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A Review on Extended Spectrum β-Lactamase and Metallo β-Lactamase Producing Bacteria: From Current Understanding to Future Course of Action

[1] Linganagouda Patil, [2] Suneel Dodamani

[1, 2] Dr Prabhakar Kore Basic Science Research Centre, KLE Academy of Higher Education and Research, Deemed to be University, Nehru Nagar, Belagavi-590010. Karnataka, India

[1, 2] Jawaharlal Nehru Medical College, Nehru Nagar, Belagavi-590010. Karnataka, India

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Corresponding Author: **Dr. Suneel Dodamani**

Abstract

The growing prevalence of multidrug-resistant Gram-negative bacteria, particularly those producing extended-spectrum β-lactamases (ESBLs) and metallo-β-lactamases (MBLs), presents a serious global health threat. These enzymes degrade a wide range of β-lactam antibiotics, undermining treatment efficacy. ESBLs (e.g., CTX-M, TEM, SHV) mainly target third-generation cephalosporins and are commonly found in *Escherichia coli* and *Klebsiella pneumoniae*. MBLs (e.g., NDM, VIM, IMP) confer broader resistance, including to carbapenems, and are not inhibited by β-lactamase inhibitors. Rapid gene transfer via mobile elements accelerates their spread in hospitals and communities.

This review outlines the molecular classification, resistance mechanisms, detection methods, and clinical impact of ESBL and MBL producers. It highlights current diagnostic challenges—especially for MBLs—and reviews phenotypic and molecular tools. Treatment options are increasingly limited, with carbapenems reserved for ESBL infections and few effective agents for MBLs. Co-existence of ESBL and MBL genes in single strains further complicates therapy and infection control. Mitigating this threat demands global surveillance, rapid diagnostics, prudent antibiotic use, and the development of novel drugs or inhibitors. A deeper understanding of resistance dynamics is essential to inform research, clinical practice, and policy.

Keywords: Extended-Spectrum β-lactamases, Metallo-β-lactamases, Antimicrobial Resistance (AMR)

Introduction

The rise in multidrug-resistant Gram-negative bacteria has been consistently observed in recent years, especially among Enterobacteriaceae that produce extended-spectrum β-lactamases (ESBLs). These enzymes can break down penicillins, as well as first-, second-, and third-generation cephalosporins and aztreonam, though they are ineffective against cephamycins and carbapenems. Their action can be inhibited by substances like clavulanic acid [5]. Organisms that produce ESBLs can cause severe, potentially life-threatening infections, which contribute to higher rates of illness, death, and increased healthcare expenses [6, 7, 8, 9]. *Klebsiella pneumoniae* and *Escherichia coli* are the most commonly detected ESBL-producing strains globally; nevertheless, ESBLs have also been found in other Enterobacteriaceae species (Jacoby 2005) [10].

An extended-spectrum β-lactamase (ESBL) is a type of β-lactamase enzyme that can cause resistance or reduced sensitivity to oxyimino-cephalosporins such as cefotaxime, ceftriaxone, and ceftazidime, as well as to monobactams like aztreonam [11]. However, ESBLs are unable to break down cephamycins (e.g., cefoxitin and cefotetan) or carbapenems (such as imipenem and meropenem), and their enzymatic activity can be blocked by β-lactamase inhibitors like clavulanic acid and tazobactam [11]. The primary ESBL-producing bacteria are *Escherichia coli* and *Klebsiella pneumoniae*, which are major contributors to both community-acquired and hospital-acquired infections (Pitout *et al*., 2008) [12].

Molecular Classification of β-Lactamases

β-Lactamases are commonly classified according to two general schemes: the Ambler molecular classification and the Bush–Jacoby–Medeiros functional classification [1]. The Ambler scheme categorizes β-lactamases into four classes based on protein homology, with classes A, C, and D containing serine β-lactamases while class B enzymes are metallo-β-lactamases [1]. The

Bush–Jacoby–Medeiros functional scheme is based on the substrate and inhibitor profiles of the enzymes [1]. ESBLs are generally defined as transmissible β-lactamases that can be inhibited by clavulanic acid, tazobactam, or sulbactam, and are encoded by genes that can be exchanged between bacteria [1]. Class B β-lactamases, or metallo-β-lactamases (MBLs), utilize a Zn^{2+} metal cofactor to catalyze the inactivation of β-lactams and can hydrolyze virtually all clinically used bicyclic β-lactams and serine β-lactamase-inhibiting drugs [3].

