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Review Article **Open Access**

Recent update on the mechanism and epidemiology of metallo-β-lactamases in nosocomial infections: A mini review

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Abstract:

Metallo-β-lactamases are different types of biological enzymes that breakdown a broad spectrum of beta-lactam antibiotics such as carbapenems. Antibiotic resistance exhibited by many Gram-negative bacteria is due to acquisition of genes encoding these enzymes, which underscores their importance in antibiotic resistance and has led to an increase in nosocomial infections caused by multi-drug-resistant pathogens. This review analyzes recent updates on the mechanism of antibiotic resistance and epidemiology of metallo-β- lactamases in nosocomial infections. Carbapenem antibiotics are regarded as effective and reserve antibiotics for the treatment of multidrug-resistant bacteria infections. Currently, there is paucity of inhibitors that prevent the activities of metallo beta-lactamase clinically. Carbapenem resistance in bacteria is a global health issue, associated with increased morbidity and mortality in the healthcare setting. There is a need for continuous research on metallo-β-lactamases inhibitors, rational use of carbapenems and appropriate infection control measures in order to curb the increase in infections. This mini-review is aimed to provide a broader scope on the current trends of antimicrobial resistance in metallo-β-lactamase-associated nosocomial infections. This will lead to a better understanding of the public health implication of the unabated spread of these infections, the need for judicious utilization of the limited therapeutic options, resulting to efficient antimicrobial stewardship.

Keywords: Metallo-β-lactamases, β-lactam, Carbapenem, Nosocomial, Multidrug resistant

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Mise à jour récente sur le mécanisme et l'épidémiologie des métallo-β-lactamases dans les infections nosocomiales: une mini-synthèse

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Résumé:

Les métallo-β-lactamases sont différents types d'enzymes biologiques qui dégradent un large spectre d'antibiotiques bêta-lactamines tels que les carbapénèmes. La résistance aux antibiotiques de nombreuses bactéries à Gram négatif est due à l'acquisition de gènes codant ces enzymes, ce qui souligne leur importance dans la résistance aux antibiotiques et a entraîné une augmentation des infections nosocomiales causées par des agents pathogènes multirésistants. Cette revue analyse les dernières avancées sur le mécanisme de résistance aux antibiotiques et l'épidémiologie des métallo-β-lactamases dans les infections nosocomiales. Les antibiotiques carbapénèmes sont considérés comme efficaces et réservés au traitement des infections bactériennes multirésistantes. Actuellement, il existe une pénurie d'inhibiteurs inhibant cliniquement l'activité des métallo-β-lactamases. La résistance bactérienne aux carbapénèmes est un problème de santé mondial, associé à une augmentation de la morbidité et de la mortalité dans le milieu de soins. Il est nécessaire de poursuivre les recherches sur les inhibiteurs des métallo-β-lactamases, d'utiliser rationnellement les carbapénèmes et de mettre en place des mesures appropriées de contrôle des infections afin de freiner l'augmentation des infections. Cette mini-revue vise à élargir le champ d'analyse des tendances actuelles en

matière de résistance aux antimicrobiens dans les infections nosocomiales associées aux métallo-β-lactamases. Elle permettra de mieux comprendre les implications pour la santé publique de la propagation incontrôlée de ces infections, la nécessité d'une utilisation judicieuse des options thérapeutiques limitées et une gestion efficace des antimicrobiens.

Mots-clés: Métallo-β-lactamases, β-lactamines, carbapénèmes, nosocomiales, multirésistance

Introduction:

Nosocomial infections are infections acquired in the hospital and are now referred to as healthcare-associated infections (HAIs). At the time of patient admission, these infections are absent and occur when caring for patients. They may also occur after patient discharge from the hospital and are the main sources of infections among healthcare workers. Nosocomial infections are a threat to the safety of patients and have major socioeconomic implications (1). These infections have a prevalent rate of up to 40% in developing nations compared to 5% in developed countries (2). Healthcare-associated infections result in increased hospital stay, death, disability, and emergence of antimicrobial resistance (3).

