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Research Article

The current knowledge on Guiana - Extended - Spectrum (GES) in Gram negative bacteria and their dissemination.

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Abstract: Extended-spectrum β-lactamases (ESBLs) are a major contributor to antimicrobial resistance in Gram-negative bacteria, posing a significant global public health challenge. Among these, the Guiana extended-spectrum β-lactamase (GES) family has emerged as an important but relatively underrecognized group of class A ESBLs. Initially identified in *Klebsiella pneumoniae* from French Guiana, GES-type enzymes have since been reported worldwide in various bacterial species, particularly *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

GES enzymes exhibit considerable heterogeneity, with certain variants demonstrating the ability to hydrolyze carbapenems, thereby complicating treatment options. The global dissemination of ESBLs, including GES types, is largely driven by mobile genetic elements such as plasmids and integrons, as well as the spread of high-risk clones like *Escherichia coli* ST131.

Detection of GES-type ESBLs remains challenging due to variability in phenotypic expression and limitations of routine diagnostic methods. Although standardized screening and confirmatory tests are recommended, molecular techniques such as PCR and sequencing provide more reliable identification.

This review highlights the epidemiology, molecular characteristics, detection challenges, and clinical significance of GES-type ESBLs. Understanding their evolution and dissemination is essential for improving surveillance, guiding appropriate antimicrobial therapy, and developing effective infection control strategies.

Keywords: *Extended-spectrum β-lactamases (ESBLs), GES enzymes, Antimicrobial resistance.*

1. Introduction

Patterns of β-lactam the resistance and β-lactamase production are becoming increasingly complex, with β-lactamases unrelated to well-described enzyme groups becoming more common. Extended-spectrum β-lactamases (ESBLs) appear to be evolving at an alarming rate, with more than 200 characterized enzymes known to date (Paterson & Bonomo, 2005). Since the descriptions of TEM- and SHV-type ESBLs in the early1980s, these two distinct groups have been extensively studied and reported on a worldwide basis (1). To date, Emergence and subsequent spread of several other ESBL families have been described, most notably the CTX-M group of enzymes (Bonnet, 2004). Another group of ESBLs, Guiana Extended-Spectrum, or GES, an Ambler class A ESBL, was described in 2000 in a clinical isolate of Klebsiella pneumoniae from the island of Guiana, French Guiana (Poirel et al., 2000). As expected, since 2000 several novel GES-type ESBLs have been described and characterized from different geographical locations. Although they were once referred to as an obscure the cluster of ESBLs, mostly recorded from Pseudomonas aeruginosa in South Africa (Livermore & Paterson, 2006). This review will familiarize readers with this novel group of the enzymes.

2. Epidemiology and Clinical Impact

The time of writing, nine different GES-type ESBLs have been isolated and described from different geographical locations, including French Guiana, South Africa, Greece, Japan, and France **(Poirel et al., 2001)**. (Table 1). In addition to its original location, GES-1 has subsequently been found in Argentina, Brazil, Portugal, South Africa, and France **(Pasteran et al., 2005)**. The occurring in two different host bacterial species, K. pneumoniae **(Duarte et al., 2003)**. And P. aeruginosa **(Castanheira et al., 2004)**. GES-1 was found to be associated with class 1 integrons in all cases **(Weldhagen, 2004)**, with exception of a class 3 integron site reported in a Portuguese isolate

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of K. pneumoniae **(Correia et al., 2003)**. An outbreak of GES-1-producing K. pneumoniae has been described from Lisbon, Portugal, clonally related isolates were collected from surgical, medical, and intensive care units between 1999 and 2001 from urine, respiratory specimens, blood, and pus. However, no specific clinical outcomes were reported in this outbreak **(Duarte et al., 2003)**. GES-2 was originally described in a multidrug-resistant clinical isolate of P. aeruginosa from South Africa **(Poirel et al., 2001)**. The isolate was obtained in May 2000 from a blood culture of a patient with cerebral malaria and nosocomial pneumonia. Compared to GES-1, GES-2 exhibited an extended hydrolysis profile to include imipenem and was less inhibited by clavulanate and tazobactam **(Poirel et al., 2001)**. During same in the same time period, drug-resistant, GES-2-producing P. aeruginosa was also implicated in the first described GES-associated nosocomial outbreak affecting patients from a variety of clinical disciplines in a South African teaching hospital. During this outbreak, clonally related P. aeruginosa isolates were recovered from eight patients on medical, surgical, neurosurgical, and gynecological wards. Only three patients were reported to have survived **(Poirel et al., 2002)**. Despite its frequent occurrence in South African isolates of P. aeruginosa and its presumed enterobacterial origin **(Poirel et al., 2001)**, GES-2 has not been detected in common fermentative bacterial species, such as ESBL-producing K. pneumoniae, that occur in the same ecological niche (unpublished data). To date, there are no published reports of GES-2 in species other than P. aeruginosa. Domain. GES-2-producing P. aeruginosa was subsequently found in Argentina **(Pasteran et al., 2004)**, and GES-3 was described from a clinical isolate of K. pneumoniae originating from a neonatal intensive care unit (ICU) in a Japanese hospital **(Wachino et al., 2004)**.

Table 1. Nomenclature and current epidemiology of GES-type ESBLs (Wachino et al., 2004).

