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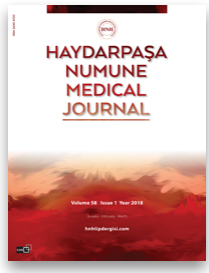

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ORIGINAL ARTICLE

Correlation Between Antimicrobial Consumption and Antimicrobial Resistance Rates of *Acinetobacter* species in a Tertiary Intensive Care Unit: A 10-year Time Series Analysis

Recep Balık[1], Tuna Demirdal[2], İlhan Afşar[3]

[1]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Istanbul, Türkiye
[2]Department of Infectious Diseases and Clinical Microbiology, Katip Çelebi University Izmir Atatürk Training and Research Hospital, Izmir, Türkiye
[3]Department of Microbiology, Katip Çelebi University Izmir Atatürk Training and Research Hospital, Izmir, Türkiye

Abstract

Introduction: Antimicrobial resistance in *Acinetobacter* spp. is a growing concern in ICU settings. The connection between antimicrobial usage and the development of resistance is complex, including the selection of resistant strains due to the extensive use of broad-spectrum antimicrobials. This study analyzes trends in antimicrobial consumption and resistance rates of *Acinetobacter* spp. and their correlation in ICU settings.

Methods: The study includes patients aged 18 and older hospitalized for more than 48 hours between 2007 and 2016. Repetitive culture results were excluded following the Centers for Disease Control and Prevention (CDC) 'Antimicrobial Use and Resistance Module' guidelines. Susceptibility testing was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) rules. The resistance rate is expressed as the proportion of resistant isolates to total isolates. Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD) measurement units for each drug were assigned to the data. Antimicrobial consumption is expressed as the number of DDDs per 1,000 patient days. Trends in consumption and resistance were analyzed using an ARIMA model, and correlations were assessed using either Pearson or Spearman tests.

Results: Consumption of ceftazidime, meropenem, sulfamethoxazole-trimethoprim, tigecycline, and colistin increased, while cefazolin, cefepime, cefuroxime, and amikacin decreased. Resistance to imipenem, meropenem, piperacillin-tazobactam, cefepime, netilmicin, cefoperazone-sulbactam, and tigecycline increased. Gentamicin, tobramycin, and sulfamethoxazole-trimethoprim susceptibility increased. There was a correlation between amikacin resistance and consumption of piperacillin-tazobactam, ceftazidime, colistin, meropenem, and tigecycline. Imipenem resistance correlated with consumption of meropenem, piperacillin-tazobactam, ceftazidime, and tigecycline. Meropenem resistance correlated with consumption of piperacillin-tazobactam and cefoperazone. Cefepime resistance correlated with consumption of netilmicin and sulfamethoxazole-trimethoprim. Netilmicin resistance correlated with consumption of colistin and netilmicin. Piperacillin-tazobactam resistance correlated with ceftazidime consumption.

Discussion and Conclusion: Monitoring antimicrobial resistance and its interaction with antimicrobial use is essential for effective antimicrobial stewardship programs.

Keywords: *Acinetobacter*, antimicrobial consumption; antimicrobial resistance.

**This article is extracted from my thesis entitled "Relationship Between Antibiotic Use and Changing of Resistance Profile in Acinetobacter Species", supervised by Prof. Dr. Tuna Demirdal (Katip Çelebi Üniversity, Atatürk Training and Researh Hospital, İzmir, 2017).*

