Acinetobacter baumannii: Epidemiology, Antimicrobial Resistance, and Treatment Options

Lisa L. Maragakis1,2 and Trish M. Perl1,2
1Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, and 2Department of Hospital Epidemiology and Infection Control, Johns Hopkins Medical Institutions, Baltimore, Maryland

Multidrug-resistant Acinetobacter baumannii is recognized to be among the most difficult antimicrobial-resistant gram-negative bacilli to control and treat. Increasing antimicrobial resistance among Acinetobacter isolates has been documented, although definitions of multidrug resistance vary in the literature. A. baumannii survives for prolonged periods under a wide range of environmental conditions. The organism causes outbreaks of infection and health care–associated infections, including bacteremia, pneumonia, meningitis, urinary tract infection, and wound infection. Antimicrobial resistance greatly limits the therapeutic options for patients who are infected with this organism, especially if isolates are resistant to the carbapenem class of antimicrobial agents. Because therapeutic options are limited for multidrug-resistant Acinetobacter infection, the development or discovery of new therapies, well-controlled clinical trials of existing antimicrobial regimens and combinations, and greater emphasis on the prevention of health care–associated transmission of multidrug-resistant Acinetobacter infection are essential.

Multidrug-resistant Acinetobacter baumannii is a rapidly emerging pathogen in the health care setting, where it causes infections that include bacteremia, pneumonia, meningitis, urinary tract infection, and wound infection. The organism’s ability to survive under a wide range of environmental conditions and to persist for extended periods of time on surfaces make it a frequent cause of outbreaks of infection and an endemic, health care–associated pathogen [1, 2].

EPIDEMIOLOGY

Risk factors for colonization or infection with multidrug-resistant Acinetobacter species include prolonged length of hospital stay, exposure to an intensive care unit (ICU), receipt of mechanical ventilation, colonization pressure, exposure to antimicrobial agents, recent surgery, invasive procedures, and underlying severity of illness [1, 3]. Widespread environmental contamination is often demonstrated, and outbreaks of infection have been traced to respiratory care equipment, wound care procedures, humidifiers, and patient care items [4–13]. Wilks et al. [8] reported a recent outbreak of multidrug-resistant Acinetobacter infection, with environmental contamination found on curtains, laryngoscope blades, patient lifting equipment, door handles, mops, and keyboards. Medical equipment has been implicated, emphasizing the need for special attention to disinfection of shared items and extra caution with respiratory care and wound care procedures [4, 5, 7]. One or more epidemic Acinetobacter clones often coexist with endemic strains, making it difficult to detect and control transmission [14, 15].

Table 1 outlines various infection control and prevention methods for multidrug-resistant Acinetobacter infection. Investigators often report interruption of transmission after reinforcement of existing infection control and prevention standards, such as hand hygiene, standard precautions, barrier precautions, and thorough environmental cleaning and disinfection [8, 16, 17]. Other transmission is more difficult to halt, requiring cohorting of patients, dedicated staff assignments, active surveillance cultures, and closure of entire ICUs [11–13, 18–23]. Most reports of successful control involve multiple interventions, making it difficult to evaluate the efficacy of each intervention individually [24]. Further investigation of the efficacy and cost-effectiveness of various infection control strat-
egies to prevent transmission of multidrug-resistant *Acinetobacter* infection are needed.

In addition to transmission, emergence of resistance occurs in the context of selective pressure from broad-spectrum antimicrobial therapy, such as therapy involving carbapenems or third-generation cephalosporins [25, 26]. The relative contributions of antimicrobial selective pressure and transmission between patients on the emergence of multidrug-resistant *Acinetobacter* species are not known.

In many health care institutions, endemic, multidrug-resistant *Acinetobacter* infection demonstrates complex epidemiologic profiles and coexistence of multiple strain types. Abbó et al. [27] studied 118 patients with multidrug-resistant *Acinetobacter* infection in Israel and found 10 different PFGE-typed clones, as well as many small clusters of patients with no common source identified, despite molecular testing and extensive investigation. Multidrug-resistant *Acinetobacter* infection has been reported among patients residing in rehabilitation and long-term care facilities, as well as in acute care hospitals [28, 29]. Several factors work together to maintain the presence of multidrug-resistant *Acinetobacter* species in the health care setting, including the presence of susceptible patients, the presence of patients already colonized or infected with the organism, selective pressure from antimicrobial use, and incomplete compliance with infection control procedures [24] (figure 1).

