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Carbapenem-Resistant *Klebsiella pneumoniae*: Resistance Mechanisms, Epidemiology, and Mortality

Karbapenem Dirençli *Klebsiella pneumoniae*: Direnç Mekanizmaları, Epidemiyoloji ve Mortalite

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ABSTRACT

Antimicrobial resistance has become an urgent global public health problem. It is predicted that deaths due to bacterial antimicrobial resistance will reach 10 million per year by 2050, if no action is taken. Antimicrobial resistance also causes prolonged hospitalization, failure of treatment, spread of resistant bacteria in the community, and a serious economic burden. Carbapenem-resistant Klebsiella pneumoniae is among the bacteria that the World Health Organization gives critical priority to and poses the greatest threat to human health. The main mechanisms of carbapenem resistance are loss of porins, activation of efflux pumps, modification of target structure, and production of beta-lactamases. There are several risk factors associated with mortality in cases of carbapenem resistance, including older age, prolonged hospitalization, high Acute Physiology and Chronic Health Evaluation II scores, as well as the presence of conditions such as diabetes mellitus, hemato-oncological diseases, chemotherapy, and corticosteroid treatment. In this review, data, extracted by PubMed and Web of Science Databases searching with the terms "carbapenem-resistant Klebsiella pneumoniae", "carbapenem resistance mechanisms", "carbapenemases", "resistance to meropenem-vaborbactam", "resistance to imipenem-relebactam", is summarized and briefly discussed with recommendations.

Key Words: *Meropenem-vaborbactam; Imipenem-relebactam; KPC; OXA-48; NDM-1*

ÖZ

Karbapenem Dirençli *Klebsiella pneumoniae*: Direnç Mekanizmaları, Epidemiyoloji ve Mortalite

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Antimikrobiyal direnç, acil bir küresel halk sağlığı sorunu haline gelmiştir. Herhangi bir önlem alınmadığı takdirde bakteriyel antimikrobiyal dirence bağlı ölümlerin 2050 yılına kadar yılda 10 milyona ulaşacağı tahmin edilmektedir. Antimikrobiyal direnç aynı zamanda hastanede yatış süresinin uzamasına, tedavi başarısızlığına, dirençli bakterilerin toplumda yayılmasına ve ciddi bir ekonomik yüke neden olmaktadır. Karbapenem dirençli Klebsiella pneumoniae, Dünya Sağlık Örgütünün antimikrobiyal ilaç geliştirmeye ihtiyaç duyulan en tehlikeli patojenlerin listesinde kritik öncelik verdiği ve insan sağlığı için en büyük tehdidi oluşturan bakteriler arasında yer almaktadır. Karbapenem direncinin ana mekanizmaları, porinlerin kaybı, akış pompalarının aktivasyonu, hedef yapının modifikasyonu

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ve beta-laktamazların üretimidir. Karbapenem direncine bağlı mortalite risk faktörleri vardır; yaşlı olmak, hastanede uzun süre kalmak, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi II skorunun yüksek olması, diyabetes mellitus varlığı, hemato-onkolojik hastalıklar, kemoterapi ve kortikosteroid tedavisi olarak sıralanabilir. Bu derlemede, PubMed ve Web of Science veri tabanlarında "Karbapenem-dirençli Klebsiella pneumoniae", "Karbapenem direnç mekanizmaları", "Karbapenemazlar", "meropenem-vaborbaktama direnç", "imipenem-relebaktama direnç" terimleriyle arama yapılarak elde edilen veriler özetlenmiş ve önerilerle birlikte kısaca tartışılmıştır.

Anahtar Kelimeler: *Meropenem-vaborbaktam; İmipenem-relebaktam; KPC; OXA-48; NDM-1*

INTRODUCTION

Klebsiella pneumoniae (*K. pneumoniae*), known since 1875, is a gram-negative fermentative bacillus belonging to the *Enterobacteriaceae* family. It is a member of a healthy human microbiome, and colonizes many parts of the body, such as the mucosal surfaces of the upper respiratory tract and gastrointestinal tract. Colonization can turn into an infection when the immune system is suppressed by comorbidities such as diabetes, corticosteroid use, organ transplantation, and malignancy. During the 1960s and 1970s, *K. pneumoniae* established itself as one of the most important causes of global nosocomial infections, particularly urinary tract infections, respiratory tract infections, and bloodstream infections. Finally, nosocomial infections due to multidrug resistant (MDR) *K. pneumoniae* have become a major problem in recent years[1]. In Türkiye, the rate of resistance to third generation cephalosporins in *K. pneumoniae* isolates is 75.4%, aminoglycoside resistance is 43.1%, quinolone resistance is 68%, and the rate of isolates with resistance to all three drug groups is 38.7%[2]. The increasing prevalence of MDR leaves patients with limited treatment options and leads to an excessive increase in the use of carbapenems, which are considered as last resort drugs. Overuse of carbapenems brings the problem of resistance. Therefore, carbapenem-resistant *K. pneumoniae* (CRKP) is among the bacteria for which new antimicrobial drugs are urgently needed and that the World Health Organization (WHO) gives critical priority, as they pose the greatest threat to human health[3]. Among invasive pathogens reported from 29 countries in Europe in 2020, *K. pneumoniae* (14.9%) ranks third, after *Escherichia coli* (38.4%) and *Staphylococcus aureus* (17.3%). Although only 10% of these isolates were reported to be carbapenem resistant, the range of rates across countries was quite wide (0.0% to 66.3%)[4]. In Türkiye, it was reported that the rate of CRKP was on the rise in every year from 2016 to 2020, respectively; 29.5%, 32.5%, 34.4%, 39.4% and 48.2%. According to the National Health Service-Associated Infections Surveillance Network report, the weighted general average of CRKP infections in our country was 63.57% in 2021[4,5].

Global rise in carbapenem resistance especially among *K. pneumoniae* strains ties into knots. The main mechanisms of carbapenem resistance are limiting uptake of drug by reduction or loss of porins, activation of efflux pumps, modification of target structure, and production of hydrolytic enzymes (beta-lactamases; carbapenemases)[6].

The dominant selection of strains with antimicrobial resistance (AMR), which can adapt to environmental conditions and evolve, is increasing for several reasons including compliance with guidelines in rational antimicrobial use and infection control policies, and exposure to sublethal doses of antibiotics through meat (farm animals) and agricultural products in daily life. Antimicrobial resistance (AMR) has become an urgent global public health problem. It is predicted that deaths due to bacterial AMR will reach 10 million per year by 2050, if no action is taken. In addition to an increase in mortality rates, AMR causes prolonged hospitalization, failure of treatment, spread of resistant bacteria in hospitals and in communities, and a serious economic burden[7].

