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Beta-Lactam Resistance in *Enterobacterales*

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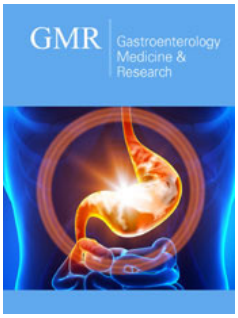

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Abstract

The order *Enterobacterales* contains a large number of genera which are mainly gut microbiota bearing similar biochemical and genetic characteristics. They are ubiquitous and the members include several that are among important opportunistic human pathogens, which cause infections including urinary tract, bloodstream, respiratory tract, (hospital and health care associated pneumonia), as well as intestinal and intra-abdominal infections. *Klebsiella pneumoniae, Escherichia coli, Proteus, Citrobacter, Enterobacter, Hafnia, Morganella, Providencia*, and *Serratia* are some of the genera that cause opportunistic infections. Other members are primary pathogens such as *Salmonella, Shigella*, and *Yersinia*. β-lactam antibiotics, which include penicillins, cephalosporins, and carbapenems, are among the most commonly prescribed antibiotics and preferred therapeutic options for infections caused by *Enterobacterales*. Resistance to these antibiotics is due to inaccessibility of the antibiotics to their target enzymes, modification of target enzymes, and direct deactivation of the antibiotics by β-lactamases. This review explores the common Extended Spectrum β-Lactamase (ESBL) and carbapenemase gene families, which are commonly involved in resistance to the β-lactams in *Enterobacterales*.

Introduction

The β-lactam antibiotic group is a class of broad-spectrum pharmaceutical antimicrobials that include all agents whose molecular structure consists of a β-lactam ring. Penicillin derivatives (penams), cephalosporins (cephems), carbapenems, and monobactams form this group [1]. Together with other antibiotics such as vancomycin, bacitracin, fosfomycin, and isoniazid, they inhibit bacterial cell wall synthesis. β-lactams are the most frequently administered antimicrobials across the world [2]. They are structurally characterized by a β-lactam ring which is highly susceptible to hydrolysis by a variety of reagents, both biotic (enzymatic and biological degradation) and abiotic (chemical degradation) processes [3]. All β-lactam compounds interfere with the synthesis of the bacterial cell wall, which is made up of extensively cross-linked peptide and glycan chains that give the cell structure stability and rigidity. These chains are made up of two amino sugars called N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG). The peptidoglycan molecule is formed by linking a pentapeptide side chain to NAM sugar. The cleavage of terminal D-alanine of the peptide chains by transpeptidases catalyzed by penicillin-binding proteins, which are transmembrane surface enzymes found in bacteria, is the final step in its synthesis. Beta-lactams inhibit cell wall synthesis by irreversibly binding to the Penicillin-Binding Proteins (PBP) required for the final crosslinking (transpeptidation) step in the synthesis of peptidoglycan for cell wall construction. Inhibition of this catalyzed process of transpeptidation results in a loosely knit structure of the cell wall. Cell wall deficient organisms result when susceptible bacteria multiply in the presence of a β-lactam compound. The interior of the bacterium is hyperosmotic which results in osmotic drive and eventual cell lysis. The most clinically important are the third generation cephalosporins, 'anti-pseudomonal' beta-lactam/beta-lactamase inhibitor combinations, and carbapenems. Being the most widely used antibiotics, beta-lactams resistance is a severe threat because they have low toxicity and are used to treat a broad range of infections.

Enzymatic inactivation resistance mechanism

The expression of beta-lactamase enzymes encoded by *bla* genes either on the chromosome or plasmid DNA, which hydrolyze the beta-lactam ring, resulting in inactivation or degradation, primarily accounts for the beta-lactam resistance [3]. *bla* genes associated with mobile genetic elements often coexist with other antimicrobial resistance determinants, increasing the possibility of multidrug resistance and dissemination [4,5]. Many different types of beta-lactamases can confer resistance to each of the most clinically important beta-lactam types, and a single amino acid difference may affect the phenotype conferred. β-lactamases can be classified as (1) Ambler molecular classes A–D or (2) Bush-Jacoby (functional) groups [6,7], which comprise Extended Spectrum β-Lactamases (ESBL), AmpC cephalosporinases, and metallo-β-lactamases. Throughout Europe and the United States of America, there has been continuous reporting of resistance mediated by Extended Spectrum β-Lactamase (ESBL) after the introduction of the broad spectrum β-lactams, especially cephalosporins into clinical practice [8]. Extended Spectrum β-Lactamases (ESBLs) comprise a category of enzymes that, in addition to penicillin, are capable of hydrolyzing a wide range of β-lactams, including cephalosporins such as ceftazidime, cefotaxime, ceftriaxone, cefepime, and monobactams like aztreonam, but not cephamycins like cefoxitin and carbapenems [9]. Earlier studies reported *Klebsiella* species and *Escherichia coli* as the main ESBL producers, but they can be widely detected in other members of the *Enterobacterales* such as *Enterobacter*, *Salmonella*, *Citrobacter*, *Serratia marcescens* and *Proteus* species [10].

