

Multidrug-resistant *Acinetobacter baumannii* isolates in pediatric patients of a university hospital in Taiwan

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Background and Purpose: *Acinetobacter baumannii* is one of the common nosocomial pathogens, and the emergence of multidrug-resistant *A. baumannii* (MDRAB) is a therapeutic problem. We describe the clinical characteristics and outcomes of MDRAB colonization/infection in pediatric patients at the National Taiwan University Hospital.

Methods: Fifty two pediatric patients with 205 MDRAB isolates collected between April 2000 and December 2005 were included for investigation of their clinical characters, presentations, and outcome.

Results: Among these 205 isolates, 20 (9.8%) were from sterile body sites (11 from blood, 8 from catheter tips, and 1 from ascites), 154 (75.1%) from respiratory sites, 18 (8.8%) from skin or wound pus, 5 (2.4%) from urine, and 8 (3.9%) from other sites. The mean age was 6 years. The common underlying diseases were hematological or oncological diseases (n = 15, 28.8%), neonatal disorders (6, 11.5%), cyanotic congenital heart diseases (10, 19.2%), neurology disorders (12, 23.1%), and gastrointestinal tract disorders (3, 5.8%). Seventeen patients (32.7%) had received major surgery, and 48 (92.3%) had used ventilators. Fourteen patients (26.9%) had neutropenia and 46 (88.5%) had used broad-spectrum antibiotics. There were 31 patients (59.6%) with suspected or proven MDRAB infections, including sepsis (9 patients), pneumonia (19), wound infections (3), urinary tract infections (2), peritonitis (1), and perineal infection (1). Seven (77.8%) of the 9 sepsis patients died. The overall mortality rate was 42.3% (22 cases).

Conclusions: The threat of MDRAB has been recognized in our hospital for several years. Host defense deficiencies, prolonged intensive care unit hospitalizations, and prior broad-spectrum antibiotic use play a major role in MDRAB infection and colonization.

Key words: *Acinetobacter baumannii*; Drug resistance, multiple, bacterial; Pediatrics

Introduction

Acinetobacter baumannii is an aerobic, Gram-negative coccobacillus. It is an important nosocomial pathogen and causes clinical infections, such as lower respiratory infections, urinary tract infections, and bacteremia [1]. Treatment of *A. baumannii* infections has become difficult because of the emerging resistance to multiple antibiotics in organisms.

Multidrug-resistant *A. baumannii* (MDRAB) has been increasingly isolated in hospitals in the last few decades [2]. The emergence of carbapenem-resistant *A. baumannii* (CRAB) was reported in the USA in 1991 [3]. Since then, CRAB nosocomial infections and hospital-wide outbreaks have been reported in many countries [4-7].

In May 1998, the first isolate of MDRAB resistant to almost all commercially available antibiotics (including all cephalosporins, aztreonam, aminoglycosides, and ciprofloxacin) was discovered at the National Taiwan University Hospital (NTUH) [8]. Since then clusters of MDRAB nosocomial infections and outbreaks have

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persisted in our hospital. In this study, we describe the clinical characteristics and outcomes of MDRAB colonization/infection in pediatric patients at the NTUH.

Methods

There were 120 beds in the pediatric general wards and the 3 intensive care units (ICUs), including 1 neonatal ICU (25 beds) and 2 pediatric ICUs (15 and 25 beds, respectively) in the pediatric department of NTUH. Laboratory records at the Clinical Microbiology Laboratory at NTUH were reviewed and medical records of patients with positive MDRAB isolations in the Department of Pediatrics were analyzed.

The Clinical Microbiology Laboratory at NTUH processed all clinical samples for bacterial cultures with conventional methods. Blood cultures were processed by the Bactec 9240 blood culture system (Becton Dickinson, Cockeysville, MD, USA). Susceptibilities to antimicrobial agents were determined by the disk diffusion method in accordance with the guidelines of the Clinical Laboratory Standard Institute [9]. MDRAB isolates were those non-susceptible to the commercially available antibiotics tested (i.e., ampicillin-sulbactam, ceftazidime, cefepime, ticarcillin-clavulanate, piperacillin-tazobactam, aztreonam, imipenem, meropenem, gentamicin, amikacin, ofloxacin, and ciprofloxacin).

