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ANTIBIOTIC RESISTANCE OF *ACINETOBACTER* STRAINS IN OUR INTENSIVE CARE UNIT: A RETROSPECTIVE STUDY

YOĞUN BAKIM ÜNİTEMİZDEKİ ACİNETOBACTER SUŞLARININ ANTİBİYOTİK DİRENCİ: RETROSPEKTİF BİR ÇALIŞMA

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ABSTRACT

Objective: Antibiotic resistance development in the treatment of *Acinetobacter* infection is a serious health care problem and responsible for high mortality in intensive care units (ICU). In our study, it was aimed to determine rates of antibiotics resistance of *Acinetobacter* strains isolated from various samples in our ICU.

Methods: We examined the records of *Acinetobacter* isolates and antibiotics resistance for one year followed up in our ICU. The samples from different patients and different type of samples of the same patients were evaluated. The data was analyzed with SPSS for Windows version 23.0. Categorical variables were expressed in terms of numbers and percentage.

Results: 50% of the samples were isolated from tracheostomy. 96.4% of the 138 isolates were *Acinetobacter baumannii* and 3.6% were the other strains. We found high resistance to all of antibiotics except colistin (3.6%) and tigecycline (13.1%).

Conclusion: *Acinetobacter* is the most important opportunistic human pathogen causing fatal nosocomial infections because its ability of developing resistance to new antibiotics is overly fast. Compared to the results reported from Dicle University Hospital in south east of our country it was determined that antibiotics resistance, especially colistin resistance ratio in our ICU was different. It is important to remember that antibiotic susceptibility may vary in regions, hospitals and even clinics, and resistance development should be constantly detected to make the appropriate initial therapy until deescalation.

Keywords: *Acinetobacter,* antibiotic resistance, multidrug resistant infections

ÖZ

Amaç: *Acinetobacter* enfeksiyonunun tedavisinde antibiyotik direnci gelişimi ciddi bir sağlık sorunudur ve yoğun bakım ünitelerinde (YBÜ) yüksek mortaliteden sorumludur. Çalışmamızda yoğun bakım ünitemizde çeşitli örneklerden izole edilen *Acinetobacter* suşlarının antibiyotik direnç oranlarının belirlenmesi amaçlanmıştır.

Yöntem: Yoğun bakım ünitemizde takip edilen bir yıllık *Acinetobacter* izolatları ve antibiyotik direnç kayıtları incelendi. Farklı hastalardan alınan numuneler ve aynı hastaya ait farklı tipteki numuneler değerlendirildi. Veriler SPSS for Windows 23.0 versiyon ile analiz edildi. Kategorik değişkenler sayı ve yüzde olarak ifade edildi.

Bulgular: Örneklerin %50 'si trakeostomiden izole edildi. 138 izolatın %96,4'ü *Acinetobacter baumannii* ve %3,6'sı diğer suşlardı. Kolistin (%3,6) ve tigesiklin (%13,1) dışındaki tüm antibiyotiklere yüksek direnç bulduk.

Sonuç: Acinetobacter, yeni antibiyotiklere aşırı hızlı direnç geliştirme yeteneği nedeniyle ölümcül hastane enfeksiyonlarına neden olan en önemli fırsatçı insan patojenidir. Ülkemizin güneydoğusundaki Dicle Üniversitesi Hastanesi'nden bildirilen sonuçlarla karşılaştırıldığında, yoğun bakım ünitemizde antibiyotiklerin dirençlerinin, özellikle kolistin direnç oranının farklı olduğu görülmektedir. Antibiyotik duyarlılığının bölgelere, hastanelere hatta kliniklere göre değişebileceğini ve direnç gelişiminin deeskalasyona kadar uygun başlangıç tedavisini yapmak için sürekli olarak saptanması gerektiğini hatırlamak önemlidir.