Antibiotic resistance develops from acquisition of resistance gene or by plasmid transfer between same or different species of bacteria. A bacterium carrying many genes that express antibiotic resistance is referred to as multi-drug resistant (MDR) or informally 'superbug'. The World Health Organization (WHO) states that 15% and 7% of patients in developing and developed countries respectively will get at least one HAI during their stay in the hospital, and an average of 10% of these patients will die from their HAIs (4). In the USA, the Centre for Disease Control (CDC) reported that 1 in 31 patients in the hospital have at least one nosocomial infection (5). Antibiotics misuse has serious effect on public health, causing emergence of 'super bugs' that results in life-threatening MDR infections.

Antibiotic resistance and nosocomial infections have been known globally for several years, and nosocomial infections such as urinary tract infection, pneumonia and bacteraemia are mostly associated with *Escherichia coli*, *Staphylococcus* and *Pseudomonas* spp (6). There is a global rise in infections caused by MDR bacteria and a looming threat of untreatable infections since the inception of the 21st century (7). The WHO reported that approximately 1.27 million global deaths are due to bacterial antimicrobial resistance (AMR) and AMR contributed to 4.95 million deaths (8). The members of the family Enterobacteriaceae producing extended spectrum beta-lactamases (ESBL) are known as very important nosocomial pathogens in the world today and their mechanism of resistance is also globally spread (9,10).

The prevalence of the pathogens causing HAIs and their methods of antibiotic resistance should determine the therapeutic pattern in different hospitals. Antibiotic resistance is mostly exhibited in bacteria that have high virulence, depends on the history of antibiotic use and could be innate or acquired (11). In this review, the global rise of carbapenem resistance in bacteria due to metallo-beta-lactamases (MBLs) and their mechanism of resistance are discussed. The types of MBLs, the classes of antibiotic they act upon, epidemiology of these enzymes in HAIs and possible therapeutic options to curb increase in nosocomial infections are also reviewed.

β-lactam antibiotics:

Antimicrobial drugs such as β-lactam antibiotics are mostly used in hospitals and their increased incidence is a great concern in clinical setting. They have a wide range of activities against different forms of bacteria. They have unique qualities making them, the most broadly used antibiotics in the world (9). They act by preventing transpeptidase enzymes and these enzymes are mainly responsible in synthesis of the bacterial cell wall peptidoglycan layer (12). The action of β-lactam antibiotics is exerted by blocking the synthesis of the peptidoglycan layer with resultant death of the bacteria (13).

Classes of β-lactam antibiotics:

Different types of β-lactams exist, and their structure determines the class they belong. The clinically important β-lactams are penicillins, carbapenems, cephalosporins and monobactams. The β-lactam ring of penicillin and cephalosporin is joined to five- and six-member rings, respectively which has carboxyl group at the C3 and C4 positions. These antibiotics have a broad-spectrum of actions against many types of bacteria (17). Unlike the penicillins and cephalosporins, the monobactams are not made up of a fusing ring but have a sulfunic acid group linked to its β-lactam at similar sites of carboxylate group as in penicillins and cephalosporins (18), and they show activities against Gram-negative pathogens that are aerobic.

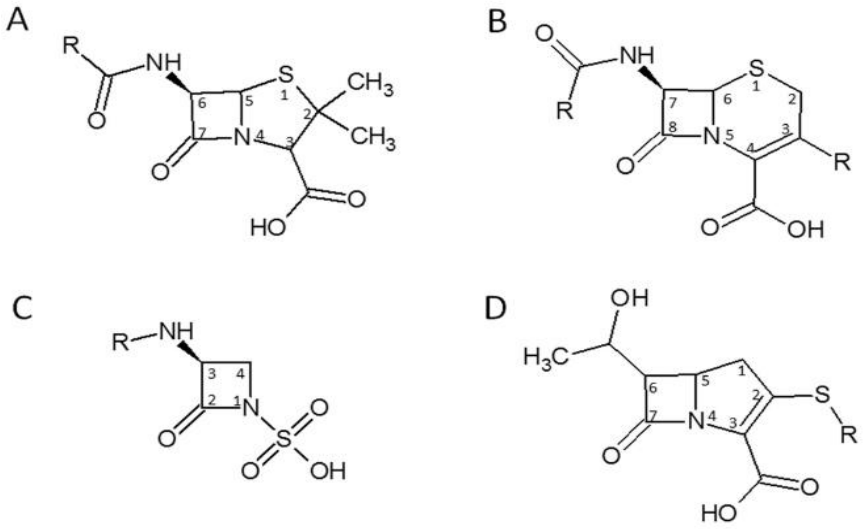

Fig 1: Classes of β-lactam antibiotics (19)

