Ad-din Medical Journal
July 2024, 2(2):34-40

Review article

Unraveling the Complexity of ESBL and MBL: Insights into Pathogenesis, Mechanisms, and Health Ramifications

Received: 01.03.2024 Accepted: 28.06.2024.

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Abstract

The emergence and spread of extended-spectrum β-lactamases (ESBLs) and metallo-β-lactamases (MBLs) among bacterial pathogens pose a formidable threat to global health. This review article provides a comprehensive examination of ESBL and MBL-related health hazards, focusing on their pathogenesis, mechanisms of action, and clinical implications. Through an extensive analysis of current literature, this review elucidates the intricate interplay between bacterial enzymes and antimicrobial agents, delineating the molecular mechanisms underlying ESBL and MBL-mediated resistance. Furthermore, it explores the epidemiology of ESBL and MBL-producing bacteria, encompassing transmission dynamics, risk factors, and global prevalence patterns. The clinical impact of ESBL and MBL-related infections is also addressed, including challenges in diagnosis, treatment options, and patient outcomes. By synthesizing insights from microbiology, epidemiology, and clinical medicine, this review aims to provide a comprehensive understanding of ESBL and MBL-related health hazards. Additionally, it discusses strategies for infection control, antimicrobial stewardship, and public health policy to mitigate the escalating threat posed by ESBL and MBL-producing bacteria..

Keywords: ESBL, MBL, AMC

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How to cite this article: Fariha RSH, Saha R. Unraveling the Complexity of ESBL and MBL: Insights into Pathogenesis, Mechanisms, and Health Ramifications. Ad-din Med J. 2024 Jul;2(2)::34-40

Introduction

The widespread dissemination of antibiotic resistance among bacterial pathogens presents a formidable challenge to global public health.[1] Among the diverse mechanisms of antimicrobial resistance, the emergence and spread of extended-spectrum β-lactamases (ESBLs) and metallo-β-lactamases (MBLs) pose significant threats to the efficacy of β-lactam antibiotics, a cornerstone of modern medicine.[2] ESBLs and MBLs are enzymes capable of hydrolyzing a broad spectrum of β-lactam antibiotics, including penicillins, cephalosporins, and carbapenems, thereby conferring resistance and limiting treatment options for bacterial infections.[3] The complex interplay between bacterial enzymes and antimicrobial agents underlies the pathogenesis, mechanisms, and health implications of ESBL and MBL-mediated antibiotic resistance. Understanding the molecular underpinnings of ESBL and MBL production is essential for unraveling the transmission dynamics, epidemiology, and clinical impact of multidrug-resistant pathogens.[4] The genetic basis of ESBL and MBL production underscores the remarkable adaptability of bacterial pathogens in response to selective pressures imposed by antibiotic use. Through horizontal gene transfer and genetic recombination, bacteria acquire genetic elements encoding ESBLs and MBLs, facilitating the dissemination of resistance determinants among diverse bacterial species and geographic locations.[5] Characterizing the evolutionary origins and genetic determinants driving ESBL and MBL production is critical for elucidating the epidemiology and evolution of antibiotic resistance.[6] At the molecular level, ESBLs and MBLs employ diverse mechanisms to confer resistance to β-lactam antibiotics.

ESBLs typically reside in the periplasmic space of Gram-negative bacteria, where they hydrolyze β-lactam antibiotics and render them ineffective against bacterial targets.[7] MBLs, on the other hand, utilize zinc ions as cofactors to catalyze the hydrolysis of β-lactam antibiotics, thereby circumventing the inhibitory effects of β-lactamase inhibitors.[8] The clinical implications of ESBL and MBL-related infections extend beyond individual patient outcomes to encompass broader public health concerns.[9] ESBL and MBL-producing bacteria are associated with increased morbidity, mortality, and healthcare costs, necessitating comprehensive infection control measures and antimicrobial stewardship programs to mitigate their impact.[10] Furthermore, the global spread of ESBL and MBL-mediated antibiotic resistance underscores the urgent need for collaborative efforts to address this growing threat on a global scale. In light of the escalating challenge posed by ESBL and MBL-producing bacteria, this review aims to provide a comprehensive exploration of their pathogenesis, mechanisms, and health implications. By synthesizing insights from microbiology, epidemiology, and clinical medicine, this review seeks to inform strategies for infection control, antimicrobial stewardship, and public health policy in the fight against antibiotic resistance.

