

REVIEW ARTICLE

CURRENT CONCEPTS

Acinetobacter Infection

L. Silvia Munoz-Price, M.D., and Robert A. Weinstein, M.D.

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

From Medical Specialists, Dyer, IN (L.S.M.-P.); and the Division of Infectious Diseases, Stroger (Cook County) Hospital, Ruth M. Rothstein CORE Center, and Rush Medical College — all in Chicago (R.A.W.). Address reprint requests to Dr. Munoz-Price at Medical Specialists, 919 Main St., Ste. 202, Dyer, IN 46311, or at simunozprice@gmail.com.

N Engl J Med 2008;358:1271-81.
Copyright © 2008 Massachusetts Medical Society.

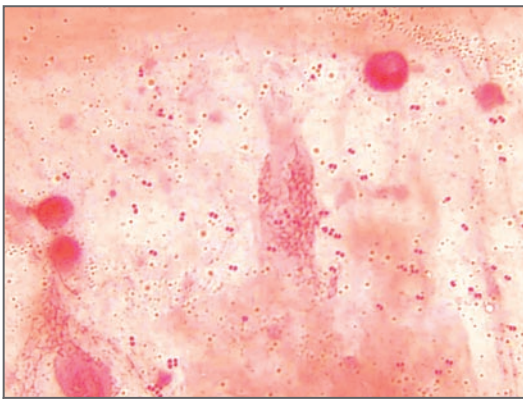


Figure 1. Gram's Staining of Sputum Specimen from a Patient with Suspected Ventilator-Associated Pneumonia.

Acinetobacter baumannii was recovered from this specimen, which shows gram-negative coccobacilli¹; 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, ISAb₁, 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

