



Susceptibility Patterns of Multidrug-Resistant *Acinetobacter baumannii*

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Abstract

Objectives To investigate the antimicrobial resistance patterns of multidrug-resistant *Acinetobacter baumannii* (MDRAB) in patients in pediatric intensive care units (PICU) in order to determine a guide for the empirical antibiotic treatment of MDRAB.

Methods The authors retrospectively evaluated the medical records of patients with MDRAB infections in the PICU during a follow-up period, between January 2015 and January 2017. The identification of *A. baumannii* was performed using a BD Phoenix 100 Automated Microbiology System. A BD Phoenix NMIC/ID-400 commercial kit was used to test antibiotic susceptibility. All data was entered into Microsoft Excel, and the data was analyzed using SPSS version 23.0.

Results The mean age of the patients was 8.1 ± 6.2 y. In all, 46 isolates were obtained from 33 patients. The most effective antimicrobial agents were colistin, trimethoprim/sulfamethoxazole, and tigecycline. Nevertheless, with the exception of colistin, no antibiotic was associated with a susceptibility rate of >45% for the isolates. Low sensitivities in 2015 to tigecycline, aminoglycosides, levofloxacin, and carbapenems had been lost in 2016.

Conclusions Many drugs that were previously effective against MDRAB, have lost their effectiveness. Currently, there is no effective drug to fight MDRAB, apart from colistin. Thus, it is clear that new drugs and treatment protocols should be developed urgently.

Keywords Multidrug-resistant *Acinetobacter baumannii* · Isolates · Susceptibility · Antibiotics · Children

Introduction

Acinetobacter baumannii is an aerobic, pleomorphic, oxidase-negative, catalase-positive, non-motile, Gram-negative bacillus. It is also an opportunistic bacterial pathogen that has emerged as an important nosocomial pathogen in recent years, especially in intensive care units (ICUs) [1]. This pathogen has been found to be associated with several clinical infections, including lower respiratory tract infections, meningitis, endocarditis, urinary tract infections, skin and soft tissue infections, burn wound infection, and bacteremia [1–3]. The strains of multidrug-resistant *Acinetobacter baumannii* (MDRAB) are defined as *A. Baumannii* and are resistant to

3 or more than 3 classes of antimicrobials [4]. MDRAB isolates are a growing problem and have been widely reported in recent years [5, 6]. The rapid global emergence of MDRAB has increased the threat to healthcare systems worldwide. It has been reported that continuous surveillance of the antimicrobial resistance of *A. baumannii* is extremely important for the selection of appropriate empirical therapies, because appropriate therapies can increase chances of patient survival [7]. Thus, in order to determine a guide for the empirical antibiotic treatment of MDRAB, the authors investigated the antimicrobial resistance patterns of MDRAB in patients in pediatric intensive care units (PICUs).

Material and Methods

The PICU of the School of Medicine, University Children's Hospital in Adiyaman, Turkey is a tertiary-level medical center with a total of 10 beds. The authors retrospectively evaluated the medical records of patients with MDRAB infections in the PICU during a follow-up period, between January 2015

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and January 2017. A total of 33 children with *A. baumannii* positive cultures (age range: 5 mo–17 y) were included in the study. The children's age, gender, date of admission, laboratory findings, radiological findings, culture, and antibiogram results were recorded.

When patients with suspected infections were included in the PICU, cultures for possible infection foci were taken. Peripheral blood culture was obtained from two separate arms from patients suspected of systemic infection during hospitalization in the PICU. Endotracheal aspirate and mini bronchoalveolar lavage (BAL) samples were obtained from intubated patients and sputum cultures were obtained from non-intubated patients suspected of respiratory tract infections. Urine culture, in case of suspected urinary tract infection (by fresh catheters or mid stream clean catch), and cerebrospinal fluid culture, in case of suspected central nervous system infection, were obtained. Additionally, wound culture was taken for localized wounds or soft tissue infections. In patients with prolonged fever or with clinical deterioration, such as tachypnea/bradypnea, tachycardia / bradycardia, hypotension, prolonged capillary filling time, oliguria, and nutritional intolerance, cultures were obtained again. The date of the first positive culture of MDRAB infection was recorded for each case. The hospitalization period was calculated by using the data.

