may cause a spectrum of infections, but most commonly affects the lower respiratory tract, followed by blood and wound [1]. *Acinetobacter* isolates collected randomly from hospitals across the USA in 2010 showed that the majority of the isolates (57.6 %) were from the respiratory tract, followed by bloodstream (23.9 %) and skin or wound (9.1 %) [5]. It was the third most common pathogen causing ventilator-associated pneumonia (8.4 % of cases) and the ninth most common cause of central line-associated bloodstream infection (2.2 %) in US hospitals between 2006 and 2007 [7]. Between 2009 and 2010, it caused 6.6 % of ventilator-associated pneumonia (ranking fifth) and 2.1 % of central line-associated bloodstream infection (ranking thirteenth) [2]. Therefore, most clinical data regarding therapy of *Acinetobacter* infection have been generated from cases of pneumonia and bloodstream infections. It should be noted, however, that for pneumonia and infections of other non-sterile sites, it is often difficult to distinguish colonization from true *Acinetobacter* infection and determine whether the affected patients require therapy directed towards this pathogen. Thus, some of the epidemiologic source data may include isolates that were not responsible for infections, but were simply colonizing ill patients, and the estimates of resistance may be biased as a result. In terms of resistance, 34 % of *Acinetobacter* isolates in the National Healthcare Safety Network were resistant to penicillins, cephalosporins, carbapenems, fluoroquinolones and aminoglycosides [8]. In another nationwide surveillance study conducted in the USA in 2010, 44.7 and 49.0 % were resistant to imipenem and meropenem, respectively [5]. Carbapenem resistance increased with age; it was present in 60–64 % of all isolates in the elderly (age >65 years) and 46–51 % of those in younger adults, while it was only present in 13–17 % of

pediatric isolates. Resistance rates to ceftazidime, levofloxacin and tobramycin were at 52.1, 52.3, and 38.9 %, respectively; 53.9 % were MDR. Notably, 5.3 % were also resistant to colistin in vitro in this study. It is clear that over the last decade, *Acinetobacter* species, in particular *A. baumannii*, have become increasingly resistant to currently available antimicrobial agents, especially carbapenems [9].

There appears to be a wide geographic and temporal variation in the distribution of genomospecies among clinical isolates of *A. baumannii* complex. In a study investigating clinical isolates from any site collected from hospitals in Germany between 2005 and 2009, 51 % of *A. baumannii* complex isolates were identified as *A. pittii*, followed by *A. baumannii* (37 %), *A. calcoaceticus* (3 %) and *A. nosocomialis* (2 %). Of note, all imipenem-non-susceptible isolates were *A. baumannii* [10]. On the other hand, in a similarly designed study conducted in Taiwan in 2006, 89 % were *A. baumannii*, 8 % *A. pittii* and 3 % *A. nosocomialis* [11]. In the USA, *A. baumannii* was the most prevalent species (63 %), followed by *A. nosocomialis* (21 %) and *A. pittii* (8 %) among blood isolates collected between 1995 and 2003 [12]. However, when carbapenem-non-susceptible isolates collected more recently (2008–2009) were studied, all were *A. baumannii* [13]. Furthermore, in a series of *A. baumannii* complex bloodstream infections, *A. baumannii* as the genomospecies has been singled out as an independent risk factor for mortality, with attributable mortality of 59, 17, and 33 % for *A. baumannii*, *A. nosocomialis* and *A. pittii*, respectively [3]. Therefore, *A. baumannii* is the most problematic genomospecies in the *A. baumannii* complex both in terms of antimicrobial resistance and unfavorable clinical outcome.

3 Clinical Relevance

A. baumannii is primarily a healthcare-associated pathogen, thus the risk factors for colonization and infection by *A. baumannii* are also healthcare associated. The risk factors for acquisition are best studied for XDR and carbapenem-resistant isolates, and include recent exposure to antimicrobial agents (in particular carbapenems), presence of central venous catheters or urinary catheters, severity of illness, duration of hospital stay, location in an intensive care unit (ICU), larger hospital size, and recent surgery [14–17].

Mortality associated with invasive *A. baumannii* infection is high, especially for carbapenem-resistant cases. Crude mortality for carbapenem-resistant *A. baumannii* infections ranges from 16 to 76 %, as opposed to 5 to 53 % for carbapenem-susceptible infections [18]. More recently, attributable mortality of 70 % has been reported for bloodstream infections due to imipenem-resistant *A. baumannii*, compared with 24.5 % for imipenem-susceptible *A. baumannii* in Taiwan [19], and 30-day mortality of 79.8 % has been reported for carbapenem-resistant *A. baumannii* bloodstream infections in Korea [20]. These studies, however, did not report specific causes of death, so determination of the contribution of *A. baumannii* to the mortality may not be accounted for in these estimates. On the other hand, mortality as low as 2 % has been reported for *A. baumannii* bloodstream infections among young, previously healthy war-related trauma patients, underscoring the significant contribution of host factors to the clinical outcome of invasive *A. baumannii* infection [21].

Independent risk factors for mortality among patients with carbapenem-resistant *A. baumannii* bloodstream infections include the severity of illness, underlying malignancy, history of transplant, higher age, septic shock, concurrent pneumonia, inappropriate antimicrobial therapy, prolonged ICU stay, and renal failure, among others [19, 20, 22–25]. High mortality rates observed in patients with carbapenem-resistant *A. baumannii* infection are believed to be mostly due to the greater severity of illness and higher risk of receiving early inappropriate antimicrobial therapy (see Sect. 5.9) [18]. For instance, an analysis of 274 patients with *A. baumannii* bloodstream infection in a US health system revealed significantly higher in-hospital mortality for carbapenem- and ampicillin–sulbactam-resistant infections compared with more susceptible ones (42 vs. 29 %; $p < 0.001$), but after adjusting for the severity of illness, the odds of dying in the hospital were similar between the two groups. The authors postulated this may be due to the fact that risk factors for carbapenem resistance were similar to risk factors for hospital mortality [26].

4 Mechanisms of Antimicrobial Resistance

A. baumannii has an armamentarium of antimicrobial drug-resistance mechanisms it can utilize or acquire to become XDR. Certain XDR strains are epidemic in hospitals worldwide, likely because of the degree of antimicrobial resistance as well as their ability to survive environmental desiccation for many weeks [27]. Here, we will briefly review the key mechanisms underlying resistance of *A. baumannii* to relevant classes of antimicrobial drugs.

