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Carbapenemases, types and epidemiology: A review

Fatima Moeen Abbas[1]* and Murtadha Hamza Ajeel[2]
[1]Dep.of Biology, College of Sciences for Women, University of Babylon, Iraq and
[2]Alhussain Military Hospital, Medical affairs Directorate, Ministry of defense, Iraq.
***Corresponding author: fatima.abas99@yahoo.com**
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Abstract
Resistance to antibiotics is one of the critical threat to public health worldwide. Carbapenems are antibiotics that provide a potential defense against a wide variety of bacteria and represent the last resort of therapy for serious infections. Carbapenem-hydrolyzing enzymes also known carbapenemases which are a set of diverse enzymes belong to β-lactamases, their genes are carried on both plasmids and chromosomes. These enzymes hydrolysis various β-lactam antibiotics including carbapenem, penicillin, cephalosporins and azteronam. The worldwide dissemination of bacteria resistant to carbapenem has resulted in in a great number of nosocomial and community acquired infections. The most important bacterial strains carrying carbapenemases are *Enterobacteriaceae* and non-fermenter bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
Keywords: Antibiotics resistance, carbapenem, carbapenemases, β lactamases.

الكاربابنيمز (Carbapenemases) الأنواع والوبائية: مراجعة

فاطمة معين عباس[1]* و مرتضى حمزة عجيل[2]
[1]قسم البايولوجي / كلية العلوم للبنات / جامعة بابل و [2]مستشفى الحسين العسكري / مديرية الشؤون الطبية / وزارة الدفاع / العراق.
***Corresponding author: fatima.abas99@yahoo.com**
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الخلاصة
تعد مقاومة المضادات الحيوية أحد التهديدات الخطيرة للصحة العامة في جميع أنحاء العالم. الكاربابنيمز هي مضادات حيوية توفر دفاعًا محتملاً ضد مجموعة واسعة من البكتيريا وتمثل الملاذ الأخير لعلاج الالتهابات الخطيرة. إنزيمات الكاربابنيم المتحللة مائيًا والمعروفة أيضًا باسم الكاربابنيمز وهي مجموعة من الإنزيمات المتنوعة تنتمي إلى البيتا لاكتاماز، وتحمل جيناتها على كل من البلازميدات والكروموسومات. تقوم هذه الإنزيمات بتحلل العديد من المضادات الحيوية من نوع بيتا لاكتام بما في ذلك الكاربابينيم والبنسلين والسيفالوسبورين والأزترونام. أدى الانتشار العالمي للبكتيريا المقاومة للكاربابنيم إلى عدد كبير من حالات العدوى المكتسبة في المستشفيات والمجتمع. أهم السلالات البكتيرية التي تحمل الكاربابنيمز هي Enterobacteriaceae والبكتيريا غير المتخمرة مثل *Pseudomonas aeruginosa* و *Acinetobacter baumannii*.
الكلمات المفتاحية: مقاومة المضادات الحياتية، الكاربابنيم، الكاربابنيمز، بيتا لاكتاميزز.

Introduction
Bacterial resistance to antibiotics is a rapidly growing issue worldwide with special regard for Gram-negative bacteria (Sosa *et al.*, 2010; Diene and Rolain, 2014). Carbapenems are a subclass of β-lactam antibiotics regarded as a last resort for therapy due to serious infections caused by resistant and multi-drug (MDR) resistant bacteria (Hansen, 2021). The most antimicrobial agents belong to carbapenems are meropenem, ertapenem, doripenem and imipenem (Potter *et al.*, 2016).

