MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Journal of Infectious Diseases & Travel Medicine
ISSN: 2640-2653

The Epidemiology and Molecular Aspect of Carbapenemase Producing Enterobactericiae (CPE). A Review

Sahile Z[1]* and Shenkute D[2]

[1]Department of Medical Laboratory Science, Debre Berhan Health Science College, Ethiopia
[2]Department of Medical Laboratory Science, Debre Berhan University, Ethiopia

***Corresponding author:** Zenawork Sahile, Department of Medical Laboratory Science, Debre Brehan Health Science College, PO.Box: 37, Debre Berhan, Ethiopia, Tel: +251915536212; Fax: +251116814296; Email: zenasahle@gmail.com

Review Article
Volume 6 Issue 1
Received Date: May 30, 2022
Published Date: June 09, 2022
DOI: 10.23880/jidtm-16000161

Abstract

Carbapenems are the last line of defense against Gram-negative and Gram-positive bacteria that cause serious infections. Although they are resistant to most B-lactamases, the presence of carbapenem hydrolyzing enzymes known as carbapenemase has put their use as a last-resort antibiotic in jeopardy. These enzymes are produced most frequently by Enterobacteriaceae. True carbapenemase in Ambler molecular classes A, B, and D are frequently expressed by genes found in mobile genetic elements such plasmids, integrons, and transposons, which frequently contain many resistance determinants, further limiting treatment options. The worldwide development of carbapenem-resistant Gram-negative bacteria has resulted in a large number of nosocomial and community-acquired illnesses, which has become a major public health issue. In vitro evidence of the advantages of combination schemes against polymyxins is still available while polymyxins are still available.

Keywords: OXA-48; OXA-181; Metallo-ß-lactamase; Antimicrobial Activities; Carbapenemases; Enterobacteriaceae

Introduction

Carbapenemase Resistance

Carbapenems are antibiotics that belong to the B-lactam class and are frequently used as last-resort medicines to treat infections caused by multidrug-resistant Enterobacteriaceae. Carbapenem resistance in Enterobacteriaceae bacteria is becoming a severe public health issue around the world. Sporadic outbreaks or endemic circumstances of antibiotic-resistant enterobacterial isolates [1].

The most important determinants sustaining carbapenem resistance are integrin acquired class A Klebsiella pneumoniae carbapenemases (KPC), class B (Imipenemase IMP, Verona Integron-encoded Metallo-ß-lactamase VIM, New Delhi Metallo-ß-lactamase NDM), or class D Oxacillinase of type (OXA-48, OXA-181) carba The related genes are typically found on plasmids and are linked to a variety of mobile genetic structures (insertion sequences, integrons, and transposons), allowing them to spread even more widely [2].

Carbapenems, such as imipenem and meropenem, are most commonly used to treat infections caused by Enterobacteriaceae that produce extended-spectrum beta-lactamases; hence the development of enzymes capable of inactivating carbapenems would limit treatment options [3].

Carbapenem-resistance Mucoid is one of the most common recognized nosogens that causes urinary tract infections, wound infections, and septicemia in

immunocompromised people. Enterobacteriaceae (CRE), which includes Klebsiella pneumoniae, is frequently mucoid-positive [4]. CRE can lead to treatment failure, posing a substantial public health risk [5]. Antimicrobial resistance genes (ARGs) can be transferred to other bacterial species, resulting in the production of various enzymes (such as beta-lactamases) that inactivate antimicrobial activities; the types of enzymes produced by carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CP-CRE) include clavulanic-acid-inhibited-lactamases [3].

Carbapenemases found in Enterobacteriaceae are different from extended spectrum B-lactamase (ESBL) in that they efficiently hydrolyze carbapenems. With the notable exception of certain Guiana carbapenemases, the protein structure of carbapenemases differs greatly from that of ESBLs in most situations. Extended spectrum B-lactamase (GES) and OXA-48-type ß-lactamases with ESBL activity that may have point-mutant equivalents [6]. Carbapenemase producers are currently the most serious clinical issue in antibiotic resistance in Gram negative bacteria, especially in Enterobacteriaceae [7].