4.1 Cephalosporins

Most clinical isolates of *A. baumannii* are resistant to cephalosporins. *Acinetobacter* spp. intrinsically produces AmpC β-lactamase, called *Acinetobacter*-derived cephalosporinase (ADC) [28, 29]. Unlike most chromosomally produced AmpC β-lactamases in Gram-negative

pathogens, ADC is not believed to be inducible [29]. However, expression of ADC is elevated when insertion sequence IS*Aba1* or IS*Aba125* is acquired upstream of the bla_{ADC} gene and provides a stronger promoter activity compared with the native promoter sequence of the bla_{ADC} gene [30, 31]. This results in elevation of cephalosporin minimum inhibitory concentrations (MICs) except cefepime, which is not a substrate of AmpC β-lactamases including ADC. Some *A. baumannii* isolates have been observed to produce extended-spectrum AmpC β-lactamases which can confer resistance to cefepime along with other cephalosporins [32].

A. baumannii may also become resistant to cephalosporins by producing extended-spectrum β-lactamase (ESBL). PER-type ESBL is the most commonly found ESBL in *A. baumannii* [33, 34], but production of VEB-type ESBL and CTX-M-type ESBL, which is the most common ESBL in *Escherichia coli*, has also been reported [35, 36].

4.2 Carbapenems

Several mechanisms are involved in carbapenem resistance. They include production of carbapenem-hydrolyzing β-lactamase ("carbapenemase"), reduced permeability of the outer membrane, and active efflux [37, 38]. Of these, the most significant mechanism is the production of carbapenemases, which can be either intrinsic or acquired.

A. baumannii naturally produces chromosomally encoded OXA-51-group carbapenemase at a low level. While this basal production of the OXA-51 group does not lead to clinically relevant carbapenem resistance, acquisition of a stronger promoter by transposition of IS*Aba1* or IS*Aba9* upstream of the OXA-51-group gene may lead to a moderate, clinically significant degree of carbapenem resistance [39, 40].

Among acquired carbapenemases, OXA-group enzymes are the most commonly encountered worldwide. There are five groups of acquired OXA-group carbapenemases in *A. baumannii*, including OXA-23, -40, -58, -143 and -235 groups [41]. Of these, the OXA-23 group is especially widely disseminated and is the most frequent cause of clinically relevant carbapenem resistance in *A. baumannii* [42]. Of note, OXA-group carbapenemases confer resistance to oxacillins and carbapenems, but not cephalosporins. However, isolates that acquire OXA-group carbapenemase are usually already resistant to cephalosporins because of the aforementioned mechanisms.

Non-OXA carbapenemases that have spread in *Enterobacteriaceae* are also being acquired by *A. baumannii*. The most significant metallo-β-lactamase found in this species is NDM group. Carbapenem-resistant *A. baumannii* producing NDM-1 has been identified worldwide since 2011 [43, 44]. Production of IMP-, VIM- and SIM-group metallo-β-lactamases has also been reported on rare occasions in this species [45–47]. Finally, *A. baumannii* producing KPC- and GES-group carbapenemases have been reported, but they appear to remain sporadic events at this point [48, 49].

4.3 Sulbactam

Sulbactam exerts its anti-*Acinetobacter* activity by binding to the penicillin-binding protein PBP2 of *A. baumannii* [50]. Reduced expression of PBP2 has been associated with resistance to sulbactam [51]. In addition, the role of production of non-ESBL β-lactamase TEM-1 has been suggested to contribute to sulbactam resistance of *A. baumannii* [52].

4.4 Rifampin

Rifampin binds to the active center of bacterial ribonucleic acid (RNA) polymerase and inhibits transcription initiation. The major mechanism underlying rifampin resistance is amino acid substitutions in the β-subunit of this target protein [53]. In addition, enzymatic modification by rifampin adenosine diphosphate (ADP) ribosyltransferase (e.g., Arr-2) and active efflux have been implicated in rifampin resistance of *A. baumannii* clinical isolates [53, 54].

4.5 Aminoglycosides

Aminoglycosides bind to the 16S ribosomal RNA of the 30S ribosomal subunit and inhibit protein synthesis. The most ubiquitous mechanism underlying aminoglycoside resistance in *A. baumannii* is production of various aminoglycoside-modifying enzymes. There are three functional groups of modifying enzymes, which include aminoglycoside acetyltransferases [e.g., AAC(6′)-Ib], aminoglycoside phosphotransferases [e.g., APH(3′)-Ia] and aminoglycoside adenylyltransferases [e.g., ANT(2″)-Ia] [55]. Commonly found aminoglycoside-modifying enzymes in *A. baumannii* are AAC(6′)-Ib, AAC(6′)-Ih (conferring tobramycin and amikacin resistance), AAC(3)-Ia, ANT(2″)-Ia and APH(3′)-Ia (conferring gentamicin resistance) [56, 57]. Another aminoglycoside resistance mechanism that appears to be emerging is production of 16S ribosomal RNA methyltransferase, especially ArmA. ArmA methylates a guanine residue in the aminoglycoside-binding site (A-site) of 16S ribosomal RNA (rRNA) [58]. ArmA-producing *A. baumannii* are highly and uniformly resistant to the aminoglycosides that are commonly used systemically (e.g., gentamicin, tobramycin and amikacin) [59, 60].

4.6 Fluoroquinolones

The primary mechanism of resistance to fluoroquinolones in *A. baumannii* is, as with any bacteria, amino acid substitutions in the quinolone resistance determining region (QRDR) of the DNA gyrase and topoisomerase IV, which interfere with binding of fluoroquinolones to these target proteins [36]. Overexpression of active efflux pumps may also cause moderate fluoroquinolone resistance and augment the level of resistance in strains with QRDR substitutions [61].

4.7 Colistin

Colistin targets lipid A of lipopolysaccharide for its activity, and resistance to colistin arises because of modifications of this target. The most commonly reported pathway in *A. baumannii* is the addition of a phosphoethanolamine moiety to the hepta-acylated lipid A, which reduces the negative charge of lipid A and lowers the affinity of colistin [62–64]. Another proposed mechanism is the loss of lipopolysaccharide, which deprives *A. baumannii* of the target [65].

4.8 Tetracyclines

Resistance to the tetracycline group of agents is mediated primarily by active efflux or target protection by production of Tet proteins that bind to the 70S ribosome [66]. Tigecycline, which was designed to resist the majority of these mechanisms, is still prone to efflux by Ade-type efflux pumps, which are produced by the majority of *A. baumannii* clinical isolates. Their overexpression therefore leads to resistance to tigecycline [67].

