REVIEW ARTICLE

CURRENT CONCEPTS

Acinetobacter Infection

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Acinetobacter is a gram-negative coccobacillus (Fig. 1)[1,2] that during the past three decades has emerged from an organism of questionable pathogenicity to an infectious agent of importance to hospitals worldwide.[3,4] Approximately one quarter of the PubMed citations for "nosocomial acinetobacter" in the past 20 years appeared in 2005 and 2006. Acinetobacter infections have long been clinically prominent in tropical countries, have been a recurrent problem during wars and natural disasters, and have recently caused multihospital outbreaks in temperate climates. Most alarming are the organism's ability to accumulate diverse mechanisms of resistance, the emergence of strains that are resistant to all commercially available antibiotics,[5] and the lack of new antimicrobial agents in development.[6] At more than 300 U.S. hospitals surveyed by the Centers for Disease Control and Prevention (CDC), rates of carbapenem resistance in 3601 isolates of *Acinetobacter baumannii*, clinically the most important of 25 acinetobacter genospecies,[1] increased from 9% in 1995 to 40% in 2004.[7]

Acinetobacter was first described in 1911 as *Micrococcus calco-aceticus*.[8] Since then, it has had several names, becoming known as acinetobacter in the 1950s.[1,2] Its natural habitats are water and soil, and it has been isolated from foods, arthropods, and the environment.[3] In humans, acinetobacter can colonize skin, wounds, and the respiratory and gastrointestinal tracts. Some strains of acinetobacter can survive environmental desiccation for weeks, a characteristic that promotes transmission through fomite contamination in hospitals.[1,9]

Acinetobacter is easily isolated in standard cultures but is relatively nonreactive in many biochemical tests commonly used to differentiate among gram-negative bacilli. This can delay isolate identification by a day. *A. baumannii*, *A. calcoaceticus*, and *A. lwoffii* are the acinetobacter species most frequently reported in the clinical literature. Because it is difficult to differentiate among acinetobacter species on the basis of phenotypic characteristics, the term *A. calcoaceticus–A. baumannii* complex is sometimes used.[1]

MECHANISMS OF RESISTANCE

Resistance mechanisms that are expressed frequently in nosocomial strains of acinetobacter include β-lactamases, alterations in cell-wall channels (porins), and efflux pumps (Fig. 2). *A. baumannii* can become resistant to quinolones through mutations in the genes *gyrA* and *parC* and can become resistant to aminoglycosides by expressing aminoglycoside-modifying enzymes.[10]

AmpC β-lactamases are chromosomally encoded cephalosporinases intrinsic to all *A. baumannii*. Usually, such β-lactamases have a low level of expression that does not cause clinically appreciable resistance; however, the addition of a promoter

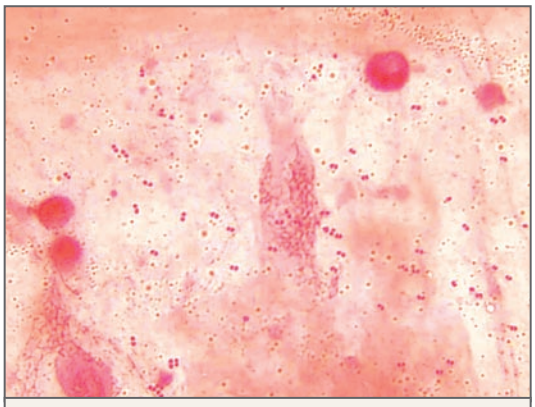

Figure 1. Gram's Staining of Sputum Specimen from a Patient with Suspected Ventilator-Associated Pneumonia.

Acinetobacter baumannii was recovered from this specimen, which shows gram-negative coccobacilli[1]; the diplococcal features help explain one of the early designations of acinetobacter as neisseria.[2] Bacilli may predominate, depending on the culture medium.[1] Photomicrograph courtesy of Kathleen G. Beavis, M.D.

insertion sequence, IS*Aba*1, next to the *ampC* gene increases β-lactamase production, causing treatment-limiting resistance to cephalosporins.[11] Although porin channels in *A. baumannii* are poorly characterized, it is known that reduced expression or mutations of bacterial porin proteins can hinder passage of β-lactam antibiotics into the periplasmic space, leading to antibiotic resistance.

Overexpression of bacterial efflux pumps can decrease the concentration of β-lactam antibiotics in the periplasmic space. To cause clinical resistance in acinetobacter, efflux pumps usually act in association with overexpression of AmpC β-lactamases or carbapenemases. In addition to removing β-lactam antibiotics, efflux pumps can actively expel quinolones, tetracyclines, chloramphenicol, disinfectants, and tigecycline.[12]

Clinically most troubling have been acinetobacter's acquired β-lactamases, including serine and metallo-β-lactamases, which confer resistance to carbapenems.[10] Acquired extended-spectrum β-lactamase carriage occurs in acinetobacter but is not as widespread as in *Klebsiella pneumoniae* or *Escherichia coli*.[13]

A recent report described a "resistance island" containing 45 resistance genes within the acinetobacter genome.[14] Resistance islands comprise one or more virulence genes located in a mosaic distribution within a large genomic region.[15]

Currently, the term "multidrug resistance" in reference to acinetobacter does not have a standard definition. It is sometimes used to denote resistance to three or more classes of drugs that would otherwise serve as treatments for acinetobacter infections (e.g., quinolones, cephalosporins, and carbapenems). The term "panresistance" has been used to describe strains of acinetobacter that are resistant to all standard antimicrobial agents tested (except colistin).[16]

EPIDEMIOLOGY

Historically, acinetobacter has been a pathogen of hot and humid climates, where it has been a major cause of infections, particularly in intensive care units (ICUs), and sometimes a cause of community-acquired pneumonia.[17-21] Acinetobacter was cited as the cause of 17% of cases of ventilator-associated pneumonias in a Guatemalan ICU — second only to pseudomonas, which caused 19% of cases — years before becoming a concern in ICUs in the United States.[21] Over the past two decades, acinetobacter infections have become an increasingly common nosocomial problem in temperate climates.

HEALTH CARE–ASSOCIATED INFECTIONS

Most information about health care–associated acinetobacter infections is based on outbreak investigations.[22] Infections with *A. baumannii* tend to occur in debilitated patients, mostly in ICUs. Residents of long-term care facilities, particularly facilities caring for ventilator-dependent patients, are at increased risk. In addition to a stay in the ICU, risk factors for colonization and infection are recent surgery, central vascular catheterization, tracheostomy, mechanical ventilation, enteral feedings, and treatment with third-generation cephalosporin, fluoroquinolone, or carbapenem antibiotics.[23,24]

Acinetobacter outbreaks have been traced to common-source contamination, particularly contaminated respiratory-therapy and ventilator equipment, to cross-infection by the hands of health care workers who have cared for colonized or infected patients or touched contaminated fomites, and to the occasional health care worker who carries an epidemic strain.[22,25,26] Once introduced into a hospital, acinetobacter often has an epidemiologic pattern of serial or overlapping outbreaks caused by various multidrug-resistant

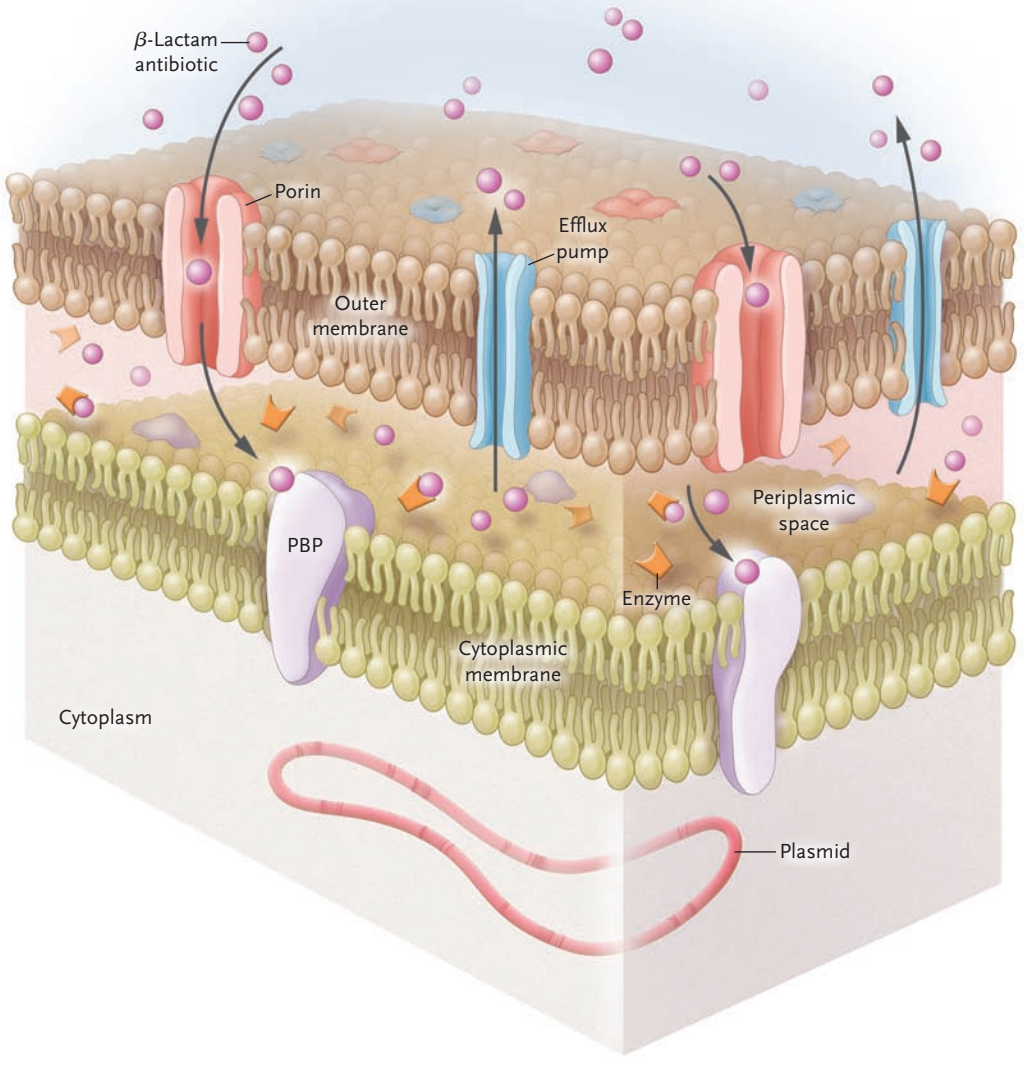

Figure 2. Potential Mechanisms of Antimicrobial Resistance in Acinetobacter.

