Changes in resistance percentage to antibiotics in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains isolated from blood cultures of intensive care unit patients

Yoğun bakım hastalarının kan kültürlerinden izole edilen *Pseudomonas aeruginosa* ve *Acinetobacter baumannii* izolatlarının antibiyotik direnç yüzdelerindeki değişim

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ÖZET

Amaç: *Pseudomonas aeruginosa* ve *Acinetobacter baumannii* enfeksiyonları özellikle yoğun bakım ünitesinde (YBÜ) yatan hastalar için en önemli sorunlardan birisidir. Bu çalışmanın amacı, YBÜ hastalarında kan dolaşımı enfeksiyonlarına sebep olan *P. aeruginosa* ve *A. baumanni* etkenlerinin antimikrobiyal direnç paternlerini belirlemek ve ampirik tedavi protokollerinin uygunluğunu değerlendirmektir.

Yöntemler: Ocak-Aralık 2010 ve Ocak-Aralık 2011 tarihlerinde YBÜ'de yatan hastalara ait hemokültür örneklerinde üreyen suşların direnç oranları ayrı ayrı incelenerek karşılaştırıldı. Bu iki zaman aralığı arasında direnç oranlarındaki farklılıklar karşılaştırılarak istatistiksel olarak analiz edildi.

Bulgular: *P. aeruginosa* suşlarının piperasilin-tazobaktam, sefaperazon - sulbaktam, seftazidim, siprofloksasin, gentamisin, amikasin ve netilmisine direnç oranlarında 2011 yılında 2010 yılına oranla azalma olduğu saptandı (p değerleri sırasıyla, 0,0059, 0,0000, 0,0048, 0,0350, 0,0000, 0,0000, 0,0003). Buna karşılık, aztreonam direnç oranında artış saptandı (p değeri, 0,0155). İmipenem direncinin benzer oranlarda

ABSTRACT

Objective: Infections of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are one of the greatest concerns for hospitalized patients, particularly those in intensive care units (ICUs). The aim of this study was to determine the antimicrobial resistance percentages and to assess empirical treatment options for bloodstream infections due to *P. aeruginosa* and *A. baumannii* strains in ICU patients.

Methods: Resistance percentages of strains isolated in January- December 2010 and January- December 2011 were separately analyzed and compared. The differences in resistance percentages between two intervals was statistically analyzed.

Results: A statistically significant decrease was found in the resistance percentage of piperacillin-tazobactam, cefoperazone-sulbactam, ceftazidime, ciprofloxacin, gentamicin, amikacin and netilmicin in the second period compared with the first (p values were 0.0059, 0.0000, 0.0048, 0.00350, 0.0000, 0.0000, 0.0003, respectively) for *P. aeruginosa* strains. Whereas resistance percentage of aztreonam was increased (p value was 0.0155). Resistance percentage of imipenem was found similar.

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olduğu görüldü. *A. baumannii* suşlarının sefepim ve amikasin direnç oranlarında ikinci periyotta ilkine oranla istatistiksel olarak anlamlı azalma saptandı (p değerleri, 0,0003 ve 0,0000). Ampisilin-sulbaktam, piperasilin-tazobaktam ve imipeneme karşı direnç oranlarında artış saptandı (p değerleri sırasıyla, 0,0003, 0,0210, 0,0033). Her iki bakteri türünde de kolistine direnç saptanmadı. *A. baumannii* izolatlarında tigesiklin direnci saptanmadı.

Sonuç: Her hastanenin özellikle yoğun bakım birimlerinden izole edilen suşların antibiyotik direnç paternlerinin aktif sürveyansla takibi, ampirik tedavi yaklaşımlarını belirlemeye hizmet eder. Bu çalışmada antibiyotik kullanım politikasının hastane enfeksiyonları ile mücadelede önemli bir adım olduğu vurgulanmıştır. Sonuç olarak, direnç oranlarını azaltmak için, enfeksiyon kontrol önlemleri alınmalı, ampirik tedavi rejimleri sürekli gözden geçirilmeli ve aktif surveyans verilerine göre belirlenmelidir.

Anahtar Sözcükler: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, antibiyotik direnci, kan kültürü, yoğun bakım ünitesi

In A.baumannii strains, a statistically significant decrease was found in resistance percentage of cefepime and amikacin in the second period compared with the first (p values were 0.0003, 0.0000). Resistance percentage of ampicillin-sulbactam, piperacillin-tazobactam and imipenem was increased (p values were 0.0003, 0.0210, 0.0033). There was no colistin resistance determined in both species. Tigecycline resistance was not found in *A. baumannii* isolates.

