Managing *Acinetobacter baumannii* infections

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Purpose of review
We reviewed recent data about epidemiology of *Acinetobacter baumannii*, resistance mechanisms, and therapeutic options for severe infections caused by multidrug-resistant strains.

Recent findings
A. baumannii is a major cause of nosocomial infections affecting mainly to debilitating patients in the ICU, although the spread to regular wards and to long-term care facilities is increasing. It is characterized by its great persistence in the environment and to have an extraordinary capability to develop resistance to all antimicrobials. Carbapenems may not be considered the treatment of choice in areas with high rates of carbapenem-resistant *A. baumannii*. Nowadays, polymyxins are the antimicrobials with the greatest level of in-vitro activity against *A. baumannii*. Colistin is the most widely used in clinical practice although polymyxin B seems to be associated with less renal toxicity. Colistin is administered intravenously as its inactive prodrug colistimethate. A loading dose of 9 million IU and subsequently high, extended-interval maintenance doses (4.5 million IU/12 h) are recommended. Combination therapy instead of monotherapy increases the rates of microbiological eradication although no clinical study has demonstrated a reduction in clinical outcomes (mortality or length of stay).

Summary
The optimal treatment for multidrug-resistant *A. baumannii* nosocomial infections has not been established. There are no compelling data to recommend combination therapy for severe *A. baumannii* infections.

Keywords
Acinetobacter baumannii, epidemiology, infection, multiresistance, treatment

INTRODUCTION

Acinetobacter baumannii is a gram-negative aerobic bacillus that primarily causes hospital-acquired infections affecting specially to debilitated patients with prolonged hospitalization and with long-term exposition to antimicrobials. Until now, the ICUs have been considered as the epicenters of *A. baumannii* infections. Nevertheless, spread to general wards and long-term care facilities have also been shown to play an important role.

A. baumannii exhibits a wide variety of mechanisms of resistance to antimicrobial agents. This phenomenon has increasingly become a cause for serious concern for stakeholders and the scientific community worldwide. Thus, the WHO published its first list of 'priority pathogens' resistant to antibiotics, which includes the 12 families of bacteria most dangerous for human health and for that new antibiotics are urgently needed. In this list, *A. baumannii* is considered as 'priority 1' (critical) [1].

EPIDEMIOLOGY

Overall, *A. baumannii* is accountable for more than 12% of the cases of hospital-acquired bloodstream infections (BSI) in ICU, with wide geographic variations: it is frequent in Southern Europe, median Eastern countries, Asia, and South America, whereas it is rare in Northern European countries and Australia [2]. *A. baumannii* is a common cause of ICU-acquired pneumonia, particularly late onset pneumonia [3]. In countries were *A. baumannii* is spreading, it is the predominant pathogen isolated from patients with hospital-acquired pneumonia (HAP). Indeed, *A. baumannii* might be accountable of more than 36% of HAP cases in Asia [4]. Nevertheless, it only represents 1–2% of nosocomial pneumonia episodes in some countries [5]. In addition, *A. baumannii* might be involved in out-of-hospital healthcare-associated infections. Thus, a

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KEY POINTS

- *Acinetobacter baumannii* is one of the most frequently isolated bacteria in the ICU but significant regional differences exist.
- *A. baumannii* harbors on its core genome multiple innate resistance mechanisms against multiple antimicrobials and it can rapidly acquire new resistances via mobile genetic elements.
- Few therapeutic options are available for multidrug resistant *A. baumannii*.
- Polymyxins in monotherapy or combined with other agents (carbapenems, tigecycline, or rifampicin) are the options more widely used.

Table 1. Risk factors for development of *A. baumannii* infections in the ICU

Prior colonization with *A. baumannii*
Severity of illness
Immunosuppression
Malignancies
Unscheduled admission
Chronic pulmonary diseases
Respiratory failure at admission
Previous antimicrobial therapy
Previous sepsis in ICU
Multiple invasive procedures
Prior central venous or urinary catheterization, mechanical ventilation, and nasogastric tube
Previous use of carbapenems and third-generation cephalosporins
Older age
Long ICU stay

comparison of two large multicenter cohort studies found an increase in out-of-hospital cases from 1.2% in 2000 to 14.2% in 2010 ($P < 0.001$) [6▪]. Conversely, the incidence of *A. baumannii* in the ICU seems to have diminished in the last years [7].