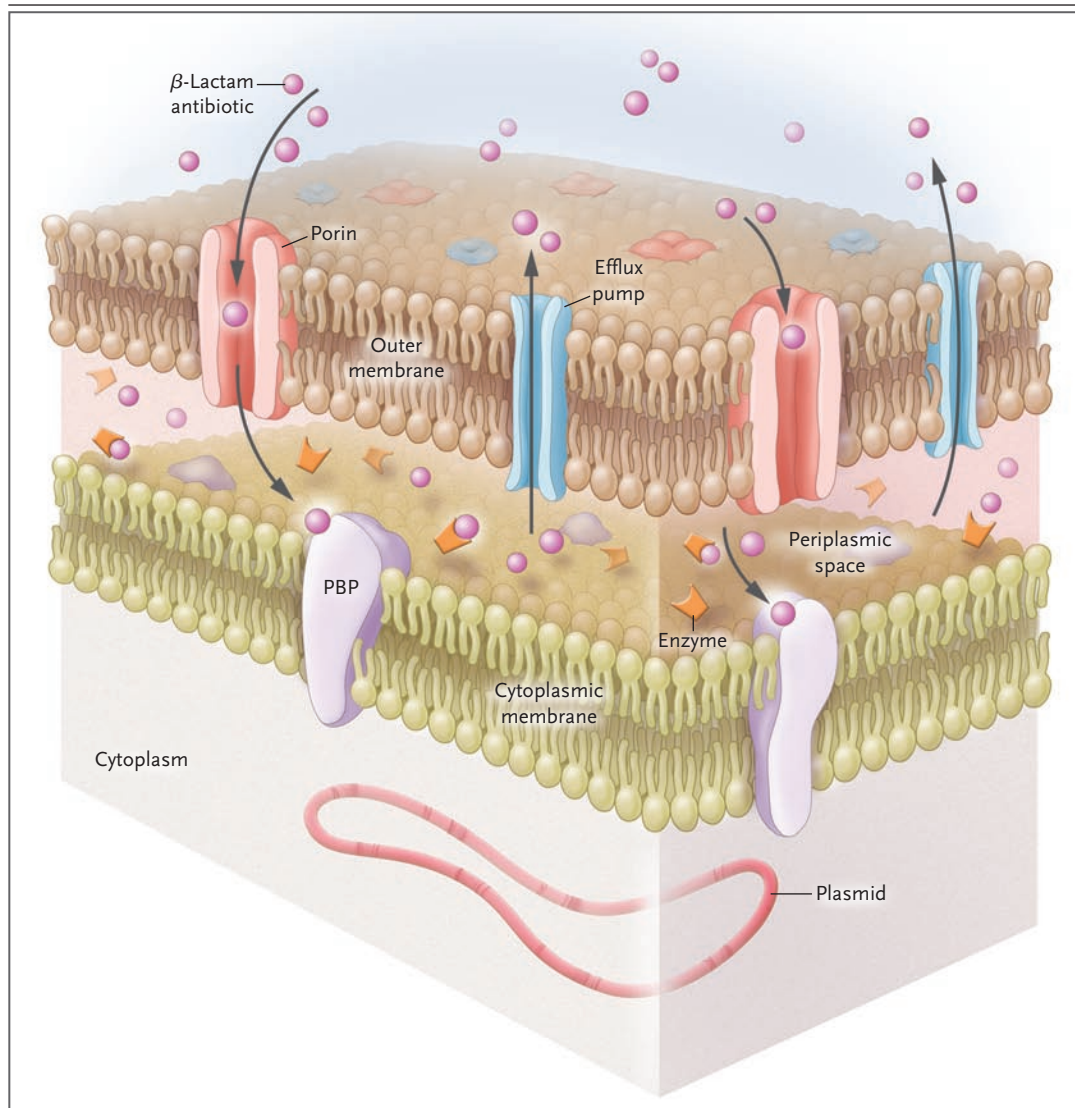


Figure 2. Potential Mechanisms of Antimicrobial Resistance in *Acinetobacter*.

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 re-appearance 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 treated⁴²; *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 enterococci⁴⁶ — 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 hospital-

ization 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 pathogens²⁴ 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 carbapenems⁵⁴), 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 infections⁶⁴⁻⁷⁶ (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 days	Clinical Improvement	Mortality‡ percent of patients	Side Effects
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 (1.5–6×10 ⁶ IU divided into 3 or 4 doses/day, inhaled; 5 patients also received 1–3×10 ⁶ IU every 8 hr, IV)§	10 (inhaled colistin); 17 (IV colistin)	86	14	None
Lung ⁶⁸	21 14	Colistin (2.5–5 mg/day, divided in 3 doses, IV) Imipenem (2–3 g/day, IV)	15 13	57 57	38 (Attributable) 36 (Attributable)	Renal failure, 24 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 Garnach-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 successful⁷¹ (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*