Carbapenem Resistance Mechanisms of *Klebsiella pneumoniae*

The first case of imipenem-resistant *K. pneumoniae* was reported 11 years after the first carbapenem was introduced to the market in 1985.

The mechanisms leading to carbapenem

resistance in *K. pneumoniae* isolates are as follows[8]:

1. Production of hydrolytic enzymes (beta-lactamases; carbapenemases)

2. Production of extreme broad-spectrum beta-lactamases (ESBL) and AmpC cephalosporinases, with reduced expression of outer membrane proteins (OMP) that cause permeability defects

3. Activation of efflux pumps

1. Carbapenemases

Beta-lactamases are of four classes (classes A, B, C, and D) according to their amino acid sequence (Ambler's molecular classification). Beta-lactamases with catalytic activity for carbapenem hydrolysis are carbapenemases in classes A, B, and D. Class C beta-lactamases (cephalosporinases, AmpC) have very weak or absent hydrolytic activities against carbapenems. However, if there are permeability defects together with their overexpression, they may play a role in carbapenem resistance[9]. Imipenem minimum inhibitory concentration (MIC) values in bacteria expressing Class A carbapenemases can range from slightly elevated (MIC< 4 µg/mL) to completely resistant. Therefore, these beta-lactamases may be missed in routine susceptibility tests. Apart from carbapenems, they have the ability to hydrolyze many beta-lactam antibiotics, including cephalosporins, penicillins and aztreonam. The antibiotic hydrolysis and inhibition properties of carbapenemases are summarized in Table 1.

Class A serine carbapenemases include *Serratia marcescens* enzyme (SME), nonmetalloenzyme carbapenemase (NMC), imipenem-hydrolysing beta-lactamase (IMI), *Serratia fonticola* carbapenemase (SFC), *K. pneumoniae* carbapenemase (KPC), and Guiana extended spectrum (GES) beta-lactamase. Although KPC carbapenemases are mostly detected in *K. pneumoniae*, they have also been reported in *Enterobacter* spp. and *Salmonella* spp.[9].

Since the first KPC enzyme was discovered in the United States in 1996, 13 KPC enzymes, which were separated from each other by single amino acid substitutions, have been identified. KPC carbapenemases hydrolyze nitrocefin, cephalothin, cephaloridine, benzylpenicillin, ampicillin, and piperacillin most potently, while they hydrolyze imipenem,

Table 1. Antibiotic hydrolysis and inhibition properties of carbapenemases[6,13]

			Hydrolysis profile*					Inhibition profileÝ	
Molecular class	Enzyme	Location	PEN	1st/2nd CEP	Extended spectrum 3rd/4th CE	AZN	C	EDTA	CLA
A	NMC	Chromosome	+	+	+	+	+	-	+
	IMI	Chromosome	+	+	+	+	+	-	+
	SME	Chromosome	+	+	±	+	+	-	+
	KPC	Plasmid	+	+	+	+	+	-	+
	GES	Plasmid	+	+	+	-	±	-	+
B	IMP	Plasmid	+	+	+	-	+	+	-
	NDM	Plasmid	+	+	+	-	+	-	-
	VIM	Plasmid	+	+	+	-	+	+	-
	GIM	Plasmid	+	+	+	-	+	+	-
	SPM	Plasmid	+	+	+	-	+	+	-
D	OXA	Plasmid (except OXA-51)	+	+	±	-	±	-	±

* +: Strong hydrolysis, ±: Weak hydrolysis, -: No detectable hydrolysis reported.
Ý +: Inhibition present, ±: Variable inhibition among enzymes, -: Inhibition not reported.
AZN: Aztreonam, C: Carbapenem, CEP: Cephalosporins, CLA: Clavulanic acid, PEN: Penicillins.

meropenem, cefotaxime, and aztreonam 10 times less efficiently. In addition, weak but measurable hydrolysis of cefoxitin and ceftazidime provides its broad spectrum to the KPC family. *K. pneumoniae* producing KPC has been found in many sequence types, especially ST258 and its related types (ST512, ST11, ST340 and ST437). KPC carbapenemases, which have become a global health problem, have two key features that differ from others: they are encoded by plasmids, and the hydrolyzed substrate spectrum also includes aminothiazoloxime cephalosporins such as cefotaxime. As the KPC gene is located in mobile genetic elements (plasmids), and is mostly found in *K. pneumoniae*, which has a high ability to accumulate and transmit resistance genes, it is highly capable of spreading among different bacterial species. Therefore, KPC is currently endemic in Greece, Israel, Latin America, the United States, and East Asia. It has been reported in many countries in Europe[8,9].

The primary features of class B metallo-beta-lactamases (MBL) are hydrolysis of carbapenems, resistance to beta-lactamase inhibitors, and inhibition by metal ion chelators. The mechanism of hydrolysis depends on the interaction of zinc ions (Zn^{+2}) in the active site of the enzyme, and beta-lactams. For this reason, when ethylene diamine tetraacetic acid (EDTA), which is a chelator for divalent cations such as Zn^{+2}, is present in the environment, their hydrolysis abilities are inhibited. The substrate spectra are quite broad; in addition to carbapenems, most of these enzymes hydrolyze cephalosporins and penicillins, but lack the ability to hydrolyze aztreonam[9]. The sulfonate group in the aztreonam molecule bonds with the second Zn^{+2} binding site of MBL, and in this case, the β-lactam ring cannot be connected by the first Zn^{+2} binding site of MBL due to staying in the configuration too far from. Therefore, it is hypothesized that aztreonam may bind weakly and inefficiently to MBLs, thereby evading their hydrolytic activity. Bactericidal efficacy is increased when aztreonam, which can evade hydrolysis of MBLs, is added to a beta-lactam/beta-lactamase inhibitor combination, such as ceftazidime-avibactam, which inhibits ESBL and AmpC beta-lactamases. Due to this in vitro efficacy and the lack of alternative treatment options, the combination of aztreonam and ceftazidime-avibactam is increasingly used clinically[10]. Class B MBLs have three subclasses: B1, B2, and B3. Clinically significant MBLs are in subclass B1, including imipenem-resistant *Pseudomonas* (IMP), New Delhi metallo-beta-lactamase (NDM), Verona integron-encoded metallo-β-lactamase (VIM), Sao Paulo metallo-β-lactamase (SPM), and German imipenemase (GIM) enzymes[9,10]. NDM-1 (New Delhi metallo-beta-lactamase-1), which was detected for the first time in 2008 in Sweden from an Indian patient, spread to Europe and America with international human mobility in the 2010s. Recent findings suggest that Balkans, African, and Middle Eastern countries may also be reservoirs. The first report in Türkiye was from an Iraqi patient in 2012. At least eight variants of NDM-1 have been found. It is predominantly detected in *K. pneumoniae* and *E. coli* isolates[6,10].

