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Extended-Spectrum Beta-Lactamases (ESBLs) and Metallo-Beta-Lactamases (MBLs): A Review

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Abstract

Gram-negative bacteria produce extended-spectrum beta-lactamases (ESBLs) and metallo-beta-lactamases (MBLs), enzymes that play a crucial role in antibiotic resistance. These enzymes enable the bacteria to withstand a wide array of beta-lactam antibiotics, including penicillins, cephalosporins, and carbapenems. The production of these enzymes, particularly by organisms, such as Escherichia coli and Klebsiella pneumoniae, complicates treatment options for severe infections, leading to increased morbidity and mortality in clinical settings. ESBLs are primarily responsible for hydrolyzing extended-spectrum cephalosporins, while MBLs can hydrolyze carbapenems, often regarded as last-resort antibiotics. The genetic basis for these resistances is typically found on plasmids, facilitating their spread among bacterial populations. The detection of ESBL and MBL-producing bacteria in both clinical and environmental settings highlights the critical necessity for improved monitoring and infection control strategies to address the escalating issue of antibiotic resistance. Understanding the mechanisms of resistance and the epidemiology of these enzymes is crucial for developing effective therapeutic strategies and public health interventions.

Keywords: Extended-spectrum beta-lactamases (ESBLs), metallo-beta-lactamases (MBLs), gram-negative bacteria, antibiotics

INTRODUCTION

Characterizing ESBLs) and MBLs producing gram-negative bacteria from both human clinical cases and environmental samples is crucial in understanding the complex dynamics of antibiotic resistance in these microorganisms. Gram-negative bacteria, especially those belonging to the *Enterobacteriaceae* family, are well-known for their capacity to produce enzymes that provide resistance to a broad spectrum of beta-lactam antibiotics, including penicillins, cephalosporins and monobactams [1]. This resistance is often mediated by the production of ESBLs and MBLs, which are enzymes that can hydrolyze the beta-lactam ring of these antibiotics, rendering them ineffective against the bacteria [2].

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ESBLs are enzymes capable of hydrolyzing a wider variety of beta-lactam antibiotics than conventional beta-lactamases, including third-generation cephalosporins and monobactams like aztreonam. Gram-negative bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae* often produce them. They are a significant cause of morbidity and mortality in hospitals due to their ability to cause severe infections, such as sepsis and meningitis [3]. In contrast, MBLs are enzymes capable of hydrolyzing a wider variety of beta-lactam antibiotics than ESBLs, including carbapenems, which are frequently regarded as the last line of defence against multidrug-resistant gram-negative bacteria. MBLs are often produced by gram-negative bacteria, such as *Pseudomonas*

aeruginosa, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*. They are a significant cause of morbidity and mortality in hospitals due to their ability to cause severe infections, such as pneumonia and sepsis. The recovery of ESBL and MBL-producing gram-negative bacteria from both human clinical cases and environmental samples highlights the importance of understanding the ecology and epidemiology of these microorganisms. Environmental samples can provide valuable insights into these microorganisms' genetic diversity and distribution and their potential to spread antibiotic-resistant genes to other bacteria [4]. Likewise, human clinical cases can offer important information regarding the clinical relevance and treatment results of infections caused by these microorganisms.

ESBLs and MBLs are enzymes that can hydrolyze the beta-lactam ring of beta-lactam antibiotics, rendering them ineffective against the bacteria. This resistance is often mediated by the production of these enzymes, which are encoded by genes that are either chromosomally or plasmidically located [5]. The prevalence of ESBLs and MBLs among gram-negative bacteria is a significant threat to public health, particularly in hospitals where the spread of these resistant bacteria can lead to severe infections, increased morbidity and mortality. The recovery of ESBL and MBL-producing gram-negative bacteria from both human clinical cases and environmental samples highlights the importance of understanding the ecology and epidemiology of these microorganisms [6, 7]. ESBLs and MBLs are significant because they grant bacteria resistance to various beta-lactam antibiotics, such as penicillins, cephalosporins, and carbapenems. This resistance often leads to multidrug resistance, making infections caused by these bacteria difficult to treat. The co-production of ESBLs and MBLs with other beta-lactamases, such as AmpC, further complicates the treatment of these infections. The background and significance of ESBLs and MBLs are also critical in understanding the mechanisms of resistance and dissemination of resistant genes. ESBLs and MBLs are frequently encoded by genes found on plasmids, which can be readily transferred between bacteria, promoting the dissemination of resistance [8]. The coexistence of ESBLs and MBLs with additional resistance mechanisms, including efflux pumps and mutations in target sites, significantly enhances the antibiotic resistance of these bacteria.

