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A Review of Extended Spectrum β-Lactamases: Definition and Types

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Abstract

Extended-spectrum β-lactamases (ESBLs) are defined as those bacterial enzymes which are capable to hydrolyze most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam and especially expanded spectrum cephalosporins such as ceftriaxone, cefotaxime, ceftazidime. Worldwide, ESBLs are considered to be a serious threat, especially in hospitalized and immunocompromised patients. There is a growing prevalence and dissemination of ESBLs in bacterial isolates all over the world. Individuals at high risk are those exposed to bacterial species harboring ESBLs as they result in treatment failure in many cases. Thus, there is an urgent need to detect ESBLs producers with the formulation of strategic initiatives that participate in controlling their prevalence and dissemination. The current review aims to illustrate the importance of ESBLs and give a simple definition of their major types emphasizing on their substrate profiles and characteristics.

1. Introduction:

It is well established that antimicrobials are employed for treating and preventing microbial, particularly bacterial, diseases in both humans and animals. They are produced from synthetic, natural, or semi-synthetic origins and inhibit or kill microbial cells [1], [2]. Antimicrobial agents have saved millions of lives worldwide in the past years by treating infections and preventing them. Unfortunately, the emergence of antimicrobial resistance has accompanied their introduction and usage in the medical field posing a growing global health challenge and threat [3]. Antimicrobial abuse, misuse, and overuse in different sectors and fields (medical, veterinary, agricultural, and industrial) are reported as the leading causes of what we can call an antimicrobial resistance pandemic [2], [3]. Deaths resulting from multidrug-resistant bacterial infections are expected to rise from seven hundred thousand to more than10 million per year, and the cost may exceed 100 trillion US dollars by the year 2050 [3], [4], [5], [6].

Bacterial possession of β-lactamases is considered as the most prevalent mechanism used to overcome the fatal effect of β-lactams through the breaking of the β-lactam ring which is crucial for the bactericidal action of the drug [7], [8], [9]. The resistance to β-lactams developed even before the discovery of the first antibiotic, penicillin. Penicillinase (the first β-lactamase known) was characterized in *Escherichia coli* (previously *Bacillus coli*) before the use of penicillin medically [10]. Chromosomally mediated β-lactamases are naturally occurring in many Gram-negative bacteria. Such enzymes are believed to be originated from bacterial penicillin binding proteins (PBPs), as their sequence share some homology with them. It is presumed that this evolution was likely because of the co-occurrence of soil microorganisms which produce β-lactam antibiotics and exert their selective pressure in the surrounding environment [11]. The enzyme TEM-1, a plasmid-encoded enzyme, was reported in the 1960s [12]. This enzyme was initially characterized in *E. coli* recovered from a Greek patient called Temoniera [13]. Being transposon and plasmid-encoded has assisted the dissemination of TEM-1 to other bacteria. Within several years, this enzyme had been spread globally in some species of the Enterobacteri-

aceae, *Haemophilus influenza*, *Pseudomonas aeruginosa*, and *Neisseria gonorrhoeae* [7], [14]. SHV-1 (sulfhydryl variable) is another plasmid-encoded enzyme found commonly in E. coli and *Klebsiella pneumoniae* strains. SHV-1 was firstly detected in 1979. In general, it is chromosomally mediated in *K. pneumoniae* strains, however, it is commonly located on plasmid in the isolates belonging to *E. coli* [15].

In an attempt to overcome the new and growing challenge imposed by β-lactamases, many semi-synthetic β-lactam antimicrobials have been introduced that were specially manufactured to resist β-lactamase activity. Though, new variants have evolved with each new class causing resistance to those antimicrobials. The selective pressure imposed by the random use and abuse of the antimicrobials in health settings has participated in the emergence of new β-lactamases with expanded hydrolytic capabilities. Oxyimino-cephalosporins was one of the new antimicrobials introduced and became broadly used for the management of serious diseases, especially those caused by multi-resistant Gram-negative bacilli in the 1980s [7], [14]. Not surprisingly, the emergence of the β-lactamase variants capable of destroying oxyimino-cephalosporins was quick. SHV-2 was the first enzyme of this group, it was firstly described in a *Klebsiella ozaenae* strain recovered in Germany [16]. Due to their extended range of action and hydrolytic activity, particularly towards oxyimino-cephalosporins, these enzymes were termed extended-spectrum β-lactamases (ESBLs). At present, several hundred variants of ESBLs have been characterized. These enzymes have been reported globally in different bacterial species especially those belonging to Enterobacterales and *P. aeruginosa* [7], [14], [17]. This review aims to give a simple definition of ESBL types and their impact on the global threat of antimicrobial resistance.

2. ESBLs:

ESBL enzymes represent an important category of serine enzymes that belong to class A of Ambler's molecular scheme and 2be subgroup of the functional scheme of Bush [18], [19]. They are widely disseminated in nature and categorized into numerous groups Table 1. ESBL-producing bacterial strains are distinguished by having the power to resist and hydrolyze numerous β-lactam agents i.e., penicillins, first cephalosporins, aztreonam (a monobactam), and oxyimino-β-lactams, such as ceftazidime, cefotaxime, with no ability to hydrolyze carbapenems or cephamycins. However, they are affected by clavulanic acid, tazobactam, and sulbactam [9]. The largest subset of 2be subgroup was a result of mutations that lead to substitutions in amino acid sequences of TEM-1, SHV-1, and TEM-2 that expanded their action to include oxyimino-β-lactams and decreased, in return, their hydrolytic power for cephaloridine and benzylpenicillin [9][14].

Subsequently, the rapidly proliferated Cefotaxime- hydrolyzing β-lactamase from Munich (CTX-M) enzymes were functionally similar to SHV and TEM enzymes and were related to the chromosomally encoded β-lactamases of Kluyvera [14]. The majority of these variants attack cefotaxime more rapidly than ceftazidime (hence the name), and a number of them can attack cefepime as well. Contrary to the SHV or TEM enzymes, CTX-M variants are inhibited by tazobactam more readily than clavulanic acid [20], [21]. Furthermore, other types of ESBLs are also present, they are less common and unrelated to CTX-M, SHV, or TEM. Examples of these enzymes are SFO-1, BEL-1, TLA-1, BES-1, TLA-2, and members of the families VEB and PER. Typically, 2be subgroup enzymes remain susceptible to clavulanic acid, this characteristic is usually employed by clinical laboratories in the detection test for ESBLs [9], [22]. Additionally, active site extension which permits the activity increase against oxyimino drugs may also make the enzymes more susceptible to inhibitors such as tazobactam and clavulanic acid [23]. Generally, ESBLs are sensitive to cephamycins, and the majority of ESBLs-producing bacteria are sensitive to cefotetan and cefoxitin. Nevertheless, it has been documented that strains expressing ESBLs can show resistance to cephamycins because of the loss of a porin protein in the outer membrane [24], [25], [26].

β-lactamase variety has numerous reasons, the serine enzymes are very ancient once. It is estimated that they have been developing and evolving for almost 2 billion years, even before the bacterial divergence into Gram-positive and Gram-negative species [27]. They have been found in different bacterial species living in varied environments and hence are exposed to various selective pressures. Furthermore, ESBL genes have used the horizontal gene transfer mechanisms, i.e., conjugation and transduction, to transfer to new bacterial hosts and to become part of multi-resistance transposable elements now spreading in clinical and environmental isolates [14], [17]. In consequence, it is unfortunately true expectation that these enzymes will persist and continue to develop. ESBL-expressing strains, usually correlated with antimicrobial-resistant infections, are continuously reported with increasing rates worldwide which represents a universal threat facing the control and treatment of hospital- and community- acquired bacterial infections, especially those caused by Gram-negative bacilli with multiple drug-resistance such as *Klebsiella spp.*, *Pseudomonas aeruginosa*, and *Escherichia coli.* which will limit therapeutic options and may lead to treatment failure [6], [9].

3. Types of ESBLs:

Many ESBL enzymes are derived from the original SHV or TEM β-lactamases and categorized in several groups with different designations Table 2 [18], [23] The ESBLs phenotype usually evolved as a consequence of point mutations at selected loci. SHV and TEM enzymes are most common in bacterial strains belonging to *Klebsiella pneumoniae* and *Escherichia coli.* As well, they have also been detected in

Table 1. Classification and characteristics of selected groups of β-lactamases (mainly ESBLs).

Functional group	Molecular class	Preferable substrate(s):	Inhibition by: CA*	EDTA	Main characteristic(s)	Example(s)
1	C	cephalosporins	no	no	hydrolyze cephalosporins more efficiently than benzylpenicillin hydrolyze cephamycins	AmpC, ACT-1, CMY-2 FOX-1, MIR-1
2a	A	Penicillins	yes	no	hydrolyze benzylpenicillin more efficiently than cephalosporins	PC1
2b	A	Penicillins, early cephalosporins	yes	no	Hydrolyze benzylpenicillin and cephalosporins equally	TEM-1, TEM-2, SHV-1
2be	A	Extended-spectrum cephalosporins, monobactams	yes	no	preferentially hydrolyze oxyimino-drugs (cefotaxime, ceftazidime, cefepime, aztreonam)	TEM-3, SHV-2, CTX-M-15, CTX-M-15, PER-1, VEB-1
2de	D	Extended-spectrum cephalosporins	variable	no	efficiently hydrolyzes oxacillin or cloxacillin and oxyimino-drugs as well	OXA-11, OXA-15
2ber	A	Extended-spectrum cephalosporins, monobactams	no	no	inhibitor resistant, hydrolyze oxyimino-drugs	TEM-50
2br	A	Penicillins	no	no	resistant to tazobactam, clavulanic acid, and sulbactam,	TEM-30, SHV-10

*CA: Clavulanic acid

other genera of Enterobacteriaceae like Providencia spp. and Proteus spp.

Table 2. Nomenclature origin of the major groups of the Extended-spectrum β-lactamase.

Group Designation	Designation Origin
TEM	Temoneira, patient name
SHV	Sulfhydryl reagent variable
CTX-M	Cefotaxime-hydrolyzing β-lactamase from Munich
IRT	Inhibitor-Resistant TEM
OXA	Active on oxacillin
GES	Guiana-extended spectrum
VEB	Vietnam Extended Spectrum β-lactamase
BEL	Belgium Extended β-Lactamase
SFO	In Serratia fonticola
OXY	In K. oxytoca
TLA	Tlahuicas Indians (Mexican people group)
PER	Pseudomonas Extended Resistant
CME	From Chryseobacterium meningosepticum
BES	Brazil Extended Spectrum

3.1 TEMs:

These enzyme variants are originated from TEM-1 enzyme, which was plasmid-mediated and firstly reported in the early 1960s [12]. It was initially characterized in an *E. coli* strain recovered in Greece from a local patient named Temoneira [13]. TEM-1 is considered the most frequently expressed enzyme in Gram-negative strains. It has been reported that almost 90% of ampicillin-resistant *E. coli* isolates are possessing this enzyme [8]. In addition, TEM-1 is also one of the major mechanisms used in resisting penicillin and ampicillin increasingly seen in *N. gonorrhoeae* and *H. influenza* clinical isolates. This enzyme can hydrolyze the first cephalosporins such as cephaloridine, cephalothin, and penicillins. TEM-2, as the first variant of TEM, has one substitution (glutamine for lysine at position 39) in comparison to the parent enzyme [28]. Although changing the isoelectric point (pI) from (5.4) to (5.6), it has no effect to alter the substrate profile. However, TEM-2 acted as the originator of several TEM variants with extended-spectrum activity [7], [14]. TEM-3, originally reported in *K. pneumoniae* in France in the late 1980s, was the first extended-spectrum TEM enzyme reported [29]. In the beginning, the enzyme was known as CTX-1, as it was more active against cefotaxime [30]. At present, nearly 243 various TEM variants have been reported and characterized, some of them are inhibitor-resistant, but most of them are ESBLs.