Burden of Carbapenemase Resistance

The incidence of blaKPC within K. pneumoniae isolates reached at 36%, according to the CDC's Intensive Care Antimicrobial Resistance Epidemiology (ICARE) [8]. The annual incident CRE cases/100,000 population in seven US localities was reported to range from 0.35 to 4.80, with an overall estimate of 2.94 annual incident CRE cases/100,000 populations [9]. A CPE was found in 21 percent of people in a multi-national observational research spanning seven Latin American countries (Argentina, Colombia, Ecuador, Guatemala, Mexico, Peru, and Venezuela) (83 percent) [10]. Patients in numerous Indian and Pakistani hospitals have been colonized with blaNDM-producing bacteria at an increasing rate, with reported carriage rates ranging from 2% to 13.5 percent in intensive care units [11]. Carbapenem resistance genes in South Africa 42 percent, 10 percent, and 6 percent for blaNDM-1, blaKPC, and blaOXA-48, respectively. The ambler class A genes, such as blaKPC, are the most commonly identified carbapenem genes, followed by class B metallo-beta lactamases (MLBs), such as blaNDM, and class D OXA-type genes, such as blaOXA-48. KPC enzymes are the most clinically important carbapenemases in the world right now [12].

KPC, which was found in 15% of East Africans, was the most common CRE gene. IMP (21.6%), VIM (12.3%), OXA-48 (4.9%), KPC (3.5%), and NDM were found to be the most common CR genes in Tanzania (3.1 percent) [13]. In various parts of Latin America, such as Colombia and Argentina, KPC manufacturers are endemic. KPC producers may be found practically everywhere in Europe, and are frequently linked to imports from endemic areas. Greece and Italy are European endemic areas. Numerous healthcare-related findings, as well as few community-acquired cases, have indicated the endemicity of KPC producers in Israel [1]. ST 258, a K. pneumoniae clone that produces KPC-2 or KPC-3, has been widely detected throughout the world. Despite the fact that NmcA was the first carbapenemase sequenced in Enterobacteriaceae in the 1990s, other forms of class a carbapenemases (NmcA, SME, IMI, GES) still have a local distribution, with GES-type ß-lactamases having a more specific distribution in South America [6]. Despite being found all over the world, VIM producers in Enterobacteriaceae are most common in Southern Europe and the Mediterranean, while IMP producers are usually found in Asia [7].

Molecular Classification (Type) of Carbapenemase

Carbapenemases are divided into two groups based on their active sites , serine carbapenemases belonging to class A penicillinases and class D oxacillinases, which have a serine in the active site and can be inactivated by b-lactamase inhibitors such as clavulanic acid and tazobactam; and Metallo-b-lactamases belonging to class B carbapenemase EDTA stops these enzymes from working.

Class a Carbapenemase

Some are chromosomal encoded (NmcA, SME, IMI-1, SFC-1), while others are plasmid encoded (KPC, IMI-2, GES, variants), but all successfully hydrolyze carbapenems and are somewhat inhibited by clavulanic acid. KPCs are the most widely used enzymes in clinical practice [14]. KPC and GES enzymes are plasmid-encoded, whereas SME, NMC, and IMI enzymes are chromosomally encoded. SME (Serratia marcescens) enzymes are normally found only in Serratia marcescens, although IMI and NMC enzymes have been found in Enterobacter cloacae on rare occasions. The genes for KPC enzymes, on the other hand, are present on transferable plasmids and are quite common, mostly in K. pneumoniae but also in other Enterobacteriaceae. K. pneumoniae integrons on transferable plasmids include the genes for GES enzymes [6,15].

KPC-2 and KPC-3 are the most widely identified of the 20 known KPC variations. They hydrolyze expanded-spectrum cephalosporins as well as all carbapenems, unlike other class A carbapenemases. KPC-lactamases are inhibited only weakly by clavulanic acid and tazobactam, and they are frequently coharbored with OXA-1, affording resistance to -lactam inhibitor combinations. They are encoded on

transferable plasmids and are not inducible. The major genetic structure promoting the spread of blaKPC-type genes has been identified as a 10-kb Tn3-type transposon Tn4401 with two insertion sequences ISKpn6 and ISKpn7. The blaKPC gene was recently discovered to be chromosol integrated in K. pneumoniae, allowing for easier gene maintenance in bacterial populations. The successful clone Klebsiella [16,17].