EXTENDED-SPECTRUM BETA-LACTAMASES (ESBLS)

Extended-spectrum beta-lactamases (ESBLs) are enzymes produced by certain bacteria that enable resistance to various beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam. These enzymes can break down extended-spectrum cephalosporins and aztreonam but remain susceptible to inhibition by beta-lactamase inhibitors like clavulanic acid [9]. Both molecular and functional traits determine the classification of ESBLs. The Ambler molecular classification categorizes β-lactamases into four primary classes (A to D), with ESBLs specifically classified under class A. The Bush-Jacoby-Medeiros functional classification categorizes β-lactamases based on their substrate and inhibitor characteristics, placing ESBLs in group 2be or group 2d (OXA-type). ESBLs are commonly encoded by genes found on large plasmids that harbor genes conferring resistance to other antimicrobial agents. This extensive antibiotic resistance poses a major challenge in clinical treatment, as it restricts the available options for managing infections caused by ESBL-producing bacteria [10]. The most prevalent bacteria that produce ESBLs are *Escherichia coli* and *Klebsiella pneumoniae*, both of which are typically found in the human gut. These bacteria can cause infections, including urinary tract infections and pneumonia, and are typically treated with antibiotics, such as penicillins and cephalosporins. However, when these bacteria produce ESBLs, they develop resistance to these antibiotics, complicating treatment efforts [11, 12]. ESBL-producing bacteria can be transmitted through direct person-to-person contact or by touching contaminated surfaces. Infections caused by ESBL-producing bacteria are prevalent in healthcare environments, where these bacteria can be easily transmitted by healthcare professionals who frequently interact with infected patients. The symptoms of infections caused by ESBL-producing bacteria depend on the bacterial strain and the affected body site [13]. Typical signs include fever, chills, nausea, vomiting, and respiratory difficulties. Treatment typically involves using less common antibiotics, such as carbapenems and may require multiple courses of treatment and different medications to resolve the infection. Prevention and control of ESBL-producing bacteria involves proper infection-control practices and barriers to prevent the

spread of the bacteria [14]. This includes increased handwashing, especially in healthcare settings, and avoiding close contact with people or animals that may be infected. ESBLs are enzymes generated by specific bacteria that provide resistance against a broad spectrum of beta-lactam antibiotics. They are categorized according to their molecular and functional traits and are frequently encoded by genes located on large plasmids. Bacteria that produce ESBLs can lead to a range of infections and are especially prevalent in healthcare environments. Treatment requires the use of less commonly prescribed antibiotics, while prevention and control rely on effective infection-control measures and barriers.

Extended-spectrum beta-lactamases (ESBLs) are enzymes that provide resistance to a wide range of beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam. These enzymes are classified based on both molecular and functional characteristics. According to the Ambler molecular classification, β-lactamases are categorized into four main classes (A to D), with ESBLs belonging to class A. The Bush-Jacoby-Medeiros functional classification organizes β-lactamases based on their substrate specificity and inhibitor susceptibility, placing ESBLs in group 2be or, in the case of OXA-type enzymes, group 2d. The Ambler classification relies on protein homology (amino acid sequence similarity) rather than phenotypic traits. Within this system, β-lactamases in classes A, C, and D are classified as serine β-lactamases, whereas class B enzymes are identified as metallo-β-lactamases. ESBLs specifically fall under molecular class A. The Bush-Jacoby-Medeiros classification system is particularly important for physicians and microbiologists in diagnostic laboratories, as it focuses on clinically significant β-lactamases and their β-lactam substrates. This system categorizes ESBLs into two groups: 2be and 2d (OXA-type). Although group 2d shares several characteristics with group 2be enzymes, it is distinct in its resistance to inhibitors [15, 16]. There is no universally accepted definition of ESBLs; however, a widely used working definition describes them as β-lactamases that enable bacteria to resist penicillins, as well as first, second, and third-generation cephalosporins, and aztreonam, except for cephamycins and carbapenems, by hydrolyzing these antibiotics. Moreover, these enzymes can be inhibited by β-lactamase inhibitors, such as clavulanic acid [17, 18].

