Review Article

Acinetobacter Infection in the Intensive Care Unit

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ABSTRACT

The rising incidence of *Acinetobacter* infection in the intensive care unit (ICU) causes a great concern to all clinicians and intensivists worldwide due to their extraordinary ability to develop resistance to multiple classes of antibiotics. *Acinetobacter* can infect virtually any body site, particularly the lower respiratory tract, the bloodstream, and the urinary tract. Infection is mainly related to the inappropriate or previous use of antibiotics and the increasing use of invasive devices in the ICU. Although carbapenem is currently considered the drug of choice for these pathogens, the occurrence of carbapenem-resistant strains has led to fewer treatment options. Due to limited therapeutic options, prevention and infection control measures are essential. (*J Infect Dis Antimicrob Agents 2005;22:77-92.*)

INTRODUCTION

Until 1970, *Acinetobacter* spp. were considered rare causes of nosocomial infections in the intensive care unit (ICU).[1] In recent years, however, the incidence of *Acinetobacter* infections has reached a point of concern and poses a threat to hospitalized populations around the world.[2 - 8] Outbreaks have been increasingly reported regularly.[4-6,9] Moreover, most of those outbreaks were caused by multidrug-resistant (MDR) strains of this organism.[2-3,6] The initial concern about MDR-*Acinetobacter* strains began in 1991 when the first hospital-wide outbreak occurred in New York.[9] Now MDR-*Acinetobacter* strains are observed worldwide.[6,10-14] In Thailand, MDR-*Acinetobacter* infections have been described repeatedly.[13-14] This phenomenon is due to their extraordinary ability to develop multiple resistance mechanisms against major antibiotic classes used in the ICU including cephalosporins, aminoglycosides, carbapenems, and quinolones.[15] In addition, their ubiquitous nature in the ICU environment and inadequate infection-control

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practice have continuously raised the incidence of *Acinetobacter* infections over the past two decades.[16-17] Despite the global alarm caused by *Acinetobacter,* relatively few studies on this issue have been published. The understanding and recognition of *Acinetobacter* infections in the ICU is critically needed. This article reviews the current aspects of microbiology, epidemiology, clinical characteristics, treatment, and prevention of *Acinetobacter* infections in the ICU.

MICROBIOLOGY

Acinetobacter is a gram-negative coccobacillus that has emerged as an important nosocomial pathogen. It is non-motile, encapsulated, and non-fermentative.[11] It belongs to the family Neisseriaceae. Frequently, it can be misidentified as *Neisseria* or *Moraxella* species on gram staining[18], although the negative oxidase reaction is useful in distinguishing *Acinetobacter* from other gram-negative organisms in the same family. Furthermore, it is indole negative and catalase positive. *Acinetobacter* is ubiquitous in the outside environment and has been isolated from hospital personnel, and hospital equipments.[4-5,11,15] It is strictly aerobic, and does not require unusual nutrients to survive in the environment. *Acinetobacter* is easily grown on routine laboratory media (e.g. Tryptic soy agar), however, the specialized culture media are also available.[19] Colonies are 1-2 mm in diameter, dome-shaped, non-pigmented, with smooth or pitted surfaces (Figure 1).

Nowadays, there are more than 20 species of *Acinetobacter* reported.[20] However, the most common one known to cause major nosocomial infections in the ICU is *Acinetobacter baumannii*, formerly known as *Acinetobacter calcoaceticus* var. *anitratus*. This species makes up to 80 percent of total *Acinetobacter* clinical isolates and has been reported worldwide.[2,4-5,13-15,21-22] *Acinetobacter* can be grown from several human sources, including skin, pharynx, sputum, urine, vaginal secretions, and stool.[23] *Acinetobacter* spp. have, therefore, been implicated in a wide spectrum of infections, including pneumonia, meningitis, bacteremia, soft tissue infections, surgical site infections, peritonitis, endocarditis, catheter-related infections, and urinary tract infections.[24-25] These infections mostly occur in critically-ill patients.

One of the most striking features of *Acinetobacter* spp. is their extraordinary ability to develop multiple resistance mechanisms against several major antibiotic classes. The precise mechanisms that explain how multiple-drug resistance occurs are not fully known. However, recent studies have shown that MDR *Acinetobacter* can produce a great diversity of chromosomal and plasmid-mediated enzymes. *Acinetobacter* spp. can produce aminoglycoside-modifying enzymes to neutralize aminoglycosides and thus become resistant to this class of antimicrobial agents.[26] β-lactamases are another type of modifying enzymes that give them potential to become resistant to penicillins, cephalosporins, and carbapenems.[27-29] More interestingly, they can also diminish uptake of antibiotics into their cells by either changes in the outer membrane porins to decrease permeability to the agents or by creating active antimicrobial efflux systems.[28] Furthermore, *Acinetobacter* can alter the target protein to prevent the antibiotics from reaching their target, and thus becomes resistant. Examples of target modification include mutational changes of topoisomerase IV gene contributing to quinolone-resistance[30], and altered penicillin-binding proteins causing penicillin resistance.[29]

EPIDEMIOLOGY

Two decades ago, *Acinetobacter* infections were rare. According to the data from the United States National Nosocomial Infection Surveillance (NNIS) System, nosocomial infections caused by *Acinetobacter* spp. were ranked in the tenth position in 1988.[21,31] Since then, the incidence of *Acinetobacter* infections