Clinical data, including demographic characteristics, clinical symptoms and signs, diagnosis, comorbid diseases, length of hospital stays, presence of catheters, invasive diagnostic and therapeutic procedures, parenteral nutrition, laboratory examinations, and antibiotic usage before and after MDRAB isolation, were reviewed.

For patients with MDRAB isolated from airway secretions, the diagnosis of pneumonia was considered if there was a definite new infiltration or patch formation noted in chest roentgenography and sputum Gram stain revealed phagocytosis. Otherwise, the cases were considered to be instances of colonizations. If MDRAB was isolated from blood cultures and the patient had unstable vital signs or shock, sepsis was considered. Mortality was deemed related to MDRAB, if no pathogen other than MDRAB was identified at the time of bacteremia. Otherwise, mortality was considered unrelated to MDRAB.

Incidence was compared using Fisher's exact test to determine the factors influencing prognosis. A *P* value <0.05 was considered significant.

Results

In total, 205 clinical isolates of MDRAB were isolated in 52 pediatric patients between April 2000 and December 2005 at the NTUH. The male-to-female ratio was 1.00:1.08 and age ranged from 3 days to 27 years, with a mean age of 6 years. Hematological or oncological diseases were the most common underlying diseases (15, 28.8%). The other diseases were congenital cyanotic heart diseases (10, 19.2%), neurological disorders (12, 23.1%), neonatal disorders (6, 11.5%), gastrointestinal tract disorders (3, 5.8%), Down syndrome, VACTERL syndrome, Lennox-Gastaut syndrome, tuberculosis, and toxic shock syndrome.

Most of the isolates were isolated from the respiratory tract (154, 75.1%). Twenty isolates (9.8%) of MDRAB were isolated from sterile sites, including 11 from blood, 8 from catheter tip and 1 from ascites. The other sources of isolation included urine, eye discharge, skin or wound pus, endometrial clots, gastric juice, and rubber drain discharge. These MDRAB isolates were found occasionally before June 2004, but increased thereafter (Fig. 1). We noted that almost all patients who stayed in the ICUs for several days could be colonized by MDRAB, following which the infection could spread to the other wards.

The common clinical manifestations in the 52 patients are described in Table 1. Forty eight patients (92.3%) received endotracheal intubation and mechanical ventilation. Seventeen patients (32.7%) had major surgery. There were 14 patients (26.9%) with neutropenia when MDRAB was isolated. Most of them had hematological or oncological diseases and received chemotherapy. The other cases with neutropenia and MDRAB isolation also had gastroschisis and prematurity with low body weights at birth. All patients, except case 6, had prolonged ICU hospitalizations (≥ 7 days), and the median duration of ICU care was 58.2 (0-201) days. Forty three patients were staying in ICUs when MDRAB was isolated. Forty six patients (88.5%) had been treated with multiple classes of antibiotics before the onset of MDRAB colonization or infection. The antimicrobial agents included cephalosporins, fluoroquinolones, broad-spectrum penicillins, aminoglycosides, macrolides, and carbapenems.

Among the 52 patients, only 31 (59.6%) were considered as MDRAB infections, and included sepsis (9 patients), pneumonia (19), wound infections (3), urinary tract infections (2), peritonitis (1), and perineal infection (1). MDRAB was isolated from blood cultures