MECHANISM OF ESBL

Extended-spectrum beta-lactamases (ESBLs) facilitate bacterial resistance by breaking down extended-spectrum cephalosporins and aztreonam. These enzymes belong to the serine beta-lactamase family, utilizing a serine residue at their active site to cleave the beta-lactam ring of antibiotic [19]. The structural composition of ESBLs includes a conserved sequence motif that is crucial for their enzymatic function, allowing the antibiotic to bind to the active site. Based on amino acid sequences and functional mechanisms, ESBLs are categorized into four major classes: A, B, C, and D. Their functional classification is determined by their substrate specificity and response to inhibitors. ESBLs fall under group 2be or group 2d (OXA-type) based on their capacity to degrade extended-spectrum cephalosporins and aztreonam, as well as their resistance to beta-lactamase inhibitors like clavulanic acid [20].

The presence of extended-spectrum beta-lactamases (ESBLs) has significant clinical consequences, as they confer resistance to a wide range of beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam. This resistance can result in treatment failures, leading to higher rates of morbidity and mortality in individuals infected with ESBL-producing pathogens. *Escherichia coli* and *Klebsiella pneumoniae* are the two most common bacteria associated with ESBL production, both of which are naturally present in the human intestinal tract. These bacteria can cause infections, including urinary tract infections and pneumonia, and are typically treated with antibiotics, such as penicillins and cephalosporins. However, when these bacteria produce ESBLs, they gain resistance to these antibiotics, complicating treatment efforts. The clinical implications of ESBLs are particularly significant in healthcare settings, where the bacteria can spread quickly through person-to-person contact or contact with contaminated surfaces. Infections caused by ESBL-producing bacteria are readily transmitted by healthcare professionals who frequently interact with infected patients [21, 22].

Symptoms of infections caused by ESBL-producing bacteria depend on the type of bacteria and the affected body area. Common symptoms include fever, chills, nausea, vomiting and difficulty breathing. Treatment typically involves using less common antibiotics, such as carbapenems and may require multiple courses of treatment and different medications to resolve the infection. Prevention and control of ESBL-producing bacteria involve proper infection-control practices and barriers to prevent the spread of the bacteria. This includes increased handwashing, especially in healthcare settings and avoiding close contact with people or animals that may be infected (Figure 1).