Classification of extended spectrum β-lactamases (ESBL)

There are two most accepted methods of classification of ESBLs.

Ambler molecular classification scheme: This scheme places β-lactamases into four major groups (A, B, C, and D). This classification system considers protein homology, or sequence similarity, as opposed to phenotypic characteristics. The beta-lactamases of classes A, C and D are categorized as serine β-lactamases in the Ambler classification scheme, while the enzymes of class B are placed under metallo-β-lactamases. However, most of the ESBLs are of molecular class A, with the exception of OXA-type enzymes (which are class D enzymes) [11].

Bush-Jacoby-Medeiros (traditional) or functional classification scheme: Based on the functional similarities (substrate and inhibitor profile), there are four main groups and multiple subgroups in this system. Additionally, this classification of ESBL belongs to group 2be or 2d (OXA-type) [12].

Group 1 Cephalosporinases: This family is a member of the molecular class C, which is encoded on the chromosomes of *Enterobacterales* and a few other microbes. They appear to be more active against cephalosporins than benzylpenicillin. Beta-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam do not inhibit cephalosporinase activity but are active on cephamycins such as cefoxitin [13].

Group 2 serine β-lactamases: This is the largest category of beta-lactamases, and corresponds to molecular classes A and D, which reflect the initial TEM and SHV genes. This group involves penicillinases and cephalosporinases. Moreover, these enzymes are inhibited at various degrees by the Beta-Lactamase Inhibitors (BLI), clavulanic acid, and tazobactam [14]. Furthermore, beta-lactamase inhibitor proteins inhibit many class A TEM beta-lactamases [15].

Group 3 Metallo-β-lactamases (MBLs): A distinct class of beta-lactamases in both structural and functional forms. Their main structural difference from the other beta-lactamases is the presence of a zinc ion at the active site. They were distinguished functionally primarily by their ability to hydrolyze carbapenems; however, some serine beta-lactamases are reported to have acquired this ability as well. Metallo-Beta-Lactamases (MBLs) have a lower affinity or hydrolytic capability for monobactams than serine beta-lactamases and are not inhibited by tazobactam or clavulanic acid. Metal ion chelators such as EDTA, on the other hand, inhibit them [14].

Group 4 β-lactamases: This category contains enzymes that have not been fully characterized and classified and may fall into one of the existing enzyme groups [15]. Moreover, this group contains penicillinases that are not inhibited by clavulanic acid, and do not belong to any of the corresponding molecular classes

Diversity of the common ESBL types

TEM β-lactamases (class A): TEM-type beta-lactamases are widespread in *E. coli* and *K. pneumoniae*, although they are reported in other Gram-negative bacteria with increasing frequency. The TEM types of ESBL are derived from the ancestral types, TEM-1 and TEM-2, the first of which was discovered in 1965 in an *E. coli* isolate from a patient in Athens, Greece [9]. An earlier report demonstrated that TEM-1 confers about 90% resistance to ampicillin and almost 140 TEM types have been described [18].

SHV β-lactamases (class A): SHV-1, which is mostly harbored by *K. pneumoniae* and shares 68% structural and sequence similarity with TEM-1, is another popular type of beta-lactamase. SHV-1 accounts for up to 20% of this species' plasmid-mediated ampicillin resistance. Furthermore, although SHV-5 and SHV-12 are the most frequent, more than 60 SHV variants have been described [19].

CTX-M β-lactamases (class A): In comparison to other oxyimino-beta-lactam substrates such as ceftazidime, ceftriaxone, or cefepime, this enzyme is more effective against cefotaxime. They are examples of beta-lactamase genes that are plasmid-acquired and are usually found on the chromosome of *Kluyvera species*, which are rare pathogenic commensal organisms. CTX-M shares 40% sequence similarity with the TEM or SHV beta-lactamases. Studies show that CTX-M enzymes contain more than 80 variants, most of which have been characterized. Evidently, they have mostly been found in the strains of *Salmonella enterica* serovar, *Typhimurium,* and *E. coli*, but have also been described in other species of *Enterobacterales* [20].