Class B Metallo-β-Lactamases

The IMP, VIM, GIM, SIM, and NDM enzymes are class B metallo-b-lactamases, and their genes are mostly found in Enterobacteriaceae transferable plasmids. This family of enzymes catalyzes -lactam hydrolysis by forming nucleophilic hydroxide, which attacks the -lactam ring further. The metallo-lactamases are further split into subclasses (B1, B2, and B3), however the B1 subclass contains the majority of clinically significant MBLs, including the Verona integron-encoded MBL (VIM), imipenemase (IMP), and New Delhi MBL (NDM). Those MBLs are frequently found within diverse integron structures, which are linked to mobile plasmids or transposons, allowing resistance genes to be transferred across bacteria [6,17,18,19].

The imipenem resistance conferring -lactamase was called IMP-1 and was found on a conjugative plasmid. This enzyme's gene was found on the class 1 integron. IMP-5 was more homologous to IMP-1, IMP-3, and IMP-4 than IMP-2. BlaIMP-5 was the lone gene cassette introduced into an In76 transfer of resistance genes between bacteria class 1 integron.

VIM enzyme is a member of another common family of integron-associated metallo-lactamases. The BlaVIM-1 gene was repeatedly found within the class1 integron, demonstrating its importance in the spread of IMP and VIM genes not only in non-fermentative bacteria but also in Enterobacteriaceae. The enzyme was chromosomally encoded and varied from VIM-1 in two amino acids, C178A and A443G, respectively. VIM-4-lactamases were discovered in K. pneumoniae and Enterobacter cloacae isolates from an Italian patient who had previously been treated with carbapenems. VIM-4 differs from VIM-1 in one amino acid (S228A), making it more active against imipenem. VIM-1 and VIM-4 enzymes are frequently carried on incompatibility group NorA/C plasmids in E.cloacae and K.pneumoniae, especially of ST147 and 11 [12,20,21].

Huge conjugative plasmids bearing the blaNDM genes can have up to 14 different antibiotic resistance determinants and can transmit this resistance to other bacteria, resulting in multidrug resistance or pan-drug resistance phenotypes [17].

Transposon Tn125 with two flanking ISAba125 elements, commonly truncated in Enterobacteriaceae and part of broad-host-range plasmid containing IncA/C, is the most common genetic platform for the blaNDM gene (predominant plasmid type). NDM producers have been identified as a source of community-acquired infections because they can acquire additional -lactamases, including carbapenemases [22]. GIM–MBL possesses two zinc ions in the active site, unlike other class B carbapenemase [23].

Class D Enzymes of the OXA-48 Type

The hydrolytic activity of these enzymes toward oxacillin is their key feature, and their genes can be found on both plasmids and chromosomes. OXA enzymes were recently classified into 12 sub-groups: OXA-23-like, OXA-24/40-like, and OXA-45-like. OXA-48, OXA-51-like, OXA-58-like, OXA-143-like, OXA-253, OXA-211, OXA-213, OXA-214, OXA-229, and OXA-235 are all OXA-48-like, OXA-51-like, OXA-58-like [17]. OXA-48-lactamase was discovered in a Klebsiella pneumoniae strain. Not just in Klebsiella pneumoniae, but also in other Enterobacteriacea, it is currently ubiquitous. The BlaOXA-48 gene is found in the IncL/M plasmid pOXA-48. This plasmid has a high conjugation rate and is self-conjugative, which helps to explain why OXA-48 enzymes are so widely used around the world [6]. The IS1999 insertion sequence positioned upstream of the Tn1999 transposon, which is commonly present on L/M plasmids, aids in the propagation of the blaOXA-48 gene [24].

OXA-48 hydrolyzes carbapenems at a low level, has very little activity against expanded-spectrum cephalosporins, and does not hydrolyze ceftazidime or cefepime appreciably, but when combined with impermeability, can lead to high-level carbapenem resistance [25]. Despite the fact that multiple class C carbapenemases have been identified (ACT-1, CMY-2, CMY-10, and ADC-68), their producers frequently have reduced carbapenem susceptibility due to low enzyme catalytic efficiency and permeability defect. However, its clinical significance is uncertain [26].

Molecular Mechanisms of Carbapenemase Resistance

Carbapenem resistance is significantly linked to carbapenemase production (carbapenemase gene acquisition), porin loss in combination with extended-spectrum-lactamases (ESBLs), and efflux pump overexpression. KPC,NDM,VIM, IMP, and OXA, which are encoded by blaKPC, blaNDM, blaVIM, blaIMP, and blaOXA genes present in both the plasmid and the chromosome, are the most common carbapenemases resistant encoding genes [27].