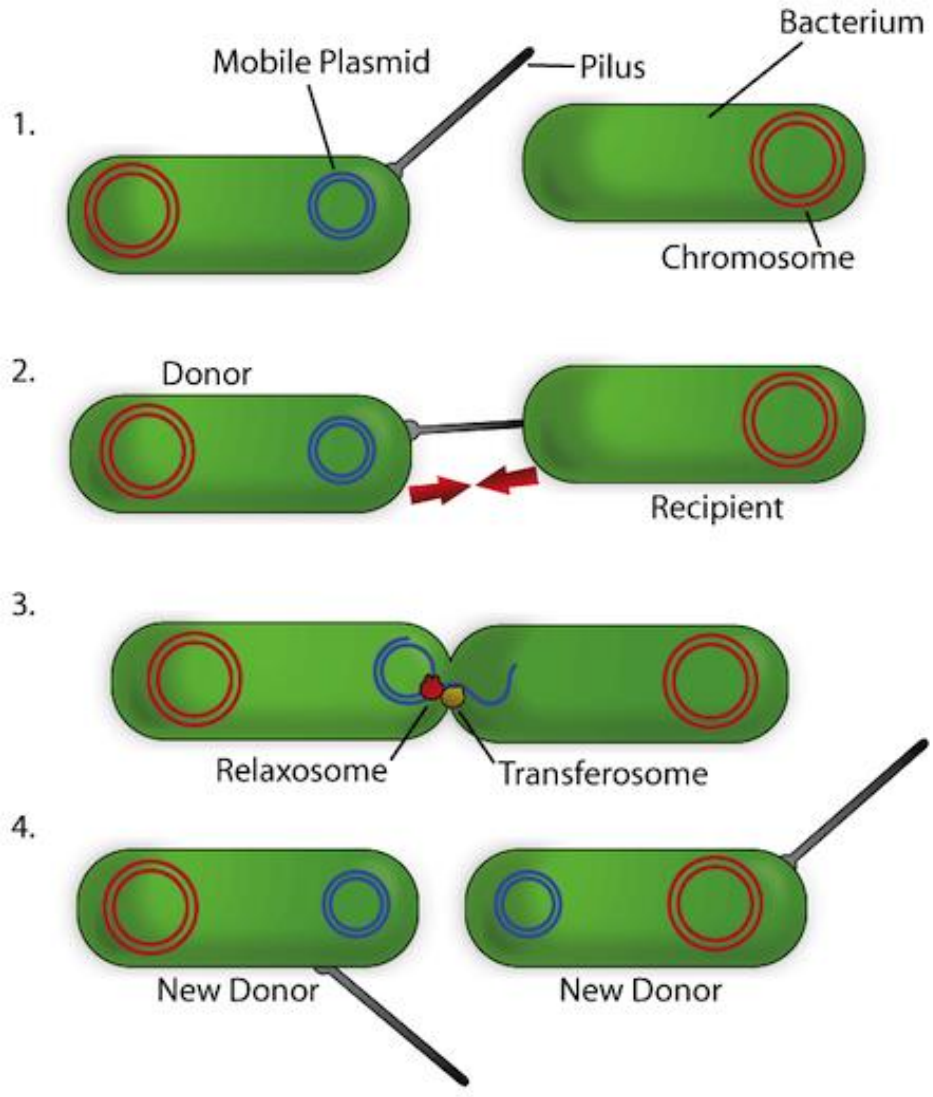

Figure 1. Mechanism of ESBL.

Metallo-β-Lactamases (MBLs)

MBLs are a varied group of enzymes that facilitate the hydrolysis of a wide array of β-lactam antibiotics, including carbapenems. They are distinguished by their dependence on a zinc ion at the active site and are typically produced alongside a second or third β-lactamase in clinical isolates [23]. MBLs are classified into three subclasses (B1, B2 and B3) based on their amino acid sequence and functional properties. Most MBLs associated with the spread of antibiotic resistance are part of the B1 subgroup. Although many characterized B3 MBLs have been identified in environmental bacteria, they are being increasingly observed in clinical samples. B3-type MBLs demonstrate greater variability in their active sites compared to other MBLs [24]. The primary resistance mechanism to β-lactams

provided by MBLs is the hydrolysis of the β-lactam ring. MBLs are distinguished from other β-lactamases by their ability to hydrolyze carbapenems, an essential class of β-lactams often used as a last-resort treatment for infections that do not respond to narrower-spectrum β-lactams [25, 26]. Metallo-β-lactamases (MBLs) can be inhibited by metal ion chelators, such as EDTA, dipicolinic acid, and 1,10-o-phenanthroline. These agents bind to zinc ions at the active site of MBLs, thereby reducing their enzymatic activity. The gene encoding MBLs can be found on various genetic elements, including integrons, transposons, plasmids, and chromosomes. Its expression is frequently regulated by a promoter located within the integrase gene [27]. The global proliferation of MBL-producing Enterobacterales poses a significant public health threat, especially given the stagnant development of effective antibiotics. Successful treatment of infections caused by these bacteria relies on the detection of β-lactamase in clinical environments. Historically, a range of antibiotics has been utilized to combat infections from MBL-producing Enterobacterales. While antimicrobials, such as aminoglycosides, tetracyclines, fosfomycin, and polymyxins exhibit promising in vitro efficacy, there is insufficient clinical data to advocate for their routine use. Currently, the combination of ceftazidime-avibactam with aztreonam shows considerable promise for treating infections caused by MBL-producing Enterobacterales and has the most substantial clinical evidence supporting its application among available antibiotic options [28–30].

MECHANISM OF MBL

The mechanisms of resistance to β-lactam antibiotics involve several vital processes that bacteria employ to evade the effects of these drugs. These mechanisms involve decreased access to penicillin-binding proteins (PBPs), reduced binding affinity for PBPs, and the degradation of the antibiotic through the production of β-lactamase enzymes that bind to and hydrolyze β-lactams. In gram-negative bacteria, resistance to β-lactams primarily arises from the production of β-lactamases, which are enzymes that hydrolyze β-lactam antibiotics, making them ineffective. The sheer number of β-lactamases identified highlights the complexity of this resistance mechanism, with 927 named β-lactamases from 24 different classes [31]. The evolution of resistance in gram-negative bacteria has occurred in waves, with the emergence of narrow-spectrum penicillinases followed by resistance to extended-spectrum cephalosporins due to point mutations within enzymes like TEM-1 and SHV-1. These mutations, combined with changes in promoter activity and reduced antibiotic access to the periplasmic space, have led to high-level resistance to extended-spectrum cephalosporins. The resistance mechanisms to β-lactam antibiotics result from a complex interaction of enzyme activity, alterations in bacterial proteins and modifications in membrane permeability, enabling bacteria to survive and thrive despite the presence of these drugs (Figure 2) [32].