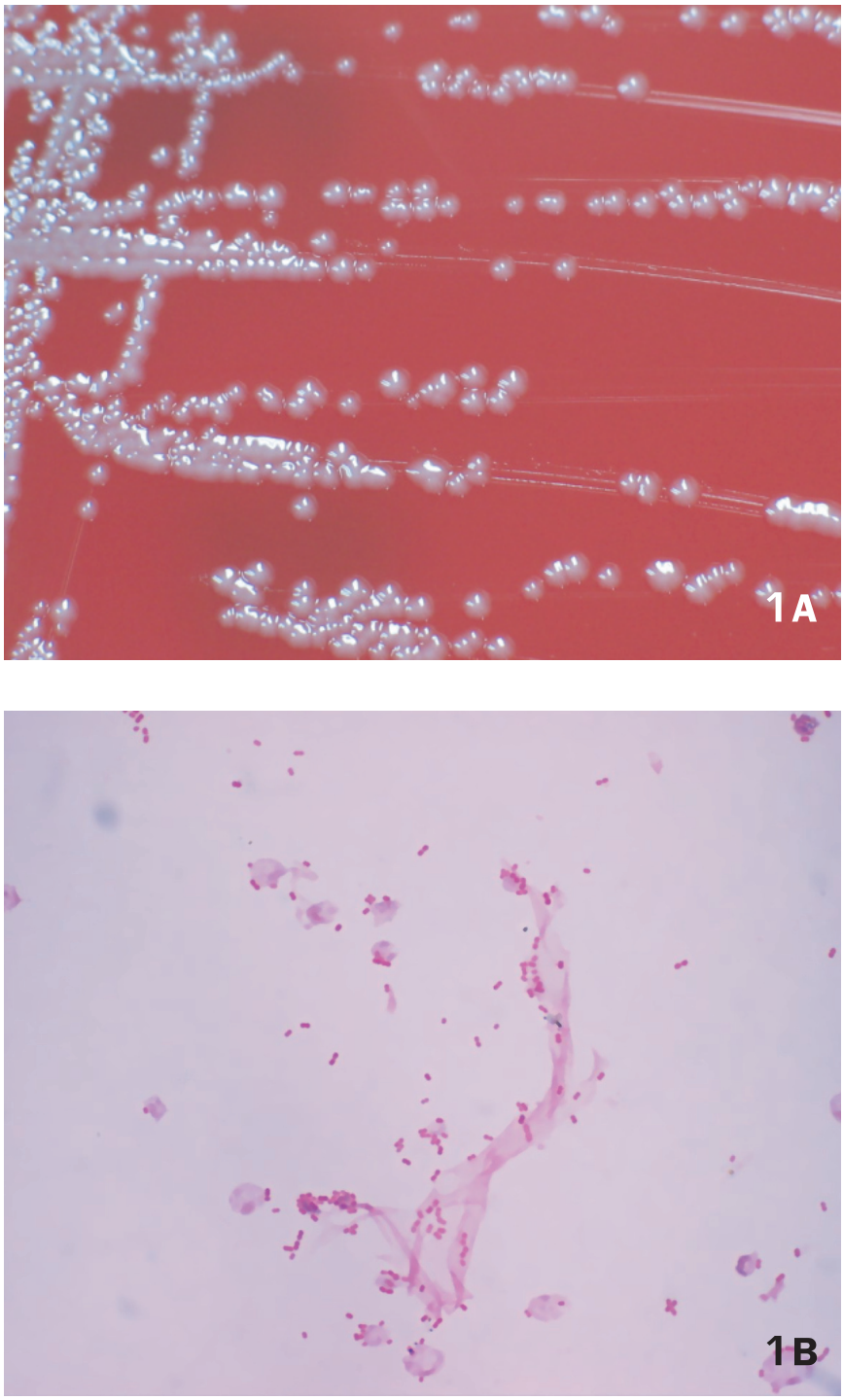

Figure 1. ***Acinetobacter calcoaceticus-baumannii*** **complex isolated from clinical specimens. (A) blood cultures from a patient with chronic lymphocytic leukemia grew** ***Acinetobacter calcoaceticus-baumannii*** **as dome-shaped, non-pigmented, smooth-surfaced colonies on blood agar. (B) a high-power view of gram stain showing encapsulated, gram-negative coccobacilli, consistent with** ***Acinetobacter*** **spp.** *(Courtesy of Salinee Phansuwan, B.Sc. (MT), Division of Laboratory Medicine, Praram 9 Hospital, Bangkok, Thailand)*

has risen significantly and continuously worldwide. Several hospital-wide outbreaks due to this organism have been reported.[4,12,16-17,28,32-34] At present, 10-30 percent of nosocomial infections in the ICU, particularly pneumonia, are associated with *Acinetobacter* spp., compared to only 2-4 percent in the last 15 years.[35]

Acinetobacter spp. are ubiquitous in the environment, both outside and inside hospital, particularly in the ICU environment. Some authors in the 1960s and late 1970s were able to isolate *Acinetobacter* from human skin in up to 25 percent of healthy adults[36], mostly from their hands.[37] In fact, *Acinetobacter* is considered to be the most common gram-negative organism colonized on the skin of hospital personnel, including ICU nurses and respiratory therapists.[15] Moreover, transient pharyngeal colonization was noted in 7 percent of healthy individuals enrolled in one study.[38] These findings indicate that hospital personnel and hospitalized patients may be the most important reservoir of this organism[37], leading to the persistently increased incidence of *Acinetobacter* nosocomial infections. Besides human skin, *Acinetobacter* has also been isolated from soil[15], water[15], fish[39], meat[39], vegetables[39], hospital air[40], tap water faucets[39], sink basins[40], bed mattresses[41], bedside urinals[41]and respiratory therapy equipments.[40] More interestingly, some reports showed that *Acinetobacter* colonization and infections occurred more commonly during the warmer and more humid months.[42-43] Additionally, infections caused by these pathogens in the ICU appeared to be more prevalent in the tropical and subtropical areas such as Australia[43]and Hong Kong.[42]

Acinetobacter spp. can cause a wide spectrum of clinical infections in the ICU, including pneumonia, meningitis, bacteremia, urinary tract infection, endocarditis, peritonitis, and soft-tissue infections.[24-25,31] Larson reviewed the incidence of nosocomial infections acquired in the ICU from January 1971 to April 1981, and showed that the most common ICU-acquired nosocomial infections caused by *Acinetobacter* spp. is the lower respiratory tract infections.[44] The incidence of other sites of infection is as shown in Figure 2.

The recent emerging of drug-resistant *Acinetobacter* has caused a great concern worldwide. A study in 2002 showed that 12 percent of *Acinetobacter* isolates were resistant to all standard antibiotics.[12] Some studies indicated that up to 80 percent were resistant to all aminoglycosides[45] and ciprofloxacin.[30] About 70 percent of isolates resisted to ceftazidime.[46-47] Twenty to 30 percent were resistant to β-lactam and β-lactamase inhibitor combinations.[47] More importantly, carbapenem-resistance rate was recently reported about 11-53 percent.[12] In fact, MDR *Acinetobacter* infection has also become a serious problem in the ICU located in several Asian countries.[13-14,22,46,48-49] Its incidence is currently on the rise in Thailand[13-14], China[22], Hong Kong[48], Taiwan[46], and Malaysia.[49] In Thailand, the most recent National Susceptibility Surveillance data indicated that drug-resistant *Acinetobacter* is prevalent in Thailand. As high as 44 percent, and 16 percent of clinical isolates were reported resistant to ceftazidime, and imipenem, respectively.[50] At the author's institution[51], in the year 2004, more than half of all *Acinetobacter* clinical isolates were multidrug-resistant, which has raised three fold in the past two years.

