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An Overview of Extended Spectrum Beta Lactamases and Metallo Beta Lactamases

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Abstract

Antibiotic resistant β-lactamases are diverse and complex enzymes produced by most of the Gram-negative bacteria that are mediated by number of plasmids. The impact of these enzymes has posed a major threat to the health sectors and has challenged the available treatment options for both community and hospital acquired infections. These include the uncomplicated most severe life-threatening infections. Moreover, with resistance to the cephalosporin drugs these Multidrug Resistance strains exhibit co-resistance patterns with different class of antibiotics which is a cause of concern that leads to narrow the limited treatment options. It is alarming situation since there is a steep rise in MDR—Beta lactamase pathogens mainly in *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Currently, the clinical detection of Extended Spectrum of β-Lactamases (ESβL) and MβL producing pathogens are carried out by antibiotic sensitivity test on the guidelines of Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) since, the other methods being too expensive. The choice of antimicrobial treatment for infections should rely on the clinical data and the tests (AST) in asymptomatic and mild cases. However, this does not imply for critical infections. The last resorts of treatment for ESβL pathogens are carbapenem and nevertheless, resistances have also been reported for the same. With increasing resistance rate to the antibiotics, it is very essential to follow the guidelines for detection, implementation of antibiotic rotation to reduce these pathogens, followed by the efficient infection control practices and strategies to avoid such outbreaks.

Keywords

ESβL, MβL, MDR

1. Introduction

Infectious diseases are the potential transmission of a pathogenic agent from one species to another and these pathogens are contagious, which are also known as communicable diseases [1]. These pathogens have shown high resistance to the antibiotics, which has become a worldwide problem with the consequences on the infectious disease's treatment. Usually antibiotics are given empirically before the laboratory results of culture are available to ensure appropriate therapy. There is an alarming increase of antibiotic resistance in bacteria that cause either community infections or hospital acquired infections. Many of these multidrug pathogens are of particular interest such as, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus*, and extensively drugs resistant *Mycobacterium tuberculosis* [2].

According to WHO (2018) reports, 750,000 deaths every year may shoot high due to bacteria exhibiting resistance if proper action is not taken. Hence, antibiotic resistance has become one of the greatest threats to global health and survival statistics, which may be linked to global problem. Dispersion of the successful clones of Multidrug Resistant (MDR) bacteria is found to be common with the importance of plasmids carrying MDR markers in *Shigella sps*., and *E. coli* first described in the seminal work in Japan over 57 years ago [3]. Leplae and his coworkers (2006) showed the mechanism of transmission of mosaic plasmids from one bacterium to other to give rise to the MDR phenotype [4].

β-lactam antibiotics are the most common drugs used for the treatment of Gram-negative bacteria and their continuous misuse has led to the resistance worldwide [5]. Bacterial strains have induced continuous production and mutation of *β*-lactamases, due to the continuous exposure Beta lactam drugs, expanding their activity even against the newly developed *β*-lactam antibiotics. Incidence and treatment of ES*β*L-producing MDR strains is a matter of scientific concern for the difficulties to resolve due to various reasons, difficulty in detecting ES*β*L production and inconsistencies in reporting [6]. Recently, a significant increase in the incidents of ES*β*L-related infections has been observed throughout the globe [7] [8].

Microorganisms that produce beta-lactamases can break and enable the beta-lactam molecules inactive thus, conferring the resistance to the pathogens. More than 500 beta-lactamases have been reported so far (http://www.lahey.org/studies). These beta-lactamases are widespread across the world that are mostly reported in Gram negative organisms with common resistance mechanism mediated by plasmid or expressed chromosomally, specifically the CTX-M-15 family. Chromosomally located inducible expression is also common, while plasmid mediated enzymes are generally expressed constitutively in these Gram-negative organisms [9] [10].

ES*β*L enzymes are commonly found in the members of *Enterobacteriaceae* family and are of over 120 types. ES*β*Ls are generally acquired by horizontal gene

transfer and confer resistance to oxyimino-cephalosporins, some being mutant derivatives of established plasmid-mediated *β*-lactamases (TEM/SHV) or mobilized from environmental bacteria (CTX-M) and these enzymes hydrolyze penicillin, broad-spectrum cephalosporins and monobactams. However, they do not affect cephamycin and carbapenems, and they are inhibited by clavulanic acid [11]. ES*β*L has generally been defined as transmissible *β*-lactamases that can be inhibited by clavulanic acid, tazobactam or sulbactam, and which are encoded by genes that can be exchanged between bacteria [11]. Clavulanic acid is used in combination with amoxicillin and ticarcillin, sulbactam sodium is used in combination with ampicillin and cefoperazone, and tazobactam in combination with piperacillin [12].

Emergence of Metallo-*β*-Lactamases (M*β*Ls) with activity against carbapenems (e.g. the VIM and IMP families of enzymes) has compromised the clinical utility of this class of antibiotics [13] [14]. Resistance to carbapenems may also be induced as a result of increased production of either AmpC or ES*β*L, coupled with a decrease in porin production or increased efflux [14] [15]. In India, the high rates of ES*β*L producers have recently increased the usage of carbapenem antibiotics, which may provide a selective pressure for the spread of strains producing carbapenems in the near future [16] [17].

