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DISEASE MANAGEMENT

Initiate antibacterial treatment early in patients with carbapenem-resistant or extensively drug-resistant *Acinetobacter baumannii* infection

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Abstract Survival is consistently improved with early initiation of appropriate antibacterial therapy in patients with carbapenem-resistant or extensively drug-resistant *Acinetobacter baumannii* infections. However, because of a general lack of data, there is no clear consensus for the optimum empirical antibacterial therapy in these patients. Regimens that include colistin, sulbactam or tigecycline have been the most widely evaluated.

Major cause of hospital infections

In recent decades, Gram-negative coccobacilli *Acinetobacter* spp. have become increasingly major pathogens in hospital-acquired and healthcare-associated infections, occurring most frequently with ventilator-associated pneumonia, bloodstream infection, wound infection and urinary tract infection [1]. Among the >30 known genomic species, *A. baumannii* is the most clinically relevant on the basis of virulence and multidrug resistance (MDR), causing invasive infections in patients with co-morbid conditions and/or pre-existing illness. Of note, *A. baumannii* is not distinguishable from three other genomic species (two of which are also clinically significant pathogens) by standard biochemical, non-genetic methods, and references to *A. baumannii* in the literature may mean either just *A. baumannii* or the *A. baumannii* complex (i.e. all four genomic species) [1].

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Characterized by resistance to multiple agents …

A. baumannii is well known for its capacity to develop resistance to multiple classes of antibacterials [1]. MDR is technically defined as the non-susceptibility of an isolate to at least one agent in three or more antibacterial classes [2] (e.g. an isolate is defined as MDR if it is resistant to ceftriaxone, ciprofloxacin and trimethoprim–sulfamethoxazole), which means that many treatment options are still available [1]. However, the use of the term extensive drug resistance (XDR; defined as non-susceptibility of an isolate to one or more agents in all but two or fewer antibacterial categories [2]), is more clinically relevant when discussing the treatment of drug-resistant *A. baumannii* infections [1]. *XDR* isolates of *A. baumannii* (e.g. isolates susceptible to colistin and tigecycline, but resistant to all other categories tested) are increasingly encountered in clinical practice, with certain XDR strains being epidemic in hospitals [3]. Most clinical isolates of *A. baumannii* are resistant to cephalosporins; other antibacterial classes for which *A. baumannii* is resistant include carbapenems, sulbactam, rifampicin (rifampin), aminoglycosides, fluoroquinolones, colistin (polymixin E), penicillins and tetracyclines [1]. *A. baumannii* can survive for weeks on dry surfaces, which further facilitate its dissemination [1].

… in particular carbapenem

Carbapenem resistance is of particular importance, as second-line options for the treatment of *A. baumannii* have less defined efficacy and are often associated with various toxicities [1]. The incidence of carbapenem resistance is increasing [4]. Carbapenem-resistant *A. baumannii* is an independent risk factor for mortality, and is associated with

higher mortality rates than other *A. baumannii* complex species [5]. In addition, carbapenem-resistant *A. baumannii* strains are often also XDR and vice versa (i.e. XDR *A. baumannii* strains are resistant to carbapenem) [1]. This article provides a summary of the treatment of carbapenem-resistant and XDR *A. baumannii infections* as reviewed by Viehman et al. [1].

Multiple acquisition and mortality risk factors

Risk factors for acquiring XDR [6] or carbapenem-resistant [7] *A. baumannii* include recent exposure to antibacterial (in particular carbapenem), the presence of central venous catheter or urinary catheter, more severe illness, relatively longer duration of hospital stay, treatment in an intensive care unit (ICU) or relatively large hospital, and recent surgery.

Mortality rates associated with invasive *A. baumannii* infections vary, but are generally high, especially for carbapenem-resistant strains (16–76 vs. 5–53 % for carbapenem-susceptible infections) [8]. The high mortality rates are generally attributed to more severe illness and early, but inappropriate, antibacterial therapy [8]. Independent risk factors for mortality in patients with bloodstream infections with carbapenem-resistant *A. baumannii* include illness severity, underlying malignancy, history of transplant, higher age, septic shock, concurrent pneumonia, inappropriate antibacterial therapy, prolonged ICU stay and renal failure [8, 9].

Treat appropriately, and early …

In order to reduce the mortality resulting from severe sepsis and septic shock in patients with resistant-Gram negative bacteria, early and appropriate antibacterial therapy is crucial [1]. If the causative *A. baumannii* strain is resistant to carbapenem, the risk of inappropriate therapy [10] or a delay in appropriate therapy [11] is increased, resulting in a significant increase in mortality rates. Currently, it is unclear whether appropriate antibacterial therapy should consist of monotherapy or combination therapy [1].