Molecular-based strain typing by PFGE or other methods can be used to identify outbreaks of infection and to monitor interinstitutional, regional, and international transmission of multidrug-resistant *Acinetobacter* species [30, 31]. Nemecz et al. [31] used ribotyping and amplified fragment–length polymorphisms to demonstrate the genetic relatedness of *Acinetobacter* isolates in western Europe. Investigators used PFGE to demonstrate interinstitutional spread of carbapenem-resistant *Acinetobacter* infection among acute care hospitals in locales including New York, Argentina, the United Kingdom, and the Iberian Peninsula [32–35]. Gales et al. [36] used PFGE to demonstrate the spread of epidemic *Acinetobacter* clones between Brazil and Argentina.

Multidrug-resistant *Acinetobacter* deep wound infections, osteomyelitis, respiratory infections, and bacteremia have been reported among military personnel with traumatic injuries during the conflicts in Iraq and Afghanistan [37–40]. Theories that previously colonized soldiers are autoinoculated or that *Acinetobacter* species from local soil or water are introduced during traumatic injury have not been supported by cultures of specimens obtained from healthy soldiers, soil samples, water samples, or samples from fresh wounds [41–44]. Current literature suggests that these infections are associated with health care processes of stabilization, emergency treatment, and evacuation through the military medical system [37, 39, 42, 43, 45, 46]. The potential for introduction of new, virulent, multidrug-resistant *Acinetobacter* strains into hospitals by returning soldiers is a concern that warrants ongoing surveillance and careful attention to infection control measures [39, 47, 48].

**IMPACT ON PATIENT OUTCOMES**

Because multidrug-resistant *Acinetobacter* infection usually occurs in severely ill patients in the ICU, the associated crude mortality rate is high, ranging from 26% to 68% [49–51]. It has proven to be difficult, however, to determine the attributable mortality of these infections independent of patients’ severe underlying illnesses. Recent studies and a systematic review concluded that *Acinetobacter* infection or colonization is associated with increased mortality [52–54]. Many of these

---

**Table 1. Methods for control and prevention of multidrug-resistant *Acinetobacter* infection.**

<table>
<thead>
<tr>
<th>Method</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point source control</td>
<td>Effective in the outbreak setting when a point source is identified</td>
</tr>
<tr>
<td>Standard precautions</td>
<td>Includes hand hygiene, correct and consistent glove use, and appropriate use of gowns and eye protection; reported compliance among healthcare personnel is often poor</td>
</tr>
<tr>
<td>Contact barrier precautions</td>
<td>Includes dedicated patient care equipment and gowns and gloves for health care personnel on entry to an isolation room</td>
</tr>
<tr>
<td>Environmental cleaning and disinfection</td>
<td>Widespread environmental contamination is often reported in the epidemic setting, and environmental reservoirs likely play a role in the endemic setting as well</td>
</tr>
<tr>
<td>Cohorting of patients</td>
<td>Grouping colonized and infected patients into a designated unit or part of a unit</td>
</tr>
<tr>
<td>Cohorting of health care personnel</td>
<td>Designating staff to care for only patients colonized or infected with the organism</td>
</tr>
<tr>
<td>Clinical unit closure</td>
<td>Required in some outbreak settings to interrupt transmission and allow for thorough environmental disinfection</td>
</tr>
<tr>
<td>Antimicrobial stewardship</td>
<td>Programs to promote judicious antimicrobial use and prevent emergence of resistance</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Passive or active surveillance can identify infected or colonized patients so that interventions can be implemented</td>
</tr>
</tbody>
</table>
studies were limited by small sample sizes, methodological differences, and failure to adequately control for patients’ severity of illness. Other studies that rigorously controlled for severity of illness did not find *Acinetobacter* infection to be independently associated with increased mortality [1, 49, 55, 56]. An alternative explanation is that *Acinetobacter* infection is a marker of increased mortality in patients with severe underlying illness but not an independent predictor of mortality [55].

Mortality may be related to the extent of antimicrobial resistance, the effectiveness of empirical therapy, and the availability of definitive therapeutic options. A recent matched cohort study from Korea found that administration of ineffective empirical antimicrobial therapy for *Acinetobacter* bacteremia was an independent predictor of 30-day mortality [51]. However, other studies have found poor correlation between patient mortality and the empirical choice of antimicrobial agents to which *Acinetobacter* infection was resistant [49, 55, 57–59].

