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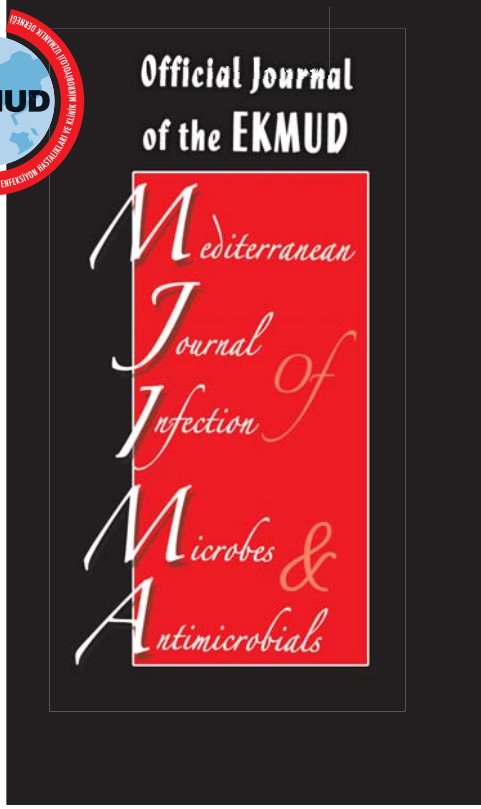

Antibiotic Resistance Profile of Acinetobacter Strains Isolated from Patients in the Intensive Care Unit: A Surveillance Study of Four Years

Yoğun Bakım Hastalarından İzole Edilen Asinetobakter Kökenlerinin Direnç Profili: Dört Yıllık Sürveyans Çalışması

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ABSTRACT

Introduction: *Acinetobacter* species can cause health care-associated infections in patients who are treated in intensive care units of hospitals. The aim of this study was to determine the antibiotic resistance rates of *Acinetobacter* species that induce health care-associated infections among intensive care unit patients in a state hospital during the period 2008-2011.

Materials and Methods: Clinical samples obtained from intensive care unit patients were cultured by regular methods. The identification and antibiotic susceptibility tests were performed using the BD Phoenix 100 system, BD Phoenix NMIC/ID-82 Id+ADT (Becton Dickinson, Belgium).

Results: During the study period a total of 320 *Acinetobacter* strains were isolated. Colistin and tigecycline were found to be the most effective antimicrobial agent against *Acinetobacter* species. When the resistance rates were compared between 2008 and 2011, significant increases were observed for imipenem, meropenem, ceftazidime, trimethoprim-sulfamethoxazole, and ampicillin-sulbactam; a significant decrease was observed for tobramycin. No statistically significant changes were observed for amikacin, cefepime, ceftriaxone, piperacillin-tazobactam, and gentamicin.

Conclusion: High antibiotic resistance rates of *Acinetobacter* species induce health care- associated infections in intensive care unit patients. It is important to undertake bacteriologic surveillance in hospitals to ascertain the common microorganisms and their antibiotic resistance rates.

Key words: *Acinetobacter,* antibiotic resistance, health care-associated infection, nosocomial

Received: 17.11.2012 • ***Accepted:*** 18.09.2013 • ***Published:*** 12.11.2013

ÖZET

Giriş: *Acinetobacter* türleri yoğun bakım ünitesinde yatan hastalarda sağlık bakımı ile ilişkili infeksiyonlara neden olmaktadır. Bu çalışmada bir devlet hastanesi yoğun bakım ünitesindeki hastalarda sağlık bakımı ile ilişkili infeksiyonlara sebep olan *Acinetobacter* türlerinin çeşitli antibiyotiklere direnç oranlarını ve 2008-2011 yılları arasında bu oranların yıllara göre değişiminin saptanması amaçlanmıştır.

Materyal ve Metod: Yoğun bakım ünitesinde yatan hastaların klinik örneklerinin kültürleri rutin yöntemlerle yapılmıştır. İzole edilen suşların identifikasyon ve antibiyogram duyarlılık testleri BD Phoenix 100 sistemiyle BD Phoenix NMIC/ID-82 İd+ADT (Becton Dickinson-Belçika) kullanılarak yapılmıştır.

Bulgular: Çalışma süresince toplam 320 *Acinetobacter* kökeni izole edilmiştir. *Acinetobacter* türlerine kolistin ve tigesiklinin en etkili antibiyotikler olduğu görülmüştür. 2008-2011 yılları arasında, seftazidim, imipenem, meropenem, trimetoprim-sülfametoksazol, ampisilin-sulbaktam direncinde istatistiksel olarak anlamlı artış saptanmıştır. Tobramisin direncinde ise istatistiksel olarak anlamlı azalma olduğu görülmüştür. Amikasin, sefepim, seftriakson, piperasilin-tazobaktam ve gentamisinde ise anlamlı bir değişme gözlenmemiştir.