5 Treatment of *Acinetobacter baumannii* Infections

For infections caused by relatively antimicrobial-susceptible *A. baumannii* strains, there usually remain a sufficient number of safe and effective antimicrobial agents that can be used for treatment. Research has thus primarily focused on how to effectively treat XDR and carbapenem-resistant *A. baumannii* infections (Tables 1, 2). While various treatment approaches have been proposed through in vitro, in vivo and clinical studies, there is a hesitant consensus that a polymyxin (colistin [polymyxin E] or polymyxin B) should be included in any regimen as the backbone for

Table 1 Agents used in the treatment of carbapenem-resistant and XDR *Acinetobacter baumannii* infections

Drug	Dosing for *A. baumannii* infections (normal renal function)	Advantages	Drawbacks	Ongoing questions
Colistin (as colistimethate) [62–64, 75, 76]	5-mg CBA/kg/day loading dose followed by 5 mg CBA/kg/day divided in 2 or 3 doses	Mainstay of therapy; used in combination with other agents	Nephrotoxicity; low serum concentrations especially early in therapy; resistance via lipid A modification	Efficacy when optimally dosed; optimal companion agent for combination therapy
Fosfomycin[a] [127, 128]	4 g every 12 h used in a randomized trial; potential for higher doses; used in combination	Bactericidal; relatively well tolerated	No approved intravenous formulation in the USA; minimal activity alone; difficulties with MIC determinations	Larger trials to prove added benefit in the context of combination therapy
Rifampin[a] [124, 125]	600 mg every 12 or 24 h; used in combination	Widely available; no renal toxicity	Monotherapy can quickly lead to resistance; liver toxicity and drug–drug interaction	Randomized trial data conflicting regarding overall benefit of adding rifampin
Sulbactam (ampicillin–sulbactam) [79, 80, 96]	3–9 g/day (9–27 g/day of ampicillin–sulbactam); alone or in combination	Widely available in combination with ampicillin; relatively inexpensive	Increasing resistance; not available alone in many countries, including the USA	Clinical correlation between MIC and outcome; optimal dosing regimen
Tigecycline [102–106]	100-mg loading dose followed by 50 mg every 12 h; alone or in combination	Widely available; active against most strains in vitro	Low serum concentrations; bacteriostatic activity; may be inferior to comparators in critically ill patients	Clinical correlation between MIC and outcome; optimal dosing regimen; benefit of combination regimens
Vancomycin[a] [134, 135]	10–15 mg/kg every 12 h; in combination with colistin	Widely available; strong in vitro synergy with colistin; often included in empiric sepsis therapy	Potential for increased nephrotoxicity; no prospective validation of clinical efficacy	Optimal dosing regimen and duration; efficacy in colistin-resistant cases

CBA colistin base activity, *MIC* minimum inhibitory concentration, *XDR* extensively drug-resistant

[a] These agents are always considered as part of combinations and are not to be used alone

Table 2 Studies comparing combination to monotherapy for carbapenem-resistant and XDR *Acinetobacter baumannii* infections

Year	Country	Design	Infection type	Combination regimen	Monotherapy regimen	Microbiology	*n*	Endpoint	Combination vs. monotherapy, %	Reference
2010	Greece	Retrospective	PNA, BSI, UTI, IAI, SSI, SSTI, CNS	Colistin + carbapenem, piperacillin–tazobactam, sulbactam or other	Colistin	Ab (some XDR)	170	Clinical cure	80.3 vs. 87	[139]
2013	Turkey	Open label RCT	VAP	Colistin + rifampin	Colistin	CR-Ab	43	Mortality	61.9 vs. 72.7	[124]
2013	Italy	Open label RCT	PNA, BSI, IAI	Colistin + rifampin	Colistin	XDR-Ab	209	Mortality	43.4 vs. 42.9	[125]
2013	Spain	Retrospective	BSI, PNA	Colistin + vancomycin	Colistin	CR-Ab	57	Clinical cure	55.2 vs. 67.9	[134]
2014	Thailand	Open label RCT	PNA, BSI, UTI, SSTI, IAI	Colistin + fosfomycin	Colistin	CR-Ab	94	Mortality	46.8 vs. 57.4	[128]
2014	Italy	Retrospective	PNA, BSI, UTI, IAI, SSI	Colistin + vancomycin	Colistin	CR-Ab	166	Mortality	41.7 vs. 35.3	[135]
2014	Turkey	Retrospective	BSI	Colistin + carbapenem, sulbactam, tigecycline or other	Colistin	XDR-Ab	240	Mortality	52.3 vs. 72.2	[23]
2014	USA	Retrospective	PNA, BSI	Colistin + carbapenem, sulbactam, tigecycline or other	Tigecycline, carbapenem, cefepime	XDR-Ab	36	Mortality	47 vs. 100	[138]

Ab Acinetobacter baumannii, *BSI* bloodstream infection, *CNS* central nervous system infection, *CR* carbapenem-resistant, *IAI* intra-abdominal infection, *PNA* pneumonia, *RCT* randomized controlled trial, *SSI* surgical site infection, *SSTI* skin/soft tissue infection, *UTI* urinary tract infection, *VAP* ventilator-associated pneumonia, *XDR* extensively drug-resistant

treatment of infections caused by colistin-susceptible isolates and likely colistin-resistant isolates as well [68, 69]. Despite the recent trend toward polymyxins, there is some hesitancy to their use. For most other infections, polymyxins were abandoned because of their toxicity profile in the 1980s. Thus many centers and clinicians favor therapy based on other agents, including sulbactam and tigecycline, both as monotherapy and in combination, for carbapenem-resistant isolates. The variation in practice has driven some of the heterogeneous studies included here.

Of note, colistin is given as its less active prodrug colistimethate (colistin methanesulfonate) intravenously, which is then converted over time to the active drug colistin in the blood. However, most scientific papers refer to colistimethate as colistin. In this review, colistin, when appearing as part of treatment regimens, refers to colistimethate. On the other hand, the active drug colistin is used for in vitro testing of susceptibility and synergy.

5.1 Colistin

Colistin (polymyxin E) is one of the two polymyxin class agents that are approved for clinical use, the other one being polymyxin B. Polymyxins are cationic polypeptides which exert their bactericidal activity through interactions with the lipid A component of lipopolysaccharide constituting the bacterial outer membrane. For intravenous use, colistin is administered as its inactive prodrug colistin methanesulfonate, or colistimethate. Colistin is much more widely available than polymyxin B worldwide, and as a result most data in the literature regarding treatment of *A. baumannii* are provided for colistin rather than polymyxin B. It is worth noting that a recent retrospective study from a single center showed higher risk of nephrotoxicity with colistin compared with polymyxin B (60.4 vs. 41.8 %), though more patients in the colistin arm were on vasopressors [70]. Also worth mentioning is the confusing terminology used to describe the amount of colistimethate, with international units (IUs) used in Europe and elsewhere and milligrams of colistin base activity (CBA) used in the Americas and elsewhere. One million IU is equivalent to approximately 30 mg of CBA, which in turn corresponds to approximately 80 mg of chemical colistimethate [71]. We will use CBA throughout this review unless otherwise specified.