Resistance to most -lactams, fluoroquinolones, and aminoglycosides has been observed in bacteria generating carbapenemases KPC and NDM. However, carbapenemases of the OXA type, namely OXA-48-like carbapenemases, are less active against carbapenems and can only cause a significant level of resistance when combined with extended-spectrum antibiotics. The IMI/NMC, SME, KPC, and GES enzymes hydrolyze the beta –lactamase and OXA b-lactamases for 'oxacillin-hydrolysing,' and their genes are present both on plasmids and in the chromosome. Only GES-2, GES-4, GES-5, GES-6, GES-14, and GES-18 have been documented to exhibit enzymatic activity against carbapenemase [17].

Possible Genes in the Future for Carbapenemase Resistance

Many reports from the Indian subcontinent describe isolates generating OXA-181, NDM-1, and VIM enzymes. Shewanella xiamenensis was recently identified as the origin of the blaOXA-181 gene in a recent study. As a result, it's thought that a chromosomal gene was mobilized to plasmid and then distributed in clinically important species. This highlights the continual interaction of microbes in the environment, community, and clinics. MBL variations (VIM-42, 43, 44, and 45, IMP-48 and -49, and NDM-16), which differ by one amino acid from previously reported enzymes, show that the genetic background of these widely distributed enzymes is still active [7,28].

Challenges and Future Perspective

Enterobacteriaceae carbapenemase producers vary from other multidrug-resistant bacteria in that they are vulnerable to few (if any) antibacterial medicines.

The following are the key characteristics of these enzymes' epidemiology:

The major reservoir is the first parameter to consider. Indeed, a specific enzyme is very likely to arise in a given geographical location where numerous favorable factors exist, such as a dense population, poor hygiene, and significant selective pressure connected to antibiotic abuse and misuse. The second parameter involves the carbapenemase gene's genetics, as certain genetic structures are known to promote gene plasticity and mobility. Some plasmids and integron or transposon architectures may really favor horizontal gene transfer. Some plasmids have a broad host range for replication, which can help with interspecies spread, while others have a limited host range. Some plasmids replicate quickly and are self-conjugative, while others are not self-conjugative or conjugate at a slow rate. The degree of human population exchanges after a reservoir has been established is the third important parameter. If a carbapenemase emerges in a geographical location where the population is mobile (a large worldwide diaspora, tourism, or medical tourism), the likelihood of seeing that resistance determinant evolve globally is significant, as previously reported enzymes have shown (Table 1).

Drugs		Mechanism of Action	Limitation
Old antibiotics	Fosfomycin	Cell wall synthesis inhibitor	Appearance of resistance
	Aminoglycosides	Protein synthesis inhibitor	Appearance of resistance
	Colistin	Cell membrane disruptor	Nephrotoxicity
	Tigecycline	Protein synthesis inhibitor	Low concentration in tissue
Dual therapy	Meropenem/	Cell wall inhibitor	Insufficient clinical data
	Vaborbactam		
	Plazomicin	Protein synthesis inhibitor	Insufficient clinical data
Novel drug	Eravacycline	Protein synthesis inhibitor	Currently in clinical trials
	Imipenem/relebactam	Cell wall inhibitor	Currently in clinical trials

Table 1: Current and future treatment options for infections caused by CRE.

How CPE Disseminate Among Humans, Animals and Environment

CPE-from Human

Incidences of blaNDM, blaKPC, blaOXA-48, and blaVIM-producing K. pneumoniae and Enterobacter spp. increased dramatically, according to data from the Nosocomial Infection Surveillance Program. Patients could disseminate CPE over multiple locations by using health-care facilities as a reservoir. Many European nations, including Greece, Italy, Spain, France, and Germany, have reported blaKPC-producing K.pneumonia outbreaks in hospitals.

In a recent investigation, blaNDM-1 and blaKPC-2-producing K. pneumonia were found in transplanted patients in Brazil. Carbapenemases have been linked to multidrug resistance genes on the same MGEs. The blaKPC gene, which encodes the KPC enzyme that hydrolyzes all -lactams, was discovered on plasmids containing numerous additional antimicrobial resistance determinants. In North America, Europe, Asia, and South America, outbreaks caused by multidrug-resistant and blaKPC-positive K. pneumoniae opportunistic pathogenic strains have been recorded [12].

Arecent study from China reported a Morganell morgana isolate, an opportunistic pathogen, harboring blaNDM-5 gene on a self-transmissible IncX3 plasmid from a stool sample of a cancer patient [29].