A - Basic penicillin structure; R - groups distinguish different types of penicillins; B - Core structure of cephalosporin; C-Basic structure of Monobactam; D - Carbapenem core structure; Atoms were numbered for reference in the discussion text

The carbapenems are very useful for the treatment of infections caused by bacteria that are MDR and they have a wide range of activities against these bacteria (15). The carbapenems are resistant to hydrolytic activities of β-lactamases and are an inhibitor of most β-lactamases. However, in the last ten years, few classes of β-lactamases are able to hydrolytically breakdown carbapenems and these are major sources of resistance (16). Fig 1 shows the classes of β-lactam antibiotics with the atoms numbered for reference (19).

Resistance to β-lactam antibiotics:

In other to withstand the antimicrobial effects of these antibiotics, bacteria developed some defensive strategies to combat the activities of antibiotics (14). The unguarded use of beta-lactam antibiotics has resulted to increased bacterial resistance thereby threatening antibiotic therapy (15). Although beta-lactam antibiotics have low toxicity and are frequently used antibiotic drugs, there are increasing resistance to these drugs (16). The subclass of the beta-lactamases determines the different enzyme processes which differ based on the number of zinc molecules bound to the enzyme active site.

The spread of genes that encode β-lactamases in Gram-negative bacteria made them a major key for resistance. One of the resistance strategies of Gram-negative bacteria against beta-lactam antibiotics is the production of metallo-β-lactamases (MBLs). Currently, MBLs cannot be prevented by any clin ically available inhibitors (14).

Mechanisms of β-lactam resistance:

The commonest method of antibiotic resistance in Gram-negative bacteria is the hydrolysis of beta-lactam ring by beta-lactamases. Other mechanisms include changes in porin channels, activities of efflux pumps leading to reduced permeability of the cell wall, by the actions of altered transpeptidases and β-lactamase inactivation of the antibiotics (15). In *Streptococcus pneumoniae*, enzymes bind loosely to β-lactam due to changes that occur in the sequences of target transpeptidases through mutation or recombination and these results to resistance. The transpeptidase in *Staphylococcus aureus*, aids in resistance by slowly binding to beta-lactam antibiotics (20).

i. β-lactamases:

Beta-lactamase breaks down the amide bond in beta-lactam ring and this results to products that are not effective, which is the basis of resistance in bacteria. The genes that express β-lactamases are mostly on the plasmids or other mobile genetic elements such as transposons and integrons of the bacteria. Basically, there are four structural classes of beta-lactamases; A, B, C and D (21). Classes A, C and D are serine-based enzymes and they activate the breakdown of β-lactam through a serine-bound acyl intermediate (22). Class B enzymes need zinc for its activities, although catalysis is not through covalent intermediate but by breakdown of hydroxide ion which the zinc in the active site stabilizes (23). Class A carbapenemases and class B MBLs are able to break down carbape-

nems and these are major sources of resistance (23).

ii. Class B Metallo beta-lactamases:

Metallo β-lactamases of class B β-lactamases have wide range of substrates and catalyzes the breakdown of most β-lactam antibiotics excluding monobactams. Their activities are not prevented by clavulanate, sulbactam, or tazobactam which are inhibitors to serine-based beta-lactamases (24). Unlike the serine-based enzymes, MBLs are destroyed by metal chelator like ethylene diamine tetra-acetic acid (EDTA) (24). Metallo-β-lactamases have been in existence for more than forty years and are encoded in the chromosome and were also found in organisms that are not pathogenic, and therefore did not pose challenge for antibiotic therapy (25). But in the 1990s there was wide dissemination of Imipenemase (IMP) and Verona integron-encoded metallo-β-lactamase (VIM) among Gram-negative bacteria such as *Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii.* Table 1 shows the characteristics of class B metallo-β-lactamases.