The first member of the imipenem-resistant *Pseudomonas* (IMP) MBL family was found in Italy as the first cassette in the class 1 integron in *Acinetobacter baumannii* (*A. baumannii*). There are 79 species identified in *A. baumannii, P. aeruginosa* and the *Enterobacteriaceae* family[9]. Another class 1 integron-related MBL, VIM ("Verona integron-encoded metallo-β-lactamase") enzyme, was first detected in a *P. aeruginosa* isolate in 1997. There are 46 variants defined mostly in *P. aeruginosa* and *P. putida*, and rarely in *Enterobacteriaceae* (Greece, VIM-1), which was also reported in Türkiye. Recently, it has become common in Europe. The most common variant of VIM is VIM-2. IMP and VIM families share common features in terms of plasmid and integron relationships[6,9,10].

Multidrug resistant isolates of *K. pneumoniae* arise with acquisition of plasmid-located resistance genes as well as acquisition of mobile genetic elements such as transposons and integrons. For instance, transposon Tn4401 is associated with KPC production, and Tn1999 is associated with OXA production. There are three well-characterized major classes of antibiotic resistance integrons classified as classes 1, 2, and 3.

The class 1 integron cassette is the most common and can be found in most of the *Enterobacteriaceae* family. The class 1 integron generally encodes a protein that causes multiple drug resistance. It was reported that the locations of VIM and IMP genes in the class 1 integron were closely related to aminoglycoside resistance (aacA4, aadA1, aadB), class D beta-lactamase (OXA gene), antiseptic resistance (qacΔG), and chloramphenicol resistance genes (catB)[11,12].

Class D serine carbapenemases (OXA beta-lactamases) were thought to have only penicillinase activity when they were first identified in the late 1970s. Today, the number of OXA variants has exceeded 102. Nine of these are broad-spectrum beta-lactamases and at least 37 are carbapenemases. The most important feature of OXA carbapenemases is that they mutate rapidly and expand their spectrum of action[9,13]. The first identification of OXA beta-lactamase with carbapenemase activity was in an *A. baumannii* strain in 1993. The enzyme was named ARI-1 (*Acinetobacter* resistant to imipenem), and when sequence analysis was performed, it was determined that it was a member of the OXA class D beta-lactamase family. Therefore, its name was changed to OXA-23[9,13]. Currently, the majority of OXA carbapenemases have been identified in *A. baumannii* isolates. While OXA-expressing *Acinetobacter* spp. strains are increasing all over the world, OXA-48 was reported in a *K. pneumoniae* isolate for the first time in Türkiye. After five years, the first OXA-48-producing CRKP outbreak was reported in Türkiye. This OXA variant was encoded by the plasmid and had <46% amino acid identity with other OXA variants. Moreover, OXA beta-lactamase had the highest hydrolysis ability according to the kinetic parameters of the OXA enzymes found[26]. Recently, OXA-48 has been frequently reported in Türkiye, the Middle East, and North Africa. Among the carbapenemases carried by the *Enterobacteriaceae* family in Türkiye, OXA-48, including IMP and NDM-1, takes the lead[9,14].

The limited treatment options available in Türkiye for CRKP infections include polymyxins (colistin), aminoglycosides, tigecycline, and ceftazidime-avibactam. Ceftazidime-avibactam can not inhibit MBLs (IMP, VIM, and NDM). Synergistic efficacy against KPC/VIM/OXA-48 producing CRKP has been demonstrated in high-dose carbapenem and colistin combination therapy[15,16].

2. Coexistence of Permeability Defects with Beta-lactamases (ESBL, AmpC)

The outer membrane (OM) of gram-negative bacteria has a unique architectural feature; it is composed of phospholipids, lipopolysaccharides, lipoproteins, and β-barrel porins. Acting as an additional barrier, OM inhibits the transport of toxic compounds such as bile acids and antimicrobials. Therefore, chemical compounds with a molecular weight of more than 600 daltons can not pass through the OM of gram-negative bacteria. Porins, which are outer membrane proteins in the β-barrel structure that form a transmembranous pore allowing passive transport of hydrophilic compounds, are found extensively in OM. Some small hydrophilic antimicrobials, such as beta-lactams, enter cells by diffusion through aqueous channels of porins[17]. The number, shape, and quality of porins differ between gram-negative bacterial species, and can be altered by mutations. Decreased expression of porins due to mutations leads to permeability defects. In this case, beta-lactam antibiotics, such as carbapenem, can not pass through porin channel and can not reach their sites of action[17]. *K. pneumoniae* has two main non-specific porins that allow passage of antimicrobials into the periplasmic space in cell: OmpK35, which belongs to the OmpF porin group with a large channel size, and OmpK36, which belongs to the OmpC porin group with a small channel size. Studies have shown that OmpK36 may play a key role in the carbapenem resistance of ESBL or AmpC-type beta-lactamase producing *K. pneumoniae* strains. OmpK35 deficiency may also be one of the factors contributing to antibiotic resistance of ESBL-producing *K. pneumoniae*. Mutation or loss of OmpF is responsible for beta-lactam resistance in *K. pneumoniae* and in many gram-negative bacteria. *K. pneumoniae* isolates that do not normally produce chromosomally encoded class C

beta-lactamases can readily acquire an AmpC or another ESBL-encoding plasmid. These enzymes may confer elevated levels of carbapenem resistance in the porin-deficient strain[18].

3. Activation of Efflux Pumps

Efflux pump proteins are a family of transport proteins localized in the cytoplasmic membrane that regulate the intake of nutrients and ions into the cell, excretion of metabolic end products and antimicrobials, and the interaction of bacteria with the environment. Active efflux pumps extrude antibiotics out of the cell before they reach the intended targets. Overexpression of these pumps by gene regulation or mutations increases their efficiency and causes AMR. This mechanism may be responsible for beta-lactam resistance in *P. aeruginosa, E. coli* and *Neisseria gonorrhoeae*[19]. However, although it is possible that activation of efflux pumps may contribute to porin defects causing carbapenem resistance in *K. pneumoniae* isolates, this has not yet been clarified.

