ORIGINAL ARTICLE / ORİJİNAL MAKALE

The Effect of Broad-Spectrum Antibiotic Use on Carbapenem Resistance in Enterobacteriaceae Species

Enterobacteriaceae Türlerinde Geniş Spektrumlu Antibiyotik Kullanımının Karbapenem Direnci Üzerine Etkisi

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Abstract

Objective: Carbapenem resistance in bacterial species belonging to the Enterobacteriaceae family has become an increasingly important health problem worldwide. We aimed to investigate the effect of broad-spectrum antibiotic use on the development of carbapenem resistance.

Methods: A total of 82673 patients whose culture samples were sent to the microbiology laboratory from various polyclinics of our hospital between January 2019 and August 2021. Those with Gram-negative enteric bacterial growth in their cultures and those with carbapenem-resistant Gram-negative enteric bacterial growth in their cultures were recorded.

Results: The patients included in the study consisted of 71 (56.8%) females and 54 (43.2%) males. Of 125 patients, 91 (73.1%) had a history of antibiotic use in the last 12 months. Carbapenem-resistant Gram-negative enteric bacterial growth was detected in the culture of 125 (33.2%) of 376 patients. Among the patients with a history of broad-spectrum antibiotic use, the ratio of those with carbapenem-resistant Gram-negative bacterial growth in their cultures was significantly higher than those without a history of antibiotic use (0.19% vs. 0.05%; p<0.001). It was determined that the risk of developing carbapenem resistance increased by 3.49 times in those with a history of antibiotic use (Odds ratio =3.49; 95% CI: 1.92-6.33).

Conclusion: The results obtained in our study indicate that broad-spectrum antibacterial use may be associated with the development of carbapenem resistance in Gram-negative enteric bacteria. Detailed studies will provide important information for a clearer determination of this possible relationship.

Keywords: Carbapenem Resistance, Carbapenemase, Enterobacteriaceae, Antibiotic Use

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Öz

Amaç: Enterobacteriaceae familyasına ait bakteri türlerinde karbapenem direnci dünya çapında önemi giderek artan bir sağlık sorunu haline gelmiştir. Geniş spektrumlu antibiyotik kullanımının karbapenem direnci gelişimi üzerine etkisini
araştırmayı amaçladık.

Yöntem: Hastanemizin çeşitli polikliniklerinden Ocak 2019 ile Ağustos 2021 arasında kültür örnekleri mikrobiyoloji laboratuvarına gönderilen toplam 82673 hasta mevcut idi. Kültürlerinde Gram negatif enterik bakteri üremesi olanlar ile karbapenem dirençli Gram negatif enterik bakteri üremesi olanların kültürleri kaydedildi.

Bulgular: Çalışmaya alınan hastaların 71'i (%56,8) kadın, 54'ü (%43,2) erkekti. 125 hastanın 91'inin (%73,1) son 12 ayda antibiyotik kullanım öyküsü vardı. 376 hastanın 125'inin (%33,2) kültüründe karbapenemlere dirençli Gram negatif enterik bakteri üremesi saptandı. Geniş spektrumlu antibiyotik kullanım öyküsü olan hastaların , antibiyotik kullanma öyküsü olmayanlara göre (%0,19'a karşı %0,05; p<0,001) kültürlerinde karbapenem dirençli Gram negatif bakteri üreme oranı anlamlı olarak daha yüksekti. Antibiyotik kullanımı öyküsü olanlarda karbapenem direnci geliştirme riskinin 3,49 kat arttığı belirlendi. (Odds oranı =3,49; %95 GA: 1,92-6,33).

Sonuç: Çalışmamızda elde edilen sonuçlar, geniş spektrumlu antibakteriyel kullanımının Gram-negatif enterik bakterilerde karbapenem direnci gelişimi ile ilişkili olabileceğini içermektedir. Bu olası ilişkinin daha net tespiti için detaylı çalışmalar önemli bilgiler sağlayacaktır.