Integron structures associated with transposons carry genes for VIM- and IMP-type enzymes within them and these genes can be inserted on the chromosome or in plasmids of the bacteria (23). The resultant effect is the basis for the dissemination of MBL genes and their existence in MDR bacteria. In 2008, the newly described New Delhi metallo-β-lactamase-1 (NDM-1) was initially discovered in *Klebsiella pneumoniae* and *Escherichia coli,* found in a patient travelling from India to Sweden (26). Since then, they have spread globally due to rapid exchange of genes among species. The rapid spread of NDM MBLs is because of the bacterial promiscuity exhibited by its genetic element (23). All MBLs hydrolyse carbapenems but not all serine based β-lactamases are carbapenemases (14) (Table 1).

Epidemiology of metallo-β-lactamases in nosocomial infections:

Carbapenemase genes were first identified in the chromosomes of Gram-positive bacilli but by 1980s, MBLs were found in non-lactose-fermenting Gram-negative bacteria (23). By 1990s, they were discovered in the plamids of many species of bacteria isolated from clinical settings (25). Metallo-β-lactamases have been reported as being ubiquitous in nosocomial settings (14). The most affected patients are those in units such as intensive care (ICUs), organ transplant receivers, burns and neonates.

There are reports from a retrospective study carried out in Serbia, that not less than one hospital-acquired infection affects about one-third of patients admitted in intensive care units (28). The WHO classified important pathogens causing MDR hospital-acquired infections based on their global risk into critical, high and medium priority (29). The first two groups are very important pathogens known as 'ESKAPE' and these include *Enterococcus faecium*, *Staphylococcus aureus, K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp. The WHO 2024 Bacterial Priority Pathogens List (WHO BPPL) is an updated version of the 2017 edition which addresses the evolving challenges of antibiotic resistance, and notable bacteria on this list are carbapenemase-producing Gram-negative bacteria (30). These pathogens cause infection with high mortality rate of patients because of their plasmid-borne MBLs (31,32).

Table 1: Characteristics of class B Metallo-β-Lactamases (23)

Ambler structural Class	Functional Class[a]	Active Site[b]	Inhibitors	Notable Gene	Mobile genetic Elements	Multilocus STs[c]	Retained β-lactam Susceptibility
B	3	Zinc	EDTA	VIM	IncN, Incl1, multiple types; class1 integrons	ST147, ST11, others	Monobactam spared
B	3	Zinc	EDTA	IMP	IncL/M, IncA/C, multiple types; class 1 integrons		Monobactams spared
B	3	Zinc	EDTA	NDM	IncA/C, multiple; ISAba125	ST101, ST11, several others	Monobactam spared

EDTA - Ethylene diamine tetra-acetic acid; IMP - Imipenem metallo-beta-lactamase; Inc - Plasmid incompatibility type; NDM - New Delhi metallo-β-lactamases; ST - Sequence type; VIM - Verona integron-encoded metallo-β-lactamase; [a]Bush-Jacob-Medeiros classification scheme [27]; [b]Hydrolytic method; [c] Only *Klebsiella pneumoniae* and *Escherichia coli*-associated STs are listed

Members of the family Enterobacteriaceae carrying MBL genes are a major world threat in healthcare environment (15). Integron-encoded IMP-1 MBL was first reported in *Serratia marcescens* in 7 Japanese hospitals in Okazaki, Japan during a plasmid-mediated outbreak. Presently, there are at least 52 variants of IMP genes in many bacteria species distributed globally, and they are endemic in Taiwan and Japan (33). The bla_{IMP} gene has both broad and narrow host-range plasmids aiding their increased dissemination and a surveillance study conducted in Australia shows further spread of these genes (34).

The VIM MBLs were found in *P. aeruginosa* in 1996 and 1997 in Verona, Italy (VIM-1) and Marseilles France (VIM-2) respectively (23). VIM-2 is the commonest type globally and has at least 46 bla_{VIM} variants which are distributed worldwide with Greece as the epicentre (26,35,36). In 2008, the bla_{NDM-1} MBL gene was discovered in ST14 *K. pneumoniae* from a Swedish patient in a hospital in New Delhi, India. There are about 24 variants of NDM MBL genes distributed worldwide with India, Middle East and Balkans as the epicentre (37,38). In a study on the outbreak of NDM-1 in South Africa, researchers found that New Dehli MBL is a major cause of hospital mortality (39). In Tuscany,Italy, a rapid spread of NDM-producing *K. pneumoniae* from 2018-2019 was reported (40). Some risk factors for nosocomial infections are existence of co-morbid disease, piperacillin or tazobactam exposure, and the use of mechanical ventillators. Metallo-β-lactamases (MBLs) have been observed to persist in environments like burn unit, thus there is a significant relationship between spread of MBLs in the burns unit environment and patient colonization subsequently (41).