… but no clear consensus for drug selection

Some clinicians suggest a polymyxin-containing regimen (colistin or the less widely available polymyxin B) to treat infections with colistin-susceptible *A. baumannii*, and also favour such a regimen for infections with colistin-resistant strains [12]. However, other clinicians prefer regimens based on other agents (e.g. sulbactam, tigecycline), because of the toxicity profiles of polymyxins [1]. Table 1 outlines the most studied treatment options for patients with carbapenem-resistant or XDR *A. baumannii*. Of note, colistin is administered intravenously in the form of its less active prodrug colistimethate (colistin methanosulfonate); one million international units of colistimethate is equivalent to ≈30 mg of colistin base activity, which corresponds to ≈80 mg of chemical colistimethate.

Is combination therapy better than monotherapy?

Treatment with a combination of concomitant antibacterials has advantages over antibacterial monotherapy. Overall efficacy may be improved, as the use of more than one antibacterial may provide multiple mechanisms of antibacterial activity and have a faster onset of action than monotherapy (e.g. colistin takes time to reach therapeutic concentrations) [1]. The increasing incidence of carbapenem-resistant *A. baumannii* may mean that colistin-based combinations are used as empirical therapy in the future, instead of as salvage therapy as currently used [1].

For colistin [24, 25] and tigecycline [22, 26], there are concerns regarding the unpredictable and suboptimal pharmacokinetics and the emergence of drug resistance during their use; for sulbactam, there are concerns regarding unclear optimal dosing and clinical outcomes that are not always predicable based on its in vitro efficacy [27]. The available trial data (Table 2) suggest that patients with carbapenem-resistant *A. baumannii* may respond better to colistin-based combination therapy than to monotherapy, but the components of the optimal combination are as yet unclear [1]. In two retrospective studies (Table 2), the use of colistin and a carbapenem was an independent predictor of survival [28], and microbiological eradiation was significantly higher with combination therapy than with monotherapy (79.9 vs. 55.6 %; $p = 0.001$) [29]. However, in two other retrospective studies, clinical cure rates did not favour various colistin combinations over colistin monotherapy [55.2 vs. 67.9 % (no significant difference) [30] and 80.3 vs. 87 % (*p*-value not reported) [31]].

Even less data for other agents

Fosfomycin has shown in vitro synergy with colistin or sulbactam [1], and a clinical trial has shown higher microbiological eradication rates with fosfomycin 4 g every 12 h plus colistin than with colistin alone (100 vs. 81.2 %; $p < 0.01$), with no significant difference in clinical outcomes or mortality rates [35]; the fosfomycin dosage used was lower than that used for other infections, and the study was underpowered to detect a difference in mortality

Table 1 Treatment options for patients with carbapenem-resistant or extensively drug-resistant *Acinetobacter baumannii* infections, as reviewed by Viehman et al. [1]