Resistance Mechanisms of New Carbapenem Combinations (Meropenem-Vaborbactam & Imipenem-Cilastatin-Relebactam)

Limited treatment options against difficult-to-treat resistant gram-negative bacilli have led to the development of several new beta-lactam/beta-lactamase inhibitor combinations. meropenem-vaborbactam (MER-VAB) and imipenem-cilastatin-relebactam (IMI-REL) are two of these, which were approved in 2017 and 2019, respectively. Clinical data on use of these drugs, which are not yet available in our country, are limited, and mostly based on nonrandomized studies in the literature[20].

Vaborbactam, a novel cyclic boronic acid beta-lactamase inhibitor, restores the activity of meropenem against KPC producing *K. pneumoniae* and several other serine beta-lactamase producing gram-negative bacteria. However, it has no activity against MBL/OXA. It has been demonstrated to be as effective as piperacillin/tazobactam in the treatment of complicated urinary tract infections, and more effective than other compounds in the treatment of carbapenem-resistant *Enterobacterales* infections (Targeting Antibiotic Nonsusceptible gram-negative organisms-I/-II, TANGO- I/-II clinical phase 3 trials). While it was previously approved for clinical use only in complicated urinary tract infections (UTIs), MER-VAB is now indicated for the treatment of aerobic gram-negative infections such as complicated intra-abdominal infections and nosocomial pneumonia. The widespread use of MER-VAB in countries where these agents have become available for clinical use, due to increasing rates of infections, which it is indicated for, has brought along the problem of resistance, as can be predicted[20,21].

Production of beta-lactamases (MBL or OXA) that are not inhibited by vaborbactam or relebactam is the most common resistance mechanism against MER-VAB and IMI-REL drugs, which are recommended as an option in the treatment of *P. aeruginosa* and *Enterobacterales* (with ESBL, KPC, and AmpC activity) isolates. Based on data thus far, the main mechanisms associated with MER/VAB resistance in KPC-producing *Enterobacterales* are overexpression of beta-lactamase, porin mutations, and activation of efflux pumps[20-22].

In recent studies, it has been reported that a decrease in the number of OmpK35/36/37 porins in KPC producing *K. pneumoniae* isolates (due to the loss of KvrA), and an efflux pump (AcrAB) mutation are associated with MER-VAB resistance[20-22].

IMI-REL is a combination of imipenem, cilastatin (renal dihydropeptidase-I inhibitor), and relebactam (a new beta-lactamase inhibitor). It is approved for use in the treatment of nosocomial/ventilator-associated bacterial pneumonia, and complicated urinary tract or intra-abdominal infections in adults with no limited or alternative treatment options. There are a few studies reporting that resistance to IMI-REL may also result from carbapenemase mutation, carbapenemase overexpression, mutation or underexpression of penicillin-binding proteins (PBPs), increased efflux, and decreased permeability, in addition to the presence of MBL or OXA carbapenemases. The mechanism of resistance to IMI-REL in *K. pneumoniae* isolates is mutation resulting in loss

of OmpK35/OmpK36 porins, and production of SHV-11/12, TEM-1/KPC beta-lactamases[20,23].

There can be cross-resistance to new carbapenem/beta-lactamase inhibitor combinations. It has been shown that resistance to IMI-REL also increases MER-VAB and CAZ-AVI MIC values[24,25].

Epidemiology, mortality, and risk factors for carbapenem-resistant *K. pneumoniae*

If all AMR infections were replaced by no infections, 4.95 million deaths could have been prevented, or if all AMR infections were replaced by antimicrobial-susceptible infections, 1.27 million deaths could have been prevented in 2019[7].

The prevalence of CRKP isolated from blood and cerebrospinal fluid cultures in Türkiye was 29.5% in 2016, 32.5% in 2017, 34.4% in 2018, 39.4% in 2019, 48.2% in 2020 and 49.1% in 2021. These rates were reported as 0.0-0.3% in Finland, and less than 1.0% in Germany, France, Norway, Sweden, England, Hungary, and Austria in 2021. However, 2021 data in Greece, Serbia, Romania, Ukraine, Belarus, Russia, and Georgia show that the resistance rate exceeds 50%[26].

The European Center for Disease Prevention and Control (ECDC) reported that 30.9% of the total burden in disability-adjusted life years (DALYs) in 2020 was due to carbapenem-resistant bacterial infections. The distribution of carbapenem-resistant isolates within the attributed burden reported for mortality was as follows: *K. pneumoniae* (4076 deaths; ~11%), *Acinetobacter* spp. (3656 deaths; ~10%), and *P. aeruginosa* (3210 deaths, ~9%). Inadequate implementation of infection control measures and rational antibiotic use are estimated to facilitate AMR rates. If no action is taken, it is predicted that the rate of resistance to second-line drugs in Europe will increase by 72% in 2030 compared to 2005, and resistance to last-line drugs will more than double. Every year, AMR is reported to be responsible for 33.000 deaths, and the financial burden to the healthcare system is €1.1 billion[26,27].

In a multicenter study in Türkiye, in which various clinical samples were included from 24 hospitals between 2015 and 2018, AMR of healthcare-associated infections (SHIE) and 30-day fatality rates were analysed. It was reported that the carbapenem resistance of *K. pneumoniae* isolates was 81% in 2015 and 75% in 2018. It was also reported that the total fatality rate was 57%, and the 30-day fatality rate was 27% in bloodstream infections. In multivariate analysis, 30-day fatality for *K. pneumoniae* was found to be associated with pneumonia, bloodstream infection, age over 65, and carbapenem resistance[28]. In another multicenter study investigating antimicrobial resistance and mortality predictors of SHIEs (n= 831) developed with gram-negative bacteria in the intensive care unit (ICU) in our country, *K. pneumoniae* (27%) was found to be the second most common cause and carbapenem resistance was found to be 40%. This CRKP rate is higher than that previously reported from Türkiye (2014; 28%), and it draws attention to the importance of local surveillance data. In terms of carbapenem resistance, AMR may be a much more important and urgent health problem for our country than previously thought. Considering the current workload and economic conditions of microbiology laboratories, we need more multicenter studies that reflect the national profile in a timely manner and provide more economic support for scientific studies. In the same study the proportion of carbapenem resistance in all causes of death was 62%, and in the multivariate analysis, carbapenem resistance, being older than 70 years, central venous catheter use, ventilator-associated pneumonia, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were reported to be statistically significant risk factors for mortality[29]. In a meta-analysis (up to December 2018) of 1843 publications to evaluate the association of CRKP infections and mortality, it was reported that the overall mortality rate was 37.2%, and monotherapy was more associated with mortality than combination therapies[30]. According to studies investigating the relationship between carbapenem-resistant other gram-negative bacteria associated SHIEs and mortality in Türkiye, it was reported

that being female, having malignancy, having bloodstream infection, and being transferred from another health center increase the fatality rate[31]. In another study, the overall mortality of *P. aeruginosa* associated SHIEs was 46%, while that of carbapenem-resistant SHIEs was 68%, and the case series had a 30-day mortality rate of 88%[32]. In a multicenter (n= 10) prospective study in Türkiye, it was reported that carbapenem resistance was 99.4 %, and the mortality rate was 58.5% in ICU patients (n= 164) with invasive MDR *A. baumannii* infection. It has been reported that risk factors associated with mortality were long hospital stay in ICU, having APACHE II score >20, presence of ventilator-associated bacteremia, being >65 years of age, presence of diabetes mellitus, liver failure, chemotherapy treatment and previous quinolone treatment[33].

