Extended-spectrum β-lactamases in North America, 1987–2006

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ABSTRACT

Extended-spectrum β-lactamases (ESBLs) derived from the TEM-1 β-lactamase were first identified in the USA in outbreak strains of *Klebsiella pneumoniae* in the middle to late 1980s, together with the SHV-5 ESBL. The TEM-10, TEM-12 and TEM-26 enzymes have remained in US hospitals, but have been joined by other ESBLs that are variants of the SHV-1 broad-spectrum β-lactamase. In the most recent surveys from hospitals in the eastern part of the USA, the most prominent ESBLs have been the SHV-7 and SHV-12 enzymes. In Canada, a wider variety of ESBLs has been identified, with multiple members of the TEM, SHV and CTX-M classes being represented in surveillance isolates. SHV-type and CTX-M ESBLs have appeared in many Canadian isolates, with an outbreak of CTX-M-14-related enzymes from Calgary, but limited TEM-derived ESBLs. Surprisingly, few CTX-M ESBLs have yet been reported in the USA, in contrast to the rest of the world, where the CTX-M enzymes have become a predominant ESBL family.

Keywords β-Lactamase, ESBL, review

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BACKGROUND

When aminothiazole-containing third-generation cephalosporins and monobactams were identified in the late 1970s and early 1980s, a major criterion for their development was a need for stability in the presence of the troublesome TEM and SHV β-lactamases that had emerged in the Enterobacteriaceae [1]. The broad-spectrum TEM-1, TEM-2 and SHV-1 enzymes, as well as the OXA-1 oxacillinase, had become the most commonly identified plasmid-encoded enzymes in multiple surveys of β-lactamase production worldwide [2]. Most importantly, they were capable of being transferred among genera of Gram-negative bacteria, as demonstrated early in the history of the TEM β-lactamase that was readily acquired by gonococci, presumably from *Escherichia coli* [3,4]. As a result, widely used β-lactams became ineffective against many of the Enterobacteriaceae that produced these enzymes.

The introduction of antibacterial agents such as cefotaxime, ceftazidime and aztreonam was met with high hopes that these drugs would control the proliferation of β-lactamase-producing Gram-negative pathogens, with the possible exceptions of the AmpC cephalosporinase-producing pseudomonads and Enterobacteriaceae. In a somewhat premature statement in 1981, C. W. Kunin stated that these agents were 'magnificent examples of good scientific thinking and good chemistry on the part of the pharmaceutical manufacturers', a response typical of many in the infectious disease community at the time [5]. Resistance to these agents was predicted to emerge, most likely as a result of hyperproduction of the chromosomal AmpC-type cephalosporinase [6].

However, it was the plasmid-encoded enzymes that proved to be more versatile in mutating to confer resistance to these new agents. Transferable cefotaxime resistance was first reported from Germany in 1983 [7], and this was followed by large outbreaks of transferable cefotaxime or ceftazidime resistance in France, beginning in 1985 [8–10]. The responsible enzymes, variants of the common TEM and SHV β-lactamases with one to four point mutations of single nucleotides in the parent gene, were named 'extended-spectrum β-lactamases' (ESBLs) because of their ability to hydrolyse the extended-spectrum β-lactams, including cephalosporins and monobactams [11].

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Early TEM β-lactamases

All the early North American ESBLs that were identified were members of the TEM family, with a number of variants that included the TEM-10, TEM-12 and TEM-26 β-lactamases, as shown in Table 1. The chronology outlining their identifications demonstrates a wide geographical diversity over a very short period.

In 1986, Bakken *et al.* submitted a paper describing a ceftazidime-resistant *E. coli* isolate from a patient who had received ceftazidime for 8 weeks; at that time, the authors did not believe that the resistance was related to the apparent TEM-1 β-lactamase in the strain [22]. The first report of a recognised ESBL in North America was from Jacoby *et al.* from Boston, in February 1988 [23], and this was followed by a report from Quinn *et al.* describing ceftazidime-resistant *Klebsiella pneumoniae* isolates identified in mid-1988 from Chicago, and later shown to be TEM-10-producers [13]. During this time-frame, the TEM-26 β-lactamase had also emerged in January 1988, in a paediatric oncology ward in Stanford CA, where ceftazidime had been used as monotherapy [18]. Curiously, in the New York Medical Center of Queens in New York City, beginning in October 1988, the same TEM-26 enzyme began to cause one of the largest ESBL outbreaks that has been recognised in the USA [19,24], 436 ceftazidime-resistant *K. pneumoniae* isolates being identified over a period of 19 months. Reports from the Boston area of three different TEM-related ESBLs during that period were later also identified as TEM-10, TEM-12 and TEM-26 ESBLs [16,23,25]. Eventually, the putative TEM-1 β-lactamase from the Bakken strain in 1986 was demonstrated to be TEM-12, a single-amino-acid variant of TEM-1 and the precursor to either TEM-10 or TEM-26 [15].

It is not surprising that other related TEM β-lactamases, such as TEM-28 and TEM-43 [20,21], were identified in the USA at later times. As seen in Table 1, all these US TEM enzymes are derived from TEM-1 rather than from its point mutant TEM-2. All these variants contain a substitution of either serine or histidine at position 164, and also contain a lysine substitution at either position 104 or position 240. Thus, one can envision a series of point mutations occurring within this family to give the set of TEM ESBLs that emerged in the USA.

Most of the TEM ESBL enzymes appear in *K. pneumoniae*, although *E. coli* has served as the host organism for some ESBLs. When ESBLs are produced in *K. pneumoniae*, multiple β-lactamases are usually present, often including a parental TEM-1 and an SHV enzyme, as well as the TEM ESBL [19]. Occasionally, both TEM-12 and TEM-10 have been identified in the same strain [17].

Early SHV β-lactamases

The emergence of SHV variants in North America was less dramatic than observed with the TEM ESBLs, with no major epidemics resulting from the early appearance of these enzymes. The first SHV-related family member in the USA was the OHIO-1 enzyme, which appeared in the mid-1980s in the state of Ohio, with >90% amino-acid

Table 1. Amino-acid substitutions associated with TEM variants identified in the USA

TEM	Location(s)	Date of first identification	Amino-acid substitution at position[a]				Reference
			104	164	182	240	
1			Glu	Arg	Met	Glu	[12]
10	Boston, MA Chicago, IL	1988	Glu	**Ser**	Met	**Lys**	[13,14]
12	Boston, MA Chicago, IL	1988	Glu	**Ser**	Met	Glu	[15–17]
26	Boston, MA New York City, NY Stanford, CA	1988	**Lys**	**Ser**	Met	Glu	[16,18,19]
28	Los Angeles, CA	1992	Glu	**His**	Met	**Lys**	[20]
43	St Louis, MO	1992–1996	**Lys**	**His**	**Thr**	Glu	[21]

[a]Bold type indicates a substitution leading to a difference from the TEM-1 amino-acid sequence.