Sepsis has been defined as “Systemic inflammatory response syndrome (SIRS) caused by infection” based on Surviving Sepsis Campaign Guidelines (SSCG) 2012 [8]. The presence of two or more of the following criteria (one of which must be abnormal temperature or leukocyte count) defines SIRS:

- Core temperature (measured by rectal, bladder, oral, or central probe) of >38.5 °C or <36 °C.
- Tachycardia, defined as a mean heart rate more than two standard deviations above normal for age, or for children younger than 1 y of age, bradycardia defined as a mean heart rate <10 th percentile for age.
- Mean respiratory rate more than two standard deviations above normal for age or mechanical ventilation for an acute pulmonary process.
- Leukocyte count elevated or depressed for age, or $>10\%$ immature neutrophils.

Nosocomial infections are defined as those occurring within 48 h of hospital admission or within 3 d of discharge or within 30 d of an operation.

In the laboratory, the samples were transferred onto eosin methylene blue (Becton Dickinson, Sparks, MD, USA) and 5% sheep blood agar via 4 mm caliber loops. The samples were then incubated at 37 °C for an average of 18–24 h. Several biochemical tests were conducted to confirm that all of the isolates belonged to *A. baumannii*. These tests included

gram staining and oxidase, catalase, and hanging drop preparation. Acinetobacter are gram-negative bacilli or coccobacilli and are either oxidase negative or catalase positive.

The identification of *A. baumannii* was performed using a BD Phoenix 100 Automated Microbiology System (Becton Dickinson, USA). A BD Phoenix NMIC/ID-400 commercial kit (Becton Dickinson Diagnostic Systems, Sparks, USA) was used for antibiotic susceptibility testing. All bacteriologic tests were standardized and performed according to the criteria of the Clinical and Laboratory Standards Institute [9]. *A. baumannii* isolate was defined as MDRAB if it was resistant to a carbapenem and at least 3 representatives of different antibiotic classes.

This study was approved by the Ethics Committee of the School of Medicine, University Children's Hospital in Adiyaman, Turkey.

All data was analyzed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistical analyses were performed. The normality of the continuous data was assessed using the Kolmogorov–Smirnov test. Because the data were not normally distributed, groups were compared using the Mann–Whitney U-test. The results were reported as mean \pm SD and median (range). Categorical variables were compared using a chi-squared test and are expressed as counts and percentages; $p < 0.05$ was considered statistically significant.

Results

The mean age of the patients was 8.1 ± 6.2 y (range: 5 mo–17 y). Of the patients, 24 (72.7%) were male and 9 (27.3%) were female. Pneumonia (84.8%), heart failure (30.3%), and sepsis (21.2%) were the most common diagnoses upon hospitalization. Nosocomial infections were detected in 18 patients and community-acquired MDRAB infections were detected in 15 patients. All patients were admitted to the intensive care unit with symptoms suggestive of infection. Twenty-five patients received mechanical ventilator (MV) support. The total number of MV stay was 210 d. In addition, the total number of central venous catheter retention time was 300 d and the number of foley catheter retention time was 84 d. Some patients had co-morbid conditions. Among these patients, four suffered from neurometabolic diseases, three had spinal muscular atrophy, two had congenital heart disease, one patient had Sandhoff disease, one had subacute sclerosing panencephalitis, and one had cerebral palsy. The most frequent indications of the culture were clinical deterioration (87.8%) and fever (33.3%). Some patients had been admitted to the PICU several times during the study period, and MDRAB growth was observed in cultures from different times and samples. While 20 patients received combined antibiotherapy; colistin alone (5 mg/kg/d intravenous) was used in 13 patients. Success was achieved with the

addition of colistin (6 patients) or trimethoprim/sulfamethoxazole (9 patients) according to the results of culture of patients using meropenem. In addition, trimethoprim/sulfamethoxazole was added to the treatment of 5 patients who received cefotaxime. Thus, the received combined antibiotherapy were meropenem + trimethoprim/sulfamethoxazole (9 patients), meropenem + colistin (6 patients), and cefotaxime + trimethoprim/sulfamethoxazole (5 patients), respectively. One patient died during the study. The clinical and demographic characteristics of the patients are summarized in Table 1.