OXA β-lactamases (class D): The OXA-type enzymes are a growing family of ESBLs that are completely different from the TEM and SHV enzymes, with only 20% sequence similarity. They are members of the molecular class D and the functional group 2d. Resistance to the antibiotics ampicillin and cephalothin is also conferred by these OXA enzymes. They are also distinguished by their high hydrolytic activity against oxacillin and cloxacillin, as well as their resistance to clavulanic acid [12].

Carbapenemases

Due to their high affinity with penicillin-binding proteins, stability against Extended-Spectrum-beta-lactamases (ESBLs), and permeability of bacterial outer membranes, carbapenems (imipenem, meropenem, ertapenem, and doripenem) have been regarded as the mainstay and most potent beta-lactams against Gram-negative bacilli [21]. Carbapenem hydrolyzing enzymes (carbapenemases) have, however, been detected in the members of the *Enterobacterales*. Carbapenemase producers are resistant to almost all beta-lactams and other antibiotic classes, and infections arising from carbapenemase producers are predominantly associated with healthcare institutions [22]. The majority of carbapenemases are class B Metallo-beta-lactamases (MBL), which are dependent on zinc ions for activity rather than the active-site serine found in classes A, C, and D, and confer resistance to carbapenem antibiotics, usually in addition to other beta-lactams except aztreonam, and to clinical beta-lactamase inhibitors [23]. The bla_{VIM} (Verona integron encoded metallo-beta-lactamase encoding gene), specifically bla_{VIM-1} and its variants, is widespread in *Enterobacterales*. Some variants of imipenemases (IMP) have also been identified in *Enterobacterales*, although they are known to occur primarily in *P. aeruginosa*. The NDM (New Delhi Metallo-beta-lactamase) enzyme, first reported in 2009, received a lot of international attention and 15 minor variants have now been identified in a variety of plasmids, strain types, and species [24]. Certain class A enzymes are categorized as carbapenemases. The most prominent being KPC (*Klebsiella pneumoniae* carbapenemase), which was first identified in the USA in 1996 and is most commonly associated with *K. pneumoniae*, often multi-locus sequence type (ST) 258 [25], but also found in *E. coli*, *Enterobacter* and other species [26]. Carbapenemase activity is also associated with some of the known GES variants, especially GES-2 and GES-5, which are associated with clinically significant resistance to carbapenems [27]. Class D enzymes (named OXA, for 'oxacillinase') are a very varied group, encompassing many different subfamilies and variants. OXA-48 and variants, and the related but distinct OXA-181, which can hydrolyze carbapenems and confer low-level resistance to these antibiotics, have been extensively reported in *Enterobacterales* in some locations [28].

Conclusion

Multiresistant *Enterobacterales* harboring extended spectrum β-lactamases, primarily CTX-M, TEM, and SHV types, and VIM, which degrade broad-spectrum cephalosporins and carbapenems, are widespread. The presence of these enzyme-encoding genes can be attributed to the development of resistance in the source population as a result of selection pressure caused by increased antibiotic use, as well as the subsequent dissemination via horizontal gene transfer mediated by bacterial plasmids.