Anahtar Kelimeler: Karbapenem Direnci, Karbapenemaz, Enterobakter, Antibiyotik Kullanımı

INTRODUCTION

Antibiotic resistance is known as the loss of the effects of antibiotics to stop the growth of bacteria or kill them. Nowadays, antibiotic resistance is gradually increasing, which is caused by the excessive and off-label use of antibiotics, widespread use of antibiotics in the food and livestock industries, and difficulties in developing new antibiotics (1). The forms of misuse that create antibiotic resistance and cause high economic costs are antibiotic use in non-infectious diagnoses, inability to choose the appropriate antibiotic, keeping the duration of treatment long or short, giving the appropriate dose less or more, and prophylactic use of broad-spectrum antibiotics. The wrong and unnecessary use of antibiotics makes the treatment of infectious diseases more difficult with each passing day. Antibiotic resistance may have very significant social and economic consequences (2,3).

A wide variety of antibacterials are used in the treatment of infections caused by Gram-negative bacteria. However, the easy development of resistance in these bacteria, especially multiple drug resistance, reduces the antibiotic options to be used (4,5). In particular, the fact that bacterial species in the Enterobacteriaceae family cause infections at a high frequency in the community increases the importance of resistance. Moreover, the rapid transmission of these bacteria in the community and the rapid spread of the resistance status among this group of bacteria require close resistance monitoring(4-6).

The increasing number of strains resistant to carbapenems, one of the most effective antibacterial groups against bacteria in the Enterobacteriaceae family, has become an important problem. Carbapenem resistance occurs as a result of the production of the carbapenemase enzyme that hydrolyzes carbapenems or the production of the cephalosporinase enzyme with mutations that prevent carbapenems from crossing the bacterial wall (6,7). The fact that these bacteria that become resistant to

carbapenems are frequently resistant to most of the antibiotic groups thoroughly restricts the treatment options for infections caused by these bacteria. Therefore, carbapenem resistance has become an increasingly important health problem nowadays(6-8).

This study aimed to investigate the effect of broad-spectrum antibiotic use on the development of carbapenem resistance in Gram-negative enteric bacteria.

METHODS

This retrospective study was approved by the local ethics committee with the number and date of GOKA/2021/15/06.

Patients

A total of 82673 patients whose culture samples were sent to the microbiology laboratory from various clinics of our tertiary care hospital between January 2019 and August 2021 were included in the study. Those with Gram-negative enteric bacterial growth in their cultures and those with a history of broad-spectrum antibiotic use in the last 12 months among these patients and those with carbapenem-resistant Gram-negative enteric bacterial growth in their cultures were recorded. All data of the patients were obtained from the hospital automation system.

Tests

The inoculation of each culture sample brought to the microbiology laboratory was performed by conventional methods. Carbapenem resistance was studied in bacteria in plaques with growth and pure colonies, using conventional methods and VITEK2 (bioMérieux, France) automated system, according to minimal inhibitory concentration (MIC) values in line with the manufacturer's recommendations. The sensitivity results were interpreted according to the EUCAST criteria (9).

Statistical Analysis

Statistical analysis was performed using the SPSS 25.0 program (IBM SPSS, Chicago, USA). Descriptive data are presented as numbers and percentages. The comparisons between the groups in terms of categorical variables were performed with the chi-square test. The odds ratio was calculated by the logistic regression test. The results were evaluated at a confidence interval of 95%, and $p<0.05$ values were considered significant.

RESULTS

There was the growth of Enterobacteriaceae in 376 (0.45%) of 82673 cultures included in the study. Carbapenem-resistant Gram-negative enteric bacterial growth was detected in the cultures of 125 patients (33.2%) (Table 1). Of the patients,73.1% had a history of antibiotic use in the last 12 months. While the mean age of the patients was 48.2±37.3, it was 49.8±35.1 in the patients with isolated carbapenem-resistant bacteria in their cultures.

Table 1. The relationship between the history of antibiotic use and the frequency of carbapenem resistance

	Carbapenem resistance				
	Available		Not available		Total
	n	%	n	%	
Antibioticusers	113	0.19	60330	99.81	60443
Non-antibiotic users	12	0.05	22343	99.95	22355
Total	125	0.24	82673		82798

p<0.001. Odds ratio =3.49 (95%CI: 1.92-6.33). Among patients with culture growth, the rate of development of carbapenem resistance in **antibiotic users** is significantly higher compared to that in non-antibiotic users.