2. Mechanism of Antibiotic Resistance by Beta-Lactamases

In the year 1940, *β*-lactam antibiotics came into clinical use and it has been observed that many strains of bacteria have emerged resistant to these drugs [18]. Resistance to these agents is in both Gram-positive and Gram-negative bacterial pathogens and occurs as a result of drug inactivation by *β*-lactamases, target site (*i.e.* PBP) alterations, diminished permeability and efflux of drugs [19]. The primary mechanism of the *β*-lactam resistance is by enzymatic cleavage of the *β*-lactam ring by *β*-lactamases produced by microbes [18].

In 1983, SHV-2, a plasmid borne ES*β*L produced by *K. ozaenae* was discovered in Germany. Other ES*β*L types, TEM and SHV were predominant until 1990. Later on, prevalence of SHV, TEM and a new CTX-M family of ES*β*L coproduced mainly by *E. coli* had emerged. CTX-M has become the predominant and CTX-M-producing *E. coli* has spread globally and has been involved in nosocomial outbreaks and community acquired infections [20]. In 1990 the first *bla*CTX-M was detected in clinically isolated *E. coli* in Germany [21] then on CTX-M-producing *Enterobacteriaceae* has been detected globally [22] [23].

Beta-lactamases producing bacteria hydrolyse beta-lactam drugs and render them inactive before it gets to the PBP (Penicillin binding proteins) target. The structural similarities with PBP makes the lactamases bind acylate and hydrolyse using water molecules and inactivate the Beta lactam drugs. These enzymes contain either serine residue (Ambler classes A, C, D) or metal ion Zn^{2+} (Ambler class B) in their active site, that attack beta-lactam ring and break the amide bond in the ring **Figure 1** [24] [25] [26].

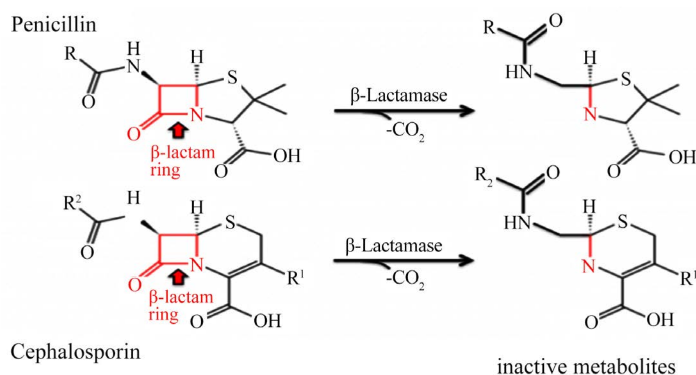

Figure 1. Interaction between antibiotic and beta-lactamases.

3. Structure of Beta Lactamases

3.1. Primary Structure/Molecular Structure

Largest group of class A-lactamases was characterized on the basis of 26 strictly conserved residues and molecular comparisons helped standard numbering scheme as indicated by the label "ABL" (for class A-lactamase) [27]. Further updated list was reported for the residues that are involved in the catalytic mechanism and/ or in substrate binding by Matange *et al.* [28] [29].

It has been reported that, 268 sequences aligned for representative of class A-lactamases from subclasses A1 and A2, 100% was confirmed and highly conserved (between 90% and 99%) residues, such as Gly45, Ser70, Lys73, Leu81, Pro107, Ser130, Asp131, Asn132, Ala134, Gly144, Gly156, Glu166, Lys/ Arg234, Thr/Ser235, and Gly236, differentiated between subclasses. The two subclasses were distinguished as A1 [28] [29] [30] and A2 (discovered more recently) as subgroups due to their different conserved residues. PER-1 and PER-2, an alignment of subclass A2-lactamase sequences revealed the presence of several insertions [31] [32]. An examination of the overall amino acid composition of lactamases revealed that representative enzymes from subclass A2 had small numbers of arginine residues (8.2 3.9 residues on average) and large numbers of lysine residues (29.0 5.5 residues).

3.2. Structure-Function Relationships of Class A Enzymes

A great diversity of amino acid sequences has been noted between the different clusters of class A *β*-lactamases and further, X-ray crystallography has been able to determine the tertiary structure of these protein molecules and helped to explore the two subclasses of A1 and A2.
(http://www.rcsb.org/pdb/home/home.do). Structures of Beta lactamases such as, TEM types, SHV types, CTX-M types, KPC-2, L2, NMC-A, OXY-1, PenA, PenI, PSE-4, SED-1, SME-1, Toho-1, and *Francisella tularensis* that are produced by Gram negative organisms have been determined with the exception of PER-1 and PER-2, belong to subclass A1 [31] [32].

Overall structures of these are found to be same with the structural features

surrounding the active sites with two subdomains generating a cleft as in **Figure 2** [28] [33] [34]. Of the two sub domains, the alpha subdomain is largely α-helical in contrast, to the alpha/beta subdomain that consists of a five-stranded *β*-sheet flanked by α-helices. Active sites are present on the cleft of the two sub-domains and contain catalytic Ser70 residue and Glu166, Asn170, and Ser70 that is deacylated with water primed by interactions.