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The main mechanism of resistance to carbapenem among Gram-negative bacteria is the production of Carbapenemases (Bonomo *et al*., 2018). Carbapenemases are enzymes have the ability to resist all antibiotics of β-lactam and have been proved to be found in *Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Canton *et al*., 2012). These enzymes are carried on mobile genetics elements and have the ability to disseminate and transmission overall the world (Cheng *et al*., 2019; Hussaini *et al*., 2023). Bacterial strains harboring these enzymes showed multiple resistant phenotype to antimicrobial agents due to overuse of these agents in human and animals (Sugden *et al*., 2016).At the first time carbapenemases were discovered in Gram-positive bacteria like *Bacillus licheniformis* and *Bacillus cereus* (Carfi *et al*.,1995; Duval *et al*., 2003). Classically resistance to antibiotics have been restricted in clinical setting (Hashemi *et al*, 2014). However, resistance also documented in natural environment (Abbas, 2022).

This review focus on carbapenemase enzymes and its definition, characterize their types, classification and epidemiology.

Classification of Carbapenemases: Carbapenemases can be classified into two classes depending on their action sites: serine carbapenemases include class A penicillinase and class D oxacillinases possess a serine residue in their active which can be inhibited by β-lactamase inhibitors like sulbactam, tazobactam , class B comprise metallo β-lactamases which utilize one or more zinic ions at their active site, hydrolyze beta lactamases and are not inhibited by beta-lactamase inhibitors like vabrobactam, tazobactam and clavulanic acid (Hansen, 2021; Sahile and Shenkut, 2022).

Class A Carbapenemases: These enzymes include imipenem-hydrolyzing β-lactamase (IMI), Guiana extended spectrum carbapenemase (GES), *Klebsiella pneumoniae* carbapenemases (KPCs), *Serratia marcescens* enzyme (SME), *Serratia fonticola* carbapenemase and nonmetallo-carbapenemase-A. (Patel and Bonomo, 2013).

Some of these enzyme are chromosomally encoded (IMI-1,SME,NmcA,SFC-1) while (KPC,GES,IMI-2) are plasmid encoded all can hydrolyze carbapenem efficiently and somewhat inhibited by β- lactamase inhibitors ,clavulanic acid (Sahile and Shenkut, 2022).

KPC enzymes are associated with transferable plasmids commonly found on *K.pneumoniae* and many members of *Enterobacteriaceae* family (Hansen, 2021).The common variants for KPC are KPC-2 and KPC-3, they can inactivate cephalosporin with expanded spectrum and carbapenem but KPC can be inhibited weakly by tazobactam and clavulanic acid. These enzymes coharbored with OXA-1 conferring resistance to β-lactam inhibitors combinations (Sahile and Shenkut, 2022).

Class B Carbapenemases: Metallo beta lactamases (MBLs) are a diverse group of enzyme capable of hydrolyzing all antibiotics of β-lactam (Abbas, 2021). The enzymes IMP,VIM,SIM and NDM are belong to class B metallo β-lactamases predominantly found in *Enterobacteriaceae* family such as *K.pneumoniae*, *K.oxytoca*, *Enterobacter* spp. and *Escherichia coli* and on transferable plasmid of other bacteria like *A. baumanni*i and *P. aeruginosa* .These enzymes are associated with mobile genetic elements like plasmid, transposon and integron (Diene and Rolain, 2014; Hansen, 2021).MBLs are divided into subclasses (B1, B2 and B3), however the important types classified in B1 subclass including imipenemases (IMP),Verona integrin-encoded MBLs (VIM) and New Delhi MBLs (NDM) (Sahile and Shenkute, 2022).

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Class D Carbapenemases: The key features of these enzymes is the hydrolytic activity against oxacillin, and their genes are carried on plasmid and chromosomes (Sahile and Shenkute, 2022). OXA- enzymes including OXA-23,OXA-24,OXA-58 groups are basically reported in *A. baumanni*i while OXA-48 have been detected in *K.pneumoniae* (Queenan and Bush, 2007).Class D beta-lactamase and variants of OXA have variable and important carbapenemase activity and not inhibited by beta-lactamase inhibitors like tazobactam, sulbactam and clavulanic acid (Drawz and Bonomo, 2010).