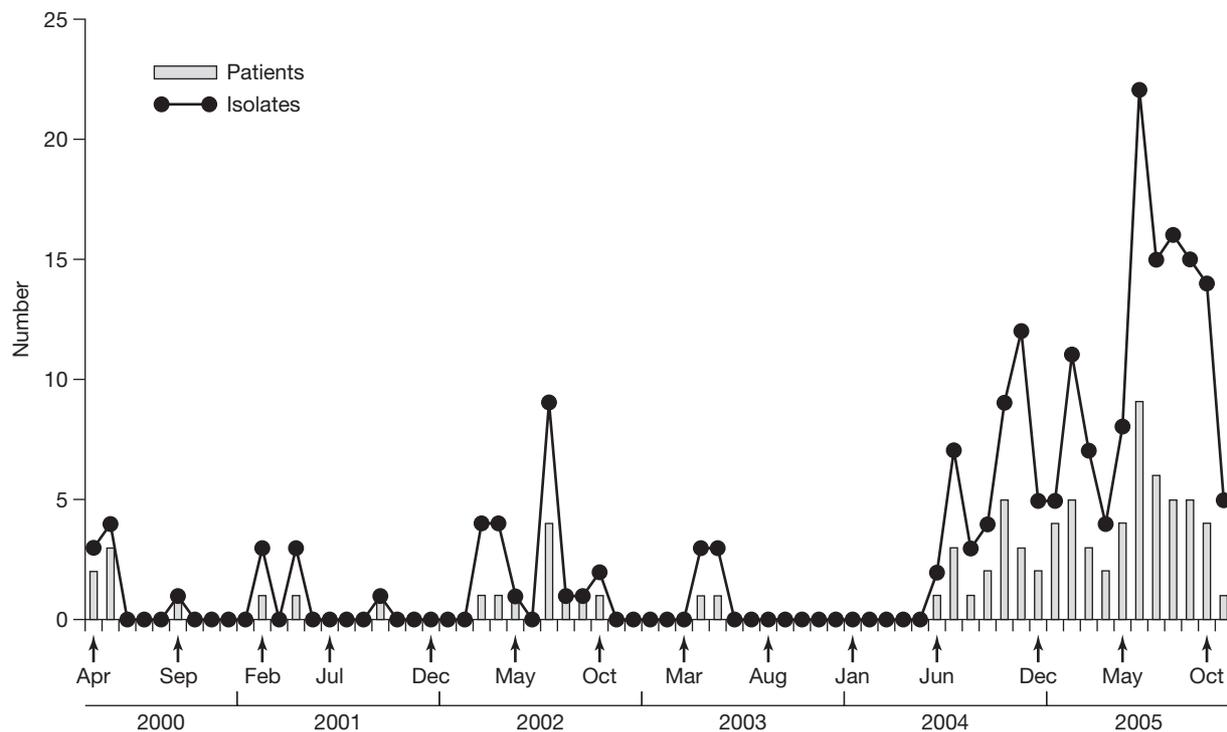


Fig. 1. Pattern of multidrug-resistant *Acinetobacter baumannii* isolated from patients in the pediatrics department at the National Taiwan University Hospital between April 2000 and December 2005.

in 8 of 9 sepsis patients. One case had a positive central venous pressure line tip culture and the clinical manifestation was compatible with septic shock without other documented pathogens. Pneumonia cases had lung infiltrations on chest X-ray and cultures from respiratory tract samples grew MDRAB. However, only a few cases had compatible Gram stain reports. Hospital death occurred in 22 patients (42.3%). Among these, 6 deaths were directly related to MDRAB sepsis, and the other deaths were considered to be the result of underlying diseases. 27 MDRAB-infected patients (51.9%) required antibiotic adjustments after MDRAB infections were impressed. Antibiotic dosage was changed to 300 mg/kg/day of ampicillin-sulbactam in 25 patients, while minocycline was used in 2 patients with MDRAB sepsis. However, the clinical efficacy of antibiotic treatment seemed unsatisfactory, as mortality and morbidity did not improve following antibiotic adjustments.

MDRAB sepsis ($p=0.05$) and sepsis with neutropenia ($p=0.0093$) were the only significant factors identified to predict in-hospital mortality in inpatients with MDRAB infections. Mechanical ventilation, hematological or oncological diseases, and major surgery were not significantly related to hospital death.

Discussion

There were 52 patients and 205 isolates of MDRAB between April 2000 and December 2005 in the pediatric wards of NTUH. There have been several outbreaks and clusters of nosocomial infections of MDRAB at NTUH [10] since its first isolation here in May 1998 [8]. The percentage of MDRAB in the isolates of *A. baumannii* has been gradually increasing, and now accounts for 15% of all cases according to our laboratory-scheduled report. It thus poses a major clinical threat.

Since June 2004, MDRAB has been a constant problem in our ICU wards. Debilitated patients transferred to the ICUs due to pressing clinical needs have increased susceptibility to MDRAB colonization. Some of these patients are immunocompromised while others have had major surgeries or require prolonged mechanical ventilation. MDRAB colonization can result in clinical disease, and increased mortality. As some cases were transferred to the general wards or the other ICU wards with colonization, they may have been the source of further nosocomial infections.