Amino acid alterations usually take place at a few specific and known number of positions [7]. These alterations result in numerous modifications in the enzyme phenotype, i.e., the ability to attack certain antimicrobials like cefotaxime and ceftazidime, or changing the enzyme isoelectric points (usual range: 5.2 - 6.5). Several residues are particularly significant for generating the extended spectrum phenotype when alterations take place at that positions. For example, arginine substitution to either histidine or serine at position 164, glutamate to lysine at position 104, glutamate to lysine at position 240, and glycine to serine at position 238. It is noteworthy that among these substitutions, the alteration of glycine to serine and glutamate to lysine appear to have the most influence on the production of the extended-spectrum phenotype of the enzyme [14]. Furthermore, newer TEM enzymes show subtle alterations in their profiles. For instance, TEM-184 with the following substitutions: glutamate to lysine (position 6), glutamic acid substitution to lysine (position 104), isoleucine to valine (position 127), arginine substitution to serine (position 164), and methionine to threonine (position 182)

can hydrolyze aztreonam more efficiently than cefotaxime or ceftazidime [31]. Although the analyzing of bacteria genomes through Whole Genome Sequencing (WGS) participated in detecting and discovering so many new TEM variants, only a few of them are phenotypically characterized. Nevertheless, network analysis with computer modeling has enabled researchers to predict whether a specific enzyme sequence has the probability to fit in the functional groups 2be (extended-spectrum), 2br (inhibitor resistant), or 2b (the original broad spectrum) [32].

Interestingly, it has been documented that the occurrence of TEM enzymes was regional to some geographical areas. For example, TEM-10 was the most prevailing enzyme in the USA [33]. In contrast, TEM- 3 was infrequently described in the USA, but it was very common in France [34]. On the other hand, the TEM-26 variant was characterized in different bacterial species worldwide [34], [35], [36], [37]. At the present, as the CTX-M enzymes came to be the prevalent ESBLs globally, TEM variants have become infrequently reported. In a recent study screening bacterial isolates in Europe for ESBLs, these enzymes were characterized in no more than 1% of ESBL-expressing Klebsiella spp. and *Escherichia coli* [14], [38].

Although TEM variants are most commonly detected in bacterial strains belonging to *E.coli* and *Klebsiella pneumoniae*, they have been reported in other Gram-negative species as well including different members of Enterobacteriaceae, i.e. Salmonella spp, *M. morganii*, *E. aerogenes*, *Pr. mirabilis*, and *E. cloacae* [8], [39], [40], [41], [42]. Furthermore, they have also been reported in non-Enterobacteriaceae, for example, TEM-42 was detected in *P. aeruginosa* isolates and TEM-17 was characterized in a Capnocytophaga ochracea strain isolated from blood [43], [44], [45], [46].

3.2 SHVs:

Sulfhydryl variable (SHV) β-lactamases were firstly reported as chromosomally determined enzymes in the strains of *K. pneumoniae* [8]. The first variant with ESBL phenotype (designated as SHV-2) was characterized in 1985 in an isolate of *K. ozaenae* recovered in Germany, this variant is varied from the SHV-1 enzyme by only one substitution (glycine to serine, position 238) [47]. Like TEM variants, most of the SHV-variants have substitutions at positions 238 (glycine to serine) and 240 (lysine to glutamine) [8]. Interestingly, both of these alterations are resemble of those found in the TEM variants. Serine substitution seems to be important for the effective breakdown of ceftazidime, while lysine substitution (position 240) is important for the effective cefotaxime hydrolysis as well [47]. The significance of amino acid substitutions concerning the phenotypic alterations in substrate profile has been studied and analyzed by mathematical modeling [48]. The SHV-1 enzyme is frequently characterized in bacterial isolates belonging to *K. pneumoniae* and it is the mechanism used in more than 20% of ampicillin resistance (usually plasmid-encoded) in these strains [49]. Noteworthy, SHV enzymes are more prevalent in clinical bacterial isolates than other types of ESBLs [50]. In many isolates of *K. pneumoniae*, blaSHV-1 has been found to be integrated into the chromosomal DNA [8]. Although the hypothesis of being part of transposable elements like plasmids, the SHV-1 encoding gene has never been characterized as so [51]. Contrary to the TEM enzymes, there are few variants of the SHV-1 enzyme. Additionally, the alterations that have been detected in the blaSHV gene to produce the variants take place in fewer positions in comparison to TEM enzyme, many of these variants express the ESBL phenotype. Though, a single variant, SHV-10, is documented to have the IR (Inhibitor Resistant) characteristics, it seems this variant has been resulted from the SHV-5 enzyme containing an extra alteration in amino acid sequence at position 130 as glycine replaced by serine [52].

Up to the present time, 228 SHV variants have been described. Nonetheless, not all of them have been phenotypically described as extended-spectrum enzymes. Globally, SHV-12 and SHV-5 are the most prevalent SHV- ESBLs documented in Enterobacterales [14], [53], [54]. Although most of the SHV- ESBLs are present in the clinically isolated *K. pneumoniae*, they have also been reported in *E. coli*, Citrobacter diversus, other Enterobacterales, Acinetobacter spp, and *P. aeruginosa* isolates [53], [54], [55], [56], [57], [58], [59], [60], [61].

In the latest European surveillance, 3.1%–17.0% of the clinical strains belonging to *K. pneumoniae* were found to harbor SHV- ESBLs [38]. Nevertheless, in a clinical study investigated clinically recovered ceftazidime resistant bacteria, SHV enzymes were infrequently detected and were only presented in isolates that also harbored a carbapenemase or a plasmid-encoded AmpC [62]. Although SHV and TEM enzymes are still reported, it seems that the influence of their occurrence amongst clinical strains is insignificant [14].

3.3 CTX-Ms:

Afterward, a new group of plasmid-encoded enzymes named CTX-M, which favorably attack cefotaxime has developed. This group of enzymes is differing from the SHV or TEM enzymes as they show approximately 40% homology with the both enzymes [63]. Initially, CTX-M was first reported in the late 1980s and their numbers are continuously growing as more than 128 variants of this enzyme have been detected worldwide [14], [46], [63]]. These enzymes are distinguished from others by hydrolyzing cefotaxime more effectively than ceftazidime, and cephalothin more efficiently than benzylpenicillin, they attack cefepime as well [63]. Unlike SHV and TEM ESBLs, no point mutation is occurred in CTX-M enzyme. It is believed that this enzyme was firstly described in the Kluyvera spp chromosome [14], [64]. The term CTX-M (standing for cefotaximase from Munich, Table 2 was firstly used in a German study [65]. Nevertheless, CTX-Ms that recognized in other areas were given diverse designations, like

Toho-1 (Japan), MEN-1 (France), and FEC-1 (Japan) [21]. Outbreaks in different countries were followed and presenting an alarm for the potential threat that these enzymes could represent. Additionally, these variants have been documented as the most prevalent ESBL enzymes, instead of SHV and TEM. Variants of CTX-M have been described amongst various members of the enteric bacteria, Acinetobacter isolates and *P. aeruginosa* strains [66], [67], [68]. Furthermore, bacterial strains harboring CTX-M genes have been identified in the community and public health establishments, the environment, food products, livestock, and the companion animals [69].

As mentioned previously, the CTX-M enzymes preferentially hydrolyze cephaloridine or cephalothin (in comparison to benzylpenicillin) and cefotaxime (in comparison to ceftazidime) [63], [70]. As for ceftazidime, although these enzymes have a minor effect on it, they could not provide the required hydrolysis activity to make the strains clinically resistant to the antimicrobial. Serine (found in all CTX-M variants at position 237) is believed to have a critical effect in the extended-spectrum action of these enzymes [63]. Likewise as proposed by molecular modeling studies, the arginine residue (at position 276) which is equivalent in position to arginine 244 in SHV or TEM ESBLs, may participate in the enzymatic hydrolysis of oxyimino-cephalosporins [71]. Additionally, CTX-M ESBLs have an extra unique characteristic of being inhibited more efficiently by tazobactam in comparison to clavulanic acid or sulbactam [63], [70], [72], [73].

Based on the sequence homologies, most of the CTX-M variants are classified into five groups: CTX-M-1, CTX-M-8, CTX-M-25, CTX-M-2, and CTX-M-9. The prevailing enzyme in the first group is CTX-M-15, then the CTX-M-3 and CTX-M-1 enzymes. CTX-M-9, CTX-M-14, and CTX-M-27 are the most common variants in CTX-M-9 group [74], [75], [76], [77], [78]. CTX-M-25, CTX-M-2, and CTX-M-8 are prevailing in their own groups. Interestingly, it is documented by the analysis and studying of the CTX-M-2 gene to be originated from Kluyvera spp. Additional investigations had confirmed that this group has resulted from the Kluyvera ascorbate KLUA-1 enzyme [79], [80]. Likewise, CTX-M-134 (CTX-M-1 group) is documented to be resulting from the *Kluyvera cryocrescens* KLUC-1 enzyme and the CTX-M-9 has a resemble like characteristics with the Kluyvera georgiana KLUG-1 enzyme [81], [82]. Accordingly, an early divergence from a common ancestor may be suggested based on the evolutionary distances among these groups [7], [83]. Noteworthy, these variants also showed basic resemblance and enzymatic activities with various class A enzymes that were described in bacterial strains recovered from the environment, such as *Rahnella aquatilis and Erwinia persicina* [84], [85].

CTX-M β-lactamases are known to hydrolyze ceftriaxone (CRO) and cefotaxime (CTX) more efficiently than ceftazidime (CAZ) [21]. Nevertheless, variants with increased hydrolytic power against ceftazidime were also reported. CTX-M-27 and CTX-M-15 are good examples of that. CTX-M-15 is a derivative from CTX-M-3 with only one amino acid alteration (aspartic acid to glycine at position 240) [86]. This substitution is responsible for the enzymatic accommodation to ceftazidime molecule, which has a larger size compared to cefotaxime [87], [88]. Similarly, CTX-M-27 has the same amino acid (position 240) which is believed to be responsible for the increased MIC values for ceftazidime in comparison to its originator CTX-M-14 [89]. Recently, a new variant (CTX-M-33) with a substitution of aspartic acid to serine (at position 109) compared with CTX-M-15 was described in a *K. pneumoniae* clinical isolate [90]. This enzyme has showed decreased hydrolytic activity against ceftazidime and elevated hydrolysis against meropenem. Interestingly, the isolate also had impaired permeability resulting in an elevated MIC for meropenem [90]. CTX-M enzymes are widely distributed and continuously emerging globally. However, even though alternative options are still available for bacterial strains carrying them alone, the concurrent occurrence of CTX-M ESBLs with other resistance mechanisms (i.e. impermeability) in the same isolate could affect the action of carbapenems or other newer agents and limit it [1].

Bacterial strains expressing various types of CTX-M enzymes have been reported from different parts of the globe, although they mostly have been related to outbreaks recorded in eastern Europe [70], [90], [91], [92], Japan, and South America [72], [93]. Furthermore, these enzymes also have been reported in bacterial strains isolated from immigrated patients in western Europe [94]. For instance, a clinical strain of *Enterobacter* cloacae with CTX-M-3 was isolated in France in 1998 [95]. Numerous laboratories and institutions in the outbreaks areas had documented the prevalence of CTX-M variants in the recovered isolates in comparison to other types of ESBLs [73]. Remarkably, some of these enzymes have been described in Salmonella enterica clinical isolates as well [70], [91], [94], [96], [97]. *S. enterica* strains possessing CTX-M enzymes were responsible for large outbreaks that occurred in both eastern Europe and South America. Additionally, these strains were documented to have multiple CTX-M enzymes. Consequently, it is questionable thing that a single origin for the existence and tendency of CTX-M enzymes within S. enterica can be existed [7], [14].