In the last 20 years, carbapenems were regarded as 'reserve' antibiotics used basically against bacteria carrying extended spectrum β-lactamase or Gram-negative bacteria that produces AmpC beta-lactamases. Lately, serine carpenemases and MBLs are more frequent and widespread in many parts of the world (14). In the United States, physicians in tertiary healthcare centres, acute care hospitals for long term diseases and nursing homes are concerned because Gram-negative bacteria that produces carbapenemases such as *K. pneumoniae* caused significant rise in death rates in patients with these bacterial infections (42). Studies in the US and Brazil shows that MBLs produced by *P. aeruginosa* resulted in higher mortality rates and an increase in severity of infections (18, 43). Another study in a tertiary hospital in Abuja, Nigeria, concluded that the increase in the occurrence of MBL-producing strains of *P. aeruginosa* is a major threat to therapeutics, and infection prevention and control. Therefore, rational use of carbapenems, regular surveillance and proper infection prevention and control measures should be put in place to curb MBLs dissemination in hospitals (44).

Metallo beta-lactamase inhibitors:

Metallo-beta-lactamases have catalytic sites, mechanism and structures different from serine beta-lactamases because both are not evolutionarily related (45). There are limited options for inhibiting the activities of pathogens that produce MBLs. One of such options is aztreonam-ceftazidime-avibactam combination, which is effective, although the optimization of pharmacokinetics of the combination has not been concluded (46). Recently, the Food and Drug Administration (FDA) approved the clinical use of β-lactam/β-lactamase inhibitor for the treatment of diseases caused by MDR ESKAPE pathogens (47). The FDA approved β-lactam/β-lactamase inhibitor combinations are ceftazidime-avibactam, imipenem-relebactam, the siderophore cephalosporin (cefiderocol), meropenem-vaborbactam and ceftolozane-tazobactam (47). Non-ribosomal peptide antibiotic such as colistin (produced by *Paenibacillus polymyxa)* is active against pathogens that are carbapenem resistant (48). Although there are six approved serine β-lactamase inhibitors, none inhibits the activities of MBLs because their catalytic sites are different (14).

Tebipenem, the foremost oral carbapenem, is undergoing clinical trials (phase 3). If approved, this could be combined with other antibacterial drugs for treatment of nosocomial MBL bacterial pathogens (46). Novel boronate compounds which are effective against MBL are taniborbactam, which is a MBL inhibitor in phase 3 clinical trial (NCT03840 138), QPX7728 in phase 1 clinical trial (NCT0 4380207) and xeruborbactam in phase 1 clinical trial (49,50). Other MBL inhibitors are metal chelators such as aspergllomarasmine A (14). Bicyclic boronates have been developed as inhibitors to serine beta-lactamases and MBLs although the genetic diversity of MBL is a major challenge in developing MBL inhibitors (49).

Conclusion:

There are basically two groups of beta-lactamases in bacteria, which are the cause of resistance to carbapenems, exhibited by many Gram-negative bacteria in clinical settings. The first is the serine carbapenemases (use serine as the active site amino acid) and the second is the MBLs (those that use a Zn^{2+} ion). In recent years, MBLs have become one of the most dreaded resistance systems due to their ability to break down

almost all beta-lactams such as carbapenems and the genes expressing these enzymes are mostly on bacteria plasmids.

Therapeutic choices for nosocomial infections caused by Gram-negative bacteria is largely limited due to the dissemination of MBLs in these pathogens. Healthcare institutions with high occurrence of MBLs should review their empirical treatments. Local, national and international monitoring system, should be developed and organised to monitor threats of MBLs infections. Research studies aimed at identyfying, observing, controlling and reviewing the threats posed by these infections should also be encouraged.

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Contributions of authors:

IFE conceptualized and wrote the manuscript, MOA edited the manuscript, MAA managed the literature searches, and OOO reviewed the final draft of the manuscript. All authors read and approved the final manuscript.

