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CURRENT PROGRESS IMPACTS AND CHALLENGES OF ANTIMICROBIAL DRUG RESISTANCE: CHALLENGES AND SOLUTIONS

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Abstract: Antimicrobial drug resistance has emerged as a significant global health threat, jeopardizing our ability to effectively treat infectious diseases. Overuse and misuse of antibiotics, coupled with the lack of development of new antimicrobial agents, have contributed to the rapid spread of resistance among bacterial, viral, fungal, and parasitic pathogens. This review provides an overview of the current status of antimicrobial drug resistance, highlighting key mechanisms of resistance, the impact on patient outcomes and healthcare systems, and the urgent need for concerted efforts to address this critical issue. Strategies to combat antimicrobial resistance include antimicrobial stewardship programs, development of novel antimicrobial agents, promotion of infection prevention and control measures, and public education campaigns to raise awareness about appropriate antibiotic use. Antimicrobial drug resistance poses a significant threat to public health globally. This review examines the current landscape of antimicrobial resistance, including its mechanisms, epidemiology, and impact on healthcare. Strategies to combat resistance, such as stewardship programs, development of new drugs, and alternative therapies, are also discussed.

Collaboration among healthcare providers, policymakers, researchers, and the pharmaceutical industry is essential to mitigate the further spread of antimicrobial resistance and safeguard the effectiveness of antimicrobial therapy for future generations.

Keywords: Antimicrobial resistance, antibiotics, drug resistance, stewardship, infection control, public health.

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Introduction: Antimicrobial drug resistance has emerged as a critical issue in healthcare, leading to increased morbidity, mortality, and healthcare costs. This section provides an overview of the problem and its implications for global health. Antimicrobial resistance can arise through various mechanisms, including genetic mutations, horizontal gene transfer, and biofilm formation. This section explores these mechanisms in detail, highlighting the diverse ways bacteria, viruses, parasites, and fungi evade antimicrobial agents. The prevalence of antimicrobial resistance varies across regions and pathogens. This section examines trends in resistance rates, the emergence of multidrug-resistant organisms, and the impact of factors such as antibiotic overuse and misuse on resistance patterns. Antimicrobial resistance complicates the management of infectious diseases, leading to treatment failures, prolonged hospital stays, and increased mortality. This section discusses the clinical consequences of resistance and the challenges it poses for patient care. Addressing antimicrobial resistance requires a multifaceted approach. This section explores strategies such as antimicrobial stewardship programs, infection prevention and control measures, development of novel therapeutics, and the use of alternative treatment options like phage therapy and immunotherapy.[1-2]

Microbes, also known as microorganisms, can be classified into several categories based on various criteria such as cell structure, metabolism, and genetic composition.

Bacteria: Bacteria are single-celled prokaryotic organisms that can be found in diverse environments. They come in various shapes (e.g., cocci, bacilli, spirilla) and play crucial roles in processes such as nutrient cycling and biotechnology.[1].

Archaea are also single-celled prokaryotic organisms, but they differ from bacteria in terms of their genetic makeup and biochemistry. Archaea can thrive in extreme environments such as hot springs, acidic environments, and deep-sea vents.[2]

Fungi: Fungi are eukaryotic organisms that include yeasts, molds, and mushrooms. They obtain nutrients through absorption and play important roles in decomposition, nutrient cycling, and food production. Some fungi can also cause diseases in plants and animals.[3]

Protozoa: Protozoa are single-celled eukaryotic organisms that are primarily found in aquatic environments. They exhibit diverse forms of locomotion and include parasites responsible for diseases such as malaria, amoebiasis, and giardiasis.[4]

Viruses are non-cellular entities that consist of genetic material (DNA or RNA) surrounded by a protein coat. They require a host cell to replicate and are responsible for a wide range of infectious diseases in humans, animals, plants, and bacteria.[5]

Algae are diverse photosynthetic organisms that can be found in aquatic and terrestrial environments. They range from unicellular to multicellular forms and play important roles in oxygen production, food chains, and bioremediation.[6]

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Pathophysiology of specific microbial pathogens

Adherence and Colonization: Adherence and colonization are fundamental processes in the establishment of microbial infections, playing pivotal roles in the pathogenesis of various diseases. This review explores the mechanisms underlying microbial adherence to host surfaces and subsequent colonization, encompassing interactions between microbial surface structures and host cell receptors. Key factors influencing adherence and colonization, including microbial adhesins, host cell adhesion molecules, and environmental conditions, are examined. Furthermore, the implications of microbial colonization, such as biofilm formation and evasion of host immune responses, are discussed in relation to infection persistence and treatment resistance. Insights into these processes are essential for the development of effective strategies to prevent and manage microbial infections. The review also underscores the importance of interdisciplinary approaches involving microbiologists, immunologists, pharmacologists, and clinicians in advancing our understanding of adherence and colonization mechanisms and developing novel therapeutic interventions.[7-12]

Microbial Adhesion to Host Tissues: Role of Adhesion Molecules and Surface Structures. Microbial adhesion to host tissues is a crucial step in the initiation of infections, enabling microorganisms to establish themselves within host environments and evade host defenses. This review examines the mechanisms and factors involved in microbial adhesion to various host tissues, including mucosal surfaces, epithelial cells, and implanted medical devices. Key microbial adhesins, host cell receptors, and environmental factors influencing adhesion are discussed, highlighting the diverse strategies employed by pathogens to interact with host tissues. Furthermore, the implications of microbial adhesion in the pathogenesis of infectious diseases, such as biofilm formation and immune evasion, are explored. Understanding the mechanisms of microbial adhesion is essential for the development of targeted interventions to prevent and treat microbial infections.[13-19]

Invasion and Penetration: The mechanisms and factors involved in microbial invasion and penetration of host cells and tissues, including the role of microbial virulence factors, host cell receptors, and signaling pathways. Key strategies employed by pathogens to facilitate invasion and penetration, such as secretion systems, adhesion molecules, and motility mechanisms, are discussed. Furthermore, the consequences of microbial invasion and penetration in disease pathogenesis, including tissue damage and dissemination, are explored. Insights into these processes are essential for the development of targeted interventions to prevent and treat microbial infections effectively.[20-26]

Bacterial invasion and evasion of host immune defenses are fundamental aspects of microbial pathogenesis, contributing to the establishment and persistence of infections. This review focuses on the mechanisms and paradigms employed by enteroinvasive pathogens to invade host cells and evade host immune responses. Specifically, it explores the role of bacterial virulence factors, such as adhesins, secretion systems, and toxins, in promoting invasion and subversion of host

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defenses. Additionally, host immune evasion strategies employed by bacterial pathogens, including modulation of phagocytosis, interference with complement activation, and manipulation of cytokine signaling pathways. Insights into these processes provide valuable insights into the pathogenesis of infectious diseases and inform the development of novel therapeutic interventions to combat bacterial infections.[27-32].