Epidemiology: In 2001, KPC (*Klebsiella pneumoniae* carbapenemase) firstly identified in United States in *K. pneumoniae* isolates (Yigit *et al*., 2001; Yigit *et al*., 2003). This enzyme disseminated into different regions in the world and across many genera of *Enterobacteriaceae* (Lee *et al*., 2016; Bush, 2018).Outbreaks due to KPC producers have been reported. In Greece, 2007 outbreak due to *K. pneumoniae* isolates has been documented and affect 22 hospitalized patients without history of travelling to area infected by this type of carbapenemases (Maltezou *et al*., 2009).

In 2008, *Klebsiella pneumoniae* harboring NDM was first described in a Swedish patient from India suffering from urinary tract infection due to isolate of *K. pneumoniae* resistant to carbapenem (Yong *et al*., 2009). NDM producing bacteria also detected in drinking and seepage water sample attained in New Delhi (Walsh *et al*., 2011). During the early 1990s a report identified chromosomal imipenem hydrolyzing enzyme *Serratia marcescens* in the United Kingdom (Yang *et al*., 1990). In France a chromosomal enzyme NmcA in *Enterobacter cloacae* (Nordmann *et al*., 1993; Naas and Nordmann, 1994). Another plasmid mediated resistant to carbapenem has reported in Japan, Italy, Greece and Portugal (Watanabe *et al*., 1991; Lauretti *et al*., 1999; Tsakris *et al*., 2000; Cardoso *et al*., 2002) with studies documented MBLs in *Pseudomonas aeruginosa,* disseminated as well in other countries from Latin America (Crespo *et al*., 2004).

OXA-48 was first described in the bacterium *K.pneumoniae* in Istanbul, Turkey,2001 (Poirel *et al*., 2004).Outbreak due to *K. pneumoniae* carrying OXA-48 was happened in Turkey, later in France and other regions (Glupczynski *et al*., 2002; Carrer *et al*., 2008; Cuzon *et al*., 2011).

Conclusions

Carbapenem is the last therapeutic line for treatment severe infections caused by MDR bacterial isolates. However, the emergence of resistance to these agents has been increased worldwide. The use of carbapenem should be controlled in clinical setting to avoid misuse and overuse of these agents, thus limit the dissemination of resistant pathogenic bacteria.

References

Abbas, F.M. (2022). Prevalence of waterborne blaNDM-1 gene producing carbapenem-resistant *Klebsiella pneumoniae* from Al Hillah river water, Babylon Province, Iraq. J. Pure. Appl. Microbiol. 16(3):1873-1877.

Abbas, F.M. (2021). Metallo -β-Lactamases: A Review. Annals of R.S.C.B., 25 (5) :1308 – 1316.

Bonomo, R.A.; Burd, E.M.; Conly, J.; Limbago, B.M.; Poirel, L.; Segre, J.A.; Westblade, L.F.(2018), CarbapenemaseProducing Organisms: A Global Scourge. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 66, 1290–1297.

Bush, K. (2018). Past and Present Perspectives on β-Lactamases. Antimicrob. Agents Chemother. 62, doi:10.1128/AAC.01076-18.

Online ISSN: 2001-6611
Print ISSN: 2001-662X

Canton, R, Akova M, Carmeli Y et al.(2012). Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin. Microbiol. Infect.; 18: 413–431.

Cardoso, O.; Leitão, R.; Figueiredo, A.; Sousa, J.C.; Duarte, A.; Peixe, L.V. (2002,). Metallo-beta-lactamase VIM-2 in clinical isolates of *Pseudomonas aeruginosa* from Portugal. Microb. Drug Resist. Larchmt. N 8, 93–97.

Carfi, A.; Pares, S.; Duée, E.; Galleni, M.; Duez, C.; Frère, J.M.; Dideberg, O.(1995). The 3-D structure of a zinc metallo-beta-lactamase from Bacillus cereus reveals a new type of protein fold. EMBO J., 14, 4914–4921.