Among the patients with a history of broad-spectrum antibiotic use, the ratio of those with carbapenem-resistant Gram-negative bacterial growth in their cultures was significantly higher than those without a history of antibiotic use (0.19% vs. 0.05%; p<0.001). It was determined that the risk of developing carbapenem resistance increased by 3.49 times in those with a history of antibiotic use (Odds ratio =3.49; 95%CI: 1.92-6.33) (Table 1).

The distribution of antibiotics used by patients with the growth of carbapenem-resistant bacteria in their cultures is presented in Table 2.

According to the distribution of bacteria-isolated samples; 61 (48.8%) urine cultures,

28 (22.4%) blood cultures, 22 (17.6%) sputum cultures, 11 (8.8%) wound cultures and 3 (2.4%) also had catheter culture. The distribution of cultures with carbapenem-resistant isolates is as follows: 120 (96%) *Klebsiella pneumoniae*, 3 (2.4%) *Klebsiella ozaena*, and 2 (1.6%) *Klebsiella oxytoca.*

Table 2. Distribution of antibiotics recently used by the patients with carbapenem-resistant isolates in their cultures

Antibiotic	**n**	**%**
Not used	12	9.6
Quinolones (Levofloxacin, Ciprofloxacin,Moxifloxacin)	14	11.2
Betalactams(Amoxicillin, Amoxicillin clavulanic acid, Ampicillin sulbactam)	9	7.2
2nd Generation Cephalosporins (Cefuroxime, Cefdinir)	3	2.4
3rd Generation Cephalosporins (Ceftriaxone, Cefixime)	4	3.2
Ciprofloxacin + fosfomycin	5	4
Amikacin + amoxicillinclavulanic acid	2	1.6
Ampicillin sulbactam	2	1.6
Nitrofurantoin	2	1.6
Ceftriaxone + Levofloxacin	2	1.6
Ceftriaxone + vancomycin + piperacillin tazobactam	2	1.6
Ciprofloxacin + teicoplanin	2	1.6
Clarithromycin	1	0.8
Vancomycin	1	0.8
Amoxicillinclavulanic acid + linezolid + metronidazole	1	0.8
Amoxicillin clavulanic acid + ciprofloxacin + clarithromycin	1	0.8
Amoxicillin clavulanic acid	1	0.8
Amoxicillin + metronidazole	1	0.8
Amoxicillin + nitrofurantoin	1	0.8
Amoxicillin + ceftriaxone	1	0.8
Ampicillin sulbactam + levofloxacin + ceftriaxone	1	0.8
Ampicillin -sulbactam + metronidazole	1	0.8
Fosfomycin + teicoplanin	1	0.8
Fosfomycin + ampicillin sulbactam	1	0.8
Fosfomycin + amoxicillinclavulanic acid	1	0.8
Fosfomycin + ceftriaxone + amoxicillin clavulanic acid	1	0.8
Fusidic acid + metronidazole	1	0.8
Fusidic acid + ceftriaxone	1	0.8
Gemifloxacin + moxifloxacin	1	0.8
Clarithromycin + amoxicillinclavulanic acid	1	0.8
Clindamycin + metronidazole	1	0.8
Clindamycin + ceftriaxone	1	0.8
Levofloxacin + ampicillin sulbactam	1	0.8
Levofloxacin + fusidic acid + metronidazole	1	0.8
Levofloxacin + ceftriaxone	1	0.8
Levofloxacin + ceftriaxone + piperacillin tazobactam	1	0.8
Levofloxacin + ciprofloxacin	1	0.8
Metronidazole + ampicillin sulbactam	1	0.8
Metronidazole + cefdinir	1	0.8

Table 2. Distribution of antibiotics recently used by the patients with carbapenem-resistant isolates in their cultures