A total of 46 isolates were obtained from 33 patients. Of these 46 isolates, 34 were from respiratory tract specimens (73.9%) and 7 were from the blood (15.2%). Twenty isolates (43.4%) were obtained in 2015 from 15 patients, and 26 isolates (56.4%) were obtained in 2016 from 18 patients. MDRAB was detected in 15 respiratory tract specimens and

3 blood samples from the cultures at admission. Cultures were taken again from the patients with prolonged fever or with clinical deterioration. In these samples, MDRAB were detected in 19 respiratory tract specimens, 4 blood samples, 3 pus samples from wounds and 2 urine samples respectively (Table 2). In total, 46 *A. Baumannii* isolates collected from various samples of patients (blood, respiratory tract specimens, urine, and pus from wounds) were evaluated. From samples of 7 (21.2%) patients with sepsis, MDRAB was produced in blood (in 5 patients), respiratory system samples (in 4 patients) and urine samples (in 2 patients). MDRAB was produced from blood + respiratory system samples in 2 patients, blood +urine samples in 2 patients, only respiratory system samples in 2 patients and only blood sample in one patient.

When their antibiotic resistance status was examined, it was noted that the isolates showed very high resistance to many drugs, especially various classes of antimicrobials, including aminoglycosides, carbapenems, antipseudomonal fluoroquinolones, penicillin, extended-spectrum cephalosporins, and penicillin+beta-lactamase inhibitors. The most effective antimicrobial agents were colistin, trimethoprim/sulfamethoxazole, and tigecycline. Nevertheless, with the exception of colistin, no antibiotic was associated with a susceptibility rate of >45% for the isolates. In 2015, low sensitivities to tigecycline, aminoglycosides, levofloxacin, and carbapenems had been lost in 2016. In 2016, the isolates were found to have a resistance rate of above 90% against all antibiotics except for colistin and trimethoprim/sulfamethoxazole (Table 3). In addition, when the resistance rates of the isolates according to isolation sites were examined, it was seen that there was a significant difference only in terms of trimethoprim/sulfamethoxazole (Table 4).

Discussion

The *Acinetobacter* species has emerged as a strong pathogen that causes life-threatening infections in communities and hospitals. *A. Baumannii* have emerged as important nosocomial pathogens that are often MDRAB and associated with life-threatening infections in ICUs [10]. The biggest problem with this pathogen is its antibiotic resistance, which is rapidly increasing worldwide. A few decades ago, infections caused by *A. baumannii* could be effectively treated with traditionally used broad-spectrum antibiotics; currently, there are no effective drugs against this pathogen, except for a small number of antibiotics. These have necessitated the use of new antibiotic-treatment strategies, including the use of tigecycline and colistin by clinicians in recent years [10]. Unfortunately, in recent years, there has also been an increasing resistance to these drugs (Table 5) [11, 12]. The increased difficulty of clinically managing the infections caused by MDRAB due to a lack of active antimicrobials has necessitated the development of

Table 1 The clinical and demographic characteristics of patients

Gender, n (%)	
Female	9 (27.3%)
Male	24 (72.7%)
Mean age (years)	8.1 ± 6.2
Diagnosis ^a , n (%)	
Pneumonia	28 (84.8)
Heart failure	10 (30.3)
Sepsis	7 (21.2)
Septic shock	2 (6.1)
Other	6 (18.8)
Co-morbid conditions, n (%)	
Neurometabolic disease	4 (12.1)
Spinal muscular atrophy	3 (9.1)
Congenital heart disease	2 (6.1)
Sandhoff disease	1 (3)
Cerebral palsy	1 (3)
Subacute sclerosing panencephalitis	1 (3)
Sample, n (%) ^b	
Respiratory tract specimens	29 (63.1)
Blood	12 (26.1)
Pus from wounds	3 (6.5)
Urine	2 (4.3)
Indications for culture ^a , n (%)	
Clinical deterioration	29 (87.8)
Fever	11 (33.3)
Inflammation at wound	1 (3.1)
Clinical Outcome, n (%)	
Recovery	32 (96.9)
Exitus	1 (3.1)