*Acinetobacter* infection is associated with increased morbidity and a prolonged length of hospital stay. A retrospective, matched cohort study found that patients with *Acinetobacter* bacteremia had a 5-day excess length of mechanical ventilator dependence and ICU stay, compared with critically ill patients without *Acinetobacter* infection [56]. Multidrug-resistant *Acinetobacter* infection was found to significantly prolong the duration of ICU stay (by 6 days) and the median duration of hospitalization (by 18 days) [49, 60]. One study found no evidence of a prolonged length of ICU stay for patients with *Acinetobacter* ventilator-associated pneumonia [61]. The impact on length of stay may depend on the type of infection and the extent of antimicrobial resistance.

**ANTIMICROBIAL RESISTANCE**

Antimicrobial resistance among *Acinetobacter* species has increased substantially in the past decade [62]. The capacity of *Acinetobacter* species for extensive antimicrobial resistance may be due in part to the organism’s relatively impermeable outer membrane and its environmental exposure to a large reservoir of resistance genes [63]. Definitions of multidrug-resistant *Acinetobacter* species vary, referring to a wide array of genotypes and phenotypes [64]. Two of the most common definitions of multidrug resistance are carbapenem resistance or resistance to ≥3 classes of antimicrobials [64]. Some strains are susceptible only to polymyxins—peptide antibiotics that are not routinely used because of earlier reports about toxicities. Strains that demonstrate resistance to all antimicrobial agents, including polymyxins, have also been reported in the literature, making treatment of these infections extremely difficult and in some cases impossible [65, 66].

**Mechanisms of resistance.** Resistance mechanisms for *Acinetobacter* species are similar to those for *Pseudomonas* species, although *Acinetobacter* species have not been studied as extensively [67, 68]. The mechanisms of resistance generally fall into 3 categories: (1) antimicrobial-inactivating enzymes, (2) reduced access to bacterial targets, or (3) mutations that change targets or cellular functions [68]. For the first category, *Acinetobacter* species possess a wide array of β-lactamases that hydrolyze and confer resistance to penicillins, cephalosporins, and carbapenems. AmpC cephalosporinases are chromosomally encoded and confer resistance to broad-spectrum cephalosporins [63, 67]. Recently, a large number of class D OXA-type
enzymes with activity against carbapenems were characterized in locations that include Scotland, Spain, France, Japan, Singapore, China, Brazil, Cuba, and Kuwait [69, 70]. Some Acinetobacter strains express class B metallo-β-lactamases (MBLs), such as VIM and IMP, which hydrolyze a broad array of antimicrobial agents, including carbapenems [67]. MBLs pose a significant threat because they are often located on mobile genetic elements easily transferred among bacteria [63, 67]. Many variants exist, and both IMP and VIM have been found worldwide in a wide array of bacterial species, including Acinetobacter species [67, 71, 72].

Porin channels and other outer membrane proteins are important for transport of antimicrobial agents into the cell to gain access to bacterial targets. Carbapenem resistance in Acinetobacter species has been linked to the loss of proteins thought to be porin channels from the outer membrane [67, 73, 74]. It is likely that β-lactamases and outer-membrane alterations work together to confer resistance to β-lactam agents [63]. Acinetobacter species possess efflux pumps that are capable of actively removing a broad range of antimicrobial agents from the bacterial cell [63].

The third category of resistance mechanisms involves point mutations that alter bacterial targets or functions, decreasing the affinity for antimicrobial agents or up-regulating cellular functions, such as the production of efflux pumps or other proteins. Resistance to colistin is thought to be mediated by changes in the bacterial cell membrane that interfere with the agent’s ability to bind bacterial targets [75]. This type of mechanism is also seen in Acinetobacter resistance to quinolone agents from mutations in the bacterial targets gyrA and parC topoisomerase enzymes [63].

Acinetobacter species can acquire resistance genes from other organisms; mutations leading to resistance can develop over time in Acinetobacter strains; or subpopulations with preexisting resistance may emerge and become dominant under antimicrobial selective pressure [69]. These 3 processes are not mutually exclusive and likely function together to explain emerging resistance among Acinetobacter species. A recent comparative genomic study of an epidemic, multidrug-resistant Acinetobacter strain in France found a large genomic “resistance island” containing 45 resistance genes that appeared to have been acquired from Pseudomonas, Salmonella, or Escherichia genera [76]. The emergence of antimicrobial-resistant Acinetobacter species is due to both selective pressure exerted by the use of broad-spectrum antimicrobials and transmission of strains among patients, although the relative contributions of these mechanisms are not yet known [14, 77].