Designation	GenBank no	Isolated from other countries	Country of origin	Bacterial host species	References
GES-1	AF156486	Brazil, Portugal, Argentina, South Africa, France	French Guiana	K. pneumoniae P. aeruginosa	3, 11
GES-2	AF326355	Argentina	South Africa	P. aeruginosa	5, 12, 13
GES-3	AB113580		Japan	K. pneumoniae	14
GES-4	AB116260		Japan	K. pneumoniae	15
GES-5[a]	Y494717	Korea	Greece	K. pneumoniae E. coli	16,17, 18
GES-6[b]	Y494718		Greece	K. pneumoniae	16
GES-7 (IBC-1)	AF208529		Greece	E. cloacae	19, 20
GES-8 (IBC-2)	AF329699		Greece	P. aeruginosa	21
GES-9	AY920928		France	P. aeruginosa	22

[a]GES-type ESBL previously designated GES-3.

[b]GES-type ESBL previously designated GES-4.

Original isolate, with high levels of resistance to broad-spectrum cephalosporins, was found in March 2002. Subsequently, several GES-type-producing and genetically related K. pneumoniae isolates were found in the same neonatal ICU over a 1-year period, although no clinical data were reported in this study **(Wachino et al., 2004)**. GES-4, a variant of GES-3 with a G170S substitution in the omega-loop region, was described by the same Japanese research group **(Wachino et al., 2004)**. GES-4 also originated from the same neonatal ICU as the GES-3-producing isolates and subsequently exhibited enhanced hydrolysis of carbapenems and cephamycins. In addition, GES-4 showed decreased affinities for β-lactamase inhibitors **(Wachino et al., 2004)**. Neither GES-3- nor GES-4-producing bacterial isolates have described or reported from locations outside of Japan. GES-5 and GES-6, originally reported from Greece, occurred in clinical isolates with decreased susceptibility to carbapenems. GES-5 was found in *Escherichia coli*, whereas GES-6 occurred in *K. pneumoniae* **(Vourli et al., 2004)**. GES-5 producing clinical isolates of *K. pneumoniae* were subsequently found in Bundang City, Republic of Korea **(Jeong et al., 2005; Ryoo et al., 2005)**. However, Korean isolates produced GES-5 with a silent mutation, G54A, compared with Greek isolates **(Vourli et al., 2004; Jeong et al., 2005)**. Gene sequences from Korean isolates initially reported as GES-3 producers were

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changed to GES-5 (GenBank accession no. AY494717) due to nomenclature issues **(Ryoo et al., 2005)**. A clinical outbreak of GES-5-producing *K. pneumonia* has been described in Korea **(Jeong et al., 2005)**, with isolates recovered from patients in intensive care, neurosurgery, pulmonary medicine, and general medicine wards. Samples yielding isolates included sputum, urine, bile, and pus, but no clinical outcomes were reported **(Jeong et al., 2005)**. GES-7, from Athens, Greece, was originally described as IBC-1 (integron-borne cephalosporinase) **(Giakkoupi et al., 2000)**. The gene was found on a transmissible plasmid as part of a class 1 integron in a clinical isolate of *Enterobacter cloacae* from a leukemia patient **(Giakkoupi et al., 2000)**. Isolates of *E. cloacae* from August 1998 to June 2000 from a Greek neonatal ICU were subsequently found to harbor blaGES-7 (blaIBC-1) and could be linked to an outbreak in that setting **(Kartali et al., 2002)**. Possible modes of transmission included colonization of the gastrointestinal tract, hands of health care workers, overcrowding, and contamination of multidose vials **(Kartali et al., 2002)**.

Was successfully managed by infection control measures, including the use of disposable gloves and gowns **(Poirel et al., 2005)**. In addition to GES-7, a structural analog, GES-8, was initially described as IBC-2 during 2001 from Greece **(Correia et al., 2003)**. GES-8 was found as the only gene cassette in the variable region of a class 1 integron in a clinical isolate of *P. aeruginosa* collected during 1998 **(Mavroidi et al., 2001)**. The emergence of GES-type ESBLs was subsequently described in several hospitals in Athens. The most recent addition to the GES lineage is GES-9, described from Paris, France **(Poirel et al., 2005)**. GES-9 was found to be associated with a clinical isolate of *P. aeruginosa* obtained from a rectal swab of a stroke patient in 2004 **(Poirel et al., 2005)**. No other clinical descriptions of GES-9 are currently known.

3. Nomenclature of GES-type ESBLs

Due to the description of GES-type ESBLs by different authors during a relatively short period of time, confusion has arisen as to the correct nomenclature of these enzymes. Because different GES-type ESBLs, which possess different hydrolytic properties, have previously been referred to by identical names (Table 1), it has been suggested that new nomenclature be developed. It was suggested **(Lee et al., 2005)**. That changes be made to alleviate the uncertainty surrounding the simultaneous descriptions of GES-3 and GES-4 in Greece and Japan **(Vourli et al., 2004; Wachino et al., 2004)**. Based on manuscript submission dates and the release of gene sequence data into the public domain, it was proposed to maintain the current nomenclature of fully characterized GES-3 and GES-4 enzymes described in Japan **(Wachino et al., 2004)**. And to rename the GES-3 and GES-4 variants described in Greece **(Vourli et al., 2004)** as GES-5 and GES-6, respectively **(Lee et al., 2005)**. Two recent papers from France and Korea **(Jeong et al., 2005; Mavroidi et al., 2001)** could not reach a consensus on the nomenclature of GES-type ESBLs, especially with regard to types 3 to 6. These conflicting reports on the nomenclature of GES-type ESBLs resulted from the absence of a final decision on the previously proposed nomenclature update **(Lee et al., 2005)**. IBC-1 and IBC-2 differ from GES-1 by only one amino acid residue **(Giakkoupi et al., 2000; Mavroidi et al., 2001)** and were subsequently renamed GES-7 and GES-8, respectively **(Jacoby, 2006)**.