Although, little is known about the spread and clinical relevance of CRE in Africa, two studies reported their prevalence in hospital and community settings among several African [23].

CPE-from Companion Animals

Carbapenems are not licensed for the treatment of infectious diseases in companion animals in most of countries. As a result, pathogenic strains of Enterobacteriaceae causing infections in companion animals are not usually screened for carbapenemase resistance genes in veterinary laboratories. The possible way companion animals may get infected with CRE is through direct contact with colonized hosts and contaminated environment. Eventually, companion animal may become a reservoir for CPE [2].

For instance, a blaOXA-48 carbapenemase-producing K. pneumoniae has been transmitted from human to companion animals (dogs) through contaminated hands. Identification of CPE in companion animals could become significant for public health due to not only host-to-host transmission but also possible gene transfers between commensals and pathogens. Due to selection pressure, treated animals (pets) may become colonized with CPE that could be transmitted to human through fecal – oral contaminations.

CPE-from the Environment

As discussed above, several studies demonstrate the spread of CPE all around the world among humans and animals. However, there are very few reports on the role of environmental contamination in the spread of CPE. The environment, surrounded by the CPE carriers, may be contaminated with these bacteria and further act as a vector for their dissemination. Dissemination of environmental CPE (eCPE) can negatively impact human health. The prevalence rate of eCPE is high especially around intensive care units, acute and long-term health care facilities. Exposure of health care personnel to infected patients and cleaning methods used in the health facilities could potentially be responsible for dissemination of eCPE [30].

A study from Egypt investigated the occurrence of β-lactamase and CRE in the integrated agriculture–aquaculture environment and isolated several *Enterobacteriaceae* strains resistant carrying predominantly the carbapenemase resistant gene blaKPC either alone or with the β-lactamase genes (blaCTX-M-15, blaSHV, blaTEM, and blaPER-1). This study suggests transmission of the resistance genes among Enterobacteriaceae strains in integrated agriculture–aquaculture system with serious public health implication [31].

The Predisposing Risk Factor for CPE

CPE is high in humans with advanced age, primarily, due to their frequent visits to hospitals, long-term stay in health care, ICU patients showing new emerging mechanisms of resistance continue to rise in the United States of America [32]. Another important factor responsible for worldwide dissemination of CRE is the international travelling and medical tourism. There are several reports demonstrating the role of travelling to affected developed countries in the epidemiology of CRE. Pathogenic strains of K. pneumoniae and Enterobacter cloacae containing blaKPCs have been isolated from patients from France and Greece hospitalized in New York. Overcrowding coupled with poor sanitation conditions including inappropriate waste management system and misuse of antibiotics could play roles in the spread of antimicrobial resistance genes in general and those for carbapenemase in particular. Furthermore, urbanization and globalization are greatly involved in spreading antimicrobial resistance pathogens all over the world [33-35].

The Way Forward To Control Carbapenemase Resistance or Treatment Options

The implementation of screening and isolation measures is more effective if the diagnosis of colonization is made at an early stage. The recommendations may also apply for the prevention of the spread of NDM or OXA-48 producers in *Enterobacteriaceae*, since person-to-person transmission through the hands of nursing and medical staff is the main route of dissemination of these resistant bacteria. The role of the contaminated environment is probably less important. Adherence to contact precaution

- Appropriate use of gown and gloves by healthcare staff for all interactions involving contact with the patient or the patient's environment.
- Isolation of carrier patients in single-patient rooms, or if not available, then cohorting of patients with the same

carbapenemase producers.

- Individual patient use of non-critical medical equipment or disposable medical items (e.g., blood pressure cuffs, disposable stethoscopes).

Antimicrobial agents currently used for treatment of infections caused by carbapenem-resistant Enterobacteriaceae (CRE) include carbapenem combinations, polymyxins, fosfomycin, tigecycline, aminoglycosides, ceftazidime—avibactam, and meropenem–vaborbactam. Trials supporting their clinical use are scarce, and many of the agents are limited by toxicities and pharmacokinetics disadvantages. New beta-lactamase combinations have been made available within the last few years, and early results suggest they are safer and more efficacious for the treatment of CRE infections compared with some of the older agents, particularly polymyxin regimens. Furthermore, new treatments with activity against CRE are currently being studied to help mitigate the threat of resistance. Meropenem/vaborbactam (Melinta) is also a new ß-lactam/ß-lactamase inhibitor consisting of a carbapenem and a novel boron-containing serine-ß-lactamase inhibitor that potentiates the activity of meropenem [6,36].