Colistin is active against Gram-negative bacteria, and most *A. baumannii* isolates remain susceptible to this agent. Among *Acinetobacter* clinical isolates collected from US hospitals in 2010, 94.7 % were susceptible to colistin when using the susceptibility breakpoint of $\leq$2 μg/mL currently endorsed by both the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [5]. The antibacterial activity of colistin is best predicted by free area under the curve (AUC)/MIC (fAUC/MIC) [72]. In time-kill studies, colistin exerts a rapid bactericidal effect, but regrowth is commonly observed even at colistin concentrations exceeding the MICs [73]. In addition, subpopulations with increased tolerance to colistin concentrations higher than the MICs can be observed when high inoculums are used for testing [74]. This hetero-resistance phenomenon raises concerns about subpopulations not adequately targeted by colistin in an apparently colistin-susceptible isolate. Emergence of resistance on therapy with colistin may be related to selection for these hetero-resistant subpopulations.

Colistin and its prodrug colistimethate have unique pharmacokinetic properties [72]. Colistimethate has a relatively short terminal half-life under normal physiology because of high renal clearance, and slowly converts to colistin in the blood. Some references estimated the colistimethate half-life at 2.2 h, whereas others give a higher estimate, closer to 4.9 h. Colistin, on the other hand, undergoes tubular reabsorption and has a longer terminal half-life (14.4–18.5 h) [75]. Of note, in patients with decreased clearance, the half-life of colistimethate was prolonged proportionally more than the colistin half-life [76]. As a result, the predicted maximum plasma concentration of colistin after a 90-mg CBA-equivalent dose is only 0.6 mg/L, and only reaches 2.3 mg/L after repeated administration every 8 h in critically ill patients [77]. The colistin MICs for the majority of *A. baumannii* clinical isolates cluster between 0.25 and 2 μg/mL (http://mic.eucast.org), implying that patients may be exposed to subtherapeutic concentrations of colistin for a prolonged period. These data suggest that a loading dose may provide clinical benefit to patients receiving colistin. When a loading dose of 180 mg (CBA equivalent) was administered, colistin concentrations averaged 1.34 mg/L, with a wide range [75]. In another study, which included 105 critically ill patients with variable renal function, the average steady-state plasma concentration of colistin ranged from 0.48 to 9.38 mg/L, with a median of 2.36 mg/L [76]. These studies highlighted the pharmacokinetic caveats of treating patients with colistin alone, where an adequate plasma level of the active form of colistin may not be achieved for the first 1 or 2 days of therapy in the absence of a loading dose, and the therapeutic window between the colistin MICs of the infecting organisms and the plasma colistin concentration remains low even at the steady state. However, nephrotoxicity of colistin limits the potential for increasing the doses at the same time. Because of these limitations of colistin monotherapy, it is increasingly proposed that colistin should be used as part of combination regimens for clinical efficacy and prevention of resistance (see also Sect. 5.8).

Given that colistin is usually used for therapy when there are no good alternatives, clinical data on the efficacy of colistin in the treatment of XDR *A. baumannii* infections are scarce. Furthermore, studies suffer from inherent limitations, including the lack of suitable comparators, heterogeneity and complexity of the patients' medical conditions, and also inconsistent dosing approaches. In a retrospective study of 35 patients with ventilator-associated pneumonia due to *A. baumannii* who were treated according to colistin or imipenem susceptibility, 21 received colistin (2.5–5 mg/kg/day) and 14 received imipenem (2–3 g/day) [78]. Clinical cure and in-hospital mortality rates were comparable at 57 % each and 61.9 vs. 64.2 %, respectively. Though a small study, the findings suggested that colistin might be a reasonable alternative for imipenem when *A. baumannii* is resistant to imipenem. On the other hand, in another study of 167 patients with invasive infections caused by carbapenem-resistant *A. baumannii* and treated with a polymyxin or ampicillin–sulbactam, therapy with a polymyxin was an independent risk factor for in-hospital mortality (odds ratio 2.07; $p = 0.041$; see also Sect. 5.2 below) [79]. There is only one prospective, randomized study that compared the efficacy of colistin and ampicillin–sulbactam among *A. baumannii* ventilator-associated pneumonia patients [80]. This small study of 28 patients used a dose of colistin (270 mg CBA/day, without loading dose) that was acceptable, but on the low end of the current recommended dosing [76], and high-dose ampicillin–sulbactam (27 g/day). The clinical efficacy was comparable in both groups (60.0 vs. 61.5 %). Overall, there does appear to be some efficacy of colistin when used against *A. baumannii* infection, which nonetheless is difficult to quantify. Given the pharmacokinetic limitations of colistin as described above and concerns over development of resistance during treatment, it is increasingly used as part of combination therapy, and, consequently, most of the efficacy data on colistin are expected to be derived in this context in the future. Efficacy data regarding colistin-containing combination therapy that are currently available are reviewed in the sections for each companion agent below.

Nebulized colistin (as its prodrug colistimethate) is often used in clinical practice, in conjunction with intravenous colistin or other regimens for the treatment of ventilator-associated pneumonia due to XDR *A. baumannii*. A pharmacokinetic study conducted in cystic fibrosis patients confirmed the higher and likely therapeutic colistin concentrations present in sputum following administration of nebulized colistin compared with intravenous colistin [81]. There were minimal systemic levels noted in the six patients tested, all of whom had normal renal function, suggesting a possible way to limit toxicity. However, it should be noted that bronchospasm is a known adverse event of this off-label use [82]. A recently conducted retrospective study on ventilator-associated pneumonia patients with Gram-negative isolates susceptible only to colistin reported increased clinical cure rates (69.2 vs. 54.8 %; $p = 0.03$) when nebulized colistin was added to the intravenous form, as compared with intravenous colistin monotherapy. The study included *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* as well as *A. baumannii*, but *A. baumannii* was the predominate pathogen in both groups. There was no observed difference in ICU death between the groups [83]. In a case-control study conducted in Taiwan, patients with respiratory secretions growing MDR *A. baumannii* eradicated the organism sooner when they were given nebulized colistin for a median of 10.9 days, with or without intravenous colistin, compared with no nebulized colistin therapy (8.2 vs. 21.5 days; $p < 0.001$) [84]. There were no differences in the rates of adverse events or in-hospital mortality. A randomized, open-label trial comparing the efficacy of nebulized colistin for 100 patients with Gram-negative ventilator-associated pneumonia was conducted in Thailand [85]. In this study, *A. baumannii* accounted for over 60 % of the causative organisms. Favorable microbiologic outcome was noted in 60.9 % of the nebulized plus intravenous colistin group and 38.2 % of the intravenous colistin only group ($p = 0.03$). However, there was no difference in the rates of favorable clinical outcome (51.0 vs. 53.1 %; $p = 0.84$). Of note, there were numerically more bronchospasm events in the nebulized colistin group (7.8 vs. 2.0 %; $p = 0.36$). These data suggest that nebulized colistin expedites eradication of *A. baumannii* from the airway, but the true benefit to the clinical outcome of the patients, and to overall mortality, along with the risks of bronchospasm and development of resistance remain unclear.