The hospital recorded only sporadic cases or small clusters of MDRAB infections prior to June 2004, but there seem to have been ongoing outbreaks of MDRAB

Table 1. Clinical characteristics of 52 patients with multidrug-resistant *Acinetobacter baumannii* infection or colonization

| Characteristic | Number of patients |
|--|---------------------------|
| Gender ratio (male:female) | 1.00:1.08 |
| Mean age (range) | 6 years (3 days-27 years) |
| Mean ICU care (days) [range] | 58.2 (0-201) |
| Underlying disease | |
| Hematological or oncological diseases ^a | 15 |
| Neurological disorders ^b | 12 |
| Cyanotic congenital heart disease | 10 |
| Neonatal disorders ^c | 6 |
| Gastrointestinal tract diseases ^d | 3 |
| Infectious diseases ^e | 2 |
| Others ^f | 3 |
| None | 1 |
| Mechanical ventilation (%) | 48 (92.3) |
| Broad-spectrum antibiotics usage (%) | 46 (88.5) |
| Neutropenia (%) | 14 (26.9) |
| Major surgery (%) | 17 (32.7) |

Abbreviation: ICU = intensive care unit

^aHematological or oncological diseases include leukemia, lymphoma, infection-associated hemophagocytosis syndrome, aplastic anemia, neuroblastoma, brain tumor, and Wilms' tumor.

^bNeurological disorders include encephalitis, seizure disorders, cerebral palsy, spinal muscular atrophy, and epilepsy.

^cNeonatal disorders include prematurity and meconium aspiration syndrome.

^dGastrointestinal tract diseases include gastroschisis, Hirschsprung disease, and liver cirrhosis.

^eInfectious diseases include tuberculosis and toxic shock syndrome.

^fOthers include Down syndrome, Lennox-Gastaut syndrome, and VACTERL syndrome.

infections since that time. Investigations by the nosocomial infection control team at NTUH have revealed that these outbreaks were not just restricted to the pediatrics ward, but involved the entire hospital, since patients were transferred between various locations, including general wards and surgical ICUs. Isolation of MDRAB was widespread; even the portable X-ray machines and beds were found to be colonized. MDRAB colonization could not be eradicated even with strict contact isolation and cohort care, due to the lack of effective therapy.

Risk factors for MDRAB infections have been described by many studies in the literature. Mahgoub et al revealed prior antibiotic usage, mechanical ventilation, ICU stay, and cardiovascular disease as the common risk factors for highly resistant *A. baumannii* infections [11]. These findings were comparable to the clinical characteristics of patients in this study. Another earlier study found that underlying heart disease,

shock, resuscitation, acute respiratory distress syndrome, mechanical ventilation, and multiple organ dysfunction score >6 were significant risk factors related to mortality in patients with MDRAB bacteremia [12]. In our study, sepsis and sepsis with neutropenia were identified as significant factors associated with in-hospital mortality, while mechanical ventilation, hematological or oncological underlying diseases, neutropenia, and congenital heart disease were not.

Among the 52 patients, there were 15 cases with underlying hematological or oncological diseases. Nine of these patients received chemotherapy before the isolation of MDRAB, and they all had neutropenia, increasing the nosocomial infection rate. Long-term and broad-spectrum antimicrobial drug usage seemed unavoidable for infection control. Our study indicated that these underlying diseases might be the risk factors predisposing patients to MDRAB infection.

Choosing appropriate and effective antibiotic therapy for MDRAB infections is a major problem for clinicians. For MDRAB strains, carbapenem was the drug of choice [13] and combinations of imipenem and amikacin exhibited better in vitro activity against the pathogen [14]. Several studies have found that isolates of CRAB are usually susceptible to sulbactam, with ampicillin-sulbactam proving to be effective in a limited number of patients [15,16]. One study even found that carbapenem-sulbactam combinations demonstrated lower minimal inhibitory concentrations for MDRAB, but did not noticeably improve clinical outcome [17]. Our laboratory data revealed that some of the isolated MDRAB clones showed resistance to ampicillin-sulbactam. In our study, 25 patients were treated with high-dose ampicillin-sulbactam (300 or 150 mg/kg/day) and 2 patients were treated with minocycline for MDRAB pneumonia and sepsis. As we did not observe any satisfactory clinical improvement, we conclude that there is limited association between the use of antibiotics for MDRAB and prognosis. We are of the opinion that patient survival depends on the severity of illness at the time of infection.

In conclusion, MDRAB has been a clinical problem in our hospital for several years. Host defense deficiency, prolonged ICU hospitalization, and prior broad-spectrum antibiotic use play a major role in MDRAB infection and colonization.

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