3.4 OXAs:

OXA β-lactamase is a growing group of ESBLs belonging to the functional group 2d and Ambler class D [18]. These enzymes, which display resistance to cephalothin and ampicillin, are well known for their specific hydrolysis of cloxacillin and oxacillin and poor inhibition by clavulanic acid [9], [18]. Generally, OXA enzymes show variability in amino acid sequences and substrate profiles. Nevertheless, many OXA enzymes have been reported to hydrolyze cephems, and/or monobactams as well as cephalosporins. Therefore, these enzymes are now classified as subgroup 2de [9]. Whether

or not OXA enzymes with expanded-spectrum activity are considered as ESBLs is still questionable [98]. Many scientists do not agree with applying the ESBLs designation to oxacillinases because the OXA variants are grouped in the 2de subgroup and not in the 2be, in addition to their resistance to inhibition by clavulanate [14].

As documented by a current review, 27 oxacillinases have been characterized as ESBLs. The substrate profile includes the new cephalosporins (3^{rd} and/or 4^{th} generation drugs) in addition to the early ones and penicillins [99]. OXA enzymes have been described mostly in bacterial isolates belonging to P. aeruginosa in addition to *Acinetobacter baumannii* strains, and not in *K. pneumoniae* and *E. coli* as other ESBLs. For instance, OXA-21 was reported in an isolate of *Acinetobacter baumannii* as the first occurrence of OXA enzymes in this species [100]. The majority of OXA ESBL variants originate from OXA-2 and OXA-10 (PSE-2). The variants originated from OXA-10 are OXA-16, -14, -13, -11, -17, -28, and -19 [101], while those derived from OXA-2 include OXA-15, -53, -34, -141, -32, -36, -161, -226, and -210, most of these variants are described in *P. aeruginosa* [99]. OXA-14 originated from the OXA-10 enzyme and differs from it by one substitution, OXA-16 and -11 differ by two, and OXA-19 and -13 differ by nine. Interestingly, amongst these enzymes, the ESBL variants have one of these amino acids alterations: aspartate for glycine (amino acid position: 157), or asparagine for serine (amino acid position: 73). Particularly, the aspartate for glycine substitution may be critical for ceftazidime resistance [102]. Either substitutions could be essential to display the extended spectrum phenotype. On the other hand, the OXA-17 variant shows resistance to ceftriaxone and cefotaxime but displays only minimal hydrolysis activity against ceftazidime [103]. Additionally, although the traditional OXA enzymes were known for their resistance to inhibition by clavulanate, the OXA-18 variant was characterized to be affected and inhibited by it [7], [103].

Although OXA-1 and OXA-30 are not considered as ESBLs, their capabilities to destroy cefepime have been documented [104], [105], [106]. These two variants were firstly reported to be different by one substitution; but it was revised later that these enzymes were actually the same [107]. Noteworthy, the OXA-1 enzyme accompanied by porin deficiency has been detected in false-ESBL phenotype-expressing E. coli strains [108]. Furthermore, an OXA-31 variant described in a *P. aeruginosa* strain had (3) alterations in comparison to OXA-1 and also showed a hydrolytic effect towards cefepime [109]. As well, OXA-405 and OXA-163 (derivatives from OXA-48) have also been reported to show hydrolytic effect towards the new cephalosporins in addition to the carbapenemase activity characteristic of OXA-48-like enzymes [14],[110], [111], [112].

4. Inhibitor Resistant β-Lactamases:

Inhibitor-resistant enzymes were firstly discovered in the early 1990s. Although these enzymes don not have the distinguished ESBL phenotype, they are regularly discussed with them because they are usually originated from the traditional SHV or TEM enzymes. They are categorized into the functional group 2br Table 1 [9], [18]. The inhibitor-resistant variants derived from TEM enzymes are often not inhibited by sulbactam and clavulanic acid, but they remain sensitive to tazobactam and avibactam [112], [113], [114], [115], [116]. It is suggested that the mutations conferring resistance to sulbactam and clavulanate are also reduce the enzyme efficiency of hydrolyzing some cephalosporins like cephalothin and penicillins [115], [117].

Inhibitor-resistant TEM variants have been detected mostly in *E. coli* clinical strains, and infrequently in *P. mirabilis*, *K. pneumoniae*, Citrobacter freundii, and Klebsiella oxytoca isolates [118], [119]. They have mainly been described in France and in some other countries within the Europe continent [115]. Although these enzymes are infrequently detected, the variant TEM-30 was characterized in a *K. pneumoniae* strain with numerous KPC-producing bacteria isolated from a carbapenem-resistant Enterobacteriaceae outbreak occurred in New York [113]. As documented by nucleotide sequencing data, the majority of these enzymes originated from TEM-1 and were previously known as " Inhibitor Resistant TEM, IRT", but now they are renamed using numerical TEM designations with 19 distinct inhibitor-resistant TEM variants known and documented so far [14], [120]. The common alterations in these enzymes are methionine at position 69, serine at position 130, arginine at position 244, arginine at position 275, and asparagine at position 276 [121]. These alterations in amino acids sequence are different from those described in the ESBL variants. Several variants of the SHV-1 and OHIO-1 have been reported to be resistant to inhibitors, such as SHV-107, -56, and -49 characterized in clinical isolates of *K. pneumoniae* in Europe [52], [116], [122], [123], [124].

In a laboratory experiment, mutants containing common substitutions for both extended spectrum and inhibitor resistant phenotypes have been constructed. These variants possessed either the IRT or the ESBL phenotype, but not both [125]. Additionally, a few TEM variants with both the inhibitor resistance and the ESBL phenotype have been reported [121]. Interestingly, these enzymes could be detected with ESBLs-screening methods depending on the clavulanic acid inhibition principle. For instance, TEM-50 enzyme with alterations characteristic of both the inhibitor-resistant and the ESBL phenotypes was reported in 1997. This variant was not affected by clavulanic acid, and displayed a minor resistance to 3^{rd}. generation cephalosporins [126]. TEM-152 is another variant of such enzymes, it was described in an *E. coli* isolate recovered from a French patient [127]. This mutant harbored the following amino acid substitutions: arginine for histidine

(position164) and glutamine for lysine (position 240) which characterize the ESBLs phenotype, in addition to methionine for valine (position 69) and asparagine for aspartic acid (position 276) which characterize the inhibitor-resistant variant TEM-36. This variant efficiently hydrolyzes ceftazidime with 50% susceptibility to clavulanic acid. This could specify the emergence likelihood of a new subgroup with a complicated profile that shares features of inhibitor-resistant and ESBL enzymes. Interestingly, these complex enzymes are susceptible to avibactam, therefore the combination of a new β-lactamase inhibitor like ceftazidime/avibactam may represent an alternative therapy to face and treat bacterial diseases caused by strains with one of these variants [127]. It is expected that the dissemination of SHV- or TEM-type IR-variants is undervalued due to the absence of a specific phenotypic screening test that could be used routinely by laboratories to identify and detect the occurrence of these enzymes [14], [128], [129].

5. Other ESBLs:

There are several extended-spectrum β-lactamases have been described that are not part of the well-known groups of β-lactamases Table 3. The PER-1 (Pseudomonas Extended Resistant) enzyme was firstly characterized in a *P. aeruginosa* isolate which was resistant to 3^{rd} generation cephalosporins and inhibited by clavulanate [130], [131]. Furthermore, this enzyme could hydrolyze many penicillins as well as cephalosporins including ceftazidime, cefoperazone, cefalotin, cefuroxime, and ceftriaxone, but not oxacillin, imipenem, and cephamycins. Soon after, it was also reported among other bacterial strains belonging to *A. baumannii* and *S. enterica* Typhimurium [132], [133], [134]. This enzyme is most commonly described in Turkey and Mediterranean countries in up to 60% of *A. baumannii* isolates that are ceftazidime-resistant [134], [135], [136]. Interestingly, the PER-1 enzyme was plasmid-mediated in several nosocomial strains of *S. enterica* Typhimurium, which might suggest the spread and acquisition of the resistance plasmid in the hospital setting [133]. Consequently, PER-2 was characterized in another *S. enterica* Typhimurium strain from Argentina with 86.4% homology with the original PER-1 enzyme [137]. Since after, PER variants have been reported in different species of Enterobacterales as well as Aeromonas spp. and *A. baumannii* isolates. PER-1 and PER-2 enzymes are the most common variants of the PER group, they have been characterized by their susceptibility to avibactam in comparison to other class A enzymes [138], [139]. Noteworthy, a recent analysis has documented that A. baumannii strains expressing PER variants can show increased minimum inhibitory concentrations against the siderophore cephalosporin, cefiderocol [140].

Table 3. Classification and characteristics of selected groups of β-lactamases (mainly ESBLs).

Enzyme	pI*	Closely related to:	Preferentially *hydrolyze**:	Ref.
VEB-1	5.35	PER-1, PER-2	CAZ, ATM	141
TLA-1	9	CME-1	CAZ, CTX, ATM	161
PER-2	5.4	PER-1	CAZ	96
GES-1	5.8	Penicillinase from P.mirabilis	CAZ	147
SFO-1	7.3	AmpA from S. fonticola	CTX	159
CME-1	>9	VEB-1	CAZ	160

*pI : isoelectric point, CAZ: ceftazidime, CTX: cefotaxime, ATM: aztreonam.

VEB-1 is related to some extent to PER-1, the abbreviation stands for Vietnamese Extended-spectrum β-lactamase Table 2, it was firstly described in a local *E. coli* strain from Vietnam [141]. Subsequently, this enzyme was described in a local *P. aeruginosa* isolate from a Thai patient [142]. VEB-1 displayed high resistance to aztreonam and ceftazidime Table 3, but only moderate susceptibility for cefotaxime and no activity against imipenem. Additionally, it was susceptible to clavulanic acid but not to avibactam [128], [143]. VEB variants were identified in different bacterial species including members of Enterobacterales, Achromobacter xylosoxidans, Vibrio spp., *A. baumannii*, and *P. aeruginosa* [144], [145], [146].

The Guiana Extended-Spectrum β-lactamases (abbreviated GES) are the most prevailing enzymes among the infrequently detected ESBLs. The GES-1 gene is not closely associated with other plasmid-encoded enzymes, even so, it has some homology (36%) with a carbenicillin-hydrolyzing enzyme identified in Proteus mirabilis Table 3 [7], [147]. These enzymes are more commonly described in *A. baumannii* and *P. aeruginosa* isolates. Noteworthy, they have been initially reported among Enterobacterales species [66], [148], [149], [150], [151]. Furthermore, these enzymes are known for their acquisition of one or two substitutions in amino acid sequences and expanding the substrate profiles to include carbapenems [12], [112].

GES-1 enzyme was firstly identified in 1998 in a strain of *K. pneumoniae* recovered from a French patient in French Guiana [147]. Concurrently, the IBC-1 enzyme was described in a strain of E. cloacae recovered in Greece [152]. Subsequently, the variants IBC-2 and GES-2 were characterized in clinically isolated strains of P. aeruginosa [153], [154]. Later, IBC-2 was renamed and given the designation GES-8 and IBC-2, GES-7. Remarkably, GES-2 differed from GES-1 in a single alteration in amino acid sequence (glycine for asparagine at position 170) and could hydrolyze carbapenems to some extent [153]. Therefore, the subsequent characterized GES variants were grouped into two categories: those with the ESBL phenotype, and those with modest activity against carbapenems. The original GES variants hydrolyze cephalosporins and penicillins, but not aztreonam [147]. They are affected by tazobactam, clavulanic acid, and newer inhibitors like vaborbactam, relebactam, and avibactam [138], [155]. Notably, GES-1 hydrolyzes ceftazidime more effi-

ciently than cefotaxime. The following substitutions; glutamine for lysine (position 104), or glycine for alanine or serine (position 243) that noticed in the latterly characterized GES enzymes have displayed a hydrolytic activity against aztreonam and cephalosporins [14], [156].