Metronidazole + ceftriaxone	1	0.8
Metronidazole trimethoprim-sulfamethoxazole	1	0.8
Moxifloxacin + fosfomycin	1	0.8
Moxifloxacin + ciprofloxacin	1	0.8
Moxifloxacin + teicoplanin	1	0.8
Moxifloxacin trimethoprim-sulfamethoxazole	1	0.8
Nitrofurantoin + ciprofloxacin	1	0.8
Piperacillin tazobactam + ampicillin sulbactam	1	0.8
Piperacillin tazobactam + fosfomycin	1	0.8
Piperacillin tazobactam + ciprofloxacin	1	0.8
Rifaximin + ciprofloxacin	1	0.8
Cefoperazone sulbactam + fosfomycin	1	0.8
Cefdinir + Levofloxacin	1	0.8
Cefdinir + metronidazole	1	0.8
Cefdinir + teicoplanin	1	0.8
Cefepime + ciprofloxacin trimethoprim-sulfamethoxazole	1	0.8
Cefixime + nitrofurantoin	1	0.8
Cefixime + cephalexin	1	0.8
Ceftriaxone + fosfomycin	1	0.8
Ceftriaxone + teicoplanin + piperacillin tazobactam	1	0.8
Cefuroxime + fosfomycin	1	0.8
Ciprofloxacin + +amoxicillin clavulanic acid + fusidic acid	1	0.8
Ciprofloxacin + amoxicillin clavulanic acid	1	0.8
Ciprofloxacin + fusidic acid	1	0.8
Ciprofloxacin + nitrofurantoin + ampicillin sulbactam	1	0.8
Ciprofloxacin + ceftriaxone	1	0.8
Teicoplanin + ceftriaxone	1	0.8
Teicoplanin + ciprofloxacin	1	0.8
Tetracycline + ceftriaxone	1	0.8
Trimethoprim sulfamethoxazole + ampicillin sulbactam	1	0.8
Trimethoprim-sulfamethoxazole + ciprofloxacin	1	0.8
Trimethoprim-sulfamethoxazole	1	0.8
Vancomycin + ceftriaxone	1	0.8
Vancomycin + amoxicillin clavulanic acid	1	0.8

Antibiotics were not used at the same time in rows with more than one antibiotic listed.

DISCUSSION

According to the OECD (Organization for Economic Co-operation and Development) Health Policy Studies report, it was indicated that the highest rates of antimicrobial resistance (approximately 35% in Turkey, Korea, and Greece) in 2015 were seven times higher than the lowest rates among member states (10). During the 2005-2015 period, the overall antibiotic use in DDD per thousand people in Turkey was reported to be 16620. While the use of antibiotics in Turkey reached 18095 DDD per thousand people in 2015, the average use of antibiotics in the EU was 9099 DDD per thousand people. At the end of the review period, broad-spectrum penicillin antibiotics constituted half of the antibiotic use in both Turkey and EU countries on average (11).

According to the recent reports of the

WHO, carbapenem resistance in *Klebsiella pneumoniae* isolates has approached 50% (12). Although data on colistin resistance were not collected by the WHO-CAESAR, studies indicate that it may reach 76% among carbapenem-resistant enterobacteria in Turkey (13).

Carbapenem resistance in enterobacteria occurs with the presence of carbapenemase on plasmids or other genetic structures (14). Other mechanisms of carbapenem resistance are the presence of extended-spectrum β-lactamases (ESBLs), increased efflux, porin alteration, and the mechanism of the expressed (suppressed) endogenous AmpC enzyme (15).

Klebsiella pneumonia carbapenemase (KPC), the most frequently detected beta-lactamase, emerged in the USA in the late 1990s and started to spread worldwide (1). Especially some regions such as Latin America, China, Australia, Canada, Italy, Greece, and Israel are considered endemic for KPC (17,18). The treatment options are very limited in infections caused by carbapenem-resistant enteric Gram-negative bacteria, and the prognosis may be worse in these cases. Although various combinations of colistin, tigecycline, gentamicin, fosfomycin, and carbapenems are applied in these cases, it has been reported that the mortality rate can reach up to 50% (8,19). Furthermore, it has also been stated that these bacteria may be hypervirulent (20).