Acinetobacter, like other gram-negative bacteria, has an outer membrane and a cytoplasmic membrane, between which (the periplasmic space) β-lactamases (carbapenemases, AmpC β-lactamases, and extended-spectrum β-lactamases) reside. Penicillin-binding proteins (PBPs), located at the level of the cytoplasmic membrane, constitute the final targets of β-lactam antibiotics. To bind to these targets, antibiotics must traverse the outer membrane through porin channels (outer-membrane proteins) into the periplasmic space. Once in the periplasmic space, β-lactam antibiotics bind to PBPs or are actively expelled from the bacterial structure through efflux pumps. Acinetobacter can harbor integrons and transposons, genetic elements on the bacterial chromosome or on plasmids, that can carry multiple cassettes with resistant genes (e.g., extended-spectrum β-lactamases and metallo-β-lactamases).

strains, with subsequent endemicity of multiple strains and a single endemic strain predominating at any one time.[22] Prolonged colonization — for up to 42 months and affecting 17% of patients in one study — may contribute to the endemicity of *A. baumannii* after an outbreak.[27]

Dramatic multihospital outbreaks have been described in Brooklyn, Chicago, northwestern Indiana, Detroit, and cities in Europe, South America, Africa, Asia, and the Middle East.[5,23,28,29] A single-strain outbreak — monoclonal, as identified by molecular typing — of carbapenemase-producing (OXA-40) acinetobacter was described recently in Chicago and neighboring northwest-

ern Indiana.[5] Since 2005, at least five hospitals, three long-term care facilities, and more than 200 patients have been affected by this outbreak. In a French multicity, monoclonal outbreak of multidrug-resistant *A. baumannii*, 290 isolates were collected in 53 hospitals from April 2003 to June 2004. The epidemic strain harbored an extended-spectrum β-lactamase known as VEB-1. Most infected patients were in ICUs, medical wards, or long-term care facilities.[28]

The occurrence of monoclonal outbreaks in multiple hospitals suggests interinstitutional spread, presumably by movement of patients or personnel, or exposure to common-source contamination of food or equipment. Such outbreaks highlight the importance of ongoing surveillance, interfacility communication, and measures to prevent the introduction of acinetobacter into, and the spread from, nursing homes.

SEASONAL VARIATION

Since 1974, the CDC has noted higher rates of nosocomial acinetobacter infections in the summer than in other seasons.[30,31] McDonald and colleagues evaluated 3447 acinetobacter infections in adults and children in ICUs that were reported to the CDC between 1987 and 1996; infection rates were approximately 50% higher from July to October than at other times of the year.[31] Possible explanations include warmer, more humid ambient air, which favors growth of acinetobacter in its natural habitats, and potentially preventable environmental contaminants, such as condensate from air-conditioning units, which has been implicated as a cause of epidemic acinetobacter infections.[31]

COMMUNITY-ACQUIRED INFECTIONS

Community-acquired infections with acinetobacter have been reported in Australia and Asia. These infections were characterized by pharyngeal carriage of the organism, aggressive pneumonia, and high case fatality rates and were linked to alcoholism and cancer.[17-19] The reason for the higher prevalence of acinetobacter infections in certain geographic areas is not known, but it may be due in part to differences in temperature and humidity that influence colonizing bacteria.

In the United States, community-acquired infections are rare. In 1979, *A. baumannii* pneumonias occurred in three foundry employees who worked within meters of each other. Postmortem evaluations in two of the patients showed severe underlying pneumoconiosis. *A. baumannii* was isolated from foundry air, but the source was not identified.[32]

MILITARY PERSONNEL

Descriptions of the role played by acinetobacter infections during war date to the 1955 report of bloodstream infection with a presumed strain of acinetobacter (then called achromobacter) in a Korean War military recruit.[33] During the Vietnam War, Tong and colleagues reported on 63 soldiers with soft-tissue acinetobacter infections.[34,35] Most recently, *A. baumannii* infections have been reported among U.S. military personnel injured in the Middle East.[36-40]

From January 2002 to August 2004, 85 bloodstream infections with *A. baumannii* were identified in soldiers in two military referral hospitals; the soldiers had been injured during Operation Enduring Freedom in Afghanistan and Operation Iraqi Freedom in the Iraq–Kuwait region. A total of 35% of the isolates were susceptible only to imipenem, and 4% showed resistance to all standard drugs.[36] According to another report, among 142 acinetobacter isolates recovered from October 2003 to November 2005, strains from deployed personnel showed a lower rate of susceptibility to imipenem than isolates from nondeployed personnel (63% vs. 87%, $P<0.01$).[37]

Several studies have assessed possible sources of wartime acinetobacter infections. Griffith and colleagues reported the results of skin cultures from 102 active-duty army personnel in Iraq; none of 303 samples yielded *A. baumannii*,[38] arguing against preinjury colonization. However, in an investigation of an outbreak, acinetobacter was recovered from environmental cultures of critical care treatment areas in seven field hospitals in the Iraq–Kuwait region.[39] Finally, 16 unique resistance genes were described recently among eight major clones of acinetobacter recovered from infected soldiers.[40] This heteroclonality and reappearance of acinetobacter in personnel participating in several military actions over the past 50 years suggest multiple sources, including local foods (also a potential source of global spread), contamination of wounds in the battlefield, and environmental spread and cross-infection in field and referral hospitals.

DISASTERS

Several recent disasters further suggest that acinetobacter should be included in the microbiologic differential diagnosis of soft-tissue infections after exposure to a tropical environment and that imported strains can cause widespread contamination and cross-infection in the hospital environment. After the Southeast Asia tsunami on December 24, 2004, a total of 17 people in critical condition were evacuated to Germany; all had severe trauma from floating debris, including large soft-tissue injuries and fractures. Multidrug-resistant acinetobacter was isolated from 20% of wounds and from blood and respiratory secretions.[41] *A. baumannii* was the most prevalent nosocomial pathogen reported in a Turkish ICU in which casualties of the 1999 Marmara earthquake were treated[42]; *A. baumannii* had previously been isolated only rarely in this ICU. After the 2002 terrorist bombing in Bali, a patient infected with *A. baumannii* was transferred to a Swiss ICU for patients with burn injuries and became the presumed source of extensive environmental contamination and an ICU outbreak.[43]

CLINICAL MANIFESTATIONS

The most frequent clinical manifestations of acinetobacter infection are ventilator-associated pneumonia and bloodstream infections.[7] Vascular catheters and the respiratory tract have been the most frequent sources of acinetobacter bacteremias,[44,45] for which crude mortality rates parallel those attributed to other gram-negative bacilli (28 to 32%).[46]

In a study of specimens from 10,852 patients with bloodstream infections, collected at 49 U.S. hospitals from 1995 to 1998, the proportion of infections due to acinetobacter was 1.5%, and 36% of the acinetobacter infections were polymicrobial. The most common coisolates were skin flora — coagulase-negative staphylococci or enterococci[46] — suggesting that some blood isolates represented specimen contamination from skin or environmental strains.[47,48] Nonetheless, a study of 48 patients with multidrug-resistant *A. baumannii* bacteremias, who were matched for severity of illness to a control group with infections from strains susceptible to treatment with drugs, showed that the group with resistant strains had a 21.8% attributable mortality, higher hospitalization costs, and longer ICU and hospital stays.[49] It is unclear whether such outcomes are due to strain virulence or whether they could be avoided by the prompt use of appropriate therapy.[50]

Acinetobacter pneumonia occurs predominantly in ICU patients who require mechanical ventilation and tends to be characterized by a late onset. Affected patients spend more days in the ICU and on a ventilator before having positive cultures than do patients with pneumonias caused by other gram-negative bacilli or uninfected patients.[24,51] The clinical effect of ventilator-associated acinetobacter pneumonias has been variable. A recent study showed higher mortality among patients with multidrug-resistant acinetobacter infections than among patients infected with susceptible acinetobacter strains or uninfected patients; however, when the severity of illness and underlying diseases were considered, the main difference was that patients with multidrug-resistant acinetobacter infections had longer hospital and ICU stays.[52]

In other studies, mortality among patients with pneumonia due to multidrug-resistant acinetobacter was similar to that among patients with infection caused by other pathogens[24] or among controls (with or without pneumonia) matched for severity of illness and length of ICU stay,[53] suggesting that coexisting conditions were the major predictors of the outcome or that in some cases acinetobacter may have been a colonizer rather than a pathogen.

