Treatment of Acinetobacter Infections

Joel Fishbain1 and Anton Y. Peleg2,3,4

1Division of Infectious Diseases, St John Hospital and Medical Center, Detroit, Michigan, and 2Division of Infectious Diseases, Massachusetts General Hospital and Beth Israel Deaconess Medical Center, Boston, Massachusetts; 3Alfred Hospital and 4Department of Microbiology, Monash University, Melbourne, Australia

Acinetobacter baumannii remains an important and difficult-to-treat pathogen whose resistance patterns result in significant challenges for the clinician. Despite the prevalence and interest in A. baumannii infections, there is relatively limited well-controlled scientific data to help the clinician select optimal empirical and subsequent targeted therapy for a variety of infections. We will review the currently available antimicrobial agents and discuss the clinical data supporting the use of the various agents.

INTRODUCTION

The challenges of treating multidrug-resistant bacteria continue to be at the forefront of the clinician’s practice in caring for hospitalized patients. Acinetobacter baumannii has proven to be an increasingly important and demanding species in health care–associated infections. The drug-resistant nature of the pathogen and its unusual and unpredictable susceptibility patterns make empirical and therapeutic decisions even more difficult.

The association of A. baumannii with pneumonia, bacteemia, wound infections, urinary tract infections, and meningitis has been well described [1]. Risk factors associated with colonization or infection (which can be difficult to distinguish) include prolonged hospitalization, intensive care unit admission, recent surgical procedures, antimicrobial agent exposure, central venous catheter use, prior hospitalization, nursing home residence, and local colonization pressure on susceptible patients [1–3].

The ability of A. baumannii to survive for extended periods on environmental surfaces is notorious and is likely important for transmission within the health care setting. Multidrug resistance is common with health care–associated A. baumannii infections. The impressive number of acquired mechanisms of resistance makes selection of an appropriate empirical antimicrobial agent exceedingly difficult. The diversity of resistance mechanisms is beyond the scope of this article but can be reviewed in Peleg et al [4]. Degradation enzymes against β-lactams, modification enzymes against aminoglycosides, altered binding sites for quinolones, and a variety of efflux mechanisms and changes in outer membrane proteins have been reported. Essentially, any and all of these elements can be combined to result in a highly drug-resistant, and at times pan-resistant, opportunistic pathogen [4].

Attributable mortality has been difficult to assess for an organism that appears to be as much a colonizer as it is a true pathogen. Although one cannot argue against the pathogenicity of an organism that is identified in bloodstream infections, A. baumannii is often identified in the sputum samples of patients with mechanical ventilation. This quandary of pathogenicity has added to the difficulty of treating these highly resistant organisms, because many therapeutic strategies are associated with significant toxicity. The in-hospital attributable mortality appears to be 8%–23%, but for the intensive care unit, it was found to be 10%–43% [5, 6]. Although most studies did not demonstrate a statistically significant difference between case patients and control subjects, all studies did show a higher mortality among the case patients. Despite the lack of consistent statistical support for the findings, one has to assume that A. baumannii is at least as important as other pathogens isolated from patients. The decision to treat on the basis of a clinical culture result remains in the hands of the clinician, and criteria for decision-making in this regard will not be reviewed in this article. We will endeavor to discuss the therapeutic options using available clinical data (Table 1). The reader is encouraged to review the in vitro and animal studies for additional information.
Table 1. Antimicrobial Agents for the Treatment of Acinetobacter Infections