One important feature of *A. baumannii* is its tendency to cause outbreaks because of its resistance to antimicrobials and its ability to survive for prolonged periods on dry surfaces. Outbreaks of multidrug resistant (MDR)-*A. baumannii* have been found to be mainly transmitted via the hands of healthcare workers, and contaminated equipment and healthcare environment [8▪,9]. The potential of cross-transmission increases if the patients is heavily colonized, if the surfaces surrounding the patients are colonized or if the number of patients colonized in the unit at the same time is high [10].

Specific resistant clones are the predominant cause of outbreaks. Three European clones (designated as I, II, and III) have disseminated in geographically distinct areas, and in specific institutional outbreaks, the majority of MDR-*A. baumannii* isolates usually belongs to a single clone. Whole genome sequencing techniques may help in differentiating outbreak from nonoutbreak strains [11].

Although limited to *A. baumannii* endemic areas, MDR-*A. baumannii* risk is highly variable according to the countries. Patients at high risk of MDR-*A. baumannii* infections are those with mechanical ventilation, particularly in case of prolonged duration, those with longer hospital or ICU stay, or those with greater degree of exposure to infected or colonized patients in the neighboring hospital environment [12,13]. The most frequently reported risk factors for *A. baumannii* infections are listed in Table 1.

ANTIMICROBIAL RESISTANCE

A. baumannii is characterized by its great persistence in the environment enabling it to spread rapidly and the extraordinary capability to develop resistance to antibiotics [14,15]. Although *A. baumannii* has innate resistance mechanisms against multiple antimicrobials on its core genome, the strains can easily acquire new resistance determinants via various mobile genetic elements. Almost all mechanisms of antimicrobial resistance have been described including enzymatic inactivation, alteration of bacterial targets, permeability barriers to uptake of antimicrobials, or active efflux pumps. In many isolates, the genes that confer resistance to antimicrobials are clustered together within an antibiotic-resistance island which accumulates in specific genetic regions of the large accessory genome [16].

Resistance to carbapenems

The mechanism by far the most common is the presence of carbapenemases, which can be of several types. Group 2 class D carbapenemases are the most common mechanism by which Ab strains become resistant to carbapenems. The Oxacilinase (OXA)-23 cluster (OXA-23, OXA-27, and OXA-49) was the first recognized in the 1980s. These enzymes are known to spread through plasmid-mediated transfer that disseminated worldwide in the mid-1990s, [17]. The OXA-58 and OXA-24 clusters are also common and diffuse widely [18].

The class B metallo-β-lactamases (mainly Verona integron-encoded metallo-β-lactamas-1 and New Delhi metallo-beta-lactamase 1 and 2) are much more efficient as they are potent hydrolyzers

of carbapenems [19,20]. They have been increasingly identified in Asia, Middle East countries, and Italy. Klebsiella pneumoniae carbapenemas class A carbapenemases are usually not a common mechanism of resistance for *A. baumannii*. However, since 2009, a new class A carbapenemase, called GES, is spreading in North Africa, Middle East countries, France, and Belgium [21].

Resistance to sulbactam

Diverse mechanisms can confer resistance to sulbactam in *A. baumannii*. Thus, the β-lactamase TEM-1 (class A) and an *Acinetobacter*-derived cephalosporinase-30 seem be involved [22].

Resistance to polymyxins

To date, polymyxins remain as the most active antimicrobial agents against *A. baumannii*. However, increasing rates of colistin-resistant *A. baumannii* isolates have been reported in different countries. Importantly, colistin resistance may be underestimated using automated testing methods [23]. Genetic alterations in the PmrA–PmrB two-component system and lipid A biosynthesis genes may be associated with colistin resistance [24]. The mcr-1 gene, which is responsible for colistin resistant strains in Enterobacteriaceae, has not been yet identified in *Acinetobacter* spp. [25].

Heteroresistance is defined as the presence of subpopulations of resistant organisms in an isolate considered susceptible by standard methods. Because heteroresistance detection requires a special method and equipment, most laboratories cannot routinely perform this test. Heteroresistance rates vary from 18.7 to 100%. It has been linked to previous exposure to colistin and has been associated with failure of colistin therapy [26,27].

Resistance to tigecycline

Two different types of specific resistance to tetracyclines have been described in *A. baumannii*, based on efflux pumps or on a ribosomal protection protein. Two efflux pumps are described, TetA and TetB, which are both specific transposon-mediated efflux pumps. Although TetB controls the efflux of both tetracycline and minocycline, TetA is only responsible for the efflux of tetracycline. The second mechanism is the ribosomal protection protein, which protects the ribosome from the effect of tetracycline. This protein is encoded by *tet (M)* gene; it helps in shielding the ribosome from tetracycline, doxycycline, and minocycline [28].