TREATMENT

Infections caused by antibiotic-susceptible acinetobacter isolates have usually been treated with broad-spectrum cephalosporins, β-lactam–β-lactamase inhibitor combinations (e.g., a combination that includes sulbactam, a drug marketed only in combination intravenous products in the United States), or carbapenems (e.g., imipenem or meropenem, although there are reports of discordant susceptibility to carbapenems[54]), used alone or in combination with an aminoglycoside.[55] The duration of treatment is generally similar to that for infections caused by other gram-negative bacilli, is largely empirical, and depends mostly on the site of infection.

For infections caused by multidrug-resistant isolates, antibiotic choices may be quite limited;

the most active agents in vitro are the polymyxins — polymyxin B and polymyxin E (colistin).[23,56,57] Polymyxins are cationic detergents that disrupt bacterial cytoplasmic membranes, causing leakage of cytoplasmic contents.[58] Clinicians abandoned polymyxins in the 1960s and 1970s, prompted by problems of nephrotoxicity and neurotoxicity (mostly paresthesias).[59]

The emergence of multidrug-resistant gram-negative bacilli has brought polymyxins back into use during the past few years; recent studies show less toxicity, possibly because of lower doses, different drug formulations, and careful ICU monitoring.[59] Current nephrotoxicity rates range up to 36%, and neurotoxicity is now uncommon.[59] The main side effect of inhaled colistin — used in the past for prevention and more recently for treatment of ventilator-associated pneumonia — is bronchoconstriction.[56,59] Recently, in vitro studies have suggested colistin heteroresistance in some phenotypically susceptible acinetobacter strains,[60,61] but the clinical importance of this phenomenon is unknown.

Tigecycline, a new glycylcycline antibiotic, is another drug that has been active in vitro and clinically against some multidrug-resistant strains of *A. baumannii*[47,62]; however, development of resistance to tigecycline has been reported recently.[63] In addition, in some outbreaks of acinetobacter infections, most isolates were not susceptible to tigecycline.[5]

Only limited conclusions can be drawn from studies of resistant acinetobacter infections[64-76] (Table 1). These studies have been mostly retrospective, small case series that often included a mix of patients with infections at different sites, and in some of the studies, combined outcomes were reported for grouped cases of multidrug-resistant bacteria. In many series, intravenous colistin has shown success rates of 50% or more for the treatment of pneumonia, but a success rate of only 25% was reported in one series of 20 cases.[72] Kwa and colleagues used inhaled colistin as monotherapy in 17 patients with acinetobacter pneumonia and reported clinical improvement in 57.1%.[77]

Data on the treatment of bloodstream infections are even more limited. During the acinetobacter outbreak in Chicago and northwestern Indiana, 81 bloodstream infections were treated. In two thirds of the cases, only a single blood culture was positive; in 25% of patients, vascular catheters were changed before the first negative

Table 1. Examples of Treatment Regimens and Outcomes of Infections Due to Multidrug-Resistant *Acinetobacter baumannii*.*

Site of Infection	No. of Patients	Antimicrobial Dose†	Mean Duration of Therapy	Clinical Improvement	Mortality‡	Side Effects
			days		*percent of patients*	
Lung[64]	27	Ampicillin–sulbactam (18 g of ampicillin and 9 g of sulbactam or 24 g and 12 g, respectively per day, IV)	8	67	48	Rash, 7; renal failure, 4; diarrhea, 4
Lung[65]	12	Ampicillin–sulbactam (up to 12 g of ampicillin and 6 g of sulbactam per day, IV)	14	75	17	None
Lung[66]	16	Colistin (1×10^6 IU 3 times/day, inhaled) and rifampin (10 mg/kg of body weight every 12 hr, IV)	15	100	0	Elevated liver-function values, 12
Lung[67]	7	Colistin ($1.5–6\times10^6$ IU divided into 3 or 4 doses/day, inhaled; 5 patients also received $1–3\times10^6$ IU every 8 hr, IV)§	10 (inhaled colistin); 17 (IV colistin)	86	14	None
Lung[68]	21	Colistin (2.5–5 mg/day, divided in 3 doses, IV)	15	57	38 (Attributable)	Renal failure, 24
	14	Imipenem (2–3 g/day, IV)	13	57	36 (Attributable)	Renal failure, 43
Lung[69]	8	Polymyxin B (2.5–3.0 mg/kg, IV, then adjusted for renal function, with or without about 2.5 mg/kg/day, divided into 4 doses, inhaled)	19	NA	35 (Attributable)	Renal failure, 6; neurotoxicity, 7¶
Lung[70]	7	Doxycycline (100 mg every 12 hr, IV) or minocycline (100 mg every 12 hr, IV)	14	86	14 (Attributable)	NA
Lung[71]	4	Imipenem (500 mg 4 times/day, IV) and rifampin (600 mg every 12 hr, IV)	12	50	50	NA

Bloodstream[65]	13	Ampicillin–sulbactam (up to 12 g of ampicillin and 6 g of sulbactam/day, IV)	14	46	38	None
Bloodstream[66]	9	Colistin (2×10^6 IU 3 times/day, IV) and rifampin (10 mg/kg every 12 hr, IV)	15	100	0	Elevated liver-function values, 11
Central nervous system[72]	5	Colistin (2.5–5.0 mg/kg/day, divided into 2 or 3 doses, IV)	13	80	NA	Renal failure, 27¶
Lung, bloodstream, intraabdominal site, urinary tract, bone, or central nervous system[73]	48	Polymyxin B (1.5–2.5 mg/kg/day, divided into 2 doses, IV)	14	NA‖	20‖	14¶
Lung, bloodstream, or surgical site[74]	33 4	Polymyxin B (1.5–2.5 mg/kg/day, divided into 2 doses, IV) Doxycycline (100 mg every 12 hr, IV)	NA NA	76 50	9 (Attributable) 0 (Attributable)	Renal failure, 21; neurotoxicity, 6 None
Lung, bloodstream, intraabdominal site, urinary tract, skin, or sinus[75]	71	Colistin (5 mg/kg/day, divided into 2 doses, IV)	12	81	46	Renal failure, 31

* IV denotes intravenous, and NA not available.
† Doses shown are for patients with normal renal function. No patients had *A. baumannii* isolates that were carbapenem-susceptible, except for those treated with imipenem by Garnacho-Montero et al.[68] One milligram of colistin base is contained in 2.4 mg of colistimethate sodium and equals 30,000 IU. Because of differences in products manufactured in different countries, package inserts and the original articles cited here should be checked to verify dosages.[76]
‡ The value given is for crude mortality (or was not specified as crude or adjusted), unless otherwise noted.
§ Two patients with aminoglycoside-susceptible *A. baumannii* also received aminoglycoside intravenously.
¶ Microbiologic improvement was reported in 88% of 41 patients.
‖ The value given is based on larger treatment cohorts with other infection sites or on pathogens treated empirically.

culture result was obtained, suggesting aborted catheter-related infections. Active antibiotic therapy was never given in 49% of the cases or was started only after blood cultures became negative in 22% of the cases.[47] These data support the notion that in some cases acinetobacter bacteremia may represent specimen contamination.

Intravenous or intrathecal colistin has been used successfully for the treatment of central nervous system infections caused by acinetobacter. Intravenous administration of the drug results in moderate penetration of inflamed meninges, with cerebrospinal fluid levels that are approximately 25% of serum levels.[78]

When faced with infections due to multidrug-resistant bacteria, clinicians frequently use combinations of antibiotics. In vitro studies have demonstrated either synergy or additive effects when polymyxins were used with imipenem, rifampin, or azithromycin against multidrug-resistant acinetobacter.[23] Motaouakkil and colleagues successfully treated 16 ventilator-associated pneumonias or bloodstream infections with the combination of colistin and rifampin.[66] Clinical use of rifampin with imipenem for carbapenem-resistant acinetobacter infections has been less successful[71] (Table 1).

INFECTION CONTROL

The primary goals for the control of multidrug-resistant acinetobacter infection are recognizing its presence in a hospital or long-term care facility at an early stage, controlling spread aggressively, and preventing the establishment of endemic strains. Control measures are based almost entirely on experiences from outbreaks of acinetobacter infection and generally address the organism's major epidemic modes of transmission (Fig. 3) and the excessive use of broad-spectrum antibiotics.[22]

Control is most successful when a common source is identified and eliminated.[3,22,48,51,55] A review of 51 hospital outbreaks showed that 25 had a common source: 13 outbreaks with predominantly respiratory tract infections and 12 with predominantly bloodstream or other infections were controlled by removal or disinfection and sterilization of contaminated ventilator (or related) equipment or contaminated moist fomites.[22]

In a single-hospital, multi-ICU outbreak of ventilator-associated pneumonia, *A. calcoaceticus*