Microbial Evasion Mechanisms of the Complement System. Microbial evasion of the complement system is a critical aspect of pathogenesis employed by various bacterial, viral, fungal, and parasitic pathogens to establish and maintain infections within host organisms. This review explores the diverse strategies utilized by microbial pathogens to evade complement-mediated immune responses, thereby evading opsonization, lysis, and clearance by the host immune system. Mechanisms of complement evasion discussed include inhibition of complement activation, interference with complement deposition on microbial surfaces, and exploitation of host complement regulatory proteins. Additionally, the review examines the implications of complement evasion in disease pathogenesis and highlights the potential of targeting complement evasion mechanisms for the development of novel therapeutic interventions.[33-38]

Toxin Production:

Bacterial Toxins: Bacterial toxins play a central role in the pathogenesis of infectious diseases by mediating host cell damage, immune evasion, and modulation of host signaling pathways. This review focuses on the diverse mechanisms of action employed by bacterial toxins to subvert host defenses and promote microbial survival. It examines the classification, structure, and function of bacterial toxins, highlighting their role in virulence, disease progression, and host-pathogen interactions. Furthermore, the review discusses the implications of bacterial toxins in the development of therapeutic strategies, including vaccines and antitoxin therapies, to combat bacterial infections effectively. [39-45]

Inflammatory Response:

Inflammation and Host Response to Injury. Inflammation and the host response to injury are complex processes involving a coordinated interplay of cellular and molecular pathways aimed at restoring tissue homeostasis and eliminating pathogens. This review provides an overview of the inflammatory response to tissue injury, encompassing the key cellular players, signaling molecules, and regulatory mechanisms involved. It examines the roles of pro-inflammatory mediators, such as cytokines, chemokines, and reactive oxygen species, in orchestrating immune cell recruitment, activation, and effector functions. Furthermore, the review explores the resolution phase of inflammation and the mechanisms underlying tissue repair and regeneration. Insights into the dynamics of inflammation and host responses to injury are essential for understanding the pathophysiology of inflammatory diseases and developing therapeutic strategies to modulate immune responses effectively. [46-52]

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Tissue Damage and Disease Manifestations:

Tissue damage is a hallmark of many diseases and contributes to the manifestation and progression of various pathological conditions. This review explores the mechanisms underlying tissue damage and its role in disease pathogenesis, encompassing both acute and chronic inflammatory responses, immune-mediated damage, and tissue remodeling processes. It examines the cellular and molecular events involved in tissue injury, including oxidative stress, inflammation, apoptosis, and fibrosis, and their contribution to the development of diverse diseases, such as autoimmune disorders, infectious diseases, and cancer. Furthermore, the review discusses the clinical manifestations and consequences of tissue damage in different organ systems, highlighting the importance of understanding these processes for the development of targeted therapeutic interventions. [53-58]

Transmission and Spread:

The transmission of pathogens is a critical aspect of infectious disease epidemiology, influencing the spread and persistence of microbial infections within populations. This review provides an overview of the various modes of pathogen transmission, including direct contact, airborne transmission, foodborne transmission, vector-borne transmission, and healthcare-associated transmission. It examines the factors influencing transmission dynamics, such as pathogen characteristics, host susceptibility, environmental conditions, and social behaviors. Furthermore, the review discusses the importance of understanding transmission routes in the control and prevention of infectious diseases, highlighting the role of public health interventions, including vaccination, hygiene practices, vector control, and infection control measures.[59-65]

List of various drugs used to combat antimicrobial resistance :

Carbapenems: Carbapenems are broad-spectrum antibiotics used to treat serious bacterial infections, including those caused by multidrug-resistant organisms such as carbapenem-resistant Enterobacteriaceae (CRE).[66]

Linezolid: Linezolid is an oxazolidinone antibiotic used to treat infections caused by Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE).[67]

Colistin: Colistin is a polymyxin antibiotic used as a last-resort treatment for infections caused by multidrug-resistant Gram-negative bacteria, including carbapenem-resistant Acinetobacter baumannii and Pseudomonas aeruginosa.[68]

Daptomycin: Daptomycin is a lipopeptide antibiotic used to treat infections caused by Gram-positive bacteria, including MRSA and vancomycin-resistant Staphylococcus aureus (VRSA).[69]

Tigecycline: Tigecycline is a glycylcycline antibiotic used to treat complicated intra-abdominal and skin and soft tissue infections caused by multidrug-resistant bacteria, including MRSA and multidrug-resistant Acinetobacter baumannii.[70]

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Mechanisms of action commonly associated with antimicrobial drug resistance:

Enzymatic Inactivation:

Some bacteria produce enzymes that modify or degrade antimicrobial drugs, rendering them ineffective. For example, beta-lactamase enzymes hydrolyze beta-lactam antibiotics such as penicillins and cephalosporins.[70]

Target Site Modification:

Pathogens may acquire mutations that alter the target sites of antimicrobial drugs, reducing drug binding affinity and efficacy. For instance, mutations in bacterial DNA gyrase and topoisomerase IV genes confer resistance to fluoroquinolone antibiotics.[71]

Efflux Pump Overexpression:

Efflux pumps are membrane proteins that actively remove antimicrobial drugs from bacterial cells, reducing intracellular drug concentrations. Overexpression of efflux pump genes can confer multidrug resistance.[72]

Decreased Permeability:

Some bacteria develop mechanisms to reduce drug permeability across their cell membranes, limiting drug entry into the bacterial cell. This can involve alterations in membrane porins or lipid composition.[73]