The clinical relevance of β-lactam resistance, particularly in *Enterobacteriaceae*, is crucial due to its impact on patient outcomes, healthcare costs and the overall management of infections caused by these bacteria. The emergence of resistance to β-lactam antibiotics, including extended-spectrum cephalosporins, poses significant challenges in treating infections caused by *Enterobacteriaceae*. This resistance can lead to increased drug toxicity, mortality rates, and healthcare costs associated with these infections. The molecular mechanisms and epidemiology of β-lactam resistance in *Enterobacteriaceae* are essential for developing effective treatment strategies and combating the spread of resistant strains. Identifying key β-lactamases, such as TEM-1, SHV-1 and KPC-2, highlights the importance of monitoring and addressing resistance mechanisms to guarantee optimal patient care and effective infection control measures [33].

Characterization of ESBLs and MBLs

Characterizing ESBLs and MBLs involves understanding their molecular structures, functions, prevalence and impact on antibiotic resistance. ESBLs are plasmid-encoded enzymes found frequently in *Enterobacteriaceae* that confer resistance to a wide range of beta-lactam antibiotics. MBLs comprise a diverse group of enzymes that facilitate the breakdown of β-lactam antibiotics, including carbapenems, by utilizing a zinc ion at their active site. The occurrence of ESBL and MBL producers among Gram-negative bacteria, including *Escherichia coli* and *Klebsiella pneumoniae*, is notable, with ESBLs

typically being the most detected carbapenemase genes, followed by MBLs [34, 35]. The coexistence of ESBL and MBL producers among various isolates underscores the complexity of antibiotic resistance mechanisms in clinical settings. Detecting ESBL and MBL producers is essential for implementing appropriate antimicrobial therapy and improving patient outcomes, particularly given the rising multidrug resistance among Gram-negative bacteria. Monitoring ESBL and MBL production and multidrug resistance patterns is essential for effective infection control and antibiotic stewardship in healthcare settings [36].

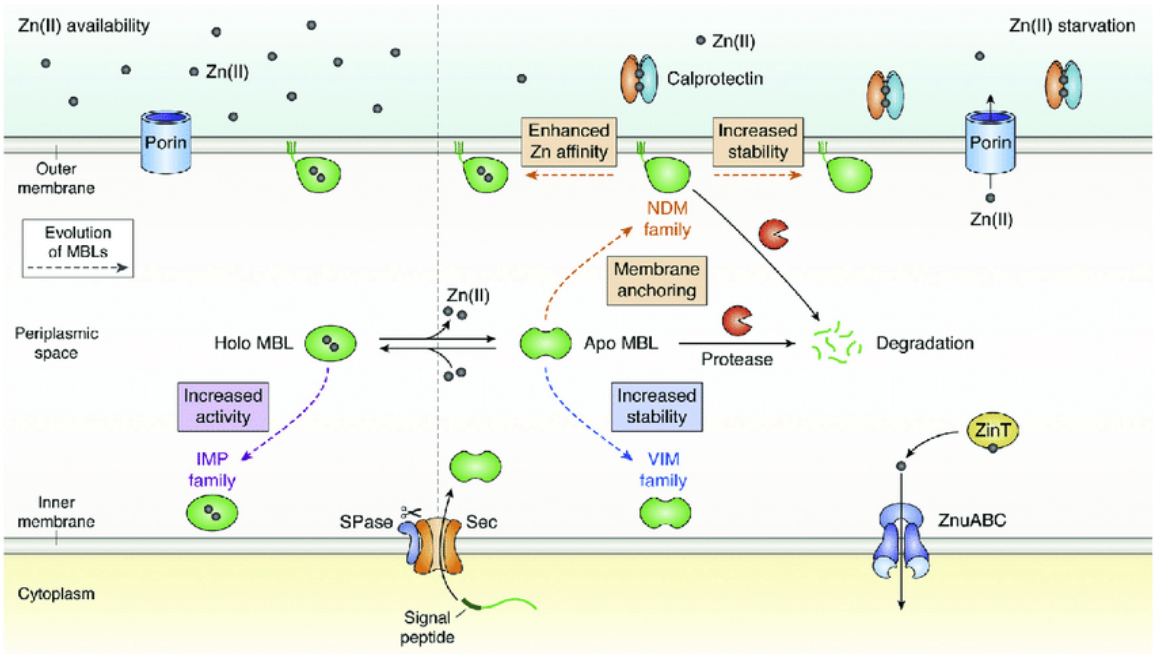

Figure 2. Mechanism of MBL.

