

# An Important Public Health Problem "Carbapenem Resistant Enterobacteriaceae Frequency": An Example From A Training And Research Hospital

Halk Sağlığında Önemli Bir Sorun "Karbapenem Dirençli Enterobacteriaceae Sıklığı": Bir Eğitim Araştırma Hastanesi Örneği

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## ABSTRACT

**Background:** Carbapenem-resistant Enterobacterales (CRE) infections are a significant threat to public health due to the limited availability of antibiotics and the effect on mortality. This study was conducted retrospectively to determine the prevalence of CRE in a teaching and research hospital in Istanbul.

**Materials and Methods:** In 2016, 2017 and in the first half of 2018 *Klebsiella* species were evaluated retrospectively in culture samples that were sent to Microbiology Laboratory in an educational hospital. The typing of *Klebsiella* species were performed with MALDITOF-MS device (Biomerieux, France). Imipenem, merapenem, ertapenem susceptibilities of the strains were evaluated with VITEC2 Compact (Biomerieux, France) according to EUCAST (European Committee on Antimicrobial Susceptibility Testing). If the strains were found to be resistant, the results were confirmed by the antibiotic gradient test.

**Results:** In our study, 257 samples; *Klebsiella oxytoca* 9 (3.49%) and *Klebsiella pneumoniae* 248 (96.51%) were detected. 130 endotracheal aspirates, 57 wounds, 34 blood, 15 urine, 9 sputum, 3 catheters, 4 tissue biopsies, 2 mediastinum, 2 peritoneal fluid and 1 pleural fluid strains were identified. While none of the *Klebsiella oxytoca* strains were resistant to carbapenems, the percentages of *Klebsiella pneumoniae* resistance against imipenem, merapenem and ertapenem were found to be 23.29%, 16.94% and 29.44% respectively.

**Conclusion:** The increasing problem of carbapenem-resistant (CR) *Klebsiella pneumoniae* in the last decade has been observed in our hospital for the last 2 years. CR strains often show increased resistance to other antibiotics and their treatment possibilities are limited. It increases the importance of controlling this factor. The application of effective infection control programs and the use of rational antibiotics are of great importance.

**Keywords:** *Klebsiella pneumoniae*; *Klebsiella oxytoca*; Carbapenem Resistance, Hospital Infections

## ÖZET

**Amaç:** Karbapenem dirençli Enterobacteriaceae (CRE) enfeksiyonları, antibiyotiklerin sınırlı varlığı ve mortalite üzerindeki etkisi nedeniyle halk sağlığı için önemli bir tehdittir. Bu çalışma İstanbul'daki bir eğitim ve araştırma hastanesinde CRE prevalansını belirlemek için retrospektif olarak yapılmıştır.

**Gereç ve Yöntemler:** Bir eğitim Araştırma hastanesi Mikrobiyoloji Laboratuvarı'na gönderilen kültür örneklerinde 2016, 2017 ve 2018'in ilk yarısında *Klebsiella* türleri retrospektif olarak değerlendirildi. *Klebsiella* türlerinin tiplendirilmesi MALDITOF-MS cihazı (Biomerieux, Fransa) ile yapıldı. Suşların imipenem, meropenem, ertapenem duyarlılıkları VITEC2 Compact (bioMerieux, Fransa) ile EUCAST'a (Avrupa Antimikrobiyal Duyarlılık Testi Komitesi) göre değerlendirildi. Suşların dirençli olduğu tespit edilirse, sonuçlar antibiyotik gradyan testi ile doğrulandı.

**Bulgular:** Çalışmamızda 257 örnek; *Klebsiella oxytoca* 9 (% 3,49) ve *Klebsiella pneumoniae* 248 (% 96,51) tespit edildi. 130 endotrakeal aspirat, 57 yara, 34 kan, 15 idrar, 9 balgam, 3 kateter, 4 doku biyopsisi, 2 mediasten, 2 periton sıvısı, 1 plevral sıvı

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susu tespit edildi. *Klebsiella oxytoca* suşlarının hiçbiri karbapenemlere dirençli olmasa da, *Klebsiella pneumoniae* suşlarının imipenem, meropenem ve ertapenem'e karşı yüzdeleri sırasıyla % 23,29, % 16,94 ve % 29,44 olarak bulundu.