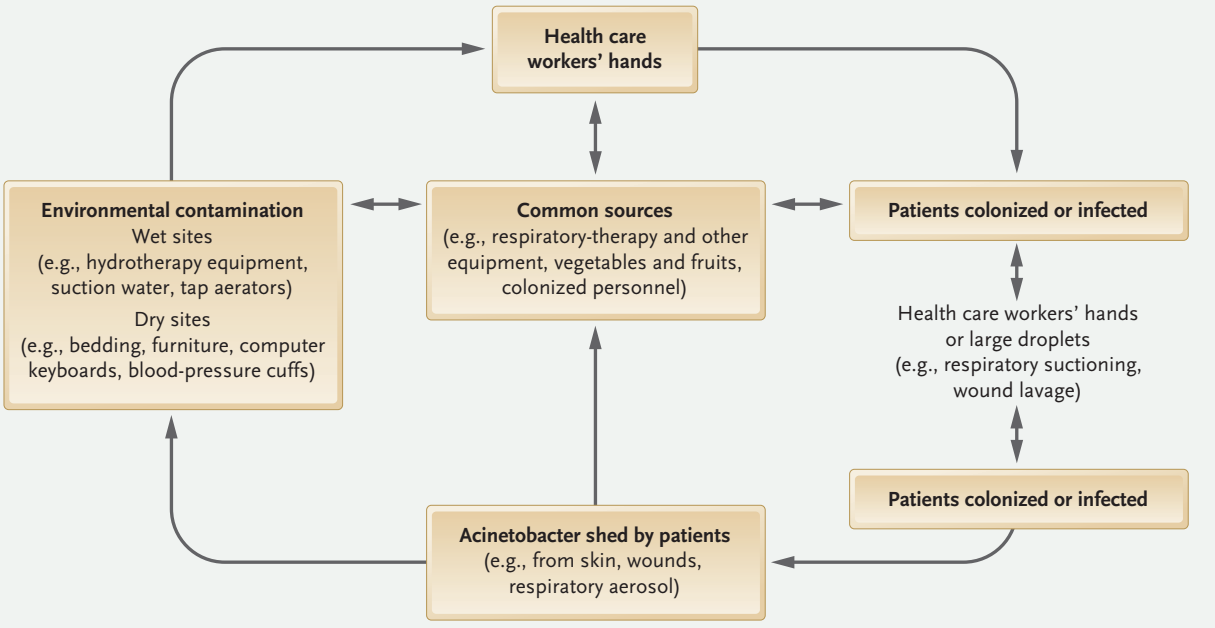

Figure 3. Reservoirs, Sources, and Transmission Patterns for Acinetobacter in Health Care Facilities.

Infection-control measures are directed against the major epidemiologic modes of transmission of acinetobacter, as determined mostly from outbreaks: common-source contamination, environmental contamination, and cross-infection due to lapses in hand hygiene.[22] Although environmental contamination is well documented as a cause of epidemic infections, there are fewer examples of environmental contribution to endemic acinetobacter.

was cultured from 18% of reusable ventilator circuits after pasteurization and from the hands of the four health care workers — one of whom was persistently colonized — who assembled circuits; both disinfection failure and recontamination of circuits by colonized workers during handling probably caused the outbreak.[25] Nevertheless, multidrug-resistant acinetobacter has remained largely susceptible to disinfectants and antiseptics; occasional reports of disinfectant failure are more likely to represent the failure of personnel to follow cleaning procedures than disinfectant resistance.

Aggressive cleaning of the general environment has been the next most frequent outbreak intervention,[22] reflecting the concern that acinetobacter's ability to survive for weeks on wet or dry surfaces facilitates nosocomial transmission.[9] A review of 1561 hospital epidemics reported over the past 40 years noted that closure, typically for cleaning, was considered necessary for outbreak control in 22.9% of 105 units affected by acinetobacter, as compared with 11.7% affected by other pathogens.[79] An outbreak attributed to dissemination of acinetobacter by high-pressure lavage of wounds demonstrated the effect of extensive environmental contamination on the risk of cross-infection.[26] Because multiple measures are usually introduced simultaneously, it has been difficult to assess the independent effect of cleaning. However, in one ICU outbreak, failure to maintain a low level of environmental contamination by *A. baumannii* correlated with an increased risk of patient colonization.[22]

When neither common sources nor environmental reservoirs are identified, control has depended on active surveillance and contact isolation for colonized and infected patients, improvements in the hand hygiene of health care workers (generally the hardest measure to implement), and aseptic care of vascular catheters and endotracheal tubes.[22,51,57,80] A few reports credit out-

break control to reduced prescribing of broad-spectrum antibiotics, such as fluoroquinolones or carbapenems.[22] Because antibiotic exposure is often a risk factor for an outbreak, these findings are plausible; however, use of multiple interventions and historical controls complicates interpretation of these studies. Finally, patient decolonization — by skin cleansing with chlorhexidine or the use of polymyxin topically, orally, or by aerosol — has been an occasional adjunctive control measure that warrants evaluation.[57]

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smaller than cigarettes and typically contain only about a quarter as much tobacco (they are wrapped in the leaf of another plant). In a comparison between smokers and nonsmokers, the relative risk of death from any medical cause did not depend on educational level, but it did depend on whether bidis or cigarettes were smoked and the amount smoked (Fig. 1). The risk ratio for a given number of bidis or cigarettes smoked was greater for cigarettes than for bidis. However, we found a dose–response relationship between smoking and mortality among men who smoked only bidis and among men who smoked only cigarettes ($P<0.001$ for both trends), with particularly elevated risk ratios for cigarette smoking.

In response to Pandey and Pandey, the additional adjustment for tobacco chewing did not materially alter the relative risk of death from any medical cause or the relative risk of death from cancer in a comparison of smokers and nonsmokers.

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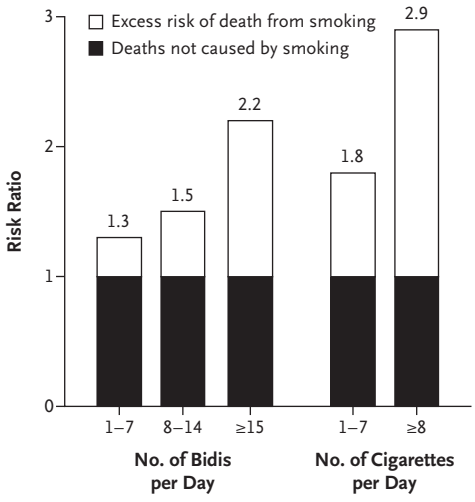

Figure 1. Risk of Death in Men between the Ages of 30 and 69 Years, According to the Type and Amount of Tobacco Smoked.

Risk ratios are for smokers as compared with nonsmokers. The mean numbers of bidis smoked per day were divided into three categories: 4.4 (1 to 7 bidis), 10.2 (8 to 14 bidis), and 23.9 (≥15 bidis). The mean numbers of cigarettes smoked per day were divided into two categories: 4.0 (1 to 7 cigarettes) and 13.7 (≥8 cigarettes). More results are available on the Web site of the Centre for Global Health Research at www.cghr.org/tobacco.

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Acinetobacter Infection

TO THE EDITOR: In their review article, Munoz-Price and Weinstein (March 20 issue)[1] state that "Acinetobacter is a gram-negative coccobacillus" and that it is "nonreactive in many biochemical tests commonly used to differentiate among gram-negative bacilli." However, acinetobacter can be gram-variable and even gram-positive on initial Gram's staining.[2,3] The appearance of the bacteria is highly dependent on its life-cycle phase: it is rod-shaped during the growth phase and coccobacillary during the stationary phase.[4,5] The oxidase-negative characteristic allows one to differentiate acinetobacter from other important gram-negative bacteria such as pseudomonas and neisseria.[4,5] This information can be useful with respect to diagnosis and time to treatment when

a clinician has a high clinical suspicion of acinetobacter infection but the Gram's stain does not show a gram-negative coccobacillus.

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TO THE EDITOR: Munoz-Price and Weinstein did not comment on abscesses as one of the clinical manifestations of acinetobacter infection. In our intensive care unit (ICU), we identified two patients with multidrug-resistant *Acinetobacter baumannii* abscesses. The first patient was a 77-year-old woman who underwent splenectomy after multiple trauma and in whom a lung abscess developed after 60 days in the ICU. This patient recovered. In the literature there is a case report of a lung abscess[1] and three cases of pneumatoceles due to *A. baumannii*.[2] The second patient was a 68-year-old man who also underwent splenectomy after multiple trauma, and in whom an intraabdominal abscess developed at the site of splenectomy 10 days after admission to the ICU. This patient died. To our knowledge, only four cases of *A. baumannii* intraabdominal abscesses have been reported in the literature.[3,4]

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TO THE EDITOR: As pointed out by Munoz-Price and Weinstein, *A. baumannii* is an important contaminant of wounds, and it is an important causative agent of infectious complications of open fractures, as reported in studies involving combat casualties.[1-3] In our reference service in Brazil for severe skeletal trauma, over the past 5 years *A. baumannii* was the second most frequent agent related to infection in open Gustilo type II and III fractures. It was isolated in 25 patients (18% of the total number of patients), and the majority of isolates were multidrug-resistant.

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THE AUTHORS REPLY: Kapoor is correct. As noted in our review article, on Gram's staining of cultures of acinetobacter, bacilli or coccobacilli may predominate, depending on the culture medium. Young acinetobacter cultures (most frequently in liquid mediums) can stain as gram-positive[1] and have coccal morphology for approximately 24 hours; the latter effect is seen in up to 25% of liquid cultures growing acinetobacter (Schreckenberger P: personal communication). This behavior is shared by other gram-negative bacilli such as neisseria and moraxella. Regarding the oxidase-negative characteristic, it is true that it will differentiate acinetobacter from oxidase-positive organisms such as pseudomonas and neisseria; however, it will not differentiate acinetobacter from oxidase-negative nonfermenting bacteria such as *Stenotrophomonas maltophilia* or oxidase-negative fermenting bacteria such as members of the Enterobacteriaceae family.