Genetic Diversity of ESBLs and MBLs

ESBLs are categorized into molecular classes (A, B, C and D) and functional groups (2be and 2d) according to their structural and functional properties [37]. The accumulation of minor mutations in the primary amino acid sequences of β-lactamases, including ESBLs, can ultimately broaden their substrate range. The most frequently identified ESBL genes are blaCTX-M, followed by blaTEM and blaSHV, indicating the proliferation of specific ESBL variants. ESBL-producing *Enterobacteriaceae*, particularly *Klebsiella pneumoniae* and *Escherichia coli*, are widely prevalent and exhibit high antibiotic resistance [38].

MBLs are a diverse group of enzymes categorized into three subclasses (B1, B2, and B3) according to their amino acid sequences and functional characteristics. Most MBLs associated with the spread of antibiotic resistance belong to the B1 subgroup, while B3-type MBLs display greater variability in their active sites. The MBL gene can reside on various genetic elements like integrons, transposons, plasmids and chromosomes, contributing to their genetic diversity and proliferation [39].

Evolutionary Trends

The genetic diversity and spread of MBLs and ESBLs present a significant challenge in effectively treating infections caused by resistant bacteria. These enzymes, commonly found in Gram-negative bacteria, are associated with a wide range of clinical isolates, particularly within the *Enterobacteriaceae* family, *Pseudomonas spp*., and *Acinetobacter baumannii* [27]. The ability of MBLs and ESBLs to reside on various genetic elements, such as integrons, transposons, and plasmids, facilitates their dissemination and contributes to the evolution of antibiotic resistance. The prevalence of ESBL and MBL producers varies across different regions and species; for instance, *E. coli* accounts for 35.71% of

MBL producers, followed by *Pseudomonas spp*. at 28.57%, *K. pneumoniae* at 21.43%, *Proteus vulgaris* at 7.14%, and *Acinetobacter baumannii*, which poses a significant threat to public health, particularly in hospital settings [28]. The emergence of novel MBL and ESBL variants and their global spread underscores the urgent need for continuous monitoring, surveillance, and the development of effective inhibitors and treatment strategies to combat this growing public health concern. The prevalence of ESBLs and MBLs in humans, animals, and wastewater also varies widely, ranging from 11% to 72%. Various factors, including antibiotic use, genetic exchange and environmental factors, influence these enzymes' emergence and spread. The epidemiology of ESBLs and MBLs highlights the widespread distribution of these enzymes among Gram-negative bacteria, particularly in clinical isolates of *Enterobacteriaceae, Pseudomonas spp*., and *Acinetobacter baumannii*. The prevalence of ESBLs and MBLs varies across different regions and species, and multiple factors influence their emergence and spread [40–42].

ESBL DETECTION METHODS

Disc Diffusion Method

This method involves detecting ESBL production by measuring the inhibition zones of specific antibiotics, including cefpodoxime, ceftazidime, aztreonam, cefotaxime, and ceftriaxone. An inhibition zone of 22 mm or less for a 10-μg cefpodoxime disc indicates potential ESBL production [29].

Combined Disc Method

This confirmatory test employs cefotaxime (CTX) and ceftazidime (CAZ), both individually and in combination with clavulanic acid (CA). A confirmed production of ESBL is indicated by an increase of 5 mm or more in the zone of inhibition for either antimicrobial agent when tested with CA compared to when tested alone.

MBL DETECTION METHODS

Initial Screening

The initial screening for MBL production includes testing with ceftazidime (CAZ) and imipenem (IPM). If the zone of inhibition measures ≤18 mm for CAZ and ≤19 mm for IPM, the isolate is regarded as a potential MBL producer [31].

Confirmation by Combined Disc Method

The combined disc method using imipenem (IPM) alone and combined with EDTA can confirm MBL production. A ≥7 mm increase in zone diameter for the IPM-EDTA disc compared to the IPM disc alone indicates MBL production.