Mechanisms of ESBL and MBL Production

The mechanisms underlying the production of extended-spectrum β-lactamases (ESBLs) and metallo-β-lactamases (MBLs) are pivotal to understanding the development of antibiotic resistance in bacterial pathogens.ESBLs and MBLs are enzymes that confer resistance to β-lactam antibiotics through various molecular mechanisms. The genetic basis of ESBL production involves the acquisition of resistance genes encoding these enzymes, often facilitated by mobile genetic elements such as plasmids and transposons. Similarly, MBLs utilize zinc ions as cofactors to catalyze the hydrolysis of β-lactam antibiotics, rendering them ineffective against bacterial targets.[11] Understanding the molecular structure and function of β-lactamases, along with the genetic determinants driving ESBL and MBL production, is essential for elucidating the mechanisms of antibiotic hydrolysis and resistance.[12]

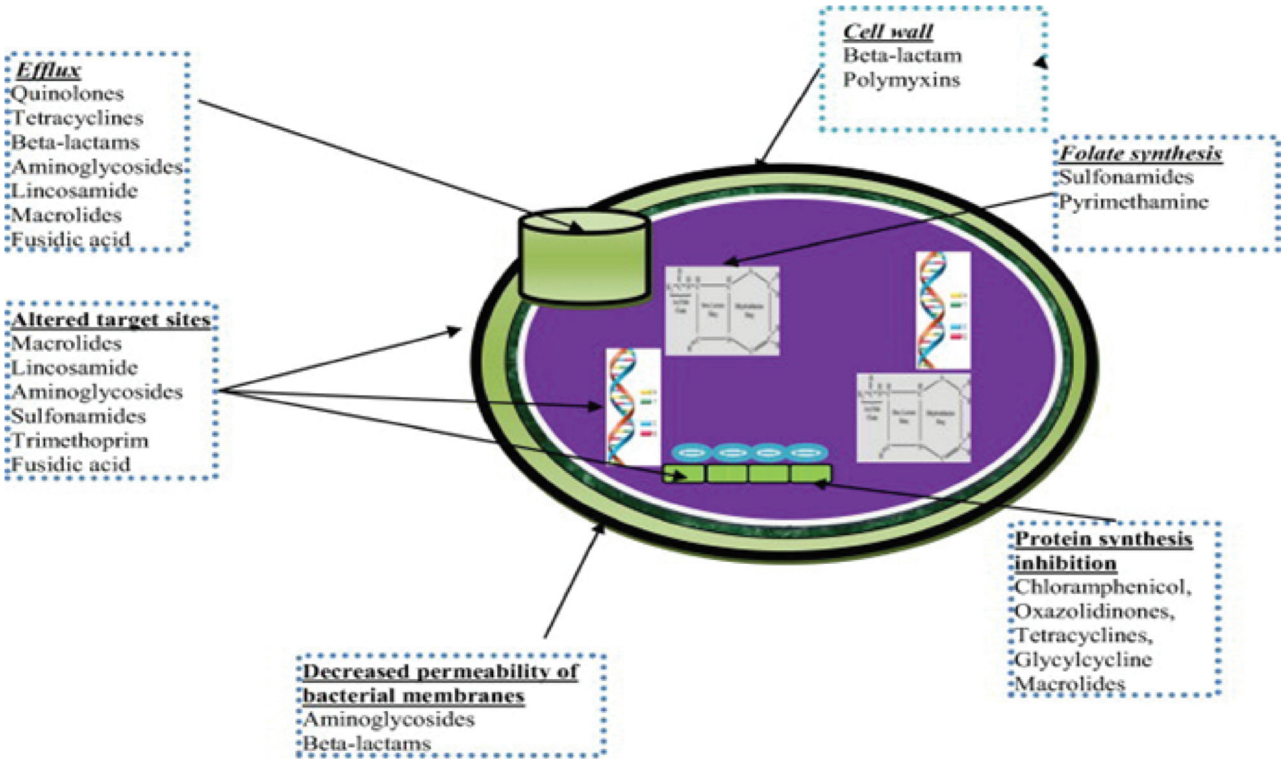

Figure 1: Antibiotic resistance vs. antimicrobial activity mechanism.[7]

This knowledge provides insights into the evolutionary dynamics of antibiotic resistance and informs the development of novel therapeutic strategies aimed at combating multidrug-resistant pathogens.

