J Microbiol Immunol Infect.
2007;40:401-405

Original Article

Multidrug-resistant *Acinetobacter baumannii* in ventilator-associated pneumonia at a medical center in southern Taiwan

Ming-Hsin Mai[1], Hung-Chin Tsai[1], Susan Shin-Jung Lee[1], Yung-Hsing Wang[1], Yao-Shen Chen[1], Shue-Ren Wann[1], Yung-Ching Liu[1,2]

[1]Section of Infectious Diseases, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung; and [2]College of Medicine, National Yang-Ming University, Taipei, Taiwan

Received: April 20, 2006 Revised: July 30, 2006 Accepted: August 11, 2006

Background and Purpose: To evaluate the significance of multidrug-resistant *Acinetobacter baumannii* (MDRAB)-related ventilator-associated pneumonia at a medical center in southern Taiwan.

Methods: We retrospectively reviewed the medical records of patients with MDRAB isolated from sputum and described the characteristics of these patients. Patients were divided into 2 groups according to their clinical pulmonary infection scores (CPIS), and their host factors and outcomes compared.

Results: In the patient group with significant MDRAB-related lung infection, Acute Physiology and Chronic Health Evaluation II scores were significantly higher than in those patients with lower CPIS scores (<6). However, the clinical outcomes, including the duration of hospitalization after isolation of MDRAB and mortality rate, were not different.

Conclusion: Our investigation showed that significant lung infections with MDRAB isolation did not result in prolonged hospitalization or increased mortality. The initial clinical severity of the group with significant MDRAB-related lung infection was significantly greater than in the other. We propose that MDRAB-related pneumonia should be regarded as a signal of the clinical severity of the patient rather than as a prognostic factor.

Key words: *Acinetobacter baumannii*; Drug resistance, multiple, bacterial; Pneumonia, ventilator-associated; Sulbactam

Introduction

Acinetobacter baumannii is a relatively harmless pathogen that has the ability to survive on equipment surfaces for long periods [1]. However, nosocomial infections and hospital-wide outbreaks caused by *A. baumannii* have increased in recent decades. Several antibiotics, such as carbapenem and amikacin, have been used in the treatment of *A. baumanni* infections, and may be the reason behind the appearance of resistant strains [2]. Initial concern about multidrug-resistant *A. baumannii* (MDRAB) was neglected until the first nosocomial outbreak occurred in the USA in 1991 [3]. With increasing reports of nosocomial infections caused by MDRAB worldwide, several groups have studied the risk factors and treatment of MDRAB-related bloodstream infections [2,4,5]. One study described the poor outcome of MDRAB-related bloodstream infections and the associated difficulty in selecting antibiotic treatment [4]. However, very few studies have addressed the significance of MDRAB infection in patients with pneumonia.

This study describes the characteristics of patients from whose sputum MDRAB was isolated. We used clinical criteria to define the significance of lung infection and its effect on clinical outcome.

Corresponding author: Dr. Yung-Ching Liu, Section of Infectious Diseases, Department of Medicine, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung, Taiwan.
E-mail: vghks8115@yahoo.com.tw

Methods

Patients

This study was conducted at the Kaohsiung Veterans General Hospital, a 1250-bed hospital located in southern Taiwan. All sputum specimens obtained from adult inpatients that yielded MDRAB between March 2004 and October 2005 were retrospectively identified from laboratory records. All relevant information, including demographic data, host and therapeutic risk factors, laboratory and bacteriology results, antibiotic therapy, and outcome were gathered from medical and laboratory records. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were used to estimate the severity of clinical condition before MDRAB isolation, when the severity was greatest.

Definitions

MDRAB was defined as an isolate of *A. baumannii* resistant to all antibiotics tested routinely (including amikacin, quinolones, ceftazidime, cefepime, and carbapenem), except polymyxin E and ampicillin-sulbactam. Susceptibility testing of polymyxin E is not available in our microbiology laboratory; the susceptibility rate of MDRAB to ampicillin-sulbactam was around 47%. Species identification and antimicrobial susceptibility testing were done using the Phoenix NMIC/ID panel (Becton Dickinson and Company, Franklin Lakes, NJ, USA).