**Sonuç:** Son on yılda artan karbapenem dirençli *Klebsiella pneumoniae*'nin sorunu hastanede son 2 yıldır gözlenmektedir. Karbapenem dirençli suşlar genellikle diğer antibiyotiklere karşı daha fazla direnç gösterir ve tedavi olanakları sınırlıdır. Bu faktörü kontrol etmenin önemini artırır. Etkili enfeksiyon kontrol programlarının uygulanması ve rasyonel antibiyotik kullanımı büyük önem taşımaktadır.

**Anahtar Kelimeler:** *Klebsiella pneumoniae*, *Klebsiella oxytoca*, Karbapenem Direnci, Hastane Enfeksiyonları

## INTRODUCTION

The approach to medicine that is concerned with the health of the community as a whole is called community health. Hospital infections (HI) related to public health continues to be an important health problem in our country as well as in the whole world. The morbidity, mortality and increased treatment costs due to HI are determined by the detection of the causes of HI made it obligatory to monitor these data over the years and develop control infection control strategies and implement them.

With well-applied infection control programs, HI is reduced, hospitalization time is shortened, and hospital expenses are reduced (Edmond & Wenzel, 2000: 2988-2991).

Nosocomial infections are an important problem that concerns the whole world with the developments in medicine (Haley, et al., 1985: 159-167). Although hospital infections are a critical factor in the quality of health services, they negatively affect the results of health services (Akalm, 2001: 169-171). Gram-negative bacterial species are among the most common causes of hospital and community infections. They are more resistant to antibiotics than Gram-positive bacteria due to the outer membrane of the cell walls of these microorganisms. In addition, multidrug resistance with genetic material transfer and/or selective pressure of antibiotics is encountered (Gür, et al., 2006:161-176).

*Klebsiella spp.* bacteria, non-motile, usually encapsulated, and Gram-negative and Enterobacterales species show the general characteristics of the broiler (Bilgehan, 2004:182-184). *Klebsiella pneumoniae* are opportunistic pathogens that cause nosocomial, upper airway, and urinary tract and wound infections which are very important for human health (Rasool, et al., 2003:243-248). Most of the *Klebsiella* infections are hospital-origin. The most common cause of nosocomial *Klebsiella* infections is *K. pneumoniae* (Yavuzdemir, 2001:196-200). Infections caused by CR *Klebsiella pneumoniae* (CRKP) strains are a problem increasing the morbidity and mortality in critically ill patients and increasing in frequency all over the world (CDS, 2009).

The most important step of infection control protocols is the prevention of infections caused by the increasing amount of CRKP strains all over the world. Despite all infection control measures to prevent infections and outbreaks associated with multidrug-resistant (MDR) microorganisms, CRKP infections have been reported to be

increasing worldwide (Çalışkan, et al., 2015: 47-53). Difficulties are encountered in the treatment of infections with *K. pneumoniae* strains showing multiple drug resistance (Patterson, et al., 2000: 455-458).

In this study, we evaluated the samples that are collected in to Educational Hospital Microbiology Laboratory. It is aimed to investigate the types, distribution and susceptibility of *Klebsiella* species isolated from various cultures between 2016 2018.

## MATERIAL AND METHODS

This study was conducted with the culture samples that were sent to the Microbiology Laboratory of an educational hospital between 2016, 2017 and the first half of 2018. The culture samples were than evaluated retrospectively. The types of *Klebsiella* species were performed with MALDİTOF-MS device (Biomerieux, France). Imipenem, merapenem and ertapenem susceptibilities of the strains were evaluated with VITEC2 Compact (Biomerieux, France) according to EUCAST (European Committee on Antimicrobial Susceptibility Testing).