Finally, numerous additional ESBLs enzymes were identified in the chromosomes of Enterobacteriaceae and other non-fermentative bacteria in different countries including Iraq [157], [158], [159], [160], [161], [162]. For instance, the OXY enzymes in *Klebsiella oxytoca* strains are undoubtedly the predominant resistance mechanism detected in this species [163], [164]. Moreover, there are other infrequently detected ESBLs have also been characterized in clinical bacterial isolates, but their incidence is somehow limited. An example of these enzymes is the SFO-1 variant, which was initially identified in an isolate of *Serratia fonticola*. This enzyme is a transferable variant, its production can be induced and enhanced by imipenem [165]. The plasmid encoding the gene blaSFO-1 also encodes ampR (regulatory gene) which is essential for expression induction of class C β-lactamases. Nevertheless, contrary to class C enzymes, SFO-1 is unable to attack cephamycins and is easily affected by clavulanate [164]. CME-1 is another related enzyme, that was identified in an isolate of *Chryseobacterium meningosepticum* [166]. Additional examples are; the TLA-1 enzyme described in an *E. coli* strain recovered from the Tlahuicas group (Mexican indigenous people), TLA-2 which was identified in Germany with 51% homology to TLA-1, BES-1 which was described in Brazil, and BEL-1 in Belgium Table 3 [144], [167], [168]. All of these enzymes display resistance to 3^{rd} generation cephalosporins, particularly ceftazidime, cefotaxime, and aztreonam. Additionally, they display limited resemblances to the chromosomally-encoded cephalosporinases described in Bacteroides spp. from which they might be originated [7], [166].

6. Conclusions:

Undoubtedly, the ESBL-producing bacteria are of great concern to the medical field as they are directly connected with an elevated mortality and morbidity rates. Additionally, it is time consuming to identify them, and subsequently their infections are difficult to treat. It is documented that the overuse and misuse of the broad-spectrum cephalosporins in the veterinary and health settings participated in the development and dissemination of ESBLs. Current therapy options for bacterial strains expressing the ESBLs enzymes is restricted to the broad-spectrum antimicrobials such as carbapenems. Nevertheless, there have already been therapeutic failure reports of these drugs as well. Bacterial strains conferring ESBLs would represent a serious challenge for clinicians and clinical microbiologists as we are heading into the next quarter of the 21^{st} century. Taking into account the globally rising prevalence rates of ESBLs-producing strains, and the lack of alternative therapy, the future is extremely concerning. Thus there is a crucial need for instant documentation and suitable strategy to control and reduce the occurrence of ESBLs. Controlling the use of broad-spectrum agents in different aspects and inspecting the environmental contamination are essential. Therefore, urgent and continuous works are mandatory to develop reliable, quicker, and cost- effective diagnostic tools as well as new active alternative antimicrobials for dealing with such ESBLs producing bacterial strains.

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References

[1] J.M. Willey, K.M. Sandman, , and D.H. Wood. *Prescott's Microbiology*. McGraw Hill Education, New York, 11^{th} edition, 2020.

[2] M.T. Madigan, K.S. Bender, D.H. Buckley, W.M. Sattley, , and D.A. Stahl. *Brock Biology of Microorganisms*. Pearson Education Ltd., New York, 15^{th} edition, 2019.

[3] C. J. Murray, K. S. Ikuta, F. Sharara, L. Swetschinski, G. R. Aguilar, A. Gray…, and M. Naghavi. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, 399(10325): 629–655, 2022, doi:10.1016/S0140-6736(21)02724-0.

[4] M. Gashaw, M. Berhane, S. Bekele, G. Kibru, L. Teshager, Y. Yilma, , and S. Ali. Emergence of high drug resistant bacterial isolates from patients with health care associated infections at jimma university medical center: a cross sectional study. *Antimicrobial Resistance Infection Control*, 7(1): 1–8, 2018, doi:10.1186/s13756-018-0431-0.

[5] M. Osman, H. Al Mir, R. Rafei, F. Dabboussi, J. Y. Madec, M. Haenni, , and M. Hamze. Epidemiology of antimicrobial resistance in Lebanese extra-hospital settings: An overview. *Journal of Global Antimicrobial Resistance*, 17: 123–129, 2019, doi:10.1016/j.jgar.2018.11.019.

[6] N. Tanko, R. O. Bolaji, A. T. Olayinka, and B. O. Olayinka. A systematic review on the prevalence of extended-spectrum β-lactamase-producing gram-negative bacteria in nigeria. *Journal of Global Antimicrobial Resistance*, 22: 488–496, 2020, doi:10.1016/j.jgar.2020.04.010.

[7] P. A. Bradford. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clinical Microbiology Review*, 14(4): 933–951, 2001, doi:10.1128/CMR.14.4.933–951.2001.

[8] D. M. Livermore. β-lactamases in laboratory and clinical resistance. *Clinical Microbiology Review*, 8(4): 557–584, 1995.

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

[10] E. P. Abraham and E. Chain. An enzyme from bacteria able to destroy penicillin. *Nature*, 146(3713)837-837: 837–837, 1940.

[11] J. M. Ghuysen. Serine β-lactamases and penicillin-binding proteins. *Annual Review Microbiology*, 45: 37–67, 1991.

[12] N. Datta and P. Kontomichalou. Penicillinase synthesis controlled by infectious r factors in enterobacteriaceae. *Nature*, 208: 239–4, 1965, doi:10.1038/208239a0.

[13] A. A. Mederiros. β-lactamases. *British Medical Bulletin*, 40(1): 18–27, 1984.

[14] M. Castanheira, P. J. Simner, and P. A. Bradford. Extended-spectrum β-lactamases: An update on their characteristics, epidemiology and detection. *JAC-antimicrobial Resistance*, 3(3): dlab092, 2021, doi:10.1093/jacamr/dlab092.

[15] C. de Champs, D. Sirot, C. Chanal, M. C. Poupart, M. P. Dumas, , and J. Sirot. Concomitant dissemination of three extended-spectrum β-lactamases among different Enterobacteriaceae isolated in a french hospital. *Journal of Antimicrobial Chemotherapy*, 27: 441–457, 1991.

[16] C. Kliebe, B. A. Nies, J. F. Meyer, R. M. Tolxdorff-Neutzling, and B. Wiedemann. Evolution of plasmid-coded resistance to broad-spectrum cephalosporins. *Antimicrobial Agents and Chemotherapy*, 28(2): 302–307, 1985.

[17] Mahmood Z. Al-Hasso, S. G. Gergees, and Z. K. Mohialdeen. Molecular characterization of ESBLs and Amp C β-lactamases in bacteria isolated from currency notes circulating in Mosul city, Iraq. *Karbala International Journal of Modern Sciences*, 8(3): 543–553, 2022, doi:10.33640/2405-609X.3239.

[18] K. Bush, G. A. Jacoby, and A. A. Medeiros. A functional classification scheme for β-lactamases and its correlation with molecular structure. *ProbStat Forum*, 39(6): 1211–1233, 1995.

[19] B. G. Hall and M. Barlow. Revised ambler classification of β-lactamases. *Journal of Antimicrobial Chemotherapy*, 55(6): 1050–1051, 2005, doi:10.1093/jac/dki155.

[20] J. Walther-Rasmussen and N. Høiby. Cefotaximases. (CTX-M-ases), an expanding family of extended-spectrum β-lactamases. *Canadian Journal of Microbiology*, 50(3): 137–165, 2004, doi:10.1139/w03-111.

[21] R. Bonnet. Growing group of extended-spectrum β-lactamases: the CTX-M enzymes. *Antimicrobial Agents and Chemotherapy*, 48(1): 1–14, 2004, doi:10.1128/AAC.48.1.1–14.2004.

[22] Clinical and Laboratory Standards Institute CLSI. *Performance Standards for Antimicrobial Susceptibility Testing, CLSI document M100, M02, M07, and M11, in: Thirty first informational supplement update*. Clinical and Laboratory Standards Institute, Wayne, PA, 2021, 33^{th} edition, 2021.

[23] G. A. Jacoby and A. A. Medeiros. More extended-spectrum β-lactamases. *Antimicrobial Agents and Chemotherapy*, 35(9): 1697–1704, 1991.

[24] L. Martinez-Martinez, S. Hernández-Allés, S. Albertí, J. M. Tomás, V. J. Benedi, and G. A. Jacoby. In vivo selection of porin-deficient mutants of klebsiella pneumoniae with increased resistance to cefoxitin and expanded-spectrum-cephalosporins. *Antimicrobial Agents and Chemotherapy*, 40(2): 342–348, 1996.

[25] B. Pangon. In vivo selection of a cephamycin-resistant, porin-deficient mutant of klebsiella pneumoniae producing a tem-3 β-lactamase. *Journal of Infectious Diseases*, 159: 1005–1006, 1989.

[26] A. C. Vatopoulos, A. Philippon, L. S. Tzouvelekis, Z. Komninou, and N. J. Legakis. Prevalence of a transferable shv-5 type β-lactamase in clinical isolates of Klebsiella pneumoniae and escherichia coli in greece. *Journal of Antimicrobial Chemotherapy*, 26(5): 635–648, 1990, doi:10.1093/jac/26.5.635.

[27] B. G. Hall and M. Barlow. Structure-based phylogenies of the serine -lactamases. *Journal of Molecular Evolution*, 57(3): 255–260, 2003.

[28] M. Barthélémy, J. Peduzzi, and R. Labia. Distinction between the primary structures of TEM-1 and TEM-2 β-lactamases. *Annales de L'institut Pasteur. Microbiologie*, 136(3): 311–321, 1985, doi:10.1016/s0769-2609(85)80093-4.

[29] W. Sougakoff, S. Goussard, , and P. Courvalin. The TEM-3 β-lactamase, which hydrolyzes broad-spectrum cephalosporins, is derived from the TEM-2 penicillinase by two amino acid substitutions. *FEMS Microbiology letters*, 56(3): 343–348, 1988.

[30] C. Brun-Buisson, A. Philippon, M. Ansquer, P. Legrand, F. Montravers, and J. Duval. Transferable enzymatic resistance to third-generation cephalosporins during nosocomial outbreak of multi-resistant klebsiella pneumoniae. *The Lancet*, 330(8554): 302–306, 1987, doi:10.1016/S0140-6736(87)90891-9.

[31] A. Piccirilli, M. Perilli, G. Amicosante, C. Tascini V. Conte, G. M. Rossolini, and T. Giani. TEM-184, a novel TEM-derived extended-spectrum β-lactamase with enhanced activity against aztreonam. *Antimicrobial Agents and Chemotherapy*, 62(9): e00688–18, 2018, doi:10.1128/AAC.00688-18.

[32] C. Zeil, M. Widmann, S. Fademrecht, C. Vogel, and J. Pleiss. Network analysis of sequence-function relationships and exploration of sequence space of tem β-lactamases. *Antimicrobial Agents and Chemotherapy*, 60(5): 2709–2717, 2016, doi:10.1128/AAC.02930-15.

[33] J. Wiener, J. P. Quinn, P. A. Bradford, R. V. Goering, C. Nathan, K. Bush, and R. A. Weinstein. Multiple antibiotic–resistant klebsiella and Escherichia coli in nursing homes. *The Journal of the American Medical Association*, 281(6): 517–523, 1999.