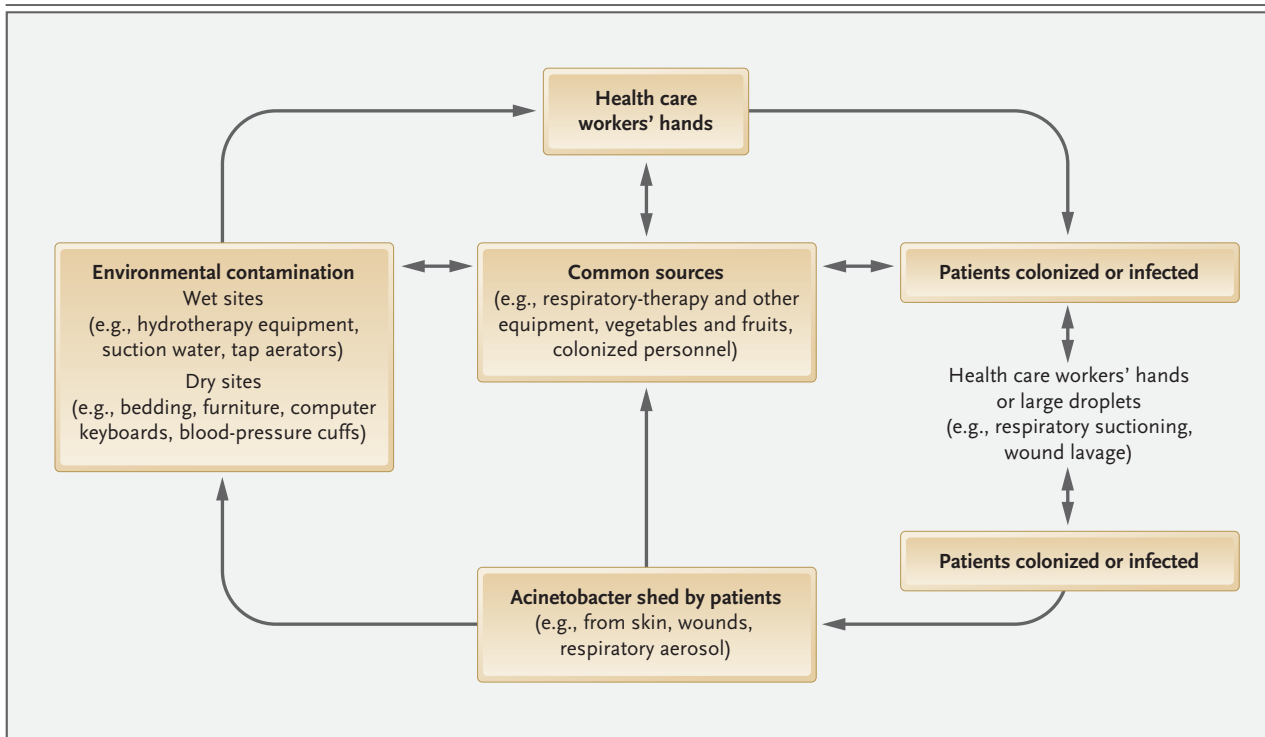


Figure 3. Reservoirs, Sources, and Transmission Patterns for *Acinetobacter* in Health Care Facilities.

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

Dr. Weinstein reports receiving consulting fees from Sage Products and joint grant support from Sage Products and the CDC for a randomized trial of chlorhexidine bathing for patients in an ICU. No other potential conflict of interest relevant to this article was reported.

We thank Dr. John P. Quinn for reviewing an earlier version of this article, Ellen Holfels for technical assistance, and Joan V. Zivich for library services.