Central nervous system (CNS) infections with *A. baumannii* are uncommon and are associated with neurosurgical procedures and devices. While carbapenems penetrate the CNS relatively well, colistin has been shown to have low CNS penetration [86]. Patients with severe and/or resistant *A. baumannii* CNS infections have been treated with intrathecal or intraventricular colistin [87]. A recent review of cases and case series showed that 72 of 81 patients treated with colistin by intrathecal/intraventricular route (in most cases with concomitant intravenous colistin) had a clinical and microbiologic cure [88]. Most of the isolates were XDR, MDR or carbapenem resistant, which explains why patients may not have been given carbapenems.

5.2 Sulbactam

Sulbactam is a synthetic β-lactamase inhibitor which has been co-formulated with ampicillin or cefoperazone to overcome β-lactamase-mediated resistance and restore the

activity of the co-formulated β-lactams. In addition, sulbactam itself has affinity for penicillin-binding proteins, in particular, types 1a and 2. As a result, it possesses intrinsic activity against *Acinetobacter* species [89, 90]. After a 1-g intravenous dose (the standard dose in the ampicillin–sulbactam 3-g formulation), a peak serum concentration of 40–60 mg/L is achieved, with an approximate half-life of 1 h [91]. Susceptibility data are somewhat limited. An ampicillin–sulbactam susceptibility of 63.6 % was reported for *Acinetobacter* spp. isolates collected from US hospitals in the early 2000s [92]. However, a steady decline in the susceptibility rate of *A. baumannii* from 89 % in 2003 to 40 % in 2008 has also been reported from a US hospital system [93].

In mouse pneumonia models of *A. baumannii*, treatment with sulbactam achieved survival and clearance of the bacteria from the lungs that was comparable to imipenem, and better than colistin in one study, when the strains were not resistant to these agents [94, 95].

The only prospective, randomized study on this topic to date was conducted in Greece, where 28 patients with ventilator-associated pneumonia from XDR *A. baumannii* were randomized to receive ampicillin–sulbactam (9 g of sulbactam/day) or colistin (270 mg CBA/day) [80]. In this trial, the clinical response rates were comparable, with 76.8 % for ampicillin–sulbactam versus 73.3 % for colistin. Bacteriologic success rates, 14- and 28-day mortality rates and the rates of adverse events were also comparable between the two groups. Of note, all isolates were resistant to ampicillin–sulbactam and susceptible to colistin in vitro and the dose of the former was more than twice higher than the standard dose of 4 g/day. This suggests that the in vitro testing against sulbactam may not reflect clinical response and may need to be studied further to reflect the pharmacodynamics and pharmacokinetics of this higher dose.

Several observational studies have attempted to explore the efficacy of sulbactam. In a study of *Acinetobacter* bloodstream infections from Korea, 35 patients received cefoperazone–sulbactam and 12 received imipenem [96]. All isolates were susceptible in vitro to the agents given. The clinical response rates were comparable (77 vs. 75 %), though there was a trend towards lower 30-day mortality among those who received cefoperazone–sulbactam (20 vs. 50 %; $p = 0.065$). However, while pneumonia was the most common source of bacteremia in both arms, 26 % of patients in the cefoperazone–sulbactam arm had a vascular catheter-related infection. No infections in the imipenem group were catheter-related, and thus the trend toward lower mortality might be explained by a more easily removable focus of infection. In another series of *A. baumannii* ventilator-associated pneumonia from the USA, 14 patients were treated with ampicillin–sulbactam and 63 with imipenem [97]. The percentages of successfully treated episodes were similar in the two groups (93 vs. 83 %). There were no differences in the rates of microbiologic clearance and mortality either. Dosing information was not provided in either of these studies. Finally, a study from Brazil examined the efficacy of ampicillin–sulbactam and polymyxins (colistin or polymyxin B) against invasive carbapenem-resistant *A. baumannii* infections [79]. Here, 85 patients received ampicillin–sulbactam and 82 received polymyxins. Almost 30 % also received a carbapenem in both groups, despite all isolates demonstrating carbapenem resistance in vitro. Clinical response was observed in 60 % of the ampicillin–sulbactam group and 39 % of the polymyxin group, and treatment with polymyxins was an independent risk factor for in-hospital mortality (odds ratio 2.07; $p = 0.04$). However, the median daily dose of colistin was 5.1 million IU, corresponding to approximately 150 mg CBA, which is substantially lower than the currently recommended dose [76]. The median daily dose of ampicillin–sulbactam was 9 g.

These data suggest that the use of sulbactam-containing regimens may have a role in the treatment of infections caused by carbapenem-resistant *A. baumannii* that remain susceptible to sulbactam. However, a recent report suggests an apparent lack of correlation between the level of sulbactam MICs and clinical response after treatment with this agent [98]. Furthermore, the declining in vitro activity of sulbactam may limit the utility of this agent in the long term.

5.3 Tigecycline

Tigecycline is the first agent in the glycylcycline class that has been approved and marketed for clinical use. It is a derivative of minocycline and exerts its activity through inhibition of protein synthesis by binding to the 30S ribosomal subunit. Tigecycline is approved for use in complicated intra-abdominal, complicated skin and skin structure infections, and also community-acquired bacterial pneumonia in the USA. It is capable of circumventing many of the efflux and ribosomal protection mechanisms underlying tetracycline resistance, and thus has a broader spectrum of activity compared with the earlier tetracyclines [99]. *A. baumannii* is broadly susceptible to tigecycline as a species [100]. Resistance to tigecycline is relatively rare but may develop through overexpression of efflux pumps, especially upon exposure to this agent [37, 101, 102].

Tigecycline has unique pharmacokinetics where the large volume of distribution results in extensive tissue distribution but also a low serum peak concentration of 0.7 to 0.8 mg/L after the standard loading dose of 100 mg [103]. The use of this agent for bloodstream infection is controversial because of the low serum concentrations, and breakthrough bacteremia during therapy has been reported

[102]. Suboptimal clinical outcome (56 % infection-related mortality) has been reported for patients with carbapenem-resistant *A. baumannii* bloodstream infection who were treated with tigecycline despite in vitro susceptibility [104]. In addition, it is generally not recommended for use in urinary tract infection since only 15–22 % is excreted unchanged in the urine [105].