PREDISPOSING FACTORS

A number of risk factors have been shown to be associated with *Acinetobacter* nosocomial infections. They include advanced age[52], immunosuppression[53-54], surgery[55], previous treatment with broad-spectrum antibiotics[35,53,56-60], use of invasive devices[61], burns[62], fecal colonization with *Acinetobacter*[63], and prolonged hospital or ICU stays.[32,53,56]

Recent evidence demonstrated that the occurrence of *Acinetobacter* nosocomial pneumonia in the

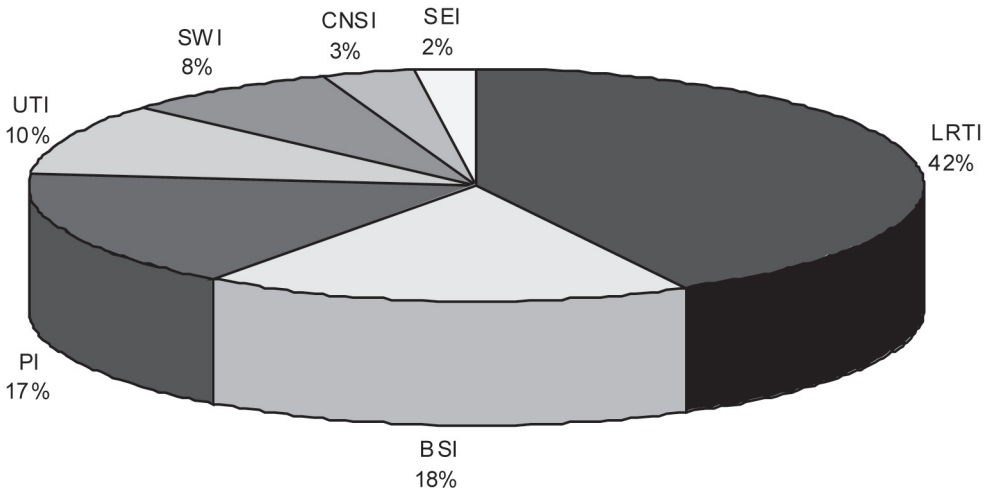

Figure 2. Major sites of infection caused by *Acinetobacter* spp. acquired in the intensive care units (adapted from Larson E[44]). Lower respiratory tract infection: LRTI, bloodstream infection: BSI, peritoneal infection: PI, urinary tract infection: UTI, surgical wound infection: SWI, central nervous system infection: CNSI, skin and eye infections: SEI.

ICU is contributed by several factors.[52-53,59,62] Immunosuppressed hosts, including neutropenic patients and HIV-infected individuals, especially those with low CD4 cell counts, are at particular risk.[54] Morever, those with severe underlying diseases, as indicated by a markedly elevated APACHE II score, are also more prone to develop *Acinetobacter* nosocomial pneumonia and ventilator-associated pneumonia (VAP).[62] Previous use of antibiotics, particularly third-generation cephalosporins[35,59], aminoglycosides[60], quinolones[35,53,56], or carbapenems[35,53,57], within 15 days preceding the pneumonic episodes is also strongly associated with the occurrence of nosocomial pneumonia caused by these pathogens. The duration of ICU or hospital stays of 5 days or more appear to be another important risk factor for nosocomial pneumonia.[32,53,56] This could partly be explained by the increased rate of bacterial colonization and translocation, as the hospital or ICU stays becomes longer. Another explanation could be attributed to the more frequent use of invasive devices in the ICU[61], including endotracheal tube[56], central venous catheter[61], and tracheostomy.[52,64-67] The patients who stay longer in the ICU may be sicker, and require more invasive monitoring and therapeutic procedures to survive; therefore, they are predisposed to the development of pneumonia. Likewise, the duration of mechanical ventilatory support (MVS) can also directly influence the occurrence of VAP.[15,56,68] Trouillet and co-workers[35] showed that there is a non-linear relationship between the risk of *Acinetobacter* VAP and duration of mechanical ventilation. They estimated the cumulative risk of VAP related to these pathogens to be 3.4 percent, 20 percent, and 48 percent at 10 days, 20 days and 30 days of MVS, respectively. Other risk factors include head injury [odds ratio (OR) 5.17, CI 0.88-30.34], especially those with Glasgow coma score ≤ 9, acute respiratory distress syndrome (ARDS) (OR 9.73, CI 1.6-59.24), and large-volume pulmonary aspiration (OR 2.9, CI 0.8-10.53).[55,69]

There are fewer data available concerning *Acinetobacter* bacteremia. The risk factors for ICU-ac-

quired bacteremia due to these pathogens are previous sepsis in the ICU (OR = 4.36), unscheduled admission to the hospital (OR = 3.29), respiratory failure at the onset of ICU admission (OR = 2.90), previous antibiotic therapy (OR = 2.35), and use of invasive devices in the ICU.[61,70] Immunosuppression, including organ transplantation, corticosteroids, and immunosuppressive therapy, is also another important risk factor for *Acinetobacter* bacteremia.[61,70-71] In a prospective cohort study of 233 critically ill patients with bacteremia who were admitted to the ICU, 42 of them (18%) were caused by *Acinetobacter* spp.[70] Almost one-third of them had hematological malignancies, and some of them were neutropenic. The risk of bacteremia was increased by three-fold among these patients, as compared to a normal host.

CLINICAL FEATURES

Acinetobacter spp. can cause infection in any body sites. However, only three sites of *Acinetobacter* infection, namely the lower respiratory tract, the bloodstream, and the urinary tract are common in the ICU. The infection of these sites are discussed in this article.

PNEUMONIA

Even though *Acinetobacter* spp. are implicated in a wide spectrum of infections, pneumonia appears to be the most dangerous one with the highest mortality rates.[71-73] Over the past several years, the incidence of *Acinetobacter* pneumonia in the ICU has increased significantly, accounting for 6-30 percent of all ICU infections.[11,35,72,74-77] *Acinetobacter* can cause either community-acquired or hospital-acquired pneumonia (HAP).[43,78-79] However, it is usually seen more often as late-onset HAP (i.e. after 4 days of hospitalization). Early-onset HAP can also occur, particularly in patients who received prior antimicrobial therapy[80] or recent hospitalization within 90 days before the onset of pneumonia.[35,81] Similar to other nosocomial pneumonia, it should be suspected when patients develop fever (temperature $\geq 38^{o}$C), increased purulent tracheal secretions, abnormal leukocyte counts, and a new or progressive radiographic infiltrate.[53] Typically, the radiographic findings of those with *Acinetobacter* pneumonia are multilobar. Some patients, however, may present with cavitation, pleural effusion, empyema, and bronchopleural fistula.[81] Secondary bacteremia and septic shock can also be seen, and are often associated with poor prognosis.[82] In a retrospective review of 15 cases[59], up to 50 percent of patients with *Acinetobacter* nosocomial pneumonia were bacteremic. Sepsis was found in 35 percent of them. Of all patients, 43 percent died.