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References:

1. Cassini, A., Diaz Högberg, L., Plachouras, D., et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19: 56–66. https://doi: 10.1016/S1473-3099(18)30605-41
2. Raoofi, S., Kan, F.P., Rafiei, S., et al. Global prevalence of nosocomial infection: A systematic review and meta-analysis. PLoS One. 2023; 18: e0274248. doi: 10.1371/journal.pone.0274248
3. Avershina, E., Shapovalova, V., and Shipulin, G. Fighting Antibiotic Resistance in Hospital-Acquired Infections: Current State and Emerging Technologies in Disease Prevention, Diagnostics and Therapy. Front Microbiol. 2021; 12: 707330 https://doi.org/10.3389/fmicb.2021.707330
4. World Health Organization: WHO. WHO launches first ever global report on infection prevention and control. World Health Organization. 2022. https://www.who.int/news/item/06-05-2022-who-launches-first-ever-global-report-on-infection-prevention-and-control.
5. HAIs: Reports and Data. 2024. https://www.cdc.gov/healthcare-associated-infections/php/data/index.html.
6. Hormozi, S. F., Saeedi, A. A., Aminianfar, M., Alishah, M. S., and Darvishi, M. Studying the Frequency of Nosocomial Infection and its Relative Factors in the Intensive Care Unit of Hospitals Based Upon NNI System. Euras J Anal Chem. 2018; 13. doi:10.29333/ejac/85014.
7. Uddin, T. M., Chakraborty, A. J., Khusro, A., et al. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. J Infect Publ Health. 2021; 14: 1750–1766. https://doi.org/10.1016/j.jiph.2021.10.02
8. World Health Organization: WHO. Antimicrobial resistance. 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.
9. Husna, A., Rahman, MdM., Badruzzaman, A. T. M., et al. Extended-Spectrum B-Lactamases (ESBL): challenges and opportunities. Biomed. 2023; 11: 2937. https://doi.org/10.3390/biomedicens11112937
10. Tilahun, M. Multi-Drug Resistance Profile, Prevalence of Extended-Spectrum Beta-Lactamase and Carbapenemase-Producing Gram Negative Bacilli Among Admitted Patients After Surgery with Suspected of Surgical Site Nosocomial Infection North East Ethiopia. Infect Drug Resist. 2022; 15: 3949–3965. https://doi.org/ 10.1186/s12866-024-03485-0
11. Hormozi, S. F., Vasei, N., Aminianfar, M., Darvishi, M., and Saeedi, A. A. Antibiotic resistance in patients suffering from nosocomial infections in Besat Hospital. Eur J Transl Myol. 2018; 28. doi:10.4081/ejtm.2018.7594.
12. Sauvage, E., Kerff, F., Terrak, M., Ayala, J. A., and Charlier, P. The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis. FEMS Microbiol Rev. 2008; 32: 234–258. https://doi.org/10.1111/j.15746976.2008.00105.x
13. Tooke, C. L., Hinchliffe, P., Bragginton, E. C., et al. Lactamases and B-Lactamase inhibitors in the 21st century. J Mol Biol. 2019; 431: 3472–3500. https://doi.org/10.1016/j.jmb 2019.04.002
14. Mojica, M. F., Rossi, M. A., Vila, A. J., and Bonomo, R. A. The urgent need for metallo-β-lactamase inhibitors: an unattended global threat. Lancet Infect Dis. 2022; 22: e28–34. https://doi.org/10.1016/S1473-3099
15. Lynch, J. P., Clark, N. M., Zhanel, G. G. Escalating antimicrobial resistance among Enterobacteriaceae: focus on carbapenemases. Expert Opin Pharmacother. 2021; 22:1455–1474. https://doi.org/10.1080/14656566.2021.1904891
16. Palacios, A. R., Rossi, M. A., Mahler, G.S., and Vila, A. J. Metallo-β-Lactamase Inhibitors Inspired on Snapshots from the Catalytic Mechanism. Biomol. 2020; 10: 854. https://doi.org/10. 3390/biom10060854
17. Kim, D., Kim, S., Kwon, Y., et al. Structural insights for B-Lactam antibiotics. Biomol. Ther. 2023; 31: 141–147. https://doi.org/10. 4062/biomolther.2023.008
18. Bush, K., and Bradford, P.A. Epidemiology of β-Lactamase-Producing Pathogens. Clin Microbiol Rev. 2020; 33. doi:10.1128/CMR.00047-19.
19. Yan, Y., Li, G., and Li, G. Principles and current strategies targeting metallo-β-lactamase mediated antibacterial resistance. Med Res Rev. 2020; 40: 1558–1592. https://doi.org/10. 1002/med.21665
20. Eichenberger, E. M., and Thaden, J. T. Epidemiology and mechanisms of resistance of extensively drug-resistant Gram-negative bacteria. Antibiotics. 2019; 8:37. https://doi.org/10. 3390/antibiotics8020037
21. Ambler, R. P., Coulson, A. F. W., Frère, J.M., et al. A standard numbering scheme for the class A beta-lactamases. Biochem J. 1991; 276: 269–270. doi:10. 1042/bj2760269