Tigecycline is not approved for use in hospital-acquired pneumonia because of a phase III approval study which resulted in inferior clinical outcome in those who received tigecycline-based regimens compared with those who received imipenem-based regimens [106]. The inferiority was driven by the lower clinical response rates among those with ventilator-associated pneumonia. Among the small subset of patients who had ventilator-associated pneumonia from *A. baumannii*, the clinical response rates for the tigecycline group and the imipenem group were 57.1 and 94.7 %, respectively. These clinical outcome data are consistent with findings in a mouse pneumonia model comparing imipenem and tigecycline, where only imipenem reduced mortality when infection was caused by either imipenem-susceptible or intermediate *A. baumannii* strains. Clearance of the bacteria from the lungs was also superior with imipenem compared with tigecycline [107]. However, recent data have suggested that clinical failure in pneumonia with tigecycline may be related to poor lung penetration and decreased AUC/MIC ratios. Given this hypothesis, a phase II trial was conducted for hospital-acquired pneumonia with doses of 75 and 100 mg of tigecycline every 12 h (standard dosing is 50 mg every 12 h), compared with imipenem. The overall cure rate in this small study was 85 % for the 100-mg dose of tigecycline, 75 % for imipenem and 70 % for the 75-mg dose of tigecycline [108]. Thus prior studies with standard-dose tigecycline in pneumonia may not have used the ideal dosing for this drug.

Observational clinical studies that compare the efficacy of tigecycline with comparators for XDR *A. baumannii* infections are scarce. The largest case series on the use of tigecycline for XDR *A. baumannii* infections comes from Taiwan, where 266 patients were treated with tigecycline alone or in combination with another agent (a carbapenem, expanded-spectrum cephalosporin or piperacillin–tazobactam), and 120 were treated with imipenem and sulbactam [109]. In both arms, the isolates were resistant to all antibiotics tested except tigecycline and colistin. The patients who received tigecycline were significantly less likely to be in an ICU, were less likely to be febrile, had lower serum creatinine, and were less likely to have sepsis, all pointing to the lower severity of illness as well as infection in the tigecycline group. Also, the tigecycline group was more likely to have pneumonia (64.7 vs. 31.7 %) and less likely to have bacteremia (18.0 vs. 43.3 %) compared with the non-tigecycline group. With these caveats in mind, there was no difference in 30-day mortality between the two groups, and there was a lower percentage of patients with unfavorable clinical outcome in the tigecycline group (30.8 vs. 50.0 %; $p < 0.001$). Since the isolates were resistant to the agents used in the non-tigecycline group, the results suggest that there may be some efficacy of tigecycline in the treatment of XDR *A. baumannii* infections.

Tigecycline, despite all its limitations, may be effective when given early. Four of five patients (80.0 %) treated with tigecycline for imipenem-resistant *A. baumannii* bloodstream infection survived when therapy was started within 2 days, as opposed to only one of nine patients (11.1 %) when therapy was started late [19]. In this study, the combination of tigecycline and colistin had a similar trend, where four of five patients (80.0 %) survived when treated early but none of five patients survived when treated late.

There remains significant concern about emergence of resistance on tigecycline monotherapy. Two clear instances of this have been reported in the literature, both with monotherapy. One was a ventilator-associated pneumonia treated with tigecycline monotherapy for an initially susceptible isolate, with subsequent resistant isolate in the lungs (greater than threefold increase in MIC) [110]. The other was a patient with a susceptible urinary isolate treated with tigecycline monotherapy, who had subsequent infection (pneumonia and epidural abscess) with a tigecycline-resistant isolate [111]. Given the pharmacokinetics of tigecycline in relation to both urinary excretion and pulmonary concentrations, it is conceivable that subtherapeutic site concentrations contributed to resistance in these cases. Given these concerns, the role of tigecycline in pathogen-specific therapy of *A. baumannii* infections may be limited, at least in the context of monotherapy and at the currently approved dose.

5.4 Minocycline

Minocycline is a derivative of tetracycline. Like tigecycline, its mode of action is inhibition of the 30S ribosomal subunits. It maintains better activity against *A. baumannii* compared with tetracycline or doxycycline since it is generally less prone to efflux-mediated resistance, though it does not overcome resistance due to ribosomal protection, whereas tigecycline does [112]. It is almost completely absorbed when taken orally, and achieves a peak serum concentration of approximately 3 mg/L after a 200-mg dose, with a prolonged serum half-life of 12–18 h [113].

Minocycline maintains good in vitro activity against contemporary isolates of *A. baumannii*. In a surveillance study of MDR *A. baumannii* isolates collected in the USA between 2005 and 2011, 72.1 % were susceptible to

minocycline, whereas only 8.7 % were susceptible to carbapenems [100]. In addition, a high rate of in vitro synergy has been observed between minocycline and colistin, meropenem or sulbactam for carbapenem-resistant *A. baumannii* [114, 115]. However, reports of clinical experience remain extremely limited. In a series of eight patients treated with oral minocycline for traumatic wound infections due to MDR *A. baumannii* (six of which were resistant to carbapenems), minocycline therapy resulted in clinical cure in seven of the patients [116]. These patients were young, otherwise healthy military service personnel. In another small series, four patients with ventilator-associated pneumonia due to XDR *A. baumannii* were treated with intravenous minocycline [117]. One also received imipenem, though the isolate was resistant to this agent. All four patients had clinical improvement, and three of them had microbiologic clearance as well. A retrospective single-center study on carbapenem-resistant *A. baumannii* ventilator-associated pneumonia found a good rate of clinical response in 36 patients treated with doxycycline or minocycline in monotherapy or combination therapy (81.8 and 80 %, respectively) [118]. Of note, 76 % of the isolates were susceptible to aminoglycosides, and these were the most common drugs used in combination.

Despite the well-maintained in vitro activity, the bacteriostatic action of minocycline and the availability of tigecycline, to which a higher proportion of carbapenem-resistant and XDR *A. baumannii* are susceptible, limit the clinical use of minocycline for *A. baumannii* infections. However, it may have roles in the context of combination therapy or as step-down therapy given the availability of both intravenous and oral formulations. Clearly, more clinical data are needed on the use of this agent to make a better assessment of its role in the therapy of *A. baumannii* infections.

5.5 Rifampin

Rifampin often retains low MICs for XDR *A. baumannii*. While rifampin cannot be used for treatment alone because of rapid emergence of resistance, its potential role in combinations with other agents, in particular, colistin, has been explored (for further discussion of combination therapy, see Sect. 5.8). In vitro synergy between colistin and rifampin has been demonstrated for MDR and carbapenem-resistant *A. baumannii* at their MICs [119, 120]. Efficacy of rifampin alone or in combination with colistin, imipenem or sulbactam was also shown in pneumonia and meningitis models [121], and rifampin alone or with colistin prolonged survival of neutropenic rats in a thigh infection model [122], both models using carbapenem-resistant *A. baumannii*. Clinical case series have also shown low infection-related mortality (21 %) among patients with XDR *A. baumannii* nosocomial pneumonia or bloodstream infection treated with this combination [123].