Anahtar Kelimeler: *Acinetobacter*, antibiyotik direnci, çoklu ilaca dirençli enfeksiyonlar

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Introduction

Acinetobacter strains are gram negative nonfermentative coco bacillus and commonly found in nature, especially in food and water.[1] It can be found in the oral, gastrointestinal, and upper respiratory tract flora of healthy people and can stay on inanimate surfaces for days.[1,2] Normally it is rare to form a disease in a healthy person because of their low virulence but it can cause serious genitourinary, respiratory and soft tissue infections in immunocompromised patients.[3,4]

Acinetobacter is the most important opportunistic human pathogen causing fatal nosocomial infections because its ability to develop resistance to new antibiotics is overly fast.[3] Uncontrolled use of antibiotics especially in hospital, increased ratio of immunocompromised patients and use of antibiotics in food industry can be counted as some of the reasons of antibiotic resistance development mechanisms of *Acinetobacter*.[5] In the genomic analyses examining resistant and susceptible strains, 52 genes responsible for resistance were detected. There are a total of 45 resistance genes localized in the same DNA region, called "resistance island". This is the largest island of resistance ever identified in a bacterium.[6]

Antibiotic resistance development in the treatment of *Acinetobacter* infection is a serious health problem and responsible for high mortality in intensive care units (ICU).[7-9] It brings along many problems, such as prolonged stay in ICU, increased treatment costs, and mortality.[10] While carbapenems were the first treatment option previously, now Acinetobacter strains have developed resistance to almost all conventional antibiotics. If precautions are not taken and new generation antibiotics can not be developed; we will have to deal with a deadly pathogen that is incurable.[6]

It is important to determine the endemic antibiotic resistance spectrum in order to defeat this pathogen, which develops resistance to antibiotics so quickly. The World Health Organization also emphasized the importance of endemic surveillance analyses in health institutions in reducing antibiotic resistance.[11] In our study, we aimed to determine the rates of resistance of *Acinetobacter* strains isolated from various samples in our ICU.

Methods

The study was carried out with the permission of the Eskişehir Osmangazi University, Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 15.05.2018 Decision No: 15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Microbiological clinical samples of patients hospitalized in our ICU for one year between May 2017 and May 2018 were analyzed retrospectively. Specimens with *Acinetobacter* growth in sample types such as tracheostomy, blood, urine, wound, and catheter tip were included in the study. All samples from different patients and different types of samples from the same patients from which *Acinetobacter* strains were isolated, were evaluated. Subtypes of the strains, resistance patterns and sample types were examined.

Clinical samples sent from the ICU to the clinical microbiology laboratory were inoculated on 5% blood agar and Eosin Methylene Blue agar and incubated at 35°C for 24 hours.

Bacterial identification and antibiotic susceptibility were determined by the automated VITEK2 (bioMérieux, France) system and the results were interpreted according to the Clinical Laboratory Standards Institute (CLSI) standards. The Kirby-Bauer disc diffusion method was used for tigecycline, which is not included in the CLSI interpretation criteria, and the zone diameter was accepted as ≤ 12 mm resistant and ≥ 16 mm sensitive. The minimum inhibitory concentration (MIC) values for colistin resistance of *Acinetobacter* species, which were determined to be multi-drug resistant based on routine antibiotic susceptibility profiles, were determined by liquid microdilution method.

The antibiotics evaluated in the study were imipenem, meropenem, amikacin, gentamicin, colistin, ciprofloxacin, levofloxacin, tigecycline, tobramycin, and trimethoprim/sulfamethoxazole (TMP/SMX), respectively. Statistical analysis SPSS 23.0 (IBM, Package program) was used. Categorical variables were expressed in terms of numbers and percentages.

Results

In a one-year period, 138 *Acinetobacter* strains were isolated and evaluated. Ninety six point four percent of the 138 isolates were *A. baumannii* and 3.6% were the other *Acinetobacter* strains. Seventy point two percent of the samples were isolated from endotracheal aspirate. The other sites for Acinetobacter isolation were followed by blood (13.8%), urine (5.8%) and wound (5.1%) cultures, respectively. The places where the samples were isolated are given in detail in Table 1.