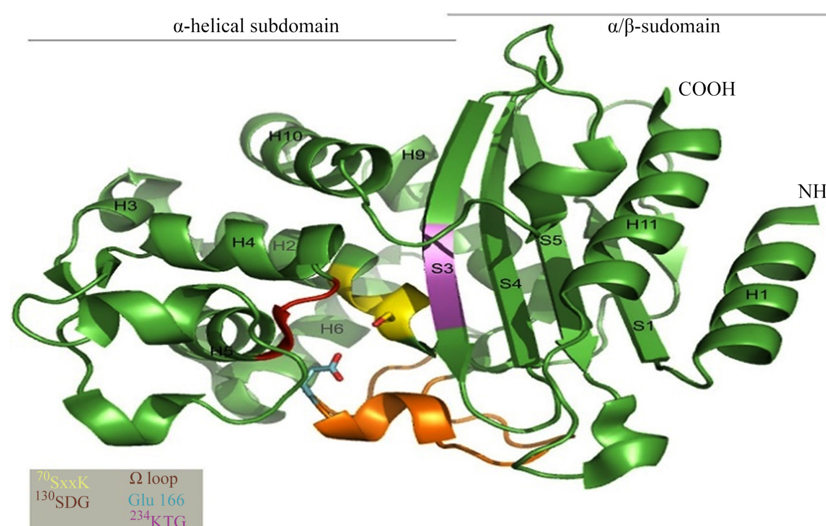

Figure 2. Secondary structures of the class A *β*-lactamase of *Mycobacterium tuberculosis*, with the spatial arrangements of the three catalytic center defining amino acid groupings, the *α* domain (left), and an *α*/*β* domain (right) [35]. The helices are represented as H1 to h11, and the strands are represented as S1 to S5. The figure was created with PyMOL (Delano Scientific).

4. Extended-Spectrum Beta-Lactamase (ES*β*L)

The term was used initially to refer to TEM and SHV enzymes that have the ability to hydrolyze oxyimino-cephalosporins. Later on, this term has been widened to include:

- Enzymes derived from other sources and have resistance spectra similar to that of TEM and SHV mutants e.g. CTX-M and VEB types.
- Enzymes exhibit wider resistance than their parents but do not belong to 2be group e.g. OXA and Amp C mutants with increased activity against cefepime [36].

Currently used definition for ES*β*L is *β*-lactamase that is able to render the bacterium resistant to the penicillin, first, second, and third-generation cephalosporins and aztreonam, but not cephamycins or carbapenems, by hydrolysis that could be inhibited by *β*-lactamase inhibitors of these antibiotics [11] [37] [38].

4.1. Classification of Beta-Lactamases

According to Ambler molecular classification scheme, which is based on the protein sequence similarity these are classified into four classes A, B, C and D.

This classification also is based on conserved and variable amino acid motifs of the proteins. Class A, C, and D include the enzymes that hydrolyze their substrates by forming acyl enzymes via the active site serine, while class B (metalloenzymes) utilizes active site zinc to facilitate *β*-lactam hydrolysis [9] [39].

Bush-Jacoby-Medeiros functional classification scheme classify these enzymes according to the similarity in their functional (substrates and inhibitors profile) characteristics. Although the molecular classification is the easiest scheme to group these diverse enzymes, the functional classification enables the clinicians and laboratory microbiologists to correlate these enzymes with their clinical roles [9]. **Table 1** reveals the detailed classification of the *β*-lactamases.

Table 1. Classification schemes and representatives of extended spectrum beta-lactamase enzymes.

Ambler (molecular) Class	Bush & Jacoby group (2009)	Substrate/target	Inhibition profile		Member examples
			Clavulanic acid	azobactam	
A	2a	Penicillins	Yes	No	PC-1
	2b	Penicillins, some of the 1st-generation cephalosporin	Yes	No	TEM-1, TEM-2, SHV-1
	2be	Extended spectrum cephalosporin, monobactam	Yes	No	TEM-3, SHV-2, CTX-M-15, PET-1, VEB-1
	2br	Penicillins	No	No	TEM-30, SHV-10
	2ber	Extended spectrum cephalosporin, monobactam	No	No	TEM-50
	2c	Carbenicillin	Yes	No	PSE-1, CARB-3
	2ce	Carbenicillin, cefepime	Yes	No	RTG-4
	2e	Extended spectrum beta-lactams	Yes	No	CepA
B	2f		Changing	No	KPC-2, 1M1-1, SME-1
	3a	Carbapenems	No	Yes	IMP-1, VIM-1, CcrA, IND-1, NDM-1
C	3b	Carbapenems	No	Yes	CphA, Sfh-1
	1	Cephalosporins	No	No	AmpC, P99, ACT 1, CMY-2, FOX-1, MIR-1
	1e	Cephalosporins	No	Yes	GC1, CMY-37
D	2d	Cloxacillin	Changeable	No	OXA-1, OXA-10
	2de	Extended spectrum cephalosporin	Changeable	No	OXA-11, OXA-15
	2df	Carbapenems	Variable	No	OXA-23, OXA-48

TYPES OF ES*β*L:

4.1.1. TEM

TEM type ES*β*Ls are derivatives of TEM-1 and TEM-2.

TEM-1 was detected for the first time in 1965 at Greece among an *E. coli* isolate recovered from a patient named Temoneira, and hence the designation TEM

[40]. TEM-1 hydrolyses ampicillin at a rate higher than that of carbenicillin, oxacillin, and cephalothin but fail to hydrolyse the extended-spectrum cephalosporins. TEM-2 has the same hydrolytic activity of TEM-1 but has more active native promotor and a different isoelectric point (5.6 instead 5.4). The plasmid mediated *β*-lactamase TEM-3 (an ES*β*L member) was detected in 1987 in *K. pneumoniae* which was isolated in France. It was originally named CTX-1 due to its higher activity against cefotaxime [41]. There is steep rise in the TEM novel variants that has been reported (**Figure 3**) from different parts of the world that can be accessed at http://www.lahey.org/Studies/temtable.asp.