Altered Metabolic Pathways:

Bacteria may develop alternative metabolic pathways or bypass mechanisms to circumvent the inhibitory effects of antimicrobial drugs. For example, dihydrofolate reductase mutations confer resistance to trimethoprim by producing a drug-insensitive enzyme.[74]

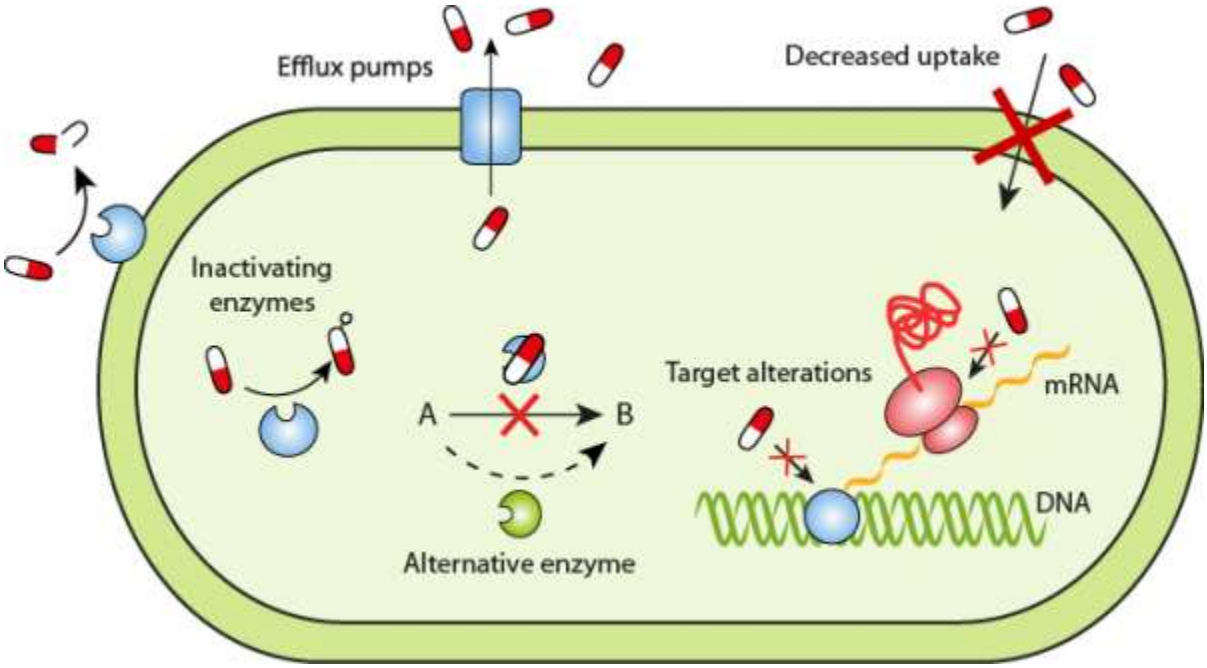

Figure 1. Antibiotic resistance strategies in bacteria.

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Methicillin-resistant Staphylococcus aureus (MRSA):

MRSA is a bacterium responsible for various infections, including skin and soft tissue infections, pneumonia, and bloodstream infections. It is resistant to multiple antibiotics, including methicillin and other β-lactam antibiotics.[75]

Multidrug-resistant Tuberculosis (MDR-TB):

MDR-TB is a form of tuberculosis caused by Mycobacterium tuberculosis strains that are resistant to at least two first-line anti-TB drugs, isoniazid and rifampicin. Treatment of MDR-TB requires second-line antibiotics, which are less effective and often associated with more adverse effects.[76]

Extended-spectrum β-lactamase (ESBL)-producing Enterobacterales:

ESBL-producing Enterobacterales are Gram-negative bacteria that produce enzymes called extended-spectrum β-lactamases, which confer resistance to a broad range of β-lactam antibiotics, including penicillins and cephalosporins.[77]

Artemisinin-resistant Plasmodium falciparum:

Artemisinin-resistant Plasmodium falciparum strains have emerged in Southeast Asia, particularly in the Greater Mekong Subregion. These strains exhibit reduced susceptibility to artemisinin-based combination therapies (ACTs), the first-line treatment for malaria.[78]

HIV Drug Resistance:

HIV drug resistance occurs when the virus mutates and becomes resistant to antiretroviral drugs used to treat HIV infection. This can happen due to inadequate adherence to treatment regimens or the transmission of drug-resistant strains.[79]

List of drugs used for antimicrobial resistance

Ampicillin - Ampicillin is a broad-spectrum beta-lactam antibiotic commonly used to treat various bacterial infections. It belongs to the penicillin group of antibiotics and works by inhibiting the synthesis of bacterial cell walls, ultimately leading to cell lysis and death.

The mechanism of action of ampicillin involves binding to penicillin-binding proteins (PBPs) present on the bacterial cell wall. PBPs are enzymes involved in the final stages of bacterial cell wall synthesis, specifically in the cross-linking of peptidoglycan strands. By binding to PBPs, ampicillin inhibits their activity, thereby preventing the formation of a functional cell wall. This disruption weakens the bacterial cell wall, making it susceptible to osmotic pressure, ultimately leading to cell lysis and death.[82-82]

Piperacillin/tazobactam is a combination antibiotic used to treat a wide range of bacterial infections. Piperacillin is a broad-spectrum penicillin antibiotic, while tazobactam is a beta-lactamase inhibitor that helps extend the spectrum of activity of piperacillin by protecting it from bacterial beta-lactamase enzymes.

Piperacillin Mechanism of Action:

Piperacillin inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), which are involved in the final steps of peptidoglycan synthesis. This leads to the disruption of the bacterial cell wall structure, weakening it and causing cell lysis.[83,84]

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Tazobactam Mechanism of Action:

Tazobactam is a beta-lactamase inhibitor that irreversibly binds to bacterial beta-lactamase enzymes. By binding to beta-lactamases, tazobactam prevents them from hydrolyzing the beta-lactam ring of piperacillin. This protects piperacillin from degradation, allowing it to exert its antibacterial activity against beta-lactamase-producing bacteria.