[34] M.J. Soilleux, A.M. Morand, and G.J. Arlet. Survey of klebsiella pneumoniae producing extended-spectrum β-lactamases: prevalence of TEM-3 and first identification of TEM-26 in france. *Antimicrobial Agents and Chemotherapy*, 40: 1027–1029, 1996.

[35] C.Urban, N. Marino, N. Rahman, A. M. Queenan, D. Montenegro, K. Bush, and J. J. Rahal. Detection of multiresistant ceftazidime-susceptible Klebsiella pneumoniae isolates lacking tem-26 after class restriction of cephalosporins. *Microbial Drug Resistance*, 6(4): 297–303, 2000, doi:10.1089/mdr.2000.6.297.

[36] K. Shannon, P. Stapleton, X. Xiang, A. Johnson, H. Beattie, F. El Bakri, and G. French. Extended-spectrum β-lactamase-producing Klebsiella pneumoniae strains causing nosocomial outbreaks of infection in the united kingdom. *Journal of Clinical Microbiology*, 36(10): 3105–3110, 1998.

[37] J. D. D. Pitout, K. S. Thomson, N. D. Hanson, A. F. Ehrhardt, E. S. Moland, and C. C. Sanders. β-lactamases responsible for resistance to expanded-spectrum cephalosporins in Klebsiella pneumoniae, escherichia coli, and Proteus mirabilis isolates recovered in South Africa. *Antimicrobial Agents and Chemotherapy*, 42(6): 1350–1354, 1998.

[38] K. M. Kazmierczak, B. L. de Jonge, G. G. Stone, and D. F. Sahm. Longitudinal analysis of ESBL and carbapenemase carriage among enterobacterales and pseudomonas aeruginosa isolates collected in Europe as part of the international network for optimal resistance monitoring (INFORM) global surveillance programme, 2013–17. *Journal of Antimicrobial Chemotherapy*, 75(5): 1165–1173, 2020, doi:10.1093/jac/dkz571.

[39] R. Bonnet, C. De Champs, D. Sirot, C. Chanal, R. Labia, , and J. Sirot. Diversity of TEM mutants in Proteus mirabilis. *Antimicrobial Agents and Chemotherapy*, 43(11): 2671–2677, 1999.

[40] T. Palzkill, K. S. Thomson, C. C. Sanders, E. S. Moland, W. Huang, , and T. W. Milligan. New variant of TEM-10 β-lactamase gene produced by a clinical isolate of proteus mirabilis. *Antimicrobial Agents and Chemotherapy*, 39(5): 1199–1200, 1995.

[41] M. Perilli, B. Segatore, M. Rosaria De Massis, M. L. Riccio, C. Bianchi, A. Zollo, and G. Amicosante. TEM-72, a new extended-spectrum β-lactamase detected in proteus mirabilis and Morganella morganii in Italy. *Antimicrobial Agents and Chemotherapy*, 44(9): 2537–2539, 2000.

[42] F. Tessier, C. Arpin, A. Allery, and C. Quentin. Molecular characterization of a TEM-21 β-lactamase in a clinical isolate of Morganella morganii. *Antimicrobial Agents and Chemotherapy*, 42(8): 2125–2127, 1998.

[43] P. Mugnier, P. Dubrous, I. Casin, G. Arlet, and E. Collatz. A TEM-derived extended-spectrum β-lactamase in pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy*, 40(11): 2488–2493, 1996.

[44] P. Nordmann and M. Guibert. Extended-spectrum β-lactamases in pseudomonas aeruginosa. *Journal of Antimicrobial Chemotherapy*, 42(2): 128–131, 1998.

[45] A. Rosenau, B. Cattier, N. Gousset, P. Harriau, A. Philippon, and R. Quentin. Capnocytophaga ochracea: characterization of a plasmid-encoded extended-spectrum TEM-17 β-lactamase in the phylum Flavobacter-Bacteroides. *Antimicrobial Agents and Chemotherapy*, 44(3): 760–762, 2000.

[46] S. Ghafourian, N. Sadeghifard, S. Soheili, and Z. Sekawi. Extended spectrum β-lactamases: definition, classification and epidemiology. *Current Issues in Molecular Biology*, 17(1): 11–22, 2015, doi:10.21775/cimb.017.011.

[47] A. Huletsky, J. R. Knox, and R. C. Levesque. Role of Ser-238 and Lys-240 in the hydrolysis of third-generation cephalosporins by SHV-type β-lactamases probed by site-directed mutagenesis and three-dimensional modeling. *Journal of Biological Chemistry*, 268(5): 3690–3697, 1993.

[48] S. Neubauer, S. Madzgalla, M. Marquet, A. Klabunde, B. Büttner, A. Göhring, and O. Makarewicz. A genotype-phenotype correlation study of SHV β-lactamases offers new insight into SHV resistance profiles. *Antimicrobial Agents and Chemotherapy*, 64(7): e02293–19, 2020, doi:10.1128/AAC.02293-19.

[49] L. S. Tzouvelekis and R. A. Bonomo. SHV-type beta-lactamases. *Current Pharmaceutical Design*, 5(11): 847–864, 1999.

[50] G. A. Jacoby. Extended-spectrum β-lactamases and other enzymes providing resistance to oxyimino-β-lactams. *Infectious Disease Clinics of North America*, 11(4): 875–887, 1997.

[51] G.A. Jacoby and L. Sutton. Properties of plasmids responsible for production of extended-spectrum β-lactamases. *Antimicrobial Agents and Chemotherapy*, 35(1): 164–169, 1991.

[52] E. E. Prinarakis, V. Miriagou, E. Tzelepi, M. Gazouli, and L. S. Tzouvelekis. Emergence of an inhibitor-resistant β-lactamase (SHV-10) derived from an SHV-5 variant. *Antimicrobial Agents and Chemotherapy*, 41(4): 838–840, 1997.

[53] M. Perilli, E. Dell'Amico, B. Segatore, M. R. De Massis, C. Bianchi, F. Luzzaro, and G. Amicosante. Molecular characterization of extended-spectrum β-lactamases produced by nosocomial isolates of Enterobacteriaceae from an italian nationwide survey. *Journal of Clinical Microbiology*, 40(2): 611–614, 2002.

[54] J. J. Yan, S. M. Wu, S. H. Tsai, J. J. Wu, and I. J. Su. Prevalence of SHV-12 among clinical isolates of Klebsiella pneumoniae producing extended-spectrum β-lactamases and identification of a novel Amp C enzyme (CMY-8) in southern taiwan. *Antimicrobial Agents and Chemotherapy*, 44(6): 1438–1442, 2000.

[55] P. A. Bradford, C. Urban, A. Jaiswal, N. Mariano, B. A. Rasmussen, S. J. Projan, and K. Bush. SHV-7, a novel cefotaxime-hydrolyzing β-lactamase, identified in escherichia coli isolates from hospitalized nursing home patients. *Antimicrobial Agents and Chemotherapy*, 39(4): 899–905, 1995.

[56] Z. El Harrif-Heraud, C. Arpin, S. Benliman, and C. Quentin. Molecular epidemiology of a nosocomial outbreak due to SHV-4-producing strains of citrobacter diversus. *Journal of Clinical Microbiology*, 35(10): 2561–2567, 1997.

[57] T. Naas, L. Philippon, L. Poirel, E. Ronco, and P. Nordmann. An SHV-derived extended-spectrum β-lactamase in pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy*, 43(5): 1281–1284, 1999.

[58] J. K. Rasheed, C. Jay, B. Metchock, F. Berkowitz, L. Weigel, J. Crellin, and F. C. Tenover. Evolution of extended-spectrum β-lactam resistance (SHV-8) in a strain of escherichia coli during multiple episodes of bacteremia. *Antimicrobial Agents and Chemotherapy*, 41(3): 647–653, 1997.

[59] Z. M. Huang, P. H. Mao, Y. Chen, L. Wu, and J. Wu. Study on the molecular epidemiology of SHV type β-lactamase-encoding genes of multiple-drug-resistant Acinetobacter baumannii. *Zhonghua liuxingbingxue zazhi*, 25(5): 425–427, 2004.

[60] L. Poirel, E. Lebessi, M. Castro, C. Fèvre, M. Foustoukou, and P. Nordmann. Nosocomial outbreak of extended-spectrum β-lactamase SHV-5-producing isolates of pseudomonas aeruginosa in athens, greece. *Antimicrobial Agents and Chemotherapy*, 48(6): 2277–2279, 2004, doi:10.1128/AAC.48.6.2277–2279.2004.

[61] T. M. Coque, F. Baquero, and R. Canton. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. *Eurosurveillance*, 13(47): 19044–54, 2008.

[62] R. E. Mendes, M. Castanheira, L. N. Woosley, G. G. Stone, P. A. Bradford, and R. K. Flamm. Characterization of β-lactamase content of ceftazidime-resistant pathogens recovered during the pathogen-directed phase 3 reprise trial for ceftazidime-avibactam: correlation of efficacy against β-lactamase producers. *Antimicrobial Agents and Chemotherapy*, 63(6): e02655–18, 2019, doi:10.1128/AAC.02655-18.

[63] L. S. Tzouvelekis, E. Tzelepi, P. T. Tassios, and N. J. Legakis. CTX-M-type β-lactamases: an emerging group of extended-spectrum enzymes. *International Journal of Antimicrobial Agents*, 14(2): 137–142, 2000.

[64] M. Radice, P. Power, J. Di Conza, and G. Gutkind. Early dissemination of CTX-M-derived enzymes in South America. *Antimicrobial Agents and Chemotherapy*, 46(2): 602–604, 2002.

[65] A. Bauernfeind, S. Schweighart, and H. Grimm. A new plasmidic cefotaximase in a clinical isolate of escherichia coli. *Infection*, 18(5): 294–298, 1990.

[66] R. C. Picao, L. Poirel, A. C. Gales, and P. Nordmann. Diversity of β-lactamases produced by ceftazidime-resistant pseudomonas aeruginosa isolates causing bloodstream infections in brazil. *Antimicrobial Agents and Chemotherapy*, 53(5): 3908–3913, 2009, doi:10.1128/AAC.00453-09.

[67] G. Celenza, C. Pellegrini, M. Caccamo, B. Segatore, G. Amicosante, and M. Perilli. Spread of blaCTX-M type and blaper-2 β-lactamase genes in clinical isolates from bolivian hospitals. *Journal of Antimicrobial Chemotherapy*, 57(5): 975–978, 2006, doi:10.1093/jac/dkl055.

[68] J. Walther-Rasmussen and N. Høiby. Cefotaximases (CTX-M-ases), an expanding family of extended-spectrum β-lactamases. *Canadian Journal of Microbiology*, 50(3): 137–165, 2004, doi:10.1139/w03-111.

[69] C. M. Liu, M. Stegger, M. Aziz, T. J. Johnson, K. Waits, L. Nordstrom, and L. B. Price. Escherichia coli ST131-H 22 as a foodborne uropathogen. *MBio, Peer-reviewed journal*, 9(4): e00470–18, 2018, doi:10.1128/mBio.00470-18.

[70] P. A. Bradford, Y. Yang, D. Sahm, I. Grope, D. Gardovska, and G. Storch. CTX-M-5, a novel cefotaxime-hydrolyzing β-lactamase from an outbreak of salmonella typhimurium in Latvia. *Antimicrobial Agents and Chemotherapy*, 42(8): 1980–1984, 1998.

[71] M. Gazouli, N. J. Legakis, and L. S. Tzouvelekis. Effect of substitution of asn for arg-276 in the cefotaxime-hydrolyzing class a β-lactamase CTX-M-4. *FEMS Microbiology Letters*, 169(2): 289–293, 1998.