Similar to other causes of nosocomial pneumonia, *Acinetobacter* can prolong the hospital stay by an average of 7-9 days per patient.[83-84] Not only that, nosocomial pneumonia caused by *Acinetobacter* spp. also carries the highest mortality rates, compared to other organisms.[71-72,76,85] This phenomenon could be attributed to the development of MDR strains of *Acinetobacter*.[86-87] Several trials have highlighted the importance of MDR *Acinetobacter* and mortality rates, which are reported to be approaching 90 percent, especially in those who required mechanical ventilation.[15,72-73,84] Fagon and coworkers found a mortality rate of 87 percent in those with VAP attributed to MDR *Acinetobacter*, compared with a mortality rate of 55 percent in patients with VAP caused by other organisms ($p<0.02$).[72] Another study among intubated patients found a mortality rate of 78.5 percent.[80]

A prospective study of 87 patients with late-onset VAP also showed that the risk of hospital mortality was increased among those due to MDR *Acinetobacter* with adjusted OR of 5.4 (95% CI 2.8-10.3, p=0.009), compared to other pathogens.[73] More interestingly, the high mortality rates decreased significantly once appropriate antibiotics were given for more than three

days.[53,56,80,88-90] This underscores the necessity of early and appropriate empirical antibiotic therapy to help improve the survival of these patients, especially those in the ICU.

BACTEREMIA

Infections of any body site caused by *Acinetobacter* spp. may progress to bacteremia. *Acinetobacter* bacteremia can affect patients of all ages, but is seen predominantly in the elderly.[61,91-92] In addition, it is commonly seen in immunosuppressed patients, as shown by Vidal et al.[71] Of 296 consecutive episodes of *Acinetobacter* bacteremia described in their study, 26.3 percent of those patients received corticosteroid therapy, and 23.6 percent were either bone marrow or solid organ transplant recipients. The most common source of bacteremia was the central venous catheter infection, accounting for almost 40 percent of all cases in one series.[61,71,93] Pneumonia and urinary tract infection (UTI) were associated with bacteremia in 10.5 percent and 5.4 percent, respectively.[71] Other sites included skin, soft tissue and wounds, as shown in a recent study demonstrating a higher incidence of *Acinetobacter* bacteremia in patients with burns on 50 percent or more of the total body surface area, compared to those without burns or with less severe burns.[91]

Once *Acinetobacter* bacteremia occurs, septic shock can be seen in up to one third of patients.[94-95] Other serious complications that have been reported include prosthetic valve endocarditis, suppurative thrombophlebitis, and subhepatic abscess.[85]

Mortality rates of 15 to 46 percent have been reported for *Acinetobacter* bacteremia.[71,86,97-98] The relatively low mortality, as compared to pneumonia, may be related to the underlying disease severity of those bacteremic patients. Most bacteremia is simply caused by catheter-related infections[61,71,93], of which much improved mortality can be promptly seen once the catheter is removed, whereas the patients with pneumonia are more frequently septic and carry severe underlying diseases.[95] More interestingly, the species of *Acinetobacter* causing bacteremia can also influence the mortality. Bacteremia due to species other than *A. baumannii* tends to be less severe.[91]

URINARY TRACT INFECTION

Although the true incidence of *Acinetobacter* UTI remains unclear, it is estimated that UTI represented about 31 percent of nosocomial infections in the ICU.[31] It is commonly found in the presence of an indwelling urinary catheter, in females, with prolonged ICU stays.[99-102] Although it is occasionally associated with pyelonephritis, and urosepsis[101,103-104], it is rarely invasive and usually limited to the lower urinary tract.[85] Diagnosis can be made by collecting a urine sample for analysis, gram stain and culture. The presence of pyuria, and organisms of at least 10^2-10^5 colony-forming unit (CFU)/ml isolated from the culture media are diagnostic. A blood culture should also be obtained before initiating therapy.[103]

THERAPY

Treatment of *Acinetobacter* infections in the ICU generally requires antimicrobial therapy, as well as supportive care. The selection of appropriate initial empirical antibiotics is the key aspect of care to help improve survival of these patients.[53,89-90,105-107] Due to the recent emerging drug-resistant *Acinetobacter* spp. in the ICU, all regimens for nosocomial infections in the ICU, particularly VAP, must be tailored to empirically cover this highly-resistant organism.[53] Nonetheless, one should keep in mind that every ICU has its own characteristic spectrum of drug-resistant pathogens. Local susceptibility patterns, therefore, have to be considered when selecting the initial empirical antibiotics for nosocomial *Acinetobacter* infections.[107-108] Once

the culture and susceptibility results become available, de-escalation of therapy is recommended to minimize the risk of colonization and superinfection due to other MDR-organisms.[53,106]

Surprisingly, despite the increasing incidence of *Acinetobacter* infections, only a limited number of clinical studies regarding the treatment of these highly-resistant pathogens are available.[109] Furthermore, these clinical studies are mostly small-sized, and some are case reports. In recent trials, carbapenems are the most reliable therapeutic agents for infections caused by these pathogens. The susceptibility rates are reportedly higher than 90 percent in some studies, although others report much lower susceptibility due to the occurrence of multidrug-resistant strains.[87,109] In one study, among all available therapeutic options, carbapenems provide the highest bactericidal efficacy.[110-111] Not all carbapenems are effective against *Acinetobacter* spp. Although the newly approved carbapenem, ertapenem, offers more convenience than the earlier ones, due to its once-daily dosing, it lacks the activity toward these organisms, and should not be used.[112-114]

Sulbactam appears to be a reasonable alternative for infections caused by *Acinetobacter* spp. It inhibits β-lactamases and blocks peptidoglycan biosynthesis of these pathogens.[115] Its efficacy has been well documented in several trials. A retrospective study by Wood and co-workers evaluated 14 patients with *Acinetobacter* VAP who were treated with ampicillin-sulbactam, compared with imipenem.[116] They found that the efficacy of ampicillin-sulbactam was comparable to imipenem. Mortality, length of ICU stays, and duration of mechanical ventilation between both groups were not different. Another study from Japan using cefoperazone-sulbactam also demonstrated good efficacy against *Acinetobacter* spp.[117] Another option for managing *Acinetobacter* infections is polymyxins, either intravenous or aerosolized forms. Both have only a limited role due to unclear efficacy against these pathogens[111,118-121] and their significant toxicity, including dose-related nephrotoxicity (up to 25%)[122-126], and neuromuscular blockade (10%).[121,127] They are reserved for use only when no other alternatives are available.

The emergence of MDR strains of *Acinetobacter* spp. has led to fewer treatment options. Only sulbactam has been shown to be effective in these circumstances, with clinical cure rate up to 70 percent.[128-130] Intravenous polymyxin E (colistin) is not a good option for pneumonic cases, according to one study which showed only a 25 percent cure rate.[118,121] However, among those with infections involving other body sites, colistin provides a better activity with clinical improvement reported in almost 60 percent of cases.[121] Other alternatives include tetracyclines, for which clinical data in humans is still limited and needs further study.[110,131]

Some authors have recommended combination therapy to treat serious cases of *Acinetobacter* infection, although available clinical data regarding this remains inconclusive.[53,116,132] The addition of an aminoglycoside and/or rifampin may provide faster bactericidal activity, and prevent the further occurrence of drug-resistance.