If the strains were found to be resistant, the results were confirmed by the antibiotic gradient test. Antimicrobial susceptibility tests are used to determine the effectiveness of the antimicrobial agent against the known bacterial species in the in vitro environment. Disc diffusion test, one of the antimicrobial susceptibility test methods, was used in our study. Disc diffusion test was performed by our study group manually. Standard fuzzy bacterial suspension is created with McFarland 0.5. The prepared suspension was inoculated on the Mueller Hilton agar (BD, Mueller Hinton II Agar) surface with a sterile swab. Antibiogram discs were placed on agar with a sterile forceps. Media were incubated at 35°C for 18-24 hours. The zones formed were measured one by one and recorded.

## RESULTS

In this study, 257 samples were tested. The distribution of sample types is given in Table 1. Based on the findings, highest sample rate was for endotracheal aspirates (130) followed by wound (57) and blood samples (34).

**Table 1.** The distribution of *Klebsiella* species that was isolated from multiple cultures

Sample Type	n (%)
Sputum	9 (3.49)
Tissue Biopsy	4 (0.78)
Endotracheal Aspirates	130 (50.39)
Urine	15 (5.81)
Blood	34 (12.79)
Catheter	3 (1.16)
Mediastinum	2 (0.78)
Peritoneal Fluid	2 (0.78)
Pleural Fluid	1 (0.39)
Wound	57 (22.09)
Total	257

According to Table 2, the distribution of *Klebsiella* species is as follows: *Klebsiella oxytoca* 9 (3.49%) and *Klebsiella pneumoniae* 249 (96.51%).

**Table 2.** Distribution of *Klebsiella* species isolated from various cultures

Bacteria Species	%	n
<i>Klebsiella oxytoca</i>	3.49	9
<i>Klebsiella pneumoniae</i>	96.51	249
Total	100.00	257

As can be seen in Table 3, CR rates are compared for the 2 bacteria. *Klebsiella pneumonia* shows resistance to Carbapenem types with the following distribution; Ertapenem (29.72%), Imipenem (23.29%) and Merapenem (16.87%).

**Table 3.** CR rates for *Klebsiella* species isolated from various cultures

Bacteria Species	Resistance Ratio n (%)		
	Ertapene m	Imipene m	Merapene m
<i>Klebsiella oxytoca</i>	0	0	0
<i>Klebsiella pneumoniae</i>	74 (29.72)	58 (23.29)	42 (16.87)

In Table 4, sensitivity rates for the *Klebsiella oxytoca* and *Klebsiella pneumoniae* are shared. As observed, both bacteria are more sensitive to Imipenem (73.26%), Merapenem (73.64%). On the other hand, the highest amount of resistance is shown to Ertapenem by 28.68% of the samples.

**Table 4.** Sensitivity rates of *Klebsiella oxytoca* and *Klebsiella pneumoniae* to antibiotics, n (%)

Antibiotic	Sensitive n (%)	Medium Sensitive n (%)	Resistant n (%)
Ertapenem	182 (70.54)	2 (0.78)	74 (28.68)
Imipenem	189 (73.26)	11 (4.26)	58 (22.48)
Merapenem	190 (73.64)	26 (10.08)	42 (16.28)

## DISCUSSION

HI continue to be an important health problem in our country as well as in the whole world. The morbidity, mortality and increased treatment costs due to HI are determined by the detection of the causes of HI made it obligatory to monitor these data over the years and develop control infection control strategies and implement them. With well-applied infection control programs, HI is reduced, hospitalization time is shortened, and hospital expenses are reduced (Edmond & Wenzel, 2000: 2988-2991).

Infections due to CR Gram-negative bacteria bring high mortality and show an urgent threat to address. Clinicians are at the beginning of a new era in which antibiotic resistance in Gram-negative bacilli is being taken care of by the availability of the new antibiotics in this area for many years (Peri, 2019:413-425).