Pathogenesis of ESBL and MBL-Producing Bacteria:

Understanding the pathogenesis of extended-spectrum β-lactamase (ESBL) and metallo-β-lactamase (MBL)-producing bacteria is essential for elucidating their role in colonization, infection dynamics, and virulence.[13] Colonization by ESBL and MBL-producing bacteria often precedes the development of clinical infections and serves as a reservoir for transmission within healthcare settings and the community.[14] Once established, these bacteria interact with the host through complex mechanisms, including adhesion, invasion, and evasion of host immune defenses. Virulence factors such as adhesins, toxins, and biofilm formation contribute to the ability of ESBL and MBL-producing bacteria to cause invasive infections and evade host immune responses.[15]

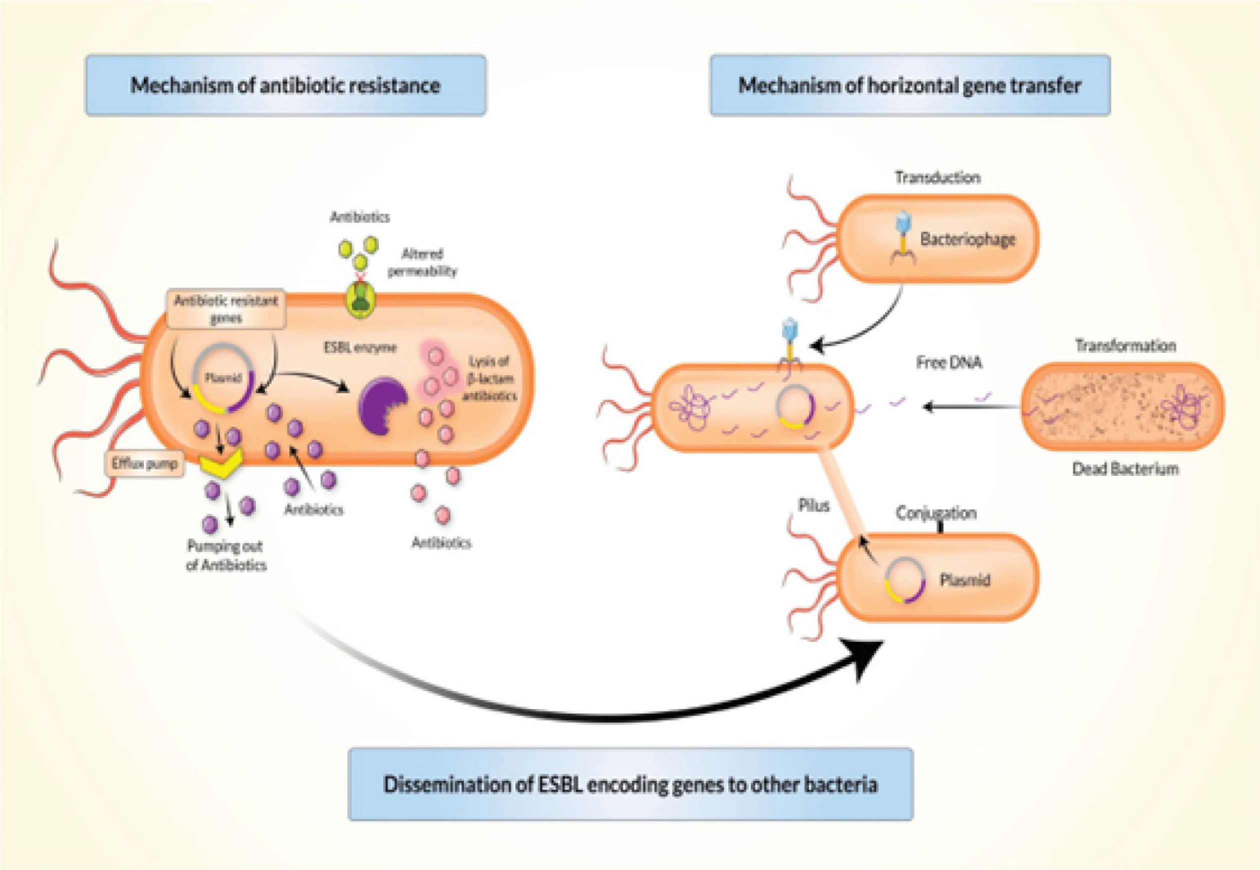

Figure 2 : Mechanism of antibiotic resistance & horizontal gene transfer[2]

Furthermore, the acquisition of antibiotic resistance genes may confer a fitness advantage, allowing these bacteria to thrive in the presence of selective pressure exerted by antimicrobial agents.[16] Understanding the interplay between colonization dynamics, host-pathogen interactions, and virulence factors is critical for devising strategies to prevent and control ESBL and MBL-related infections.

Epidemiology and Transmission Dynamics

The epidemiology and transmission dynamics of extended-spectrum β-lactamase (ESBL) and metallo-β-lactamase (MBL)-producing bacteria play a crucial role in shaping the global burden of antibiotic resistance.[17] Distinctions between healthcare-associated and community-acquired infections highlight the diverse settings in which ESBL and MBL-producing bacteria can emerge and spread.[18] Healthcare-associated infections often occur in hospital settings, where factors such as prolonged hospital stays, invasive procedures, and exposure to antimicrobial agents contribute to the selection and dissemination of multidrug-resistant pathogens.[19]