THE CHALLENGES AND LIMITATIONS

Achieving high sensitivity in detecting ESBL and MBL producers is essential, particularly in cases where these enzymes may be present at low levels, necessitating sensitive detection methods for accurate identification. Ensuring specificity in detection methods is equally crucial to accurately distinguish between ESBL and MBL producers and non-producers, as cross-reactivity or false-positive results can lead to misdiagnosis and inappropriate treatment. The complexity of some detection methods, which may require specialized equipment, trained personnel, and specific laboratory conditions, poses a challenge for their widespread use, especially in resource-limited settings. Additionally, the costs associated with implementing advanced detection methods can be prohibitive for healthcare facilities with limited financial resources. Time-consuming procedures can further delay results, impacting timely patient management and infection control measures. The continuous emergence of new variants of ESBL and MBL enzymes presents ongoing challenges in detection, necessitating constant updates and adaptations of detection methods. Accurate interpretation of results is vital to prevent misinterpretation and ensure the correct identification of ESBL and MBL producers, highlighting the need for trained personnel and standardized protocols.

Clinical Impact and Treatment Challenges

Infections caused by bacteria that produce ESBL and MBL greatly contribute to higher morbidity and mortality rates because of their resistance to various antibiotics, resulting in restricted treatment choices. These infections often result in prolonged hospital stays, elevated healthcare costs, and higher mortality rates, particularly among immunocompromised patients, such as those undergoing chemotherapy or suffering from chronic diseases. The rising occurrence of these resistant bacteria worsens the antibiotic resistance crisis, reducing the efficacy of existing treatments and heightening the threat of infections that may no longer be treatable. Furthermore, the complex nature of infections caused by ESBL and MBL producers necessitates specialized care and multidisciplinary approaches to management, which can be costly and resource intensive. The implications extend beyond individual patient outcomes, posing significant public health challenges as outbreaks can strain healthcare systems and affect community health at large. Implementing effective antibiotic stewardship programs is essential to enhance antibiotic usage and reduce the spread of these resistant strains.

Infection Control Strategies

To effectively curb the spread of bacteria that produce ESBL and MBL, healthcare facilities must adopt a range of thorough infection control strategies. Standard precautions, such as rigorous hand hygiene, appropriate use of personal protective equipment (PPE), and proper handling of patient care equipment are essential. Additionally, transmission-based precautions should be adopted, including contact, droplet, and airborne precautions for patients infected or colonized with these resistant bacteria. Effective environmental cleaning and disinfection of patient care areas are essential to reducing the risk of pathogen transmission. Additionally, implementing antimicrobial stewardship programs can help optimize antibiotic usage and prevent the emergence of resistance. Active screening and surveillance in high-risk areas, like intensive care units, are vital for identifying carriers and implementing necessary infection control measures. Education and training for healthcare personnel on infection control practices and the importance of adherence to protocols are also crucial. The environmental impact of ESBL and MBL-producing bacteria is significant, as they can be found in sewage, soil, and animals, indicating potential reservoirs outside healthcare settings. Factors, such as temperature, biological activity in soil and water, and cattle density contribute to their prevalence in the environment, suggesting a potential transmission route between animals and humans through environmental pathways. These multifaceted strategies are essential for reducing healthcare-associated infections and improving patient safety outcomes.

Environmental Factors

Environmental factors significantly influence the prevalence and dissemination of ESBL and MBL-producing bacteria. Temperature is a key factor, as elevated temperatures can boost biological activity in soils and water, subsequently affecting the presence of antimicrobial resistance (AMR) in environmental bacteria, including those producing ESBL and MBL. Seasonal variations have been documented, with studies indicating fluctuations in the prevalence of ESBL-producing bacteria, like *E. coli* in sewage water throughout different seasons, peaking during warmer months. Additionally, cattle density is significantly associated with the presence of these resistant bacteria, suggesting a link between animal reservoirs and their environmental spread. Furthermore, antimicrobial pollution from various sources contributes to the persistence and transmission of AMR to wildlife and the broader environment, exacerbating the issue of ESBL and MBL-producing bacteria. These resistant strains have been identified in various environmental samples, including sewage, soil, animals and abattoir settings, indicating that they may serve as reservoirs outside healthcare facilities. The identification of ESBL and MBL-producing bacteria in food-producing animals and wildlife highlights the broad environmental implications of these resistant strains [41].