**TREATMENT**

**Carbapenems.** Increasing antimicrobial resistance leaves few therapeutic options, and there are no well-designed clinical trials to compare treatment regimens for multidrug-resistant Acinetobacter infection. Available data are from in vitro, animal, and observational studies. Carbapenems remain the treatment of choice if isolates retain susceptibility to this antimicrobial class. The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) surveillance program has documented discordance that favors imipenem as the more potent agent, compared with meropenem, for treatment of multidrug-resistant Acinetobacter infection [78, 79]. The converse result was reported in Greece [80]. Efflux pumps may affect meropenem to a greater degree, whereas specific β-lactamases hydrolyze imipenem more efficiently [80]. Susceptibility testing of imipenem does not predict susceptibility to meropenem or vice versa [78]. Unfortunately, carbapenem-resistant Acinetobacter isolates are increasingly reported worldwide.

**β-Lactamase inhibitors.** β-Lactamase inhibitors, particularly sulbactam, have intrinsic activity against many Acinetobacter strains. The presence of a β-lactam agent (e.g., ampicillin) in combination with the β-lactamase inhibitor does not appear to contribute activity or synergy [81, 82]. Monotherapy with sulbactam is not recommended for severe Acinetobacter infection. However, Wood et al. [83] reported successful use of sulbactam to treat 14 patients with multidrug-resistant Acinetobacter ventilator-associated pneumonia, finding no difference in clinical outcomes between sulbactam-treated patients and 63 patients who received imipenem. Levin et al. [84] reported a cure rate of 67% using ampicillin-sulbactam to treat carbapenem-resistant Acinetobacter infection, but good patient outcomes were associated with lower severity of illness. The results of antimicrobial susceptibility tests (e.g., with agar dilution or the Etest) of β-lactam/β-lactamase combinations at fixed concentrations must be interpreted with caution, because they may indicate susceptibility when an isolate is actually resistant [82].

**Tigecycline.** Tigecycline, a relatively new glycyclcline agent, has bacteriostatic activity against multidrug-resistant Acinetobacter species [85, 86]. High-level resistance to tigecycline has been detected among some multidrug-resistant Acinetobacter isolates, and there is concern that the organism can rapidly evade this antimicrobial agent by upregulating chromosomally mediated efflux pumps [68, 87–91]. Peleg et al. [89] reported 2 cases of multidrug-resistant Acinetobacter bacteremia that occurred while patients were receiving tigecycline for another indication. Two recent studies documented overexpression of a multidrug efflux pump in Acinetobacter isolates with decreased susceptibility to tigecycline [92, 93]. Given these findings and concern about whether adequate peak serum concentrations can be achieved, tigecycline is best reserved for salvage therapy, with administration determined in consultation with an infectious diseases specialist [89].

**Aminoglycosides.** Aminoglycoside agents, such as tobramycin and amikacin, are therapeutic options for infection with
multidrug-resistant *Acinetobacter* isolates that retain susceptibility. These agents are usually used in conjunction with another active antimicrobial agent. Many multidrug-resistant *Acinetobacter* isolates retain intermediate susceptibility to amikacin or tobramycin; resistance to this class of agents is increasingly associated with aminoglycoside-modifying enzymes or efflux pump mechanisms. 

**Polymyxin therapy.** Given limited therapeutic options, clinicians have returned to the use of polymyxin B or polymyxin E (colistin) for the most drug-resistant *Acinetobacter* infections [94, 95]. Colistin acts by disturbing the bacterial cell membrane, thus increasing permeability, leading to cell death [94]. Colistin is bactericidal against *Acinetobacter* species, and its effect is concentration dependent [95]. Resistance to polymyxins has been reported, possibly as a result of outer cell membrane alterations or an efflux pump mechanism [65, 66, 94, 95]. Observational studies have reported rates of cure or improvement for colistin of 57%–77% among severely ill patients with multidrug-resistant *Acinetobacter* infections, including pneumonia, bacteremia, sepsis, intra-abdominal infection, and CNS infection [96–99]. Although high-quality pharmacokinetic data are lacking, colistin is reported to have relatively poor lung and CSF distribution, and clinical outcomes vary for different types of infections [96]. Despite an overall “good outcome” rate of 67%, Levin et al. [96] found a lower response rate of 25% for patients with pneumonia due to multidrug-resistant, gram-negative bacilli who were treated with parenteral colistin. Other studies have reported more favorable clinical response rates (56%–61%) for parenteral colistin treatment of multidrug-resistant *Acinetobacter* ventilator-associated pneumonia [100–103].