^a Some patients had more than one

^b Some patients had more than one sample

Table 2 Baseline culture results and culture results when admitted later

	Respiratory tract specimens	Blood	Pus from wounds	Urine
Baseline culture results (n)	<i>A. baumannii</i> (15)	<i>A. baumannii</i> (3)	<i>S. epidermidis</i> (5)	<i>E. coli</i> (2)
	<i>K. pneumoniae</i> (4)	<i>K. pneumoniae</i> (1)	<i>P. aeruginosa</i> (1)	<i>K. pneumoniae</i> (3)
	<i>P. aeruginosa</i> (2)	<i>P. aeruginosa</i> (2)		<i>P. mirabilis</i> (2)
	Other (2)	Other (1)		
Culture results when admitted later (n)	<i>A. baumannii</i> (19)	<i>A. baumannii</i> (4)	<i>A. baumannii</i> (3)	<i>A. baumannii</i> (2)
	<i>K. pneumoniae</i> (3)	<i>K. pneumoniae</i> (1)	<i>S. epidermidis</i> (1)	<i>E. coli</i> (1)
	<i>P. aeruginosa</i> (1)	<i>P. aeruginosa</i> (1)		<i>K. pneumoniae</i> (1)

novel strategies for managing said infections. In this study, the goal was to discuss the current situation of 3 drugs with resistance below 90% and to increase the awareness about this issue.

Colistin is an old antibiotic in the treatment of these infections, which has become popular again [22]. An alarming development is the increasing resistance to this drug, which is used as the first choice of treatment for MDRAB patients.

Although colistin resistance was around 0 in many studies up to 10 y ago, the levels of resistance have increased and reached 36% in recent years [15]. Reddy et al. reported that in MDRAB isolates from 2008, 8 (2.7%) were not susceptible to colistin [14]. In a study conducted in Algeria, it was stated that all of the 71 MDRAB isolates identified in 2012 were sensitive to colistin [6]. Similarly, Wei et al. [17] stated that all 67 MDRAB isolates they identified in NICU between 2010

Table 3 *A. baumannii* clinical isolates and their antibiotic resistance patterns, organized by year

Parameter	Total	2015	2016	p
Sample, n (%)				
Respiratory tract specimens	34 (73.9)	17 (85)	17 (65.4)	
Blood	7 (15.2)	0	7 (26.9)	
Pus from wounds	3 (6.5)	2 (10)	1 (3.8)	
Urine	2 (4.3)	1 (5)	1 (3.8)	
Antimicrobial resistance profile, n (%)				
Tigecycline	34 (73.9)	10 (50)	24 (92.3)	0.002*
Levofloxacin	42 (91.3)	16 (80)	26 (100)	0.030*
Amikacin	45 (97.8)	19 (95)	26 (100)	0.435
Amoxicillin/Clavulanate	46 (100)	20 (100)	26 (100)	
Ampicillin/Sulbactam	44 (95.7)	18 (90)	26 (100)	0.184
Aztreonam	46 (100)	20 (100)	26 (100)	
Cefepime	46 (100)	20 (100)	26 (100)	
Cefixime	46 (100)	20 (100)	26 (100)	
Ceftazidime	46 (100)	20 (100)	26 (100)	
Ceftriaxone	46 (100)	20 (100)	26 (100)	
Ciprofloxacin	44 (95.7)	19 (95)	25 (96.2)	0.686
Colistin	1 (2.2)	0 (0)	1 (3.8)	0.380
Ertapenem	45 (97.8)	19 (95)	26 (100)	0.435
Gentamicin	44 (95.7)	19 (95)	25 (96.2)	0.686
Imipenem	45 (97.8)	19 (95)	26 (100)	0.435
Meropenem	45 (97.8)	19 (95)	26 (100)	0.435
Nitrofurantion	45 (97.8)	19 (95)	26 (100)	0.435
Piperacillin/Tazobactam	46 (100)	20 (100)	26 (100)	
Trimethoprim/Sulfamethoxazole	27 (58.7)	19 (95)	8 (30.8)	<0.001*

