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Changing trends of carbapenem resistance of escherichia coli and klebsiella pneumoniae strains isolated from intensive care units, inpatient services and outpatient's clinics: a five years retrospective analysis

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Abstract

Carbapenem resistance (CR) was rarely reported in Klebsiella pneumoniae and Escherichia coli strains until ten years ago. In recent years, increasing carbapenem resistance in gram negative bacteria is a substantial concern. Objectives: In this study; we aimed to evaluate the changing frequency of CR in K. pneumoniae and E. coli strains that were isolated from the patients from intensive care units, inpatient services and outpatients' clinics in the last five years. Data of antimicrobial susceptibility belonging to clinical isolates of K. pneumoniae and E. coli strains determined between 2013 and 2017 were retrospectively collected from Laboratory Information System. Results were statistically analyzed. A total 4002 K. pneumoniae and 13462 E. coli strains were included. The CR of K. pneumoniae strains were found as 11.6%; while of E. coli's were found as 0.6%. The highest CR frequency was detected among intensive care units' isolates of K. pneumoniae as 20.1%. We determined that CR significantly increased in intensive care unit isolates of E. coli and K. pneumoniae about 5-10 folds throughout the study period; however, there was no remarkable change in the CR of E. coli strains from the outpatients' clinics. We determined that the resistances of K. pneumoniae and E. coli strains to carbapenems were progressively increasing by years, especially in intensive care units and inpatient services. Therefore, appropriate antimicrobial use policies sought to be considered against to this growing problem.

Keywords: Carbapenems, escherichia coli, klebsiella pneumoniae, intensive care units.

Introduction

Klebsiella pneumoniae and Escherichia coli are among the most common human pathogens. These pathogens have the potential to cause a wide variety of infectious diseases, including; urinary tract, cardiovascular system, soft tissue, bloodstream, respiratory tract infections, meningitis, intra-abdominal and genital region infections [1]. It is reported that K. pneumoniae and E. coli are responsible for the 32%-51% of all nosocomial infections, and 43%-80% of community-acquired infections [2-4].

Carbapenems are the last group of antimicrobials active against multidrug-resistant (MDR) gram-negative organisms. They are particularly indispensable in various life-threatening infections caused by extended-spectrum (ESBL) and AmpC β-lactamase-producing strains.

Furthermore, carbapenems have excellent tissue distribution and lower side effects than polymxyins and tigecycline which can be used against MDR K. pneumoniae and E. coli. Also, carbapenems may be used more safely in children' and adults' treatments [1,5].

Today, the high proportion of ESBL producing strains has been limited beta-lactam group of antibiotics. Therefore, in the treatment of these infections, the importances of carbapenems are increasing. Thus, in the treatment of ESBL-producing K. pneumoniae and E. coli strains carbapenems are taking the first choise [5,6].

The evolution of antibiotic resistance in bacteria is directly related with using of irregular antibiotics. Therefore, in recent years, CR is increasing rapidly due to irregular using of carbapenems in these strains [1,7]. The infections caused by CR strains in patients especially with underlying disease that increases the morbidity and mortality. And incidences of infections with CR strains are increasing in the world [5,6].

Carbapenem resistance is often observed with other beta-lactam antibiotics, aminoglycosides, fluoroquinolones and cotrimoxazole. Hence it can be increased the selection of MDR microorganisms. Colonization of hospitals with MDR gram-negative bacteria leads to treatment problems, long period's hospitalization and high treatment costs and also increases the morbidity and mortality [8].

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Antibiotics are often initiated empirically to treatment of infections. Treatment options can be changed according to reproducing bacteria and antibiotic susceptibility results. Hence, it is important to know the antibiotic resistance rates of the strains isolated from the community or hospital-acquired infections to guide the empirical treatment.

In this study, we aimed to evaluate and compare the resistance profile of E. coli and K. pneumoniae strains to carbapenems, last five years isolated from patients' in inpatient services (IS), intensive care units (ICU) and outpatient's clinics (OC) in our hospital, retrospectively.

