**Acinetobacter baumannii:** Epidemiology, Antimicrobial Resistance, and Treatment Options

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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-
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ologic profiles and coexistence of multiple strain types. Abbo 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).

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>

strategies 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 is not known.

In many health care institutions, endemic, multidrug-resistant Acinetobacter infection demonstrates complex epidemiologic profiles and coexistence of multiple strain types. Abbo 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]. Nemec 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 and are acquired by soldiers in medical facilities during the 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 re-review concluded that Acinetobacter infection or colonization is associated with increased mortality [52–54]. Many of these
Figure 1. Factors leading to the emergence and transmission of multidrug-resistant (MDR) Acinetobacter species. ICU, intensive care unit.

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-lactamas that hydrolyze and confer resistance to penicillins, cephalosporins, and carbapenems. AmpC cephalosporinase 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 glycycline 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 2. Studies of antimicrobial combinations against multidrug-resistant *Acinetobacter* infection.

<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.</td>
<td>2001</td>
<td>In vitro</td>
<td>Colistin and rifampin</td>
<td>In vitro synergy</td>
</tr>
<tr>
<td>Petrosillo et al.</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.</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>Glessen et al.</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.</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.</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.</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.</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.</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.</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.</td>
<td>2005</td>
<td>In vitro</td>
<td>Meropenem and sulbactam</td>
<td>In vitro synergy</td>
</tr>
<tr>
<td>Sader et al.</td>
<td>2005</td>
<td>In vitro</td>
<td>Cefepime and sulbactam</td>
<td>In vitro synergy</td>
</tr>
<tr>
<td>Kasiakou et al.</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>Sobieszczzyk et al.</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.

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