To prevent future misleading nomenclature of GES-type genes, researchers must frequently consult the β-lactamase web site which currently serves as the only repository where sequences, literature references, or database accession numbers are posted and numbered for most β-lactamase families. (Table 1) shows nomenclature of well-described GES-type ESBLs as currently presented on Lahey Clinic web site.

4. Laboratory Detection

Because there is considerable variation in the phenotypic behavior of different ESBLs, detection of these resistance mechanisms by routine diagnostics can range from surprisingly easy to extremely difficult. Because of this variability, the Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) continues to recommend that clinical microbiology laboratories perform specialized testing for the detection of ESBLs. Recommended methods may include screening of isolates using either disc diffusion susceptibility testing or dilution antimicrobial susceptibility testing, preferred antimicrobial substrates for these assays include Cefpodoxime, ceftazidime, aztreonam, cefotaxime, and ceftriaxone **(Paterson & Bonomo, 2005)**.

Sensitivity is improved when more than one substrate is used simultaneously. However, phenotypic confirmation is mandatory to verify any positive screening test result. Confirmation is based on the phenomenon whereby the susceptibility or activity of an antibiotic is restored in the presence of a β-lactamase inhibitor, with clavulanic acid being the agent of choice. The most commonly used methods include double disk synergy tests, combination disk tests, and broth microdilution tests. A variety of commercial tests, including the Etest, are available to meet this need. For GES-type ESBLs, detection in the clinical microbiology laboratory may be more difficult than for other ESBLs. GES-1-type ESBLs can be phenotypically detected by double-disc diffusion testing, with synergy between clavulanate-containing discs and one or more of the following: ceftazidime, cefotaxime, and aztreonam **(Poirel et al., 2000)**.

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Synergy may also be observed between a clavulanate-containing disc and cefepime or imipenem in Enterobacteriaceae. Phenotypic detection of GES-1 in *P. aeruginosa* could be performed using Etest strips containing ceftazidime/ceftazidime-clavulanate and Cefepime/Cefepime-clavulanate **(Castanheira et al., 2004)**. GES-2 may be very difficult to detect in its current host species, *P. aeruginosa*. In addition to resistance mediated by efflux and impermeability, resistance to extended-spectrum cephalosporins may arise from (i) the de-repression of chromosomal cephalosporinase biosynthesis, (ii) the acquired secondary β-lactamases, or (iii) both mechanisms in tandem **(Weldhagen et al., 2003)**.

Phenotypic detection using the double-disc method failed to detect GES-2. More complex EDTA-based, disc diffusion assays may be helpful to phenotypically detect GES-2 in *P. aeruginosa*, as described in Argentina **(Marchiaro et al., 2005)**. Ceftazidime resistance using CLSI breakpoints also failed to reliably detect GES-2 in this species compared to molecular methods **(Weldhagen & Prinsloo, 2004)**. Although GES-2 partially hydrolyzes imipenem in *E. coli*, experimentally cloning blaGES-2 into a high copy number vector did not significantly alter susceptibility to imipenem, making a simple susceptibility test unlikely to detect this ESBL in Enterobacteriaceae on this basis alone **(Poirel et al., 2001)**.

Similar to GES-2, phenotypic detection using the double-disc method failed to detect GES-3 **(Wachino et al., 2004)**. GES-4-producing isolates may exhibit high-level resistance to oxyimino-cephalosporins and cephalosporins, with intermediate susceptibility to imipenem **(Wachino et al., 2004)**. GES-5-producing isolates may exhibit resistance to ceftazidime, while susceptibility to cefotaxime and aztreonam and slightly elevated imipenem MIC values may be found **(Vourli et al., 2004)**. A modified cloverleaf carbapenemase assay has been used to detect GES-5 in blaGES-5 transconjugant isolates in Korea **(Jeong et al., 2005)**.

GES-6 producers, however, may exhibit high levels of resistance to most β-lactams, while susceptibility to ceftazidime and imipenem is restored in the presence of clavulanate **(Vourli et al., 2004)**. GES-7 can confer resistance to ceftazidime and cefoxitin while maintaining susceptibility to cefotaxime, ceftriaxone, aztreonam, and cefpirome **(Giakkoupi et al., 2000)**. A double-disc synergy test with ceftazidime and imipenem was used to detect GES-7-producing *E. cloacae* isolates in a Greek hospital **(Kartali et al., 2002)**. Similarly, GES-8 showed a marked synergy between imipenem and oxyimino-cephalosporin-containing discs **(Mavroidi et al., 2001)**, whereas GES-9 showed a synergy between aztreonam and amoxicillin-clavulanate **(Poirel et al., 2005)**.