[72] L. Ma, Y. Ishii, M. Ishiguro, H. Matsuzawa, and K. Yamaguchi. Cloning and sequencing of the gene encoding toho-2, a class a β-lactamase preferentially inhibited by tazobactam. *Antimicrobial Agents and Chemotherapy*, 42(5): 1181–1186, 1998.

[73] M. Sabaté, R. Tarrago, F. Navarro, E. Miró, C. Vergés, J. Barbé, and G. Prats. Cloning and sequence of the gene encoding a novel cefotaxime-hydrolyzing β-lactamase (CTX-M-9) from escherichia coli in Spain. *Antimicrobial Agents and Chemotherapy*, 44(7): 1970–1973, 2000.

[74] G. Peirano, T. Lynch, Y. Matsumara, D. Nobrega, T. J. Finn, R. DeVinney, and J. D. Pitout. Trends in population dynamics of escherichia coli sequence type 131, calgary, alberta, canada, 2006–2016. *Emerging Infectious Diseases*, 26(12): 2907–2915, 2020, doi:10.1128/mBio.00470-18.

[75] C. Colmenarejo, M. Hernández-García, J. R. Muñoz-Rodríguez, N. Huertas, F. J. Navarro, A. B. Mateo, and R. Del Campo. Prevalence and risks factors associated with ESBL-producing faecal carriage in a single long-term-care facility in Spain: emergence of CTX-M-24- and CTX-M-27-producing escherichia coli ST131-H 30R. *Journal of Antimicrobial Chemotherapy*, 75(9): 2480–2484, 2020, doi:10.1093/jac/dkaa219.

[76] H. Ghosh, S. Doijad, L. Falgenhauer, M. Fritzenwanker, C. Imirzalioglu, and T. Chakraborty. blaCTX-M-27 encoding escherichia coli sequence type 131 lineage C1-M27 clone in clinical isolates, germany. *Emerging Infectious Diseases*, 75(9): 1754–1756, 2017, doi:10.3201/eid2310.170938.

[77] Y. Matsumura, J. D. Pitout, R. Gomi, T. Matsuda, T. Noguchi, M. Yamamoto, and S. Ichiyama. Global escherichia coli sequence type 131 clade with blaCTX-M-27 gene. *Emerging Infectious Diseases*, 22(11): 1900–1907, 2016, doi:10.3201/eid2211.160519.

[78] S. C. Flament-Simon, V. García, M. Duprilot, N. Mayer, M. P. Alonso, I. García-Meniño, , and J. Blanco. High prevalence of st131 subclades C2-H30Rx and C1-M27 among extended-spectrum β-lactamase-producing Escherichia coli causing human extraintestinal infections in patients from two hospitals of Spain and France during 2015. *Frontiers Cellular and Infection Microbiology*, 10(125): 1–9, 2020, doi:10.3389/fcimb.2020.00125.

[79] A. Oliver, J. C. Perez-Dıaz, T. M. Coque, F. Baquero, and R. Canton. Nucleotide sequence and characterization of a novel cefotaxime-hydrolyzing β-lactamase (CTX-M-10) isolated in Spain. *Antimicrobial Agents and Chemotherapy*, 45(2): 616–620, 2001, doi:10.1128/AAC.45.2.616–620.2001.

[80] C. Humeniuk, G. Arlet, V. Gautier, P. Grimont, R. Labia, and A. Philippon. β-lactamases of kluyvera ascorbata, probable progenitors of some plasmid-encoded CTX-M types. *Antimicrobial Agents and Chemotherapy*, 46(9): 3045–3049, 2002, doi:10.1128/AAC.46.9.3045–3049.2002.

[81] J. W. Decousser, L. Poirel, and P. Nordmann. Characterization of a chromosomally encoded extended-spectrum class a β-lactamase from kluyvera cryocrescens. *Antimicrobial Agents and Chemotherapy*, 45(12): 3595–3598, 2001, doi:10.1128/AAC.46.9.3045–3049.2002.

[82] L. Poirel, P. Kampfer, and P. Nordmann. Chromosome-encoded ambler class a β-lactamase of kluyvera georgiana, a probable progenitor of a subgroup of CTX-M extended-spectrum β-lactamases. *Antimicrobial Agents and Chemotherapy*, 46(12): 4038–4040, 2002, doi:10.1128/AAC.46.12.4038–4040.2002.

[83] R. A. Bonomo, S. A. Rudin, and D. M. Shlaes. Tazobactam is a potent inactivator of selected inhibitor-resistant class a β-lactamases. *FEMS Microbiology Letters*, 148(1): 59–62, 1997.

[84] S. Vimont, L. Poirel, T. Naas, and P. Nordmann. Identification of a chromosome-borne expanded-spectrum class a β-lactamase from Erwinia persicina. *Antimicrobial Agents and Chemotherapy*, 46(11): 3401–3405, 2002, doi:10.1128/AAC.46.11.3401–3405.200.

[85] S. Bellais, L. Poirel, N. Fortineau, J. W. Decousser, and P. Nordmann. Biochemical-genetic characterization of the chromosomally encoded extended-spectrum class a β-lactamase from rahnella aquatilis. *Antimicrobial Agents and Chemotherapy*, 45(10): 2965–2968, 2001, doi:10.1128/AAC.45.10.2965–2968.2001.

[86] SL. Poirel, M. Gniadkowski, and P. Nordmann. Biochemical analysis of the ceftazidime-hydrolysing extended-spectrum β-lactamase CTX-M-15 and of its structurally related β-lactamase CTX-M-3. *Journal of Antimicrobial Chemotherapy*, 50(6): 1031–1034, 2002, doi:10.1093/jac/dkf240.

[87] Y. Chen, J. Delmas, J. Sirot, B. Shoichet, and R. Bonnet. Atomic resolution structures of CTX-M β-lactamases: extended spectrum activities from increased mobility and decreased stability. *Journal of Molecular Biology*, 348(2): 349–362, 2005, doi:10.1016/j.jmb.2005.02.010.

[88] G. M. Rossolini, M. M. Dandrea, and C. Mugnaioli. The spread of CTX-M-type extended-spectrum β-lactamases. *Clinical Microbiology and Infection*, 14: 33–41, 2008.

[89] R. Bonnet, C. Recule, R. Baraduc, C. Chanal, D. Sirot, C. De Champs, and J. Sirot. Effect of d240g substitution in a novel esbl CTX-M-27. *Journal of Antimicrobial Chemotherapy*, 52(1): 29–35, 2003, doi:10.1093/jac/dkg256.

[90] L. Poirel, J. M. O. De la Rosa, A. Richard, M. Aires de Sousa, and P. Nordmann. CTX-M-33 is a CTX-M-15 derivative conferring reduced susceptibility to carbapenems. *Antimicrobial Agents and Chemotherapy*, 63(12): e01515–19, 2019, doi:10.1128/AAC.01515-19.

[91] M. Gazouli, S. V. Sidorenko, E. Tzelepi, N. S. Kozlova, D. P. Gladin, and L. S. Tzouvelekis. A plasmid-mediated β-lactamase conferring resistance to cefotaxime in a salmonella typhimurium clone found in st petersburg, Russia. *Journal of Antimicrobial chemotherapy*, 41(1): 119–121, 1998.

[92] M. Gniadkowski, I. Schneider, A. Pałucha, R. Jungwirth, B. Mikiewicz, and A. Bauernfeind. Cefotaxime-resistant Enterobacteriaceae isolates from a hospital in Warsaw, Poland: identification of a new CTX-M-3 cefotaxime-hydrolyzing β-lactamase that is closely related to the CTX-M-1/MEN-1 enzyme. *Antimicrobial Agents and Chemotherapy*, 42(4): 827–832, 1998.

[93] R. C. Picao, L. Poirel, A. C. Gales, and P. Nordmann. Further identification of CTX-M-2 extended-spectrum β-lactamase in pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy*, 53(9): 2225–2226, 2009, doi:10.1128/AAC.01602-08.

[94] L. S. Tzouvelekis, M. Gazouli, N. J. Legakis, and E. Tzelepi. Emergence of resistance to third-generation cephalosporins amongst Salmonella typhimurium isolates in Greece: report of the first three cases. *Journal of Antimicrobial Chemotherapy*, 42(2): 273–275, 1998.

[95] F. Doucet-Populaire, J. C. Ghnassia, R. Bonnet, and J. Sirot. First isolation of a CTX-M-3-producing enterobacter cloacae in France. *Antimicrobial Agents and Chemotherapy*, 44(11): 3239–3240, 2000.

[96] A. Bauernfeind, M. Holley, R. Jungwirth, P. Mangold, T. Röhnisch, S. Schweighart, and M. Goldberg. A new plasmidic cefotaximase from patients infected with salmonella typhimurium. *Infection*, 20(3): 158–163, 1992.

[97] M. Gazouli, E. Tzelepi, A. Markogiannakis, N. J. Legakis, and L. S. Tzouvelekis. Two novel plasmid-mediated cefotaxime-hydrolyzing β-lactamases (CTX-M-5 and CTX-M-6) from salmonella typhimurium. *FEMS Microbiology Letters*, 165(2): 289–293, 1998.

[98] D. M. Livermore. Defining an extended-spectrum β-lactamase. *Clinical Microbiology and Infection*, 14: 3–10, 2008.

[99] E. J. Yoon and S. H. Jeong. Class d β-lactamases. *Journal of Antimicrobial Chemotherapy*, 76(4): 836–864, 2021, doi:10.1093/jac/dkaa513.

[100] J. Vila, M. Navia, J. Ruiz, and C. Casals. Cloning and nucleotide sequence analysis of a gene encoding an OXA-derived β-lactamase in Acinetobacter baumannii. *Antimicrobial Agents and Chemotherapy*, 41(12): 2757–2759, 1997.

[101] B. A. Evans and S. G. Amyes. OXA β-lactamases. *Clinical Microbiology Reviews*, 27(2): 241–263, 2014, doi:10.1128/CMR.00117-13.

[102] L. N. Philippon, T. Naas, A. T. Bouthors, V. Barakett, and P. Nordmann. OXA-18, a class d clavulanic acid inhibited extended-spectrum β-lactamase from pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy*, 41(10): 2188–2195, 1997.

[103] A. Beceiro, S. Maharjan, T. Gaulton, M. Doumith, N. C. Soares, H. Dhanji, and N. Woodford. False extended-spectrum β-lactamase phenotype in clinical isolates of escherichia coli associated with increased expression of OXA-1 or TEM-1 penicillinases and loss of porins. *Journal of Antimicrobial Chemotherapy*, 66(9): 2006–2010, 2011, doi:10.1093/jac/dkr265.

[104] L. K. Siu, J. Y. C. Lo, K. Y. Yuen, P. Y. Chau, M. H. Ng, and P. L. Ho. β-lactamases in shigella flexneri isolates from Hong Kong and Shanghai and a novel OXA-1-like β-lactamase, OXA-30. *Antimicrobial Agents and Chemotherapy*, 44(8): 2034–2038, 2000.

[105] V. Dubois, C. Arpin, C. Quentin, J. Texier-Maugein, L. Poirel, and P. Nordmann. Decreased susceptibility to cefepime in a clinical strain of Escherichia coli related to plasmid-and integron-encoded OXA-30 β-lactamase. *Antimicrobial Agents and Chemotherapy*, 47(7): 2380–2381, 2003, doi:10.1128/AAC.47.7.2380–2381.2003.

[106] D. A. Boyd and M. R. Mulvey. OXA-1 is oxa-30 is OXA-1. *Journal of Antimicrobial Chemotherapy*, 58(1): 224–225, 2006, doi:10.1093/jac/dkl149.