By combining piperacillin with tazobactam, piperacillin/tazobactam effectively targets a broader spectrum of bacteria, including those that produce beta-lactamase enzymes, making it a valuable antibiotic in the treatment of various infections.[85,86]

Ceftriaxone is a third-generation cephalosporin antibiotic used to treat a wide range of bacterial infections. It works by interfering with bacterial cell wall synthesis, leading to cell death. Here's a brief overview of its mechanism of action:

Inhibition of Cell Wall Synthesis:

Ceftriaxone belongs to the beta-lactam class of antibiotics, which inhibit bacterial cell wall synthesis by binding to and inhibiting the activity of penicillin-binding proteins (PBPs).

PBPs are enzymes involved in the final steps of peptidoglycan synthesis, which is essential for maintaining the structural integrity of bacterial cell walls.

By binding to PBPs, ceftriaxone prevents the cross-linking of peptidoglycan chains, leading to weakened cell walls and eventual cell lysis. Ceftriaxone's broad spectrum of activity and long half-life make it suitable for the treatment of various bacterial infections, including those caused by Gram-positive and Gram-negative bacteria, as well as certain anaerobic bacteria. [87-88]

Ceftazidime - Ceftazidime is a third-generation cephalosporin antibiotic commonly used to treat a variety of bacterial infections. Its mechanism of action is similar to other beta-lactam antibiotics, primarily targeting bacterial cell wall synthesis.

Inhibition of Cell Wall Synthesis:

Ceftazidime inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs) located on the bacterial cell membrane.

PBPs are enzymes involved in the final stages of peptidoglycan synthesis, which is essential for the structural integrity of the bacterial cell wall.

By binding to PBPs, ceftazidime interferes with the transpeptidation reaction, preventing the cross-linking of peptidoglycan strands and weakening the bacterial cell wall.

The weakened cell wall is unable to withstand the osmotic pressure gradient, leading to cell lysis and bacterial death.

Ceftazidime's broad spectrum of activity makes it effective against a wide range of Gram-negative bacteria, including Pseudomonas aeruginosa, Enterobacter spp., and some strains of Escherichia coli and Klebsiella pneumoniae. It is commonly used in the treatment of respiratory tract infections, urinary tract infections, skin and soft tissue infections, and sepsis.[89-91]

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Cefotaxime – Cefotaxime is a third-generation cephalosporin antibiotic used to treat various bacterial infections. Its mechanism of action is similar to other beta-lactam antibiotics, primarily targeting bacterial cell wall synthesis.

Inhibition of Cell Wall Synthesis:

Cefotaxime inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs) located on the bacterial cell membrane.

PBPs are enzymes involved in the final stages of peptidoglycan synthesis, which is essential for the structural integrity of the bacterial cell wall.

By binding to PBPs, cefotaxime interferes with the transpeptidation reaction, preventing the cross-linking of peptidoglycan strands and weakening the bacterial cell wall.

The weakened cell wall is unable to withstand the osmotic pressure gradient, leading to cell lysis and bacterial death. Cefotaxime's broad spectrum of activity makes it effective against a wide range of Gram-positive and Gram-negative bacteria, including Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Escherichia coli, and Klebsiella pneumoniae. It is commonly used in the treatment of respiratory tract infections, urinary tract infections, skin and soft tissue infections, and meningitis.[92]

Meropenem - Meropenem is a broad-spectrum carbapenem antibiotic used to treat severe bacterial infections. Its mechanism of action involves inhibiting bacterial cell wall synthesis, leading to cell death. Here's an overview of its mechanism:

Inhibition of Cell Wall Synthesis:

Meropenem inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), which are essential enzymes involved in peptidoglycan synthesis.

By binding to PBPs, particularly those with high affinity for beta-lactam antibiotics, meropenem disrupts the cross-linking of peptidoglycan chains, weakening the bacterial cell wall.

This disruption leads to impaired cell wall integrity and eventual cell lysis, resulting in bacterial death. Meropenem's broad spectrum of activity makes it effective against a wide range of bacteria, including Gram-positive, Gram-negative, and anaerobic bacteria. It is often used in the treatment of severe infections, such as pneumonia, intra-abdominal infections, urinary tract infections, and sepsis, particularly in hospitalized patients or those with compromised immune systems.[93-95]

Imipenem/Cilastatin - Imipenem/cilastatin is a combination antibiotic medication used to treat a variety of bacterial infections. Imipenem is a broad-spectrum carbapenem antibiotic, while cilastatin is a renal dehydropeptidase inhibitor that prevents the degradation of imipenem in the kidneys. The mechanism of action of imipenem/cilastatin involves inhibiting bacterial cell wall synthesis, leading to cell death. Here's an overview:

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Inhibition of Cell Wall Synthesis:

Imipenem inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), which are essential enzymes involved in peptidoglycan synthesis.

By binding to PBPs, particularly those with high affinity for beta-lactam antibiotics, imipenem disrupts the cross-linking of peptidoglycan chains, weakening the bacterial cell wall.

This disruption leads to impaired cell wall integrity and eventual cell lysis, resulting in bacterial death.

Renal Dehydropeptidase Inhibition:

Cilastatin inhibits renal dehydropeptidase, an enzyme responsible for the degradation of imipenem in the kidneys.

By inhibiting renal dehydropeptidase, cilastatin prolongs the half-life of imipenem, allowing for increased systemic exposure to the antibiotic and improved efficacy.

Imipenem/cilastatin is effective against a broad spectrum of bacteria, including both Gram-positive and Gram-negative organisms, as well as some anaerobic bacteria. It is commonly used in the treatment of severe infections, such as pneumonia, intra-abdominal infections, urinary tract infections, and sepsis.[96-98]

Discussion

Antimicrobial drug resistance poses a significant global health challenge, threatening the effective treatment of infectious diseases and compromising patient outcomes. The emergence and spread of resistant pathogens have been fueled by various factors, including the overuse and misuse of antimicrobial agents, inadequate infection control measures, and the widespread dissemination of resistance genes through horizontal gene transfer.

Mechanisms of Antimicrobial Drug Resistance

Resistance mechanisms can vary depending on the type of antimicrobial agent and the specific pathogen involved. Common mechanisms include:

Enzymatic Inactivation: Many bacteria produce enzymes, such as beta-lactamases, that degrade or modify antimicrobial drugs, rendering them ineffective.