Apart from phenotypic detection, the most specific method for detecting GES-type ESBLs is still PCR and sequencing of PCR products **(Weldhagen & Prinsloo, 2004; Weldhagen, 2004)**. Most scientific papers describe routine PCR and agarose gel electrophoresis detection methods with well-tested oligonucleotide primers **(Poirel et al., 2001; Weldhagen & Prinsloo, 2004)**. In addition to routine PCR, highly sensitive real-time PCR and a novel peptide nucleic acid-based sequence-selective PCR method have been described for the detection of blaGES-2 **(Weldhagen, 2004)**.

5. Placement of ESBLs in the β-lactamase classification scheme

The first classification scheme for β-lactamases that recognized ESBLs was established by Karen Bush in 1989, which defined group 2b' β-lactamase enzymes as those capable of hydrolyzing oxyimino-β-lactams such as cefotaxime, ceftazidime, and aztreonam at rates at least 10% that of benzyl penicillin and that were strongly inhibited by clavulanate. Subsequently, these enzymes were designated as group 2be in the functional classification scheme developed by Bush, Jacoby, and Medeiros **(Bush et al., 1995)**. In this scheme, ESBLs retained the strict definition of class A β-lactamases that can hydrolyze these extended-spectrum β-lactam antibiotics and are also susceptible to inhibition by the original β-lactamase inhibitors clavulanate, sulbactam, and tazobactam. The original classification scheme also included only plasmid-mediated enzymes, but the updated scheme recognizes the fluidity of genes expressing ESBLs between plasmids and chromosomes **(Bush & Jacoby, 2010)**. Traditional ESBLs are inhibited by all β-lactamase inhibitors, including the older inhibitors clavulanate, sulbactam, and tazobactam, as well as newer inhibitors such as avibactam, relebactam, and vaborbactam. Although the notion of including any enzyme that can hydrolyze the oxyimino-β-lactams in the classification as an ESBL has been proposed, the strict definition of an ESBL remains that inhibition by clavulanate is a requirement for designation in this group **(Bush & Jacoby, 2010; Bush et al., 2009)**.

6. ESBL Families.

Although ESBLs share common biochemical properties with respect to hydrolysis of extended-spectrum β-lactam antibiotics and inhibition by clavulanate, the genes encoding these enzymes are diverse in nature and can be grouped into several families (Table 2) **(Bradford, 2001)**. Some of these families, such as the TEM- and SHV-type ESBLs, are closely related, with variants differing by only a few amino acid substitutions. Other families, such as the CTX-M type ESBLs, are much more genetically diverse. Each of the ESBL families has some unique characteristics **(Bradford, 2001)**.

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Table 2. ESBL families

Family	Nomenclature	Characteristic
TEM	Temoneira,thepatientinfectedwith the first isolate expressing TEM-1	A Point mutation variants of TEM-1 or TEM-2
SHV	Sulfhydrylreagentvariable	The Point mutation variants of SHV-1
CMT	ComplexmutantderivedfromTEM-1	TEM variants that are resistant to inhibition by the clavulanate and sulbactam and also have ESBL phenotype
CTX-M	Cefotaxime-hydrolyzing b-lactamase isolated in Munich	Derived from chromosomal b-lactamase from Kluyvera spp. Preferentially hydrolyses cefotaxime
IRT	Inhibitor-resistant TEM	TEM variants that are the resistant to inhibition by the clavulanate and sulbactam, but do not have ESBL phenotype
GES	Guiana-extended spectrum	The More prevalent in P. aeruginosa than Enterobacterales Some variants also hydrolyze carbapenems
PER	Pseudomonas extended resistant	The More prevalent in P. aeruginosa and A. baumannii than Enterobacterales Inhibition by newer b-lactamase inhibitors is variable
BEL	Belgium extended β-lactamase	Preferentially hydrolyses ceftazidime and aztreonam compared with the cefotaxime
VEB	Vietnam extended-spectrum β-lactamase	Preferentially hydrolyses ceftazidime and aztreonam compared with the cefotaxime Inhibition by newer b-lactamase inhibitors is variable
TLA	Named after the Tlahuica Indians (Mexico), from whom the first isolate was obtained	The Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime
SFO	From Serratia fonticola	Inducible
OXY	From Klebsiella oxytoca	Chromosomally encoded

Adapted from Jacoby (Jacoby, 2006).

6.1 TEM

TEM-type ESBLs are variants of the original plasmid-mediated β-lactamase, TEM-1, described in the early 1960s **(Datta & Kontomichalou, 1965)**. This enzyme was named because it was originally found in an isolate of *Escherichia coli* from a blood culture of a Greek patient named Temoniera **(Medeiros, 1984)**. The first derivative of TEM, TEM-2, has a single amino acid substitution of Gln39Lys from the original TEM-1 β-lactamase **(Barthélémy et al., 1985)**. This change did not alter the substrate profile of TEM-1. This change did not alter the substrate profile of TEM-1, but TEM-2 served as the progenitor for many of the TEM-type ESBLs **(Paterson & Bonomo, 2005)**. The first TEM-type variant to exhibit the ESBL phenotype was TEM-3, which was reported in 1989 **(Sougakoff et al., 1988)**.

To date, 243 different TEM variants have been described, although not all are ESBLs. Amino acid substitutions that occur in the TEM enzyme occur at a limited number of positions. The amino acid residues (Ambler numbering) most commonly involved in conferring the ESBL phenotype to TEM-type enzymes are Gly238 and Glu240, located on the β3 β-pleated sheet; Arg164, located on the neck of the Ω-loop; and Glu104, located directly opposite Gly238/Glu240 at the opening of the active site cavity (Figure 1) **(Knox, 1995)**. Of these, the Gly238Ser and Glu240Lys substitutions appear to have the greatest impact on producing the ESBL phenotype.