HOW TO DIFFERENTIATE *ACINETOBACTER* COLONIZATION FROM INFECTION

The respiratory tract, urinary tract, surgical wounds, and biological fluids may be locations for infection or colonization. *A. baumannii* has the capability to form biofilms on the surface of the endotracheal tube, which explain the high levels of colonization in the lower part of the respiratory tract in intubated patients [29].

It is often challenging to differentiate colonization from infection, especially in the critical care setting. In critically ill patients, up to half of the cases in which *A. baumannii* is isolated represents a mere colonization [30].

Many biomarkers, but especially procalcitonin levels, can have an important place in the process of discriminating the presence or absence of bacterial infections. However, no clinical study has been conducted to assess the accuracy of any biomarker for distinguishing *A. baumannii* infection from colonization.

THERAPEUTIC OPTIONS

Inadequate empirical therapy of severe infections caused by *A. baumannii* is associated with increased mortality [30,31]. Therefore, it is crucial to know the available therapeutic options and, more importantly, their rate of susceptibility at your own institution. The recommended doses of the antibiotics with activity against *A. baumannii* is outlined in Table 2 [32▪▪,33].

Carbapenems

Carbapenems have been considered the treatment of choice for infections caused by MDR *A. baumannii*. In the last years, many *A. baumannii* isolates exhibit carbapenem resistance, which is strongly associated with prior use of carbapenems.

Meropenem has a lower affinity for certain oxacillinase enzymes than imipenem [34]. Its stability in extended infusion and a comparatively lower seizure threshold than imipenem makes meropenem a rational choice for *A. baumannii*. Unfortunately, rising minimum inhibitory concentrations (MIC) of meropenem substantially decrease the probability of achieving the relevant pharmacokinetic/pharmacodynamic index with the routine dosing regimens of 1 g every 8 h. A 2-g q8 h regimen in extended infusion is more likely to achieve the required %T more than MIC target. Nevertheless, these carbapenem-resistant-*A. baumannii* strains exhibit high MIC levels (>32 mg/l) making necessary the use of other antimicrobials. Therefore,

Table 2. Recommended doses of antimicrobials for severe *A. baumannii* infections

Antibiotic	Loading dose	Daily dose				Dose on CRRT	Observations
		>50	50–30	30–10	<10		
Meropenem[a]	Not required	2 g/8 h	1 g/8 h	1 g/12 h	1 g/24 h	0.5–1 g/8–12 h	Extended infusion (3–4 h) is recommended. If extended infusion is used, the first dose should be administered in 30 min
Sulbactam	Not required	9–12 g/day (in three doses)	9–12 g/day (in three doses)	6–9 g/day (in two to three doses)	3 g/day	2–3 g/12 h	4-h infusion is recommended
Colistin	9 M IU	9 M IU/day in two doses	6 M IU/24 h in two doses	4.5 M IU/24 h	3 M IU/24 h	9 M IU/day in two doses	Loading dose is necessary including patients with renal dysfunction
Polymyxin B	2–2.5 mg/kg	1.5–3 mg/kg/day in two doses	NC	NC	NC	NC	Continuous infusion may be suitable. Same doses in patients on CRRT
Tigecycline	100 mg 200 mg	50 mg/12 h 100 mg/12 h	NC NC	NC NC	NC NC	NC NC	May be adequate for approved indications (abdominal infections and SSTI) For other indications, especially pulmonary infections (without approval by regulatory agencies) use high dose (200 mg/day)
Minocycline	200 mg	100 mg/12 h	NC	NC	NC	NC	
Rifampicin	Not required	600 mg/day or 600 mg/12 h	600 mg/day or 600 mg/12 h	600 mg/day	600 mg/day	600 mg/day	Always in combination therapy
Fosfomycin	Not required	12–24 g in 3 or 4 doses	4 g/12 h	4 g/24 h	2 g/24 h	8 g/12 h	Always in combination therapy

CRRT, Continuous renal replacement therapy; M IU: millions international units; NC, no change; SSTI, Skin and soft tissue infection.

carbapenems cannot be used empirically, at least in monotherapy, for severe infections in areas with a high rate of resistance to carbapenems.

Sulbactam

Sulbactam is a penicillanic acid sulfone which, as well as being a β-lactamases inhibitor, with intrinsic activity against *A. baumannii*. A pharmacokinetic/pharmacodynamic study performed in healthy volunteers concluded that a 4-h infusion of 3 g of sulbactam every 8 h constitutes the best treatment option for less susceptible isolates [35]. Multiple clinical studies corroborate that high-dose sulbactam (9 g/day) is a valid option in the management of severe *Acinetobacter* infections. In a retrospective study analyzing infections caused by carbapenem-resistant-*A. baumannii*, polymyxin (colistin or polymyxin B) treatment was significantly associated with higher mortality than sulbactam. The use of a polymyxin was identified as an independent risk factor for mortality [36].