Conclusion

The carbapenemase *KPC, IMP, VIM, NDM,* and *OXA* types have been mainly reported in nosocomial K.pneumoniae strains. Pathogenic E.coli strains carrying *bla*NDM-1 and *bla*OXA-48 genes also have been found in community acquired infections. Therefore, proper identification and surveillance programs of carbapenem resistance pathogens and non-pathogenic strains have become necessary to support the control of CRE infections in both animals and humans. Source attribution studies along with developing alternative infection control strategies are warranted.

Author Contributions

All authors contributed significantly to the conception, article writing and revision as well as decisions to the journal to which the article would be submitted, gave final approval to the version for publication, and agreed to be accountable for all aspects of the work.

Funding

This study did not receive any funding in any form.

Disclosure

The authors report no conflicts of interest.

References

1. Nordmann P, Poirel L (2019) Epidemiology and diagnostics of carbapenem resistance in gram negative bacteria. Clinical Infectious Diseases 69(7): S521-S528.
2. Cheng VCC, Wong SC, Wong SCY, Ho PL, Yuen KY, et al. (2019) Control of Carbapenemase-producing Enterobacteriaceae: Beyond the hospital. EClinicalMedicine 6(2): 3-4.
3. Ebomah KE, Okoh AI (2020) Detection of Carbapenem-Resistance Genes in Klebsiella Species Recovered from Selected Environmental Niches in the Eastern Cape Province, South Africa. Antibiotics 9(7): 425.
4. Muntean MM, Muntean AA, Popa MI (2017) Carbapenemases in Enterobacteriaceae–overview and importance. Infectio ro (49): 13-16.
5. Bush K (2015) A resurgence of β-lactamase inhibitor combinations effective against multidrug-resistant Gram-negative pathogens. Int J Antimicrob Agents 46(5): 483-493.
6. Poirel PPNDL (2020) Carbapenem Resistance From diagnosis to outbreak management.
7. Taggar G, Attiq Rheman M, Boerlin P, Diarra MS (2020) Molecular Epidemiology of Carbapenemases in Enterobacteriales from Humans, Animals, Food and the Environment. Antibiotics (Basel) 9(10): 693.
8. Van Duin D, Doi Y (2017) The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence 8(4): 460-469.
9. Guh AY, Bulens SN, Mu Y, Jacob JT, Reno J, et al. (2015) Epidemiology of carbapenem-resistant Enterobacteriaceae in 7 US communities, 2012-2013. Jama 314(14): 1479-1487.
10. Villegas MV, Pallares CJ, Escandón-Vargas K, Hernández-Gómez C, Correa A, et al. (2016) Characterization and clinical impact of bloodstream infection caused by carbapenemase-producing Enterobacteriaceae in seven Latin American countries. PLoS One 11(4): e0154092.
11. Bharadwaj R, Joshi S, Dohe V, Gaikwad V, Kulkarni G, et al. (2012) Prevalence of New Delhi metallo-β-lactamase (NDM-1)-positive bacteria in a tertiary care centre in Pune, India. Int J Antimicrob Agents 39(3): 265-266.
12. Nordmann P, Naas T, Poirel L (2011) Global spread of carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis 17(10): 1791-1798.
13. Ssekatawa K, Byarugaba DK, Wampande E, Ejobi F (2018) A systematic review: the current status of carbapenem

resistance in East Africa. BMC Res Notes 11(1): 629.

14. Djahmi N, Dunyach-Remy C, Pantel A, Dekhil M, Sotto A, et al. (2014) Epidemiology of carbapenemase-producing Enterobacteriaceae and Acinetobacter baumannii in Mediterranean countries. Biomed Res Int 2014: 305784.

15. Cantón R, Akóva M, Carmeli Y, Giske CG, Glupczynski Y, et al. (2012) Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect 18(5): 413-431.

16. Pitout JD, Nordmann P, Poirel L (2015) Carbapenemase-producing Klebsiella pneumoniae, a key pathogen set for global nosocomial dominance. Antimicrob Agents Chemother 59(10): 5873-5884.

17. Diene SM, Rolain JM (2014) Carbapenemase genes and genetic platforms in Gram-negative bacilli: Enterobacteriaceae, Pseudomonas and Acinetobacter species. Clin Microbiol Infect 20(9): 831-838.