As mentioned by Myrianthefs et al. and Lima et al., acinetobacter can manifest as wound infections. As we noted, in one series of patients affected by a natural disaster, 20% of wounds were infected with acinetobacter; acinetobacter was also a common cause of infected wounds in the battlefield and burn injuries. Our experience in the greater Chicago area is that acinetobacter detected in wounds more frequently tends to be a contaminant than an actual pathogen. Nevertheless, in the majority of settings, the most common presentations are respiratory, urinary, and blood infections.

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Does Preventive Care Save Money?

TO THE EDITOR: In the Perspective article by Cohen et al. (Feb. 14 issue),[1] a narrow construction of what constitutes prevention leads to erroneous conclusions about its potential impact and cost-effectiveness. The authors do not address preventive interventions that occur outside the doctor's office. These include basic public health services and many other policies that bear directly on health (e.g., seat-belt laws and smoke-free policies). Health gains achieved through population-based approaches often exceed those that can be accomplished clinically, and these approaches are often cost-saving or highly cost-effective.[2]

Even if one considers only prevention in clinical settings, many high-value services are substantially underutilized. For example, less than 50% of the target population receives smoking-cessation services, counseling about aspirin use, colorectal-cancer screening, and influenza vaccines. Increasing use of these four services to 90% would save more than 100,000 lives annually.[3]

Policymakers should support investment in prevention for the right reasons — namely, to improve health at an acceptable cost, even if the services will not reduce overall spending. If reduced spending is the goal, then policymakers should discourage use of low-value services, both therapeutic and preventive.

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THE AUTHORS REPLY: Fielding and colleagues correctly highlight community-based interventions as important preventive strategies to evaluate, but they fail to note that our analysis of 1500 comparisons described in 599 articles drawn from the Tufts Medical Center Cost-Effectiveness Analysis Registry (www.cearegistry.org) did in fact include a number of community-based interventions. Like clinical preventive services, nonclinical interventions are sometimes expensive (e.g., a ban on cell-phone use while people are driving, which costs $380,000 per quality-adjusted life-year, or QALY[1]) and sometimes cost-saving (e.g., folic acid fortification of grains[2] and condom distribution[3]). Other interventions cost the health care system more money than they save but generally deliver good value,[4] meaning that they cost less than commonly recognized benchmarks for cost per QALY.[5]

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From Laboratory Medicine

A Review of *Acinetobacter baumannii* as a Highly Successful Pathogen in Times of War

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Abstract and Introduction

Abstract

Acinetobacter baumannii has emerged as a significant hospital pathogen, quickly becoming resistant to commonly prescribed antimicrobials. It has recently gained notoriety as a cause of debilitating soft tissue infections in soldiers returning from Iraq and Afghanistan. Current literature supports the belief that it is the widespread contamination of increasingly antimicrobial-resistant *A. baumannii* in both military and civilian hospitals that contributes to the rising rates of infections.

Introduction

In 1911, a Dutch microbiologist by the name of Martinus Willem Beigerinck discovered an aerobic, gram-negative, non-fermentative bacterium we now know to be of the genus Acinetobacter.[1] Acinetobacter began to be recognized as a significant hospital pathogen in the late 1970s, but at that time it was easily treated as it was susceptible to commonly used antimicrobials. In 1986 a pair of researchers, Bouvet and Grimont, delineated 12 DNA groups of Acinetobacter using DNA-DNA hybridization and proposed 4 new species.[3] These 4 included *A. baumannii*, which has emerged as a formidable, increasingly antimicrobial-resistant pathogen ubiquitous in the clinical environment today.[4–7] *Acinetobacter baumannii* and its close relatives, Genomic species 3 and 13TU, form what is called the "*A. baumannii* complex." These are the 3 species of the most clinical importance, causing a vast majority of Acinetobacter infections, but they cannot be differentiated by routine diagnostic tests. They are often just referred to as *A. baumannii* in most literature unless stated otherwise. *Acinetobacter baumannii* is just 1 of many Acinetobacter species that can cause disease in humans, but in 2004, the Centers for Disease Control (CDC) reported that *A. baumannii* accounts for approximately 80% of all reported Acinetobacter infections.[8]

As a hospital pathogen, *A. baumannii* mainly affects patients in the intensive care unit (ICU), including burn patients, trauma patients, and patients requiring mechanical ventilation.[2,7–10] Also, any immunocompromised patient or anyone who has an underlying disease, such as chronic lung disease or diabetes, is at an increased risk for *A. baumannii* infection.[8] As an opportunistic pathogen, *A. baumannii* usually poses no threat to healthy people. It can colonize the skin of healthy people, but it will generally not cause infection.[2,7–9,11] In immunocompromised and intensive care populations, however, *A. baumannii* can cause a variety of infections. According to the published literature, some infections associated with *A. baumannii* include ventilator-associated pneumonia, skin and soft-tissue infections, secondary meningitis, urinary tract infections, wound and blood stream infections, endocarditis, intra-abdominal abscess, and surgical site infections.[9,12] In soldiers, cases of osteomyelitis have been shown to develop from deep wound infections.[9]

Acinetobacter baumannii is a gram-negative, nonmotile, obligate aerobic coccobacillus harboring a number of effective virulence factors.[11] These factors include the attachment to and persistence on solid and dry surfaces, the ability to obtain essential nutrients such as iron, the adhesion to and subsequent destroying of epithelial cells, and the ability in some strains to produce gelatinases and proteinases that damage host tissues.[13] *Acinetobacter baumannii* has the added ability to colonize the skin of patients or healthy individuals without causing illness.[4] The transmission of colonized bacteria to a susceptible patient, however,

can result in infection. *Acinetobacter baumannii* also has the ability to form biofilms, which may play a role in the process of colonization. A biofilm is an aggregate of microorganisms in which the cells adhere to one another or to a surface in a self-produced matrix of extracellular DNA, proteins, and polysaccharides.[4] The cells forming the biofilm are morphologically, metabolically, and physiologically different from their planktonic counterparts. Biofilms help the bacteria resist disinfection while also allowing the participating cells to trade resistance genes, further facilitating the persistence of the pathogen.[4]

Acinetobacter baumannii is no longer isolated only rarely in hospitals, and the cause of this increase in detection is not clear. An increase in the use of broad-spectrum antibiotics may contribute to the isolating of more antimicrobial resistant bacteria, but war and natural disasters may also play a part. This is not only evidenced by the current war, but also by traumatic disasters such as earthquakes, like the Marmara earthquake in 1999. The GATA Haydarpasa Training Hospital, 1 of the major treatment facilities after this disaster, recovered *A. baumannii* from 31.2% of all the ICU patients. Before the earthquake, the bacteria was isolated from only approximately 7.3% of patients.[10] Furthermore, multi-drug-resistant strains of *A. baumannii* were being recovered where there had been none previously.[10] The Brooke Army Medical Center (BAMC) at Fort Sam Houston in San Antonio, TX, treats a population of both active and retired military personnel, their dependents, and a limited number of civilian trauma patients. Until the medical center began seeing soldiers with infected wounds, *A. baumannii* was rarely encountered. In the 14 months prior to March 1, 2003, only 2 active-duty soldiers of the 326 admitted to BAMC had any Acinetobacter infection.[9] Both patients had underlying disease. During the study period however, from March 1, 2003, to May 31, 2004, the rate of Acinetobacter isolation increased 3-fold. Most isolates were from admitted deployed soldiers with gunshot and explosives wounds. All isolates were of the *Acinetobacter baumannii* complex. Of these isolates, 76% were multi-drug resistant (MDR); almost half of them being resistant to every tested antimicrobial except Imipenem.[9] At the Walter Reed Army Medical Center (WRAMC) in Washington, DC, 75 patients were found to be positive for Acinetobacter. Of these patients, 63% had positive Acinetobacter cultures less than 3 days after admittance. Of the isolates, 89% were resistant to at least 3 drugs, meeting the criteria for multidrug resistance.[14]

A. Baumannii and War

Many of these patients with *A. baumannii* infections are soldiers who were previously healthy.[9,14] The reservoir for these infections is not well known and may be different for each treatment facility, but the evidence strongly suggests the high numbers of wounded soldiers and the transfer of these soldiers from 1 treatment facility to another aids the transmission and the growing resistance of *A. baumannii*.[14,15] A common misconception is that soldiers get these infections from the soil of Iraq and Afghanistan or have become infected from explosive devices placed inside animal carcasses—rumors with their beginnings in military hospitals—but *A. baumannii* is a pathogen mainly found in a health care setting and is not isolated from the soil.[2] *Acinetobacter baumannii* has been isolated from every hospital on the aeromedical evacuation route from Iraq and Afghanistan.[15] Furthermore, a study by Scott and colleagues (2007) tested 49 soil samples for *A. baumannii* and recovered only 1 isolate, but this isolate was not genetically related to any of the 86 clinical isolates recovered from 7 military treatment facilities. Also, soldiers did not test positive for *A. baumannii* upon admission after injury.[15]

It should be noted that war-time infection is by no means a new adversary. However, the organism doing so much widespread damage currently to both servicemen and civilian alike is a hospital pathogen, not an environmental 1 like trench fever in War World I or malaria in World War II.