Carrer, A, Poirel L, Eraksoy H, Cagatay AA, Badur S, Nordmann P.(2008). Spread of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* isolates in Istanbul, Turkey. Antimicrob. Agents Chemother. 52(8), 2950–2954 .

Cheng, VCC, Wong SC, Wong SCY, Ho PL, Yuen KY, et al. (2019) Control of Carbapenemase producing *Enterobacteriaceae:* Beyond the hospital. EClinical Medicine 6(2): 3-4.3.

Crespo, M.P.; Woodford, N.; Sinclair, A.; Kaufmann, M.E.; Turton, J.; Glover, J.; Velez, J.D.; Castañeda, C.R.; Recalde, M.; Livermore, D.M. (2004).Outbreak of carbapenem-resistant *Pseudomonas aeruginosa* producing VIM-8, a novel metallo-beta-lactamase, in a tertiary care center in Cali, Colombia. J. Clin. Microbiol. 42, 5094– 5101.

Cuzon, G, Ouanich J, Gondret R, Naas T, Nordmann P. (2011). Outbreak of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* isolates in France. Antimicrob.. Agents Chemother. 55(5), 2420–2423.

Diene, S.M. and Rolain, J.-M. (2014). Carbapenemase genes and genetic platforms in Gram-negative bacilli: *Enterobacteriaceae*, *Pseudomonas* and *Acinetobacter* species. Clin. Microbiol. Infect. 20: 831–838 .

Drawz, SM, Bonomo RA.(2010). Three decades of b-lactamase inhibitors. Clin Microbiol; Rev. 23: 160–201.

Duval, V.; Swinnen, M.; Lepage, S.; Brans, A.; Granier, B.; Franssen, C.; Frère, J.-M.; Joris, B.(2003). The kinetic properties of the carboxy terminal domain of the Bacillus licheniformis 749/I BlaR penicillin-receptor shed a new light on the derepression of beta-lactamase synthesis. Mol. Microbiol., 48, 1553–1564.

Glupczynski, Y, Huang T-D, Bouchahrouf W et al.(2002). Rapid emergence and spread of OXA-48-producing carbapenem-resistant *Enterobacteriaceae* isolates in Belgian hospitals. Int. J. Antimicrob. Agents 39(2), 168–172

Hansen, G.T.(2021). Continuous Evolution: Perspective on the Epidemiology of Carbapenemase Resistance Among Enterobacterales and Other Gram-Negative Bacteria. Infect. Dis. Ther. 10:75–92.

Hashemi, A, Fallah F, Erfanimanesh S, Hamedani P, Alimehr S, Goudarzi H.(2014). Detection of β-lactamases and outer membrane porins among *Klebsiella pneumoniae* strains isolated in Iran. 726179.

Hussaini, IM, Suleiman AB, Olonitola OS, Oyi RA.(2023). Phenotypic and molecular detection of carbapenemase producing *Escherichia coli* and *Klebsiella pneumoniae*. Microbes Infect, Dis .; 4(1): 151-159.

Lauretti, L.; Riccio, M.L.; Mazzariol, A.; Cornaglia, G.; Amicosante, G.; Fontana, R.; Rossolini, G.M. (1999). Cloning and characterization of blaVIM, a new integron-borne metallo-beta-lactamase gene from a *Pseudomonas aeruginosa* clinical isolate. Antimicrob. Agents Chemother. 43, 1584–1590.

Online ISSN: 2001-6611
Print ISSN: 2001-662X

Lee, C.-R.; Lee, J.H.; Park, K.S.; Kim, Y.B.; Jeong, B.C.; Lee, S.H.(2016). Global Dissemination of carbapenemase producing *Klebsiella pneumoniae:* epidemiology, genetic context, treatment options, and detection methods. Front. Microbiol. 7, 895. 24.