Sonuç: Dirençli *Acinetobacter* türleri yoğun bakımda yatan hastalarda sağlık bakımı ile ilişkili infeksiyonlara neden olmaktadır. Hastanelerde sık rastlanan etkenleri ve antibiyotik direnç oranlarını bilmek için bakteriyolojik sürveyans yapılması önemlidir.

Anahtar kelimeler: *Acinetobacter,* antibiyotik direnci, sağlık bakımı ile ilişkili infeksiyon, nozokomiyal

Geliş Tarihi: 17.11.2012 • ***Kabul Ediliş Tarihi:*** 18.09.2013 • ***Yayınlanma Tarihi:*** 12.11.2013

INTRODUCTION

Acinetobacter species are gram-negative, non-fermentative, immobile aerobe coccobacilli. They form translucent, opaque, convex colonies 0.5-2 mm in diameter on a blood agar plate in 24 hours. They exhibit natural resistance to several antibiotics because of their intrinsic resistance mechanism; therefore, it is difficult to treat outbreaks of health care-associated infections. *Acinetobacter* species are prevalent, and exist on the skin flora of healthy people, hospital staff and the hospital environment. Despite the low virulence of the bacteria, they may cause opportunistic infections in patients with underlying disease, newborn babies, and in the elderly. The intensive care unit (ICU) is where patients in poor general condition are followed up and invasive devices are frequently applied. Approximately 25% of health care-associated infections develop in ICUs[1,2]. However, it is known that the resistance rates of the infections in ICUs are higher[3]. A large number of antibiotic-resistant *Acinetobacter* outbreaks have been reported in many ICUs[4-6]. Because the antibiotic resistance rates vary between hospitals, is important to ascertain the bacterial resistance status for each hospital in order to select the appropriate antibiotics for empiric therapy.

In this study, it was aimed to determine the antibiotic resistance rates of *Acinetobacter* strains isolated from clinical specimens of ICU patients and the distribution of these ratios during the period 2008-2011.

MATERIALS and METHODS

A prospective and active surveillance was performed among patients treated in a state hospital ICU between 2008 and 2011. The diagnosis of health care-associated infection was based on the Centers for Disease Control and Prevention (CDC) criteria[7]. A total of 320 *Acinetobacter* spp. isolated from the patients who had health care-associated infection in the ICU and the antibiotic resistance of the isolates were investigated in the study. The samples were inoculated on 5% sheep blood agar and EMB agar. The identification and antibiotic susceptibility tests were performed using the BD Phoenix 100 system, BD Phoenix NMIC/ID-82 Id+ADT (Becton Dickinson, Belgium). Strains defined as *Acinetobacter* spp. were evaluated for resistance to antimicrobials. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for Windows (SPSS Inc., Chicago, IL, USA) program and the non-parametric chi-square test.

RESULTS

A total of 320 *Acinetobacter* strains were isolated (Table 1); 245 (76.5%) of the strains were identified as *A. baumannii*, 40 (12.5%) as *A. lwoffii* and 35 (10.9%) were other *Acinetobacter* spp. with respect to the distribution of the species obtained according to clinical specimens, 40% were from tracheal aspirate, 22.5% from sputum, 10% from blood, 18.1% from wound, 7.1% from urine, and 2% from other samples (Table 2).

Table 1. The distribution of the *Acinetobacter* strains

Acinetobacter strains	2008 n (%)	2009 n (%)	2010 n (%)	2011 n (%)	Total 320 (%)
A. baumannii	26 (61.9%)	54 (72%)	61 (73.4%)	104 (86.6%)	245 (76.5%)
A. lwoffii	14 (33.3%)	16 (21.3%)	8 (9.6%)	2 (1.6%)	40 (12.5%)
Acinetobacter spp.	2 (4.7%)	5 (6.6%)	14 (16.8%)	14 (11.6%)	35 (10.9%)

Table 2. The distribution of the samples (%)

	2008 (n= 42)	2009 (n= 75)	2010 (n= 83)	2011 (n= 120)	Total (n= 320)
Sputum	13 (30.9%)	16 (21.3%)	17 (20.4%)	26 (21.6%)	72 (22.5%)
Tracheal aspirate	4 (9.5%)	43 (57.3%)	32 (38.5%)	49 (40.8%)	128 (40%)
Blood	5 (11.9%)	8 (10.6%)	5 (6%)	14 (11.6%)	32 (10%)
Wound	12 (28.5%)	5 (6.6%)	15 (18%)	26 (21.6%)	58 (18.1%)
Urine	7 (16.6%)	2 (2.6%)	10 (12%)	4 (3.3%)	23 (7.1%)
Other	1 (2.3%)	1 (1.3%)	4 (4.8%)	1 (0.8%)	7 (2.1%)