22. Ghuysen, J. M. Serine β-lactamases and penicillin-binding proteins. Annu Rev Microbiol. 1991; 45: 37–67. doi: 10.1146/annurev.mi.45.100191.000345
23. Logan, L. K., and Weinstein, R. A. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: the impact and evolution of a global menace. J Infect Dis. 2017; 215: S28–S36. https://doi.org/10. 1093/infdis/jiw282
24. Drawz, S. M., Bonomo, R. A., and Bonomo, R. A. Three Decades of β-Lactamase Inhibitors. Clin Microbiol Rev. 2010; 23: 160–201. https://doi: 10.1128/CMR.00037-09
25. Patel, G., and Bonomo, R. A. "Stormy waters ahead": global emergence of carbapenemases. Front Microbiol. 2013; 4. doi:10.3389/fmicb.2013.00048.
26. Yong, D., Toleman, M. A, Giske, C. G., et al. Characterization of a New Metallo-β-Lactamase Gene, bla NDM-1, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in Klebsiella pneumoniae Sequence Type 14 from India. Antimicrob Agents Chemother. 2009; 53: 5046–5054. https://doi.org/10. 1128/AAC.00774-09
27. Bush, K., and Jacoby, G. A. Updated Functional Classification of β-Lactamases. Antimicrob Agents Chemother. 2010; 54: 969–976. https://doi.org/10.1128/aac.01009-0
28. Despotovic, A., Milosevic, B., Milosevic, I., et al. Hospital-acquired infections in the adult intensive care unit-Epidemiology, antimicrobial resistance patterns, and risk factors for acquisition and mortality. Am J Infect Control. 2020; 48: 1211–1215. https://doi: 10.1016/j.ajic.2020.01.009
29. World Health Organization: WHO publishes list of bacteria for which new antibiotics are urgently needed. World Health Organization. 2017. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed.
30. Division, A. R. WHO bacterial priority pathogens list, 2024: Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. 2024. https://www.who.int/publications/i/item/9789240093461.
31. Santajit, S., and Indrawattana, N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. BioMed Res Int. 2016; 2016: 1–8. https://doi.org/ 10.1155/2016/2475067
32. Xuan, Y. MA., Wang, C. Y., Li, Y. Y., et al. Considerations and Caveats in Combating ESKAPE Pathogens against Nosocomial Infections. Adv Sci. 2019; 7. doi:10.1002/advs.201901872.
33. Nordmann, P., Naas, T., and Poirel, L. Global spread of Carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 2011; 17: 1791 – 1798. doi: 10.3201/eid1710.110655
34. Matsumura, Y., Peirano, G., Motyl, M. R., et al. Global Molecular Epidemiology of IMP-Producing Enterobacteriaceae. Antimicrob Agents and Chemother. 2017; 61. doi:10.1128/aac.02729-16.
35. Papadimitriou-Olivgeris, M., Bartzavali, C., Lambropoulou, A., et al. Reversal of carbapenemase-producing *Klebsiella pneumoniae* epidemiology from *bla*KPC- to *bla*VIM-harbouring isolates in a Greek ICU after introduction of ceftazidime/avibactam. J Antimicrob Chemother. 2019; 74: 2051–2054. https://doi.org/10.10193/jac/dkz125
36. Walsh, T. R., Toleman, M. A., Poirel, L., and Nordmann, P. Metallo-β-Lactamases: The Quiet before the Storm? Clin Microbiol Rev. 2005; 18: 306–325. https://doi.org/10.1128/cmr.18.2.306-325.2005
37. Wu, W., Feng, Y., Tang, G., Qiao, F., McNally, A., and Zong, Z. NDM Metallo-B-Lactamases and their bacterial producers in health care settings. Clin Microbiol Rev. 2019; 32. doi:10.1128/cmr.00115-18.