* $P < 0.05$

Table 4 *A. baumannii* clinical isolates and their antibiotic resistance patterns, organized by isolation sites

Antimicrobial resistance profile, n (%)	Respiratory tract specimens (n = 35)	Blood (n = 7)	Pus from wounds (n = 3)	Urine (n = 2)	<i>p</i>
Tigecycline	25 (71.4)	7 (100)	2 (66.7)	1 (50)	0.258
Levofloxacin	31 (88.6)	7 (100)	3 (100)	2 (100)	0.743
Amikacin	34 (97.1)	7 (100)	3 (100)	2 (100)	0.950
Amoxicillin/Clavulanate	35 (100)	7 (100)	3 (100)	2 (100)	
Ampicillin/Sulbactam	35 (100)	7 (100)	3 (100)	2 (100)	
Aztreonam	35 (100)	7 (100)	3 (100)	2 (100)	
Cefepime	35 (100)	7 (100)	3 (100)	2 (100)	
Cefixime	35 (100)	7 (100)	3 (100)	2 (100)	
Ceftazidime	35 (100)	7 (100)	3 (100)	2 (100)	
Ceftriaxone	35 (100)	7 (100)	3 (100)	2 (100)	
Ciprofloxacin	34 (97.1)	6 (85.7)	3 (100)	2 (100)	0.450
Colistin	0 (0)	1 (14.3)	0 (0)	0 (0)	0.255
Ertapenem	34 (97.1)	7 (100)	3 (100)	2 (100)	0.950
Gentamicin	33 (94.3)	7 (100)	3 (100)	2 (100)	0.869
Imipenem	34 (97.1)	7 (100)	3 (100)	2 (100)	0.950
Meropenem	34 (97.1)	7 (100)	3 (100)	2 (100)	0.950
Nitrofurantion	34 (97.1)	7 (100)	3 (100)	2 (100)	0.950
Piperacillin/Tazobactam	35 (100)	7 (100)	3 (100)	2 (100)	
Trimethoprim/Sulfamethoxazole	24 (68.6)	0 (0)	2 (66.7)	2 (100)	0.001*

**P* < 0.05

and 2013 were sensitive to colistin. In an alarming study that supported previous studies, Maraki et al. [7] reported that colistin resistance, which was 0 in 2010, was 7.9% in 2014. In a worrying study of MDRAB antibiotic susceptibility, it was reported that the colistin resistance rate increased to 35.7% in Iran [19]. In the present study, while all isolates in

2015 were sensitive to colistin, colistin resistance was found to be at 3.8% in 2016. The present results suggest that while colistin is currently a suitable option for the treatment of MDRAB, colistin resistance in authors' region may increase in coming years, in accordance with the findings of previous studies.

Table 5 Comparison of antibiotic resistance rates of drugs that can be used in multidrug-resistant *Acinetobacter baumannii* infections by years and countries

Studies and years when isolates were detected	Antimicrobial resistance rates (%)		
	Tigecycline	Colistin	Trimethoprim/Sulfamethoxazole
Palestine (2005) [13]	–	–	77.5
United States (2008) [14]	80.4	2.7	55.3
Turkey (2011) [15]	18.9	0	95.6
United States (2012) [16]	–	5.3	55.3
Algeria (2012) [6]	61.9	0	–
Taiwan (2013) [17]	*	0	100
Greece (2014) [7]	41.3	7.9	59.4
Iran (2014) [18]	98	–	–
Iran (2015) [19]	–	35.7	92.5
India (2015) [20]	20	0	73.3
Pakistan (2011) [21]	20	50	95.5
Present study (2016)	92.3	3.8	30.8