Altered Target Sites: Mutations in bacterial genes encoding antimicrobial drug targets, such as PBPs for beta-lactams or ribosomal subunits for macrolides, can reduce drug binding affinity and confer resistance.

Efflux Pumps: Bacterial efflux pumps can actively pump antimicrobial drugs out of the bacterial cell, reducing intracellular drug concentrations and promoting resistance.

Reduced Permeability: Some bacteria develop mechanisms to decrease the permeability of their cell membranes, limiting the entry of antimicrobial drugs into the cell and reducing their efficacy.

Biofilm Formation: Biofilms provide a protective environment for bacteria, allowing them to evade antimicrobial agents and facilitate the development of resistance.

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Impact of Antimicrobial Drug Resistance

The consequences of antimicrobial drug resistance are profound, affecting patient care, public health, and healthcare systems globally. Resistant infections are associated with increased morbidity, mortality, and healthcare costs, as they often require prolonged hospital stays, more expensive treatments, and alternative, potentially less effective therapies.

Addressing Antimicrobial Drug Resistance

Addressing antimicrobial drug resistance requires a multifaceted approach involving collaboration between healthcare professionals, policymakers, researchers, and the general public. Key strategies include:

Antimicrobial Stewardship: Promoting the appropriate use of antimicrobial agents through stewardship programs can help minimize the development and spread of resistance.

Infection Prevention and Control: Implementing effective infection prevention and control measures, such as hand hygiene, environmental cleaning, and antimicrobial prophylaxis, can reduce the transmission of resistant pathogens in healthcare settings.

Research and Development: Investing in research and development efforts to discover new antimicrobial agents, alternative therapies, and diagnostic tools can help address gaps in treatment options and combat emerging resistance.

Surveillance and Monitoring: Establishing robust surveillance systems to monitor antimicrobial resistance trends, track resistant pathogens, and identify high-risk areas can inform targeted interventions and guide public health policies.

Conclusion: Antimicrobial drug resistance is a complex and evolving problem that requires concerted efforts at local, national, and global levels to mitigate its impact. By implementing comprehensive strategies to promote antimicrobial stewardship, enhance infection prevention and control measures, support research and development initiatives, and strengthen surveillance efforts, we can work towards preserving the effectiveness of antimicrobial agents and safeguarding public health for future generations.

Reference:

1. Madigan, M. T., Martinko, J. M., Bender, K. S., Buckley, D. H., & Stahl, D. A. (2017). Brock Biology of Microorganisms (15th ed.). Pearson.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

2. Cavicchioli, R., Curmi, P. M., Saunders, N., & Thomas, T. (2003). Pathogenic archaea: do they exist? Bioessays, 25(11), 1119-1128.

3. de Hoog, G. S., Guarro, J., Gené, J., & Figueras, M. J. (2019). Atlas of Clinical Fungi (3rd ed.). CBS-KNAW Fungal Biodiversity Centre.

4. Molyneux, D. H., & Savioli, L. (1999). Engaging the Corporate Sector in Neglected Disease Drug Discovery: The Role of Patent Pools. PLoS Medicine, 6(2), e1000102.

5. Knipe, D. M., Howley, P. M., Cohen, J. I., Griffin, D. E., Lamb, R. A., Martin, M. A., ... & Straus, S. E. (Eds.). (2013). Fields virology (6th ed.). Lippincott Williams & Wilkins.

6. Leliaert, F., Smith, D. R., Moreau, H., Herron, M. D., Verbruggen, H., Delwiche, C. F., & De Clerck, O. (2012). Phylogeny and molecular evolution of the green algae. Critical Reviews in Plant Sciences, 31(1), 1-46.

7. Otto, M. (2008). Staphylococcal biofilms. Microbiology Spectrum, 6(2), 1-24. [DOI: 10.1128/microbiolspec.10.0004.2014]

8. Donlan, R. M., & Costerton, J. W. (2002). Biofilms: survival mechanisms of clinically relevant microorganisms. Clinical Microbiology Reviews, 15(2), 167-193. [DOI: 10.1128/cmr.15.2.167-193.2002]

9. Kline, K. A., & Lewis, A. L. (2016). Gram-positive uropathogens, polymicrobial urinary tract infection, and the emerging microbiota of the urinary tract. Microbiology Spectrum, 4(2), 1-35. [DOI: 10.1128/microbiolspec.UTI-0012-2012]

10. Li, Y. H., & Tian, X. (2012). Quorum sensing and bacterial social interactions in biofilms. Sensors, 12(3), 2519-2538. [DOI: 10.3390/s120302519]

11. Haque, M. A., & Russell, A. D. (1973). Antimicrobial activity of chlorhexidine digluconate. Journal of Applied Bacteriology, 36(4), 757-758. [DOI: 10.1111/j.1365-2672.1973.tb04192.x]

12. Valotteau, C., & du Merle, L. (2020). Biofilm formation in Escherichia coli: an optimized protocol for bacterial biofilm quantification. Journal of Visualized Experiments, 155, e60610. [DOI: 10.3791/60610]

13. Abraham, S. N., & Beachey, E. H. (1988). Trends in Microbiology, 10(4), 157-161. [DOI: 10.1016/0966-842x(88)90061-3]

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

14. Cascales, E., & Buchanan, S. K. (2020). Duche, a Type IX secretion system substrate, is required for Citrobacter rodentium colonization in vivo. Journal of Bacteriology, 202(3), e00699-19. [DOI: 10.1128/JB.00699-19]

15. Sharon, N. (2006). Carbohydrates as future anti-adhesion drugs for infectious diseases. Biochimica et Biophysica Acta (BBA) - General Subjects, 1760(4), 527-537. [DOI: 10.1016/j.bbagen.2005.11.010]

16. Wiles, T. J., & Mulvey, M. A. (2013). The RTX pore-forming toxin α-hemolysin of uropathogenic Escherichia coli: progress and perspectives. Future Microbiology, 8(1), 73-84. [DOI: 10.2217/fmb.12.135]