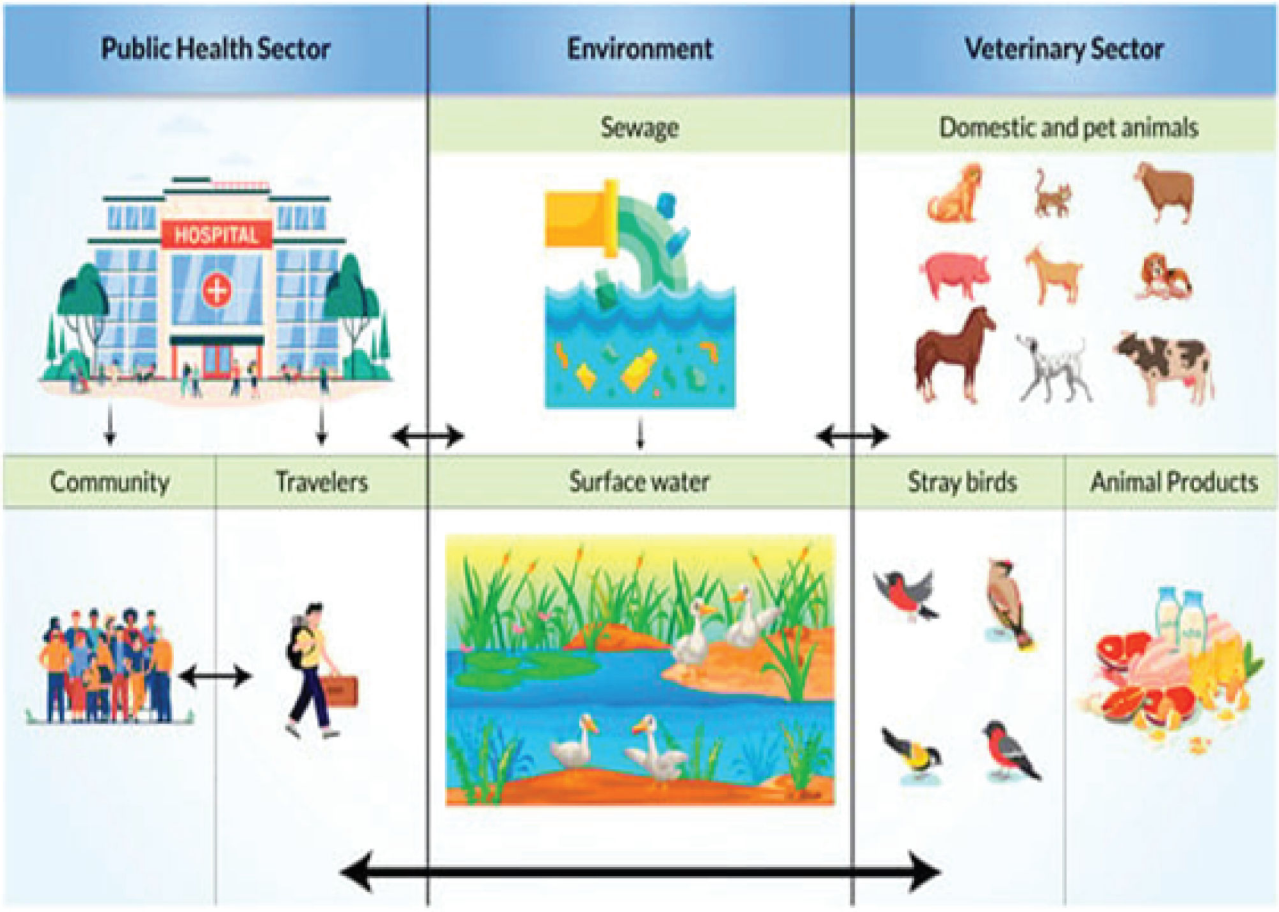

Figure 3 : Possible transmission pathways of Extended-Spectrum β-Lactamase (ESBL)-producing bacteria[2]

Conversely, community-acquired infections may arise in individuals with no recent healthcare exposure, underscoring the importance of community-based surveillance and infection control measures. Global surveillance data provide valuable insights into the prevalence and distribution of ESBL and MBL-producing bacteria, facilitating the identification of emerging hotspots and trends in antimicrobial resistance.[20] Factors contributing to the transmission and spread of ESBL and MBL-producing bacteria include inadequate infection control practices, international travel, and the dissemination of resistance genes through mobile genetic elements.[7] Addressing these challenges requires a multifaceted approach that encompasses enhanced surveillance, infection prevention strategies, and antimicrobial stewardship efforts.

The clinical implications of extended-spectrum β-lactamase (ESBL) and metallo-β-lactamases

The clinical implications of extended-spectrum β-lactamase (ESBL) and metallo-β-lactamase (MBL)-producing bacteria extend beyond individual patient outcomes to encompass broader challenges in healthcare delivery and antimicrobial stewardship.9 Infections caused by ESBL and MBL-producing bacteria are associated with increased morbidity, mortality, and healthcare costs compared to infections caused by susceptible strains.[21] The limited treatment options for multidrug-resistant pathogens further compound these challenges, often necessitating the use of last-line antibiotics with associated risks of toxicity and treatment failure. Antimicrobial stewardship efforts face significant hurdles in the management of ESBL and MBL-related infections, including difficulties in empiric therapy selection, optimal dosing regimens, and the potential for treatment failure due to resistance mechanisms.