There are case reports of successful treatment of multidrug-resistant *Acinetobacter* meningitis with parenteral colistin, but its efficacy for this condition remains unclear [104, 105]. Several case reports and case series report the use of intraventricular or intrathecal polymyxin therapy, with or without parenteral therapy, for the treatment of gram-negative bacterial meningitis [104, 106–108]. A recent review of 31 reports involving 64 episodes of gram-negative bacterial meningitis found a cure rate of 80%, including cure for 10 (91%) of 11 patients with *Acinetobacter* meningitis [109]. The majority of patients received systemic antimicrobial therapy in addition to local administration of polymyxin. Neurologic toxicity occurred primarily in reports published before 1970, and the most common

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study method</th>
<th>Combination</th>
<th>Results/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giamarellos-Bourboulis et al. [110]</td>
<td>2001</td>
<td>In vitro</td>
<td>Colistin and rifampin</td>
<td>In vitro synergy</td>
</tr>
<tr>
<td>Petrosillo et al. [111]</td>
<td>2005</td>
<td>Case series</td>
<td>Colistin and rifampin</td>
<td>Microbiologic cure in 64% of 14 patients with VAP</td>
</tr>
<tr>
<td>Pantopoulou et al. [112]</td>
<td>2007</td>
<td>Animal study</td>
<td>Colistin and rifampin</td>
<td>Enhanced activity against experimental-thigh infection in neutropenic rats</td>
</tr>
<tr>
<td>Gleeson et al. [123]</td>
<td>2005</td>
<td>Case report</td>
<td>Meropenem and rifampin</td>
<td>Successful treatment of meningitis after meropenem monotherapy failed</td>
</tr>
<tr>
<td>Montero et al. [113]</td>
<td>2004</td>
<td>Animal study</td>
<td>Colistin and rifampin, imipenem and rifampin, tobramycin and rifampin, imipenem and tobramycin</td>
<td>The best regimens in a mouse pneumonia model</td>
</tr>
<tr>
<td>Saballs et al. [114]</td>
<td>2006</td>
<td>Clinical pilot study</td>
<td>Imipenem and rifampin</td>
<td>Cautions against use of this regimen due to high failure rate and emergence of rifampin resistance in 70% of patients</td>
</tr>
<tr>
<td>Rodriguez-Hernandez et al. [115]</td>
<td>2000</td>
<td>Animal study</td>
<td>Imipenem and amikacin</td>
<td>Combination offered no advantage over imipenem monotherapy in a mouse pneumonia model</td>
</tr>
<tr>
<td>Bernabeu-Wittet et al. [116]</td>
<td>2005</td>
<td>Animal study</td>
<td>Imipenem and amikacin</td>
<td>Combination was worse than imipenem alone in a guinea pig pneumonia model, despite evidence of in vitro synergy</td>
</tr>
<tr>
<td>Haddad et al. [117]</td>
<td>2005</td>
<td>In vitro</td>
<td>Imipenem and amikacin; imipenem and colistin</td>
<td>In vitro synergy</td>
</tr>
<tr>
<td>Ko et al. [118]</td>
<td>2004</td>
<td>Animal study</td>
<td>Meropenem and sulbactam</td>
<td>In vitro synergy and increased survival in a mouse infection model</td>
</tr>
<tr>
<td>Kiffer et al. [119]</td>
<td>2005</td>
<td>In vitro</td>
<td>Meropenem and sulbactam</td>
<td>In vitro synergy</td>
</tr>
<tr>
<td>Sader et al. [122]</td>
<td>2005</td>
<td>In vitro</td>
<td>Cefpirime and sulbactam</td>
<td>In vitro synergy</td>
</tr>
<tr>
<td>Kasiakou et al. [102]</td>
<td>2005</td>
<td>Case series</td>
<td>Colistin and another agent*</td>
<td>67% of 80 patients with severe <em>Acinetobacter</em> or <em>Pseudomonas</em> infection were “cured or improved”</td>
</tr>
<tr>
<td>Sobieszczyk et al. [121]</td>
<td>2004</td>
<td>Case series</td>
<td>Colistin and another agent*</td>
<td>79% of 25 patients with <em>Acinetobacter</em> or <em>Pseudomonas</em> pneumonia survived until the end of therapy</td>
</tr>
</tbody>
</table>

**NOTE.** ICU, intensive care unit; VAP, ventilator-associated pneumonia.

* Other agents included meropenem, imipenem, aminoglycosides, ampicillin-sulbactam, piperacillin-clavulanate, and ciprofloxacin.
manifestation was meningeal irritation, which was apparently dose-dependent and reversible [109]. Overall, there is insufficient evidence to draw conclusions regarding the efficacy, safety, or pharmacokinetic properties of colistin for treatment of CNS infection, although it remains an important option for salvage therapy [104].