17. Wurpel, D. J., Beatson, S. A., Totsika, M., Petty, N. K., Schembri, M. A. (2013). Chaperone-usher fimbriae of Escherichia coli. PLoS ONE, 8(1), e52835. [DOI: 10.1371/journal.pone.0052835]

18. Thanassi, D. G., & Bliska, J. B. (2019). Active transport of proteins by the bacterial Tat pathway. In K. S. Makarova, L. Aravind, E. V. Koonin (Eds.), Horizontal Gene Transfer (pp. 127-149). Academic Press. [DOI: 10.1016/B978-0-12-815288-5.00005-4]

19. Bhattacharjee, S., & Mishra, S. K. (2019). Adhesion, adhesins and their regulation in Shiga toxin-producing Escherichia coli: mechanism and significance in pathogenesis. Journal of Applied Microbiology, 127(1), 11-25. [DOI: 10.1111/jam.14197]

20. Sansonetti, P. J. (2001). Science, 293(5532), 2093-2098. [DOI: 10.1126/science.1062049]

21. Galán, J. E. (2001). Salmonella interactions with host cells: type III secretion at work. Annual Review of Cell and Developmental Biology, 17(1), 53-86. [DOI: 10.1146/annurev.cellbio.17.1.53]

22. Cossart, P., & Sansonetti, P. J. (2004). Bacterial invasion: the paradigms of enteroinvasive pathogens. Science, 304(5668), 242-248. [DOI: 10.1126/science.1090124]

23. Burns, D. L. (2003). Type IV transporters of pathogenic bacteria. Current Opinion in Microbiology, 6(1), 29-34. [DOI: 10.1016/S1369-5274(03)00002-6]

24. Finlay, B. B., & Falkow, S. (1989). Common themes in microbial pathogenicity revisited. Microbiological Reviews, 53(2), 210-230. [PMID: 2675391]

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

25. Gao, Q., & Garcia, E. C. (2021). Pili multicityling: novel strategies for pilus formation in bacteria. Annual Review of Microbiology, 75, 529-551. [DOI: 10.1146/annurev-micro-090820-004017]

26. Stevens, J. M., & Galyov, E. E. (2004). Exploitation of host cells by Burkholderia pseudomallei. International Journal of Medical Microbiology, 293(7-8), 549-555. [DOI: 10.1078/1438-4221-00283]

27. Cossart, P., & Sansonetti, P. J. (2004). Bacterial invasion: the paradigms of enteroinvasive pathogens. Science, 304(5668), 242-248. [DOI: 10.1126/science.1090124]

28. B. B., & Falkow, S. (1989). Common themes in microbial pathogenicity revisited. Microbiological Reviews, 53(2), 210-230. [PMID: 2675391]

29. Lambris, J. D., Ricklin, D., & Geisbrecht, B. V. (2008). Complement evasion by human pathogens. Nature Reviews Microbiology, 6(2), 132-142. [DOI: 10.1038/nrmicro1824]

30. Skaar, E. P. (2010). The battle for iron between bacterial pathogens and their vertebrate hosts. PLoS Pathogens, 6(8), e1000949. [DOI: 10.1371/journal.ppat.1000949]

31. Beuzón, C. R., & Holden, D. W. (2001). Use of mixed infections with Salmonella strains to study virulence genes and their interactions in vivo. Microbes and Infection, 3(14-15), 1345-1352. [DOI: 10.1016/S1286-4579(01)01498-5]

32. Littman, D. R., & Pamer, E. G. (2011). Role of the commensal microbiota in normal and pathogenic host immune responses. Cell Host & Microbe, 10(4), 311-323. [DOI: 10.1016/j.chom.2011.10.004]

33. Lambris, J. D., Ricklin, D., & Geisbrecht, B. V. (2008). Complement evasion by human pathogens. Nature Reviews Microbiology, 6(2), 132-142. [DOI: 10.1038/nrmicro1824]

34. Blom, A. M., & Ram, S. (2008). Contribution of interactions between complement inhibitor C4b-binding protein and pathogens to their ability to establish infection. Frontiers in Immunology, 2, 2-8. [DOI: 10.3389/fimmu.2011.00008]

35. Meri, T., Amdahl, H., Lehtinen, M. J., Hyvärinen, S., McDowell, J. V., Bhattacharjee, A., ... & Jarva, H. (2013). Microbes bind complement inhibitor factor H via a common site. PLoS Pathogens, 9(4), e1003308. [DOI: 10.1371/journal.ppat.1003308]

36. Zipfel, P. F., Hallström, T., & Riesbeck, K. (2013). Human complement control and complement evasion by pathogenic microbes—tipping the balance. Molecular Immunology, 56(3), 152-160. [DOI: 10.1016/j.molimm.2013.05.222]

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

37. Stoermer, K. A., & Morrison, T. E. (2011). Complement and viral pathogenesis. Virology, 411(2), 362-373. [DOI: 10.1016/j.virol.2010.12.045]

38. Lambris, J. D., & Gros, P. (2016). Complement evasion by bacteria and parasites. Cold Spring Harbor Perspectives in Medicine, 6(5), a016892. [DOI: 10.1101/cshperspect.a016892]

39. Popoff, M. R. (2011). Microbial Pathogenesis, 16(2), 89-103. [DOI: 10.1016/0882-4010(94)90087-6]

40. Lacy, D. B., & Stevens, R. C. (1999). Sequence homology and structural analysis of the clostridial neurotoxins. Journal of Molecular Biology, 291(5), 1091-1104. [DOI: 10.1006/jmbi.1999.3029]

41. Krantz, B. A., & Melnyk, R. A. (2003). Crystal structure of the bacterial virulence factor CNF1 reveals molecular details of toxin activation and membrane targeting. Nature Structural & Molecular Biology, 10(6), 456-464. [DOI: 10.1038/nsb933]

42. Stevens, D. L., & Bryant, A. E. (2002). The role of clostridial toxins in the pathogenesis of gas gangrene. Clinical Infectious Diseases, 35(S1), S93-S100. [DOI: 10.1086/341903]

43. Collier, R. J., & Young, J. A. T. (2003). Anthrax toxin. Annual Review of Cell and Developmental Biology, 19(1), 45-70. [DOI: 10.1146/annurev.cellbio.19.111301.140655]