We determined the antibiotic resistance rates for a four-year average as follows: 93.4% for ceftazidime, 93.2% for cefepime, 93.1% for ceftriaxone, 92.6% for ciprofloxacin, 91.4% for gentamicin, 89.4% for ampicillin-sulbactam, 88.9% for piperacillin-tazobactam, 88.9% for amikacin, 84.5% for tetracycline, 87.9% for trimethoprim-sulfamethoxazole, 68.5% for meropenem, 67.6% for cefoperazone-sulbactam, 65.8% for imipenem, 37% for tobramycin, 2.5% for colistin, and 10% for tigecycline (Figure 1).

The annual distribution of these ratios is shown in Table 3. When the resistance rates were compared between 2008 and 2011, significant increases were observed for imipenem ($p< 0.001$), meropenem ($p< 0.001$), ceftazidime ($p< 0.001$), trimethoprim-sulfamethoxazole ($p< 0.01$), and ampicillin-sulbactam ($p< 0.05$). Further, significant increases were observed for cefoperazone-sulbactam between 2009 and 2011. Although a significant decrease was observed for tobramycin ($p< 0.001$), we found no statistically significant changes for amikacin, cefepime, ceftriaxone, piperacillin-tazobactam, and gentamicin (Table 3).

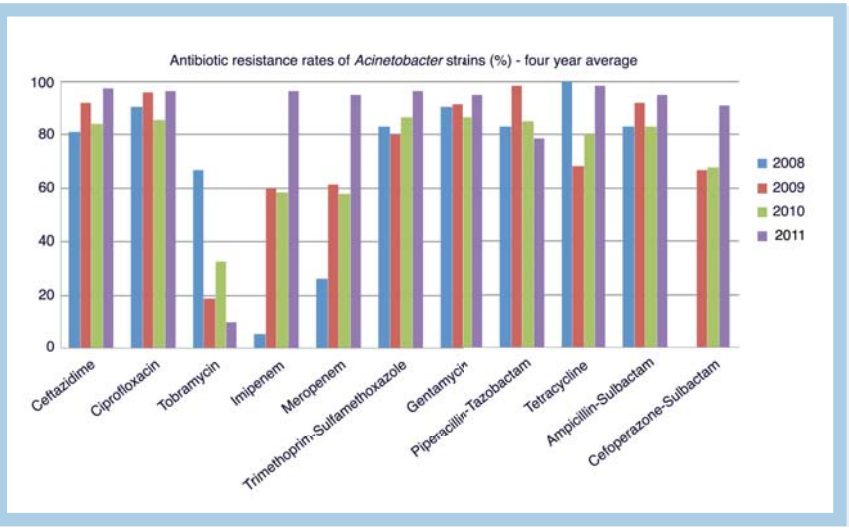

Figure 1

Antibiotic resistance rates of *Acinetobacter* strains (%).

Table 3. Antibiotic resistance rates of *Acinetobacter* strains between years 2008-2011 (%)

	2008 (n= 42)	2009 (n= 75)	2010 (n= 83)	2011 (n= 120)
Amikacin	90.3%	92%	86.6%	91.5%
Ceftazidime	81%	91.9%	84.2%	97.5%
Ciprofloxacin	90.5%	96%	85.4%	96.6%
Tobramycin	66.6%	18.7%	32.6%	9.9%
Colistin	-	-	3%	2.1%
Tigecycline	-	-	9.6%	10%
Imipenem	5.6%	60%	58.6%	96.3%
Meropenem	26.2%	61.3%	58.1%	95%
Trimethoprim-Sulfamethoxazole	83.4%	80%	86.6%	96.7%
Ceftriaxone	100%	97.9%	92.3%	96.6%
Cefepime	90.5%	96.8%	89.9%	96.5%
Cefoperazone-Sulbactam	-	66.6%	67.8%	91%
Gentamycin	90.5%	91.4%	86.6%	95%
Piperacillin-Tazobactam	83.4%	98.4%	85%	78.6%
Tetracycline	100%	68.1%	80.3%	98.3%
Ampicillin-Sulbactam	83.4%	91.9%	83.4%	94.9%