Two prospective clinical trials have been conducted on this topic. In an open-label, randomized trial comparing the efficacy of colistin alone and colistin plus rifampin conducted in Turkey, 43 patients with ventilator-associated pneumonia due to carbapenem-resistant *A. baumannii* were enrolled [124]. Twenty-two patients were treated with colistin alone, and 21 were treated with the combination. The dose of colistin was 300 mg CBA/day. The two groups were comparable with the exception of the mean Sequential Organ Failure Assessment (SOFA) score, which was higher for the combination group. The crude in-hospital mortality was nominally higher for the colistin group (72.7 %) compared with the combination group (61.9 %), and so was the pneumonia-related mortality (63.6 vs. 38.1 %). Synergy was observed between colistin and rifampin for all isolates in vitro. Twenty-three percent developed nephrotoxicity, but none had hepatotoxicity from rifampin. Overall this study was underpowered to detect relevant differences in mortality and other key outcomes.

The other, larger study was conducted in Italy [125]. This was a multicenter, open-label, randomized trial comparing the efficacy of colistin alone and colistin plus rifampin. Patients with life-threatening infection due to XDR *A. baumannii* which remained susceptible to colistin were enrolled. The study was powered to detect a 20 % absolute difference in 30-day mortality between the two groups. A total of 210 patients were enrolled, and 209 received at least one dose of the study drug(s). The baseline characteristics were comparable, with most patients located in ICUs. There was no mortality difference between the two groups (43.4 % for the combination group, 42.9 % for the colistin group). This was the case even when patients who had rifampin-resistant isolates were excluded. However, the microbiologic eradication rate was significantly higher in the combination group (60.6 vs. 44.8 %; $p = 0.034$). In terms of adverse events, renal impairment occurred evenly (26.2 % overall), but hepatic dysfunction was nominally more common in the combination group, presumably due to rifampin use (20.8 vs. 11.9 %; $p = 0.13$). Several aspects of this study are worth a mention. The dose of colistin was approximately 180 mg CBA/day, which is lower than the dosing recommended currently based on contemporary pharmacokinetic assessments [76], though this would have affected both groups equally if anything. In addition, meropenem was added in the colistin group more frequently than in the combination group (15.9 vs. 3.9 %), which may have improved the outcome in the colistin group compared with what might have been achieved with colistin alone.

Taken together, the beneficial effect of adding rifampin in the treatment of XDR *A. baumannii* infection, which had

been suggested repeatedly by in vitro and animal studies, has not been demonstrated in two randomized, controlled trials. Also, given the potential for hepatotoxicity and significant drug interactions due to the induction of cytochrome P450 3A4, the use of rifampin is currently not recommend in the treatment of *A. baumannii* infection.

5.6 Fosfomycin

Fosfomycin is an inhibitor of peptidoclycan biosynthesis which has a broad spectrum of activity across Gram-positive and Gram-negative pathogens, but not *A. baumannii* [126]. However, in vitro synergy has been reported between fosfomycin and colistin or sulbactam among carbapenem-resistant *A. baumannii* [127].

The results of a randomized controlled trial of colistin versus colistin plus fosfomycin for infections caused by carbapenem-resistant *A. baumannii* were presented recently from Thailand [128]. In this study, 99 patients were enrolled and 94 were included in the analysis, 47 in each group. Fosfomycin was given at 4 g every 12 h intravenously to patients in the combination arm, and colistin was given at 5 mg CBA/kg/day to both groups for 7–14 days. The two groups did not differ in favorable clinical outcomes (59.6 vs. 55.3 %; $p = 0.835$) nor mortality at 28 days (46.8 vs. 57.4 %; $p = 0.409$). However, microbiologic eradication rates at the end of treatment were significantly higher in the combination group (100 vs. 81.2 %; $p = 0.01$). Of concern, the dose of fosfomycin was lower than has been used in other infections. In addition, this study was grossly underpowered to detect a relevant difference in mortality, but, like with rifampin, microbiologic clearance was significantly improved when combination therapy was used. Therefore, the combination of colistin and fosfomycin appears to merit further investigation.

5.7 Glycopeptides

Glycopeptides, including vancomycin, teicoplanin and telavancin, exert their activity by inhibiting peptidoglycan synthesis, but they do not penetrate the Gram-negative bacterial outer membrane and are considered inactive against Gram-negative pathogens. However, disruption of the outer membrane may allow them to reach their targets in Gram-negative bacteria. This phenomenon was initially suggested in colistin-resistant *A. baumannii* [129]. Subsequently, a series of investigations, both in vitro and using waxworm infection models, have reported potent synergy between glycopeptides and colistin [130–132]. A recent study evaluating *A. baumannii* clinical isolates from a Greek hospital found that seven of the ten colistin-susceptible isolates had synergy with daptomycin via time-kill methodology. This suggests that daptomycin, similarly to vancomycin, may be useful when combined with colistin [133].

An observational study conducted in Spain compared the outcome of patients who had carbapenem-resistant *A. baumannii* ventilator-associated pneumonia or bacteremia, 29 of them treated with colistin and vancomycin and 28 of them treated with colistin without vancomycin [134]. The clinical cure rate was similar in both treatment groups (55.2 vs. 67.9 %; $p = 0.32$), and microbiologic eradication was documented in 65.2 % of patients treated with colistin and in 54.2 % of patients treated with combined therapy ($p = 0.44$). However, the rate of renal failure was significantly higher in the combination therapy group (55.2 vs. 28.6 %; $p = 0.04$).

A similar study from Italy, where 166 patients who were given colistin for any Gram-negative infections were surveyed, showed somewhat opposing results [135]. Approximately 60 % of the infections were due to carbapenem-resistant *A. baumannii*. Sixty-eight received a colistin–glycopeptide combination, and 98 received colistin without a glycopeptide. The combination group had more bloodstream infections and less ventilator-associated pneumonia. The 30-day mortality for patients with carbapenem-resistant *A. baumannii* infection was comparable (41.7 vs. 35.3 %; $p = 0.54$) and so was the rate of nephrotoxicity (10.4 vs. 15.7 %; $p = 0.55$). Of note, colistin–glycopeptide combination therapy given for 5 days or longer was an independent protective factor for survival (hazard ratio 0.41; $p = 0.04$).

Given these inconclusive data, more clinical studies are needed on this topic, ideally as a prospective controlled study, especially given the difficulty in controlling for the differences in Gram-positive co-infections.

5.8 Role of Combination Therapy

While colistin is a key drug in the therapy of XDR *A. baumannii* infections, there are concerns regarding its unpredictable and suboptimal pharmacokinetics [76, 77] and documentation of emergence of colistin resistance during therapy [136, 137]. Similar concerns about suboptimal pharmacokinetics and resistance emerging on therapy exist for tigecycline [108, 110, 111]. Regarding sulbactam, optimal dosing is unclear and there is concern about in vitro efficacy not necessarily predicting clinical outcomes [98]. Given these concerns, various combination regimens have been studied mostly with colistin serving as one of the agents. The studies which have focused on comparing combination and monotherapy are listed in Table 2.