44. Aktories, K., & Barbieri, J. T. (2005). Bacterial cytotoxins: targeting eukaryotic switches. Nature Reviews Microbiology, 3(5), 397-410. [DOI: 10.1038/nrmicro1155]

45. Paton, A. W., & Paton, J. C. (1998). Detection and characterization of Shiga toxigenic Escherichia coli by using multiplex PCR assays for stx1, stx2, eaeA, enterohemorrhagic E. coli hlyA, rfbO111, and rfbO157. Journal of Clinical Microbiology, 36(2), 598-602. [DOI: 10.1128/JCM.36.2.598-602.1998]

46. Medzhitov, R. (2008). Origin and physiological roles of inflammation. Nature, 454(7203), 428-435. [DOI: 10.1038/nature07201]

47. Nathan, C., & Ding, A. (2010). Nonresolving inflammation. Cell, 140(6), 871-882. [DOI: 10.1016/j.cell.2010.02.029]

48. Serhan, C. N., & Savill, J. (2005). Resolution of inflammation: the beginning programs the end. Nature Immunology, 6(12), 1191-1197. [DOI: 10.1038/ni1276]

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

49. Ward, P. A. (2010). The harmful role of c5a on innate immunity in sepsis. Journal of Innate Immunity, 2(5), 439-445. [DOI: 10.1159/000314857]

50. Schreiber, J., & Jenner, R. G. (2010). Host cell invasion by adenoviruses. Current Topics in Microbiology and Immunology, 343, 93-124. [DOI: 10.1007/82_2010_7]

51. Xu, J., & Jiang, Y. Y. (2011). Host and pathogen interaction during Candida infections in immune compromised hosts. Frontiers in Bioscience, E3(1), 371-384. [DOI: 10.2741/E225]

52. Kohl, B. A., Deutschman, C. S. (2006). Surgical Clinics of North America, 86(6), 1239-1251. [DOI: 10.1016/j.suc.2006.08.001]

53. Kubes, P., & Mehal, W. Z. (2012). Sterile inflammation in the liver. Gastroenterology, 143(5), 1158-1172. [DOI: 10.1053/j.gastro.2012.09.008]

54. Rock, K. L., & Kono, H. (2008). The inflammatory response to cell death. Annual Review of Pathology: Mechanisms of Disease, 3(1), 99-126. [DOI: 10.1146/annurev.pathmechdis.3.121806.151456]

55. Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., & Li, Y. (2018). Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 9(6), 7204-7218. [DOI: 10.18632/oncotarget.23208]

56. Netea, M. G., Balkwill, F., Chonchol, M., Cominelli, F., Donath, M. Y., Giamarellos-Bourboulis, E. J., ... & Joosten, L. A. B. (2017). A guiding map for inflammation. Nature Immunology, 18(8), 826-831. [DOI: 10.1038/ni.3790]

57. Geissmann, F., Manz, M. G., Jung, S., Sieweke, M. H., Merad, M., & Ley, K. (2010). Development of monocytes, macrophages, and dendritic cells. Science, 327(5966), 656-661. [DOI: 10.1126/science.1178331]

58. Wynn, T. A., & Ramalingam, T. R. (2012). Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nature Medicine, 18(7), 1028-1040. [DOI: 10.1038/nm.2807]

59. Baldacchino, F., Muenworn, V., Desquesnes, M., Desoli, F., Charoenviriyaphap, T., Duvallet, G. Transmission of Pathogens by Stomoxys Flies (Diptera, Muscidae): A Review. (2013). Parasite, 20, 26. [DOI: 10.1051/parasite/2013026]

60. Anderson, R. M., & May, R. M. (1991). Infectious Diseases of Humans: Dynamics and Control. Oxford University Press.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

61. Morse, S. S. (1995). Factors in the emergence of infectious diseases. Emerging Infectious Diseases, 1(1), 7-15. [DOI: 10.3201/eid0101.950102]

62. Woolhouse, M. E. J., & Gowtage-Sequeria, S. (2005). Host range and emerging and reemerging pathogens. Emerging Infectious Diseases, 11(12), 1842-1847. [DOI: 10.3201/eid1112.050997]

63. Keeling, M. J., & Rohani, P. (2008). Modeling Infectious Diseases in Humans and Animals. Princeton University Press.

64. World Health Organization. (2007). Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care is Safer Care. World Health Organization.

65. Centers for Disease Control and Prevention. (2020). Vector-Borne Diseases. Retrieved from https://www.cdc.gov/ncezid/dvbd/index.html

66. Nordmann, P., Dortet, L., & Poirel, L. (2012). Carbapenem resistance in Enterobacteriaceae: here is the storm! Trends in Molecular Medicine, 18(5), 263–272. [DOI: 10.1016/j.molmed.2012.03.003]

67. Dong, K., & Zhao, S. (2017). The prevention and control of linezolid-resistant Gram-positive bacteria. Expert Review of Anti-infective Therapy, 15(11), 1027–1037. [DOI: 10.1080/14787210.2017.1391062]

68. Nation, R. L., & Li, J. (2009). Colistin in the 21st century. Current Opinion in Infectious Diseases, 22(6), 535–543. [DOI: 10.1097/QCO.0b013e328332e672]

69. Silverman, J. A., Perlmutter, N. G., & Shapiro, H. M. (2003). Correlation of daptomycin bactericidal activity and membrane depolarization in Staphylococcus aureus. Antimicrobial Agents and Chemotherapy, 47(8), 2538–2544. [DOI: 10.1128/AAC.47.8.2538-2544.2003]

70. Bush, K., & Jacoby, G. A. (2010). Updated functional classification of β-lactamases. Antimicrobial Agents and Chemotherapy, 54(3), 969-976. [DOI: 10.1128/AAC.01009-09]

71. Hooper, D. C. (2001). Mechanisms of fluoroquinolone resistance. Drug Resistance Updates, 4(6), 377-391. [DOI: 10.1054/drup.2001.0210]

72. Nikaido, H. (2011). Structure and mechanism of RND-type multidrug efflux pumps. Advances in Enzymology and Related Areas of Molecular Biology, 77, 1-60. [DOI: 10.1002/9780470920541.ch1]