DISCUSSION

The broad-spectrum antibiotic application leads to the emergence of resistant microorganisms in ICUs related to high rates of infection. Aging, immune suppression, surgery, invasive procedures, antibiotic use, and long-term hospitalization are the risk factors for these resistant bacterial infections. The most common species of *Acinetobacter* that cause health care-associated infections are *A. baumannii*[8]. We also determined that *A. baumannii* (76.5%) was the most frequently isolated strain (Table 1). *Acinetobacter* species may lead to sepsis, pneumonia, urinary tract infections, wound infections, meningitis, and surgical site infections in ICU patients. Although studies vary, the respiratory tract and blood samples are the most frequently isolated samples of *Acinetobacter*[1,9-11]. As shown in Table 2, tracheal aspirate culture was the most frequently examined sample in our study, followed by sputum (22.5%), wound (18.1%), blood (10%), urine (7.1%), and other (2.1%) cultures. Multidrug resistant (MDR) *Acinetobacter* are an important cause of morbidity and mortality in hospitalized patients in the ICU[12]. In our country, in the many studies investigating antibiotic resistance among *Acinetobacter* strains that cause infections in ICU patients, the resistance ratios were determined as follows: 15-100% for cephalosporins, 65-100% for quinolones, 39-100% for aminoglycosides, 61-100% for penicillins, 68-100% for trimethoprim-sulfamethoxazole, 22-92% for tobramycin, and 0-90% for carbapenems (Table 4)[3,9,13-20]. There may be different rates of resistance according to hospitals or years. Due to their constitution of cephalosporinase, 3rd generation cephalosporins have low efficiency against *Acinetobacter*. Colistin resistance was detected as zero for *A. baumannii* in a study involving 19 centers in Spain; however, it was reported in a study performed in Turkey as 6% in 2009 and 5% in 2010[21,22]. In the same study, resistance to tigecycline was found as 13.7%[21]. We found resistance to colistin as 2.5% and to tigecycline as 10% in our study. In our study, colistin was found to be the most effective antimicrobial agent against *Acinetobacter* spp. In recent years, colistin has been used as a therapeutic agent because of these MDR strains. Widespread use of this antibiotic increases the resistance rates to colistin. When the resistance rates were compared between 2008 and 2011, significant increases were observed for imipenem ($p< 0.001$), meropenem ($p< 0.001$), cef-

Table 4. Antibiotic resistance rates of *Acinetobacter* strains isolated from various ICU patients (%)

	Pala-biyikoglu et al.* 1997-8	Akkurt et al.* 1999-2000	Inan et al.* 2000	Aygün et al. 2000	Kiremitci et al.* 2003	Kucuk-bayrak et al.* 2003	Ozer et al.* 2003-4	Serefhanoglu et al.* 2003-7	Cetin et al.* 2005-6	2008-2010
n	50	17	75	50	133	4	36	18	56	245
Amikacin	88	54	80	70	83	-	94	39	68	89
Ceftazidime	96	100	88	98	90	-	94	67	90	93
CRO	100	-	65	76	78	100	86	67	95	93
Tobramycin	-	54	22	-	70	-	92	-	-	37
Colistin	-	-	-	-	-	-	-	-	-	2.5
Tigecycline	-	-	-	-	-	-	-	-	-	10
Imipenem	64	0	9	34	60	-	56	22	80	66
Meropenem	-	0	-	36	-	25	56	-	-	69
SXT	-	-	-	92	69	100	-	-	-	88
Cefepime	-	46	78	86	80	100	-	50	-	93
SCF	-	15	95	20	-	100	8	28	58	68
Gentamycin	-	92	-	88	73	100	94	61	74	91
TZP	-	62	-	90	-	100	92	61	95	89
Tetracycline	-	-	-	-	-	-	-	-	-	85
SAM		-	-	-	-	100	33	61	-	90

CRO: Ceftriaxone, SXT: Trimethoprim-sulfamethoxazole, SCF: Cefoperazone-sulbactam, TZP: Piperacillin-tazobactam, SAM: Ampicillin-sulbactam.

tazidime ($p< 0.001$), trimethoprim-sulfamethoxazole ($p< 0.01$), and ampicillin-sulbactam ($p< 0.05$), while a significant decrease was observed for tobramycin ($p< 0.001$). There were no statistically significant changes for amikacin, cefepime, ceftriaxone, piperacillin-tazobactam, and gentamicin. The cause of the increasing resistance to carbapenems was based on their frequent use for empirical treatment of serious infections in patients[23]. Tobramycin has not been available in our country since 2006. Since it has not been used for treatment, the resistance rates to this antibiotic are decreasing. For the treatment of severe *Acinetobacter* infections, combination therapy should be applied by considering antibiotic sensitivity tests. The best approach is combinations of carbapenem, colistin, rifampin, and ampicillin-sulbactam[8]. It is determined that MDR strains cause infections in ICU patients. These infections increase the cost of treatment, morbidity and mortality. Accurate empirical treatment of these patients will be lifesaving. Management of these infections is very difficult because of MDR, including to carbapenems. For empirical therapy, it is important to know the frequent pathogens and their antibiotic resistance, which vary in each hospital.

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