Unfortunately, nowadays the percentage of resistance to sulbactam has reached such a high level [22] that its use as empirical therapy against infections caused by *A. baumannii* is discouraged [32▪▪].

Polymyxins

Polymyxins are a group of polypeptide cationic antibiotics. Only polymyxin B and polymyxin E (colistin) are used in clinical practice. Colistin is by far the most extensively used polymyxin. It is administered as colistimethate (CMS), a prodrug that needs to be hydrolyzed to its active form (colistin).

CMS is mostly excreted unchanged in urine (70%) and is partly transformed to colistin (30%), whereas renal excretion of colistin is negligible (1–2%). As renal function decreases, a progressively larger fraction of a dose of CMS will be converted to colistin. The elimination of colistin is nonrenal because it undergoes extensive renal tubular reabsorption, and nonbiliary by unknown mechanism. In the last years, our knowledge on the clinical pharmacokinetic of colistin has increased substantially. The ratio of the area under the curve (AUC) to the MIC (AUC/MIC ratio) is the best pharmacokinetic–pharmacodynamic index to describe its efficacy profile. A dosing regimen should allow for colistin plasma concentrations of about 2 mg/l to assure the efficacy against colistin susceptible *A. baumannii*. A meta-analysis of 32 studies confirmed the clinical benefit of high doses of colistin (MIC ≤ 2 mg/l) [37]. The risk of nephrotoxicity increases as plasma colistin concentration exceeds 2.5 mg/l [38]. This problem of heteroresistance to colistin can be overcome with high doses of colistin or with the use of another active agent [39].

Polymyxin B is available for direct intravenous administration. Polymyxin B dosages should be calculated based on body weight and the plasma concentration is not influenced by renal function [40]. Of note, the incidence of renal failure seems to be lower with polymyxin B than with colistin [41].

Minocycline

Minocycline exhibits bactericidal activity against *A. baumannii* as well as synergistic effects with different antimicrobials. In retrospective studies, the use of intravenous minocycline provided high rates of clinical success or improvement and was generally well tolerated among patients with MDR or carbapenem-resistant-*A. baumannii* infections [42].

Tigecycline

Serious doubts exist about the role of tigecycline in monotherapy for MDR-*A. baumannii* infections. The currently approved dosage is a 100-mg loading dose followed by a 50-mg dose administered twice daily. Tigecycline possesses a large distribution volume but C_{max} in the serum does not exceed 0.87 mg/l with the standard regimen; treatment of intravascular/bacteremic infections by *A. baumannii* seems impossible with the approved regimen [43]. Similarly, tigecycline concentrations in pulmonary endothelial lining fluid with conventional dosing are insufficient (0.01–0.02 mg/l) to treat *A. baumannii* pneumonia [44].

A matched cohort analysis concluded that the tigecycline-based therapy resulted in higher in-hospital mortality than the colistin-based therapy (61 vs. 44%, respectively) in critically ill patients with pneumonia caused by multidrug-resistant *A. baumannii*. This lower efficacy of tigecycline might be because of *A. baumannii* isolates with MIC more than 2 mg/l [45]. Two meta-analyses discourage the use of a tigecycline for the treatment of MDR-*A. baumannii* infections because, compared with other active antimicrobials, the use of tigecycline was associated with higher in-hospital mortality, lower microbial eradication rate and longer length of stay [46,47▪▪]. Nevertheless, a high-dose regimen (200 mg/day), usually in combination with another antimicrobial, may be an effective and well-tolerated alternative for severe *A. baumannii* infections including HAP [48].

MONOTHERAPY OR COMBINATION THERAPY

The use of combination therapy is an attractive approach based on the results of experimental

models and justified by the high mortality rates of these infections, the lack of proven valid therapeutic options, and the rapid development of resistance. Notwithstanding, the advantages of combination therapy is doubtful.

Observational studies

A recent observational study that evaluated multiple combinations (colistin and tigecycline followed by carbapenem and tigecycline were the most common combinations) compared with monotherapy (colistin and carbapenems were the most common drugs used in monotherapy) failed to demonstrate any benefits in term of mortality in patients with sepsis because of multidrug-resistant *A. baumannii*. Various observational studies evaluating different colistin-based combination therapy against monotherapy with colistin have reported a higher eradication rate but no impact on mortality with the used of combination therapy [49,50]. It is worth mentioning a retrospective study that compared monotherapy with colistin with patients that received combination therapy (colistin and carbapenem, sulbactam, tigecycline, or other agents) in MDR-*A. baumannii* BSI. Rates of 14-day survival and microbiological eradication were significantly higher in the combination group but without differences in hospital mortality [49].