Table 1. General characteristics of *Acinetobacter* strains

	n (%)
Isolated bacteria	
A. baumannii	133 (96.4%)
Other subspecies	5 (3.6%)
Material	
Endotracheal aspirate	97 (70.2%)
Blood	19 (13.8%)
Urine	8 (5.8%)
Wound	7 (5.1%)
Sputum	1 (0.7%)
Other	6 (4.3%)

While the highest antibiotic resistance was seen to be meropenem (99.3%), the lowest resistance rate was found to be against colistin (3.6%). Antibiotic resistance rates are detailed in Table 2.

When we evaluated the antibiotic resistance patterns according to the places where *Acinetobacter* strains were isolated, the highest resistance was found against ciprofloxacin and meropenem in endotracheal aspirate samples, while levofloxacin resistance took the first place in blood samples. It was seen that all colistin resistant *Acinetobacter* samples were endotracheal aspirate samples (Table 3).

Table 2. Antibiotic resistance rates of *Acinetobacter* strains.

	Antibiogram		
	Susceptible	**Intermediate susceptibility**	**Resistant**
Amikacin	43 (31.2%)	14 (10.1%)	81 (58.7%)
Ciprofloxacin	3 (2.2%)	-	135 (97.8%)
Colistin	133 (96.4%)	-	5 (3.6%)
Gentamicin	67 (48.9%)	-	70 (51.1%)
Imipenem	4 (3.4%)	13 (11.1%)	100 (85.5%)
Levofloxacin	1 (0.9%)	-	114 (99.1%)
Meropenem	1 (0.7%)	-	137 (99.3%)
Tigecycline	68 (68.7%)	18 (18.2%)	13 (13.1%)
Trimethoprim/Sulfamethoxazole	39 (28.3%)	-	99 (71.7%)
Tobramycin	53 (43.1%)	-	70 (56.9%)

Table 3. Antibiotic resistance patterns according to where *Acinetobacter* strains were isolated.

	A	**CI**	**CO**	**G**	**I**	**L**	**M**	**T**	**TMX-SMX**	**TO**
Material										
Endotracheal aspirate	61(62.8%)	95 (97.9%)	5(5.1%)	58 (59.7%)	69 (71.1%)	79 (81.4%)	97 (100%)	11 (11.3%)	73 (75.2%)	53 (54.6%)
Blood	11 (57.9%)	18 (94.7%)	-	4 (21.1%)	13 (86.7%)	15 (100%)	18 (94.7%)	1 (7.7%)	11 (57.9%)	8 (44.4%)
Urine	4 (50%)	8 (100%)	-	4 (50%)	7 (87.5%)	8 (100%)	8 (100%)	-	7 (87.5%)	4 (50%)
Sputum	1 (100%)	1 (100%)	-	-	-	-	1 (100%)	-	1 (100%)	1 (100%)
Wound	1 (14.3%)	7 (100%)	-	4 (57.1%)	6 (100%)	6 (100%)	7 (100%)	-	5 (71.4%)	3 (50%)
Other	3 (50%)	6 (100%)	-	-	5 (83.3%)	6 (100%)	6 (100%)	1 (25%)	2 (33.3%)	1 (16.7%)

A: Amicasin, CI: Ciprofloxacin, CO: Colistin, G: Gentamicin, I: Imipenem, L: Levofloxacin, M: Meropenem, T: Tigecycline, TMX-SMX: Trimethoprim/sulfamethoxazole, TO: Tobramycin

Discussion

In our study, we evaluated the *Acinetobacter* strains of our own clinics and we found that the carbapenem resistance rate was high, and the tigecycline and colistin resistance rates were lower than other studies in the literature. We have shown that tigecycline and colistin are the most effective agents for *Acinetobacter* strains in our own endemic region.[4,7-9]

In studies comparing the isolated places of *Acinetobacter* strains, the highest rate was observed in deep tracheal aspirate and tracheostomy cultures.[7,12] Parallel to this, in our study, the most common place isolated was endotracheal aspirate culture. This was followed by blood and urine cultures, respectively.