Data are lacking on the pharmacokinetics, pharmacodynamics, and toxicodynamics of colistin. Earlier methods of measuring serum concentrations of the drug were unable to adequately distinguish concentrations of colistimethate, the nonactive prodrug, from concentrations of colistin [95]. There are inconsistencies among manufacturers regarding the recommended dosing of colistin and the units of measurement employed [95]. Data suggest that current recommended dosing regimens may lead to serum levels of colistin that are less than the MIC for Acinetobacter infection [95]. These problems highlight the need for careful pharmacologic studies and the importance of attention to formulation and dosing in clinical care and research studies.

Synergy and combination therapy. A lack of controlled clinical trials makes it difficult to evaluate the role of synergy or combination therapy for multidrug-resistant Acinetobacter infection. Most available data are from uncontrolled case series, animal models, or in vitro studies. The studies summarized in Table 2 investigated various combinations of rifampin, sulbactam, aminoglycoside agents, colistin, carbapenems, and other agents against multidrug-resistant Acinetobacter infection [102, 110–123].

Studies have found conflicting results for the same antimicrobial combinations. Montero et al. [113] studied a mouse model of multidrug-resistant Acinetobacter pneumonia and found that the combinations of rifampin with imipenem, tobramycin, or colistin were the most effective regimens. A follow-up clinical pilot study, however, cautioned against the use of rifampin plus imipenem for treatment of carbapenem-resistant Acinetobacter infection, because investigators observed a high failure rate and documented the emergence of rifampin resistance in 70% of the patients who were treated with this regimen [114]. In a guinea pig model, the combination of imipenem and amikacin was found to be worse than imipenem alone for treatment of imipenem-resistant pneumonia, despite the demonstration of in vitro synergy between the agents [116]. The clinical utility of in vitro synergy remains unclear. Most results for combination therapy are comparable to cure rates reported for parenteral colistin alone, and the wide variety of other agents used limits the ability to draw conclusions regarding combination therapy. Controlled clinical studies are needed to determine whether any antimicrobial combinations translate into useful therapeutic strategies.

Li et al. [124] found heteroresistance (i.e., subpopulations with varying levels of resistance to colistin) in 15 of 16 colistin-susceptible Acinetobacter isolates studied in vitro. Serial passage of the isolates in the presence of colistin increased the proportion of colistin-resistant subpopulations. Owen et al. [125] also found in vitro evidence of heteroresistance, suggesting that combination therapy may be advisable to prevent the emergence of colistin resistance during monotherapy.

CONCLUSIONS

Despite a reputation for relatively low virulence, multidrug-resistant Acinetobacter infection poses a formidable threat to patients. The cause of many outbreaks, this organism is increasingly endemic in the health care setting. Antimicrobial resistance is increasing, likely as a result both of the emergence of resistance in the context of antimicrobial pressure and of health care–associated transmission of drug-resistant strains. Multidrug-resistant Acinetobacter infections have an extremely high crude mortality rate and occur most frequently in severely ill patients. Although the attributable mortality of multidrug-resistant Acinetobacter infections is debatable, these infections are clearly associated with increased time on mechanical ventilation, in the ICU, and in the hospital. Treatment options are severely limited, and there have been, to our knowledge, no controlled trials to guide therapeutic choices. Carbapenems and colistin are the agents of choice for the most drug-resistant infections. The role of other agents and combination therapy remains unclear. More data are needed on the pharmacokinetics, pharmacodynamics, and appropriate dosing of colistin, especially in light of the discovery of heteroresistance. Given the lack of good therapeutic options, the development of new therapies, well-controlled clinical trials of existing regimens and antimicrobial combinations, more research, and greater emphasis on the prevention of health care–associated transmission of multidrug-resistant Acinetobacter infection are essential.

Acknowledgments

We thank Benedict John Frederick for his assistance developing figure 1.

Financial support. Centers for Disease Control and Prevention (1 K01 CI000300 and 1 R01 CI00530).

Potential conflicts of interest. T.M.P. has been on advisory boards for Pfizer, Replidyne, and 3M; has received recent research funding from 3M and Sage; and has received a speaker honorarium from Ortho McNeil. L.L.M.: no conflicts.