Colistin (administered as the prodrug colistimethate)
Mechanism of action interacts with the lipid A component of the lipopolysaccharide that makes up the bacterial outer membrane
Dosage 5 mg CBA/kg/day loading dose, followed by 5 mg CBA/kg/day in two or three divided doses; use as combination therapy
A higher loading dose may be beneficial in some pts with renal impairment (half-life of the prodrug may be prolonged)
Evidence of efficacy is conflicting: effective alternative to imipenem for imipenem-resistant strains (in terms of similar in-hospital mortality and clinical cure rates) [13], but was an independent risk factor for in-hospital mortality in pts with carbapenem-resistant strains (odds ratio 2.07; $p = 0.041$), although this study used a very low dosage of colistin ($\approx$150 mg CBA/day) [14]; the clinical efficacy of a relatively low dosage of colistin (270 mg CBA/day) without a loading dose was similar to that of a very high dosage of ampicillin/sulbactam 27 g/day in a small randomized study in pts with VAP [15]
Nebulized colistin (off-label use): may increase local drug concentrations without increasing systemic drug concentrations, thereby minimizing the risk of nephrotoxicity (however, bronchospasm may occur) [16–18]
Advantages mainstay of therapy because most *A. baumannii* strains remain susceptible
Limitations associated with nephrotoxicity; low serum concentrations especially early in therapy; resistance via lipid A modification
Uncertainties efficacy when optimally dosed; optimal companion agent for combination therapy
Sulbactam
Mechanism of action synthetic β-lactamase, co-formulated with ampicillin or cefoperazone to overcome β-lactamase-mediated resistance and restore activity of the co-formulated β-lactam; affinity for penicillin-binding proteins, in particular types 1a and 2
Dosage 3–9 g/day alone or as combination therapy (e.g. combined with ampicillin or cefoperazone)
Efficacy of ampicillin/sulbactam was similar to that of colistin (study described above) [15]; observational studies suggest that the efficacy of cefoperazone/sulbactam [19] and ampicillin/sulbactam [20] is similar to that of imipenem/cilastatin
Advantages widely available in combination with ampicillin; relatively inexpensive
Limitations increasing resistance
Uncertainties clinical correlation between MIC and outcome; optimal dosing regimen
Tigecycline
Mechanism of action minocycline derivative that inhibits protein synthesis by binding to 30S ribosomal subunit; has a broader spectrum of activity than the earlier tetracyclines
Dosage 100 mg loading dose, followed by 50 mg every 12 h; use alone or as combination therapy
Poor outcomes with tigecycline-based regimens relative to imipenem-based regimens in pts with VAP may be related to poor drug penetration in the lung and low AUC/MIC [21]; higher dosages of 75 and 100 mg every 12 h (with loading doses of 150 or 200 mg, respectively) showed similar clinical cure rates as imipenem/cilastin 1 g every 8 h (69.6 and 85.0 vs. 75.0 %) in pts with hospital-acquired pneumonia [22]; significantly fewer unfavourable clinical outcomes were reported with tigecycline-based regimens than with imipenem + sulbactam (30.8 vs. 50.0 %; $p < 0.001$) in an observational study (no difference in 30-day mortality rates) [23]
In a small retrospective study, survival rates were significantly ($p < 0.05$) higher in pts receiving early treatment (within 2 days) with colistin alone, tigecycline alone or colitin + tigecycline than in pts receiving late (inappropriate) treatment with the same therapies (62 vs. 12 %; 80 vs. 11 % and 80 vs. 0 %, respectively) [9]
Advantages widely available; active against most strains in vitro (resistance is currently relatively rare; more likely with monotherapy at lower dosages)
Limitations generally not suitable for urinary tract infections (15–22 % of the drug is excreted unchanged in the urine); serum concentrations are low (making its use in bloodstream infections controversial); bacteriostatic activity; may be less effective in critically ill pts
Uncertainties clinical correlation between MIC and outcome; optimal dosing regimen; benefit of combination regimens

AUC area under the plasma concentration–time curve, *CBA* colistin base activity, *MIC* minimum inhibitory concentration, *pts* patients, *VAP* ventilator-associated pneumonia

rates. Given that fosfomycin is bactericidal and relatively well tolerated (with the possibility of using higher dosages), the combination of fosfomycin and colistin in treating *A. baumannii* infections warrants further investigation [1].

The use of minocycline has been superseded by the use of tigecycline (Table 2); however, micocycline may be of use in combination therapy or as step-down therapy, as it is available in intravenous and oral formulations [1].

Glycopeptides (e.g. vancomycin) do not generally penetrate the outer membrane of Gram-negative bacteria, although their addition to colistin showed strong in vitro synergy against such bacteria, including *A. baumannii*. However, conflicting results were reported in clinical studies [30, 34], and more studies are needed to evaluate this combination [1].

Despite good in vitro synergy and in vivo activity [1], clinical trials did not show a benefit with using rifampicin

Table 2 Summary of studies comparing mortality rates with a combination of concomitant antibacterials vs. antibacterial monotherapy in patients with carbapenem-resistant or extensively drug-resistant *Acinetobacter baumannii* infections

Type of resistant infection(s)	Regimens (combination therapy vs. monotherapy)	Mortality rate (% of patients)
Open-label trial in patients with carbapenem-resistant *A. baumannii* infection		
Ventilator-associated pneumonia ($n = 43$) [32]	Colistin + vancomycin vs. colistin	61.9 vs. 72.7[a]
Open-label trial in patients with extensively drug-resistant *A. baumannii* infection		
Pneumonia, bloodstream infection, intra-abdominal infection ($n = 209$) [33]	Colistin + rifampin vs. colistin	43.4 vs. 42.9
Retrospective study in patients with carbapenem-resistant *A. baumannii* infection		
Pneumonia, bloodstream infection, urinary tract infection, intra-abdominal infection, surgical site infection ($n = 166$) [34]	Colistin + vancomycin vs. colistin	41.7 vs. 35.3
Retrospective studies in patients with extensively drug-resistant *A. baumannii* infection		
Bloodstream infection ($n = 240$) [29]	Colistin + carbapenem, sulbactam, tigecycline or other vs. colistin	52.3 vs. 72.2*
Pneumonia, bloodstream infection ($n = 36$) [28]	Colistin + carbapenem, sulbactam, tigecycline or other vs. tigecycline, carbapenem or cefepime	33 vs. 100*

* $p = 0.03$

[a] Study was not powered to detect a statistically significant between-group difference

plus colistin compared with using colistin alone [32, 33]; given its association with hepatotoxicity and likelihood of cytochrome P450 3A4-related drug interactions, the use of rifampicin is not recommended to treat *A. baumannii* infections [1].

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