[22] Furthermore, the global dissemination of ESBL and MBL-producing bacteria complicates the landscape of infectious diseases, requiring collaborative efforts among healthcare providers, policymakers, and researchers to develop and implement effective strategies for infection control and antimicrobial stewardship.[2]

Health Hazards Associated with ESBL and MBL

The health hazards associated with extended-spectrum β-lactamase (ESBL) and metallo-β-lactamase (MBL)-producing bacteria are profound, encompassing increased morbidity and mortality rates, complications in vulnerable populations, and broader implications for public health and infection control.19 Infections caused by ESBL and MBL-producing bacteria are often associated with adverse clinical outcomes, including treatment failure, prolonged hospital stays, and increased healthcare costs.[23] Vulnerable populations, such as elderly individuals, immuno-compromised patients, and those with underlying medical conditions, are at particular risk of experiencing severe complications from ESBL and MBL-related infections. Moreover, the global dissemination of multidrug-resistant pathogens poses significant challenges for infection control efforts, requiring stringent measures to prevent transmission within healthcare settings and the community.[24] Addressing the health hazards associated with ESBL and MBL-producing bacteria necessitates a multifaceted approach that encompasses enhanced surveillance, antimicrobial stewardship, and infection prevention strategies to mitigate the impact of antibiotic resistance on public health.[25]