TRANSMISSION & PREVENTION

Several hospital-wide outbreaks have been previously described.[4-6,9] Most of these outbreaks indicated that hospital personnel are the most important reservoir of these highly-resistant pathogens in the ICU, and have led to cross contamination during patient care.[15,36-38,133] Hand and skin transmission of this organism by health-care personnel have been well documented.[36-37,133] The study by Larson and co-workers showed that 12.3 percent of patients in the United States were colonized with *Acinetobacter* spp.[134] In Thailand, *Acinetobacter* colonization on the human skin appears to be more prevalent. Thamlikitkul and colleagues[135] evaluated microbial skin flora in 350 outpatients and 500 inpatients. *Acinetobacter* was found on the skin in more than one-third of hospitalized patients. Cur-

rently, although there is no clear explanation for this high prevalence of *Acinetobacter* skin colonization in Thailand, the warmer climate could be relevant.

ICU environmental contamination appears to be another important source. The significant environmental reservoirs in the ICU include room surfaces[16], ventilators[17], ventilator tubing[136], resuscita-tion bags[33], mattresses[33-34], hand-washing sinks[16,40], gowns and gloves.[16] More interestingly, it is possible that airborne dispersal could be an indirect source, especially during a hospital outbreak, as has been described in a previous study.[137]

To prevent the occurrence and transmission of this organism in the ICU, infection control measures are essential. Measures described in the clinical trials include hand disinfection using either alcohol hand gel or chlorhexidine[138] and contact isolation using glove, gown, and barrier precautions.[139] In most circumstances, however, these two measures alone may not be sufficient. Specialized infection control measures are therefore needed. As indicated in numerous studies, the major focus is the antibiotic control strategy, which consists of restricted use of third generation cephalosporins and carbapenems[5,75,139,141], antibiotic cycling schedules[75,140], and implementation of antimicrobial prescribing guidelines.[139] Other measures include rigorous cleaning and disinfection of the ICU environment using 1,000 ppm hypochlorite solution[142]; surveillance cultures of patients, environmental surfaces, and staffs[4,34,139]; continuous educational and quality control programs for all ICU personnel[9]; and adequate ICU staffing. Moreover, partial structural redesign of the units and placement of hand-washing facilities within the rooms have been reported to be highly effective in achieving successful transmission control.[143] Although some above mentioned measures seem to be costly, most of them are simple and have been proven to be effective.[144-145]

SUMMARY

Emerging infections due to MDR strains of *Acinetobacter* spp. in the ICU is a therapeutic concern for clinicians worldwide. Few treatment options are currently available, including sulbactam and polymyxins. Due to limited therapeutic options, prevention and infection control measures are essential. These should include not only traditional infection control measures, but also antibiotic control strategies in the ICU.

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References

1. Villers D, Espaze E, Coste-Burel M, et al. Nosocomial *Acinetobacter baumannii* infections: microbiological and clinical epidemiology. Ann Intern Med 1998; 129:182-9.
2. Afzal-Shah M, Livermore DM. Worldwide emergence of carbapenem-resistant *Acinetobacter* spp. 1998. J Antimicrob Chemother 1998;41:576-7.
3. Tomasz A. Multiple-antibiotic-resistant pathogenic bacteria. N Engl J Med 1994;330:1247-51.
4. Corbella X, Montero A, Pujol M, et al. Emergence and rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant *Acinetobacter baumannii*. J Clin Microbiol 2000; 38:4086-95.
5. Houang ETS, Chu YW, Leung CM, et al. Epidemiology and infection control implications of *Acinetobacter* spp. in Hong Kong. J Clin Microbiol 2001;39:228-34.
6. Fridkin SK. Increasing prevalence of antimicrobial resistance in intensive care units. Crit Care Med

2001;29 (Suppl 4):N64-8.

7. Costantini M, Donisi PM, Turrin MG, Diana L. Hospital acquired infections surveillance and control in intensive care services. Results of an incidence study. Eur J Epidemiol 1987;3:347-55.
8. Kanafani ZA, Kara L, Hayek S, Kanj SS. Ventilator-associated pneumonia at a tertiary-care center in a developing country: incidence, microbiology, and susceptibility patterns of isolated microorganisms. Infect Control Hosp Epidemiol 2003;24:864-9.
9. Go ES, Urban C, Burns J, et al. Clinical and molecular epidemiology of *Acinetobacter* infections sensitive only to polymyxin B and sulbactam. Lancet 1994; 344:1329-32.
10. Karlowsky JA, Draghi DC, Jones ME, Thornsberry C, Friedland IR, Sahm DF. Surveillance for antimicrobial susceptibility among clinical isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from hospitalized patients in the United States, 1998 to 2001. Antimicrob Agents Chemother 2003;47:1681-8.
11. Chastre J, Trouillet JL. Problem pathogens (*Pseudomonas aeruginosa* and *Acinetobacter*). Semin Respir Infect 2000;15:287-98.
12. Landman D, Quale JM, Mayorga D, et al. Citywide clonal outbreak of multiresistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Brooklyn, NY: the preantibiotic era has returned. Arch Intern Med 2002;162:1515-20.
13. Srifuengfung S, Sangsawang M, Komolpis P, Dhiraputra C, Chompanee B. Bacterial pathogens (non-myco bacterium) from sputum culture and antimicrobial susceptibility. Southeast Asian J Trop Med Public Health 1998;29:96-9.
14. Thongpiyapoom S, Narong MN, Suwalak N, et al. Device-associated infections and patterns of antimicrobial resistance in a medical-surgical intensive care unit in a university hospital in Thailand. J Med Assoc Thai 2004;87:819-24.
15. Chastre J. Infections due to *Acinetobacter baumannii* in the ICU. Semin Resp Crit Care Med 2003;24:69-78.
16. Tankovic J, Legrand P, De Gatines G, Chemineau V, Brun-Buisson C, Duval J. Characterization of a hospital outbreak of imipenem-resistant *Acinetobacter baumannii* by phenotypic and genotypic typing methods. J Clin Microbiol 1994;32:2677-81.
17. Castle M, Tenney JH, Weinstein MP, Eickhoff TC. Outbreak of a multiply resistant *Acinetobacter* in a surgical intensive care unit: epidemiology and control. Heart Lung 1978;7:641-4.
18. Joyce M, Woods CW. Antibacterial susceptibility testing in the clinical laboratory. Infect Dis Clin N Am 2004;18:401-34.
19. Mandel AD, Wright K, McKinnon JM. Selective medium for selection of *Mima* and *Herellea* organisms. J Bacteriol 1964;88:1524-5.
20. Bergogne-Berezin E, Towner KJ. *Acinetobacter* spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. Clin Microbiol Rev 1996;9: 148-65.
21. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990- May 1999, issued June 1999. Am J Infect Control 1999;27: 520-32.
22. Yu YS, Yong Q, Xu XW, Kong HS, Xu GY, Zhong BY. Typing and characterization of carbapenem-resistant *Acinetobacter calcoaceticus*-baumannii complex in a Chinese hospital. J Med Microbiol 2004;53(Pt 7): 653-6.
23. Agusti C, Pujol M, Argerich MJ, et al. Short-term effect of the application of selective decontamination of the digestive tract on different body site reservoir ICU patients colonized by multiresistant *Acinetobacter baumannii*. J Antimicrob Chemother 2002;49:205-8.