Material and Methods

Study design

CR of the K. pneumoniae and E. coli strains were performed in 2013, 2014, 2015, 2016 and 2017 which were sent from the ICU, IS and OC in our hospital. Only one strain was included for each patient in the study.

Identification and susceptibility

K. pneumoniae and E. coli strains were identified by conventional methods and Maldi-tof MS (BioMérieux, France) from the clinical specimens. In-vitro antimicrobial susceptibility tests of E. coli and K. pneumoniae strains to imipenem and meropenem were determined on the basis of criteria of Clinical and Laboratory Standards Institute (CLSI) by Kirby-Bauer disk diffusion method and automated system (Vitek2, BioMérieux, France) [9]. If the strains were resistant to both or anyone of imipenem or meropenem, we accepted CR strain. E. coli strain ATCC 25922 was used as a standard.

Data evaluation

Statistical analyses were performed using SPSS for Windows, version 13.0 (IBM-SPSS Inc, Armonk, NY). P values were determined using Chi-Square test.

Results

In this study; we investigated 4002 K. pneumoniae, 13462 E. coli total 17464 strains among the years 2013–2017. The distributions of strains to clinics are shown in Table. The resistance of K. pneumoniae strains were determined to carbapenems; 11.6% (3.4% vs 18.9%, $p < 0.00001$), while the E. coli strains resistance to carbapenems; 0.6% for five years average (0.2% vs 1.1%, p=0.000031).

Table. The distributions of strains to clinics

	Intensive care units	Inpatient services	Outpatient's clinics
K. pneumoniae	1830	1282	890
E. coli	2950	5028	5484
Total	4780	6310	6374

The resistances of K. pneumoniae strains isolated from ICU to carbapenems were found as 20.1% (5.4% vs 36.5%, p=0.01618), while the E. coli strains were 1.4% (0.5% vs 2.3%, p= 0.008163) respectively determined according to five years average (Figure 1).

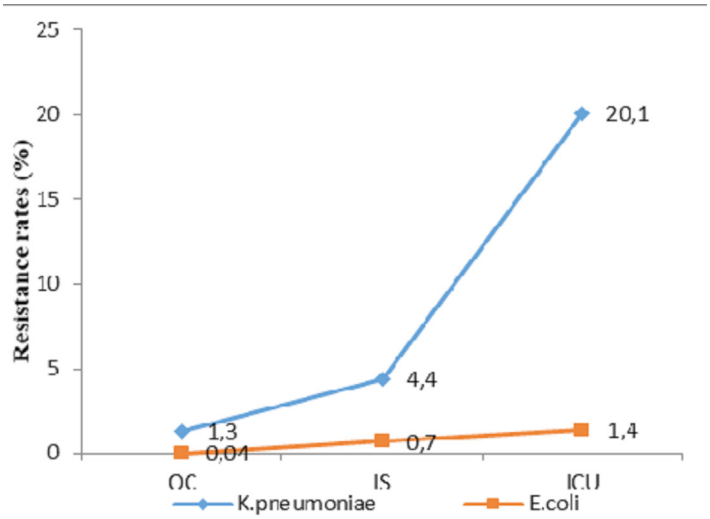

Figure 1 CR of K. pneumoniae and E. coli in ICU, IS, OC for five years avarage

If we investigated the resistance according to the years; K. pneumoniae strains were in 2013; 5.4% and in 2014; 7.7%. However, the resistances were increasing with a peak for carbapenems significantly as 5-7-fold, 19.7%, 33.1% and 36.5% in 2015, 2016 and 2017 years in ICU (Figure 2). Similarly, resistances of E. coli strains increased as 2–5 fold between 2013 and 2017 (Figure 3).