Strategies for prevention and control for ESBL & MBL

Extended-spectrum beta-lactamase (ESBL) and metallo-beta-lactamase (MBL) producing bacteria pose significant challenges in healthcare settings due to their resistance to multiple antibiotics. Effective prevention and control strategies are essential to mitigate their spread and impact.[2] Key measures include stringent infection control practices such as hand hygiene, environmental cleaning, and appropriate use of personal protective equipment. Antibiotic stewardship programs play a crucial role in optimizing antibiotic use, thereby reducing selective pressure for resistance development.[26] Surveillance for ESBL and MBL-producing organisms, along with timely detection through laboratory testing, facilitates early intervention and containment efforts.[27] Additionally, implementing measures to prevent horizontal gene transfer, such as limiting unnecessary antimicrobial exposure and employing molecular typing techniques, can aid in understanding transmission dynamics.[28] Comprehensive strategies integrating these components are pivotal for combating the dissemination of ESBL and MBL-producing bacteria in healthcare settings, ultimately safeguarding patient outcomes and public health.[25]

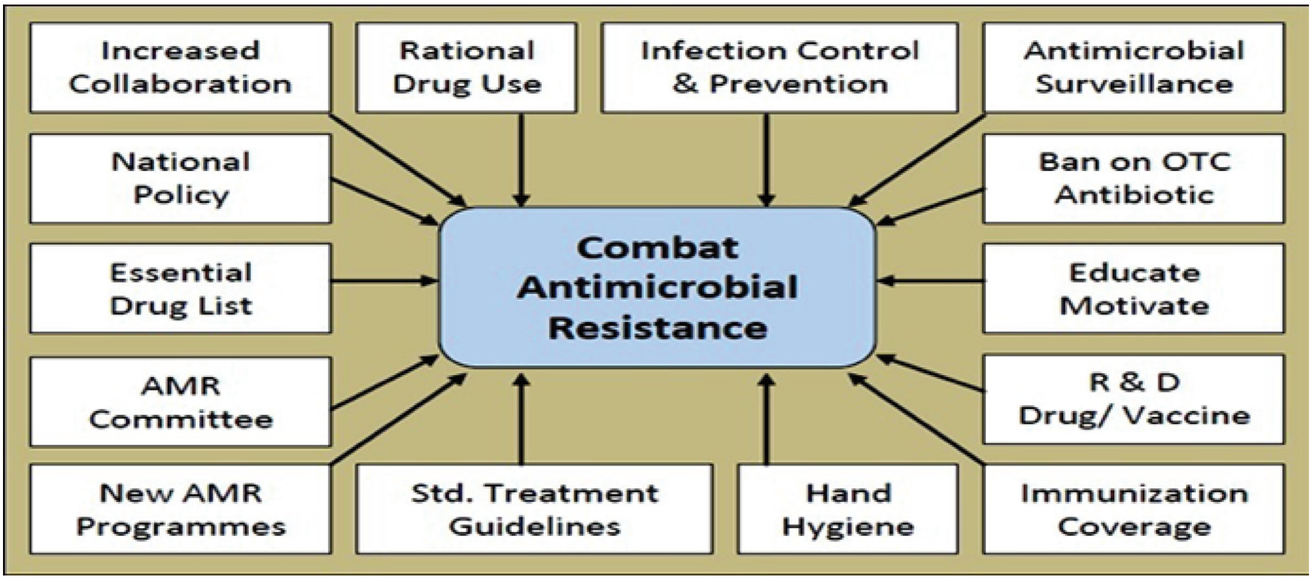

Figure4: The key points to AMR control strategies[29]