REFERENCES

- Schreckenberger PC, Daneshvar MI, Weyant RS, Hollis DG. *Acinetobacter*, *Achromobacter*, *Chryseobacterium*, *Moraxella*, and other nonfermentative gram-negative rods. In: Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA, eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: ASM Press, 2007:770-802.
- Euzéby JP. Dictionnaire de bactériologie vétérinaire. (Accessed February 19, 2008, at <http://www.bacterio.cict.fr/bacdico/aa/acinetobacter.html>.)
- Fournier PE, Richet H. The epidemiology and control of *Acinetobacter baumannii* in health care facilities. *Clin Infect Dis* 2006;42:692-9.
- Dima S, Kritsotakis EI, Roubelaki M, et al. Device-associated nosocomial infection rates in intensive care units in Greece. *Infect Control Hosp Epidemiol* 2007;28:602-5.
- Lolans K, Rice TW, Munoz-Price LS, Quinn JP. Multicity outbreak of carbapenem-resistant *Acinetobacter baumannii* isolates producing the carbapenemase OXA-40. *Antimicrob Agents Chemother* 2006;50:2941-5.
- Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. *Clin Infect Dis* 2006;42:657-68.
- Carey RB, Banerjee SN, Srinivasan A. Multidrug-resistant *acinetobacter* infections, 1995-2004. Presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 27–30, 2006.
- Beijerinck MW. Über Pigmentbildung bei Essigbakterien. *Cent Bakteriol Parasitenk* 1911;29:169-76.
- Getchell-White SI, Donowitz LG, Gröschel DH. The inanimate environment of an intensive care unit as a potential source of nosocomial bacteria: evidence for long survival of *Acinetobacter calcoaceticus*. *Infect Control Hosp Epidemiol* 1989;10:402-7.
- Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2006;43:Suppl 2:S49-S56.
- Poirel L, Nordmann P. Carbapenem resistance in *Acinetobacter baumannii*: mechanisms and epidemiology. *Clin Microbiol Infect* 2006;12:826-36.
- Peleg AY, Adams J, Paterson DL. Tigecycline efflux as a mechanism for nonsusceptibility in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2007;51:2065-9.
- Jacoby GA, Munoz-Price LS. The new beta-lactamases. *N Engl J Med* 2005;352:380-91.
- Fournier PE, Vallenet D, Barbe V, et al. Comparative genomics of multidrug resistance in *Acinetobacter baumannii*. *PLoS Genet* 2006;2(1):e7.
- Schmidt H, Hensel M. Pathogenicity islands in bacterial pathogenesis. *Clin Microbiol Rev* 2004;17:14-56. [Erratum, *Clin Microbiol Rev* 2006;19:257.]
- Paterson DL. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. *Clin Infect Dis* 2006;43:Suppl 2:S43-S48.
- Chen MZ, Hsueh PR, Lee LN, Yu CJ, Yang PC, Luh KT. Severe community-acquired pneumonia due to *Acinetobacter baumannii*. *Chest* 2001;120:1072-7.
- Anstey NM, Currie BJ, Hassell M, Palmer D, Dwyer B, Seifert H. Community-acquired bacteremic *Acinetobacter* pneumonia in tropical Australia is caused by diverse strains of *Acinetobacter baumannii*, with carriage in the throat in at-risk groups. *J Clin Microbiol* 2002;40:685-6.
- Leung WS, Chu CM, Tsang KY, Lo FH, Lo KF, Ho PL. Fulminant community-acquired *Acinetobacter baumannii* pneumonia as a distinct clinical syndrome. *Chest* 2006;129:102-9.
- Houang ET, Chu YW, Leung CM, et al. Epidemiology and infection control implications of *Acinetobacter* spp. in Hong Kong. *J Clin Microbiol* 2001;39:228-34.
- Berg DE, Hershov RC, Ramirez CA, Weinstein RA. Control of nosocomial infections in an intensive care unit in Guatemala City. *Clin Infect Dis* 1995;21:588-93.
- Villegas MV, Hartstein AL. *Acinetobacter* outbreaks, 1977-2000. *Infect Control Hosp Epidemiol* 2003;24:284-95.
- Manikal VM, Landman D, Saurina G, Oydna E, Lal H, Quale J. Endemic carbapenem-resistant *Acinetobacter* species in Brooklyn, New York: citywide prevalence, interinstitutional spread, and relation to antibiotic usage. *Clin Infect Dis* 2000;31:101-6.
- Garnacho-Montero J, Ortiz-Leyba C, Fernández-Hinojosa E, et al. *Acinetobacter baumannii* ventilator-associated pneumonia: epidemiological and clinical findings. *Intensive Care Med* 2005;31:649-55.
- Hartstein AI, Rashad AL, Liebler JM, et al. Multiple intensive care unit outbreak of *Acinetobacter calcoaceticus* subspecies *anitratus* respiratory infection and colonization associated with contaminated, reusable ventilator circuits and resuscitation bags. *Am J Med* 1988;85:624-31.
- Maragakis LL, Cosgrove SE, Song X, et al. An outbreak of multidrug-resistant *Acinetobacter baumannii* associated with pulsatile lavage wound treatment. *JAMA* 2004;292:3006-11.
- Marchaim D, Navon-Venezia S, Schwartz D, et al. Surveillance cultures and duration of carriage of multidrug-resistant *Acinetobacter baumannii*. *J Clin Microbiol* 2007;45:1551-5.
- Naas T, Coignard B, Carbonne A, et al. VEB-1 extended-spectrum beta-lactamase-producing *Acinetobacter baumannii*, France. *Emerg Infect Dis* 2006;12:1214-22.
- Coelho JM, Turton JF, Kaufmann ME, et al. Occurrence of carbapenem-resistant *Acinetobacter baumannii* clones at multiple hospitals in London and Southeast England. *J Clin Microbiol* 2006;44:3623-7.
- Smith PW. Seasonal incidence of *Acinetobacter* infection. *J Infect Dis* 1979;140:275-6.
- McDonald LC, Banerjee SN, Jarvis WR. Seasonal variation of *Acinetobacter* infections: 1987-1996. *Clin Infect Dis* 1999;29:1133-7.
- Cordes LG, Brink EW, Checko PJ, et al. A cluster of *Acinetobacter* pneumonia in foundry workers. *Ann Intern Med* 1981;95:688-93.
- Lindberg RB, Wetzler TF, Marshall JD, Newton A, Strawitz JG, Howard JM. The bacterial flora of battle wounds at the time of primary debridement: a study of the Korean battle casualty. *Ann Surg* 1955;141:369-74.
- Tong MJ. Septic complications of war wounds. *JAMA* 1972;219:1044-7.
- Murray CK, Yun HC, Griffith ME,