24. Forster DH, Daschner FD. *Acinetobacter* species as nosocomial pathogens. Eur J Clin Microbiol Infect Dis 1998;17:73-7.

25. Gales AC, Jones RN, Forward KR, Linares J, Sader HS,

Verhoef J. Emerging importance of multidrug-resistant *Acinetobacter* species and *Stenotrophomonas maltophilia* as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY Antimicrobial Surveillance Program (1997-1999). Clin Infect Dis 2001;32 (Suppl 2): S104-S13.

26. Miller GH, Sabatelli FJ, Hare RS, et al. The most frequent

aminoglycoside resistance mechanisms--changes with time and geographic area: a reflection of aminoglycoside usage patterns? Aminoglycoside Resistance Study Groups. Clin Infect Dis 1997;24 (Suppl 1):S46-S62.

27. Danes C, Navia NM, Ruiz J, et al. Distribution of β-lactamases in *Acinetobacter baumannii* clinical isolates and the effect of Syn 2190 (Amp C inhibitor) on the MICs of different β-lactam antibiotics. J Antimicrob Chemother 2002;50:261-4.

28. Bou G, Cervero G, Dominguez MA, Quereda C, Martinez-

Beltran J. Characterization of a nosocomial outbreak caused by a multiresistant *Acinetobacter baumannii* strain with a carbapenems-hydrolyzing enzyme: high-level carbapenems resistance in *A.baumannii* is not due solely to the presence of beta-lactamases. J Clin Microbiol 2000;38:3299-305.

29. Quale J, Bratu S, Landman D, Heddurshetti R. Molecular

epidemiology and mechanisms of carbapenem resistance in *Acinetobacter baumannii* endemic in New York City. Clin Infect Dis 2003;37:214-20.

30. Vila J, Ruiz J, Goni P, Jimenez de Anta T. Quinolone-resistance mutations in the topoisomerase IV parC gene of *Acinetobacter baumannii*. J Antimicrob Chemother 1997;39:757-62.

31. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med 1999;27:887-92.

32. Scerpella EG, Wanger AR, Armitage L, Anderlini P, Ericsson CD. Nosocomial outbreak caused by a multiresistant clone of *Acinetobacter baumannii*: results of the case-control and molecular epidemiologic investigations. Infect Control Hosp Epidemiol 1995;16:92-7.

33. Sherertz RJ, Sullivan ML. An outbreak of infections with *Acinetobacter calcoaceticus* in burn patients: contamination of patients'mattresses. J Infect Dis 1985;151:252-8.

34. Simor AE, Lee M, Vearncombe M, et al. An outbreak due to multiresistant *Acinetobacter baumannii* in a burn unit: risk factors for acquisition and management. Infect Control Hosp Epidemiol 2002;23:261-7.

35. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998;157:531-9.

36. Al-Khoja MS, Darrell JH. The skin as the source of *Acinetobacter* and *Moraxella* species occurring in blood cultures. J Clin Pathol 1979;32:497-9.

37. Larson EL. Persistent carriage of gram-negative bacteria

on hands. Am J Infect Control 1981;9:112-9.

38. Baltimore RS, Duncan RL, Shapiro ED, Edberg SC. Epidemiology of pharyngeal colonization of infants with aerobic gram-negative rod bacteria. J Clin Microbiol 1989;27:91-5.

39. Villegas MV, Hartstein AI. *Acinetobacter* outbreaks, 1977-2000. Infect Control Hosp Epidemiol 2003;24: 284-95.

40. Bergogne-Berezin E. The increasing significance of outbreaks of *Acinetobacter* spp.: the need for control and new agents. J Hosp Infect 1995;30 Suppl:441-52.

41. Neely AN. A survey of gram-negative bacteria survival

on hospital fabrics and plastics. J Burn Care Rehabil 2000;21:523-7.

42. Chu YW, Leung CM, Houang ET, et al. Skin carriage

of

Acinetobacters in Hong Kong. J Clin Microbiol 1999;37:2962-7.

43. Anstey NM, Currie BJ, Withnall KM. Community-acquired *Acinetobacter* pneumonia in the Northern Territory of Australia. Clin Infect Dis 1992;14:83-91.

44. Larson E. A decade of nosocomial *Acinetobacter*. Am

J Infect Control 1984;12:14-8.

45. Fridkin SK, Steward CD, Edwards JR, et al. Surveillance

of antimicrobial use and antimicrobial resistance in United States hospital: project ICARE phase 2. Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE) hospitals. Clin Infect Dis 1999;29:245-52.

46. Lauderdale TL, Clifford McDonald L, Shiau YR, et al. The status of antimicrobial resistance in Taiwan among gram-negative pathogens: the Taiwan surveillance of antimicrobial resistance (TSAR) program, 2000. Diagn Microbiol Infect Dis 2004;48:211-9.

47. Turner PJ, Greenhalgh JM. The activity of meropenem

and comparators against *Acinetobacter* strains isolated from European hospitals, 1997-2000. Clin Microbiol Infect 2003;9:563-7.

48. Siau T, Yuen KY, Ho PL, Wong SS, Woo PC. *Acinetobacter* bacteremia in Hong Kong: prospective study and review. Clin Infect Dis 1999;28:26-30.

49. Rozaidi SW, Sukro J, Dan A. The incidence of nosocomial infection in the intensive care unit, hospital Universiti Kebangsaan Malaysia: ICU-acquired nosocomial infection surveillance program 1998-1999. Med J Malaysia 2001;56:207-22.

50. Dejsirilert S, Apisarnthanarak A, Kijphati R, et al. The

status of antimicrobial resistance in Thailand among gram-negative pathogens bloodstream infection: NARST data, 2000-2003 [abstract]. In: Program and abstracts of the 9th Western Pacific Biennial Congress of Chemotherapy and Infectious Diseases. Bangkok, Thailand, 2004.

51. Microbiology laboratory annual data and susceptibility

testing results. Nakornnayok: Microbiology Laboratory,

HRH Princess Maha Chakri Sirindhorn Medical Center, 2004.