38. Dortet, L., Poirel, L., and Nordmann, P. Worldwide dissemination of the NDM-Type carbapenemases in Gram-Negative Bacteria. BioMed Res Int. 2014; 2014: 1–12. https://doi.org/10.1155/2014/249856
39. De Jager, P., Chirwa, T., Naidoo, S., Perovic, O., and Thomas, J. Nosocomial Outbreak of New Delhi Metallo-β-Lactamase-1-Producing Gram-Negative Bacteria in South Africa: A Case-Control Study. PLoS One. 2015; 10. doi: 10.1371/journal.pone.0123337.
40. Tavoschi, L., Forni, S., Porretta, A., et al. Prolonged outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacterales (NDM-CRE), Tuscany, Italy, 2018 to 2019. Eurosurveill. 2020; 25. doi:10.2807/1560-7917.es.2020.25.6.2000085.
41. Leung, G. H., Gray, T. J., Cheong, E. Y., Haertsch, P., and Gottlieb, T. Persistence of related *bla*$_{IMP-4}$ metallo-beta-lactamase producing Enterobacteriaceae from clinical and environmental specimens within a burn unit in Australia - a six-year retrospective study. Antimicrob Resist Infect Contr. 2013; 2. doi: 10.1186/2047-2994-2-35.
42. Endimiani, A., DePasquale, J.M., Forero, S., et al. Emergence of *bla*$_{KPC}$-containing Klebsiella pneumoniae in a long-term acute care hospital: a new challenge to our healthcare system. J Antimicrob Chemother. 2009; 64: 1102–1110. https://doi.org/10. 1093/jac/dkp327
43. Zavascki, A. P. The influence of metallo-lactamase production on mortality in nosocomial *Pseudomonas aeruginosa* infections. J Antimicrob Chemother. 2006; 58: 387–392. https://doi.org/10. 1086/665730
44. Zubair, K. O., and Iregbu, K. C. Resistance Pattern and Detection of Metallo-beta-lactamase Genes in Clinical Isolates of Pseudomonas aeruginosa in a Central Nigeria Tertiary Hospital. Niger J Clin Pract. 2018; 21: 176–182. https://doi.org/10.4103/njcp.njcp_229_17
45. Liu, B., Trout, R. E. L., Chu, G.H., et al. Discovery of Taniborbactam (VNRX-5133): a Broad-Spectrum serine- and metallo-B-lactamase inhibitor for Carbapenem-Resistant bacterial infections. J Med Chem. 2019; 63: 2789–2801. https://doi.org/10.1021/acs.jmedchem.9b01518
46. Timsit, J. F., Paul, M., Shields, R. K., et al. Cefiderocol for the treatment of infections due to Metallo-B-lactamase–Producing pathogens in the CREDIBLE-CR and APEKS-NP Phase 3 randomized studies. Clin Infect Dis. 2022; 75: 1081–1084. https://doi.org/10. 1093/cid/ciac078
47. Barbier, F., Hraiech, S., Kernéis, S., et al. Rationale and evidence for the use of new beta-lactam/beta-lactamase inhibitor combinations and cefiderocol in critically ill patients. Ann Intensive Care. 2023; 13. doi: 10.1186/s13613-023-01153-6.
48. Tambadou, F., Caradec, T., Gagez, A.L., et al. Characterization of the colistin (polymyxin E1 and E2) biosynthetic gene cluster. Arch Microbiol. 2015; 197: 521-532. https://doi.org/10. 1007/s00203-015-1084-5
49. Kang, S. J., Kim, D. H., and Lee, B. J. Metallo-β-lactamase inhibitors: A continuing challenge for combating antibiotic resistance. Biophys Chem. 2024; 309: 107228. http//doi.org/10.1016/j.bpc.2024.107228.
50. Tsivkovski, R., Totrov, M., and Lomovskaya, O. Biochemical characterization of QPX7728, a new Ultrabroad-Spectrum Beta-Lactamase inhibitor of serine and Metallo-Beta-Lactamases. Antimicrob Agents Chemother. 2020; 64. doi: 10.1128/aac.00130-20.