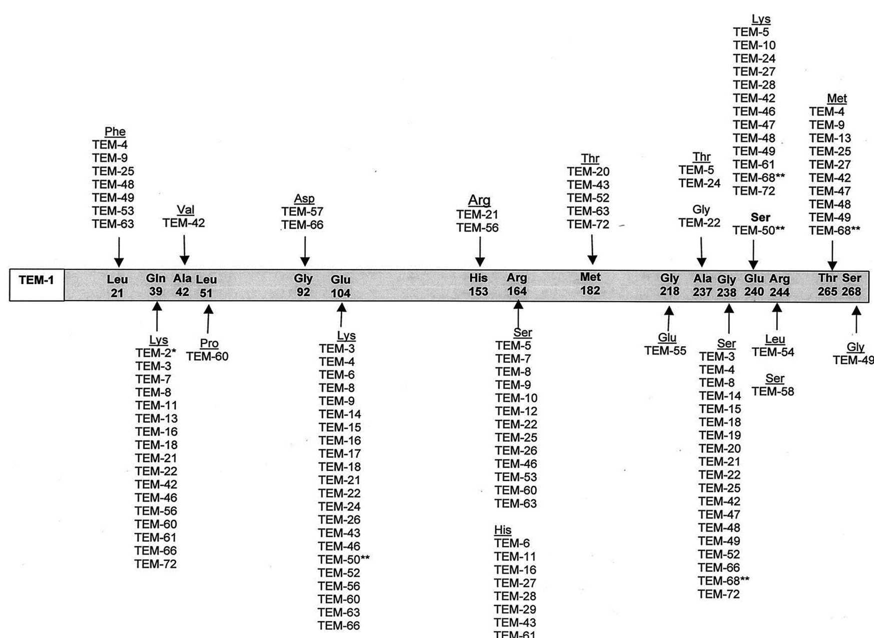

Figure 3. Shows the amino acid substitutions in the different TEM variants in comparison with TEM-1 adapted from Bradford (2001).

4.1.2. SHV

SHV-type ES*β*L was the most frequently detected in clinical isolates [42]. This is referred to sulfhydryl *v*ariable because it was thought that the inhibition of the enzyme activity by p-chloromercuribenzoate was substrate-dependent and variable according to the substrate used in the assay [43]. In 1983, a new SHV-*β*-lactamase (designated SHV-2) efficiently hydrolyzes cefotaxime and to lesser extent ceftazidime had been detected in *K. ozaenae* in Germany [44]. SHV-2 differs from SHV-1 by only one amino acid at the 238th position (glycine replaced by serine). This substitution (Gly238Ser) that resulted from a point mutation accounts for the activity of this enzyme against extended-spectrum cephalosporin. SHV-2 spread globally due to the selection pressure exerted by third- generation cephalosporins being detected in a wide range of *Enterobacteriaceae* but mainly in *Klebsiella sps*. [11] [45] [46]. The amino acid sequence compositions for 193 different variants have been reported (**Figure 4**) and the data can be accessed at http://www.lahey.org/Studies/.

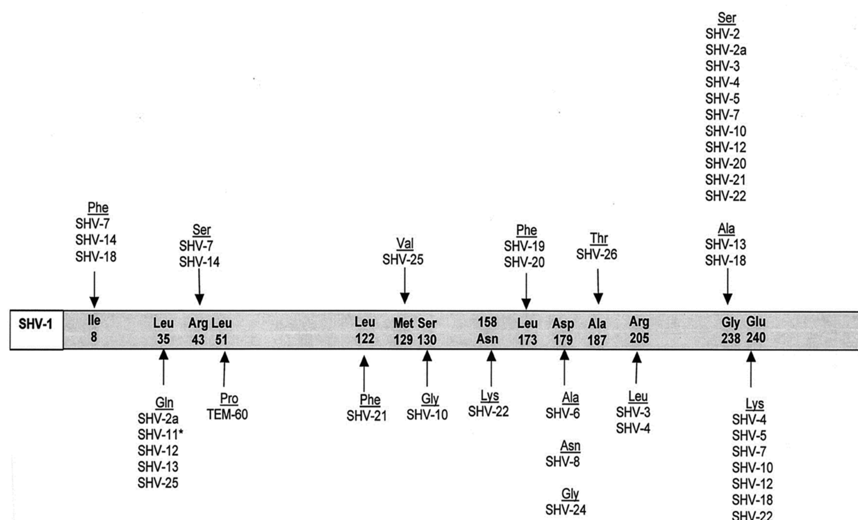

Figure 4. Depicts the amino acid substitutions in the different SHV variants in comparison with SHV-1 adapted from Bradford (2001).

4.1.3. CTX-M

The designation CTX refers to the potent hydrolytic activity of these enzymes against cefotaxime. However, some CTX-M-types hydrolyze ceftazidime and also cefepime with high efficiency [11] [47] [48]. The hydrolytic activity of CTX-M is inhibited by *β*-lactamase inhibitors. Tazobactam exhibits 10-fold greater inhibitory activity than clavulanic acid [39]. CTX-M-type *β*-lactamases are related to the chromosomal *β*-lactamase of *Kluyvera sps*. [49].