Robust evidence suggests the excessive use of broad-spectrum antibiotics may also be to blame for the evolution of drug-resistant strains of *A. baumannii*.[4,6,8,9] When a patient presents with a bacterial infection, broad-spectrum antibiotics are the most likely drug to provide effective treatment without identifying the organism behind the infection. Overuse of broad-spectrum antibiotics, however, can contribute to the persistence of MDR bacteria. Zarrilli and colleagues (2004) discovered that 2 epidemics of MDR *A. baumannii* were caused by 2 distinct clones selected in part by the high use of broad-spectrum antibiotics in the ICU. To limit the use of broad-spectrum antibiotics while still ensuring the infection is being treated, culture-directed antimicrobial therapy is highly recommended.[6,15] This approach helps to prevent selection of antimicrobial-resistant bacteria by guiding physicians toward effective and appropriate initial treatment.[6,15] Erbay and colleagues (2009) considered "appropriate" initial treatment to include at least 1 antibiotic that is active against the pathogen *in vitro*. This study concluded that a 48-hour or more delay in administration of appropriate antimicrobial therapy had an adverse influence on the clinical outcome in patients with *A. baumannii* bacteremia.

Protocols for using antibiotics in the military have changed dramatically over the years. Antibiotics were not introduced until World War II and the Korean War, where soldiers carried pouches of sulfanilamide powder and simply dumped it into wounds to stave off infection.[17] Penicillin was used increasingly after its first use in 1942 when the British used it to sterilize wounds and the U.S. medics saved the then powerful drug for systemic administration. By the end of World War II, penicillin was the go-to drug for

aggressive debridement and wound management.[18] Both penicillin and streptomycin were commonly used in the Korean War to prevent infection in wounds, the consequences of which were observed when soldiers presented with wounds infected by organisms resistant to both drugs.[19] Hospital-acquired infection and transmission also became a hot topic during World War II, and medical personnel as well as patients began to wear masks. Instruments were sterilized and infection control practices were put into place, most of which are still used and accepted today.[20–22] These practices are important during this current war, where we are seeing an increased ratio of wounded:fatal casualties. Along with this increase in wounded soldiers, there is a surge in wound infections and transmission.[23,24] The military has greatly improved its treatment methods for wounded soldiers, and it has adopted methods to reduce the rate of isolation of resistant organisms. When a soldier presents to a field hospital with an injury, aggressive debridement and culture-directed antimicrobial therapy are the primary tools of fighting infection (no longer broad-spectrum antibiotics), but it is extremely difficult to prevent infection by an organism lurking on the walls, the tables, and even the bed sheets.[15,25,26] Strict infection control and a thorough understanding of the organism itself is a critical part of stopping the spread of *A. baumannii* from 1 ICU to the next.

Inter- and Intrahospital Transmission

Since *A. baumannii* is a well-documented hospital pathogen and most infections involve ICU and trauma patients, it is understandable that this organism should thrive in military treatment hospitals. These hospitals receive wounded servicemen directly from the field or from other hospitals, sometimes 2 or 3. This intrahospital transmission poses a threat not just for military treatment facilities, but also for civilian hospitals.[2] *Acinetobacter baumannii* has the ability to live on dry environmental surfaces in an ICU for up to 13 days—10 days more than other gram-negative bacteria.[27] Other studies have shown similar abilities by *A. baumannii* in humid conditions and on bed rails.[28,29] It is this ability to survive for long periods coupled with its ability to demonstrate a number of antimicrobial resistance genes that have made *A. baumannii* a successful hospital pathogen.[2,27,30]

Acinetobacter baumannii is ubiquitous in the hospital setting. It is entirely too easy to carry the pathogen from 1 patient to another or from 1 hospital to another, as was seen in both a nationwide outbreak in France and a city-wide outbreak in Brooklyn, NY. In early September 2003, an alert went out through France's national hospital acquired infection notification system when, within a month, 4 hospitals in a single district reported 5 clusters of *A. baumannii*, all of which had similar susceptibility profiles and harbored a gene usually found within enterics and *Pseudomonas aeruginosa*, VEB-1. VEB-1, an extended spectrum β-lactamase gene, gives the organism resistance to all penicillins, cephalosporins, extended-spectrum cephalosporins, and monobactams.[31] In this case study, the isolates were resistant to all drugs save for colistin and imipenem. This clonal outbreak spread from 4 hospitals to 53 hospitals and from Northern France to 4 distant regions. In 1999, 15 hospitals in Brooklyn, NY, reported high rates of MDR *A. baumannii* infection. Twelve percent of the strains were resistant to all commonly used drugs, and the only effective treatment was an older, fairly toxic drug. Ribotyping of the isolates revealed that 1 strain was responsible for two-thirds of the infections and was present in each of the 15 hospitals.[32] After an investigation into the cause of this *A. baumannii* epidemic, it was believed that the transfer of colonized patients from hospital to hospital along with the rotation of medical staff and students may have contributed to the spread of *A. baumannii*.[32]

Infection Control

As easily transmitted as *A. baumannii* is, it is becoming increasingly important for hospitals to update their infection control procedures. In 2006, the CDC released a report describing guidelines to prevent the transmission of MDR organisms. The steps the CDC recommends all health care facilities take include improvement of hand hygiene, use of contact precautions until the patient tests culture-negative for the target organism, active surveillance cultures, education of hospital personnel, improved environmental cleaning, and better communication about patients with these infections to not just personnel within the facility but also between facilities.[33] Several hospitals found success placing all admitted soldiers from Operation Iraqi Freedom or Operation Enduring Freedom (OIF/OEF) under contact precautions until cultures showed neither infection nor colonization with *A. baumannii*.[9,34–36] One particular study found that each time a patient underwent pulsatile lavage debridement of wounds, that patient's risk of developing a MDR *A. baumannii* infection increased by 60% due to the aerosolization of the pathogen during the procedure. This aerosolization lead to widespread environmental contamination, and the hospital had to remove all upholstered items from the ICU and stopped pulsatile lavage therapy in the ICU patients, after which there was a significant decrease in the number of infections.11 Obviously, stress needs to be placed on environmental disinfecting. Studies have reported lower rates of infection when the rooms and equipment were cleaned completely and more frequently.[2,27,33] Bleach solutions and other disinfectants should be used in rooms and on equipment often and thoroughly to effectively control transmission of *A. baumannii*. In 1 study, it was found that an outbreak of Acinetobacter was caused by the incomplete disinfection of reusable ventilator tubing.[37] Desiccation is also a popular way to stave off environmental contamination as it keeps the area dry and free of the effects of

humidity. However, a few studies have found clinical and outbreak strains of *A. baumannii* to be more resistant to desiccants than culture-type strains from the American Type Culture Collection (ATCC). The reason for this is not well understood, but it may be due to natural selection.[38,39] Another type of cleaning used to prevent the formation of biofilms is biocides. Biofilms further facilitate the persistence of *A. baumannii* in the clinical environment by the exchange of resistance genes and resistance mechanisms.[40] Furthermore, biofilm-forming bacteria are more resistant to disinfectants such as biocides.[40] One study found that residual biocide in the environment actually contributed to an increased range of drug resistance. This is due to the fact that biocides at the subminimum inhibitory concentration induced biofilm formation. This, of course, raises concerns about the inappropriate use of biocides and disinfectants.[41] Despite the fact that *A. baumannii* poses a serious risk to patients, it is possible to prevent transmission and infection in the hospital. In fact, the CDC reports that from 1982 to 2005, more than 100 reports have been published documenting the success of various control interventions to lessen the burden of not only *A. baumannii* but methicillin-resistant *Staph aureus* (MRSA) and other MDR pathogens.[33] Several of these interventions are listed in Table 1.

Table 1. A List of Interventions for Controlling the Transmission of MDR Hospital Pathogens[33]

Effective Control Measures for MDR Pathogens
Education of staff, patients, and visitors
Emphasis on hand washing
Use of antiseptics for hand washing
Contact precautions and glove use
Segregation of cases
Change in antimicrobial use
Surveillance cultures of patients
Surveillance cultures of staff
Environmental cultures
Extra cleaning and disinfection
Dedicated equipment

Molecular Characterization of Resistance Mechanisms

One of the chief problems facing hospitals, clinicians, and military health care personnel in regards to *A. baumannii* today is multi-drug resistance. The CDC describes any species resistant to 3 or more antimicrobials as MDR.[33] It is no surprise that *A. baumannii* has become resistant to a number of antimicrobials. It is bombarded by drugs and is in close association with other gram negatives in the clinical setting. As such, it has acquired an impressive array of resistance mechanisms on top of its own intrinsic abilities. *Acinetobacter baumannii*, along with other gram negative pathogens, can acquire new mechanisms via plasmids, integrons, and transposons. These structures and their basic functions are depicted in Figure 1. Interestingly, studies have observed that many outbreak strains of *A. baumannii* have a class 1 integron. The class 1 integron is responsible for the transferring and recruitment of multiple resistance genes and has been demonstrated to be present in 88% of biofilm-forming *A. baumannii* strains in 1 study. Class 1 integrons have also been linked to outbreak strains in military treatment facilities treating repatriated soldiers in both the United States and the United Kingdom.[4,42] A resistance mechanism common to *A. baumannii* and other gram negative bacteria are enzymes. Genes coding for these enzymes can be passed from cell to cell via the mechanisms discussed previously. A common enzyme is β-lactamase, which hydrolyzes and confers resistance to the penicillins, cephalosporins, and carbapenems.[43–45] Other enzymes *A. baumannii* can acquire are acetyltransferases, phosphotransferases, and nucleotidyl transferases, which all promote resistance to fluoroquinolones and aminoglycosides. Mutated genes can also be acquired from other bacteria. Mutations can alter bacterial targets of antimicrobials, reducing their affinity for the bacteria and increasing the minimum inhibitory concentration (MIC) for the drug. An example of a point mutation would be a mutation in the gyrA and parC genes. If there were point mutations in both genes, the isolate would have an increased MIC for all available fluoroquinolones.[43] Table 2 lists the most common resistance genes and genes coding for resistance mechanisms found in *A. baumannii*.