The Public Health Implications

Infections caused by bacteria that produce ESBL and MBL are linked to higher rates of morbidity and mortality due to the limited treatment options available and the increased likelihood of treatment

failures. Studies indicate that patients with these infections experience significantly elevated mortality rates [12]. These resistant bacteria contribute to the global antibiotic resistance crisis, complicating effective treatment and raising the risk of untreatable infections. They are frequently linked to healthcare-associated infections, resulting in longer hospital stays, increased healthcare costs, and potential outbreaks within healthcare settings. Moreover, ESBL and MBL-producing bacteria have been found to spread beyond healthcare environments, posing a public health risk through person-to-person transmission and environmental contamination. The emergence of these resistant strains limits available treatment options, often necessitating the use of more potent and less commonly prescribed antibiotics, which can further complicate antimicrobial stewardship efforts and contribute to resistance development. The global spread of ESBL and MBL-producing bacteria represents a significant public health threat that necessitates coordinated efforts in surveillance, infection control, and antibiotic stewardship to effectively address this growing challenge. Overall, these resistant bacteria have profound implications for patient outcomes, healthcare systems, and community health, underscoring the need for a comprehensive approach that includes infection control measures, antimicrobial stewardship programs, active surveillance and ongoing research to combat their spread.

FUTURE DIRECTIONS

To effectively address the spread of ESBL and MBL-producing bacteria, it is crucial to implement several strategic initiatives. Improved surveillance systems should be established to track the prevalence and transmission of these resistant strains in both healthcare environments and the community. This data will help guide infection control measures and treatment approaches [40]. Strengthening antimicrobial stewardship programs is crucial for optimizing antibiotic use, preventing resistance development, and curbing the spread of ESBL and MBL strain [41]. Additionally, investing in research and development is necessary to create novel antibiotics, alternative treatment options, and advanced diagnostic tools to address the challenges posed by these resistant bacteria [42]. Public health interventions must also be enacted to raise awareness about the risks associated with ESBL and MBL-producing bacteria, promoting effective infection control practices while educating both healthcare providers and the public on appropriate antibiotic usage. Furthermore, adopting a One Health approach that integrates human, animal and environmental health will help tackle the complex dynamics of antimicrobial resistance across various sectors. Comprehensive epidemiological studies are needed to better understand the prevalence, distribution and risk factors related to these resistant bacteria in different settings. Investigating their genetic characterization will aid in identifying novel resistance mechanisms and potential intervention targets.

Therapeutic Innovations

The development of novel antibiotics and antibiotic combinations is crucial to address the limited treatment options for infections caused by ESBL and MBL-producing bacteria, researchers are investigating new antimicrobial agents and strategies to address resistance mechanisms. One proposed approach is combination therapy, which involves pairing cefotaxime or ceftazidime with clavulanic acid. This strategy may aid in the detection and confirmation of these resistant strains, potentially improving treatment effectiveness. Additionally, advancements in rapid diagnostic tests, including phenotypic detection methods, like disc diffusion and combined disc methods, are essential for timely identification of ESBL and MBL-producing bacteria, enabling more targeted treatment strategies. Effective infection control measures, including standard precautions and antimicrobial stewardship programs, are essential to prevent the transmission of these resistant pathogens. Furthermore, enhanced surveillance and comprehensive epidemiological studies are necessary to understand the prevalence, distribution and risk factors associated with ESBL and MBL-producing bacteria, guiding the implementation of effective control measures.

CONCLUSIONS

The review paper emphasizes the critical role of ESBLs and MBLs in the growing challenge of antibiotic resistance among gram-negative bacteria. Enzymes, like those produced by pathogens, such as *Escherichia coli* and *Klebsiella pneumoniae* confer resistance to a broad range of beta-lactam

antibiotics, including penicillins, cephalosporins, and even carbapenems, which are typically reserved as last-line treatments. The presence of these resistant strains in healthcare environments makes managing infections more challenging, leading to increased rates of morbidity and mortality. Therefore, it is crucial to conduct comprehensive surveillance and characterization of these enzymes in both clinical and environmental samples to better understand their spread and genetic variation. Additionally, this underscores the need for effective infection control measures to curb the transmission of these resistant pathogens. As the landscape of antibiotic resistance continues to evolve, ongoing research into novel therapeutic strategies and the mechanisms driving resistance is essential for safeguarding public health and improving patient outcomes. Addressing these challenges requires a coordinated effort involving healthcare professionals, researchers and policymakers to develop comprehensive strategies aimed at combating the threat posed by ESBLs and MBLs.

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