*Unworked for five isolates

Tigecycline is a new glycolcycline, and it is 1 of the 2 preferred drugs for the treatment of MDRAB. Although there are differences between countries, and although tigecyclines such as colistin previously had high susceptibility rates, it has experienced high resistance rates in a short time when compared to colistin. The tigecycline resistance rate, which was at roughly 3% at the beginning of 2010, increased to 98% in 2018. Reddy et al. reported that of the 348 (28%) MDRAB isolates from 2008, 280 (80.4%) were not susceptible to tigecycline in the Detroit Medical Center [14]. In a study reported from Greece, the tigecycline resistance rate, which was 2.9% in 2010, increased to 41.3% in 2014 [7]. Hasan et al. [21] reported that between July 2010 and August 2011, a total of 90 clinical isolates of *A. baumannii* were obtained from patients and isolates, and they showed only a 20% resistance to tigecycline. In a study carried out in Algeria in the following year, the tigecycline resistance rate for 2012 was reported to be 61.9% [6]. In a recent (and alarming) study reported from Iran, the tigecycline resistance rate was expressed as 98% [18]. When all isolates were taken into consideration, the rate of tigecycline resistance was 73.9% in the present study. However, the tigecycline resistance rate, which was 50% in 2015, increased to 92.3% in 2016. These results suggest that tigecycline may not be the right choice for MDRAB in authors' region and many other countries.

While trimethoprim/sulfamethoxazole is not traditionally recommended to treat MDRAB infections, it may be recommended in combination with other therapies [23]. Different results have been reported in different countries and in different times regarding the resistance to trimethoprim/sulfamethoxazole. In a study conducted in Taiwan, all 30 isolates obtained between 2010 and 2013 had detected resistance to trimethoprim/sulfamethoxazole [17]. In a study reported from Palestine, 40 isolates were obtained from NICU in 2004–2005, and 77.5% of them were found to be resistant to trimethoprim/sulfamethoxazole [13]. In 2 recent studies conducted in Iran and India, the trimethoprim/sulfamethoxazole resistance rate was detected as 92.5% and 73.3%, respectively [19, 20]. In a recent survey describing secular trends in the resistance of 39,230 *A. baumannii* isolates in the United States from 2003 to 2012, it was stated that the rate of resistance to trimethoprim/sulfamethoxazole varied between 52.5–57.5% during the study period, and the total resistance rate was 55.3% [16]. In a study reported from Greece, the rate of resistance to trimethoprim/sulfamethoxazole, which was 91.5% in 2010, decreased to 59.4% in 2014 [7]. When all isolates were taken into consideration, the rate of trimethoprim/sulfamethoxazole resistance was 58.7% in the present study. However, the trimethoprim/sulfamethoxazole resistance rate, which was 95% in 2015, decreased to 30.8% in 2016. The authors believe that the decreasing resistance of *A. baumannii* isolates to trimethoprim/sulfamethoxazole over the past 2 y is likely due to the limited use of this bacteriostatic agent in

recent years. These results suggest that trimethoprim/sulfamethoxazole might be considered in combination with other therapies to treat MDRAB in authors' region.

In conclusion, the remaining therapeutic options for critically ill patients who suffer from MDRAB infections are extremely limited. Many of the drugs that were previously effective have lost their effectiveness. Currently, and apart from colistin, there is no effective drug for the treatment of MDRAB. Unfortunately, MDRAB has also begun to develop resistance to colistin. Trimethoprim/sulfamethoxazole has sufficient efficacy to be recommended in combination with other therapies. The most important reason for this change in antibiotic resistance rates may be unconscious antibiotic consumption. In addition, the presence of co-morbid conditions and a history of recurrent hospitalization in some patients may have led to changes in resistance rates. From the results of this study and others, it is clear that new drugs and treatment protocols should be developed.

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Authors' Contributions MG: Data collection; MT: Writing of the manuscript; CK: Performer of the analysis, writing and preparation of the manuscript and will act as guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None.

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