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage*</th>
<th>Route</th>
<th>Toxicity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulbactam (amp/sulb in the United States)</td>
<td>6 g per day</td>
<td>IV</td>
<td>Dermatologic, GI, nephritis</td>
<td>Adjust for renal function; daily dose based on sulbactam</td>
</tr>
<tr>
<td>Imipenem-cilastatin</td>
<td>500 mg every 6 h up to 1 g every 6–8 h</td>
<td>IV</td>
<td>Phlebitis, GI, anaphylaxis, seizures, nephritis</td>
<td>Extended infusions have been used, limited data</td>
</tr>
<tr>
<td>Meropenem</td>
<td>500 mg to 1 g every 8 h</td>
<td>IV</td>
<td>GI, headache, dermatologic, hematology, angioedema, seizure</td>
<td>Extended infusions have been used, limited data</td>
</tr>
<tr>
<td>Doripenem</td>
<td>500 mg every 8 h</td>
<td>IV</td>
<td>Dermatologic, GI, anemia, anaphylaxis, seizure</td>
<td>Consider extended infusion</td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen 1</td>
<td>15 mg/kg daily</td>
<td>IV</td>
<td>Nephrototoxicity, ototoxicity, neuromuscular blockade</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen 1</td>
<td>4–7 mg/kg daily</td>
<td>IV</td>
<td>Nephrototoxicity, ototoxicity, neuromuscular blockade</td>
<td>Peak and trough measurements as appropriate for dosing regimen selected</td>
</tr>
<tr>
<td>Regimen 2</td>
<td>300 mg (1 ampule) twice daily</td>
<td>IH</td>
<td>Nephrototoxicity, ototoxicity, neuromuscular blockade</td>
<td>Tobi inhaled formulation</td>
</tr>
<tr>
<td>Regimen 3</td>
<td>5–20 mg</td>
<td>IT/IVent</td>
<td>Not for children</td>
<td>Not FDA approved for this route of administration</td>
</tr>
<tr>
<td>Colistin (colistimethate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen 1</td>
<td>5 mg/kg/day, 2–4 divided doses</td>
<td>IV</td>
<td>Nephrotoxicity and neurotoxicity</td>
<td>Additional data still required on ideal dosing</td>
</tr>
<tr>
<td>Regimen 2</td>
<td>1–3 million IU every 8 h</td>
<td>IH</td>
<td>Must be used immediately after reconstitution to prevent accumulation of colistin–lung toxicity</td>
<td>1 million IU is 80 mg of colistimethate. A variety of doses used in studies</td>
</tr>
<tr>
<td>Polymyxin B [25]</td>
<td>50,000 units daily (5 mg)</td>
<td>IT</td>
<td>Meningeal irritation</td>
<td>Has been used as intraventricular injection but not FDA labeled as approved by this route</td>
</tr>
<tr>
<td>Polymyxin E (colistin [25])</td>
<td>10 mg daily</td>
<td>IT/IVent</td>
<td>Meningeal irritation</td>
<td>Has not been FDA approved for either route of administration</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100 mg once then 50 mg every 12 h</td>
<td>IV</td>
<td>GI, shock, pancreatitis, anaphylaxis</td>
<td>Avoid use in blood stream infections due to large volume of distribution and low mean maximum steady-state levels</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100 mg every 12 h</td>
<td>IV</td>
<td>GI, hepatic, dermatologic</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt; lower than that of doxycycline; limited data on use in severe infections; most active of all the tetracyclines [33] (excluding tigecycline because of lack of established breakpoints)</td>
</tr>
</tbody>
</table>

NOTE. Amp/sulb, ampicillin-sulbactam; FDA, US Food and Drug Administration; GI, gastrointestinal (eg, nausea, vomiting, and diarrhea); H, inhalational; hepatic, jaundice and hepatitis; IT, intrathecal; IV, intravenous; IVent, intraventricular.

* Based on adults with normal renal function.

**SPECIFIC THERAPEUTIC OPTIONS**

**Sulbactam.** Of the β-lactamase inhibitors, sulbactam possesses the greatest intrinsic bactericidal activity against *A. baumannii* isolates [4]. Results of clinical investigations have documented the efficacy of sulbactam (commercially available in the United States in combination with ampicillin) in mild-to-severe *A. baumannii* infections. Urban et al [7] have reported one of the earliest experiences using ampicillin-sulbactam and observed that 9 of 10 patients who were seriously ill and receiving mechanical ventilation demonstrated clinical improvement using ampicillin-sulbactam at a dosage of 3 g of amicillin and 1.5 g of sulbactam intravenously every 6 or 8 h. Sulbactam-containing regimens appeared to be comparable to regimens of other agents when the infecting organisms were susceptible to sulbactam in patients with *A. baumannii* pneumonia and blood stream infections [8–10]. A study from Israel identified that treatment with ampicillin-sulbactam was the only statistically significant variable associated with reduced mortality in patients with multidrug-resistant *A. baumannii* bloodstream infection [11]. Mixed results have been reported for use of sulbactam to treat *A. baumannii* meningitis, and this likely relates to impaired drug penetration. The optimal dosage of sulbactam to treat serious *A. baumannii* infections is unknown, but most authors recommend at least 6 g per day in divided doses for patients with normal renal function (Table 1). Whether higher dosages are more efficacious or reduce the risk
of resistance, or even whether ampicillin-sulbactam should be used in combination with other agents (as recommended by others), is yet to be determined [8].

