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Acinetobacter Infection in the ICU

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The increase of infections worldwide caused by multidrug-resistant organisms has resulted in a growing challenge to provision of adequate patient care, especially to patients who are critically ill. Professional societies, including the Infectious Diseases Society of America, have sought legislation to increase antimicrobial research and development to combat these multidrug-resistant pathogens [1]. One of the identified pathogens of primary concern is the gram-negative bacteria of the genus *Acinetobacter*. Although historically considered organisms of low virulence (and pathogenicity), *Acinetobacter* are increasingly recognized as the cause of infections, especially in intensive care units.

The bacteria

The taxonomy of *Acinetobacter* has not been defined adequately. Currently, the genus includes named (Box 1), proposed, and genomic species (or genospecies) (www.bacterio.cict.fr/a/acintobacter.html). Most disease is caused by a complex of four phenotypically similar genospecies (1, 2, 3, and 13TU). Two of them are named *A calcoaceticus* (genospecies 1) and *A baumannii* (genospecies 2), and the group are commonly referred to as the *A calcoaceticus-A baumannii* complex. *Acinetobacter* are gram-negative aerobic coccobacilli with a tendency to retain crystal violet on Gram

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Box 1. Named species of *Acinetobacter*

Acinetobacter (genus) (1954)
- *A baumannii* (1986)
- *A baylyi* (2003)
- *A bouvetii* (2003)
- *A calcoaceticus* (1911)
- *A gerneri* (2003)
- *A grimontii* (2003)
- *A haemolyticus* (1963)
- *A johnsonii* (1986)
- *A junii* (1986)
- *A lwoffii* (1940)
- *A parvus* (2003)
- *A radioresistens* (1988)
- *A schindleri* (2001)
- *A tandoii* (2003)
- *A tjernbergiae* (2003)
- *A towneri* (2003)
- *A ursingii* (2001)

Year in parentheses represents year of description in the literature.

Data from Euzeby JP. List of prokaryotic names with standing in nomenclature. Available at: http://www.bacterio.cict.fr/a/acinetobacter.html.

staining, thus they are occasionally misidentified as gram-positive bacteria. They can persist on inanimate surfaces for prolonged periods of time (3 days to 5 months) and can be detected on various hospital equipment, including bedrails, curtains, and ventilation equipment (eg, ventilation [ambu] bags and ventilation filters) [2–4]. Colonization of patients, health care workers, and healthy individuals occurs, although there is substantial genotypic and phenotypic variability between isolates recovered from these groups; isolates from patients with prolonged hospitalizations typically are more resistant [5–7]. Long-term colonization has been documented [8].

Epidemiology

Within the United States, *Acinetobacter* is a common cause of nosocomial infections. It caused 6.9% of nosocomial pneumonias, 2.4% of bloodstream, 2.1% of surgical site, and 1.6% of urinary tract infections in 2003 [9]. Outbreaks are recognized as being associated with hospital equipment, including that used in wound treatment (pulsatile lavage) [10]. An increasing incidence of *Acinetobacter* infections is being recognized

worldwide. In one report from an Israeli teaching hospital, *Acinetobacter* advanced from the fourth most common bacteria resulting in bloodstream infections in 1997 to the most frequent cause in 2002 [11]. Since the involvement of the US military in overseas operations in Iraq and Afghanistan, numerous casualties have been infected or colonized with *Acinetobacter* [12–14]. Disease in this group of patients has included bone and soft tissue infections after combat trauma, pneumonia, bloodstream, and central nervous system infections. Currently, the most likely source of these infections seems to be nosocomial transmission throughout the medical evacuation chain in Iraq, Germany and US hospitals [15]. Isolates recovered from military personnel are genetically related or identical to isolates recovered in England and throughout Europe [16,17]. Apart from the military, there also have been reports of *Acinetobacter* in civilian patients medically evacuated across international borders [18]. Interhospital transmission of resistant *Acinetobacter* has been associated with transferring patients between hospitals [19]. The role of community-associated infections, especially pneumonia, is under debate because patients reported in these studies are often at higher risk because of comorbidities [20–23].

Virulence

The true disease impact (attributable morbidity and mortality) of *Acinetobacter* has been an ongoing debate for the past 30 years, chiefly because of the difficultly of differentiating colonization from infection with these organisms. The recent military experience with *Acinetobacter* has not been able to find attributable mortality in our young, healthy population, but rather an association with longer hospital stays and more surgical procedures [12–14,24]. Numerous studies in nonmilitary patients have reported increased morbidity, including longer length of hospitalizations, more intensive care unit days, and an overall increase in hospital costs [25–27]. Some studies have reported attributable mortality, especially in patients with imipenem-resistant isolates who were not provided adequate therapy initially [28–30].

Risk factors associated with poor outcomes with *Acinetobacter* infections include elevated APACHE II scores, underlying chronic disease, mechanical ventilation, multiple trauma, neutropenia, previous antimicrobial exposure, blood transfusion, and colonization density [31–35]. Interestingly, appropriate or inappropriate antimicrobial therapy has not always been predictive of mortality [13,30,36].