Table 2. Genes Conferring Antibiotic Resistance and Resistance Mechanisms in Acinetobacter Baumannii

Enzyme Group, Gene Name	Description	Antibiotic Resistance	Clinical Significance	References
β-Lactamase Genes				
ADC	Chromosomally integrated cephalosporinase	Extended-spectrum cephalosporins	*A. baumannii's* most common mechanism of resistance to β-lactam antibiotics	14
VIM	Acquired metallo-β-lactamase	All β-lactams except monobactams, evades all β-lactamase inhibitors	Hydrolyzing capabilities and ability to transfer to other gram negatives make VIM a new nosocomial threat	14, 61
IMP	Stronger carbapenem-hydrolyzing activity than OXA	Carbapenem resistance	Has a history of spreading very quickly to many other gram-negative organisms and to other countries	32, 60
OXA	A group of carbapenem-hydrolyzing oxacillinases	Carbapenem resistance	There are more than 15 oxacillinase genes. They are separated into at least 4 groups. More genes of this type continue to be discovered.	32, 60
TEM	A broad-spectrum enzyme	Narrow-spectrum cephalosporins, all penicillins except temocillin	TEM-1 has been found to sustain many combinations of mutations in its active site, broadening the list of antibiotics it can become resistant to.	14, 68
SHV	Plasmid-mediated. Includes SHV-1 and at least 23 variants	Extended-spectrum cephalosporins, ampicillin	Considered the most prevalent extended-spectrum beta-lactamases	14, 69
AME Genes—Aminoglycoside-Modifying Enzymes				
aadB	Enzymatic inactivation by adenylation	Kanamycin, tobramycin, and gentamicin	aadB is a gene cassette sometimes found in integrons, namely Integron 1	62, 64, 66
aacC1	Enzymatic inactivation by acetylation	Gentamicin, apramicin, lividomicin resistance	A common gene first found in enterics	62
aacC2	Enzymatic inactivation by acetylation	A number of aminoglycosides, including those above	Also involved in nosocomial epidemics caused by enterics. One of a number of genes transferred from one gram negative to another	62
aphA6	Enzymatic inactivation by phosphorylation	Kanamycin, neomycin, gentamicin, gentamicin B, paromomycin, amikacin, and others	Primarily associated with *Acinetobacter* and rarely isolated from other gram negatives	62
aadA1	Modifies the 3"-hydroxyl position of streptomycin and the 9"-hydroxyl position of	Streptomycin and spectinomycin	Ubiquitous in gram-negative bacteria	62

	spectinomycin			
Gene-Encoding Efflux Pumps				
adeABC	Composed of AdeA, AdeB, and AdeC proteins	Aminoglycosides, quinolones, tetracyclines and trimethoprim	Forms a proteinaceous transporter in the cytoplasmic membrane or extrusion of antibiotics	67
Point Mutations				
gyrA	Point mutation at Ser83	Quinolones		**14**
parC	Point mutation at Ser80	Quinolones	Hujer and colleagues reported that 88% of his *A. baumannii* isolates had 1 or both genes.	14

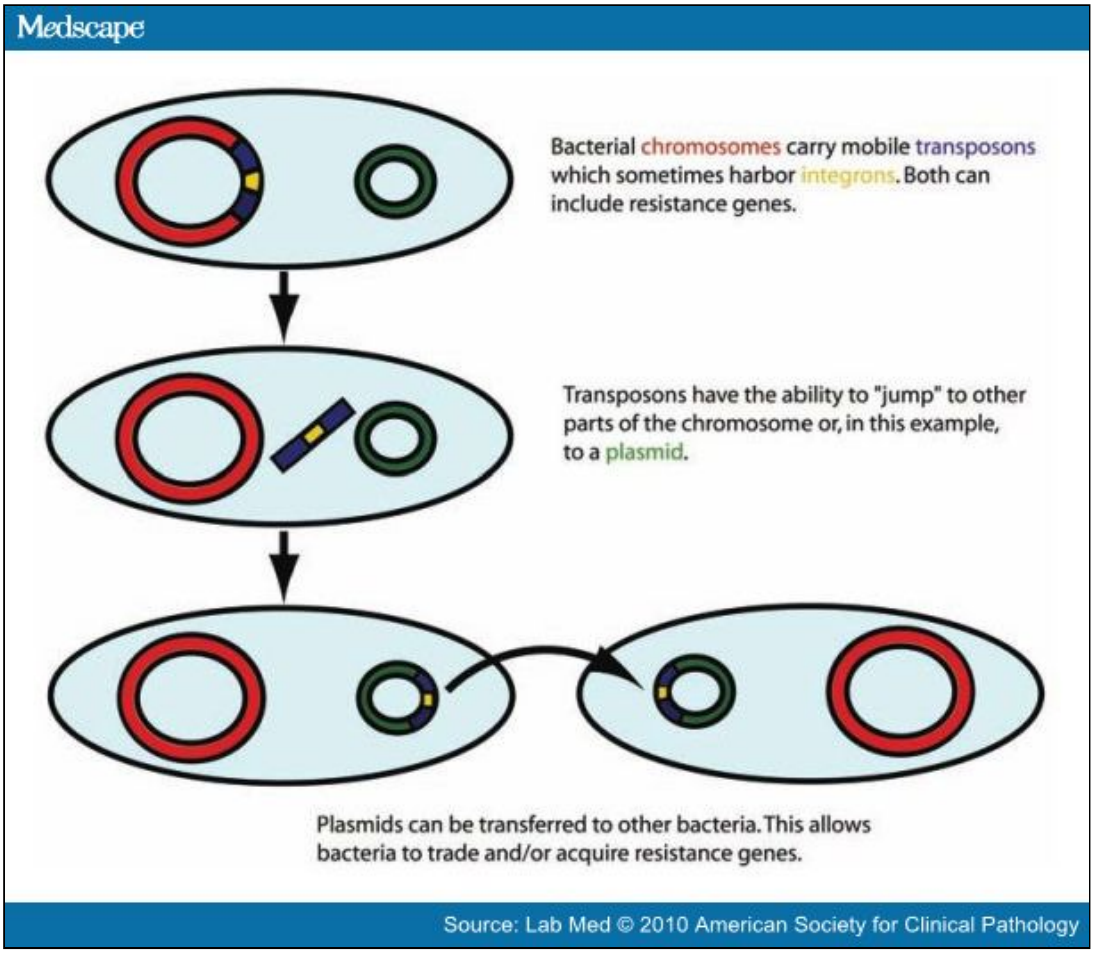

Figure 1. Plasmids are extra-chromosomal elements occurring naturally in bacteria and can be transferred between bacteria, facilitating antimicrobial resistance if resistance genes jump to a plasmid.

Acinetobacter baumannii also has a set of its own intrinsic mechanisms. These include porins and efflux pumps. Porins are specialized outer membrane proteins (OMP) that allow for the passage of small metabolites such as sugar, amino acids, and ions.[46] More porins in the outer membrane of a cell makes the cell more permeable to certain antimicrobials. *Acinetobacter baumannii* is considerably less permeable than other gram-negative bacteria, and researchers suggest the small number and size of porins in the outer membrane could be a reason for the intrinsic resistance attributable to *A. baumannii*.[47] Also interesting is the observation that there are 3 porins missing in *A. baumannii* strains resistant to imipenem, 1 of the very few drugs still successful against most strains.[48] More research is required to elucidate the meaning behind these different porins and their

association with antimicrobial resistance. Another impressive mechanism *A. baumannii* has is the efflux pump. Efflux pumps can actively remove antimicrobials from the bacterial cell, preventing the bacteria's exposure to it.[49] The action of efflux pumps in conjunction with porins is believed to be a very powerful resistance mechanism.[49] To put all of these mechanisms into perspective, if an *A. baumannii* isolate acquired mutations in both the gyrA and parC genes and had efflux overexpression as well as a loss of porins, the isolate would be highly resistant to all available drugs: a physician's worst nightmare.[12]

Despite everything happening inside and outside the cell walls of *A. baumannii*, there are still some drugs that have some potential activity against the bacteria terrorizing ICUs. These include monobactams, some aminoglycosides, carbapenems, polymixins, fluoroquinolones, sulbactams, and glycylcyclines.[2] Of these drugs, carbapenems have become the mainstay of treatment for MDR *A. baumannii* isolates, but there are already numerous reports of resistance caused by carbapenem-hydrolyzing beta lactamases.[50–54] Consequently, susceptibility should be determined for each and every isolate to ensure proper and effective treatment and to prevent delay and unnecessary morbidity.[6]