References

1. Holten KB, Onusko EM (2000) Appropriate prescribing of oral beta-lactam antibiotics. Am Fam Physician 62(3): 611-620.
2. Korzeniewska E, Harnisz M (2020) Sources, occurrence, and environmental risk assessment of antibiotics and antimicrobial-resistant bacteria in aquatic environments of Poland, pp. 179-193.
3. Deshpande A, Baheti K, Chatterjee N (2004) Degradation of β-lactam antibiotics. Current science 87(12): 1684-1695.
4. Tennstedt T, Szczepanowski R, Braun S, Puhler A, Schluter A (2003) Occurrence of integron-associated resistance gene cassettes located on antibiotic resistance plasmids isolated from a wastewater treatment plant. FEMS Microbiol Ecol 45(3): 239-252.
5. Schluter A, Szczepanowski R, Puhler A, Top EM (2007) Genomics of IncP-1 antibiotic resistance plasmids isolated from wastewater treatment plants provides evidence for a widely accessible drug resistance gene pool. FEMS Microbiol Rev 31(4): 449-477.
6. Ambler RP (1980) The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci 289(1036): 321-331.
7. Bush K, Jacoby GA (2010) Updated functional classification of beta-lactamases. Antimicrob Agents Chemother 54(3): 969-976.
8. Livermore DM, Hawkey PM (2005) CTX-M: Changing the face of ESBLs in the UK. J Antimicrob Chemother 56(3): 451-454.
9. Bradford PA (2001) Extended-spectrum β-lactamases in the 21st century: Characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 14(4): 933-951.
10. Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO (2001) Extended-spectrum beta-lactamase-producing Escherichia coli and *Klebsiella pneumoniae*: Risk factors for infection and impact of resistance on outcomes. Clin Infect Dis 32(8): 1162-1171.
11. Paterson DL, Bonomo RA (2005) Extended-spectrum beta-lactamases: A clinical update. Clin Microbiol Rev 18(4): 657-686.
12. Rasmussen BA, Bush K (1997) Carbapenem-hydrolyzing beta-lactamases. Antimicrob Agents Chemother 41(2): 223-232.
13. Gurung M, Moon DC, Tamang MD, Kim J, Lee YC, et al. (2010) Emergence of 16S rRNA methylase gene armA and carriage of blaIMP-1 in *Pseudomonas aeruginosa* isolates from South Korea. Diagn Microbiol Infect Dis 68(4): 468-470.
14. Picão RC, Poirel L, Gales AC, Nordmann P (2009) Further identification of CTX-M-2 extended-spectrum β-lactamase in *Pseudomonas aeruginosa*. Antimicrob agents Chemother 53(5): 2225-2226.
15. Jacoby GA (2009) AmpC beta-lactamases. Clin Microbiol Rev 22(1): 161-182.
16. Bonnet R (2004) Growing group of extended-spectrum beta-lactamases: The CTX-M enzymes. Antimicrob Agents Chemother 48(1): 1-14.
17. Marchiaro P, Ballerini V, Spalding T, Cera G, Mussi MA, et al. (2008) A convenient microbiological assay employing cell-free extracts for the rapid characterization of gram-negative carbapenemase producers. J Antimicrob Chemother 62(2): 336-344.
18. Datta N, Kontomichalou P (1965) Penicillinase synthesis controlled by infectious R factors in *Enterobacteriaceae*. Nature 208(5007): 239-241.
19. Jacoby GA, Munoz-Price LS (2005) The new beta-lactamases. N Engl J Med 352(4): 380-391.

20. Sykes RB, Karen B (1982) 3-Physiology, biochemistry, and inactivation of β-lactamases. The Biology of Beta-Lactam Antibiotics 3: 155-207.

21. Zavascki AP, Carvalhaes CG, Picao RC, Gales AC (2010) Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: Resistance mechanisms and implications for therapy. Expert Rev Anti Infect Ther 8(1): 71-93.

22. Woodford N, Wareham DW, Guerra B, Teale C (2014) Carbapenemase-producing *Enterobacteriaceae* and non-*Enterobacteriaceae* from animals and the environment: An emerging public health risk of our own making? J Antimicrob Chemother 69(2): 287-291.

23. Cornaglia GH, Giamarellou GM, Rossolini (2011) Metallo-β-lactamases: A last frontier for β-lactams? Lancet Infect Dis 11(5): 381-393.

24. Johnson AP, Woodford N (2013) Global spread of antibiotic resistance: The example of New Delhi Metallo-β-lactamase (NDM)-mediated carbapenem resistance. J Med Microbiol 62(Pt 4): 499-513.

25. Woodford N, Turton JF, Livermore DM (2011) Multiresistant gram-negative bacteria: The role of high-risk clones in the dissemination of antibiotic resistance. FEMS Microbiol Rev 35(5): 736-755.

26. Nordmann P, Cuzon G, Naas T (2009) The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. The Lancet infect Dis 9(4): 228-236.

27. Frase H, Shi Q, Testero SA, Mobashery S, Vakulenko SB (2009) Mechanistic basis for the emergence of catalytic competence against carbapenem antibiotics by the GES family of beta-lactamases. J Biol Chem 284(43): 29509-29513.

28. Poirel L, Potron A, Nordmann P (2012) OXA-48-like carbapenemases: The phantom menace. J Antimicrob Chemother 67(7): 1597-1606.