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). 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. Outbreaks have been increasingly reported regularly. Moreover, most of those outbreaks were caused by multidrug-resistant (MDR) strains of this organism. The initial concern about MDR-Acinetobacter strains began in 1991 when the first hospital-wide outbreak occurred in New York. Now MDR-Acinetobacter strains are observed worldwide. In Thailand, MDR-Acinetobacter infections have been described repeatedly. 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. In addition, their ubiquitous nature in the ICU environment and inadequate infection-control...
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 staining18, 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, bacteraemia, 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-resistance30, 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.\textsuperscript{4,12,16-17,28,32-34} At present, 10-30 percent of nosocomial infections in the ICU, particularly pneumonia, are associated with \textit{Acinetobacter} spp., compared to only 2-4 percent in the last 15 years.\textsuperscript{15}

\textit{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 \textit{Acinetobacter} from human skin in up to 25 percent of healthy adults\textsuperscript{36,37}, mostly from their hands.\textsuperscript{37} In fact, \textit{Acinetobacter} is considered to be the most common gram-negative organism colonized on the skin of hospital personnel, including ICU nurses and respiratory therapists.\textsuperscript{15} Moreover, transient pharyngeal colonization was noted in 7 percent of healthy individuals enrolled in one study.\textsuperscript{38} These findings indicate that hospital personnel and hospitalized patients may be the most important reservoir of this organism\textsuperscript{37}, leading to the persistently increased incidence of \textit{Acinetobacter} nosocomial infections. Besides human skin, \textit{Acinetobacter} has also been isolated from soil\textsuperscript{15}, water\textsuperscript{15}, fish\textsuperscript{39}, meat\textsuperscript{39}, vegetables\textsuperscript{39}, hospital air\textsuperscript{40}, tap water faucets\textsuperscript{39}, sink basins\textsuperscript{40}, bed mattresses\textsuperscript{41}, bedside urinals\textsuperscript{41} and respiratory therapy equipments\textsuperscript{40}. More interestingly, some reports showed that \textit{Acinetobacter} colonization and infections occurred more commonly during the warmer and more humid months.\textsuperscript{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\textsuperscript{43} and Hong Kong.\textsuperscript{42}

\textit{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.\textsuperscript{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 \textit{Acinetobacter} spp. is the lower respiratory tract infections.\textsuperscript{44} The incidence of other sites of infection is as shown in Figure 2.

The recent emerging of drug-resistant \textit{Acinetobacter} has caused a great concern worldwide. A study in 2002 showed that 12 percent of \textit{Acinetobacter} isolates were resistant to all standard antibiotics.\textsuperscript{12} Some studies indicated that up to 80 percent were resistant to all aminoglycosides\textsuperscript{45} and ciprofloxacin.\textsuperscript{30} About 70 percent of isolates resisted to ceftazidime.\textsuperscript{46-47} Twenty to 30 percent were resistant to β-lactam and β-lactamase inhibitor combinations.\textsuperscript{47} More importantly, carbapenem-resistance rate was recently reported about 11-53 percent.\textsuperscript{12} In fact, MDR \textit{Acinetobacter} infection has also become a serious problem in the ICU located in several Asian countries.\textsuperscript{13-14,22,46-49} Its incidence is currently on the rise in Thailand\textsuperscript{13-14}, China\textsuperscript{22}, Hong Kong\textsuperscript{48}, Taiwan\textsuperscript{46}, and Malaysia.\textsuperscript{49} In Thailand, the most recent National Susceptibility Surveillance data indicated that drug-resistant \textit{Acinetobacter} is prevalent in Thailand. As high as 44 percent, and 16 percent of clinical isolates were reported resistant to ceftazidime, and imipenem, respectively.\textsuperscript{50} At the author’s institution\textsuperscript{51}, in the year 2004, more than half of all \textit{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 \textit{Acinetobacter} nosocomial infections. They include advanced age\textsuperscript{52}, immunosuppression\textsuperscript{53-54}, surgery\textsuperscript{55}, previous treatment with broad-spectrum antibiotics\textsuperscript{35,53,56-60}, use of invasive devices\textsuperscript{61}, burns\textsuperscript{62}, fecal colonization with \textit{Acinetobacter}\textsuperscript{63}, and prolonged hospital or ICU stays.\textsuperscript{32,53,56}

Recent evidence demonstrated that the occurrence of \textit{Acinetobacter} nosocomial pneumonia in the
ICU is contributed by several factors. Immunosuppressed hosts, including neutropenic patients and HIV-infected individuals, especially those with low CD4 cell counts, are at particular risk. Moreover, 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). Previous use of antibiotics, particularly third-generation cephalosporins, aminoglycosides, quinolones, or carbapenems, 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. 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, including endotracheal tube, central venous catheter, and tracheostomy. 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. Trouillet and co-workers 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).

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 antimicrobial 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 therapy40 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 ≥38°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 cases59, 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 co-workers 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 infections61,71,93, 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 urosepsis101,103-104, 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 $10^2$-$10^7$ 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 pathogens111,118-121 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.110,111

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 colleagues135 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, ventilators, resuscitation bags, mattresses, hand-washing sinks, gowns and gloves. 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.

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 and contact isolation using glove, gown, and barrier precautions. 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, antibiotic cycling schedules, and implementation of antimicrobial prescribing guidelines. Other measures include rigorous cleaning and disinfection of the ICU environment using 1,000 ppm hypochlorite solution; surveillance cultures of patients, environmental surfaces, and staffs; continuous educational and quality control programs for all ICU personnel; 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. Although some above mentioned measures seem to be costly, most of them are simple and have been proven to be effective.

**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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