Conclusion: Active surveillance of antibiotic resistance percentages of isolated strains especially in ICUs serves to determine empirical treatment regimens in every institution. The present study emphasized that antibiotic usage policy is an important step to combat hospital infections. Consequently, infection control measures should be taken, empirical treatment regimens should be constantly reviewed, and should be determined according to active surveillance data in order to decrease resistance percentages.

Key Words: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Antibiotic resistance, Blood culture, Intensive care unit

INTRODUCTION

Nosocomial infections pose a threat in difficult to treat patients, especially in the high-risk departments such as Intensive Care Units (ICUs) (1). Bloodstream infections are being reported as a leading cause of morbidity and mortality worldwide. Moreover, bloodstream infections represent about 15% of all nosocomial infections and causes of health care costs (2, 3).

Pseudomonas aeruginosa and *Acinetobacter baumannii* are nonfermentative gram-negative bacteria that have minimal nutritional requirements and can survive on a wide variety of surfaces and in aqueous environments. Infections with *P. aeruginosa* or *A. baumannii* are of greatest concern for hospitalized patients, particularly those in ICUs, where these opportunistic pathogens are capable of developing severe invasive infections in critically ill and immunocompromised patients (4). In recent years, multiple antimicrobial resistance patterns of these bacteria have become as a major problem and a factor that complicates the treatment (5). Uncontrolled and intensive use of antimicrobials is one of the most important reasons for the increase of resistant strains. Each hospital should have data about their antimicrobial susceptibility patterns of nonfermentative bacteria to choose appropriate empirical treatment regimens for reducing morbidity and mortality. To have data about resistance percentage is required not only for assessment of treatment options but also to monitor the spread of resistant organisms or resistance genes throughout the hospital and community. Therefore each hospital must regularly follow their isolates, determine resistance percentage of antibiotics and regulate their own empirical treatment protocols according to these results (6). The present study was designed for this aim.

MATERIAL AND METHODS

The study was performed retrospectively in an 1100-bed tertiary training hospital at the western part of Turkey. ICU bed ratio was 7% of all bed capacity. *P. aeruginosa* and *A. baumannii* which was isolated from blood cultures of ICU patients between January 2010 and December 2011 was examined. All results evaluated in 2 periods (first period January -December 2010, second period January- December 2011). Totally 470 strains included in the study 157 (33.4%) *P. aeruginosa* and 313 (66.6%) *A. baumannii* strains). In the first period, 84 (36%) *P. aeruginosa* and 152 (64%) *A. baumanni* and in the second period 73 (31%) *P. aeruginosa* and 161 (69%) *A. baumannii* strains were evaluated.

Automated blood culture system (Bactec 9240™, Becton-Dickinson Diagnostic Instrument Systems, USA) was used for isolation of bacterial strains from blood specimens. Identification was performed based on conventional methods. Confirmation and antimicrobial resistance results of the isolated strains to 16 antibacterial agents was made by automated system (BD Phoenix 100™ System, Beckton Dickinson, USA). Antimicrobials tested for *P. aeruginosa* was piperacillin-tazobactam, ceftazidime, cefepime, imipenem, aztreonam, gentamicin, amikacin, netilmicin, ciprofloxacin, and colistin, for *A. baumanni* was ampicillin-sulbactam, piperacillin-tazobactam, cefotaxime, ceftriaxone, ceftazidime, cefepime, imipenem, gentamicin, amikacin, ciprofloxacin, tigecycline, trimetoprim-sulfamethoxazole, and colistin. Antimicrobial susceptibility of the isolated strains was determined using Kirby-Bauer Disk diffusion method for cefoperazone-sulbactam. All studies performed according to the CLSI standards (7). Zone diameter of cefoperazone was used for cefoperazone-sulbactam whose limit values are not standard approved by CLSI. Tigecycline breakpoints approved by the US Food and Drug Administration (FDA) for indicated Enterobacteriaceae species was applied for comparison purposes. Moderately susceptible strains were accepted as resistant (8). *P. aeruginosa* ATCC 27853 was used as quality control strain.

Differences in resistance percentage to antibiotics between these two periods was analyzed. Statistical analyses was performed by using Epi İnfo version 7 program (CDC, Atlanta). Chi-square test was applied where appropriate. For all analyses, a P value of less than 0.05 was considered statistically significant.