Correspondence: Recep Balık, M.D. Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Istanbul, Türkiye
Phone: +90 532 697 49 64 **E-mail:** dr.recepbalik@gmail.com
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The annual number of patients admitted to intensive care units (ICUs) has steadily increased, reaching 5 million patients annually[1]. According to the Hospital Prevalence Survey on Hospital-Acquired Infections (HAIs), it was estimated that hospitals in the United States documented approximately 687,000 cases of HAIs and around 72,000 associated deaths during hospitalization[2]. Patients in ICUs are more susceptible to infections due to invasive interventions such as intravenous catheters, urinary catheters, and endotracheal intubation, which bypass natural barriers[3]. These infections result in longer hospital stays, increased mortality, morbidity, and economic losses[4]. In line with the rising trend of HAI incidence, global antimicrobial consumption also rose by 65% between 2000 and 2015, with the highest consumption rates observed in ICUs[5]. Although there was a decrease in the consumption of penicillins and quinolones, the use of tetracyclines, cephalosporins and other beta-lactams, and sulfonamides and trimethoprim significantly increased in hospital settings in Europe between 2012 and 2021[6]. The relationship between antimicrobial consumption and the emergence of resistance is intricate. One established mechanism involves the selection of resistant strains due to the widespread use of broad-spectrum antimicrobials at both hospital and community levels[7]. *Acinetobacter* spp. are highly capable of developing resistance through mechanisms such as enzymatic hydrolysis, alterations in the target area, loss of porins, and efflux pumps[8]. Various resistance mechanisms can be observed among different regions, hospitals, and even different departments within the same hospital. This paper focuses on the correlation between antimicrobial consumption and antimicrobial resistance in *Acinetobacter* spp. within ICU settings from 2006 to 2016.

Materials and Methods

This study was approved by İzmir Katip Çelebi University Non-interventional Clinical Studies Ethical Committee (Date: 16/11/2016, Number: 290). Patients admitted to the anesthesiology and reanimation intensive care unit between 2007 and 2016 and diagnosed with nosocomial infections were included in the study, according to the diagnostic criteria for hospital infections defined by the Centers for Disease Control and Prevention (CDC)[9]. Susceptibility results from cultures were obtained for patients aged 18 and older who had been hospitalized for more than 48 hours, as documented in electronic records. Repetitive results were excluded from the study in accordance with CDC's "Antimicrobial Resistance (AR) Option" rules[10].

Identification and susceptibility testing were performed using the Phoenix 100 ID/AST system (Becton Dickinson Co., Sparks, Md.), following guidelines set by EUCAST (The European Committee on Antimicrobial Susceptibility Testing)[11]. The resistance rate, expressed as the proportion of resistant isolates, was calculated by dividing the number of resistant isolates by the total number of isolates for each quarter.

Quarterly antimicrobial consumption data from 2006 to 2016 were obtained from the pharmacy department. The Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD) measurement units (ATC/DDD version 2016) were assigned to the data and expressed in defined daily doses (DDD) per 1000 patient-days (PD)[12].

Statistical Analysis

All statistical tests were performed using R 3.3.3 (The R Foundation for Statistical Computing). To assess deviations from the normality assumption of continuous variables, Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted, and histograms and normal-quantile plots were examined. All series were found to be stationary, as confirmed by Kwiatkowski-Phillips-Schmidt-Shin (KPSS) tests.

Consumption patterns and resistance rates of each antimicrobial were initially evaluated over time using the autoregressive-integrated moving average (ARIMA) modeling method[13]. The appropriate model was identified using Akaike's information criterion to minimize the residual variance of parameters[14]. To examine lag-time effects, the relationship between the resistance rate and antimicrobial consumption in the previous year was assessed using either the parametric Pearson's or non-parametric Spearman's correlation coefficient. Statistical significance was defined as a p-value of$\leq$0.05.

Results

The mean hospital stay duration was 6±4 days (min 1, max 291). Between 2007 and 2016, a total of 1149 *Acinetobacter* spp. isolates were obtained from 750 patients, but only 1114 isolates met the inclusion criteria. Tracheal aspirate samples accounted for the highest percentage of *Acinetobacter* spp. isolates (42%), followed by blood (26%), sputum (11%), urine (8%), wound swabs (8%), and other (1%) samples.