Some of the newer TEM variants have subtle changes in the substrate profile. For example, TEM-184 (amino acid substitutions at Q6K, E104K, I127V, R164S, and M182T) hydrolyzed aztreonam more efficiently than ceftazidime or cefotaxime **(Piccirilli et al., 2018)**. Although so many new variants are being discovered by WGS, few are being phenotypically characterized to determine whether they have the properties of an ESBL. However, computational modeling and network analysis have made it possible to predict whether a particular sequence is likely to belong to the 2b (original broad-spectrum), 2be (ESBL), or 2br (inhibitor-resistant) functional groups **(Zeil et al., 2016)**.

As the prevalence of TEM-type ESBLs increased, the prevalence of some of the variants varied regionally. For example, TEM-3 was very common in France, but rarely seen in the USA. In contrast, TEM-10 was the most prevalent TEM-type ESBL in the USA. Interestingly, TEM-26 was detected in isolates from all over the world **(Urban et al., 2000)**. As CTX-M-type β-lactamases became the most common ESBL worldwide, TEM-type enzymes became less common. In a recent survey of European isolates, TEM-type ESBLs were detected in less than 1% of ESBL-producing *E. coli* and *Klebsiella pneumoniae* **(Kazmierczak et al., 2020)**.

6.2 SHV

The SHV-type β-lactamases (so named for their sulfhydryl reagent variability) originated as chromosomally encoded enzymes in *K. pneumoniae*. The first ESBL, SHV-2, was

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described in 1985 in a strain of *Klebsiella ozaenae* that differed from *Klebsiella pneumoniae* in its use of amino acids. The first ESBL described in 1985 was SHV-2, which was found in a single *Klebsiella ozaenae* strain isolated in Germany and differed from SHV-1 by a substitution of Gly for Ser at position 238. Similar to what is seen in TEM-type ESBLs, the majority of SHV-type ESBLs also have mutations at Ambler positions 238 **(Huletsky et al., 1993)** (Gly for Ser) and 240 (Lys for Glu) (Fig 1) **(Paterson & Bonomo, 2005)**. The serine substitution at position 238 appears to be critical for efficient hydrolysis of ceftazidime, whereas the Lys substitution at residue 240 is critical for efficient hydrolysis of cefotaxime **(Huletsky et al., 1993)**.

The relevance of the different amino acid substitutions with respect to phenotypic changes in the substrate profile has recently been investigated using a mathematical model **(Neubauer et al., 2020)**. To date, 228 sequence variants of SHV have been identified, although not all have been functionally characterized to determine whether they possess the ESBL phenotype (https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/SHV). Worldwide, SHV-5 and SHV-12 are the most common ESBL variants found in Enterobacterales. SHV-type ESBLs are most commonly found in clinical isolates of *K. pneumoniae*, but these enzymes have also been found in other genera of Enterobacterales and *P. aeruginosa* **(Perilli et al., 2002)**.

Figure1: Amino acid alignments of TEM-1, SHV-1 and CTX-M-1. The amino acid sequences WP_000027057.1 (TEM-1), WP_001620095.1 (SHV-1) and WP_013188473.1 (CTX-M-1) were obtained from NCBI and aligned using Crustal Omega.224–226 Numbering according to Ambler.227 Asterisk (*) indi cates positions that have a single, fully conserved residue. Colon (:) indicates conservation between groups of strongly similar properties. Period (.) indicates conservation between groups of weakly similar properties. The yellow highlights show the active site Ser70-X-X-Lys active site common to all serine b-lactamases. Red amino acids denote residues where substitutions provide ESBL phenotype (TEM and SHV). Blue amino acids denote where substitutions provide inhibitor resistance phenotype. Green indicates position 240 in CTX-M-1, which has been identified as being associated with increased hydrolysis of cefotaxime (Perilli et al., 2002).

6.3 Inhibitor-resistant b-lactamases

Inhibitor-resistant β-lactamases are derivatives of TEM and SHV enzymes that have amino acid substitutions that confer resistance to inhibition by the β-lactamase inhibitors clavulanate and sulbactam. In the functional classification scheme, they belong to functional group 2br. Most of these enzymes remain susceptible to inhibition by tazobactam and avibactam **(Lahiri et al., 2016)**. The majority of inhibitor-resistant β-lactamases are derivatives of TEM-1 and were formerly designated IRT (for inhibitor-resistant TEM), but are now given a sequential TEM number **(Bush & Jacoby, 1997)**. Common substitutions in the TEM variants have been characterized

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at amino acid positions Met69, Ser130, Arg244, Arg275, and Asn276 (Fig 1) **(Cantón et al., 2008)**.

It appears that the cost of mutations conferring resistance to clavulanate and sulbactam is a reduction in the efficiency of hydrolysis of some penicillins and cephalosporins, such as cefalotin **(Bret et al., 1997)**. Although these mutants are rarely detected, a strain of *K. pneumoniae* expressing the inhibitor-resistant TEM-30 was identified in several KPC-producing isolates from an outbreak of carbapenem-resistant Enterobacteriaceae (CRE) in New York City. Several SHV-type β-lactamases have been characterized as inhibitor-resistant, including SHV-49, -56, and -107, which were identified in *K. pneumoniae* clinical isolates from patients in Europe **(Mendonça et al., 2009)**.