A clinical pulmonary infection score (CPIS) was used to define significant lung infection, and this scoring system included both clinical and laboratory aspects, i.e., body temperature, leukocyte count, the amount and appearance of tracheal secretion, chest film findings and results, arterial blood gas data, demanded oxygen pressure fraction, sputum smear, and culture results. Pugin and coworkers first proposed CPIS to aid in the clinical diagnosis of ventilator-associated pneumonia [6]. Subsequently, Singh et al defined patients with pulmonary infiltration and CPIS >6 as those who needed antibiotic treatment [7]. Patients with CPIS >6 points in the period of 1 day around the time of MDRAB isolation were identified as having significant lung infections and included in the analysis.

Statistical analysis

Fisher's exact test was used to analyze differences in discrete variables and the Mann-Whitney rank sum test was used to analyze continuous variables. All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) software (Version 12.0; SPSS Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Results

Demographic characteristics of patients

During the study period, sputum specimens from 81 patients tested positive for MDRAB. However, as 6 patients did not require mechanical ventilator support, 75 patients were included in the study. Of these, 32 patients (42.7%) had CPIS scores >6 points, and their MDRAB-related lung infections were regarded as significant. They were mostly male (56, 74.6%), with an average patient age of 70.9 years (range, 15-92).

Clinical symptoms in the 75 MDRAB-positive patients included underlying hypertension (49.3%), diabetes mellitus (41.3%), chronic obstructive pulmonary disorder (26.7%) and malignancy (18.7%). Other underlying conditions, such as chronic renal disease (5.3%) and liver cirrhosis (2.7%), were less common. The average duration of hospitalization was 44.7 days (range, 1-163) and the median APACHE II score was 20 (range, 9-37), which represented the predictive mortality rate of around 35%. However, the crude mortality of these patients was 52%. During hospitalization, antibiotics used within the month prior to MDRAB isolation included aminoglycosides (44 patients), quinolones (17 patients), carbapenems (16 patients), vancomycin (16 patients), sulbactam (14 patients), and third- or fourth-generation cephalosporins (9 patients). Only 17 of the 75 patients received antibiotic treatment directed at MDRAB, such as ampicillin-sulbactam.

CPIS scoring

The medical records of 75 patients under mechanical ventilator support, whose sputum specimen yielded MDRAB, were reviewed. The 75 patients were divided in 2 groups: CPIS >6 and CPIS ≤6. The demographic characteristics and underlying conditions are listed in Table 1. There was no statistical difference with respect to age and gender. The duration of hospitalization following MDRAB isolation was also not significantly different. However, the initial clinical severity was greater in the group with CPIS >6 (APACHE II median, 22 vs 18; p=0.01). The incidence of underlying diseases, including diabetes, hypertension, liver cirrhosis, chronic heart diseases, chronic renal diseases, chronic obstructive pulmonary disorder and malignancy, was not statistically

Table 1. Demographic characteristics and clinical outcome of patients with multidrug-resistant *Acinetobacter baumannii* (MDRAB) isolated from sputum

Characteristic	Total (n = 75) No. (%)	CPIS >6 (n = 32) No. (%)	CPIS ≤6 (n = 43) No. (%)	*p*
Age (years; mean ± SD)	70.9 ± 14.6	73.1 ± 10.7	69.3 ± 16.8	0.32
Hospitalization[a] (days; mean ± SD)	24.3 ± 24.1	24.8 ± 28.1	23.9 ± 21	0.48
APACHE II score (median) [range]	20 (9-37)	22 (11-37)	18 (9-35)	0.01
Male gender	56 (74.7)	26 (81.2)	30 (69.8)	0.20
Sulbactam-based antibiotic treatment	17 (22.7)	12 (37.5)	5 (11.6)	0.12
Underlying disease				
Hypertension	37 (49.3)	16 (50.0)	21 (48.8)	0.55
Diabetes mellitus	31 (41.3)	13 (40.1)	18 (41.9)	0.55
Chronic obstructive pulmonary disease	20 (26.7)	11 (34.4)	9 (21.0)	0.15
Malignancy	14 (18.7)	3 (9.4)	11 (25.6)	0.07
Chronic heart disease	10 (13.3)	5 (15.6)	5 (11.6)	0.43
Chronic renal disease	4 (5.3)	1 (3.1)	3 (7.0)	0.43
Liver cirrhosis	2 (2.7)	1 (3.1)	1 (2.3)	0.67
Deaths	39 (52.0)	16 (50.0)	23 (53.5)	0.47

Abbreviations: CPIS = clinical pulmonary infection score; SD = standard deviation; APACHE = Acute Physiology and Chronic Health Evaluation

[a]Interval between time of MDRAB isolation and discharge.

different, and there was also no statistical difference between the crude mortality of these 2 groups.