Imipenem (10.85%) was the most prescribed antimicrobial, followed by piperacillin/tazobactam (9.8%), ceftriaxone (8.29%), and meropenem (8.11%). The consumption of ceftazidime ($p<0.001$), meropenem ($p<0.001$), sulfamethoxazole-trimethoprim ($p<0.001$), tigecycline ($p<0.001$), and colistin ($p<0.001$) showed a significant upward trend between 2006 and 2016. Conversely, consumption of cefazolin ($p<0.001$), cefepime ($p<0.001$),

cefuroxime (p=0.008), and amikacin (p=0.002) exhibited a gradual reduction (Table 1).

The resistance rate of *Acinetobacter* spp. significantly increased for imipenem (p<0.001), meropenem (p<0.001), piperacillin-tazobactam (p=0.012), cefepime (p=0.010), netilmicin (p=0.010), cefoperazone-sulbactam (p<0.001), and tigecycline (p=0.003). In contrast, the resistance rate for gentamicin (p<0.001), tobramycin (p=0.022), and sulfamethoxazole-trimethoprim (p=0.002) significantly decreased over the study period (Table 2). Significant posi-

Table 1. Change in antimicrobial consumption between 2006-2015 (DDD†/1000PD‡)

Antimicrobials	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P
Amikacin*	2.01	5.16	5.03	1.52	2.61	0.94	2.20	1.03	1.37	1.47	**0.002**
Ampicillin-Sulbactam	0.34	0.04	0.33	0.13	0.06	0.72	0.54	0.24	0.16	1.01	0.679
Cefazolin*	8.98	15.50	7.76	5.90	4.83	9.51	4.48	2.10	2.16	1.92	**0.001**
Cefepime*	1.36		0.53	0.93	0.08	0.16	0.05	0.22	0.15	0.63	**0.001**
Cefoperazone-Sulbactam	2.47	7.74	11.50	10.85	9.07	6.63	6.80	6.11	2.44	3.81	0.334
Ceftazidime¥	0.83	0.16	0.25	0.95	0.18	0.84	1.02	1.36	1.75	4.01	**0.001**
Ceftriaxone	4.22	9.27	15.76	8.06	4.15	10.71	16.31	14.80	9.01	4.08	0.842
Cefuroxime*	1.10	0.22	1.17	0.37	0.44	0.11	0.25	0.06	0.16	0.15	**0.008**
Ciprofloxacin	1.18	0.83	0.94	1.07	2.36	0.75	2.61	0.82	1.89	2.28	0.122
Colistin¥						3.42	5.67	6.26	7.48	13.15	**0.001**
Ertapenem			0.03	0.36	0.77	0.63	0.54	1.15	0.53	0.71	0.993
Gentamicin	1.07	0.68	0.69	0.77	0.64	0.42	0.30	0.12	0.63	0.55	0.133
Imipenem	5.27	19.38	26.30	16.02	14.54	15.00	9.21	10.98	9.90	2.40	0.057
Levofloxacin	1.71		0.03	0.68	0.92	0.91	1.36	4.59	1.05	2.34	0.980
Meropenem¥	4.34	4.02	6.55	7.93	4.62	7.17	11.43	11.23	9.55	15.37	**0.001**
Netilmicin	0.32	0.89	5.76	7.69	4.26	2.25	2.47	0.05			0.724
Piperacillin-Tazobactam	7.40	11.95	10.13	6.41	6.09	10.48	14.49	8.04	12.18	14.30	0.121
Tigecycline¥			0.26	0.32	0.46	1.68	2.60	3.42	6.73	3.36	**0.001**
Tmp-Smx¥	0.06		0.23	0.29	0.03	0.12	0.34	0.56	0.36	0.82	**0.001**

Annual Antimicrobial Consumption; ¥: Increasing Trend; *: Decreasing Trend; †: Daily Defined Dose; ‡: Patient Days.