CTX-M *β*-lactamases are typical ES*β*Ls that belong to Bush's group 2be and Ambler's class A. There are at least 128 CTX-M types that have been described so far. *bla* CTX-M is a 291 amino acid encoding enzyme and the change in any one of them result in a new CTX-M variant [50]. By using amino-acid sequence relatedness, phylogeny tree of CTX-M *β*-lactamases has been constructed. They are divided into five clusters, namely CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9 and CTX-M-25 [41]. So far, the database availability for the 172 CTX-M variants shows distinct (http://www.lahey.org/Studies) with distinct amino acid sequence and functional characteristics.

Few members are shown below:

CTX-M-1 cluster: CTX-M-1, -3, -10, -12, -15, -22, -23

CTX-M-2 cluster: CTX-M-2, -4, -5, -6, -7, -20, -76, -77

CTX-M-8 cluster: CTX-M-8, -40, -63

CTX-M-9 cluster: CTX-M-9, -14, -15, -16, -17, -18, -19

CTX-M-25 cluster: CTX-M-25, -26, -39, -41, -91

4.1.4. Oxa-Beta-Lactamase

OXA name refers to the oxacillin-hydrolysing ability of these *β*-lactamases. They hydrolyze oxacillin and cloxacillin at a higher rate than 50% that of benzylpenicillin [39]. OXA-*β*-lactamases are mainly found in *P. aeruginosa* [51]. The most common OXA-type *β*-lactamase is OXA-1. It has been detected in up to 10% of

E. coli isolates [52]. Most OXA-type *β*-lactamases do not hydrolyze the extended spectrum cephalosporin and hence are not regarded as ES*β*Ls. OXA-ES*β*Ls includes, OXA-10 (weak), -11, -14, -16, -17. -19, -15, -18, -28, -31, -32, -35 and -45 [11] [41]. Altogether, OXA type *β*-lactamases is explosively increasing based on the amino acid sequence variations and so far 498 variants have been reported and arranged in the database (http://www.lahey.org/Studies/other).

4.1.5. Other ES*β*L-Types

It includes PER-1 (for *Pseudomonas* extended resistance), PER-2, VEB-1 (for Vietnamese extended spectrum), VEB-2, GES (Guiana-extended spectrum) and SFO (*Serratia fonticola*) which share only 25% and 27% homology with TEM and SHV types. It was observed that, PER-1 with 86% amino acid homology and PER-2 incidence was high in Turkey and South America respectively. VEB-1 and TLA-1 were discovered in *E. coli* clinical isolates from Vietnamese patient hospitalized in France and Mexico respectively [53]. PER-1, PER-2, VEB-1 and TLA-1 are related to *Bacteroides sps*. with reference to their homology to the chromosomal *β*-lactamase [53]. These novel enzymes are found infrequently and the details of these enzymes are reviewed elsewhere [42] [54].

4.2. Inhibitors for ES*β*L

The agent that inhibits *β*-lactamase enzymes by irreversible binding to its active site leads to permanent inactivation. The first clinically used *β*-lactamase inhibitor was clavulanic acid isolated from *S. clavuligerus* which exhibited weak antimicrobial activity. But, if combined with amoxicillin, it significantly increases the antimicrobial activity of the later. *β*-lactamase inhibitors are most effective against class-A *β*-lactamase including CTX-M, TEM and SHV-ES*β*Ls [55].

4.3. Epidemiology of ES*β*Ls

ES*β*Ls are currently a universal problem in hospitalized patients as well as community settings. Prevalence of ES*β*Ls among clinical isolates is variable with respect to different institutions, countries and continents [56]. Recent studies have shown a significant global increase in the ES*β*L rate. In North America the ES*β*L rate in *Klebsiella sps*., *E. coli* and *P. mirabilis* ranges from 4.2% - 44%, 3.3% - 4.7% and 3.1% - 9.5%, respectively. In Latin America, the ES*β*L rate of *Klebsiella sps*., *E. coli* and *P. mirabilis* lie in the ranges 40% - 47.3%, 6.7% - 25.4% and 9.5% - 35.5%, respectively. In the Far East-Western Pacific area, the ES*β*L rate in *Klebsiella sps*., *E. coli*, *Salmonella sps.* and *P. mirabilis* ranges between 11.3% - 51%, 7.9% - 23.6%, 3.4% and 1.4% - 1.8%, respectively [57].

The highest rate was detected in Egypt and Greece (38.5% and 27.4%, respectively) and the lowest rate was in Netherlands and Germany (2% and 2.6%, respectively) according to the Pan European Antimicrobial Resistance Local Surveillance (PEARLS) study done between the years 2001-2002 [58]. However, in comparison to other countries in United States (US) the prevalence of ES*β*L-encoding *Enterobacteriaceae* was around 3%. A study reflects that lower ES*β*L

prevalence in Northern European countries compared to South-Eastern European countries [53] [59]. Whereas in Spain, only 1.5% among 1962 invasive *E. coli* isolates in 2001 were found to produce ES*β*L [60]. In contrary, France had 11.4% *K. pneumoniae* and 47.7% *E. aerogenes* isolates were seen which produced ES*β*L in a surveillance covering many medical centres during 1996 to 2000 [61]. Northern European countries still have the lowest prevalence of ES*β*L-producing *Enterobacteriaceae* ranging from <1% in the Netherlands to 3% in Sweden.