Although carbapenems are a broad-spectrum antibiotic group used in *Acinetobacter* infection, it has been shown that resistance has increased over the years in studies conducted throughout the world and our country.[5,13,14] Doruk et al. examined the four year *Acinetobacter* antibiotics resistance profile in their study and showed that while carbapenem resistance was 28.6% in 2009, this resistance increased to 100% in 2011-2013.[13] In another study of Şafak et al. the six year resistance profile was analyzed and it was shown that the resistance of meropenem increased from 78.5% in 2010 to 96.2% in 2016.[15] In our study, it was observed that carbapenem resistance was high and this rate was 85.5% for imipenem and 99.3% for meropenem, respectively. Studies have shown that patients infected with *Acinetobacter* strains with high carbapenem resistance are associated with high mortality.[16,17] We can attribute the high meropenem resistance in our clinic to the fact that we use meropenem too much in empirical antibiotic selection. We need to plan interventions to prevent colonization of this resistant strain.

Intravenous or inhaler colistin is popularly preferred especially in our country in the treatment of carbapenem-resistant A*cinetobacter* infections. Colistin is a polymyxin group antibiotic, and its systemic use was limited in the 1960s due to its nephrotoxic and neurotoxic side effects, but today it has been re-used due to hospital-acquired infections of multi-drug-resistant nonfermentative gram-negative bacteria.[18,19] However,

colistin resistance reported in recent studies has confronted clinicians with the same problem. In the study by Talan et al, in which they examined the colistin-resistant *Acinetobacter* infections, they found colistin resistance in 9 of 33 *Acinetobacter* infections (33%). They found that the length of stay in ICU was numerically higher in patients infected with resistant strains .[20] In the study conducted in the Dicle University hospital located in the southeast of Turkey, the resistance rate was found to be 6%.[21] In our study, colistin resistance rate was quite low and found to be 3.6%.

The study conducted by Celik et al.[22], reported that the antibiotic to which *Acinetobacter* species was most sensitive, apart from colistin, was trimethoprim/sulfamethoxazole and recommended it for empirical treatment. This study was conducted in 2014 and 2016 (in a three-year period) and it showed how antibiotic susceptibility changed over the years. Surveillance is a dynamic process and its importance was emphasized in this study. The most important limitation of our study was that we only evaluated the one-year resistance profile. Again, in a study by Duran et al., all antibiotic resistances except colistin resistance were examined and it was seen that the antibiotic to which it was most sensitive was TMP-SMX.[23] In our study, the TMP-SMX resistance was high and was 71.7%. This situation once again showed us how important it is to know our own endemic flora when starting empirical antibiotics.

It is known that *Acinetobacter* strains rapidly develop resistance to fluoroquinolone group antibiotics.[24] Yıldız et al.[25], in a study they conducted, looked at the pattern of resistance to fluoroquinolones and showed that this rate was 98.8% to ciprofloxacin and 98.2% to levofloxacin. They interpreted this situation as the development of resistance due to its frequent use as an empirical antibiotic in combination therapy over the years.[25] In our study, the rates were found to be similar, and it was observed that they were 97.8% for ciprofloxacin and 99.1% for levofloxacin, respectively.

In the studies, the resistance rate of tigecycline varies considerably according to the geographical regions, and it has been reported that the resistance rate is between 7-78%.[26,27] While Zer et al. found tigecycline resistance as 19%, Kuşçu et al. found this rate as 5%.[26,28] In our study, tigecycline was found to be the most sensitive antibiotic after colistin.(13.1%). Due to its lack of antipseudomonal and bactericidal activity, it is still not recommended for empirical treatment in sepsis.[29] Its use in combination therapy in multidrug-resistant *Acinetobacter* infections is still controversial.[30,31]

Compliance with Ethical Standards

This study was approved by Eskişehir Osmangazi University, Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 15.05.2018 Decision No: 15).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

AA, EK and BY: Study idea, hypothesis, study design; AA,EK and BY: Material preparation, data collection and analysis; AA,EK,BY: Writing the first draft of the article; AA, EK and BY: Critical review of the article finalization and publication process.

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