Table 2. Annual Antibiotic Resistance Rates of *Acinetobacter* Spp. between 2007-2016

Antimicrobials	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	P
Amikacin	41.7%	60.0%	83.9%	71.4%	30.7%	48.8%	62.6%	55.3%	80.0%	90.3%	0.160
Ampicillin-Sulbactam		100.0%	95.1%	99.1%	96.0%	97.3%	86.7%	93.3%	96.4%	100.0%	0.816
Cefepime¥	36.4%	83.3%	98.3%	99.0%	94.0%	95.8%	92.1%	91.3%	98.2%	100.0%	**0.010**
Cefoperazone-Sulbactam¥	7.7%	53.8%	68.8%		100.0%	33.3%	41.7%	89.9%	84.6%		**0.001**
Cefotaxime	100.0%	100.0%	100.0%	96.6%	98.8%	100.0%	100.0%	100.0%	100.0%	100.0%	0.693
Ceftazidime	83.3%	91.7%	96.7%	99.0%	94.7%	97.0%	93.8%	93.8%	96.5%	90.5%	0.065
Ceftriaxone	90.9%	88.9%	100.0%	100.0%	100.0%	100.0%	96.2%	95.7%	100.0%	100.0%	0.210
Ciprofloxacin	100.0%	83.3%	93.0%	97.2%	88.9%	90.5%	88.3%	92.6%	96.4%	99.0%	0.591
Colistin				0.0%	2.2%	1.6%	0.0%	1.1%	0.7%	3.2%	0.838
Gentamicin*	80.0%	71.4%	91.2%	81.6%	79.1%	83.5%	75.0%	69.7%	66.2%	61.9%	**0.001**
Imipenem¥	40.0%	53.8%	76.3%	86.9%	91.8%	94.2%	93.1%	90.6%	96.7%	96.8%	**0.001**
Levofloxacin			89.5%	94.8%	86.8%	90.4%	88.9%	91.7%	95.8%	91.3%	0.441
Meropenem¥	50.0%	66.7%	83.7%	87.2%	93.4%	95.7%	94.8%	90.7%	96.7%	95.0%	**0.001**
Netilmicin¥	20.0%	28.6%	63.0%	68.3%	36.7%	14.6%	2.2%	8.3%	77.3%	88.0%	**0.010**
Piperacillin-Tazobactam¥	83.3%	57.1%	78.0%	90.1%	95.8%	96.8%	93.9%	91.5%	98.0%	93.3%	**0.012**
Tigecycline¥		0.0%	0.0%		0.0%	11.1%	0.0%	6.3%	24.2%	14.3%	**0.003**
Tobramycin*	75.0%	36.4%	80.8%	60.9%	33.6%	95.6%	12.5%	18.2%	60.0%	0.0%	**0.022**
TMP-SMX*	80.0%	63.6%	81.4%	91.2%	85.5%	75.4%	61.5%	52.7%	65.8%	70.2%	**0.002**

Annual Resistance Rate; ¥: Increasing Trend; *: Decreasing Trend.

Table 3. Correlation Between Antimicrobial Consumption and Resistance Rates in *Acinetobacter* spp.

Consumption	Resistance	R	P
Colistin	Amikacin	0.663	**0.002**
Meropenem	Amikacin	0.478	**0.002**
Tigecycline	Amikacin	0.471	**0.011**
Ceftazidime	Amikacin	0.446	**0.009**
Piperacillin-Tazobactam	Amikacin	0.38	**0.017**
Netilmicin	Cefepime	0.513	**0.012**
Sulfamethoxazole-Trimethoprim	Cefepime	0.505	**0.017**
Piperacillin-Tazobactam	Imipenem	0.51	**0.001**
Ceftazidime	Imipenem	0.463	**0.006**
Meropenem	Imipenem	0.453	**0.003**
Tigecycline	Imipenem	0.414	**0.026**
Piperacillin-Tazobactam	Meropenem	0.51	**0.001**
Cefoperazone	Meropenem	0.441	**0.019**
Netilmicin	Netilmicin	0.583	**0.006**
Colistin	Netilmicin	0.582	**0.009**
Ceftazidime	Piperacillin-Tazobactam	0.426	**0.013**

Correlation Between Antimicrobial Consumption and Resistance Rate.