Distribution of carbapenemases in the world

Clinically important carbapenemases in the *Enterobacteriaceae* family as follows[34]:

- KPC (Class A carbapenemases),
- VIM, IMP and NDM (Class B metallo-β-lactamases), and
- OXA-48 (Class D carbapenemases).

KPC, which was first detected in a *K. pneumoniae* strain in North Carolina in 1996, is now circulating in 38 states of the United States, Canada, South America, Australia, China, and India. NDM-1, which was first detected in India, is endemic in India and Pakistan. NDM-1 is sporadically detected in the USA, Canada, Colombia, Northern Europe, Saudi Arabia, Türkiye, China, and Australia. OXA-48, which was first reported in Türkiye, is currently endemic in Türkiye. And this endemicity is also present in Saudi Arabia, Algeria, Egypt, Morocco, and India. It is sporadically detected in Europe[34].

While carbapenemase-producing Enterobacteriaceae spread in the form of interregional epidemics only in Italy and Poland in 2010, Belgium, Denmark, France, Hungary, Romania, Slovakia, and Spain were added to these countries in 2015. Moreover, it was reported to be endemic in Türkiye, Italy, Greece, and Malta. By 2018, it was reported that endemicity continued in the same countries, and Croatia, Serbia, and Ireland were added to the countries where there was a spread between regions[35]. The cross-border spread of MDR *K. pneumoniae* isolates producing OXA-48 and NDM-1 in Europe has been demonstrated by whole genome sequencing (WGS). It was noted that a history of previous hospitalization (in the last six months) or travel to a country with a high prevalence of MDR was an important risk factor. Failure to detect carriage of MDR is not only harmful to the individual, but also increases the possibility of undetected transmission in healthcare settings. Appropriate management of carbapenemase-producing bacteria requires good clinical laboratory capacity (sufficient WGS capacity), interdisciplinary collaboration, strong infection prevention and control methods, good antimicrobial management practices, and rapid data sharing internationally[36,37].

In Europe, the most frequently detected carbapenemases in carbapenemase-producing *Enterobacteriacea* (EuSCAPE study) were reported as KPC (42%) and OXA-48 (38%). Carbapenem resistance mechanisms detected in *K. penumoniae* isolates were reported as follows: KPC (31.5%), other mechanisms (porin, efflux, other β-lactamases such as AmpC (29.3%), OXA-48 (25.8%), NDM (7.7%), and VIM (5.7%)[34].

In North America, it was reported that the most frequently detected carbapenemases in the *Enterobacteriaceae* family were KPC (47.9%), NDM, VIM, and OXA. They were KPC (66.9%), NDM-1 (17.3%), and OXA-48 in Canada. In Latin America, the most frequently detected carbapenemases were KPC and IMP in *K. pneumoniae* isolates[34].

In Southeast Asia, the most common carbapenemases in *K. penumoniae* were NDM, other MBLs (IMP, VIM), and OXA-48[35]. In a multicenter (n= 36) study, in China, investigating carbapenemases in the *Enterobacteriaceae* family members (n= 935), 97.4% of the isolates had carbapenemases, and 51.6% of them were KPC-2 (most commonly in *K. pneumoniae* isolates; 64.6%). The others were NDM (35.7%), and OXA-48 (7.3%)[38].

In a surveillance study (ATLAS Programme) conducted in African (South Africa, Morocco, and Nigeria) and Middle Eastern countries (Israel, Kuwait, Jordan, Qatar, and Saudi Arabia), 6.2% of *Enterobacterales* (n= 5457) isolates produced at least one carbapenemase (n= 337; mostly, OXA-48 and OXA-181, in Africa), and almost half of them (n= 167) were MBL (mostly, NDM in Africa). OXA-232 and KPC dominated in the Middle East (primarily Qatar), and interestingly, Israeli strains had the lowest rate of carbapenemase production (0.9%)[39]. In Tunisia, VIM and NDM-1 were detected more frequently than KPC and IMP, with OXA-48 dominance in carbapenemase producing *Enterobacteriaceae*[40].

Table 2. Distribution of carbapenemases in Türkiye

Pathogen	Isolates (n)	Carbapenemase (%)	City	Isolation year	Reference
K. pneumoniae	42	OXA-48 (81), OXA-48 + NDM (11.9) OXA-48 + KPC (7.1), NDM, IMP, VIM (Ø)	Isparta	2018-2020	(41)
Enterobacterales	53	OXA-48 (58.4), OXA-48 + VIM (5.6), OXA-48 + SPM (3.7)	Adana, Ankara	2018-2019	(42)
K. pneumoniae	366	OXA-48 (52.2), KPC (16.4), NDM-1(15), OXA-48 + NDM-1 (12.6)	Multicenter (n= 28)	2019	(43)
K. pneumoniae	93	OXA-48 (100), OXA-48 + NDM-1 (2.1) KPC, IMP, VIM (Ø)	Ankara	2017-2019	(44)
K. pneumoniae	10	NDM (100), KPC (100)	Ankara	2018	(45)
K. pneumoniae	132	NDM (52.9), OXA-48 (39.2), KPC (2.0), OXA-48 + NDM-1 (5.9), IMP, VIM (Ø)	İstanbul	2017	(46)
Enterobacterales	75	OXA-48 (69.3), NDM-1 (22.6) VIM-5 (2.6), KPC, IMP(Ø)	İstanbul	2017	(47)
K. pneumoniae	50	OXA-48 (86), NDM (14)	Adana	2012-2016	(48)
K. pneumoniae	40	NDM (7.5)	Adana	2014	(49)
K. pneumoniae	124	OXA-48 (83.1), NDM (6.5), VIM (3.2), OXA-48 + NDM (2.4), OXA-48 + VIM (2.4), NDM + VIM (0.8) IMP (1.6)	Multicenter (n= 18)	2013-2014	(50)
K. pneumoniae	94	OXA-48 (91.5), NDM-1 (4.3) 0XA-48 + NDM-1 (1) IMP, KPC (Ø)	Kayseri	2013	(51)
Enterobacterales	112	OXA-48 (74.1), VIM (8.0) OXA-48 + VIM (6.3), NDM (1.7)	Ankara	2010-2014	(52)
K. pneumoniae	279	OXA-48 (96.7), IMP (0.3)	Ankara	2009-2013	(53)