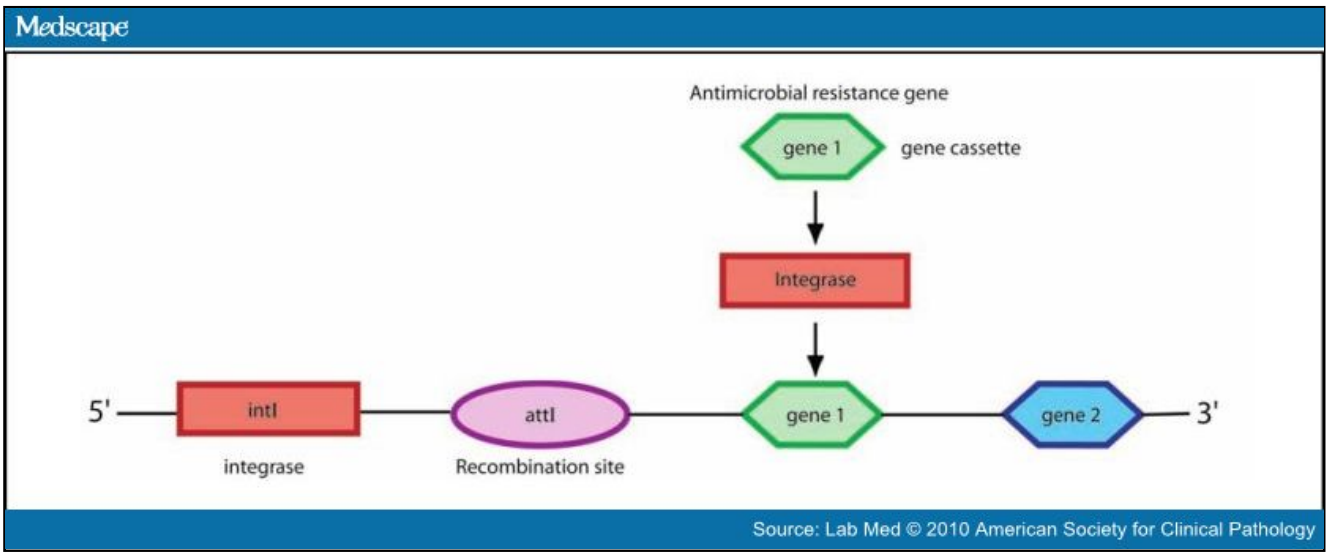

Figure 2. Integrons are another kind of mobile DNA element that can capture and carry genes in "cassettes." Being mobile, they can integrate into transposons and a whole cassette of resistance genes can thereby easily move from bacterium to bacterium. (59).

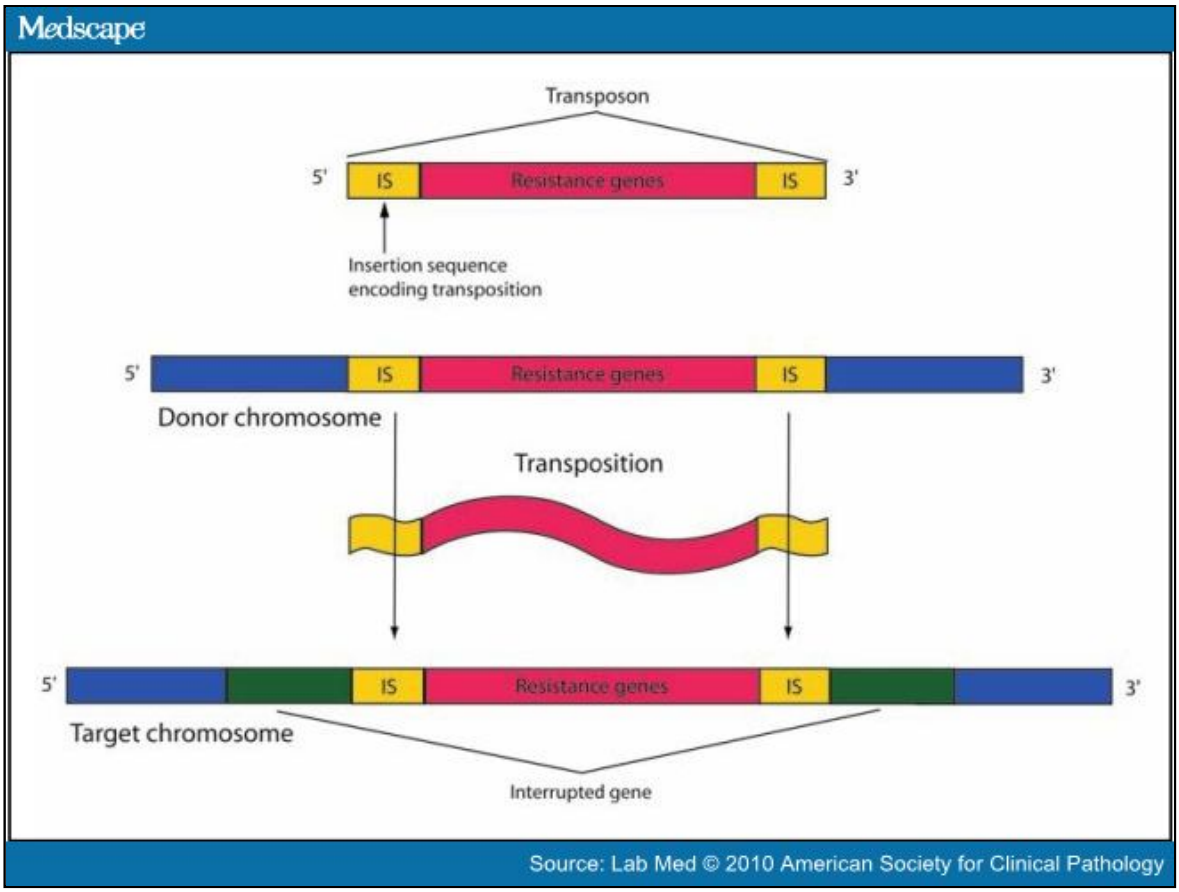

Figure 3. Transposons are segments of DNA that can move from 1 place in the genome to another. Occasionally, these transposons contain genes conferring antimicrobial resistance. If a transposon jumps to a plasmid, those resistance genes can move from one host cell to another (58).

Laboratory Diagnostic Techniques

Early and appropriate treatment is obviously extremely important when dealing with a hospital-acquired infection. In order to begin appropriate treatment, the organism behind the infection must be identified as quickly as possible. Acinetobacter is gram negative and in the coccobacillus form when in its stationary phase but can be rod-shaped during periods of rapid growth.[15] It is oxidase negative, indole negative, catalase positive, and hemolytic. Acinetobacter can be cultured on routine laboratory media due to its ability to use various sources of nutrition and will grow at 44°C.[15] These standard laboratory techniques will identify the genus but will not identify the species.[55] There are automated methods available today to quickly and accurately identify an isolate at the species level. These methods are phenotypic, utilizing biochemistry and assimilation tests usually done manually to identify the genus and species of bacteria in less time. To identify an *A. baumannii* isolate, a couple of analyzers that could be used are Microscan WalkAway (Dade Behring, West Sacramento, CA) and Vitek 2 (bioMérieux, Marcy l'Etoile, France).[55–57] However, while these analyzers will identify the isolate as *A. baumannii*, they are really only identifying the *A. baumannii* complex, but these analyzers have the added benefit of automated susceptibility testing to guide the physician in making appropriate treatment decisions.[55]

Another method of identification is molecular testing. Molecular testing can identify an isolate down to the genotype. A couple of molecular methods used in laboratories today are pulsed-field gel electrophoresis (PFGE) and 16s rRNA sequencing.[58,59] Pulsed-field gel electrophoresis is a type of gel electrophoresis used to separate large molecules of DNA up to 2000 kb. This procedure uses 3 electric fields instead of 1.[58] One electric field runs through the central axis of the gel as in traditional electrophoresis, and 2 more run at an angle of 120° on each side. The electric fields are alternately pulsed to slowly separate the large DNA molecule. Pulsed-field gel electrophoresis allows a resolution of up to 1 bp, allowing the user to differentiate between strains of bacteria, which is extremely useful in cases of an outbreak where transmission of the bacteria must be tracked.[58]

A second molecular method employed in bacterial identification is 16s ribosomal DNA (rDNA) sequencing.[59] In this method, DNA is isolated from bacterial colonies and amplified with primers selective for the 16s rDNA. The rDNA can then be sequenced and results can be compared to Acinetobacter genotypes on public-domain sequence databases such as GenBank.[59] These molecular methods are not only useful in identifying causes of bacterial infection, but they can aid a hospital in its infection control measures, highlighting areas of weakness, and can identify the source of hospital-acquired infections.[59]

Conclusion

Acinetobacter baumannii has evolved as a hospital pathogen, due in part to excessive and inappropriate use of antibiotics. Its transmission has been associated with war, natural disasters, and just about any other instance where one observes an influx in hospital trauma admissions and increased transfer of patients and staff from 1 hospital to the next.[10,15,31,42] Patients infected with a clinical isolate of *A. baumannii* have an average of $60,913 in additional patient charges due to the infection, and they stay in the hospital for an average of 13 days longer than a patient without an *A. baumannii* infection.[11] While *A. baumannii* may not be particularly virulent, it can cause unnecessary disease and expense in the critically ill patients affected by it, and the transmission of such a pathogen should be limited. Measures to prevent the inter- and intrahospital transmission of *A. baumannii* must be established in health care settings. Success in infection control has been attained by numerous others, and it can be attained by all if health care workers are educated about the proper way to manage MDR *A. baumannii*.

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Abbreviations

ICU, intensive care unit; MDR, multi-drug resistant; WRAMC, Walter Reed Army Medical Center; OIF, Operation Iraqi Freedom; OEF, Operation Enduring Freedom; ATCC, American Type Culture Collection; MIC, minimum inhibitory concentration; OMP, outer membrane protein; PFGE, pulsed field gel electrophoresis; rDNA, ribosomal DNA; BAMC, Brooke Army Medical Center; MRSA, methicillin-resistant *Staph aureus*; CDC, Centers for Disease Control

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