It has been observed that ES*β*L allele may be restricted to certain country or a certain geographical region, like *bla*TEM-10 that has been detected in the United States in several outbreaks for many years before the detection of this allele was found in Europe [62]. Another example demonstrated by *bla*TEM-3 which has not been detected in the United States but is been frequently observed in France [63]. In contrast, there are ES*β*L alleles which are commonly encountered worldwide like SHV-5 and CTX-M-15 [53].

Travel plays an important role in the dissemination of antibiotic resistance [50]. The global dissemination of CTX-M-14 and CTX-M-15 producing/ST131 *E. coli* is attributed to the colonization or infection of travellers returning from high risk area like Indian subcontinent and the Middle East Asia confirming that returning travellers are most likely to acquire the predominant ES*β*L-determinant in the visited country. Such acquisition can be achieved even without hospitalization or contact with the health care system in the visited country [64].

Several outbreaks have been reported, majority of which occurred in tertiary hospitals where the transfer of a colonized patient provide a chance for dissemination of the ES*β*L-producing organism [65]. In a French Hospital, SHV-5 expressing *K. pneumoniae* were isolated from six peripartum women and two neonates. PFGE profiles of these strains indicated that all of the strains have PFGE-patterns identical to that of a strain isolated from contaminated ultrasonography coupling gel [66]. ES*β*L-producing *E. coli* and *K. pneumoniae* having different PFGE-types, but carrying identical plasmid encoding TEM-10 have been isolated from many patients in different hospitals in Chicago. The occurrence of the same plasmid in the strains of different PFGE-genotypes is a clue for plasmid transfer [62] [67].

More interestingly, *bla*TEM-24 encoding, 180 kb, conjugative plasmid was detected in four different enterobacterial species *E. coli*, *K. pneumoniae*, *E. aerogenes* and *P. rettigeri* isolated from the same patient suggesting horizontal transfer between the normal flora of the gut [68]. The findings of bla_{TEM} were reported to be 75 percent among ES*β*L-producing *K. pneumoniae* isolates [69] [16].

In India, reports have shown high rates of ES*β*Ls since 1990s [70]. ES*β*L producing *Enterobacteriaceae* are well established in the community were a study conducted showed 24% of ES*β*L producers and 74% and 76% had a history of prior use, at some time of a cephalosporin and quinolone, respectively [71].

Relatively very few genotyping studies have been carried out, SHV-12 in *K. pneumoniae* has been reported from Southern India to be linked to the qnrB plasmid-mediated quinolone resistance determinant, the first report being from *S. marcescens* [72] [73]. There is a report of SHV-5 produced by *Salmonella Senftenberg* causing an outbreak on a burns ward in Delhi [74]. The only genotype of a TEM ES*β*L is TEM-104, reported in ten isolates of *K. pneumoniae* from New Delhi in 2001-2002 [75].

CTX-M-15 *β*-lactamase is now widely distributed across the world, but was first described in a small number of isolates from Delhi in 2000 [76]. A very recent survey from three widely dispersed centers in India showed that 95/130 cefpodoxime-resistant *E. coli* and *K. pneumoniae* isolates obtained between 2003 and 2005 carried a *bla* CTX-M gene, and when genotyped confirmed as *bla*CTX-M-15 in all the cases [77]. The study by Ensor *et al.* (2006) prompted a letter reporting on isolates of *Klebsiella spp*. and *E. coli* collected in the late 1990s from six widely dispersed centers; 47 isolates were examined using PCR and DNA sequencing, and 37 were found to carry *bla*CTX-M-15, which was the only CTX-M genotype found [78]. CTX-M-15 was also identified from two of the *K. pneumoniae* isolates collected during 2002-2003 in Coimbatore, South India [72]. India, therefore, not only appears to have very high rates of ES*β*L production across the country, but is entirely dominated by *bla*CTX-M-15 gene.

Currently, the emergence and rapid dissemination of CTX-M positive ES*β*L producing bacteria have caused a change in ES*β*L epidemiology [11] [79]. Furthermore, the recent identification of ES*β*L producing isolates that have acquired carbapenemases has further limited the therapeutic options available for treatment of these multidrug resistant microorganisms [16] [63].

The recognition of the importance of ES*β*L's as a major mechanism of *β*-lactam resistance throughout the region came with presentation of data from the 1998-1999 SENTRY antimicrobial surveillance programme [80]. The incidence of ES*β*L production (no genotyping was undertaken) among *E. coli* isolates in the four Chinese sites varied from 13% to 35%. In India, the rate of ES*β*L producers from pregnant women in *E. coli* isolates was 36.8% [81]. Rates >20% for the ES*β*L phenotype in *K. pneumoniae* in all participating mainland Chinese centers (one reaching 60%), in one each of three Japanese and Taiwanese centers, and in the single Singapore center and Philippines center, were confirmed. Such high rates had previously been reported only from South America, in a follow-up study (1998-2002) lower rates were found in *K. pneumoniae* isolates from Australia and Japan (<10%), but that in China was 30% and comparatively, low incidence rate in India have also been reported [81] [82]. The other area of Asia that is the Indian subcontinent high rates of ES*β*L production has been reported.

A number of other studies in India reported the incidence of ES*β*L producers to be 6.6% to 68%. In south India, Subha *et al.* (2002) [83] reported 6.6% ES*β*L producers whereas Babypadmini *et al.* (2004) [84] reported 40.3%. The ES*β*L

production which was reported among Gram negative bacteria by Mathur *et al*. (2002) [85] was 68% and Singhal, *et al*. (2005) [86] detected ES*β*L in 64% isolates and Rodrigues, *et al*. (2004) [87] reported 53% ES*β*L production. Other studies in India have also reported a very high prevalence of ES*β*L producing *Enterobacteriaceae*. Accordingly, in North India about 46% of uropathogens belonging to *Enterobacteriaceae* were found to be ES*β*L producers [88].