18. Nordmann P, Poirel L (2002) Emerging carbapenemases in gram-negative aerobes. Clin Microbiol Infect 8(6): 321-331.

19. Arakawa Y, Murakami M, Suzuki K, Ito H, Wacharotayankun R, et al. (1995) A novel integron like-element carrying the metallo-β-lactamase gene blaIMP. Antimicrob Agents Chemother 39(7): 1612-1615.

20. Mojica MF, Bonomo RA, Fast W (2016) B1-metallo-β-lactamases: Current Drug Targets 17(9): 1029-1050.

21. Arabaghian H, Salloum T, Alousi S, Panossian B, Araj GF, et al. (2019) Molecular characterization of carbapenem resistant Klebsiella pneumoniae and Klebsiella quasipneumoniae isolated from Lebanon. Sci Rep 9(1): 1-12.

22. Khan AU, Maryam L, Zarrilli R (2017) Structure, genetics and worldwide spread of New Delhi metallo-β-lactamase (NDM): A treat to public health. BMC Microbiol 17(1): 101.

23. Manenzhe RI, Zar HJ, Nicol MP, Kaba M (2015) The spread of Carbapenemase-producing bacteria in Africa. A systematic review. J Antimicrob Chemother 70(1): 23-40.

24. Pfeifer Y, Schlatterer K, Engelmann E, Schiller RA, Frangenberg HR, et al.(2012) Emergence of OXA-48-type carbapenemase-producing Enterobacteriaceae in German hospitals. Antimicrob Agents Chemother 56(4): 2125-2128.

25. Gülmez D, Woodford N, Palepou MF, Mushtaq S, Metan G, et al. (2008) Carbapenem resistant Escherichia coli and Klebsiella. Int J Antimicrob Agents 31(6): 523-526.

26. (2018) Pneumoniae isolates from Turkey with OXA-48 like carbapenemase and outer membrane protein loss. Journal of Antimicrobial Agents.

27. Meletis G (2016) Carbapenem resistance: Overview of the problem and future perspectives. Ther Adv Infect Dis 3(1): 15-21.

28. Tian X, Zheng X, Sun Y, Fang R, Zhang S, et al. (Molecular Mechanisms and Epidemiology of Carbapenem-Resistant Escherichia coli Isolated from Chinese Patients. Infect Drug Resist 13: 501-512.

29. Bouganim R, Dykman L, Fakeh O, Motro Y, Oren R, et al. (2020) The Clinical and Molecular Epidemiology of Noncarbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae: A Case-Case-Control Matched Analysis. Open Forum Infect Dis 7(8): ofaa299.

30. Jin C, Zhang J, Wang Q, Chen H, Wang X, et al. (2018) Molecular characterization of carbapenem-resistant Enterobacter cloacae in 11 Chinese cities. Front Microbiol 9: 1597.

31. Lerner A, Adler A, Abu-Hanna J, Meitus I, Navon-Venezia S, et al. (2012) Environmental contamination by Carbapenem-resistant Enterobacteriaceae. Journal of Clinical Microbiology 51: 177-181.

32. Hamza D, Dorgham S, Ismael E, El-Moez SIA, Elhariri M, et al. (2020) Emergence of β-lactamase-and Carbapenemase-producing Enterobacteriaceae at integrated fish farms. Antimicrob Resist Infect Control 9(1): 67.

33. Tamma PD, Kazmi A, Bergman Y, Goodman KE, Ekunseitan E, et al. (2019) The likelihood of developing a Carbapenem-resistant infection during the hospital stay. Antimicrob Agents Chemother 63(8): e00757-19.

34. Naas T, Nordmann P, Vedel G, Poyart C (2005) Plasmid-mediatedCarbapenem-hydrolyzingβ-Lactamase KPC-2 in a Klebsiella pneumoniae isolate from France Antimicrob Agents Chemother 49(10): 4423-4424.

35. Swaminathan M, Sharma S, Poliansky Blash S, Patel G, Banach DB, et al. (2013) Prevalence and risk factors for acquisition of carbapenem-resistant Enterobacteriaceae in the setting of endemicity. Infect Control Hosp Epidemiol 34(8): 809-817.

36. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A (2018) Treatment of Infections Caused by Extended-Spectrum-BetaLactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clin Microbiol Rev 31(2): e00079-e000117.