Antimicrobial resistance

One of the hallmarks of *Acinetobacter* is its ability to develop resistance to a wide range of antimicrobial agents. Resistance has been associated with an 86-kb chromosomal region, or resistance island, that is responsible for

production of resistance to a large number of antimicrobial agents [24,37,38]. Surveillance studies have revealed an increase of multidrug-resistant isolates being recovered from Europe, the Asian-Pacific region, Latin America, and North America over the last 3 to 5 years [38–40]. *Acinetobacter* isolates have been noted to develop resistance while on therapy even to recently approved antimicrobial agents, such as tigecycline [38,41,42]. Different resistance patterns have been reported even within hospital outbreaks with proven clonal isolates of *Acinetobacter*, which makes the antibiotic profile (antibiogram) an inaccurate method for assessing clonality [43–45]. This inaccuracy makes evaluation or even recognition of *Acinetobacter* outbreaks in a hospital environment that much more difficult. Emergence of resistance within any health care facility is likely caused by antimicrobial pressure and cross-transmission between patients with resistant isolates [46–48].

Management of *Acinetobacter* infections is challenging because of the broad array of resistance and the pathogen's ability to rapidly develop new resistance. Even the testing for antimicrobial resistance in *Acinetobacter* continues to present difficulties to the treatment of infections because of these bacteria. The standard for determining antimicrobial resistance profiles—broth microdilution—exhibits subtle differences in growth patterns, particularly for β-lactams, which leads to discrepancies in defining the level of resistance for ampicillin-sulbactam, piperacillin, cefepime, cefotaxime, ceftriaxone, tetracycline, and doxycycline [38,49]. The agent with the most consistent in vitro activity, colistin, is faced with its own testing challenges. Results produced by E-test do not always correlate with those obtained by microdilution testing [50].

Recently, in vitro testing of *Acinetobacter* revealed subpopulations that are resistant (heteroresistance) to colistin, which results in growth of the bacteria in the face of high levels of colistin. The recovered heteroresistant organisms may be less fit, have increased susceptibilities to other antimicrobial agents, and have decreased ability to form biofilms [38,51–53]. Colistin susceptibility testing in the clinical microbiology laboratory is commonly performed by disk diffusion with colistin sulfate–impregnated disks. In clinical practice, colistimethate sodium is used because it is less toxic than colistin sulfate and is available in intravenous formulations. Colistimethate sodium is also less potent than colistin sulfate [54].

In vitro synergy testing has been evaluated with numerous combinations, including azithromycin, rifampin, doxycycline, and imipenem. These studies have reported variable synergistic and antagonistic activity and varying results based on different testing methods used [52,53,55–57]. When synergistic combinations have been tested in animal models, the outcome benefit between mono- and dual therapy also has been mixed [58–60]. An assessment of an infrequently used testing method—peak and trough serum bactericidal activity—found that peak concentrations of antimicrobial agents had a moderate correlation but not causal association with outcome [61].

Antimicrobial selection

Antimicrobial agents that are typically active against *Acinetobacter* infections are the carbepenems (ie, imipenem/cilastatin and meropenem) (although isolates are typically more susceptible to imipenem), amikacin, sulbactam, colistin, rifampin, and tetracyclines. In some studies, less than 75% of isolates are susceptible to many or all of these agents [38–40]. The use of combination therapy is controversial in the treatment of gram-negative bacterial infections in general, because there is no proven improvement in mortality or decrease in length of stay, and some studies report increased toxicity [62,63]. At this time, therapy for *Acinetobacter* infections should rely on in vitro testing to select antimicrobial agents (Table 1).

In the face of broad-spectrum antimicrobial resistance, colistin typically retains activity; however, the clinical impact of colistin heteroresistance reported with some isolates is currently unknown. Colistin was historically considered too nephrotoxic and neurotoxic for routine clinical use, but recent use revealed that its toxicity profile is not dissimilar to other agents used in critically ill patients [54,64]. There is concern about the penetration

Table 1
Antimicrobial agents suggested for use in the treatment of *Acinetobacter* infections

Antimicrobial class	Specific agent (route)	Comments
Polymyxin	Colistimethate sodium (IV)	Agents with the overall highest susceptibility rates Concern of the recently described heteroresistance
Carbapenem	Imipenem-cilastatin (IV)	Imipenem typically is associated with higher susceptibility rates than meropenem
Aminoglycoside	Amikacin (IV)	Amikacin typically is associated with higher susceptibility rates than tobramycin, which are higher than gentamicin
Tetracycline	Minocycline (PO)	Minocycline typically is associated with higher susceptibility rates than doxycycline, which are higher than tetracycline There are no CLSI criteria for tigecycline susceptibility; however, clinical resistance has been reported and can develop on therapy These are bacteriostatic agents with unproven efficacy in severely ill patients Minocycline is available only in oral formulation in the United States

Abbreviations: CLSI, Clinical and Laboratory Standards Institute (formerly National Committee on Clinical Laboratory Standards [NCCLS]); IV, intravenous; PO, oral.

of this agent into lung tissue when given parenterally, although clinical success has been reported. There currently seems to be increased use of colistin in a nebulized form, although this is not an FDA-approved indication for this drug [65,66]. Colistin therapy for patients with imipenem-resistant isolates seems to have equal efficacy to therapy with imipenem in patients with imipenem-susceptible isolates [64].