β-Lactamase Resistance

The production of extended-spectrum β-lactamases (ESBLs) represents a significant resistance mechanism that impedes antimicrobial treatment of infections caused by Enterobacteriaceae and poses a serious threat to our current antibiotic arsenal [1]. These enzymes are capable of hydrolyzing a variety of β-lactam antibiotics, including extended-spectrum cephalosporins, rendering them ineffective [1]. Similarly, metallo-β-lactamases (MBLs) production is a common mechanism of resistance to carbapenems and most other β-lactam antibiotics in Gram-negative bacteria, creating serious challenges for antimicrobial therapy and leading to poor patient outcomes [4]. The rising prevalence of these enzymes has necessitated the development of innovative approaches for detection and treatment to combat these increasingly resistant pathogens [1]. With β-lactam antibiotics accounting for more than half of all parenterally administered antibiotic prescriptions in the United States, the emergence of resistance poses a significant threat to public health [3].

Mechanisms of Antibiotic Resistance

Bacteria have developed several strategies to counter the effects of antibiotics [1]. The primary mechanisms of antibiotic resistance include antibiotic inactivation through hydrolysis, enzymatic modifications, alterations in target sites, decreased membrane permeability, and efflux pumps. For β-lactamase-producing organisms, the hydrolysis of the β-lactam ring is the most common mechanism of resistance [1]. Extended-spectrum β-lactamases can hydrolyze penicillins, third-generation cephalosporins, and aztreonam but not cephamycins or carbapenems [1]. Metallo-β-lactamases, on the other hand, can hydrolyze virtually all β-lactam antibiotics except monobactams like aztreonam [3]. The genes encoding these enzymes are often located on mobile genetic elements such as plasmids, allowing for rapid dissemination among different bacterial species [1].

Types of Extended-Spectrum β-Lactamases

There are several major types of ESBLs that have been identified worldwide. TEM-type ESBLs, derived from TEM-1 and TEM-2, were among the first ESBLs discovered and can hydrolyze penicillins and first-generation cephalosporins [1]. SHV-type ESBLs, originating from Klebsiella spp., confer resistance to broad-spectrum penicillins. CTX-M-type enzymes, which preferentially hydrolyze cefotaxime over ceftazidime, have become the most prevalent globally [1]. Other less common ESBLs include OXA-type, PER-type, VEB-type, and GES-type enzymes, each with their unique substrate profiles and geographical distributions. The CTX-M family is thought to originate from chromosomal ESBL genes found in Kluyvera spp., an environmental opportunistic pathogen [1]. Unlike SHV-ESBLs and TEM-ESBLs which evolved through amino acid substitutions of their parent enzymes, CTX-M ESBLs were acquired through horizontal gene transfer from other bacteria [1].

Molecular Detection of ESBLs and MBLs

Molecular methods for ESBL detection include PCR amplification of the blaTEM, blaSHV, and blaCTX-M genes. For TEM and SHV ESBLs, sequencing is essential to differentiate between the non-ESBL parent enzymes and ESBL variants. For CTX-M enzymes, PCR amplification without sequencing is usually sufficient [1]. Various molecular approaches have been developed for rapid screening of ESBL-positive organisms, including multiplex PCR, real-time PCR, pyrosequencing, and reverse-line hybridization [1]. For MBLs, there are several FDA-approved molecular and biochemical rapid diagnostic methods available, including the Nanosphere Verigene BC-GN, Biofire BCID2 Panel, and GenMark Diagnostics ePlex BCID-GN [4]. These platforms can detect multiple bacterial species and their resistance mechanisms directly from positive blood cultures or respiratory samples [3].

MBL Detection Challenges and Solutions

MBL detection presents unique challenges as there are no standardized clinical guidelines for their identification. Phenotypic tests for MBLs often involve the use of chelating agents like EDTA to inhibit the zinc-dependent enzymes [2]. The metallo-β-lactamase production is typically detected by the ceftazidime-EDTA and imipenam-EDTA double disc synergy test, with an increase in inhibition zone of ≥5 mm considered positive for MBL production [14]. For molecular detection, PCR assays targeting specific MBL genes (blaNDM, blaVIM, blaIMP) are commonly used [3]. Several commercial platforms now incorporate MBL gene detection, including the Cepheid Xpert Carba-R, BD MAX Check-Points CPO, and GenePOC Carba assays, which are primarily intended for infection control purposes [3].