RESULTS

A statistically significant decrease was found in resistance percentage of piperacillin-tazobactam, cefoperazone-sulbactam, ceftazidime, netilmicin, amikacin, gentamicin, and ciprofloxacin in the second period compared with the first (p values were 0.0059, 0.0000, 0.0048, 0.0003, 0.0000, 0.0000 and 0.0350, respectively) for *P. aeruginosa* strains. Whereas resistance percentage of aztreonam was increased. This result was also statistically significant (p value was 0.0155). Resistance percentage of cefepime and imipenem was also slightly decreased but this result was statistically insignificant. Colistin resistance was not found in both periods. The antimicrobial resistance percentage of the *P. aeruginosa* strains in both periods was listed in Table 1.

In *A. baumannii* strains, a statistically significant decrease was found in resistance percentage of cefepime, and amikacin in the second period compared with the first one (p values were 0.0003 and 0.0000, respectively). In contrast resistance percentage of ampicillin-sulbactam, piperacillin-tazobactam, and imipenem was increased (p values were 0.0003, 0.0210, 0.0033, respectively). Changes in resistance percentage of cefoperazone-sulbactam, ceftazidime, gentamicin, and ciprofloxacin were statistically insignificant. The resistance percentages of cefotaxime, ceftriaxone and trimetoprim-sulfamethoxazole for *A. baumannii* isolates were %100 in first period and 97%, 97% and 95%, respectively in

the second period. Colistin and tigecycline resistance was not found in both periods. The antimicrobial resistance percentages of the *A. baumannii* isolates in both periods was listed in Table 2.

Table 1. The antimicrobial resistance profiles of the *P. aeruginosa* isolates

Antimicrobials	*Pseudomonas* spp.				P	X²
	2010		2011			
	n	(%)	n	(%)		
Piperacillin-Tazobactam	53	63	30	41	0,0059*	7,5860
Cefoperazone-sulbactam	59	70	26	36	0,0000*	18,8558
Ceftazidime	50	60	27	37	0,0048*	7,9384
Cefepime	55	66	37	51	0,0606	3,5222
İmipenem	16	19	13	18	0,8418	0,0398
Aztreonam	62	74	65	89	0,0155*	5,8623
Gentamicin	67	80	17	23	0,0000*	50,0726
Amikacin	35	42	9	12	0,0000*	16,6659
Netilmicin	33	39	8	11	0,0003*	12,8579
Ciprofloxacin	44	52	26	36	0,0350*	4,429
Colistin	0	0	0	0	-	-
Totally tested isolates	**84**	**100**	**73**	**100**	**-**	**-**

* P values as statistically significant

Table 2. The antimicrobial resistance profiles of the *A. baumannii* isolates

Antimicrobials	*Acinetobacter* spp.				P	X²
	2010		2011			
	n	(%)	n	(%)		
Sulbactam-Ampicillin	140	92	161	100	0,0003*	13,2173
Piperacillin-Tazobactam	132	87	152	94	0,0210*	5,3265
Cefoperazone-sulbactam	82	54	91	57	0,6471	0,2096
Cefotaksime	152	100	156	97	-	-
Ceftriaxone	152	100	156	97	-	-
Ceftazidime	147	97	152	94	0,3251	0,9685
Cefepime	152	100	148	92	0,0003*	12,8051
İmipenem	111	73	139	86	0,0033*	8,6145
Gentamicin	146	96	149	93	0,1830	1,7732
Amikacin	88	58	51	32	0,0000*	21,7691
Ciprofloxasin	124	82	131	81	0,9614	0,0023
Tigecycline	0	0	0	0	-	-
Trimetoprim-Sulfamethoxazole	152	100	153	95	-	-
Colistin	0	0	0	0	-	-
Totally tested isolates	**152**	**100**	**161**	**100**	**-**	**-**

* P values as statistically significant

DISCUSSION

Hospital-acquired Pseudomonas species and Acinetobacter species are frequently resistant to a broad range of antibiotics. *Pseudomonas* spp. is intrinsically resistant to most antibiotics. Antimicrobial resistance develops rapidly under antimicrobial selection pressure, and multiple mechanisms are responsible such as hyper-production of enzymes, beta-lactamases and DNA-gyrases, active efflux pumps and permeability changes. Besides, multi-drug resistant and pan-drug resistant *A. baumannii* strains becomes an important problem in many hospital (9).

Resistance percentage can be reduced through effective antibiotic use policies and infection control measures. The present study demonstrated that colistin, imipenem and aminoglycosides was the most effective agents to *P. aeruginosa* strains, tigecycline and colistin were the most effective agents to *A. baumannii*. Currently, a limited number of broad-spectrum antimicrobials are available to combat multidrug-resistant organisms (10). Tigecycline is one of these agents. Different results were reported in studies conducted with tigecycline. It was reported that resistance percentage of *A. baumannii* strains against tigecycline was 7-78% (11,12,13). In the current study, resistance was not detected in *A. baumannii* strains. This variability in results may be due to geographical differences.