A few complex TEM mutant (CMT) β-lactamases have been described, which are mutants of TEM β-lactamases that have both the ESBL phenotype and inhibitor resistance. These CMT variants are not detected by any of the screening methods used to detect ESBLs because these tests rely on inhibition with clavulanic acid. One such complex mutant, TEM-152, was found in an *E. coli* isolate from a patient hospitalized in France **(Robin et al., 2007)**. This mutant had the amino acid substitutions Arg164His and Glu240Lys, previously observed in ESBLs, plus Met69V and Asn276Asp, previously observed in the inhibitor-resistant enzyme TEM, which resulted in efficient hydrolysis of ceftazidime and a 50% reduction in inhibition by clavulanate.

Because these complex mutants are not resistant to avibactam, ceftazidime/avibactam or one of the other new β-lactamase inhibitor combinations may be a viable option for treating infections caused by organisms expressing one of these enzymes. It is likely that the prevalence of TEM- or SHV-type inhibitor-resistant β-lactamases is underestimated because there is no phenotypic test that laboratories can routinely use to identify these strains **(Kaye et al., 2004)**.

6.4. CTX-M

CTX-M-type β-lactamase enzymes were first reported in the late 1980s and appeared simultaneously in several locations. The nomenclature CTX-M (cefotaximase from Munich) was initially used in a report from Germany **(Bauernfeind et al., 1990)**. However, CTX-M enzymes found in other regions were given different names, including FEC-1 (Japan), Toho-1 (Japan), and MEN-1 (France and an Italian patient) **(Bonnet, 2004)**. These initial reports were followed by outbreaks in several countries. The global spread of isolates carrying these ESBLs would later be referred to as the "CTX-M pandemic." Since the early 2000s, CTX-M-type enzymes have been recognized as the most common ESBL group, replacing TEM and SHV as the dominant ESBL type.

CTX-M variants have been identified in several members of the order Enterobacterales and in *P. aeruginosa* and *Acinetobacter* spp. **(Picão et al., 2009)**. Isolates carrying CTX-M-encoding genes have been detected in nosocomial and community settings, as well as in pets, the environment, food, and livestock **(Liu et al., 2018)**. Most CTX-M enzymes can be classified into five groups based on sequence homologies: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25. By far the most abundant CTX-M-1 group is CTX-M-15, followed by CTX-M-3 and CTX-M-1 **(Bonnet, 2004)**.

In the CTX-M-9 group, CTX-M-9 and CTX-M-14 were the most abundant enzymes, but recently CTX-M-27 has been reported frequently **(Peirano et al., 2020)**. CTX-M-2, CTX-M-8, and CTX-M-25 are the most abundant variants within their own groups. Analysis of the upstream sequences flanking the gene encoding the CTX-M-2 group showed that this group is derived from KLUA-1, an enzyme from *Kluyvera ascorbata* **(Humeniuk et al., 2002)**.

Similarly, CTX-M-134 (CTX-M-1 group) is derived from KLUC-1 from *Kluyvera cryocrescens* and the CTX-M-9 group has similarity to KLUG-1 from *Kluyvera cryocrescens*. *Kluyvera georgiana*. Notably, CTX-M enzymes also share structural similarities and hydrolytic profiles with other classes of β-lactamases from environmental organisms, such as *Erwinia persicina* and *Rahnella aquatilis* **(Vimont et al., 2002)**.

6.5. ESBL Phenotype OXA-type b-lactamases

OXA-type b-lactamases hydrolyze Oxacillin and are grouped as Ambler class D and Bush-Jacoby-Medeiros functional group 2D enzymes. In general, OXA-type enzymes are a broad group with variability in substrate profiles and amino acid sequences .However, several OXA-type variants have been identified that hydrolyze cephalosporins, cephems, and monobactams. These OXA enzymes with an ESBL phenotype are categorized in the Bush functional subgroup 2de. Whether or not these oxacillinases with activity against extended-spectrum cephalosporins are defined as ESBLs is controversial. Many researchers do not apply the ESBL terminology to oxacillinase because these enzymes are not classified in the 2de group and are refractory to inhibition by clavulanate or other inhibitors in the same way as the true ESBLs .According to a recent review, 27 oxacillinase enzymes are described as extended spectrum. The substrates of these enzymes include third- and/or fourth-generation cephalosporins, as well as penicillins and early cephalosporins [60]. Most extended-spectrum oxacillinase are derived from OXA-10 (also called PSE-2)

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and OXA-2 .OXA-10 derivatives include OXA-11, OXA-13, OXA-14, OXA-16, OXA-17, OXA-19, and OXA-28 (Evans & Amyes, 2014). In addition, only a partial sequence of OXA-16 has been submitted for initial description (GenBank #AF043100). Among the OXA-2 derivatives, OXA-15, OXA-32, OXA-34, OXA-36 (partial sequence), OXA-53, OXA-141, OXA-161, OXA-210, and OXA-226 have been described [60]. Many OXA-2 and OXA-10 derivatives have been detected in isolates of P. aeruginosa. Although not considered extended-spectrum oxacilli, OXA-1 and OXA-30 were named for their ability to hydrolyzeepime (Beceiro et al., 2011). OXA-1 and OXA-30 were initially reported to differ by one amino acid; however, it was later corrected that these enzymes were identical (Boyd & Mulvey, 2006).