In a large retrospective study from 27 Turkish hospitals, the clinical outcome of patients with XDR *A. baumannii*

bloodstream infections was investigated [23]. Thirty-six of them received colistin monotherapy, whereas 214 received colistin-based combination therapy (102 with a carbapenem, 69 with ampicillin–sulbactam or sulbactam, and 43 with other agents). The baseline characteristics were comparable among the groups, and all isolates were susceptible to colistin and not more than one additional class, but no specific microbiologic breakdown was reported. None received a loading dose of colistin, and the standard dose of colistin was 5 mg CBA/kg/day. The in-hospital mortality rate was significantly lower in the combination group compared with the monotherapy group (52.3 vs. 72.2 %; $p = 0.03$), and the rate of microbiologic eradication was also significantly higher in the combination group than the monotherapy group (79.9 vs. 55.6 %; $p = 0.001$). When the combination group was broken down by the agent that accompanied colistin, no difference in mortality was observed.

In another observational study, including 69 patients with solid organ transplantation who developed XDR *A. baumannii* infection, where most developed ventilator-associated pneumonia, treatment with a combination of colistin and a carbapenem was an independent predictor of survival, whereas none of four patients who received any monotherapy survived; however, none in the monotherapy group received colistin [138]. In yet another single-center study, in which all patients on colistin were evaluated for clinical cure versus deterioration, 87 % of patients on colistin monotherapy and 84 % of those on colistin and meropenem combination had a clinical cure, whereas the rate of cure with colistin and piperacillin–tazobactam combination was 68 % and the rate of cure with colistin and sulbactam was 73 % for *A. baumannii* infection. Of note, in this study, lower dose colistin was associated with poor outcomes compared with higher doses [139]. The inadequacy of monotherapy for resistant *A. baumannii* infections may be due to a lack of highly effective drugs and/or the lack of adequate site concentrations of drugs. The possibility of synergy with, for example, glycopeptides, may mitigate the first consideration. In addition, combination therapy for drugs with pharmacokinetic challenges may help mitigate the concern for resistance on therapy with colistin and tigecycline. These concerns, together with the unique pharmacokinetic properties of colistin (which is administered as a prodrug), support the use of combination regimens for the treatment of invasive XDR *A. baumannii* infections.

Many questions remain unanswered, however. Is combination therapy still beneficial when dosing of colistin is optimized? Are patients at a higher risk for adverse events, especially nephrotoxicity, when multiple agents are used together? How can we best prevent the emergence of colistin resistance? The results from the ongoing randomized trials comparing colistin monotherapy and colistin–carbapenem combination therapy for the treatment of XDR Gram-negative pathogens, including XDR *A. baumannii*, should help address these questions.

5.9 Importance of Early Appropriate Therapy

Early appropriate antimicrobial therapy [i.e., therapy including agent(s) that have in vitro activity] is crucial in reducing mortality due to severe sepsis and septic shock, in particular, for cases caused by resistant Gram-negative pathogens, including *A. baumannii* [140, 141]. Furthermore, the risk of inappropriate early antimicrobial therapy increases substantially when the infecting strain is carbapenem resistant [24]. Evidence is accumulating that this is also the case for *A. baumannii*, in that higher mortality for XDR and carbapenem-resistant infections is strongly correlated with delay in the institution of appropriate therapy.

For imipenem-resistant *A. baumannii* bloodstream infection studied in Taiwan, patients given early appropriate therapy with colistin alone, tigecycline alone, or a combination of colistin and tigecycline had lower mortality (37.5, 20, 20 %) than those not given early appropriate therapy with the same agents (88.2, 88.9, 100 %) ($p = 0.017$, 0.023, 0.048) [12]. Another study from Taiwan investigated the appropriateness of therapy and clinical outcome among 252 cases of *A. baumannii* bloodstream infection [142]. Here, administration of appropriate therapy within 48 h of the onset of bloodstream infection was an independent predictor of survival at 14 days (odds ratio 0.22; $p < 0.001$). When adjusted for the severity of illness, early appropriate therapy predicted survival among patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 25 or greater. The protective effect of early appropriate therapy has also been demonstrated in a study of *A. baumannii* bloodstream infections conducted in Turkey (30-day mortality of 39.5 % for appropriate therapy vs. 65.0 % for inappropriate therapy; $p = 0.011$) [143] and a Brazilian study describing *A. baumannii* infections among solid organ transplant recipients, where early appropriate therapy was associated with significantly lower *A. baumannii*-related mortality (odds ratio = 0.04; $p = 0.03$) [144].

Early administration of an agent which has activity against the offending strain of *A. baumannii* is therefore critical in improving survival of patients, especially for those who are critically ill. Rapid identification of *A. baumannii*, and possibly XDR or carbapenem resistance, would be crucial in shortening the time until appropriate therapy is instituted, at least presumptively. At this point, it is not clear whether adequate therapy means one or multiple agents with activity. If, as some data suggest, combination therapy for *A. baumannii* is superior to

monotherapy, it may be that multiple active agents, at optimal dosing, early in the course of infection, will be the most effective way to treat these infections. Advances in diagnostics, such as direct species identification from clinical samples using matrix-assisted laser desorption ionization–time of flight (MALDI–TOF), can be leveraged to achieve this goal.

6 Concluding Remarks

A. baumannii is a significant healthcare-associated pathogen, causing invasive infections in patients with co-morbid conditions and pre-existing illnesses. The current data suggest that carbapenem-resistant strains are likely to respond better to colistin-based combination therapy compared with monotherapy. At this point, it remains unclear what the optimal companion agent is in the setting of carbapenem resistance. There are at least two advantages of combination therapy. The first involves decreasing time to effective therapy, especially given the time it takes for colistin to achieve therapeutic levels in the blood. The second relates to targeting multiple cellular mechanisms to enhance the overall antibacterial activity when the activities of single agents are no longer considered reliable.

Given the increase in carbapenem resistance in the last decade, this once-reliable drug class now offers only slightly better than 50 % coverage of this pathogen. A priori prediction of resistance is difficult as *A. baumannii* has multiple related mechanisms of resistance. If carbapenem resistance continues to increase in *A. baumannii*, empiric coverage for carbapenem-resistant and XDR strains will likely require colistin-based combination therapy even prior to determination of antimicrobial susceptibilities in critically ill patients. This would represent a major shift from current practice where the use of colistin is usually considered only in the context of definitive, salvage therapy, rather than empiric therapy. The ongoing clinical trials may indicate which specific colistin-containing regimens are most effective while minimizing toxicity in this population and give some guidance in these situations.

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