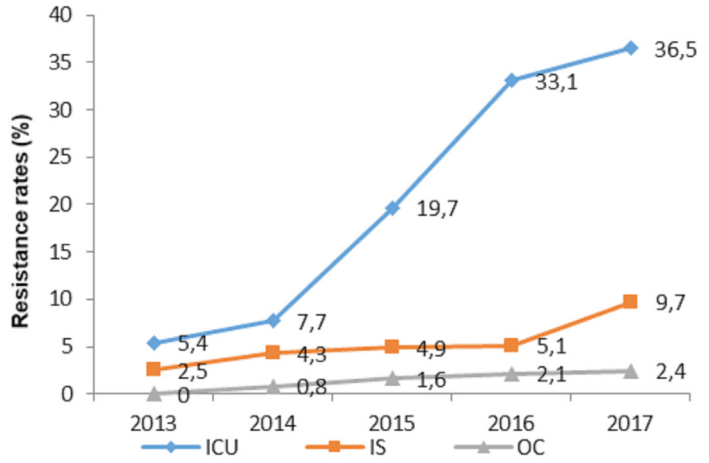

Figure 2. CR of K. pneumoniae in ICU, IS, OC according to the years

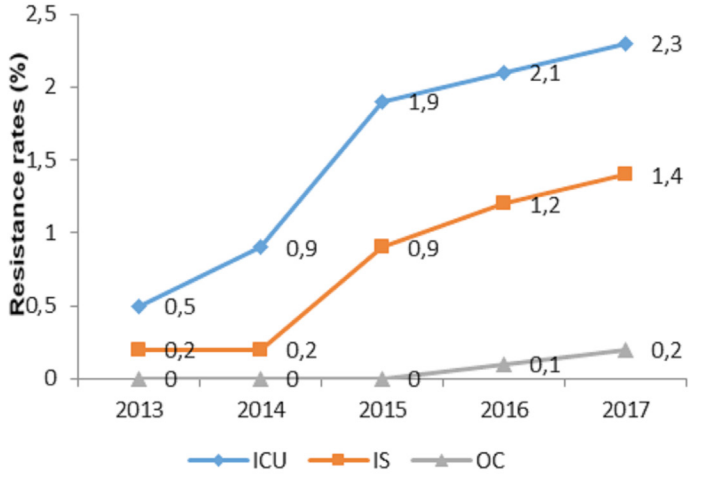

Figure 3. CR of E. coli in ICU, IS, OC according to the years

The resistances of K. pneumoniae strains to carbapenems, isolated from IS were 4.4% (2.5% vs 9.7%, p=0.452388), while the E. coli strains were 0.7% (0.2% vs 1.4%, p=0.001763) respectively determined according to five years average (Figure 1). Carbapenem resistance of IS isolates of E. coli as 5-7-fold and K. pneumoniae as 2-4 fold increased between 2013 and 2017. Resistances of strains in IS are shown in Figures 2 and 3 according to the years.

The resistance of K. pneumoniae strains isolated from the OC were found to be; for carbapenems; 1.3% (0% vs 2.4%, p=0.300857) while the E. coli strains were 0.04% for five years average (Figure 1). Resistances of strains according to the years in OC are shown in Figures 2 and 3.

Discussion

As a result of quickly spreading of ESBL-producing K. pneumoniae and E. coli strains to all over the world, antimicrobial resistance has become an issue of public health concern. It is a major factor contributing to mortality and morbidity in settings with limited treatment options. Thus, it has led to use of carbapenems antibiotics as the first choice in the treatment of these strains infections [5].

Carbapenems have the widest spectrum in the class of beta-lactam antibiotics and are showing rapid bactericidal effect. CR K. pneumoniae and E. coli strains were being reported rarely up to ten years ago. In recent years, the infections due to CR or carbapenemase producing K. pneumoniae and E. coli have started to be reported very frequently [1]. According to the data of National Healthcare Safety Networks; the CR of E. coli strains reported 0.9–4% and K. pneumoniae strains reported 3.6–10.8%, in 2008 [10].

E. coli is usually the most frequently isolated pathogen from clinical specimens, while the K. pneumoniae is second most common pathogen among the Enterobacteriaceae family [8]. K. pneumoniae and E. coli are regarded as the most important pathogens causing nosocomial urinary tract system, lungs, cardiovascular system and soft tissue infections [1]. In the last decade, E. coli and K. pneumoniae strains have become clinically more important microorganisms due to increased antibiotic resistance, morbidity and mortality. The widespread use of antibiotics and the migration of antibiotic resistance genes between bacterial genus and species facilitate the emergence of MDR K. pneumoniae and E. coli strains [1,7].