[107] D. M. Livermore, M. Day, P. Cleary, K. L. Hopkins, M. A. Toleman, D. W. Wareham, and N. Woodford. Oxa-1 β-lactamase and non-susceptibility to penicillin/β-lactamase inhibitor combinations among ESBL-producing Escherichia coli. *Journal of Antimicrobial Chemotherapy*, 74(2): 326–333, 2019, doi:10.1093/jac/dky453.

[108] D. Aubert, L. Poirel, J. Chevalier, S. Leotard, J. M. Pages, and P. Nordmann. Oxacillinase-mediated resistance to cefepime and susceptibility to ceftazidime in Pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy*, 45(6): 1615–1620, 2001, doi:10.1128/AAC.45.6.1615–1620.2001.

[109] L. Poirel, M. Castanheira, A. Carrër, C. P. Rodriguez, R. N. Jones, J. Smayevsky, and P. Nordmann. OXA-163, an OXA-48-related class D β-lactamase with extended activity toward expanded-spectrum cephalosporins. *Antimicrobial Agents and Chemotherapy*, 55(6): 2546–2551, 2011, doi:10.1128/AAC.00022-11.

[110] L. Dortet, S. Oueslati, K. Jeannot, D. Tandé, T. Naas, and P. Nordmann. Genetic and biochemical characterization of OXA-405, an OXA-48-type extended-spectrum β-lactamase without significant carbapenemase activity. *Antimicrobial Agents and Chemotherapy*, 59(7): 3823–3828, 2015, doi:10.1128/AAC.05058-14.

[111] F. Danel, L. M. Hall, B. Duke, D. Gur, and D. M. Livermore. OXA-17, a further extended-spectrum variant of OXA-10 β-lactamase, isolated from Pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy*, 43(6): 1362–1366, 1999.

[112] C. L. Tooke, P. Hinchliffe, E. C. Bragginton, C. K. Colenso, V. H. Hirvonen, Y. Takebayashi, and J. Spencer. β-lactamases and β-lactamase inhibitors in the 21^{st} Century. *Journal of Molecular Biology*, 431(18): 3472–3500, 2019, doi:10.1016/j.jmb.2019.04.002.

[113] P. A. Bradford, S. Bratu, C. Urban, M. Visalli, N. Mariano, D. Landman, and J. Quale. Emergence of carbapenem-resistant klebsiella species possessing the class a carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 β-lactamases in New York City. *Clinical Infectious Diseases*, 39(1): 55–60, 2004.

[114] S. D. Lahiri, P. A. Bradford, W. W. Nichols, and R. A. Alm. Structural and sequence analysis of class a β-lactamases with respect to avibactam inhibition: impact of ω-loop variations. *Journal of Antimicrobial Chemotherapy*, 71(10): 2848–2855, 2016, doi:10.1093/jac/dkw248.

[115] E. B. Chaibi, D. Sirot, G. Paul, and R. Labia. Inhibitor-resistant TEM β-lactamases: phenotypic, genetic and biochemical characteristics. *Journal of Antimicrobial Chemotherapy*, 43(4): 447–458, 1999.

[116] R. A. Bonomo, C. Currie-McCumber, and D. M. Shlaes. OHIO-1 β-lactamase resistant to mechanism-based inactivators. *FEMS Microbiology Letters*, 92(1): 79–82, 1992.

[117] L. Bret, E. B. Chaibi, C. Chanal-Claris, D. Sirot, R. Labia, and J. Sirot. Inhibitor-resistant TEM (IRT) β-lactamases with different substitutions at position 244. *Antimicrobial Agents and Chemotherapy*, 41(11): 2547–2549, 1997.

[118] L. Bret, C. Chanal, D. Sirot, R. Labia, and J. Sirot. Characterization of an inhibitor-resistant enzyme IRT-2 derived from TEM-2 β-lactamase produced by Proteus mirabilis strains. *Journal of Antimicrobial Chemotherapy*, 38(2): 183–191, 1996.

[119] J. Lemozy, D. Sirot, C. Chanal, C. Huc, R. Labia, H. Dabernat, and J. Sirot. First characterization of inhibitor-resistant TEM (IRT) β-lactamases in Klebsiella pneumoniae strains. *Antimicrobial Agents and Chemotherapy*, 39(11): 2580–2582, 1995.

[120] K. Bush and G. Jacoby. Nomenclature of TEM β-lactamases. *Journal of Antimicrobial Chemotherapy*, 39(1): 1–3, 1997.

[121] R. Canton, M. I. Morosini, O. Martin, S. De la Maza, and E. G. G. De La Pedrosa. IRT and CMT β-lactamases and inhibitor resistance. *Clinical Microbiology and Infection*, 14: 53–62, 2008.

[122] V. Dubois, L. Poirel, C. Arpin, L. Coulange, C. Bebear, P. Nordmann, and C. Quentin. SHV-49, a novel inhibitor-resistant β-lactamase in a clinical isolate of Klebsiella pneumoniae. *Antimicrobial Agents and Chemotherapy*, 48(11): 4466–4469, 2004, doi:10.1128/AAC.48.11.4466–4469.2004.

[123] V. Dubois, L. Poirel, F. Demarthe, C. Arpin, L. Coulange, L. A. Minarini, and C. Quentin. Molecular and biochemical characterization of SHV-56, a novel inhibitor-resistant β-lactamase from Klebsiella pneumoniae. *Antimicrobial Agents and Chemotherapy*, 52(10): 3792–3794, 2008, doi:10.1128/AAC.00387-08.

[124] N. Mendonça, E. Ferreira, D. Louro, and M. Caniça. Molecular epidemiology and antimicrobial susceptibility of extended-and broad-spectrum β-lactamase-producing Klebsiella pneumoniae isolated in Portugal. *International Journal of Antimicrobial Agents*, 34(1): 29–37, 2009, doi:10.1016/j.ijantimicag.2008.11.014.

[125] P. D. Stapleton, K. P. Shannon, and G. L. French. Construction and characterization of mutants of the TEM-1 β-lactamase containing amino acid substitutions associated with both extended-spectrum resistance and resistance to β-lactamase inhibitors. *Antimicrobial Agents and Chemotherapy*, 43(8): 1881–1887, 1999.

[126] D. Sirot, C. Recule, E. B. Chaibi, L. Bret, J. Croize, C. Chanal-Claris, , and J. Sirot. A complex mutant of TEM-1 β-lactamase with mutations encountered in both IRT-4 and extended-spectrum TEM-15, produced by an Escherichia coli clinical isolate. *Antimicrobial Agents and Chemotherapy*, 41(6): 1322–1325, 1997.

[127] F. Robin, J. Delmas, C. Schweitzer, O. Tournilhac, O. Lesens, C. Chanal, and R. Bonnet. Evolution of TEM-type enzymes: biochemical and genetic characterization of two new complex mutant TEM enzymes, TEM-151 and TEM-152, from a single patient. *Antimicrobial Agents and Chemotherapy*, 51(4): 1304–1309, 2007, doi:10.1128/AAC.01058-06.

[128] S. D. Lahiri and R. A. Alm. Identification of novel VEB β-lactamase enzymes and their impact on avibactam inhibition. *Antimicrobial Agents and Chemotherapy*, 60(5): 3183–3186, 2016, doi:10.1128/AAC.00047-16.

[129] K. S. Kaye, H. S. Gold, M. J. Schwaber, L. Venkataraman, Y. Qi, P. C. De Girolami, and F. C. Tenover. Variety of β-lactamases produced by amoxicillin-clavulanate-resistant Escherichia coli isolated in the northeastern United States. *Antimicrobial Agents and Chemotherapy*, 48(5): 1520–1525, 2004, doi:10.1128/AAC.48.5.1520–1525.2004.

[130] P. Nordmann, E. Ronco, T. Naas, C. Duport, Y. Michel-Briand, and R. Labia. Characterization of a novel extended-spectrum β-lactamase from Pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy*, 37(5): 962–969, 1993, doi:10.1128/AAC.48.5.1520–1525.2004.

[131] G.A. Jacoby. β-lactamase nomenclature. *Antimicrobial Agents and Chemotherapy*, 50(4): 1123–1129, 2006, doi:10.1128/AAC.50.4.1123–1129.2006.

[132] H. Vahaboglu, L. M. C. Hall, L. Mulazimoglu, S. Dodanli, I. Yildirim, and D. M. Livermore. Resistance to extended-spectrum cephalosporins, caused by PER-1 β-lactamase, in M Salmonella typhimurium from Istanbul, Turkey. *Journal of Medical Microbiology*, 43(4): 294–299, 1995.

[133] H. Vahaboglu, S. Dodanli, C. Eroglu, R. Oztürk, G. Soyletir, I. Yildirim, and V. Avkan. Characterization of multiple-antibiotic-resistant Salmonella typhimurium stains: molecular epidemiology of PER-1-producing isolates and evidence for nosocomial plasmid exchange by a clone. *Journal of Clinical Microbiology*, 34(12): 2942–2946, 1996.

[134] H. Vahaboglu, R. Oztürk, G. Aygün, F. Coşkunkan, A. Yaman, A. Kaygusuz, and M. Otkun. Widespread detection of per-1-type extended-spectrum β-lactamases among nosocomial Acinetobacter and Pseudomonas aeruginosa isolates in Turkey: a nationwide multicenter study. *Antimicrobial Agents and Chemotherapy*, 41(10): 2265–2269, 1997.

[135] F. Kolayli, G. Gacar, A. Karadenizli, A. Sanic, and H. Vahaboglu. Per-1 is still widespread in turkish hospitals among pseudomonas aeruginosa and Acinetobacter spp. *FEMS Microbiology Letters*, 249(2): 241–245, 2005, doi:10.1016/j.femsle.2005.06.012.

[136] K. Ranellou, K. Kadlec, A. Poulou, E. Voulgari, G. Vrioni, S. Schwarz, and A. Tsakris. Detection of Pseudomonas aeruginosa isolates of the international clonal complex 11 carrying the bla PER-1 extended-spectrum β-lactamase gene in Greece. *Journal of Antimicrobial Chemotherapy*, 67(2): 357–361, 2012, doi:10.1093/jac/dkr471.

[137] A. Bauernfeind, I. Stemplinger, R. Jungwirth, P. Mangold, S. Amann, E. Akalin, and J. M. Casellas. Characterization of β-lactamase gene blaPER-2, which encodes an extended-spectrum class a β-lactamase. *Antimicrobial Agents and Chemotherapy*, 40(3): 616–620, 1996.

[138] J. M. Ortiz de la Rosa, P. Nordmann, and L. Poirel. esbls and resistance to ceftazidime/avibactam and ceftolozane/tazobactam combinations in Escherichia coli and Pseudomonas aeruginosa. *Journal of Antimicrobial Chemotherapy*, 74(7): 1934–1939, 2019, doi:10.1093/jac/dkz149.

[139] M. Ruggiero, K. M. Papp-Wallace, F. Brunetti, M. D. Barnes, R. A. Bonomo, G. Gutkind, and P. Power. Structural insights into the inhibition of the extended-spectrum β-lactamase PER-2 by avibactam. *Antimicrobial Agents and Chemotherapy*, 63(9): e00487–19, 2019, doi:10.1128/AAC.00487-19.

[140] N. Kohira, M. A. Hackel, Y. Ishioka, M. Kuroiwa, D. F. Sahm, T. Sato, and Y. Yamano. Reduced susceptibility mechanism to cefiderocol, a siderophore cephalosporin, among clinical isolates from a global surveillance programme (SIDERO-WT-2014). *Journal of Global Antimicrobial Resistance*, 22: 738–741, 2020, doi:10.1016/j.jgar.2020.07.009.