52. Mahgoub S, Ahmed J, Glatt AE. Underlying characteristics of patients harbouring highly resistant *Acinetobacter baumannii*. Am J Infect Control 2002;30:386-90.

53. American Thoracic Society & Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

54. Manfredi R, Nanetti A, Valentini R, Chiodo F. *Acinetobacter* infections in patients with human immunodeficiency virus infection: microbiological and clinical epidemiology. Chemotherapy 2001;47:19-28.

55. Baraibar J, Correa H, Mariscal D, Gallego M, Valles J, Rello J. Risk factors for infection by *Acinetobacter baumannii* in intubated patients with nosocomial pneumonia. Chest 1997;112:1050-4.

56. Garnacho-Montero J, Ortiz-Leyba C, Fernandez-Hinojosa

E, et al. *Acinetobacter baumannii* ventilator-associated pneumonia: epidemiological and clinical findings. Intensive Care Med 2005;31:649-55.

57. 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.

58. Cardenosa Cendrero JA, Sole-Violan J, Bordes Benitez A, et al. Role of different routes of tracheal colonization in the development of pneumonia in patients receiving mechanical ventilation. Chest 1999;116:462-70.

59. Husni RN, Goldstein LS, Arroliga AC, et al. Risk factors

for an outbreak of multidrug-resistant *Acinetobacter* nosocomial pneumonia among intubated patients.

Chest 1999;115:1378-82.

60. Zarilli R, Crispino M, Bagattini M, et al. Molecular epidemiology of sequential outbreaks of *Acinetobacter baumannii* in an intensive care unit shows the emergence of carbapenem resistance. J Clin Microbiol 2004;42:946-53.
61. Valero C, Garcia Palomo JD, Matorras P, et al. *Acinetobacter* bacteremia in a teaching hospital, 1989-1998. Eur J Intern Med 2001;12:425-9.
62. Lortholary O, Fagon JY, Hoi AB, et al. Nosocomial acquisition of multiresistant *Acinetobacter baumannii*: risk factors and prognosis. Clin Infect Dis 1995;20: 790-6.
63. Carbella X, Piyol M, Ayats J, et al. Relevance of digestive tract colonization in the epidemiology of nosocomial infections due to multiresistant *Acinetobacter baumannii*. Clin Infect Dis 1996;23: 329-34.
64. Rello J, Lorente C, Diaz E, et al. Incidence, etiology, and outcome of nosocomial pneumonia in ICU patients requiring percutaneous tracheotomy for mechanical ventilation. Chest 2003;124:2239-43.
65. Wright SE, VanDahm K. Long-term care of the tracheostomy patient. Clin Chest Med 2003;24:473-87.
66. Cook DJ, Walter SD, Cook RJ, et al. Incidence and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 1998;129:433-40.
67. Georges H, Leroy O, Guery B, et al. Predisposing factors for nosocomial pneumonia in patients receiving mechanical ventilation and requiring tracheotomy. Chest 2000;118:767-74.
68. Diaz O, Diaz E, Rello J. Risk factors for pneumonia in the intubated patient. Infect Dis Clin North Am 2003;17:697-705.
69. Akca O, Koltka K, Uzel S, et al. Risk factors for early-onset, ventilator-associated pneumonia in critical care patients: selected multiresistant versus nonresistant bacteria. Anesthesiology 2000;93:638-45.
70. Garcia-Garmendia JL, Ortiz-Leyba C, Garnacho-Montero J, et al. Risk factors for *Acinetobacter baumannii* nosocomial bacteremia in critically ill patients: a cohort study. Clin Infect Dis 2001;33:939-46.
71. Vidal F, Mensa J, Almela M, et al. Bacteremia in adults due to glucose non-fermentative gram-negative bacilli other than *P. aeruginosa*. QJM 2003;96:227-34.
72. Fagon JY, Chastre J, Domart Y, et al. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. Am Rev Respir Dis 1989;139: 877-84.
73. Kollef MH, Silver P, Murphy DM, Travillion E. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. Chest 1995;108:1655-62.
74. Rello J, Torres A. Microbial causes of ventilator-associated pneumonia. Semin Respir Infect 1996;11: 24-31.
75. Gruson D, Hilbert G, Vargas F, et al. Rotation and restricted use of antibiotics in a medical intensive care unit. Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. Am J Respir Crit Care Med 2000;162(3 Pt 1): 837-43.
76. Torres A, Aznar R, Gatell JM, et al. Incidence, risk, and prognostic factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 1990;142:523-28.
77. Kofteridis DP, Papadakis JA, Bouros D, et al. Nosocomial lower respiratory tract infections: prevalence and risk factors in 14 Greek hospitals. Eur J Clin Microbiol Infect Dis 2004;23:888-91.
78. 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.

79. Achar KN, Johny M, Achar MN, Menon NK. Community-acquired *Acinetobacter* pneumonia with survival. Postgrad Med J 1993;69:934-7.

80. Rello J, Ausina V, Ricart M, Castella J, Prats G. Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. Chest 1993;104:1230-5.

81. Keenan SP, Heyland DK, Jacka MJ, Cook D, Dodek P. Ventilator-associated pneumonia. Prevention, diagnosis, and therapy. Crit Care Clin 2002;18:107-25.

82. Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. Am J Respir Crit Care Med 1999;159(4 Pt 1): 1249-56.

83. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002;122:2115-21.

84. Garcia-Garmendia JL, Ortiz-Leyba C, Garnacho-Montero J, Jimenez-Jimenez FJ, Monterrubio-Villar J, Gili-Miner M. Mortality and the increase in length of stay attributable to the acquisition of Acinetobacter in critically ill patients. Crit Care Med 1999;27:1794-9.

85. Glew RH, Moellering RC Jr, Kunz LJ. Infections with *Acinetobacter calcoaceticus (Herellea vaginicola)*: clinical and laboratory studies. Medicine (Baltimore) 1977;56:79-97.

86. Quinn JP. Clinical problems posed by multiresistant nonfermenting gram-negative pathogens. Clin Infect Dis 1998;27 (Suppl 1):S117-24.

87. Jones ME, Draghi DC, Thornsberry C, Karlowsky JA, Sahm DF, Wenzel RP. Emerging resistance among bacterial pathogens in the intensive care unit--a European and North American Surveillance Study (2000-2002). Ann Clin Microbiol Antimicrob 2004;3:14.

88. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med 2003;115:529-35.

89. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate treatment for ventilator-associated pneumonia. Chest 2002;122:262-8.

90. Kollef MH. The importance of appropriate initial antibiotic therapy for hospital-acquired infections. Am J Med 2003;115:582-4.