Carbapenem resistance rates are reaching elevated levels in these strains which used in empiric treatment especially in ICU. Our study is one of the rare studies that show the development of resistances to carbapenems antibiotics over the years, simultaneously compare in ICU, and in IS and in OC [11].

In our study, CR of K. pneumoniae strains were determined 11.6%, while the E. coli strains resistances to carbapenems were 0.6% for five years average. But resistances of K. pneumoniae strains in ICU were found 20.1%. If we investigate resistance rates in ICU according to the years, we found 5.4% and 7.7% in 2013 and 2014 years. After 2014 the resistance rates were increased with a peak as 5-7 folds to 19.7%, 33.1% and 35.6% in 2015 to 2017 years. We believe that this rapid increase of resistance may be due to either by excessive and prolonged use of carbapenem group antibiotics in empirical therapy or by colonization of patients with CR K. pneumoniae in intensive care unit. Furthermore, we determine a peak of as 2–5 fold increased to carbapenems against E. coli isolates in the ICU between 2013 and 2017.

Gozutok et al. [12] reported resistance rates of carbapenems in E. coli strains were 6.8%, in K. pneumoniae strains 16.6% in a study conducted in 2013 in internal medicine ICU. Inci et al. [13] determined CR of K. pneumoniae 11% and E. coli 5% in ICU. Ertürk et al. [14] reported no resistance in K. pneumoniae strains, but they found resistance to carbapenems 7% for E. coli. We found the resistances of K. pneumoniae strains isolated from ICU to carbapenems; 20.1%, while the E. coli strains to carbapenems; 1.4%.

The widespread use of carbapenems in the empirical treatment of infections to hospitalized patients is rapidly increasing the rates of resistance accompanying. In our study, we found resistances of K. pneumoniae strains to carbapenems isolated from IS were; 4.4%, while the E. coli strains to carbapenems; 0.7% respectively determined for five years. The resistance rates of K. pneumoniae strains isolated between the years 2013–2017 with the order of inpatient services; to carbapenems 2.5%, 4.3%, 4.9%, 5.1%, 9.7% while the E. coli strains to carbapenems; 0.2%, 0.2%, 0.9%, 1.2%, 1.4%. Carbapenems in the empirical treatment of nosocomial infections despite the rapid increase in resistance is still located in the first row. According to the results of MYSTIC work carried out between 2000 and 2003; the resistance rates of Enterobacteriaceae to carbapenems has been reported 2.4%, in our country [15]. Similarly, there was not found CR in E. coli strains in the results of HITIT–2 study observed in 2007, while imipenem resistance in K. pneumoniae strains were found 3.2% [16]. The EARRS–2008 study reported that CR in Turkey was between 1–5% [17]. Numerous studies done in our country; Gozukucuk [18] and Saglam [19] reported no resistance against carbapenems, Guzel et al. [20] reported 6.7% CR to ESBL producing K. pneumoniae and E. coli strains, in 2015. Aykan et al. [21] reported 2.9% CR in hospitalized patients between 2008 and 2012 in a meta-analysis study. Similarly, Eser et al. [22] determined 5.7% CR to the ESBL producing Enterobacteriaceae isolates, in 2014. The CR provided as 6.1% in SENTRY study that carried out in 42 centers in the United States [23].

Today, the rapid spread of CR Enterobacteriaceae worldwide “big players” NDM, KPC and OXA–48 play a significant role. OXA–48 is often being detected in Turkey and North Africa, KPC in United States, Israel, Greece and Italy, NDM are frequently in India [7]. Now it is common to see infections due to CR strains in patients who are not admitted to the hospital or traveling to an endemic region. This illustrates need to be more careful in hospitals to prevent the spread of CR strains and selection. It is likely that CR strains emerging from the hospital to the community spread. Therefore, the fact that this type of bacteria can be spread during the transfers of patients to different health centers must be strictly observed.