Dosing of colistin is based on the manufacturer recommendations, with doses of 2.5 to 5.0 mg/kg/d in two to four doses suggested for Coly-Mycin M Parenteral (Monarch Pharmaceutical, Inc., Bristol, Tennessee) and 1 to 2 million IU three times a day for Colomycin Injection (Pharmax Limited, Bexley, Kent, United Kingdom) [54]. In vitro data looking at postantibiotic effect and the development of heteroresistant colonies suggest that more frequent dosing may allow improved efficacy and decrease toxicity [67,68]. Tetracyclines, including doxycycline, minocycline, and tigecycline, have activity in vitro and seem to be effective in reports of clinical use. Further evaluation is needed because these agents are only bacteriostatic and resistance occurring on therapy has been described [69,70]. Positive results with the use of doxycyline or the combination of polymyxin B and doxycycline have been reported [69]. Rifampin is another antimicrobial agent that typically retains in vitro activity against *Acinetobacter*. As in other indications for use of this agent, rifampin should not be used as monotherapy in these infections. There have been reports of rifampin resistance developing when this agent is used in combination with other antibiotics to which resistance is known [71].

The most common infections seen with *Acinetobacter* are nosocomial pneumonias, bacteremia, surgical site infections, and urinary tract infections, but occasionally patients develop endocarditis or central nervous system infections. For endocarditis, especially prosthetic valve infections, the overall outcome is favorable after initiating therapy with an active antimicrobial agent [72]. Central nervous system infections also typically have good outcomes. Imipenem and meropenem have adequate central nervous system penetration. In the case of multidrug-resistant isolates infecting the central nervous system, combination therapy, including systemic and intraventricular or intrathecal colistin therapy, has been used with overall good outcomes [73–75]. Some courses of therapy were associated chemical meningitis [73,74].

Alternative techniques to improve efficacy of antimicrobial therapy, especially with isolates that are resistant to all agents tested in vitro, include prolonging infusion times (meropenem and imipenem) and using continuous infusion (colistin) [76,77]. Sulbactam, although traditionally thought not to have significant antibacterial activity when used alone, has activity against *Acinetobacter*. High doses of ampicillin-sulbactam have been used clinically and seem to be effective in treating infections without report of increased adverse events [78]. Randomized, controlled studies are needed to determine the ideal antimicrobial therapy and the best methods to deliver

the selected agents in the treatment of infections caused by *Acinetobacter* [79].

Infection control

Given the broad array of resistance associated with *Acinetobacter*, the role of preventing spread of this pathogen to other patients is paramount. The recently released Centers for Disease Control and Prevention (CDC) infection control recommendations indicate that hospitals with increased rates of multidrug-resistant *Acinetobacter* should take more aggressive infection control measures to control and prevent further nosocomial transmission [80]. Although challenging, implementation of aggressive infection control measures can control outbreaks of *Acinetobacter* infections [81–83]. Measures that are more likely to be effective include increased staff education, single-use items for individual patients, hand hygiene, cohorting, and isolation. Antibiotic control programs also seem effective in modifying the development of resistance to antibiotics under restriction [84]. These control programs may lead to the development of resistance to other antimicrobials, however, as was the case in one report in which controlling the use of ciprofloxacin and ceftazidime resulted in increased *Acinetobacter*-associated imipenem and amikacin resistance [84]. Antibiotic control programs also can alter (select for other) pathogens responsible for infections within the hospital. Because antibiograms cannot always predict the clonality of an outbreak strain, consideration of molecular typing *Acinetobacter* isolates should be considered.

Summary

Acinetobacter is a formidable challenge to managing critically ill patients. This pathogen's ability to rapidly develop antimicrobial resistance to all currently available antimicrobial agents is concerning because increasing data support attributable mortality to these bacteria when associated with hospitalized patients with comorbidities and severe illness. Individual patient therapy should be directed by in vitro testing. Although imipenem-cilastatin seems to be a preferred agent for treating these infections, resistance to this antimicrobial also seems to be increasing. The role of dual therapy is currently unclear and might be associated with increased toxicities without proven synergy or ability to prevent the development of resistance. Colistin seems to be a reliable alternative treatment agent, but reports of the development of resistance in vitro after drug exposure are concerning. Infection control and antibiotic control measures might have the greatest impact on these bacteria. Continued efforts are needed to develop new antimicrobial agents against this pathogen and assess the ideal currently available agents.

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