**Carbapenems.** Despite the absence of randomized controlled trials, the carbapenems (imipenem, meropenem, or doripenem) remain one of the most important therapeutic options for serious infections caused by multidrug-resistant *A. baumannii*. They have excellent bactericidal activity and stability toward a range of β-lactamases. Unfortunately, increasing carbapenem resistance is creating therapeutic challenges, especially considering that most *A. baumannii* strains that are resistant to the carbapenems are also resistant to the majority of other antibiotics (except the polymyxins or tigecycline). Susceptibility to the carbapenems ranges from >90% to as low as 32% depending on the geographic region and the carbapenem tested [12–16]. Discordance in susceptibilities between the carbapenems is well described. Norskov-Lauritsen et al [13] reported that 13% of isolates were resistant to imipenem, yet 23% were resistant to meropenem. Conversely, Ikonomidis et al [16] reported that 59% of isolates were meropenem susceptible, whereas only 32% were imipenem susceptible. A clear understanding of local susceptibility patterns and sufficient laboratory support to test the carbapenems of interest are required when deciding on treatment. One cannot equate imipenem results with meropenem. The clinical impact of discordant results is exemplified in the case report by Lesho et al [17]. They describe a fatal case of *A. baumannii* pneumonia in which meropenem was administered on the basis of imipenem susceptibility, yet the isolate was later proven to be meropenem resistant. Doripenem is a new carbapenem with equivalent in vitro activity against *A. baumannii* isolates. There does not appear to be any advantage of doripenem when compared with imipenem and meropenem, however [18]. Discordant results between doripenem and imipenem or meropenem have been reported against a few isolates of *A. baumannii* [18].

**Aminoglycosides.** Amikacin and tobramycin are the 2 agents that appear to retain activity against many *A. baumannii* isolates. As with all antimicrobial agents and multidrug-resistant pathogens, resistance is increasing, and susceptibility testing is required to ensure activity. A recent analysis of discordant susceptibility testing by Akers et al [19] has generated some significant concerns about automated testing for aminoglycoside activity against *A. baumannii*. The percentage of isolates with amikacin susceptibility was reported as 53% by Vitek 2 (bioMérieux), compared with only 17% by Etest (AB Biodisk) and broth microdilution [19]. Results were similar for tobramycin, but gentamicin did not display any discordance. Tobramycin maintained the highest overall susceptibility rates [19].

Aminoglycosides are not often used as single agents for treatment, and the toxicity profiles often hinder their use (especially for longer treatment courses). There has been much debate on the usefulness of these agents in pneumonia, but a detailed review of this issue is well beyond the scope of this article. One study by Gounden et al [20] demonstrated tobramycin’s comparative activity and toxicity in treating *A. baumannii* infections with that of colistin. In that study, 32 patients (retrospective cohort) were found to have received therapy in each group. They found no statistically significant difference in intensive care unit mortality (total in-house mortality favored colistin), increase in serum creatinine over baseline, or time to microbiologic clearance [20].

The efficacy of inhaled antibiotics, including aminoglycosides, outside the cystic fibrosis population is of increasing interest. Unfortunately, very little clinical data exists for inhaled aminoglycosides (outside of cystic fibrosis patients). Tobi (Novartis Pharmaceuticals), a specific formulation of inhaled tobramycin, has been approved by the US Food and Drug Administration (FDA) for pseudomonas infections in cystic fibrosis patients only. Hallal et al [21] investigated the utility of inhaled versus intravenous tobramycin, both in combination with an intravenous β-lactam, in a pilot randomized study (*n* = 10). All 5 patients in the intravenous tobramycin group survived, but only 3 survived in the intravenous tobramycin group. It should be noted, however, that these 2 patients had higher multiple organ dysfunction scores [21]. Historically, aminoglycosides have been used mostly in combination therapy, and at least for *Pseudomonas aeruginosa*, monotherapy appears to be inferior to other agents.

**Polymyxins.** Unfortunately, familiarity with this older class of antibiotic is now increasing in many parts of the world. The polymyxins include colistin or polymyxin E and polymyxin B, and this class of drug has been a savior for the treatment of highly drug-resistant gram-negative bacteria. Colistin is most commonly used in the United States, and it is administered intravenously as a pro-drug known as colistimethate sodium (CMS). Colistin sulfate is used topically but, most importantly, is also the form that should be used in the laboratory for susceptibility testing. Current Clinical and Laboratory Standards Institute breakpoints for colistin are ≤2 μg/mL (susceptible) and ≥4 μg/mL (resistant).