Some reports have also described the molecular epidemiology of the ES*β*L producers [78]. One of the reasons contributing to the high prevalence of ES*β*L producers in India may be the crowded hospital conditions, including implementation of optimal hygienic practices, likely fueled by unrestricted use of antimicrobials without doctor's prescription [89]. A study reported that ES*β*L producing *Enterobacteriaceae* families were responsible for the onset of community infections in India [71]. CTX-M-15 is known to be having a peculiar association with the community onset of *E. coli* and *K. pneumoniae* [16] [90] [91].

5. Metallo Beta Lactamases (M*β*L)

Metallo *β*-lactamase was first identified in 1966 as *β*-lactamase II (BcII) in *Bacillus cereus*, when the cephalosporinase activity was shown to be inhibited by metal chelators like EDTA [92]. The early reported M*β*L determinants were located on the chromosome and were produced by organisms of minor clinical relevance, e.g. *Flavobacterium odoratum*, *B. cereus*, and *Legionella gormanii*, that were regarded as rare curiosities [93].

The first report of transferable M*β*L was recorded in *P. aeruginosa* from Japan in 1991 [94] and then on M*β*Ls were discovered with more clinically relevant genera such as *Serratia*, *Bacteroides*, and *Pseudomonas* [93]. The class B *β*-lactamases exhibit resistance to commercially available *β* lactamase inhibitors, but are inhibited by metal ion chelators, such as EDTA. This class of enzymes is of particular interest and concern owing to the ability to hydrolyze and thus provide resistance to virtually all classes of *β*-lactams, including the carbapenems. A number of clinical *Burkholderia cepacia* isolates producing an inducible metalloenzymes (PCM-I) that also shows preferential hydrolysis of carbapenems/imipenem have also been described [95]. A limited number of *B. fragilis* isolates have been shown to produce a chromosomal metalloenzyme, CfiA/CcrA that provides resistance to imipenem [96].

5.1. Classification of M*β*Ls

M*β*Ls are a group of clinically important hydrolytic enzymes belonging to the molecular class B *β*-lactamases or group 3 according to the Bush-Jacoby-Medeiros functional classification [39]. These enzymes are about 250 amino acid residues in length [97] and require divalent cation(s), usually Zinc, for their hydrolysing activities [93] [95]. M*β*Ls act on carbon nitrogen bond of *β*-lactam ring [97], but they are mechanically different from other *β*-lactamases, which have serine at the active site [93]. Some of these require only one Zinc ion per mole-

cule, while others require two Zinc ions per molecule (a binuclear active site) [97]. The metal ion(s) at the active site enables them to hydrolyze broad spectrum *β*-lactam agents including carbapenems, but their ability can be inhibited by metal ion chelators, such as EDTA, 1,10-*o*-phenanthroline, and mercapto compounds [95].

M*β*Ls are generally encoded by genes carried on mobile genetic elements, such as plasmids, transposons, and integrons [94] [98]. General characteristics of IMP type M*β*Ls were capable to hydrolyze carbapenems, but not monobactam. In fact, the *bla*IMP genes were often mediated by integrons, where aminoglycoside acetyl transferase and dihydropteroate synthetase genes also co-exist [99] [100].

5.1.1. Types of M*β*L

Currently, 21 variants of IMP type M*β*Ls have been reported in the clinical isolates of *Enterobacteriaceae*, *Pseudomonadaceae*, and other non-fastidious Gram-negative non-fermenters. These M*β*L includes, IMP-1 from Japan, Singapore, and the United Kingdom [101] [102] [103]; IMP-2, IMP-12, and IMP-13 from Italy [100] [104] [105]; IMP-3, IMP-6, and IMP-10 from Japan [106] [107] [108]; IMP-4 from Hong Kong and China [109] [110]; IMP-5 from Portugal [111]; IMP-7 from Canada and Malaysia [112] [113]; IMP-8 from Taiwan [92]; IMP-9 from China (accession no: AY033653), IMP-11 from Japan (accession no: AB074437); IMP-14 and IMP-15 from Thailand (accession no: AY553332 and AY553333, respectively); IMP-16 from Brazil (accession no: AJ584652); IMP-18 from United States of America (accession no: AY780674); IMP-19, IMP-20, and IMP-21 from Japan (accession no: AB184977, AB196988, and AB204557, respectively).

5.2. Inhibitors for M*β*L

Currently there are no clinically validated inhibitors of M*β*Ls are available. Inhibitors that covalently modify M*β*Ls include small thiol modifying reagents, such as mercuric (II) salts, *p*-chloromercuribenzoate [114], iodoacetic acid and mercaptoacetic acid thiol esters [115]. Inhibitors that chelate the active site of Zinc include EDTA, 1, 10-*o*-phenanthroline, dipicolinic acid, two phenazines from *Streptomyces sps*. [116], bis (1-N-tetrazol-5-yl) amine [117] and EDTA. More promising compounds are those which reversibly block the active site by competitive inhibition, since these offers the potential for modification of the structure to improve the specificity of the inhibitor for M*β*Ls alone. Such compounds include biphenyl tetrazoles [117], mercaptophenyl acetic acid derivatives, which do not covalently modify the enzyme (probably because the phenyl ring sterically hinders the hydrolysis of the carbonyl thiol bond) [115], trifluoro methyl alcohols and ketones [118], N-(2'-mercaptoethyl)-2-phenylacetamide [119], thiomandelic acid [120], D- and L-captopril inhibitors [121], 6-(mercaptomethyl) and penicillinases [122].