In a rewiev the resistance to carbapenems among E. coli strains 0–3% and 0–5% of Klebsiella strains has been reported between the years 2000–2010, community-acquired isolates in our country [24]. Between 2008 and 2012, Aykan and colleagues [21], found the resistance to carbapenem as 4.12%, in OC in the meta-analysis. Resistance rates of carbapenems in K. pneumoniae and E. coli strains are reported to be between 0 to 4.7% in studies conducted after 2010 [25-27]. In our study, resistances of K. pneumoniae strains to carbapenems isolated from the OC were found 1.3% for five years. If we investigate the resistance of K. pneumoniae strains

year by year; it was determined; 0%, 0.8%, 1.6%, 2.1%, 2.4% as in the years 2013–2017, respectively. The resistance for E. coli in 2016 was 0.1% and in 2017 0.2%. Our datas for carbapenems were similar with previous studies. This case suggests that the following hospital resistant strains can spread to society.

The development of resistances to carbapenems against K. pneumoniae and E. coli strains are spreading quickly around the world, especially in the last decade. In our study, the resistances of K. pneumoniae from ICU, IS and OC that started to increase from 2014. Also, resistances of K. pneumoniae were particularly noteworthy that reached very high levels in 2015, 2016 and 2017 as observed in Figures. Similarly, the resistance rates for E. coli isolates were increasing over 2-7 fold the years.

Conclusion

We determined that; the resistances of K. pneumoniaee and E. coli strains to carbapenems were significantly increased as 5-10 folds between 2013 and 2017, especially in ICU and IS. As a result, it is understood that the resistance ratio of carbapenems for K. pneumoniae and E. coli should be monitored, especially in hospitalized patients. Because of the carbapenems were the first choise of treatment in ICU and IS. It should not be forgotten; CR E. coli and K. pneumoniae strains can cause outbreaks in hospitals and they may be become hypervirulent strains by winning other virulence and resistance genes. Therefore, we believe that this data would be helpful for taking of the necessary infection control measures to prevent the spread of these strains and the selection of empirical treatment for community and hospital infections. Also, it can be show the importance of determining and monitoring antibiotic resistance profiles for each hospital, periodically.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
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References

1. Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among Enterobacteriaceae worldwide. Clin Microbiol Infect. 2014;20:821-30.
2. Couto RC, Carvalho EA, Pedrosa TM, et al. A 10 year prospective surveillance of nosocomial infections in neonatal intensive care units. Am J Infect Control. 2007;35:183-9.
3. Tao XB, Qian LH, Li Y, et al. Hospital-acquired infection rate in a tertiary care teaching hospital in China: a cross-sectional survey involving 2434 inpatients Int J Infect Dis. 2014;27:7-9.
4. Stefaniuk E, Suchocka U, Bosacka K, et al. Etiology and antibiotic susceptibility of bacterial pathogens responsible for community-acquired urinary tractinfections in Poland. Eur J Clin Microbiol Infect Dis. 2016;35:1363-9.
5. Centers for Disease Control and Prevention. Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities. MMWR. 2009;58:256-60.
6. Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: a potential threat. JAMA. 2008; 300:2911-3.
7. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase producing Enterobacteriaceae. Emerg Infect Dis. 2011;17:1791-8.
8. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. Euro Surveillance. 2008;13.pii: 19045.
9. Clinical and laboratory Standards Institute. Performance Standard for Antimicrobial Susceptibility Testing. twentyfifth Informational supplement. Document M100-S25. CLSI, Wayne, PA, 2015.
10. Hidron AI, Edwards JR, Patel J,et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol. 2008;29:996-1011.
11. Bassetti M, Nicolini L, Esposito S, et al. Current status of newer carbapenems. Curr Med Chem. 2009;16:564-75.
12. Gozutok F, Sarıguzel FM, Aydın B, et al. Kayseri Eğitim ve Araştırma Hastanesi Dahiliye Yoğun Bakım Ünitesi'nde 2013 Yılında Gelişen Hastane İnfeksiyonlarının Değerlendirilmesi. Ankem Derg. 2014;28:86-93.
13. Inci A, Güven D, Atasoy R. Microorganisms Isolated from Various Clinical Samples of Intensive Care Unit Patients and their Antibiotic Susceptibilities. J Clin Anal Med. 2014;5:466-8.
14. Erturk A, Çiçek AÇ, Köksal E, et al. Yoğun Bakım Ünitesinde Yatan Hastaların Çeşitli Klinik Örneklerinden İzole Edilen Mikroorganizmalar ve Antibiyotik Duyarlılıkları. Ankem Derg. 2012;26:1-9.
15. Korten V, Ulusoy S, Zarakolu P, et al. Antibiotic resistance surveillance over a 4-year period (2000–2003) in Turkey: results of the MYSTIC Program. Diagn Microbiol Infect Dis. 2007;59:453-7.
16. Gur D, Hascelik G, Aydin N, et al. Antimicrobial resistance in gram-negative hospital isolates: results of the Turkish HITIT–2 Surveillance Study of 2007. J Chemother. 2009;21:383-9.
17. European Antimicrobial Resistance Surveillance System, EARSS. http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/EuropeanAntimicrobialResistanceSurveillanceSystemEARSS/EARSSSurveillanceReports/2008Reports/ accessed date February 2017
18. Gözüküçük R, Çakıroğlu B, Nas Y. Toplum kaynakli üriner sistem enfeksiyonu etkeni olarak saptanan Escherichia coli izolatlarının antibiyotik duyarlılıkları. JAREM. 2012;2:101-3.
19. Sağlam HS, Öğütlü A, Demiray V, et al. Üriner enfeksiyonlarda toplum kökenli escherichia coli'nin yeri ve gelişen antibiyotik direnci. Nobel Med. 2012;8:67-71.
20. Güzel M, Genç Y, Aksoy A, iInvestigation of three different methods for detection of ESBL production and antibiotic resistance percentage of ESBL producing Gram negative bacteria. Turk Hij Den Biyol Derg. 2015;72:131-8.
21. Aykan ŞB, Çiftci İH. Türkiye'de idrar kültürlerinden izole edilen escherichia coli suşlarinin antibiyotiklere direnç durumu: bir meta-analiz. Mikrobiyol Bul. 2013;47:603-8.
22. Eser ÖK, Uludağ HA, Ergin A, et al. İnvazif enfeksiyonlara neden olan GSBL pozitif Enterobacteriaceae İzolatlarında Karbapenem Direnci. Mikrobiyol Bul. 2014;48:59-69.
23. Kaiser DM, Castanheira M, Jones RN, et al. Trends in Klebsiella pneumoniaee carbapenemase-positive K. pneumoniaee in US hospitals: report from the 2007–2009 SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis. 2013;76:356-60.
24. Coskun O, Erdem H, Avci A. Management of community-acquired acute bacterial cystitis in Turkey. Turk J Med Sci. 2011;41:149-57.
25. Gündem NS, Çıkman A, Gülhan B. Extended spectrum beta-lactamase (ESBL) production and antibiotic resistances of Escherichia coli and Klebsiella spp. strains isolated from urine cultures. J Clin Exp Invest. 2013;4:56-62.
26. Çalışkan E, Dede A, Aytar AA, et al. Ayaktan Başvuran Hastalarda Üriner Sistem İnfeksiyonuna Neden Olan Esherichia coli ve Klebsiella spp. Suşlarının Çeşitli Antibiyotiklere Direnç Oranlarının ve Genişlemiş Spektrumlu Beta-Laktamaz Varlığının Değerlendirilmesi. Ankem Derg. 2015;29:47-53.
27. Duman Y, Bozkurt İ, Tekerekoğlu MS. Investigation of Antibiotic Resistance and ESBL-Presence of Community-Acquired Escherichia Coli Strains, Isolated from UTI in Afşin State Hospital. Med Science. 2014;3:1408-18.