[141] L. Poirel, T. Naas, M. Guibert, E. B. Chaibi, R. Labia, and P. Nordmann. Molecular and biochemical characterization of VEB-1, a novel class a extended-spectrum β-lactamase encoded by an Escherichia coli integron gene. *Antimicrobial Agents and Chemotherapy*, 43(3): 573–581, 1999.

[142] T. Naas, L. Poirel, A. Karim, and P. Nordmann. Molecular characterization of In50, a class 1 integron encoding the gene for the extended-spectrum β-lactamase VEB-1 in Pseudomonas aeruginosa. *FEMS Microbiology Letters*, 176(2): 411–419, 1999.

[143] S. Mushtaq, M. Warner, and D. M Livermore. In vitro activity of ceftazidime+ NXL104 against Pseudomonas aeruginosa and other non-fermenters. *Journal of Antimicrobial Chemotherapy*, 65(11): 2376–2381, 1999, doi:10.1093/jac/dkq306.

[144] T. Naas, L. Poirel, and P. Nordmann. Minor extended-spectrum β-lactamases. *Clinical Microbiology and Infection*, 14: 42–52, 2008.

[145] R. Li, L. Ye, Z. Zheng, E. W. C. Chan, and S. Chen. Genetic Characterization of a blaVEB-2 carrying plasmid in Vibrio parahaemolyticus. *Antimicrobial Agents and Chemotherapy*, 60(11),: 6965–6968, 2016, doi:10.1128/AAC.01749-16.

[146] S. Jain, R. Gaind, C. Kothari, R. Sehgal, A. Shamweel, S. S. Thukral, and H. K. Chellani. VEB-1 extended-spectrum β-lactamase-producing multidrug-resistant Proteus mirabilis sepsis outbreak in a neonatal intensive care unit in India: clinical and diagnostic implications. *JMM Case Reports*, 3(4): 1–7, 2016, doi:10.1099/jmmcr.0.005056.

[147] L. Poirel, I. Le Thomas, T. Naas, A. Karim, and P. Nordmann. Biochemical sequence analyses of GES-1, a novel class a extended-spectrum β-lactamase, and the class 1 integron In52 from Klebsiella pneumoniae. *Antimicrobial Agents and Chemotherapy*, 44(3): 622–632, 2000.

[148] A. N. Zeka, L. Poirel, O. R. Sipahi, R. A. Bonnin, B. Arda, M. Özinel, and P. Nordmann. GES-type and OXA-23 carbapenemase-producing Acinetobacter baumannii in Turkey. *Journal of Antimicrobial Chemotherapy*, 69: 1145–1153, 2014, doi:10.1093/jac/dkt465.

[149] R. A. Bonnin, P. Nordmann, A. Potron, H. Lecuyer, J. R. Zahar, and L. Poirel. Carbapenem-hydrolyzing gestype extended-spectrum β-lactamase in Acinetobacter baumannii. *Antimicrobial Agents and Chemotherapy*, 55(1): 349–354, 2011, doi:10.1128/AAC.00773-10.

[150] M. Castanheira, R. E. Mendes, T. R. Walsh, A. C. Gales, and R. N. Jones. Emergence of the extended-spectrum β-lactamase GES-1 in a Pseudomonas aeruginosa strain from Brazil: report from the SENTRY antimicrobial surveillance program. *Antimicrobial Agents and Chemotherap*, 48(6): 2344–2345, 2004, doi:http://dx.doi.org/10.1128/AAC.48.6.2344–2345.2004.

[151] M.Castanheira, S. E. Costello, L. N. Woosley, L. M. Deshpande, T. A. Davies, and R. N. Jones. Evaluation of clonality and carbapenem resistance mechanisms among Acinetobacter baumannii-Acinetobacter calcoaceticus complex and Enterobacteriaceae isolates collected in European and Mediterranean countries and detection of two novel β-lactamases, GES-22 and VIM-35. *Antimicrobial Agents and Chemotherapy*, 58(12): 7358–7366, 2014, doi:10.1128/AAC.03930-14.

[152] P. Giakkoupi, L. S. Tzouvelekis, A. Tsakris, V. Loukova, D. Sofianou, and E. Tzelepi. IBC-1, a novel integron-associated class a β-lactamase with extended-spectrum properties produced by an Enterobacter cloacae clinical strain. *Antimicrobial Agents and Chemotherapy*, 44(9): 2247–2253, 2000.

[153] L. Poirel, G. F. Weldhagen, T. Naas, C. De Champs, M. G. Dove, and P. Nordmann. Ges-2, a class a β-lactamase from pseudomonas aeruginosa with increased hydrolysis of imipenem. *Antimicrobial Agents and Chemotherapy*, 45(9): 2598–2603, 2001, doi:10.1128/AAC.45.9.2598–2603.2001.

[154] A. Mavroidi, E. Tzelepi, A. Tsakris, V. Miriagou, D. Sofianou, and L. S. Tzouvelekis. An integron-associated β-lactamase (IBC-2) from Pseudomonas aeruginosa is a variant of the extended-spectrum β-lactamase IBC-1. *Journal of Antimicrobial Chemotherapy*, 48(5): 627–630, 2001.

[155] H. S. Sader, P. R. Rhomberg, R. K. Flamm, R. N. Jones, and M. Castanheira. WCK 5222 (cefepime/zidebactam) antimicrobial activity tested against Gram-negative organisms producing clinically relevant β-lactamases. *Journal of Antimicrobial Chemotherapy*, 72(6): 1696–1703, 2017, doi:10.1093/jac/dkx050.

[156] S. Bontron, L. Poirel, and P. Nordmann. In vitro prediction of the evolution of GES-1 β-lactamase hydrolytic activity. *Antimicrobial Agents and Chemotherapy*, 59(3): 1664–1670, 2015, doi:10.1128/AAC.04450-14.

[157] Z. G. Nanakali and Z. F. Ahmad. Antibiotic resistance study and detection of virulence gene among uropathogenic E.coli. *Kirkuk University Journal-Scientific Studies*, 10(3): 205–29, 2015, doi:10.32894/kujss.2015.104995.

[158] Mahmood. Z. Al-Hasso and Z. K. Mohialdeen. Phenotypic and molecular detection of CTX-M β-lactamases in Salmonella enterica local isolates from different origins in mosul. *Malaysian Journal of Microbiology*, 19(2): 1–10, 2023, doi:10.21161/mjm.220019.

[159] F. S. Al Mayahi and S. M. Jaber. A preliminary study of multiple antibiotic resistance (MAR) and extensively drug-resistant (XDR) of bacterial causing typhoid fever isolated from stool specimens in Al-Diwaniya, Iraq. *EurAsian Journal of Biosciences*, 14(1): 2369–2378, 2020.

[160] H. A. Salman, A. M. Abdulmohsen, M. N. Falih, and Z. M. Romi. Detection of multidrug-resistant Salmonella enterica subsp. enterica serovar Typhi isolated from Iraqi subjects. *Veterinary World*, 14(7): 1922–1928, 2021, doi:10.14202/vetworld.2021.1922-1928.

[161] Z. S. Shallal, A. S. K. AL-Suraifi, and A. H. Hadil. Detection of extended spectrum β-lactamase (ESBL) among Gram-negative bacteria isolates from workers in a restaurant in Wasit province, Iraq. *Journal of Pharmaceutical Sciences and Research*, 11(4): 1602–1609, 2019.

[162] Mahmood. Z. Al-Hasso and S. H. Khalaf. Comparison of five methods for detection of extended spectrum β-lactamases in Gram negative enteric bacteria. *Karbala International Journal of Modern Science*, 6(1): 62–68, 2020.

[163] C. Fevre, M. Jbel, V. Passet, F. X. Weill, P. A. Grimont, and S. Brisse. Six groups of the OXY β-lactamase evolved over millions of years in Klebsiella oxytoca. *Antimicrobial Agents and Chemotherapy*, 49(8): 3453–3462, 2005, doi:10.1128/AAC.49.8.3453–3462.2005.

[164] M. Castanheira, S. E. Farrell, L. M. Deshpande, R. E. Mendes, and R. N. Jones. Prevalence of β-lactamase-encoding genes among Enterobacteriaceae bacteremia isolates collected in 26 US hospitals: report from the SENTRY Antimicrobial Surveillance Program (2010). *Antimicrobial Agents and Chemotherapy*, 57(7): 3012–3020, 2013, doi:10.1128/AAC.02252-12.

[165] Y. Matsumoto and M. Inoue. Characterization of SFO-1, a plasmid-mediated inducible class a β-lactamase from Enterobacter cloacae. *Antimicrobial Agents and Chemotherapy*, 43(2): 307–313, 1999.

[166] G. M. Rossolini, N. Franceschini, L. Lauretti, B. Caravelli, M. L. Riccio, M. Galleni, and G. Amicosante. Cloning of a Chryseobacterium (Flavobacterium) meningosepticum chromosomal gene (blaACME) encoding an extended-spectrum class a β-lactamase related to the bacteroides cephalosporinases and the VEB-1 and PER β-lactamases. *Antimicrobial Agents and Chemotherapy*, 43(9): 2193–2199, 1999.

[167] Mahmood Z. Al-Hasso and N.A. Al-Sharifi. Antimicrobials sensitivity of Gram-positive and Gram-negative bacteria isolated from urinary tract infections in Mosul city. *Kirkuk University Journal-Scientific Studies*, 12(3): 737–62, 2017, doi:10.32894/kujss.2017.131535.

[168] J. Silva, C. Aguilar, G. Ayala, M. A. Estrada, U. Garza-Ramos, R. Lara-Lemus, and L. Ledezma. TLA-1: a new plasmid-mediated extended-spectrum β-lactamase from Escherichia coli. *Antimicrobial Agents Chemotherapy*, 44(4): 997–1003, 2000.

مراجعة في أنزيمات البيتالاكتاميز واسعة الطيف: تعريفها وأنواعها

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الخلاصة

تعرف انزيمات البيتالاكتاميز واسعة الطيف بأنها تلك الانزيمات البكتيرية القادرة على تحليل السيفالوسبورينات واسعة المدى مثل السيفوتاكسيم والسيفترياكسون والسيفتازديم بالاضافة الى الاوكسي امينو مونوباكتام. تمثل هذه الانزيمات تهديدا جديا خاصة للأشخاص المرضى المضعفين مناعيا والمدخلين للمستشفيات، فهناك انتشار واسع ومتنام لهذه الأنزيمات في العزلات البكتيرية على مستوى العالم. ويعد الاشخاص المعرضون للبكتريا الحاملة لهذه الانزيمات ذوو احتمالية وخطورة عالية لفشل العلاج في كثير من الحالات. لذا، فان هناك حاجة ملحة للتحري عن السلالات البكتيرية المنتجة لهذه الأنزيمات مع اطلاق مبادرات استراتيجية تساهم في السيطرة على انتشار وسيادة هذه السلالات. تهدف المقالة الحالية الى توضيح أهمية هذه الأنزيمات وإعطاء تعريف بسيط للأنواع الرئيسة منها خاصة فيما يتعلق بصفاتها والمواد الأساس التي تعمل عليها.

الكلمات الدالة: أنزيمات البيتالاكتاميز واسعة الطيف؛ مقالة؛ المقاومة للمضادات المايكروبية.

التمويل: لايوجد.

بيان توفر البيانات: جميع البيانات الداعمة لنتائج الدراسة المقدمة يمكن طلبها من المؤلف المسؤول.

اقرارات:

تضارب المصالح: يقر المؤلفون أنه ليس لديهم تضارب في المصالح.

الموافقة الأخلاقية: لم يتم نشر المخطوطة أو تقديمها لمجلة أخرى، كما أنها ليست قيد المراجعة.