Several in-vitro studies have documented the existence of a potent synergism of the combination of colistin with anti-gram-positive antibiotics [51–53]. In a retrospective series, clinical benefit of the combination of colistin and vancomycin was not documented in patients with *A. baumannii* ventilator-associated pneumoni (VAP) and BSI. In addition, the rate of renal failure was significantly higher in patients on combination therapy compared with those on monotherapy with colistin [54]. Conversely, a multicenter study that included a heterogeneous group of infections caused by different gram-negative bacilli concluded that therapy with colistin and a glycopeptide at least five days was a protective factor for 30-day mortality [55].

Randomized clinical trials

Colistin and rifampicin

A randomized, open label trial found no difference in mortality or length of hospitalization between a colistin-rifampicin group and colistin monotherapy in serious MDR-*A. baumannii* infections. However, an increased rate of *A. baumannii* eradication with combination therapy was observed [56]. The results were identical in another clinical trial that compared colistin and rifampicin with colistin in 43 patients with VAP caused by carbapenem-resistant-*A. baumannii*. [57].

Colistin and fosfomycin

A recent randomized open-trial evaluated monotherapy with colistin compared with the combination of colistin and fosfomycin for 7–14 days in patients infected with carbapenem-resistant *A. baumannii*. Microbiological response at the first 72 h and at the end of treatment were significantly higher in the combination group but without differences in clinical cure rate or 28-day mortality [58].

Colistin and meropenem

Experimental studies suggest that for *A. baumannii* infections, polymyxin–carbapenem combinations are synergistic and increased bactericidal activity compared with polymyxins alone. A recent randomized controlled trial that enrolled 406 patients with severe infections caused by carbapenem-resistant gram-negative bacteria concluded that combination therapy (colistin and meropenem) did not result in better outcomes compared with colistin monotherapy. Specifically, for *A. baumannii* infections, no differences existed between monotherapy and combination therapy for clinical failure (primary outcome), or 14-day and 28-day mortality [59▪▪].

Meta-analyses

Diverse meta-analyses have assessed the use of combination therapy in severe *A. baumannii* infections. A meta-analysis that included five observational studies and two randomized controlled trials concluded that the combination of colistin and rifampicin compared with colistin alone did not impact on mortality rate or length of hospitalization although microbiological eradication rate was significantly higher in the combination group. The use of rifampicin was associated with a nonsignificant trend toward a higher incidence of liver toxicity [60]. However, the variability in the doses administered including the low doses of colistin used in these studies and the lack of colistin loading dose warrant further investigation of this antimicrobial combination. Another meta-analysis concluded that the combination of polymyxins with other antibiotics achieved similar hospital mortality and clinical response rates than monotherapy [61].

It is worth mentioning a recent meta-analysis that concluded that colistin in combination with sulbactam was associated with a significantly higher microbiological cure rate compared with colistin in combination with tigecycline (RR 1.23; 95% CI 1.03–1.47) and colistin monotherapy (RR 1.21;

95% CI 1.06–1.38) although mortality rates were unaffected. As expected by its pharmacokinetic properties, tigecycline-based therapy was significantly less effective for achieving a microbiological cure in BSIs [47▪▪]. Finally, a Bayesian network meta-analysis analyzed the comparative effectiveness of different antimicrobials in monotherapy or combined for MDR-*A. baumannii* HAP in critically ill patients. Intravenous colistin monotherapy was chosen as comparator. For survival benefit, sulbactam appears to be the best treatment option. Among combinations, colistin and fosfomycin achieved the highest survival benefit [62].

CONCLUSION

The treatment for *A. baumannii* infections often represents a challenge because of the paucity of active agents, the limited data about their efficacy and concerns about serious side-effects. As carbapenem and sulbactam resistances are rising worldwide, polymyxins in monotherapy or combined with other agents are widely used. Colistin is considered to be suboptimal to β-lactams or sulbactam but it represents frequently the last resort for drug resistant *A. baumannii* infection.

Recent meta-analyses coincide in the lack of clinical efficacy (cure rate or mortality) using combination therapy instead of monotherapy for *A. baumannii* severe infections although microbiological eradication rates are significantly higher with the use of two active antimicrobials. Furthermore, side-effects can be significantly higher with some of these combinations.

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- ▪ of special interest
- ▪▪ of outstanding interest

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