6.6. Other ESBL families

The GES (Guiana extended-spectrum β-lactamase) family is the most prevalent group of nonetheless common ESBLs. The gene encoding GES-1 is not closely related to any other plasmid-mediated β-lactamase, but shares 36% homology with a carbenicillin-hydrolyzing enzyme from *Proteus mirabilis*. Although first reported among species of Enterobacterales, GES enzymes are more common among *P. aeruginosa* and *A. baumannii* isolates **(Zeka et al., 2014)**. GES enzymes are characterized by their ability to acquire single or double amino acid substitutions and expand their spectrum of activity to carbapenems.

The ESBL GES-1 was first described in 1998 in a *K. pneumoniae* isolate collected in France from a patient recently hospitalized in French Guiana **(Poirel et al., 2000)**. At the same time, another group described a similar enzyme, named IBC, from an *E. cloacae* isolate from Greece **(Giakkoupi et al., 2000)**. Subsequent enzymes, GES-2 and IBC-2, were both found in isolates of *P. aeruginosa*. IBC-1 was later renamed GES-7 and IBC-2, GES-8. Interestingly, GES-2 had a single amino acid substitution (Gly170Asp) compared to GES-1 and showed some hydrolytic activity against carbapenems **(Poirel et al., 2001)**.

Subsequently described GES β-lactamases fell into two categories: enzymes that were ESBLs and those that showed some modest carbapenemase activity. The original GES enzymes were ESBLs that hydrolyzed penicillins and cephalosporins well, but not aztreonam. These enzymes are inhibited by clavulanate, tazobactam, and then by newer carbapenem inhibitors such as avibactam, relebactam, and vaborbactam. This means that isolates expressing GES enzymes are often susceptible to ceftazidime/avibactam but not to ceftolozane/tazobactam. GES-1 hydrolyzes ceftazidime better than cefotaxime, and amino acid substitutions of Glu104Lys or Gly243Ala/Ser, detected in GES variants described later, have been shown to confer greater resistance to cephalosporins and aztreonam **(Bontron et al., 2015)**.

The Pseudomonas extended resistant (PER-1) β-lactamase was originally described from a *P. aeruginosa* isolate that exhibited resistance to cephalosporins and inhibition to clavulanate. This enzyme hydrolyzed most penicillins well and cephalosporins, including cefalotin, cefoperazone, cefuroxime, ceftriaxone, and ceftazidime. PER-1 did not hydrolyze oxacillin, cephamycins, or imipenem. A few years later, PER-2 was described in a *P. aeruginosa* isolate from Argentina that was 86.4% homologous to PER-1. PER enzymes have since been described in *A. baumannii* and *Aeromonas* spp. and in several species of Enterobacterales **(Bauernfeind et al., 1996)**.

PER-1 and PER-2 are the most abundant members of the PER family. These enzymes have been reported to be less inhibited by avibactam than other class A β-lactamases, with significant differences in MIC values for avibactam and relebactam when tested in combination with other β-lactams **(Ruggiero et al., 2019)**. More detailed studies are warranted because of the difference in activity between these two inhibitors of the same class. Recent analyses have shown that *A. baumannii* isolates harboring PER enzymes can have elevated MICs against cefiderocol, a siderophore cephalosporin **(Kohira et al., 2020)**. PER enzymes are most commonly found in isolates from Turkey and Mediterranean countries **(Ranellou et al., 2012)**.

VEB-1 (Vietnamese extended-spectrum β-lactamase) was first detected in an *E. coli* isolate obtained from a Vietnamese man in France **(Poirel et al., 1999)**. VEB-1 conferred high MICs for ceftazidime and aztreonam, but only a modest increase in MICs for cefotaxime when expressed on an *E. coli* background. A 4-fold increase in MICs for cefepime and no activity against imipenem was observed. This enzyme was well inhibited by clavulanate, but avibactam was initially reported not to reduce ceftazidime MIC values for *P. aeruginosa* isolates containing these enzymes **(Mushtaq et al., 2010)**.

Further studies showed that when various VEB enzymes were expressed in an *E. coli* isogenic background, the ceftazidime/avibactam MIC value was reduced in a concentration-dependent manner, with ceftazidime MIC values reduced 0.8-fold when 4 mg/mL inhibitor was used **(Lahiri & Alm, 2016)**. VEB-1 and other VEB variants have been described with various Gram-negative pathogens, including several species of Enterobacterales, *Vibrio* spp., *Achromobacter xylosoxidans*, and more clinically relevant species such as *P. aeruginosa* and *A. baumannii* **(Jain et al., 2016)**.

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7. Molecular characterization of ESBL-producing isolates

7.1 Genetic environment of ESBL genes

Mobile genetic elements (MGEs) such as plasmids, transposons, insertion sequences, integrons and bacteriophages contribute to the spread of various ESBL-encoding genes. MGEs can move themselves and/or genes from one location to another within the cell or be transferred horizontally from cell to cell by conjugation, transformation, or, in the case of bacteriophages, transduction **(Partridge et al., 2018)**. In most cases, MGEs carry multiple resistance genes that confer an MDR phenotype to their hosts, some of the key elements of MGEs that carry different types of ESBLs are highlighted in the section below **(Rodríguez-Baño & Pascual, 2008)**.