- Hospenthal DR, Tong MJ. Acinetobacter infection: what was the true impact during the Vietnam conflict? *Clin Infect Dis* 2006;43:383-4.
36. *Acinetobacter baumannii* infections among patients at military medical facilities treating injured U.S. service members, 2002–2004. *MMWR Morb Mortal Wkly Rep* 2004; 53:1063-6.
 37. Hawley JS, Murray CK, Griffith ME, et al. Susceptibility of acinetobacter strains isolated from deployed U.S. military personnel. *Antimicrob Agents Chemother* 2007;51:376-8.
 38. Griffith ME, Lazarus DR, Mann PB, Boger JA, Hospenthal DR, Murray CK. Acinetobacter skin carriage among US army soldiers deployed in Iraq. *Infect Control Hosp Epidemiol* 2007;28:720-2.
 39. Scott P, Deye G, Srinivasan A, et al. An outbreak of multidrug-resistant Acinetobacter baumannii-calcoaceticus complex infection in the US military health care system associated with military operations in Iraq. *Clin Infect Dis* 2007;44:1577-84.
 40. Hujer KM, Hujer AM, Hulten EA, et al. Analysis of antibiotic resistance genes in multidrug-resistant Acinetobacter sp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center. *Antimicrob Agents Chemother* 2006;50:4114-23.
 41. Maegele M, Gregor S, Steinhäuser E, et al. The long-distance tertiary air transfer and care of tsunami victims: injury pattern and microbiological and psychological aspects. *Crit Care Med* 2005;33: 1136-40.
 42. Oncül O, Keskin O, Acar HV, et al. Hospital-acquired infections following the 1999 Marmara earthquake. *J Hosp Infect* 2002;51:47-51.
 43. Zanetti G, Blanc DS, Federli I, et al. Importation of Acinetobacter baumannii into a burn unit: a recurrent outbreak of infection associated with widespread environmental contamination. *Infect Control Hosp Epidemiol* 2007;28:723-5.
 44. Seifert H, Strate A, Pulverer G. Nosocomial bacteremia due to Acinetobacter baumannii: clinical features, epidemiology, and predictors of mortality. *Medicine (Baltimore)* 1995;74:340-9.
 45. Cisneros JM, Reyes MJ, Pachon J, et al. Bacteremia due to Acinetobacter baumannii: epidemiology, clinical findings, and prognostic features. *Clin Infect Dis* 1996; 22:1026-32.
 46. Wisplinghoff H, Edmond MB, Pfarrer MA, Jones RN, Wenzel RP, Seifert H. Nosocomial bloodstream infections caused by Acinetobacter species in United States hospitals: clinical features, molecular epidemiology, and antimicrobial susceptibility. *Clin Infect Dis* 2000;31:690-7.
 47. Muñoz-Price LS, Baig MO, Lavin MA, et al. Clinical features and outcomes of Imipenem resistant (Imi-R) *Acinetobacter baumannii* (Ab) bloodstream infections (BSI). Presented at the 46th Interscience Conference of Antimicrobial Agents and Chemotherapy, San Francisco, September 27–30, 2006.
 48. Snyderman DR, Maloy MF, Brock SM, Lyons RW, Rubin SJ. Pseudobacteremia: false-positive blood cultures from mist tent contamination. *Am J Epidemiol* 1977; 106:154-9.
 49. Lee NY, Lee HC, Ko NY, et al. Clinical and economic impact of multidrug resistance in nosocomial Acinetobacter baumannii bacteremia. *Infect Control Hosp Epidemiol* 2007;28:713-9.
 50. Kwon KT, Oh WS, Song JH et al. Impact of imipenem resistance on mortality in patients with Acinetobacter bacteremia. *J Antimicrob Chemother* 2007;59: 525-30.
 51. Buxton AE, Anderson RL, Werdegar D, Atlas E. Nosocomial respiratory tract infection and colonization with Acinetobacter calcoaceticus: epidemiologic characteristics. *Am J Med* 1978;65:507-13.
 52. Sunenshine RA, Wright MO, Maragakis LL, et al. Multidrug-resistant Acinetobacter infection mortality rate and length of hospitalization. *Emerg Infect Dis* 2007; 13:97-103.
 53. Garnacho J, Sole-Violan J, Sa-Borges M, Diaz E, Rello J. Clinical impact of pneumonia caused by Acinetobacter baumannii in intubated patients: a matched cohort study. *Crit Care Med* 2003;31:2478-82.
 54. Lesho E, Wortmann G, Moran K, Craft D. Fatal Acinetobacter baumannii infection with discordant carbapenem susceptibility. *Clin Infect Dis* 2005;41:758-9.
 55. Bergogne-Bérézin E, Towner KJ. Acinetobacter spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. *Clin Microbiol Rev* 1996; 9:148-65.
 56. Linden PK, Paterson DL. Parenteral and inhaled colistin for treatment of ventilator-associated pneumonia. *Clin Infect Dis* 2006;43:Suppl 2:S89-S94.
 57. Urban C, Segal-Maurer S, Rahal JJ. Considerations in control and treatment of nosocomial infections due to multidrug-resistant Acinetobacter baumannii. *Clin Infect Dis* 2003;36:1268-74.
 58. Horton J, Pankey GA. Polymyxin B, colistin, and sodium colistimethate. *Med Clin North Am* 1982;66:135-42.
 59. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* 2006;10(1):R27.
 60. Owen RJ, Li J, Nation RL, Spelman D. In vitro pharmacodynamics of colistin against Acinetobacter baumannii clinical isolates. *J Antimicrob Chemother* 2007;59: 473-7.
 61. Li J, Rayner CR, Nation RL, et al. Heteroresistance to colistin in multidrug-resistant Acinetobacter baumannii. *Antimicrob Agents Chemother* 2006;50:2946-50.
 62. Rice LB. Challenges in identifying new antimicrobial agents effective for treating infections with Acinetobacter baumannii and Pseudomonas aeruginosa. *Clin Infect Dis* 2006;43:Suppl 2:S100-S105.
 63. Peleg AY, Potoski BA, Rea R, et al. Acinetobacter baumannii bloodstream infection while receiving tigecycline: a cautionary report. *J Antimicrob Chemother* 2007;59:128-31.
 64. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant Acinetobacter baumannii. *Scand J Infect Dis* 2007;39:38-43.
 65. Levin AS, Levy CE, Manrique AE, Medeiros EA, Costa SF. Severe nosocomial infections with imipenem-resistant Acinetobacter baumannii treated with ampicillin/sulbactam. *Int J Antimicrob Agents* 2003;21:58-62.
 66. Motaouakkil S, Charra B, Hachimi A, et al. Colistin and rifampicin in the treatment of nosocomial infections from multidrug-resistant Acinetobacter baumannii. *J Infect* 2006;53:274-8.
 67. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. *Crit Care* 2005;9(1):R53-R59.
 68. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, et al. Treatment of multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. *Clin Infect Dis* 2003;36:1111-8.
 69. Sobieszczyk ME, Furuya EY, Hay CM, et al. Combination therapy with polymyxin B for the treatment of multidrug-resistant Gram-negative respiratory tract infections. *J Antimicrob Chemother* 2004;54: 566-9.
 70. Wood GC, Hanes SD, Boucher BA, Croce MA, Fabian TC. Tetracyclines for treating multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia. *Intensive Care Med* 2003;29:2072-6.
 71. Saballs M, Pujol M, Tubau F, et al. Rifampicin/imipenem combination in the treatment of carbapenem-resistant Acinetobacter baumannii infections. *J Antimicrob Chemother* 2006;58:697-700.
 72. Levin AS, Barone AA, Penco J, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. *Clin Infect Dis* 1999;28:1008-11.
 73. Ouderkirk JP, Nord JA, Turett GS, Kislak JW. Polymyxin B nephrotoxicity and efficacy against nosocomial infections caused by multiresistant gram-negative bacteria. *Antimicrob Agents Chemother* 2003;47:2659-62.