The distribution of carbapenemases detected in CRKP isolates in Türkiye is shown in Table 2[41-53]. In Türkiye, the most frequently detected carbapenemases in CRKP isolates are predominantly OXA-48 and NDM, as well as KPC, VIM and IMP. Determination of the AMR mechanism in microbiology laboratories is not required for routine antimicrobial susceptibility testing. However, the correct direction of treatment is important for infection control measures, prevention of spread and surveillance.

CONCLUSION

The increase in multidrug resistant *K. pneumoniae* leads to an irrational use of carbapenems, which are considered as last resort antimicrobials, and this causes carbapenem resistance. The mechanisms of carbapenem resistance in *K. pneumoniae* isolates are associated with production of carbapenemases, production of ESBL and AmpC cephalosporinases with permeability defects, and activation of efflux pumps. Clinically important carbapenemases are KPC (Class A carbapenemases), VIM, IMP, NDM (Class B metallo-β-lactamases), and OXA-48 (Class D carbapenemases). In Türkiye, the most frequently detected carbapenemases in CRKP isolates are predominantly OXA-48 and NDM, as well as KPC, VIM and IMP. Determination of the AMR mechanism in microbiology laboratories is not required for routine antimicrobial susceptibility testing. However, the correct direction of treatment is important for infection control measures, prevention of spread and surveillance. MDR usually spreads among bacteria with the acquisition of resistance genes via mobile genetic elements (plasmids, transposons, and integrons). CRKP rates may be higher than previously reported in our national surveillance reports. Therefore, having local surveillance data is crucial.

CONFLICT OF INTEREST

The authors declare no competing interest. All the figures and tables in our article are originally created by the authors.

REFERENCES

1. *Wyres KL, Lam MMC, Holt KE. Population genomics of Klebsiella pneumoniae. Nat Rev Microbiol 2020;18:344-59. https://doi.org/10.1038/s41579-019-0315-1*
2. *ECDC. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022-2020 data. Avaliable from: https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2022-2020-data (Accessed date: 21 Aralık 2022).*
3. *WHO. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. Avaliable from: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed (Accessed date: 21 Aralık 2022).*
4. *T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü Bulaşıcı Hastalıklar ve Erken Uyarı Dairesi Başkanlığı. Ulusal sağlık hizmeti ilişkili enfeksiyonlar sürveyans ağı (USHİESA) özet raporu 2021. Avaliable from: https://www.researchgate.net/publication/364113964_ULUSAL_SAGLIK_HIZMETI_ILISKILI_ENFEKSIYONLAR_SURVEYANS_AGI_USHIESA_OZET_RAPORU_2021/stats (Accessed date: 21 Aralık 2022)*
5. *Aurilio C, Sansone P, Barbarisi M, Pota V, Giaccari LG, Coppolino F, et al. Mechanisms of action of carbapenem resistance. Antibiotics 2022;11:421. https://doi.org/10.3390/antibiotics11030421*
6. *Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: A system analysis. Lancet 2022;399:629-55. https://doi.org/10.1016/S0140-6736(21)02724-0*
7. *Lan P, Jiang Y, Zhou J, Yu Y. A global perspective on the convergence of hypervirulence and carbapenem resistance in Klebsiella pneumoniae. J Glob Antimicrob Resist 2021;25:26-34. https://doi.org/10.1016/j.jgar.2021.02.020*
8. *Codjoe FS, Donkor ES. Carbapenem resistance: A review. Medical Sciences (Basel) 2017;6:1. https://doi.org/10.3390/medsci6010001*
9. *Shields RK, Doi Y. Aztreonam combination therapy: An answer to Metallo-β-Lactamase-producing gram-negative bacteria? Clin Infect Dis 2020;71:1099-101. https://doi.org/10.1093/cid/ciz1159*
10. *Diene SM, Rolain JM. Carbapenemase genes and genetic platforms in gram-negative bacilli: Enterobacteriaceae, Pseudomonas and Acinetobacter species. Clin Microbiol Infect 2014;20:831-8. https://doi.org/10.1111/1469-0691.12655*
11. *Cortés-Ortíz IA, Juárez-Gómez JC, Cu-Quijano C, Flores-Paz R, Durán-Manuel EM, Cruz-Cruz C, et al. Klebsiella pneumoniae blaNDM-1 carrying a class 1 integron causing a hospital outbreak in a Mexican attention center. J Infect Dev Ctries 2021;15:657-64. https://doi.org/10.3855/jidc.12996*

12. *Evans BA, Amyes SG. OXA β-lactamases. Clin Microb Rev 2014;27:241-63. https://doi.org/10.1128/CMR.00117-13*

13. *Ahmed SS, Alp E, Ulu Kılıç A, Dinç G, Aktaş Z, Ada B, et al. Spread of carbapenem-resistant international clones of Acinetobacter baumannii in Turkey and Azerbaijan: A collaborative study. Eur J Clin Microbiol Infect Dis 2016;35:1463-8. https://doi.org/10.1007/s10096-016-2685-x*

14. *Wistrand-Yuen P, Olsson A, Skarp KP, Friberg LE, Nielsen EI, Lagerbäck P, et al. Evaluation of polymyxin B in combination with 13 other antibiotics against carbapenemase-producing Klebsiella pneumoniae in time-lapse microscopy and time-kill experiments. Clin Microbiol Infect 2020;26:1214-21. https://doi.org/10.1016/j.cmi.2020.03.007*

15. *Erdem F, Díez-Aguilar M, Oksuz L, Kayacan C, Abulaila A, Oncul O, et al. Time kill-assays of antibiotic combinations for multidrug resistant clinical isolates of OXA-48 carbapenemase producing Klebsiella pneumoniae. Acta Microbiol Immunol Hung 2022;69:215-9. https://doi.org/10.1556/030.2022.01785*