tive correlations were found between the consumption of piperacillin-tazobactam, ceftazidime, colistin, meropenem, and tigecycline and the resistance rate of amikacin (r=0.380, p=0.017; r=0.446, p=0.009; r=0.663, p=0.002; r=0.478, p=0.002; and r=0.471, p=0.011, respectively). Similarly, significant correlations were observed between the consumption of meropenem, piperacillin-tazobactam, ceftazidime, and tigecycline and the resistance rate of imipenem (r=0.453, p=0.003; r=0.510, p<0.001; r=0.463, p=0.006; and r=0.414, p=0.026, respectively). Further significant correlations were found between piperacillin-tazobactam and cefoperazone consumption and the resistance rate of meropenem (r=0.510, p<0.001 and r=0.441, p=0.019, respectively). Additionally, netilmicin and sulfamethoxazole-trimethoprim consumption were correlated with the resistance rates of cefepime (r=0.513, p=0.012 and r=0.505, p=0.017, respectively), while colistin and netilmicin consumption were correlated with the resistance rate of netilmicin (r=0.582, p=0.009 and r=0.583, p=0.006). Lastly, ceftazidime consumption was correlated with the resistance rate of piperacillin-tazobactam (r=0.426, p=0.013, Table 3).

Discussion

Bacterial infections, especially those caused by MDR (multi-drug resistant) isolates, require prompt and appropriate treatment to minimize morbidity and mortality. Local resistance rate data are necessary for selecting the appropriate therapy. *Acinetobacter* spp. can colonize the human respiratory tract and contaminate respiratory circuits, making them a significant HAI pathogen over the past 30 years. In our study, we found the highest number of pathogens isolated from respiratory samples. As mentioned earlier, the dissemination routes of *Acinetobacter* spp. play a crucial role in hospital-acquired pneumonia (HAP)[15]. Therefore, carbapenems have become the first choice in ICUs for patients diagnosed with HAP, which explains the high imipenem consumption observed in our study.

The consumption of ceftazidime, meropenem, sulfamethoxazole-trimethoprim, tigecycline, and colistin showed a significant upward trend between 2006 and 2016. Piperacillin-tazobactam is considered a first-line agent for empiric treatment of serious infections to avoid overusing carbapenems. This led to increased consumption of piperacillin-tazobactam in the EU/EAA population between 2011 and 2021. Greece, which has similar resistance rates of *Acinetobacter* spp. to those in Türkiye, reported an increase in colistin consumption over the years. Studies from South Asia and Europe reported a sharp rise in the consumption of fluoroquinolones, carbapenems, ceftazidime, and piperacillin/tazobactam. The differences in consumption are likely due to local epidemiological variations, which influence prescription practices. Increased antimicrobial consumption is a common outcome[6,16].

In our ICU, the incidence of resistant pathogens is

higher than in other European countries. This has led to a shift in antimicrobial prescription practices from piperacillin-tazobactam to imipenem and meropenem, similar to a study conducted by Lee et al.[17] Tigecycline consumption increased in our hospital due to the limited availability of effective agents against *Acinetobacter* spp. Sulfamethoxazole-trimethoprim consumption showed the highest increase rate, likely due to the rising rate of Stenotrophomonas spp. infections, for which sulfamethoxazole-trimethoprim is considered first-line therapy[8]. Conversely, the consumption of drugs ineffective against MDR pathogens, such as cefazolin and cefuroxime, and drugs with safer alternatives like amikacin, significantly decreased. The decrease in aminoglycoside consumption is associated with a decrease in aminoglycoside resistance rates, possibly explaining the declining resistance rates of gentamicin and tobramycin[16].

Similar to our study, many studies have reported an increased prevalence of aztreonam, ceftazidime, piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem, amikacin, ceftazidime, and ciprofloxacin-resistant pathogens over time.[16,18] According to an ECDC (European Centre for Disease Prevention and Control) report, carbapenem resistance to *Acinetobacter* spp. significantly increased in Greece, Cyprus, and Bulgaria, in which resistance rates are similar to those in Türkiye[19].