A wide range of observational studies have now been published on the clinical efficacy and toxicity of colistin for treating modern day gram-negative bacteria [4]. Efficacy ranges from 55% to 80% depending on the study and appears to be equal to that of other antibiotics in similar populations. Nephrotoxicity and neurotoxicity remain as key concerns for increasing use in an era of multidrug-resistant pathogens [22]. Nephrotoxicity is a particular issue for those with preexisting renal impairment, the elderly population, and those who receive concomitant nephrotoxins. Many authors who have reported on the use of colistin have been pleasantly surprised with its tol-
erability. As has been discussed elsewhere, dosing remains confusing, because formulations differ between countries [23]. Current parenteral formulations in the United States are available as either Coly-Mycin M Parenteral (Parkdale Pharmaceuticals) or generically via a variety of manufacturers. The recommended dosages are 2.5–5.0 mg/kg per day of colistin base given in 2–4 divided doses (equivalent to 6.67–13.3 mg/kg per day of CMS) in those with normal renal function. Additional work is still required to determine the ideal dosing of intravenous colistin to maintain efficacy and minimize toxicity. Promising data are available for the use of inhaled CMS as adjunctive treatment for pneumonia caused by multidrug-resistant A. baumannii. However, more data are still required. Concerns about lung toxicity, drug distribution, alveolar penetration, emergence of resistance, and selection for organisms inherently resistant to colistin are all justified and still need clarification [24]. According to a recent FDA health alert, those prescribing nebulized CMS should use it immediately after preparation to prevent build up of the active colistin form, which can be toxic to the lungs.

Although A. baumannii meningitis remains an uncommon health care-associated infection, its incidence is increasing, and it is often caused by multidrug-resistant organisms [25]. Carbapenems should be used to treat these infections if the organism is susceptible, with or without an intrathecal or intraventricular aminoglycoside. For carbapenem-resistant cases, intravenous polymyxin (colistin or polymyxin B) plus an intrathecal or intraventricular polymyxin or aminoglycoside, with or without intravenous rifampin, would be recommended [25]. Multiple case series and reports have now been published on the favorable efficacy and toxicity profile of intraventricular/ intrathecal colistin [25, 26]. Chemical meningitis appears to be uncommon. The dosing recommended by the Infectious Diseases Society of America for adults is 10 mg daily of colistin or 5 mg daily of polymyxin B [27].

**Tigecycline.** Tigecycline is the first of a new class of antibiotics known as the glycyclines. It is a semisynthetic derivative of minocycline and inhibits the 30S ribosomal subunit. Its advantage over other tetracycline antibiotics is its ability to evade the traditional tetracycline-specific resistance mechanisms—tet(A-E) and tet(K) efflux pumps and the tet(O) and tet(M) determinants that provide ribosomal protection—and therefore it has a broader spectrum of activity. Recent global in vitro data suggest that the 90% minimum inhibitory concentration (MIC90) for carbapenem-resistant A. baumannii isolates is 2 μg/mL [28]. Susceptibility breakpoints from the Clinical and Laboratory Standards Institute have not yet been determined. Despite tigecycline’s in vitro activity against A. baumannii, clinical data remains limited. Studies are observational and are often clouded by the effects of combination antibiotic therapy [29]. Favorable clinical responses have been reported for serious infections [30]. However, because of the rapid movement of tigecycline into tissues after intravenous administration, we would recommend avoiding tigecycline use alone for A. baumannii bloodstream infections (especially if the MIC is ≥1 μg/mL) [31]. Mean maximum serum steady-state concentrations are only 0.63 μg/mL because of the large volume of distribution [4].

**Tetracyclines.** Minocycline and doxycycline are both available by intravenous infusion and minocycline is approved by the FDA for use in acinetobacter infections. In vitro susceptibility testing is required for each agent to demonstrate susceptibility. Tetracycline cannot be used as a surrogate marker, because many tetracycline-resistant isolates prove to be susceptible to minocycline [32]. As with the aminoglycosides, Akers et al [33] also reported discordant susceptibility results between broth microdilution and Etest/disk diffusion among all 3 agents tested. A study by Hawley et al [34] examined 142 A. baumannii isolates from US soldiers. They found that the MIC90 for minocycline was 4, compared with 8 for tigecycline and >16 for doxycycline, thus supporting the concept of clinical use in A. baumannii infections [34]. Clinical data is surprisingly limited for minocycline and doxycycline. One study demonstrated success in 7 of 8 patients who received minocycline for wound infections, and another study found 6 of 7 patients with ventilator-associated pneumonia were successfully treated with one of these agents [32].