16. *Ghai I, Ghai S. Understanding antibiotic resistance via outer membrane permeability. Infect Drug Res 2018;11:523-30. https://doi.org/10.2147/IDR.S156995*

17. *Hamzaoui Z, Ocampo-Sosa A, Fernandez Martinez M, Landolsi S, Ferjani S, Maamar E, et al. Role of association of OmpK35 and OmpK36 alteration and blaESBL and/or blaAmpC genes in conferring carbapenem resistance among noncarbapenemase-producing Klebsiella pneumoniae. Int J Antimicrob Agents 2018;52:898-905. https://doi.org/10.1016/j.ijantimicag.2018.03.020*

18. *AlMatar M, Albarri O, Makky EA, Koksal F. Efflux pump inhibitors: New updates. Pharmacol Rep 2021;73:1-16. https://doi.org/10.1007/s43440-020-00160-9*

19. *Yahav D, Giske CG, Gramatniece A, Abodakpi H, Tam VH, Leibovici L. New β-lactam-β-lactamase inhibitor combinations. Clin Microbiol Rev 2021;34:e00115-20. https://doi.org/10.1128/CMR.00021-21*

20. *Lupia T, Corcione S, Shbaklo N, Montrucchio G, de Benedetto I, Valentina Fornari V, et al. Meropenem/Vaborbactam and Cefiderocol as combination or monotherapy to treat multi-drug resistant gram-negative infections: A regional cross-sectional survey from Piedmont Infectious Disease Unit Network (PIDUN). J Funct Biomater 2022;13:174. https://doi.org/10.3390/jfb13040174*

21. *Gaibani P, Giani T, Bovo F, Lombardo D, Amadesi S, Lazzarotto T, et al. Resistance to Ceftazidime/Avibactam, Meropenem/Vaborbactam and Imipenem/Relebactam in gram-negative MDR Bacilli: Molecular mechanisms and susceptibility testing. Antibiotics 2022;11:628. https://doi.org/10.3390/antibiotics11050628*

22. *Hujer AM, Bethel CR, Taracila MA, Marshall SH, Rojas LJ, Winkler ML, et al. Imipenem/Relebactam resistance in clinical isolates of extensively drug resistant Pseudomonas aeruginosa: Inhibitor-resistant β-Lactamases and their increasing importance. Antimicrob Agents Chemother 2022;66:e0179021. https://doi.org/10.1128/aac.01790-21*

23. *Gaibani P, Bianco G, Amadesi S, Boattini M, Ambretti S, Costa C. Increased blaKPC copy number and OmpK35 and OmpK36 porins disruption mediated resistance to Imipenem/Relebactam and Meropenem/Vaborbactam in a KPC-Producing Klebsiella pneumoniae clinical isolate. Antimicrob Agents Chemother 2022;66:e0019122. https://doi.org/10.1128/aac.00191-22*

24. *Hernández-García M, Castillo-Polo JA, Cordero DG, Pérez-Viso B, García-Castillo M, de la Fuente JS, et al. Impact of ceftazidime-avibactam treatment in the emergence of novel KPC variants in the ST307-Klebsiella pneumoniae high-risk clone and consequences for their routine detection. J Clin Microbiol 2022;60:e0224521. https://doi.org/10.1128/jcm.02245-21*

25. *World Health Organization. Surveillance of antimicrobial resistance in Europe, 2021 data. Avaliable from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2021-data (Accessed date: 21 Aralık 2022).*

26. *Aydın M, Azak E, Bilgin H, Menekse S, Asan A, Mert HTEM, et al. Changes in antimicrobial resistance and outcomes of health care-associated infections. Eur J Clin Microbiol Infect Dis 2021;40:1737-42. https://doi.org/10.1007/s10096-020-04140-y*

27. *Ergonul O, Aydin M, Azap A, Basaran S, Tekin S, Kaya S, et al. Healthcare-associated gram-negative bloodstream infections: Antibiotic resistance and predictors of mortality. J Hosp Infect 2016;94:381-5. https://doi.org/10.1016/j.jhin.2016.08.012*

28. *Agyeman AA, Bergen PJ, Rao GG, Nation RL, Landersdorfer CB. Mortality, clinical and microbiological response following antibiotic therapy among patients with carbapenem-resistant Klebsiella pneumoniae infections (a meta-analysis dataset). Data in Brief 2020;20:104907. https://doi.org/10.1016/j.dib.2019.104907*

29. *Ergonul O, Tokca G, Keske S, Donmez E, Madran B, Komur A, et al. Elimination of healthcare-associated Acinetobacter baumannii infection in a highly endemic region. Int J Infect Dis 2022;114:11-4. https://doi.org/10.1016/j.ijid.2021.10.011*

30. *Vatansever C, Menekse S, Dogan O, Gucer LS, Ozer B, Ergonul O, et al. Coexistence of OXA-48 and NDM-1 in colistin resistant Pseudomonas aeruginosa ST235. Emerg Microbes Infect 2020;9:152-4. https://doi.org/10.1080/22221751.2020.1713025*

31. *Boral B, Unaldi O, Ergin A, Durmaz R, Eser OK, Acinetobacter Study Group. A prospective multicenter study on the evaluation of antimicrobial resistance and molecular epidemiology of multidrug-resistant Acinetobacter baumannii infections in intensive care units with clinical and environmental features. Ann Clin Microbiol Antimicrob 2019;18:19. https://doi.org/10.1186/s12941-019-0319-8*

32. *Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in gram-negative bacteria. Clin Infect Dis 2019;69:521-8. https://doi.org/10.1093/cid/ciz824*

33. *Brolund A, Lagerqvist N, Byfors S, Struelens MJ, Monnet DL, Albigeret B, et al. Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018. Eur Surveill 2019;24:pii=1900123. https://doi.org/10.2807/1560-7917.ES.2019.24.9.1900123*

34. *Ludden C, Lötsch F, Alm E, Kumar N, Johansson K, Albiger B, et al. Cross-border spread of blaNDM-1- and blaOXA-48-positive Klebsiella pneumoniae: A European collaborative analysis of whole genome sequencing and epidemiological data, 2014 to 2019. Euro Surveill 2020;25:pii=2000627. https://doi.org/10.2807/1560-7917.ES.2020.25.20.2000627*

35. *Neidhöfer C, Buechler C, Neidhöfer G, Bierbaum G, Hannet I, Hoerauf A, et al. Global distribution patterns of carbapenemase encoding bacteria in a new light: Clues on a role for ethnicity. Front Cell Infect Microbiol 2021;11:659753. https://doi.org/10.3389/fcimb.2021.659753*