Therapeutic Challenges with ESBL and MBL Producers

Infections caused by ESBL and MBL-producing organisms present significant therapeutic challenges [1]. For ESBL producers, carbapenems (imipenem, meropenem, ertapenem, doripenem) are often considered the first choice for serious infections [1]. However, with the emergence of carbapenem-resistant Enterobacteriaceae, treatment options have become increasingly limited [1]. For MBL-producing organisms, the situation is even more dire, as these enzymes can hydrolyze most β-lactams, including carbapenems [3]. The spread of MBL-producing Enterobacteriaceae worldwide without a concurrent increase in active antibiotics makes these organisms an urgent public health threat [3].

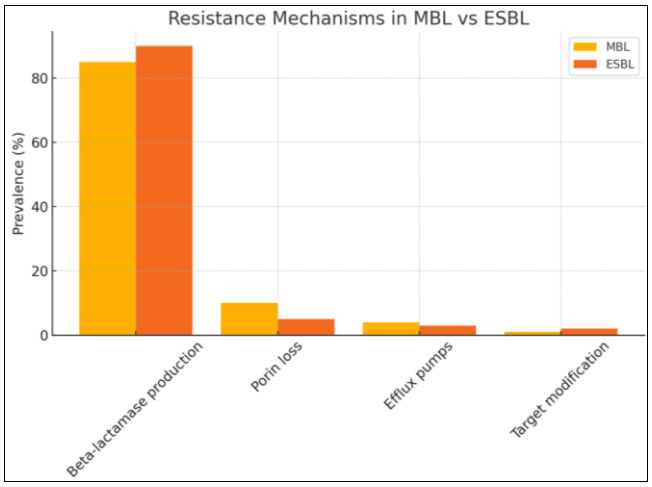

Fig 1: Comparative Prevalence of Resistance Mechanisms in MBL and ESBL Producers [15,17,18]

Extended-Spectrum β-Lactamases (ESBLs) and Metallo-β-Lactamases (MBLs) are key enzymes contributing to antibiotic resistance in Gram-negative bacteria. ESBLs, such as CTX-M, TEM, and SHV types [15], are commonly found in *E. coli* and *Klebsiella pneumoniae*, conferring resistance to third-generation cephalosporins but not to carbapenems. MBLs, including NDM-1, VIM, and IMP [17, 18] provide broader resistance, including against carbapenems, and are not inhibited by β-lactamase inhibitors. MBL producers often carry multiple resistance genes, leading to multidrug or pan-drug resistance. While ESBL producers are more widespread, MBL producers pose a greater clinical challenge due to their broader spectrum of resistance. Increasing reports of co-production further complicate treatment options (Fig 1).

Conclusion

Bacteria that produce Extended Spectrum β-Lactamases (ESBLs) and Metallo β-Lactamases (MBLs) pose a significant threat to public health, as they can neutralize a wide range of β-lactam antibiotics, including penicillins, cephalosporins, and carbapenems. The widespread emergence of these resistant pathogens in both healthcare and community environments highlights the pressing need for robust surveillance systems, precise diagnostic tools, and effective infection control measures. Although scientific understanding of their genetic mechanisms, transmission pathways, and epidemiology has improved, treatment options remain scarce and often inadequate.

Addressing this issue calls for a multifaceted strategy, including the discovery of new antimicrobial agents, the development of β-lactamase inhibitors, and exploration of alternative treatments such as phage therapy and antimicrobial peptides. Just as crucial are strong antibiotic stewardship programs, enforceable regulatory frameworks, and widespread public education to reduce inappropriate antibiotic use. Collaborative efforts in genomics and resistance gene tracking will play a pivotal role in forecasting resistance patterns and crafting focused interventions. Overcoming the challenge posed by ESBL and MBL producers will require coordinated international action and long-term dedication to preserve the effectiveness of both existing and future antibiotics.

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