We found significant correlations between meropenem, piperacillin-tazobactam, ceftazidime, tigecycline consumption, and imipenem resistance rates. Additionally, we observed a correlation between piperacillin-tazobactam and cefoperazone consumption and the resistance rate of meropenem. Recent studies have reported a positive correlation between the prevalence of carbapenem-resistant *Acinetobacter spp*. and the consumption of piperacillin-tazobactam, broad-spectrum cephalosporins, quinolones, and aminopenicillins-beta-lactamase inhibitors[20,21].

Colistin resistance is rare and usually occurs due to lipopolysaccharide structure modification, requiring at least two mutations[22]. Susceptibility testing of colistin remains problematic[23], which may explain the lack of a significant correlation between colistin consumption and colistin resistance rate.

Although amikacin resistance rates remain stable, and amikacin consumption has decreased, we observed a positive correlation between piperacillin-tazobactam, ceftazidime, colistin, meropenem, and tigecycline consumption and the resistance rate of amikacin.

The prevalence of ESBL+ (extended spectrum beta-lactamases) organisms is associated with the consumption of broad-spectrum cephalosporins, particularly ceftazidime, which also expresses AmpC β-lactamases and may be co-transferred with plasmids mediating aminoglycoside resistance[24]. Another mechanism that confers resistance to aminoglycosides and cefepime in *Acinetobacter* spp. is the AdeABC efflux pump. Several antimicrobials, including aminoglycosides, tetracyclines, erythromycin, chloramphenicol, trimethoprim, fluoroquinolones, some β-lactams, ethidium bromide, and recently tigecycline, have been identified as its substrates[25]. In contrast to these findings, cefepime consumption did not correlate with cefepime resistance rate, as reported by Mohr et al.[26] However, a significant statistical association was found between netilmicin and sulfamethoxazole-trimethoprim consumption and the resistance rate of cefepime in *Acinetobacter* spp., which is consistent with a similar relationship reported in P. aeruginosa[26].

Despite differences in resistance trends to certain bacteria, all these studies share a common result: carbapenem resistance rates are increasing, whether in the intensive care unit (ICU) or non-ICU inpatient settings. Variations in the correlations between antimicrobial consumption and resistance rates may be attributed to differences in study methodologies and local epidemiology. The spread of drug-resistant bacteria is multifaceted. While selective pressure plays a significant role in antimicrobial resistance, the lack of adherence to infection control measures is also a crucial factor in transmitting resistant pathogens among patients. In the aggregate analysis of the data, potential methodological limitations may introduce ecological bias, preventing the adaptation of these results on a patient-by-patient basis[27].

Study Limitations

In this study, antimicrobial consumption at the patient level or prior exposure to antimicrobials was not evaluated. Furthermore, antimicrobial exposure from food was not considered, even though antimicrobials given to animals constitute nearly five-sixths of total global antimicrobial consumption[28]. This study was conducted retrospectively in a single center, and genetic relationships between the isolated pathogens were not evaluated. Despite these limitations, we believe that a better understanding of the relationship between antimicrobial resistance and its use can be achieved through well-organized, multicenter studies.

Conclusion

In conclusion, we found an increased proportion of resistance among *Acinetobacter* isolates. Notably, we identified significant correlations between consumption and resistance rates within the same group of antimicrobials as well as across different groups. Many studies support this idea, but it's important to note that this relationship can only be interpreted as a correlation, not causation. Monitoring antimicrobial resistance and consumption in the hospital is a crucial component of antimicrobial stewardship programs[29]. We believe that understanding the relationship between antimicrobial therapy and resistance development will be valuable for making informed decisions about antimicrobial treatment at the local level.

Ethics Committee Approval: The study was approved by İzmir Katip Çelebi University Non-interventional Clinical Studies Ethics Committee (No: 290, Date: 16/11/2016). All experiments were carried out in compliance with the relevant laws and guidelines, in accordance with the ethical standards of the Declaration of Helsinki.

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