The use of antibiotics, when strictly indicated, and the preference for narrow-spectrum antibiotics as much as possible were stated to be the most effective methods of combating the development of bacterial resistance (8,21). Carbapenem use has been demonstrated to be associated with carbapenem resistance in bacteria such as *Pseudomonas* and *Acinetobacter* (21). However, due to the fact that the frequency of carbapenem resistance in bacterial species in the Enterobacteriaceae family is not very high yet, the relationship between carbapenem use and the development of carbapenem resistance in these bacteria could not be demonstrated (22-25). In this study, it was determined that only a few patients who were detected to have bacteria with carbapenem resistance had a history of carbapenem use. However, some studies demonstrated that carbapenem use was associated with carbapenem resistance in enteric bacteria (26-29). In a meta-analysis, it was indicated that ertapenem was not an agent that induced carbapenem resistance, and it was shown that the use of ertapenem did not lead to an increase in carbapenem resistance in enteric bacteria (30). Two separate studies reported that the use of antibiotics other than carbapenem was not associated with the development of carbapenem resistance in *Escherichia coli* and *K. pneumoniae* isolates (31,32). However, in a meta-analysis performed by Liu et al. (27), it was determined that the use of aminoglycosides, glycopeptides, quinolones, and antipseudomonal penicillin in addition to carbapenems was significantly associated with the emergence of carbapenem-resistant *Klebsiella pneumoniae* isolates, it was reported that there was no association between the use of cephalosporins, metronidazole, and beta-lactams and the development of carbapenem resistance. In our study, among the patients with a history of broad-spectrum antibiotic use, the ratio of those with carbapenem-resistant Gram-negative bacterial growth in their cultures was found to be significantly higher compared to those without a history of antibiotic use (0.19% vs. 0.05%). In the meta-analysis performed by Liu et al. (27), it was revealed that the risk of developing carbapenem resistance increased by 4.01 times in carbapenem users, 2.28 times in quinolone users, 2.4 times in glycopeptide users, 2.05 times in aminoglycoside users, and 2.67 times in those using anti-pseudomonal penicillin. Our study demonstrated that the risk of developing carbapenem resistance increased by 3.49 times in those with a history of antibiotic use. All these results indicate that recently used broad-spectrum antibiotics may play a significant role in the development of carbapenem resistance.

This study observed that 73.1% of the patients had a history of antibiotic use in the last 12 months. These results indicate that the rate of broad-spectrum antibiotic use is very high, which facilitates the development of resistance in bacteria.

This study found that the antibiotics used in the last 12 months by the patients with the growth of carbapenem-resistant bacteria in their cultures had a wide distribution and variety. This result indicates that the development of carbapenem resistance cannot be directly attributed to a group

of antibiotics. The fact that the antibiotics used were broad-spectrum supports the relationship between carbapenem resistance and this situation.

In a study conducted in Spain, carbapenem resistance was detected most frequently in *Klebsiella pneumoniae* isolates (33). All isolates in our study were *Klebsiella* species. This finding demonstrates that carbapenem resistance is more common among *Klebsiella* strains. Accordingly, it is observed that it is necessary to determine carbapenem resistance in cultures with *Klebsiella* growth.

In the present study, the fact that a molecular test was not performed with the thought that it would not make a significant contribution to the planned aim, and accordingly, the fact that it was not investigated whether carbapenem resistance was due to carbapenemases and which carbapenemase was effective in this resistance are among the limitations of our study. Furthermore, the prognosis of patients with carbapenem-resistant isolates in their culture was not evaluated in the study.

The results obtained in our study indicate that broad-spectrum antibacterial use may be associated with the development of carbapenem resistance in Gram-negative enteric bacteria. Further and detailed studies will provide important information for a clearer determination of this possible relationship.

CONCLUSION

The results obtained in our study indicate that broad-spectrum antibacterial use may be associated with the development of carbapenem resistance in Gram-negative enteric bacteria. Detailed studies will provide important information for a better determination of this possible relationship.

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Conflict of Interest

On behalf of all authors, I, as the corresponding author, accept and declare that; we have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Support Resources

No financial support was used by authors during this study.

Ethical Declaration

Ethical permission was obtained from the Health Sciences University Samsun Training and Research Hospital, Non-Invasive Clinical Research Ethics Committee for this study with date 25.08.2021 and number GOKA 2021/15/6, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MU, MK, Design: SG, Supervising: MU, HE, Financing and equipment: MAO, MK Data collection and entry: MU, SG, Analysis and interpretation: MAO, HE, Literature search: MU, Writing: MU, Critical review: MK, HE

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