Treatment and outcome

In the 32 patients with significant lung infections, 12 patients received ampicillin-sulbactam after microbiology reports showed MDRAB. According to the susceptibility tests, MDRAB was susceptible to ampicillin-sulbactam in nine of 12 patients whose CPIS score was >6, and these received ampicillin-sulbactam treatment (Group 1). The other 23 patients who did not receive in vitro-active antibiotics were managed according to their clinical presentations and the judgment of infectious disease specialists (Group 2). The demographic characteristics and underlying conditions of the 2 groups are compared in Table 2. There was no difference in gender, age, and APACHE II scores between the 2 groups. Two outcome variables, duration of hospitalization (including ordinary ward and intensive care unit) following MDRAB isolation and mortality rate, were compared (Table 2). The period of hospitalization was statistically longer in Group 1 patients (30.3 ± 15.9 vs 22.7 ± 31.6, p=0.02). The mortality rate was 22.2% (2/9) in patients who received antibiotics active against MDRAB in vitro, and 60.8% (14/23) in those who did not (p=0.11).

Discussion

A. baumannii infections were often ignored in the past, as the organism was known to widely colonize the surface of equipment and its low virulence was common knowledge. In recent years, however, several studies have reported that MDRAB could be a serious concern in hospital-acquired infections and for infection control strategies. Epidemiologic surveys of several large

Table 2. Demographic characteristics and clinical outcome of 32 patients treated with or without in vitro-active drug(s) and with clinical pulmonary infection score >6

Characteristic	Treated with in vitro-active drug(s) [n = 9]	Treated without in vitro-active drug(s) [n = 23]	*p*
Age (years; mean ± SD)	73.3 ± 10.8	73.1 ± 10.9	0.46
Hospitalization[a] (days; mean ± SD)	30.3 ± 15.9	22.7 ± 31.6	0.02
APACHE II score (median) [range]	20 (11-33)	20 (12-37)	0.29
Male gender (no.) [%]	8 (88.9)	18 (78.3)	0.45
Deaths (no.) [%]	2 (22.2)	14 (60.8)	0.11

Abbreviations: SD = standard deviation; APACHE = Acute Physiology and Chronic Health Evaluation

[a]Interval between time of multidrug-resistant *Acinetobacter baumannii* isolation and discharge.

outbreaks have used methods such as antibiogram typing [8], pulsed-field gel electrophoresis [9], and arbitrarily primed polymerase chain reaction [10] to find resolutions to these outbreaks. Studies have reported that sufficient hand washing and barrier precautions involving colonized and infected patients, their beds, and the surrounding equipment are important requirements [11,12]. Wang et al found that prior exposure to third-generation cephalosporins, fluoroquinolones, and carbapenems was associated with the subsequent development of MDRAB in patients [2]. In our study, 30 patients (40%) had prior exposure to at least one of these antibiotics.

The MDRAB strain was resistant to all routinely used antibiotics, except polymyxin E and ampicillin-sulbactam. Several antibiotic regimens have been reported as effective, including monotherapy (such as sulbactam, sulbactam-ampicillin, and polymyxin E) and combination therapies (such as imipenem plus sulbactam, imipenem plus amikacin, and imipenem plus rifampicin) [13-15]. However, the issue of whether or not to treat MDRAB infections still remains. One study of the use of sulbactam-ampicillin in MDRAB bloodstream infections showed that sulbactam-ampicillin use reduced the mortality rate from 91.7% to 41.4% [4]. The results showed that MDRAB should be treated appropriately, if isolated from the bloodstream. On the other hand, Mahgoub et al have proposed that colonization with MDRAB does not necessarily portend a worse outcome and that it seems merely to be a marker associated with certain risk factors [5]. The present study found that the duration of hospitalization and crude mortality were not statistically different in the 2 groups despite higher APACHE II scores in patients with CPIS >6 and irrespective of whether MDRAB caused a significant lung infection or not. However, in the 9 patients with CPIS >6, there was a trend towards reduced mortality with ampicillin-sulbactam treatment. This aspect, however, needs further study. Besides, contact isolation of patients is performed in our hospital following MDRAB isolation, and such intervention may have improved prognosis.