**COMBINATION THERAPY**

A significant amount of time and energy has been devoted to studying combination therapy for the treatment of A. baumannii infection. Much of the current information is derived from in vitro or animal studies. There are surprisingly limited data from comparative studies involving human A. baumannii infections. Petrosillo et al [35] produced a nice review on colistin versus combination therapy. They found only 4 relevant clinical studies, and only 1 study demonstrated any statistical significance with respect to mortality, favoring monotherapy. The heterogeneity of combinations and infections studied, as well as the small numbers of patients involved, makes interpretation very difficult [35]. Bassetti et al [36] conducted a prospective noncomparative study of colistin-rifampin combination involving critically ill patients with pneumonia and bacteremia. They observed a clinical and microbiological response rate of 76% with a mortality rate of 21%. All findings are considered to be within previously reported ranges of treatment outcomes. The noncomparative nature of the study makes any concrete conclusions difficult. Lee et al [37] reported successful treatment with carbapenem-sulbactam combination therapy in 4 patients (1 of whom received meropenem and 3 of whom received imipenem) despite all isolates showing resistance to both agents. Falagas et al [38] conducted a retro-
Prolonged infusion β-lactams

Because of the emergence of broad-spectrum antibiotic resistance in Acinetobacter species and the dearth of new antibacterials, greater emphasis has been placed on optimizing the use of currently available agents. Significant attention has been justifiably directed toward using pharmacokinetic and pharmacodynamic parameters to tailor antibacterial dosing. This logical approach accounts for characteristics of the drug, the pathogen, and the host. Despite the long-term knowledge and understanding of time-dependent versus concentration-dependent antimicrobial activity, physicians are only recently modifying their antibiotic dosing in an attempt to incorporate these principles.

Clinical literature is emerging on the use of extended-infusion β-lactams to treat gram-negative bacteria, especially with ceftazidime, piperacillin-tazobactam, and the carbapenems (meropenem, imipenem, and doripenem). One of the key advantages of extended-infusion β-lactams is the ability to achieve drug concentrations above the MIC for a greater time for less-susceptible organisms, especially those with an MIC between 4 μg/mL and 16 μg/mL. For example, Li et al [40] have shown that the likelihood of achieving bactericidal target attainment with meropenem, which equates to a T >MIC of at least 40%, increases from 64% to 90% when the infusion time of 1 g is increased from 0.5 h to 3 h for an organism with an MIC of 4 μg/mL (susceptible breakpoint). Importantly, modeling studies that use data from patients with ventilator-associated pneumonia support such findings and have shown that, by increasing the dose of meropenem to 2 g every 8 h and increasing the infusion time to 3 h, bactericidal target attainment can be achieved for organisms with an MIC of 16 μg/mL (intermediate breakpoint) [41]. Data are also available for extended-infusion imipenem. Both imipenem and meropenem have short half-lives (≤4 h), and this limits their usefulness for infusions beyond 3 h. Conversely, doripenem has a longer half-life [18] and has been administered as an extended-infusion in licensing studies. Despite modeling and retrospective clinical studies that have shown benefits for extended-infusion β-lactams [42], prospective clinical trials are lacking. It must also be highlighted that the pharmacokinetic and pharmacodynamic benefits of extended-infusion β-lactams attenuate in patients with increasing renal impairment, which is a common comorbidity in patients with Acinetobacter infection who are hospitalized in intensive care units. Finally, it is unknown whether the use of extended-infusion carbapenems will reduce the emergence of antibiotic resistance in Acinetobacter; however, promising results exist for Pseudomonas aeruginosa [43].

Summary

Acinetobacter infections remain difficult to treat. The prevalence of drug-resistant strains is increasing, and treatment options are increasingly limited. Effective therapy remains likely when the organism is proven to be susceptible. Recent data would suggest that, for some agents, a single testing method may result in incorrect susceptibility results and lead the clinician to select a potentially ineffective agent. Because of some of the unusual and potentially toxic options, one must maintain a high index of suspicion for A. baumannii infection and select empirical therapy wisely. The challenge for the clinician is to combine local susceptibility patterns with the agents that are most likely to be effective. The use of combination therapy, whether empirical or targeted, has yet to be demonstrated, and hopefully future studies will elucidate a greater number of definitive and practical options.

Acknowledgments

Potential conflicts of interest. A.P. has been a consultant for Abbott Molecular and Ortho-McNeil-Janssen. J.F.: no conflicts.

References

8. Wood GC, Hanes SD, Croce MA, Fabian TC, Boucher BA. Comparison of ampicillin-sulbactam and imipenem-cilastatin for the treatment of