74. Holloway KP, Roupael NG, Wells JB, King MD, Blumberg HM. Polymyxin B and doxycycline use in patients with multidrug-resistant *Acinetobacter baumannii* infections in the intensive care unit. *Ann Pharmacother* 2006;40:1939-45.
75. Koomanachai P, Tiengrim S, Kiratisin P, Thamlikitkul V. Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Siriraj Hospital, Bangkok, Thailand. *Int J Infect Dis* 2007;11:402-6.
76. Falagas ME, Kasiakou SK. Use of international units when dosing colistin will help decrease confusion related to various formulations of the drug around the world. *Antimicrob Agents Chemother* 2006;50:2274-5.
77. Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2005;41:754-7.
78. Jiménez-Mejías ME, Pichardo-Guerrero C, Márquez-Rivas FJ, Martín-Lozano D, Prados T, Pachón J. Cerebrospinal fluid penetration and pharmacokinetic/pharmacodynamic parameters of intravenously administered colistin in a case of multidrug-resistant *Acinetobacter baumannii* meningitis. *Eur J Clin Microbiol Infect Dis* 2002;21:212-4.
79. Hansen S, Stamm-Balderjahn S, Zuscneid I, et al. Closure of medical departments during nosocomial outbreaks: data from a systematic analysis of the literature. *J Hosp Infect* 2007;65:348-53.
80. Chan PC, Huang LM, Lin HC, et al. Control of an outbreak of pandrug-resistant *Acinetobacter baumannii* colonization and infection in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2007;28:423-9.

Copyright © 2008 Massachusetts Medical Society.