Unveiling the Pathogenesis, Mechanisms, and Imperatives of ESBL and MBL Resistance

Our journey through the pathogenesis and mechanistic intricacies of Extended-Spectrum Beta-Lactamase (ESBL) and Metallo-Beta-Lactamase (MBL) resistance has illuminated the formidable challenges posed by these enzymes, stemming from genetic mutations within bacterial populations.[13] ESBLs neutralize penicillins and cephalosporins, while MBLs extend resistance to carbapenems and beyond, showcasing the adaptability of bacterial pathogens.4The ramifications are profound, elevating morbidity, mortality rates, and straining healthcare resources.[30] Urgent action is warranted through enhanced surveillance, infection control protocols, and novel therapeutic strategies. Looking ahead, a unified, multidisciplinary approach involving healthcare providers, researchers, policymakers, and the public is crucial in combating this global threat, preserving antimicrobial efficacy, and safeguarding public health.[31] In closing, our exploration underscores the imperative for concerted action, determination, and resilience in confronting antimicrobial resistance.

Conclusion

In conclusion, our journey through the intricacies of ESBL and MBL resistance has provided invaluable insights into their pathogenesis, mechanisms, and health ramifications. As we unravel the complexity of these enzymes, it becomes increasingly clear that they pose significant challenges to public health, necessitating urgent action. By enhancing surveillance, implementing stringent infection control measures, and fostering innovation in therapeutic strategies, we can hope to mitigate the impact of multidrug-resistant bacterial strains. However, confronting antimicrobial resistance requires a unified, multidisciplinary effort involving healthcare professionals, researchers, policymakers, and the public. Together, we must remain vigilant, resilient, and committed to preserving the efficacy of antimicrobial agents for the well-being of current and future generations.

Conflict of interest

The authors hereby declare that no conflict of interest exists.

Acknowledgement

We would like to express our gratitude to all the members of Microbiology Department of BAMC for their unwavering support, as well as the editorial board members of ADMJ for their direction.

References

1. Muteeb G, Rehman MT, Shahwan, M. Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review - PMC. 2023; 16: 1615.

2. Husna A, Rahman MdM, Badruzzaman, ATM. Extended-Spectrum β-Lactamases (ESBL): Challenges and Opportunities - PMC. 2023; 11: 2937.

3. Paterson DL, Bonomo RA. Extended-Spectrum β-Lactamases: a Clinical Update. ClinMicrobiol Rev 2005; 18: 657–686.

4. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment - PMC, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4281622/ (accessed 4 May 2024).

5. Safari M, MozaffariNejad AS, Bahador A, et al. Prevalence of ESBL and MBL encoding genes in Acinetobacter baumannii strains isolated from patients of intensive care units (ICU). Saudi J BiolSci 2015; 22: 424–429.

6. Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. MicrobiolMolBiol Rev MMBR 2010; 74: 417–433.

7. Shaikh S, Fatima J, Shakil S, et al. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi J BiolSci 2015; 22: 90–101.

8. Sychantha D, Rotondo CM, Tehrani KHME, et al. Aspergillomarasmine A inhibits metallo-β-lactamases by selectively sequestering Zn2+. J BiolChem 2021; 297: 100918.

9. Kotapati S, Kuti JL, Nightingale CH, et al. Clinical implications of extended spectrum beta-lactamase (ESBL) producing Klebsiella species and Escherichia coli on cefepime effectiveness. J Infect 2005; 51: 211–217.

10. Oberoi L, singh N, sharma P. ESBL, MBL and Ampc β Lactamases Producing Superbugs – Havoc in the Intensive Care Units of Punjab India - PMC. 2013; 7: 70–73.

11. Palacios AR, Rossi M-A, Mahler GS, et al. Metallo-β-Lactamase Inhibitors Inspired on Snapshots from the Catalytic Mechanism - PMC. 2020; 10: 854.

12. Bahr, G, González, LJ, vila AJ. Metallo-β-lactamases in the age of multidrug resistance: from structure and mechanism to evolution, dissemination and inhibitor design - PMC. Chem Rev 2021; 121: 7957-8094.