36. *Han R, Shi Q, Wu S, Yin D, Peng M, Dong D, et al. Dissemination of carbapenemases (KPC, NDM, OXA-48, IMP, and VIM) among carbapenem-resistant enterobacteriaceae isolated from adult and children patients in China. Front Cell Infect Microbiol 2020;10:314. https://doi.org/10.3389/fcimb.2020.00314*

37. *Karlowsky JA, Bouchillon SK, El Mahdy Kotb R, Mohamed N, Stone GG, Sahm DF. Carbapenem-resistant Enterobacterales and Pseudomonas aeruginosa causing infection in Africa and the Middle East: A surveillance study from the ATLAS programme (2018-20). JAC-Antimicrob Res 2022;4:dlac060. https://doi.org/10.1093/jacamr/dlac060*

38. *Dziri O, Dziri R, Ali El Salabi A, Chouchani C. Carbapenemase producing gram-negative bacteria in Tunisia: History of thirteen years of challenge. Infect Drug Resist 2020;13:4177-91. https://doi.org/10.2147/IDR.S259562*

39. *Köle M, Sesli Çetin E, Şirin MC, Arıdoğan BC. Seftazidim-avibaktam, meropenem ve kolistinin tek başına ve ikili kombinasyonlarının çeşitli klinik örneklerden izole edilen karbapenem dirençli Klebsiella pneumoniae suşlarına karşı in-vitro etkinliğinin araştırılması. Mikrobiyol Bul 2022;56:230-50. https://doi.org/10.5578/mb.20229804*

40. *Hortaç İştar E, Alışkan HE, Göçmen JS. Diverse efficacy of CarbaNP test among OXA-48 carbapenemase producing enterobacterales in an endemic region. Acta Microbiol Immunol Hung 2021;68:34-9. https://doi.org/10.1556/030.2021.01220*

41. *Süzük Yıldız S, Şimşek H, Bakkaloğlu Z, Çevik YN, Hekimoğlu CN, Kılıç S, et al. Türkiye'de 2019 yılı içinde izole edilen Escherichia coli ve Klebsiella pneumoniae izolatlarında karbapenemaz epidemiyolojisi. Mikrobiyol Bul 2021;55:1-16. https://doi.org/10.5578/mb.20124*

42. *Hazırolan G, Karagöz A. Emergence of carbapenemase-producing and colistin resistant Klebsiella pneumoniae ST101 high-risk clone in Turkey. Acta Microbiol Immunol Hung 2020;67:216-21. https://doi.org/10.1556/030.2020.01275*

43. *Tekeli A, Dolapci İ, Evren E, Oguzman E, Karahan ZC. Characterization of Klebsiella pneumoniae coproducing KPC and NDM-1 carbapenemases from Turkey. Microb Drug Resist 2020;26:118-25. https://doi.org/10.1089/mdr.2019.0086*

44. *Sağıroğlu P, Hasdemir U, Altınkanat Gelmez G, Aksu B, Karatuna O, Söyletir G. Performance of "RESIST-3 O.K.N. K-SeT" immunochromatographic assay for the detection of OXA-48 like, KPC, and NDM carbapenemases in Klebsiella pneumoniae in Turkey. Braz J Microbiol 2018;49:885-90. https://doi.org/10.1016/j.bjm.2018.02.002*

45. *Cizmeci Z, Aktas E, Otlu B, Acikgoz O, Ordekci S. Molecular characterization of carbapenem-resistant Enterobacteriaceae yields increasing rates of NDM-1 carbapenemases and colistin resistance in an OXA-48-endemic area. J Chemother 2017;29:344-50. https://doi.org/10.1080/1120009X.2017.1323149*

46. *Erdem F, Oncul O, Aktas Z. Characterization of resistance genes and polymerase chain reaction-based replicon typing in carbapenem-resistant Klebsiella pneumoniae. Microbial Drug Res 2019;25:551-7. https://doi.org/10.1089/mdr.2018.0231*

47. *Guven Gokmen T, Nagiyev T, Meral M, Onlen C, Heydari F, Koksal F. NDM-1 and rmtC-producing Klebsiella pneumoniae isolates in Turkey. Jundishapur J Microbiol 2016;9:e33990.https://doi.org/10.5812/jjm.33990*

48. *Çakar A, Akyön Y, Gür D, Karatuna O, Öğünç D, Özhak Baysan B, ve ark. Türkiye'de 2014 yılı içinde izole edilen karbapeneme dirençli Escherichia coli ve Klebsiella pneumoniae izolatlarında karbapenemaz varlığının araştırılması. Mikrobiyol Bul 2016;50:21-33. https://doi.org/10.5578/mb.10695*

49. *Alp E, Perçin D, Colakoğlu S, Durmaz S, Kürkçü CA, Ekincioğlu P, et al. Molecular characterization of carbapenem-resistant Klebsiella pneumoniae in a tertiary university hospital in Turkey. J Hosp Infect 2013;84:178-80.https://doi.org/10.1016/j.jhin.2013.03.002*

50. *Kutlu HH, Us E, Tekeli A. Bir üniversite hastanesinde 2010-2014 yılları arasında izole edilen Enterobacteriaceae türlerinin karbapenemaz genlerinin araştırılması ve moleküler epidemiyolojisinin belirlenmesi. Mikrobiyol Bul 2018;52:1-12. https://doi.org/10.5578/mb.66156*

51. *Zarakolu P, Eser OK, Aladag E, Al-Zahrani IA, Day KM, Atmaca O, et al. Epidemiology of carbapenem-resistant Klebsiella pneumoniae colonization: A surveillance study at a Turkish university hospital from 2009 to 2013. Diagn Microbiol Infect Dis 2016;85:466-70. https://doi.org/10.1016/j.diagmicrobio.2016.05.012*

52. *Kutlu HH, Us E, Tekeli A. Bir üniversite hastanesinde 2010-2014 yılları arasında izole edilen Enterobacteriaceae türlerinin karbapenemaz genlerinin araştırılması ve moleküler epidemiyolojisinin belirlenmesi. Mikrobiyol Bul 2018;52:1-12. https://doi.org/10.5578/mb.66156*

53. *Zarakolu P, Eser OK, Aladag E, Al-Zahrani IA, Day KM, Atmaca O, et al. Epidemiology of carbapenem-resistant Klebsiella pneumoniae colonization: a surveillance study at a Turkish university hospital from 2009 to 2013. Diagn Microbiol Infect Dis 2016;85:466-70. https://doi.org/10.1016/j.diagmicrobio.2016.05.012*

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