Naas, T.; Nordmann, P. (1994).Analysis of a carbapenem-hydrolyzing class A beta-lactamase from Enterobacter cloacae and of its LysR-type regulatory protein. Proc. Natl. Acad. Sci. USA . 91, 7693–7697.

Nordmann, P.; Mariotte, S.; Naas, T.; Labia, R.; Nicolas, M.H.(1993). Biochemical properties of a carbapenemhydrolyzing beta-lactamase from Enterobacter cloacae and cloning of the gene into Escherichia coli. Antimicrob. Agents Chemother. 37, 939–946.

Maltezou, HC, Giakkoupi P, Maragos A et al. (2009). Outbreak of infections due to KPC-2-producing *Klebsiella pneumoniae* in a hospital in Crete (Greece). J. Infect. 58(3), 213–219.

Patel, G, Bonomo RA. (2013).“Stormy waters ahead”: global emergence of carbapenemases. Front. Microbiol. 4, 48–64 .

Poirel, L., Heritier C, Tolun V, Nordmann P. (2004).Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. 48(1), 15–22 .

Potter, R.P., Souza,A.W.D. Dantas**,G. (**2016**).** The rapid spread of carbapenem-resistant *Enterobacteriaceae***.** Drug Resist.Updat.29:30-46.

Queenan, A.M .and Bush, K.(2007). Carbapenemases: the versatile beta-lactamases. Clin. Microbiol .Rev. 20 : 440–458.

Sahile, Z. and Shenkute, D..(2022). The Epidemiology and molecular aspect of carbapenemase producing Enterobactericiae (CPE). A Review. J. Inf .Dis. Trav.Med.6(11).0000161.

Sosa, A de J, Byarugaba DK, Amabile C, Hsueh PR, Kariuki S, Okeke IN (Eds). (2010). Antimicrobial Resistance in Developing Countries. Springer, NY, USA.

Sugden R, Kelly R, Davies S. (2016).Combatting antimicrobial resistance globally. Nat. Microbiol. 1(10), 16187 .

Tsakris, A.; Pournaras, S.; Woodford, N.; Palepou, M.F.; Babini, G.S.; Douboyas, J.; Livermore, D.M. (2000). Outbreak of infections caused by *Pseudomonas aeruginosa* producing VIM-1 carbapenemase in Greece. J. Clin. Microbiol. 38, 1290–1292.

Walsh, TR, Weeks J, Livermore DM, Toleman MA. (2011). Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect. Dis. 11(5), 355–362.

Watanabe, M.; Iyobe, S.; Inoue, M.; Mitsuhashi, S.(1991).Transferable imipenem resistance in *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother. 35, 147–151.

Yang, Y.J.; Wu, P.J.; Livermore, D.M. (1990). Biochemical characterization of a beta-lactamase that hydrolyzes penems and carbapenems from two Serratia marcescens isolates. Antimicrob. Agents Chemother. 34, 755– 758.

Yigit, H.; Queenan, A.M.; Anderson, G.J.; Domenech-Sanchez, A.; Biddle, J.W.; Steward, C.D.; Alberti, S.; Bush, K.; Tenover, F.C.(2001). Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenemresistant strain of Klebsiella pneumoniae. Antimicrob. Agents Chemother. .45, 1151–1161.

Online ISSN: 2001-6611
Print ISSN: 2001-662X

Yigit, H.; Queenan, A.M.; Rasheed, J.K.; Biddle, J.W.; Domenech-Sanchez, A.; Alberti, S.; Bush, K.; Tenover, F.C. (2003). Carbapenem-resistant strain of Klebsiella oxytoca harboring carbapenem-hydrolyzing beta-lactamase KPC-2. Antimicrob. Agents Chemother. .47, 3881–3889. 23.

Yong, D., Toleman MA, Giske CG et al. (2009). Characterization of a new metallo-β-lactamase gene, blaNDM-1, and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence Type 14 from India. Antimicrob. Agents Chemother. 53(12), 5046–5054.