13. Nepal K, Pant ND, Neupane B. Extended spectrum beta-lactamase and metallo beta-lactamase production among Escherichia coli and Klebsiella pneumoniae isolated from different clinical samples in a tertiary care hospital in Kathmandu, Nepal - PMC. 16: 62.

14. Bush K, Bradford PA. Epidemiology of β-Lactamase-Producing Pathogens - PMC. 2020; 33: e00047-19.

15. Sora VM, Meroni G, Martino PA, et al. Extraintestinal Pathogenic Escherichia coli: Virulence Factors and Antibiotic Resistance. Pathogens 2021; 10: 1355.

16. Liao C, Huang X, Wang Q. Virulence Factors of Pseudomonas Aeruginosa and Antivirulence Strategies to Combat Its Drug Resistance - PMC. 2022; 12: 926758.

17. Hilty M, Betsch BY, Bögli-Stuber K, et al. Transmission Dynamics of Extended-Spectrum β-lactamase–Producing Enterobacteriaceae in the Tertiary Care Hospital and the Household Setting. Clin Infect Dis OffPubl Infect Dis Soc Am 2012; 55: 967–975.

18. Wilson H, Torok ME. Extended-spectrum β-lactamase-producing and carbapenemase-producing Enterobacteriaceae - PMC. 2018; 4: e000197.

19. Chen Q, Li D, Beiersmann C. Risk factors for antibiotic resistance development in healthcare settings in China: a systematic review - PMC. 2021; 149: e141.

20. Sintondji K, Fabiyi, K, Hougbenou, J. Prevalence and characterization of ESBL-producing Escherichia coli in

healthy pregnant women and hospital environments in Benin: an approach based on Tricycle - PMC. 2023; 11: 1227000.

21. Woldemichael GB, Belachew EB, Derese SG. High burden of ESBL and carbapenemase-producing gram-negative bacteria in bloodstream infection patients at a tertiary care hospital in Addis Ababa, Ethiopia - PMC. 2023; 18: e0287453.

22. Ramos, JR, -Vergé, LE, López, ÁEM-. The Interventions and Challenges of Antimicrobial Stewardship in the Emergency Department - PMC.2023; 12: 1522.

23. Pana ZD, Zaoutis T. Treatment of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLs) infections: what have we learned until now? F1000Research 2018; 7: F1000 Faculty Rev-1347.

24. Coque TM, Cantón, R, Cobas AEP. Antimicrobial Resistance in the Global Health Network: Known Unknowns and Challenges for Efficient Responses in the 21st Century - PMC. 2023; 11: 1050.

25. Majumder, MAA, Rahman S, Cohall D. Antimicrobial Stewardship: Fighting Antimicrobial Resistance and Protecting Global Public Health - PMC. 2020; 13: 4713-4738.

26. Ha DR, Haste NM, Gluckstein DP. The Role of Antibiotic Stewardship in Promoting Appropriate Antibiotic Use.Am J Lifestyle Med 2017; 13: 376–383.

27. Shrestha A, Acharya J, Amatya J, et al. Detection of Beta-Lactamases (ESBL and MBL) Producing Gram-Negative Pathogens in National Public Health Laboratory of Nepal. Int J Microbiol; 2022.Epub ahead of print 2022. DOI: 10.1155/2022/5474388.

28. Lee C-R, Cho IH, Jeong BC.Strategies to Minimize Antibiotic Resistance - PMC. 2013sep; 10: 4274-4305.

29. Uchil RR, Kohli GS, Katekhaye VM, et al. Strategies to Combat Antimicrobial Resistance. J ClinDiagn Res JCDR 2014; 8: ME01–ME04.

30. National Academies of Sciences E, Medicine NA of, Nursing 2020–2030 C on the F of, et al.The Role of Nurses in Improving Health Care Access and Quality. In: The Future of Nursing 2020-2030: Charting a Path to Achieve Health Equity. National Academies Press (US), https://www.ncbi.nlm.nih.gov/books/NBK573910/ (2021, accessed 8 May 2024).

31. Salam MdA, Al-Amin MdY, Salam MT, et al. Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. Healthcare 2023; 11: 1946.