5.3. Epidemiology of M*β*L

During the past decade, both the global dimension of this problem and an unanticipated diversity of enzymes have been revealed, as acquired M*β*Ls have been detected in clinical isolates from Asia as well as from Europe, North and South America [92] [100] [109] [112] [123]. Currently, the most prevalent and widespread acquired M*β*Ls are the IMP-type and VIM type enzymes, of which several variants are known. Other types of acquired M*β*Ls SPM-1, GIM-1, and SIM-1 have also been identified [98] [124].

Peleg and his colleagues (2005) for the first time reported the emergence and rapid dissemination of an acquired M*β*L determinant in a hospital setting in Australia, a continental resistance [125]. The M*β*L gene involved in the outbreak was *bla*IMP-4, an allelic variant of *bla*IMP-1 gene previously identified in clinical isolates of *Acinetobacter sps.* and *Citrobacter youngae* from Hong Kong and the People's Republic of China [109] [110]. It was likely imported to Australia from those areas via international travelers and following the first detection in *P. aeruginosa*, the M*β*L gene was found in hospital acquired isolates of Gram-negative pathogens of 5 different species, including *P. aeruginosa*, *K. pneumoniae*, *Serratia marcescens*, *Enterobacter cloacae*, *and E. coli*. This is the first report for a rapid emergence in a single hospital of the same acquired M*β*L determinant in several different species, as well as in different strains of the same species (clonal diversity was observed among the M*β*L positive isolates of *K. pneumoniae and S. marcescens*) [125]. In fact, M*β*L producers usually exhibit complex MDR phenotypes because of their nosocomial origin and because of the frequent links between M*β*L genes and other resistance genes on the mobile DNA elements that are involved in their dissemination [126].

Only a low number of M*β*L producing isolates appeared to be carbapenem resistant [125] [127]. It is known that, unlike *P. aeruginosa* and *Acinetobacter species*, members of *Enterobacteriaceae* with acquired M*β*L genes tend to exhibit carbapenem MICs that remain lower than the breakpoint for resistance, unless permeability is also impaired [126]. This phenomenon has major implications for the detection of similar isolates (and consequently for surveillance) and also for the selection of antimicrobial chemotherapy.

6. Classification Based on Sequence Similarities by Hidden Markov Models (HMM) for *β*-Lactamase Annotation

Most widely used classification scheme for BLs is the Ambler structural classification, which is based on sequence similarity and it's still the best currently used. It classifies the BLs into 4 classes: the classes A, C, and D of serine-*β*-lactamases (SBLs) and the Class B of metallo-*β*-lactamases (M*β*Ls), where Class B is further divided into subclasses B1, B2, and B3, using sequence conservation data [27] [128] [129]. Even though SBLs and MBLs are able to break amide and ester bonds they do not belong to a common ancestor due to 2 distinct protein superfamilies [130]. SBL's tertiary structures are similar enough among themselves to

be homologous [131] while, the differences lie between their primary structures and catalytic mechanisms that divide them into classes A, C, and D [132].

The 3 subclasses of MBL, B1 and B2 have detectable sequence similarity and a common ancestor between them but not with B3 [133] [134]. The scheme proposed by Hall and Barlow (2005), based on structural information the former subclasses B1 and B2 were merged and renamed as class MB, whereas subclass B3 was renamed as class ME. Thus, the 5 BL classes which are considered as third classification level namely, SA, SC, SD, MB, and ME with subclasses MB1 and MB2 represent the fourth and last hierarchical level [132].

In few studies, phylogenetic and amino acid-based sequence similarities showed further division of classes SA and SD into 2 different new BL subclasses [35] [135]. Molecular classification of BLs does not represent currently to its actual sequence diversity and no precise definition for various classes and subclasses have been precised. Silveria *et al.* (2018) proposed new BL class with fused domains and extended action spectrum. This classification is based on a previous hierarchical scheme, profiles of Hidden Markov Models (HMM) and sequence clustering using similarity was proposed [136] that provides genomes in BL annotation and know the BLs distribution among bacteria phyla suggesting new BL subclasses.

7. Conclusion

Beta-lactamases producing bacteria causing nosocomial infections have resulted in a steep rise in their incidence in recent years. The scientific community reported extensively about the high morbidity-mortality rates due to these β-lactamases resistant MDR strains. Henceforth, detection of community and hospital transmission by β-lactamase pathogens becomes a paramount importance. Rapid identification of ESβL pathogens and their antibiotic resistance patterns will help the clinicians to select appropriate drug regimens like combination therapy and reduce their further spread. Since the epidemiology of ESβL and MβL producing bacteria is becoming more complex in both hospitals and community, it is important to regulate and monitor MDR among clinical isolates. "Super bug", bacteria might evolve in the near coming future for relatively all the antibiotics if we are not cautious in handling them. This alarms the development and spreading of the disease globally and incapability to cure the infection, and ultimately leading to mortality or death. In this situation, a constant monitoring, dispense of antibiotics for non-emergency cases only on the clinical reports and careful worldwide surveillance is urgently warranted.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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