References


ANTIMICROBIAL RESISTANCE • CID 2008;46 (15 April) • 1259


Acinetobacter baumannii–calcoaceticus complex infection in the US
military health care system associated with military operations in Iraq.
44. Griffith ME, Lazarus DR, Mann PB, Boger JA, Hospenthal DR, Murray
CK. Acinetobacter skin carriage among US army soldiers deployed in
45. Griffith ME, Ceremuga JM, Ellis MW, Guymon CH, Hospenthal DR,
Murray CK. Acinetobacter skin colonization of US Army Soldiers.
infections in critically injured Canadian Forces soldiers. BMC Infect
Dis 2007; 7:95.
Acinetobacter spp infections with casualties from Iraq. Lancet Infect
baumannii isolates from the United Kingdom and the United States
that were associated with repatriated casualties of the Iraq conflict. J
49. Sunenshine RH, Wright MO, Maragakis LL, et al. Multidrug-resistant
Acinetobacter infection mortality rate and length of hospitalization.
50. Seifert H, Strate A, Pulverer G. Nosocomial bacteremia due to Aci-
etobacter baumannii: clinical features, epidemiology, and predictors
mortality in patients with Acinetobacter baemacteria. J Antimicrob
52. Falagas ME, Kopterides P, Siempos II. Attributable mortality of
Acinetobacter baumannii infection among critically ill patients. Clin Infect
Dis 2006; 43:389–90.
resistance in nosocomial Acinetobacter baumannii bacter-
54. Abbo A, Carmeli Y, Navon-Venezia S, Siegman-Igra Y, Schwaber MJ.
Impact of multi-drug-resistant Acinetobacter baumannii on clinical
infection on the mortality of burn patients. J Am Coll Surg 2006;
56. Blot S, Vandewoude K, Colardin F. Nosocomial bacteremia involving
Acinetobacter baumannii in critically ill patients: a matched cohort
57. Chen HP, Chen TL, Lai CH, et al. Predictors of mortality in Acine-
38:127–36.
59. Falagas ME, Kasiakou SK, Rafailidis PI, Zougaklis G, Morfou P.
Comparison of mortality of patients with Acinetobacter baumannii bac-
teraemia receiving appropriate and inappropriate empirical therapy.
60. The cost of antibiotic resistance: effect of resistance among Staph-
ylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, and
Pseudomonas aeruginosa on length of hospital stay. Infect Control
61. Garnacho J, Sole-Violan J, Sa-Borges M, Diaz E, Rello J. Clinical
impact of pneumonia caused by Acinetobacter baumannii in intubated
resistance among gram negative bacilli as causes of infections in inten-
sive care unit patients in the United States between 1993 and 2004.
63. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in Aci-
etobacter species and Pseudomonas aeruginosa. Clin Infect Dis
64. Falagas ME, Koletsi PK, Bliziotis IA. The diversity of definitions of
multidrug-resistant (MDR) and pandrug-resistant (PDR) Acinetobac-
ter baumannii and Pseudomonas aeruginosa. J Med Microbiol
65. Gales AC, Jones RN, Sader HS. Global assessment of the antimicrobial
activity of polymyxin B against 54 731 clinical isolates of gram-neg-
ative bacilli: report from the SENTRY antimicrobial surveillance pro-
66. Urban C, Mariano N, Rahal JJ, et al. Polymyxin B-resistant Acine-
etobacter baumannii clinical isolate susceptible to recombinant BPI and
67. Thomson MJ, Bonomo RA. The threat of antibiotic resistance in
gram-negative pathogenic bacteria: beta-lactams in peril! Curr Opin
68. Rice LB. Challenges in identifying new antimicrobial agents effective
for treating infections with Acinetobacter baumannii and Pseudomonas
69. fzl-Shah M, Woodford N, Livermore DM. Characterization of OXA-
25, OXA-26, and OXA-27, molecular class D beta-lactamases asso-
ciated with carbapenem resistance in clinical isolates of Acinetobacter
70. Brown S, Amyes S. OXA-β-lactamases in Acinetobacter: the story so
71. Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo-beta-lacta-
mases: the quiet before the storm? Clin Microbiol Rev 2005; 18:
306–25.
72. Lee K, Lee WG, Uh Y, Ha GY, Cho J, Chong Y. VIM- and
IMAP-type metallo-beta-lactamase-producing Pseudomonas spp. and
Acinetobacter spp. in Korean hospitals. Emerg Infect Dis 2003;
73. Bou G, Oliver A, Martinez-Beltran J. OXA-24, a novel class D beta-
lactamase with carbapenemase activity in an Acinetobacter baumannii
74. Mussi MA, Limansky AS, Viale AM. Acquisition of resistance to car-
bapenems in multidrug-resistant clinical strains of Acinetobacter ba-