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

73. Nikaido, H. (2003). Molecular basis of bacterial outer membrane permeability revisited. Microbiology and Molecular Biology Reviews, 67(4), 593-656. [DOI: 10.1128/MMBR.67.4.593-656.2003]

74. Roberts, M. C. (1996). Tetracycline resistance determinants: mechanisms of action, regulation of expression, genetic mobility, and distribution. FEMS Microbiology Reviews, 19(1), 1-24. [DOI: 10.1111/j.1574-6976.1996.tb00251.x]

75. Liu, C., Bayer, A., Cosgrove, S. E., Daum, R. S., Fridkin, S. K., Gorwitz, R. J., ... & Chambers, H. F. (2011). Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clinical Infectious Diseases, 52(3), e18-e55. [DOI: 10.1093/cid/ciq146]

76. World Health Organization. (2020). Global tuberculosis report 2020. World Health Organization. [Link: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2020]

77. Paterson, D. L., & Bonomo, R. A. (2005). Extended-spectrum β-lactamases: a clinical update. Clinical Microbiology Reviews, 18(4), 657-686. [DOI: 10.1128/CMR.18.4.657-686.2005]

78. World Health Organization. (2020). World malaria report 2020: 20 years of global progress and challenges. World Health Organization. [Link: https://www.who.int/publications/i/item/9789240015791]

79. Bennett, D. E., Bertagnolio, S., Sutherland, D., Gilks, C. F. (2008). The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. Antiviral Therapy, 13(Suppl 2), 1-13. [PMID: 18575193]

80. Delcour, A. H. (2009). Outer membrane permeability and antibiotic resistance. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1794(5), 808-816.

81. Bush, K., & Jacoby, G. A. (2010). Updated functional classification of β-lactamases. Antimicrobial Agents and Chemotherapy, 54(3), 969–976. [DOI: 10.1128/AAC.01009-09]

82. Livermore, D. M. (1995). Beta-lactamases in laboratory and clinical resistance. Clinical Microbiology Reviews, 8(4), 557–584. [DOI: 10.1128/cmr.8.4.557]

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

83. Bush, K., & Bradford, P. A. (2016). β-Lactams and β-Lactamase Inhibitors: An Overview. Cold Spring Harbor Perspectives in Medicine, 6(8), a025247. [DOI: 10.1101/cshperspect.a025247]

84. Lovering, A. L., Safadi, S. S., & Strynadka, N. C. (2012). Structural perspective of peptidoglycan biosynthesis and assembly. Annual Review of Biochemistry, 81, 451-478. [DOI: 10.1146/annurev-biochem-061809-112742]

85. Drawz, S. M., & Bonomo, R. A. (2010). Three decades of beta-lactamase inhibitors. Clinical Microbiology Reviews, 23(1), 160-201. [DOI: 10.1128/CMR.00037-09]

86. Bush, K., & Jacoby, G. A. (2010). Updated functional classification of beta-lactamases. Antimicrobial Agents and Chemotherapy, 54(3), 969-976. [DOI: 10.1128/AAC.01009-09]

87. Bush, K., & Bradford, P. A. (2016). β-Lactams and β-Lactamase Inhibitors: An Overview. Cold Spring Harbor Perspectives in Medicine, 6(8), a025247. [DOI: 10.1101/cshperspect.a025247]

88. Tipper, D. J., & Strominger, J. L. (1965). Mechanism of action of penicillins: a proposal based on their structural similarity to acyl-D-alanyl-D-alanine. Proceedings of the National Academy of Sciences of the United States of America, 54(4), 1133-1141. [DOI: 10.1073/pnas.54.4.1133]

89. Bush, K., & Bradford, P. A. (2016). β-Lactams and β-Lactamase Inhibitors: An Overview. Cold Spring Harbor Perspectives in Medicine, 6(8), a025247. [DOI: 10.1101/cshperspect.a025247]

90. Tipper, D. J., & Strominger, J. L. (1965). Mechanism of action of penicillins: a proposal based on their structural similarity to acyl-D-alanyl-D-alanine. Proceedings of the National Academy of Sciences of the United States of America, 54(4), 1133-1141. [DOI: 10.1073/pnas.54.4.1133]

91. Paterson, D. L., & Bonomo, R. A. (2005). Extended-spectrum β-lactamases: a clinical update. Clinical Microbiology Reviews, 18(4), 657-686.

92. Ben-Ami, R., Rodriguez-Bano, J., Arslan, H., Pitout, J. D., Quentin, C., Calbo, E. S., ... & Carmeli, Y. (2009). A multinational survey of risk factors for infection with extended-spectrum β-lactamase-producing enterobacteriaceae in nonhospitalized patients. Clinical Infectious Diseases, 49(5), 682-690.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

93. Lutgring, J. D., & Limbago, B. M. (2016). The problem of carbapenemase-producing-carbapenem-resistant-Enterobacteriaceae detection. Journal of Clinical Microbiology, 54(3), 529-534.

94. Livermore, D. M. (1995). beta-Lactamases in laboratory and clinical resistance. Clinical Microbiology Reviews, 8(4), 557-584. [DOI: 10.1128/CMR.8.4.557]

95. Bush, K., & Jacoby, G. A. (2010). Updated functional classification of beta-lactamases. Antimicrobial Agents and Chemotherapy, 54(3), 969-976. [DOI: 10.1128/AAC.01009-09]

96. Bonomo, R. A. (2011). New Delhi metallo-β-lactamase and multidrug resistance: a global SOS? Clinical Infectious Diseases, 52(4), 485-487.

97. Livermore, D. M. (1995). beta-Lactamases in laboratory and clinical resistance. Clinical Microbiology Reviews, 8(4), 557-584. [DOI: 10.1128/CMR.8.4.557]

98. Bush, K., & Jacoby, G. A. (2010). Updated functional classification of beta-lactamases. Antimicrobial Agents and Chemotherapy, 54(3), 969-976. [DOI: 10.1128/AAC.01009-09]

99. Centers for Disease Control and Prevention. (2020). Antibiotic Resistance Threats in the United States, 2019. Retrieved from https://www.cdc.gov/drugresistance/biggest-threats.html

100. World Health Organization. (2020). Antimicrobial Resistance. Retrieved from https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.