Colistin was reported as the most effective antibiotic in many studies to *P. aeruginosa* and *A. baumannii* strains similar to the present study. Colistin, a polymyxin (polymyxin E) was known from the 1960s, its systemic usage has been limited due to toxic effects such as nephrotoxicity, and neurotoxicity (14). Usage of colistin has come raised again due to nosocomial infections of multidrug-resistant nonfermentative gram-negative bacteria.

In the present study, althought imipenem was found one of the most effective agent againts *P. aeruginosa* isolates, decreased activity was found against *A. baumannii* isolates. Increase in resistance of imipenem has been found statistically significant especially in *A. baumannii* strains. In the report of European MYSTIC study group, the highest percentage of resistance to imipenem reported from Turkey (15). In some studies, imipenem and meropenem were the most effective agent against the nonfermenters (16,18,20). In a different study, resistance percentage of meropenem and imipenem were 16-54.3% for *A. baumannii* strains and 15-29% for *P. aeruginosa* strains (17,19). Consequently, carbapenems remain the most effective agents despite the increasing resistance percentages. The current study has shown that imipenem is still a good option for *P. aeruginosa* strains but resistance percentage of *A. baumannii* strains are increasing. In this study, the lack of data about carbapenems such as meropenem and doripenem is a major shortcoming.

It is reported that the combination of meropenem and aminoglycoside is effective against almost all *P. aeruginosa* strains which included meropenem-resistant strains (21). According to the results of this study aminoglycoside is one of the most effective antibiotics and resistance percentages were decreased. Iseri et al was found that the resistance of amikacin decreased for *P. aeruginosa* isolates in four years period (22). Surveillance studies reported that resistance percentage of amikacin for *P. aeruginosa* was 2.6% in Canada (23), 10% in Belgium (24), and the Grand Duchy of Luxembourg and 4% in USA (25). SENTRY study determined that the most potent antibiotic was amikacin against Pseudomonas strains (18).

Resistance percentage of sulbactam-ampicilin and piperacillin-tazobactam was also increased like resistance percentage of imipenem against *A. baumannii* strains. This increase may result due to intensive use of beta lactam and beta lactamases combinations for treatment in our hospital. Cefoperazone-sulbactam is a preferred drug especially in the treatment of Acinetobacter

spp. infections but bacteria has become resistant to this drug over the years (26). Unlike our results, piperacillin-tazobactam was the most effective antipseudomonal drug in HITIT-2 and SENTRY studies (16, 18). Resistance percentage of piperacillin-tazobactam was reported 9.3% in Canada, 16% in USA, and 17.8% in Belgium (23-25). *A. baumannii* isolates was highly resistant to many of the antimicrobial agents but the lowest percentage of resistance was observed against cefoperazone-sulbactam (52%) in HITIT-2 (16). But resistance percentage was reported 21%-70% in various studies (27-29). Cefoperazone-sulbactam is not included in the CLSI interpretive criteria. Therefore, it should not be ignored that the amount and percentage of cefoperazone and sulbactam in antibiogram disk becomes unacceptable to resistance detection and gave the wrong sensitivity to an extent that was not be accepted (27).

Ciprofloxacin may be a good option due to low toxicity. In our study, resistance percentage of ciprofloxacin was decreased in *P. aeruginosa* and it is statistically significant. Ciprofloxacin resistance percentage was reported 24% by Eldere et al, 32% by Cavallo et al, and 41% by Landman et al for *P. aeruginosa* strains (24, 25, 30). Iseri et al found that the resistance of ciprofloxacin increased for *P. aeruginosa* isolates in four years period (22).

Conclusion, extensive and uncontrolled use of antibiotics in ICU patients generally results with increase of resistance percentages to antibiotics. That is why rational use of antibiotics and sharing data of resistance percentages with physicians is essential. Regular surveillance of antibiotics resistance percentages serves to determine empirical treatment regimens in every institution. These results should be taken into consideration to determine antibiotic use policy in hospital. Higher resistance percentages of imipenem, sulbactam and piperacillin-tazobactam against Acinetobacter spp strains is still an important issue in our institution. New measures should apply to improve this situation.

Briefly, infection control measures should be taken, empirical treatment regimens should be constantly reviewed, and empirical treatment approaches should be determined according to active surveillance data in order to decrease resistance percentages.

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