These structures were initially named TnA and exhibit 99% nucleotide homology, with most nucleotide differences identified near the resolvase (res) site. A limited number of studies have reported specifically on the MGE-carrying blaTEM-encoding ESBL enzymes. In an early study, blaTEM-12 was reported to be part of Tn841, which shares homology with Tn3 **(Heritage et al., 1992)**. The gene encoding TEM-3 was located on an interrupted copy on Tn1. Tn2 was reported to carry blaTEM-10, while blaTEM-24 was associated with Tn1. In all cases, these structures were embedded in plasmids.

A study by Marcadé et al. evaluating the replicon types of conjugative plasmids carrying ESBL genes revealed that 67% of the plasmids carrying ESBL genes were of the IncA/C type. Most of these plasmids carried blaTEM-24, but the plasmids also carried blaTEM-3, blaTEM-10 and blaTEM-21. Others confirmed the occurrence of blaTEM-encoding ESBLs in IncA/C plasmids. Notably, blaTEM-52 reported by Marcadé et al. was embedded in IncI1 plasmids **(Marcadé et al., 2008)**.

7.2 Common strain types for ESBL-producing isolates

MLS has been used extensively to track and monitor the spread of resistance determinants in bacterial pathogens. Several common sequence types have been found in epidemics and outbreaks due to resistant clones that are highly associated with specific resistance mechanisms. Until the mid-2000s, it appeared that CTX enzymes spread in a seemingly random pattern, with no major clones responsible for their spread **(Cantón & Coque, 2006)**.

However, over the past two decades, the spread of CTX-M-producing enzymes has been associated primarily with the spread of *E. coli* belonging to a new clonal group, ST131. *E. coli* ST131 is derived from phylogenetic group B2 and serotype O25b:H4 and possesses multiple virulence factors, including adhesins, siderophores, toxins, and a group 2 capsule. ST131 isolates differ from most other MDR *E. coli* in that they are quite pathogenic **(Nicolas-Chanoine et al., 2014)**.

E. coli belonging to ST131 cause a wide variety of infections, but are most commonly found in urinary tract infections, including cystitis, pyelonephritis, and urosepsis. *E. coli* ST131 isolates have been reported to carry a variety of β-lactamases and several CTX-M types, most commonly CTX-M-15. Five groups (A through E) have been described according to the virulence factors identified in *E. coli* ST131 isolates. These clones vary by geographic region. Interestingly, virotypes A, B, and more than half of virotypes C carry blaCTX-M-15, whereas virotypes D isolates carry other β-lactamase genes, including blaCTX-M group 9 genes and blaSHV-12 **(Pitout et al., 2005)**.

In addition to blaCTX-M-15, other characteristics of virotypes A, B, and C include resistance to fluoroquinolones and the type 1 fimbria gene fimH30. This group also carries an ISL3-like transposase within the fimH gene. Typing of fimH revealed that the H30, H30-R, and H30-Rx subgroups are associated with MDR clones of *E. coli* ST131. These groups appear to have evolved in a stepwise fashion, first by acquiring fluoroquinolone resistance for H30-R and then by incorporating blaCTX-M-15 for the H30-Rx group. The occurrence of *E. coli* ST131 isolates carrying blaCTX-M-15 has been well documented worldwide. In an early survey, Coque et al. reported that ST131 *E. coli* isolates producing CTX-M-15 and belonging to ST131 were detected in all seven countries for which isolates were analyzed. Among clinical *E. coli* isolates collected as part of the SENTRY and MYSTIC programs in 2007, 54/127 (47.1%) isolates were found to belong to ST131 **(Johnson et al., 2010)**.

8. Conclusion

9. GES-type ESBLs have emerged from obscurity to become a recognized resistance threat. GES-type genes have been found throughout the world, with some clinical isolates being collected incidentally for research purposes in the late 1990s. However, description and full characterization did not begin until 2000, when nine variants with different physical properties were the described. Recent extensive international travel and the spread of humans, food, and animals have been proposed as possible causes for currently observed scattered global the pattern, but selective research interests may also be an important reason. Because several research groups are working on these genes simultaneously, different genes have received the same name, making correct nomenclature of paramount importance to researchers.

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The description of GES-2 resulted in the first class AESBL to significantly hydrolyze a carbapenem, the trait that seems to be the perpetuated in discovery of other GES-type enzymes. Difficulties have also been encountered in the detection of these enzymes, especially when they occur in P. aeruginosa, giving rise to specific and, in one case, novel molecular identification methods. Scientific publications on these enzymes tend to focus strongly on research aspects, with little clinical, treatment and infection control data. Therefore, it is critical that clinical aspects of infections with GES-producing isolates be studied and documented in order to successfully control them, especially those with carbapenemase properties. Antimicrobial resistance is a significant worldwide problem that is an unwelcome consequence of modern medicine. ESBL-producing enterobacteria remain the most commonly encountered mechanism of resistance to extended-spectrum cephalosporins in these pathogens, both in healthcare and community settings. ESBLs have led to spread of virulent clones such as E. coli ST131. With today's modern technologies, the detection and molecular characterization of ESBLs has become commonplace. However, with so many ESBL variants, often produced in combination with other b-lactamases, deciphering this information is not always easy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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