CRKP problem which has increased in the last 10 years, has been observed in our hospital for the last 2 years. CR strains often show increased resistance to other antibiotics and their treatment possibilities are limited. It increases the importance of controlling this factor. The application of effective infection control programs and the use of rational antibiotics are of great importance.

In our country, in the hospital infectious agents, Gram-negative bacteria are in the front row. The major ones are *P. aeruginosa*, *A. baumannii*, *K. pneumoniae* and *E. coli*. This is followed by *S. aureus*. Gültekin et al. reported that imipenem was the most effective antibiotic to *K. pneumoniae* and *E. coli* isolates of hospital infection and found imipenem resistance in an ESBL positive *K. pneumoniae* and an *E. coli* strain (Gültekin, et al., 1999: 515).

Infections caused by CRKP strains, increasing the morbidity and mortality in critically ill patients and increasing frequency all over the world is an increasing problem (Stefaniuk, et al., 2016: 1363-1369; Schwaber-Carmeli, 2008: 2911-2913).

In a study by Kocazeybek et al. Enterobacteriales family of the most effective antibiotics imipenem, amikacin and ciprofloxacin, while the most effective antibiotics in the work of Gültekin and his friends were reported as ofloxacin,



imipenem, amikacin and cefepim (Gültekin, et al., 1999: 515; Kocazeybek, 2001: 396-408).

*Klebsiella* species are found to be 5% colonized in the nasopharynx and intestine of healthy individuals. Generally, *Klebsiella* infections are caused by colonized strains in the host. Antibacterial drug use and hospitalization increase *Klebsiella carriage* (Çetinkaya, et al., 2005:1-4).

Resistance increase against antibiotics is a global problem. In order to combat this problem, maximum attention should be paid to infection control measures. In this direction, all units and especially intensive care units within the hospital active and uninterrupted surveillance, antibiotics should be used at the appropriate dose and time, cultures should be taken carefully and antimicrobials to be started until culture results are obtained should be started by taking into consideration the clinical condition of the patient and the flora of the current environment. The culture antibiogram results should be monitored and antibiotic therapy should be rearranged according to the antibiogram results with current guidelines.

Before ten years ago, CR was seldomly reported in *Klebsiella pneumoniae* and *E. coli* strains. Recently, augmenting CR in gram negative bacteria is a critical concern (Duman, et al., 2018: 536-539). The peak CR frequency was determined among intensive care units' that separates of *K. pneumoniae* as 20.1%. We understood that CR clearly increased in intensive care unit isolates of *E. coli* and *K. pneumoniae* about 5-10 folds through the study. It was understood that the resistances of *K. pneumoniae* carbapenems were progressively increasing by years, especially in intensive care units and inpatient services (Duman, et al., 2018: 536-539).

In another study, a total of 1055 samples that belong to the family Enterobacterales were studied. From the family Enterobacterales, 348 (27%) of the bacilli were determined to be CR. Among those most common bacteria was *Klebsiella pneumoniae* (Pokharel, et al., 2018: 931-935). Where as in our study, 257 samples; *Klebsiella oxytoca* 9 (3.49%) and *Klebsiella pneumoniae* 248 (96.51%) were detected. While none of the *Klebsiella oxytoca* strains were resistant to carbapenems, the percentages of *Klebsiella pneumoniae* resistance against imipenem, meropenem and ertapenem were found to be 23.29%, 16.94% and 29.44%, respectively.

In our study, CR has been shown to be a significant proportion of the members of Enterobacterales. Measures to ensure the control of CRE origins in the community and in the hospital and measures to ensure rational antibiotic use are needed.

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**Ethics Committee Approval:** This study was Educational approved by Health Sciences University Haydarpaşa

Numune Educational Research Hospital (Ethical code: HNEAH-KAEK 2018/93).

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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