umannii: natural insertional inactivation of a gene encoding a mem-
er of a novel family of beta-barrel outer membrane proteins. Antimicrob
75. Li J, Nation RL, Milne RW, Turnbull JD, Coulthard K. Evaluation of
collistin as an agent against multidrug-resistant gram-negative bacteria.
76. Fournier PE, Vallenet D, Barbe V, et al. Comparative genomics of
multidrug resistance in Acinetobacter baumannii. PLoS Genet 2006;
2:7.
77. Harris AD, McGregor JC, Furuno JP. What infection control inter-
ventions should be undertaken to control multidrug-resistant gram-
78. Jones RN, Sader HS, Fritsche TR, Rhomberg PR. Carbapenem sus-
ceptibility discords among Acinetobacter isolates. Clin Infect Dis
2006; 42:158.
79. Jones RN, Deshpande L, Fritsche TR, Sader HS. Determination of
epidemic clonality among multidrug-resistant strains of Acinetobacter
spp. and Pseudomonas aeruginosa in the MYSTIC Programme (USA,
80. Ikonomidis A, Pourarras S, Maniatis AN, Legakis NJ, Tsakris A. Dis-
cordance of meropenem versus imipenem activity against Acinetobac-
81. Brauers J, Frank U, Kresken M, Rodloff AC, Seifert H. Activities of
various beta-lactams and beta-lactam-beta-lactamase inhibitor com-
binations against Acinetobacter baumannii and Acinetobacter DNA
82. Higgins PG, Wipplinghoff H, Stefanik D, Seifert H. In vitro activities
of the beta-lactamase inhibitors clavulanic acid, sulbactam, and
ta-zobactam alone or in combination with beta-lactams against epide-
mycocercic resistance.
mio logically characterized multidrug-resistant Acinetobacter bauman-
83. Wood GC, Hanes SD, Croce MA, Fabian TC, Boucher BA. Com-
parison of ampicillin-sulbactam and imipenem-cilastatin for the treat-
ment of Acinetobacter ventilator-associated pneumonia. Clin Infect
84. Levin AS, Levy CE, Manrique AE, Medeiros EA, Costa SF. Severe
nosocomial infections with imipenem-resistant Acinetobacter bau-
mannii treated with ampicillin/sulbactam. Int J Antimicrob Agents
85. Seifert H, Stefanik D, Wisplinghoff H. Comparative in vitro activi-
ties of tigecycline and 11 other antimicrobial agents against 215 epide-
miologically defined multidrug-resistant Acinetobacter baumannii iso-
86. Pachon-Ibanez ME, Jimenez-Mejias ME, Pichardo C, Llanos AC, Pa-
chon J. Activity of tigecycline (GAR-936) against Acinetobacter bau-
87. Insa R, Cercenado E, Goyanes MJ, Morente A, Bouza E. In vitro
activity of tigecycline against clinical isolates of Acinetobacter bau-
mannii and Stenotrophomonas maltophilia. J Antimicrob Chemother
88. Jones RN, Ferraro MJ, Reller LB, Schreckenberger PC, Swenson JM, Sader HS. Multicenter studies of tigecycline disk diffusion suscepti-
89. Peleg AT, Potsoki BA, Rea R, et al. Acinetobacter baumannii blood-
stream infection while receiving tigecycline: a cautionary report. J
90. Reid GE, Grim SA, Aldeza CA, Janda WM, Clark NM. Rapid devel-
opment of Acinetobacter baumannii resistance to tigecycline. Phar-
91. Navon-Venezia S, Leavitt A, Carmeli Y. High tigecycline resistance in
multidrug-resistant Acinetobacter baumannii. J Antimicrob Chemother
92. Peleg AT, Adams J, Paterson DL. Tigecycline efflux as a mechanism
for nonsusceptibility in Acinetobacter baumannii. Antimicrob Agents
93. Ruzin A, Keeney D, Bradford PA. AdeABC multidrug efflux pump
is associated with decreased susceptibility to tigecycline in Acineto-
bacter calcoaceticus-Acinetobacter baumannii complex. J Antimicrob
94. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the
management of multidrug-resistant gram-negative bacterial infec-
95. Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic
for multidrug-resistant gram-negative bacterial infections. Lancet
96. Levin AS, Barone AA, Penco J, et al. Intravenous colistin as therapy
for nosocomial infections caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. Clin Infect Dis 1999; 28:
1008–11.
Acinetobacter baumannii ventilator-associated pneumonia: epidemi-
98. Holloway KP, Rouphael NG, Wells JB, King MD, Blumberg HM.
Polymyxin B and doxycycline use in patients with multidrug-resistant
Acinetobacter baumannii infections in the intensive care unit. Ann
for nosocomial infections caused by multidrug-resistant bacteria in the
Treatment of multidrug-resistant Acinetobacter baumannii ventilator-
associated pneumonia (VAP) with intravenous colistin: a comparison