Accurate diagnostic criteria for the reliable diagnosis of pneumonia do not exist. In this study, we used CPIS as the criterion to discern significant lung infections that required further intervention despite the specificity and sensitivity of CPIS being only around 56% and 78% [16]. Nevertheless, we used CPIS data because of our need for an objective criterion for the screening of patients. Another drawback of the study is that these cases of MDRAB-related pneumonia were not evaluated by bronchoalveolar lavage to distinguish between instances of true infection and colonization. In spite of this, we can conclude that clinically, MDRAB-related lung infection should be regarded as an indicator of the clinical severity rather than as a prognostic factor for patients with ventilator-associated pneumonia.

In conclusion, MDRAB-related bloodstream infections should be treated because of the associated improved outcome. However, pneumonia associated with MDRAB may be merely a marker of poor clinical condition. We propose that treatment of MDRAB culture-positive pneumonia should be based on clinical observation and experience, and treatment directed at MDRAB is recommended only when true infection caused by MDRAB is confirmed by isolation from bronchoalveolar lavage.

References

1. Roberts SA, Findlay R, Lang SD. Investigation of an outbreak of multidrug-resistant *Acinetobacter baumannii* in an intensive care burns unit. J Hosp Infect. 2001;48:228-32.
2. Wang SH, Sheng WH, Chang YY, Wang LH, Lin HC, Chen ML, et al. Healthcare-associated outbreak due to pan-drug resistant *Acinetobacter baumannii* in a surgical intensive care unit. J Hosp Infect. 2003;53:97-102.
3. Go ES, Urban C, Burns J, Kreiswirth B, Eisner W, Mariano N, et al. Clinical and molecular epidemiology of *Acinetobacter* infections sensitive only to polymyxin B and sulbactam. Lancet. 1994;344:1329-32.
4. Smolyakov R, Borer A, Riesenberg K, Schlaeffer F, Alkan M, Porath A, et al. Nosocomial multidrug-resistant *Acinetobacter baumannii* bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. J Hosp Infect. 2003;54: 32-8.
5. Mahgoub S, Ahmed J, Glatt AE. Completely resistant *Acinetobacter baumannii* strains. Infect Control Hosp Epidemiol. 2002;23:477-9.
6. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis. 1991; 143:1121-9.
7. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med. 2000;162:505-11.
8. Bernards AT, van der Toorn J, van Boven CP, Dijkshoorn L. Evaluation of the ability of a commercial system to identify

Acinetobacter genomic species. Eur J Clin Microbiol Infect Dis. 1996;15:303-8.

9. Maslow JN, Slutsky AM, Arbeit RD. Application of pulsed-field gel electrophoresis to molecular epidemiology. In: Persing DH, Smith TF, Tenover FC, White TJ, eds. Diagnostic molecular microbiology: principles and applications. Washington, DC: American Society for Microbiology; 1993:563-72.
10. Grundmann HJ, Towner KJ, Dijkshoorn L, Gerner-Smidt P, Maher M, Seifert H, et al. Multicenter study using standardized protocols and reagents for evaluation of reproducibility of PCR-based fingerprinting of *Acinetobacter spp.* J Clin Microbiol. 1997;35:3071-7.
11. Aygün G, Demirkiran O, Utku T, Mete B, Urkmez S, Yilmaz M, et al. Environment contamination during a carbapenem-resistant *Acinetobacter baumannii* outbreak in an intensive care unit. J Hosp Infect. 2002;52:259-62.
12. Levin AS, Gobara S, Mendes CM, Cursino R, Sinto S. Environmental contamination by multidrug-resistant *Acinetobacter baumannii* in an intensive care unit. Infect Control Hosp Epidemiol. 2001;22:717-20.
13. Hsueh PR, Teng LJ, Chen CY, Chen WH, Yu CJ, Ho SW, et al. Pandrug-resistant *Acinetobacter baumannii* causing nosocomial infections in a university hospital, Taiwan. Emerg Infect Dis. 2002;8:827-32.
14. Urban C, Segal-Maurer S, Rahal JJ. Considerations in control and treatment of nosocomial infections due to multidrug-resistant *Acinetobacter baumannii*. Clin Infect Dis. 2003;36: 1268-74.
15. Kuo LC, Teng LJ, Yu CJ, Ho SW, Hsueh PR. Dissemination of a clone of unusual phenotype of pandrug-resistant *Acinetobacter baumannii* at a university hospital in Taiwan. J Clin Microbiol. 2004;42:1759-63.
16. Fartoukh M, Maitre B, Honoré S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med. 2003;168:173-9.