91. Wisplinghoff H, Edmond MB, Pfaller 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.

92. Lee SO, Kim NJ, Choi SH, et al. Risk factors for acquisition of imipenem-resistant *Acinetobacter baumannii*: a case-control study. Antimicrob Agents and Chemother 2004;48:224-8

93. Beck-Sague CM, Jarvis WR, Brook JH, et al. Epidemic bacteremia due to *Acinetobacter baumannii* in five intensive care units. Am J Epidemiol 1990;132:723-33.

94. Seifert H, Strake A, Pulverer G. Nosocomial bacteremia due to *Acinetobacter baumannii*. Clinical features, epidemiology, and predictors of mortality. Medicine (Baltimore) 1995;74:340-9.

95. 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.

96. Graff LR, Franklin KK, Witt L, et al. Antimicrobial therapy of gram-negative bacteremia at two university-affiliated medical centers. Am J Med 2002;112:204-11.

97. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1994;271:1598-601.

98. Valles J, Leon C, Alvarez-Lerma F. Nosocomial bacteremia in critically ill patients: a multicenter study

evaluating epidemiology and prognosis. The Spanish Collaborative Group for Infections in Intensive Care Unit of SEMIUC. Clin Infect Dis 1997;24:387-95.

99. Barsic B, Beus I, Marton E, Himbele J, Klinar I. Nosocomial infections in critically ill infectious disease patients: results of a 7-year focal surveillance. Infection 1999;27:16-22.
100. Stapleton A. Urinary tract infections in patients with diabetes. Am J Med 2002;113 (Suppl 1 A): 80S-84S.
101. Rosser CJ, Bare RL, Meredith JW. Urinary tract infections in the critically ill patient with a urinary catheter. Am J Surg 1999;177:287-90.
102. Laupland KB, Zygun DA, Davis HD, Church DL, Louie TJ, Doig CJ. Incidence and risk factors for acquiring nosocomial urinary tract infection in the critically ill. J Crit Care 2002;17:50-7.
103. Avecillas JF, Mazzone P, Arroliga AC. A rational approach to the evaluation and treatment of the infected patient in the intensive care unit. Clin Chest Med 2003;24:645-69.
104. Johnson JR, Vincent LM, Wang K, Roberts PL, Stamm WE. Renal ultrasonographic correlates of acute pyelonephritis. Clin Infect Dis 1992;14:15-22.
105. Chastre J. Antimicrobial treatment of hospital-acquired pneumonia. Infect Dis Clin North Am 2003;17:727-37.
106. Alcón A, Fàbregas N, Torres A. Hospital-acquired pneumonia: etiologic considerations. Infect Dis Clin North Am 2003;17:679-95.
107. Bowton DL. Nosocomial pneumonia in the ICU--year 2000 and beyond. Chest 1999;115 (3 Suppl):28S-33S.
108. Ioanas M, Ewig S, Torres A. Treatment failures in patients with ventilator-associated pneumonia. Infect Dis Clin North Am 2003;17:753-71.
109. Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med 2001;134:298-314.
110. Rodriguez-Hernández MJ, Pachón J, Pichardo C, et al. Imipenem, doxycycline, and amikacin in monotherapy and in combination in *Acinetobacter baumannii* experimental pneumonia. J Antimicrob Chemother 2000;45:493-501.
111. Montero A, Ariza J, Corbella X, et al. Efficacy of colistin *versus* β-lactams, aminoglycosides, and rifampin as monotherapy in a mouse model of pneumonia caused by multiresistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2002;46:1946-52.
112. Martin SI, Kaye KM. Beta-lactam antibiotics: newer formulations and newer agents. Infect Dis Clin North Am 2004;18:603-19.
113. Shah PM, Isaacs RD. Ertapenem, the first of a new group of carbapenems. J Antimicrob Chemother 2003;52:538-42.
114. de Roux A, Lode H. Recent developments in antibiotic treatment. Infect Dis Clin North Am 2003;17:739-51.
115. Williams JD. Beta-Lactamase inhibition and *in vitro* activity of sulbactam and sulbactam/cefoperazone. Clin Infect Dis 1997;24:494-7.
116. Wood GC, Hanes SD, Croce MA, Fabian TC, Boucher BA. Comparison of ampicillin-sulbactam and imipenem-cilastatin for the treatment of *Acinetobacter* ventilator-associated pneumonia. Clin Infect Dis 2002;34:1425-30.
117. Ishii Y, Alba J, Kimura S, Shiroto K, Yamaguchi K. Evaluation of antimicrobial activity of beta-lactam antibiotics using E-test against clinical isolates from 60 medical centres in Japan. Int J Antimicrob Agents 2005;25:296-301.
118. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez 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.
119. Kaye D. Current use for old antibacterial agents: polymyxins, rifampin, and aminoglycosides. Infect Dis Clin North Am 2004;18:669-89.

120. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant *Pseudomonas aeruginosa* with aerosolized colistin. Am J Respir Crit Care Med 2000;162:328-30.

121. 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.

122. Evans ME, Feola DJ, Rapp RP. Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant gram-negative bacteria. Ann Pharmacother 1999;33:960-7.

123. 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.

124. Hermsen ED, Sullivan CJ, Rotschafer JC. Polymyxins: pharmacology, pharmacokinetics, pharmacodynamics, and clinical applications. Infect Dis Clin North Am 2003;17:545-62.

125. 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:R53-9.

126. Maddison J, Dodd M, Webb AK. Nebulized colistin causes chest tightness in adults with cystic fibrosis. Respir Med 1994;88:145-7.

127. Conway SP, Pond MN, Watson A, Etherington C, Robey HL, Goldman MH. Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis. Thorax 1997;52:987-93.

128. Urban C, Go E, Mariano N, et al. Effect of sulbactam on infections caused by imipenem-resistant *Acinetobacter calcoaceticus* biotype *anitratus*. J Infect Dis 1993;167:448-51.

129. Smolyakov R, Borer A, Riesenberger K, et al. Nosocomial multi-drug resistant *Acinetobacter baumannii* bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. J Hosp Infect 2003;54:32-8.

130. 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.

131. 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.

132. Giamarellos-Bourboulis EJ, Xirouchaki E, Giamarellou H. Interactions of colistin and rifampin on multidrug-resistant *Acinetobacter baumannii*. Diagn Microbiol Infect Dis 2001;40:117-20.

133. 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.

134. Larson EL, Cronquist AB, Whittier S, Lai L, Lyle CT, Della Latta P. Differences in skin flora between inpatients and chronically ill outpatients. Heart Lung 2000;29:298-305.

135. Thamlikitkul V, Santiprasitkul S, Suntanondra L, et al. Skin flora of patients in Thailand. Am J Infect Control 2003;31:80-4.

136. Cefai C, Richards J, Gould K, McPeake P. An outbreak of *Acinetobacter* respiratory tract infection from incomplete disinfection of ventilatory equipment. J Hosp Infect 1990;15:177-82.