Prevalence of extended-spectrum \( \beta \)-lactamases in South America

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ABSTRACT

In South American countries, the class A extended-spectrum \( \beta \)-lactamases (ESBLs) so far recognised belong to the CTX-M, \textit{Pseudomonas} Extended Resistance (PER), SHV and TEM families. ESBL rates in South America are among the highest in the world, probably due to multiple factors. SHV- and TEM-type ESBLs have been frequently encountered, but CTX-M is endemic and widely dominant. PER-type ESBLs seem to be restricted to the southern ‘cone’ of South America. Community-acquired ESBLs are starting to appear.

Keywords: CTX-M, extended-spectrum \( \beta \)-lactamases, \textit{Pseudomonas} Extended Resistance, review, SHV, South America, TEM

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EPIDEMIOLOGICAL AND GEOGRAPHICAL DISTRIBUTION OF EXTENDED-SPECTRUM \( \beta \)-LACTAMASES

The first reports of extended-spectrum \( \beta \)-lactamase (ESBL) enzymes came from Germany in 1985 [1,2], describing the discovery of SHV variants, specifically SHV-2. By 1986–1987, \textit{Klebsiella} isolates with transmissible resistance to cefotaxime and other \( \beta \)-lactams had emerged also in France [3] and, soon after that, there was an explosion of reports of ESBLs throughout the world. South America was not the exception, and it has been proposed that ESBLs, including CTX-M types, were common in South America as early as 1989 [4].

In general, the spread of infections due to ESBL producers has been greater in countries with lower economic resources. This is very clear when comparing prevalence data from Sweden (3%) with those from Greece, Turkey, Portugal (>25%) [5,6] or South America (>30%) [7–9]. Several reasons may account for this disparity: (i) poorer social and economic conditions; (ii) crowded hospitals, frequently with high patient/nurse ratios; (iii) self-prescription of antibiotics, which are sold over the counter in most of South America; and (iv) deficient hospital hygiene, resulting in high rates of colonisation and infection with \textit{Klebsiella} spp. This last factor is very important because \textit{Klebsiella} spp. have a particular ability to acquire plasmids determining ESBL production.

Based on recent multi-continent surveys, \textit{Klebsiella} isolates from Latin America have the highest ESBL prevalence in the world (45.4–51.9%) [10,11]. The prevalence among \textit{Escherichia coli} isolates, ranging from 8.5% to 18.1% in Latin American countries, was also higher than in developed countries [11]. However, ESBL rates among \textit{Proteus mirabilis} isolates differ widely in different continents. They were lower in northern South America while very frequent in South America as in Argentina (33% to 40%) [8,10,24] (6.2%) than in eastern and southern Europe (21.3% and 20.5%, respectively) [11].

Differences among South American countries are observed too, although analysis is complicated, depending on the isolates selected for each study. \textit{Klebsiella} isolates from intensive care units in Brazil, Colombia and Venezuela had ESBL rates ranging from 30% to 60% [12–18], while 56.6% of \textit{Klebsiella pneumoniae} isolates from blood samples in Brazil were ESBL producers [19]. Among \textit{Escherichia coli} blood isolates from Uruguay and Chile, ESBLs were expressed in 4.5% and 12%, respectively. In Colombia, our studies of isolates...
from multiple sources showed higher rates of ESBLs—up to 16.7%—and revealed a few clonally related producers [20]. The absence of clonality in most cases suggests that improved infection control will not be an adequate control measure by itself; better antibiotic use will also be required.

**TEM-type ESBLs**

Most TEM-derived ESBLs, derived from TEM-1, an extremely common enzyme known since 1965 [21,22], are more active against ceftazidime than cefotaxime or ceftriaxone. The first report of a TEM-type enzyme in South America was made by Paterson et al. in 2003, when they discovered a TEM-10 enzyme in bloodstream isolates of *K. pneumoniae* from Argentina [23]. TEM-10 and TEM-26 are among the most common TEM ESBLs in the USA and many European countries [20], and Jacoby and Muñoz-Price recently stated that they are also frequent in South America. However, there are marked geographical differences. In Colombia, TEM (and SHV) ESBLs are widely prevalent among *E. coli* and actually seldom found [21] in southern South America [24].

**SHV-type ESBLs**

SHV-type ESBLs are all derived from SHV-1 by point mutations, with more than 90 ESBL variants so far described (http://www.lahey.org/studies/). This family of ESBLs currently predominates in surveys of resistant isolates in South America [21,25–27]. The first reports of SHV-type enzymes in South America came from Argentina and Chile in 1988 and 1989, and concern SHV-2 and SHV-5 [21]. A *K. pneumoniae* isolate collected during a preclinical study of cefotaxime in Buenos Aires, and kept lyophilised since 1982, proved to be a producer of an SHV-5 enzyme when retrospectively tested, which proves that ESBLs were circulating long before they were recognised in South America, or elsewhere (J. M. Casellas, Abstracts of the International Congress of Chemotherapy, Birmingham, UK, 1999). Today, SHV-5 and SHV-12 are among the most common members of this family [28].

**CTX-M-type ESBLs**

In 1990, Bauernfeind et al., from München University, reported an *E. coli* clinical isolate obtained in East Germany that produced a non-SHV, non-TEM ESBL that hydrolysed cefotaxime but had only trace activity against ceftazidime. The enzyme was designated CTX-M-1, thus creating the ‘ceftaximase family’ (CTX-M family), which now comprises more than 60 enzymes [22,29]. These enzymes are increasingly more prevalent than the classic TEM- and SHV-type ESBLs [30].

Although the description of the first CTX-M enzymes came from Europe, South America was the first continent where they became prevalent [29]. It now appears that CTX-M enzymes had been widely distributed in South America from 1989 [4]. In that year, non-typhoidal *Salmonella* strains producing the CTX-M-2 enzyme began to spread from neonatal units, initially in La Plata and Buenos Aires, Argentina. From there, these enzymes spread to neighbouring South American countries, including Paraguay, Uruguay and Brazil [31]. By 1994, CTX-M-2 was being reported in *Klebsiella* isolates from Paraguay and *E. coli* and *P. mirabilis* isolates from Argentina [4]. Other bacteria known to harbour this enzyme in South America include *Shigella sonnei*, *Morgannella morganii*, *Citrobacter freundii*, *Serratia marcescens*, *Enterobacter aerogenes*, *Vibrio cholerae* and *Aeromonas hydrophyla* [4,21]. By 2002, CTX-M-2 was the enzyme present in c. 75% of ESBL-producing Enterobacteriaceae in Buenos Aires, making it clearly the predominant ESBL in the country [29,32]. CTX-M-31 (a variant of CTX-M-2) has also been reported from Argentina [8].

Other CTX-M enzymes, including CTX-M-8, CTX-M-9 and CTX-M-16, have been discovered in Enterobacteriaceae from Brazil since 1996 [33]. In Colombia, seven *K. pneumoniae* isolates, collected in 2004 from three hospitals, were positive for CTX-M-1-group enzymes, and CTX-M-12 was identified in one isolate [33]. This was the first report of CTX-M-12 outside of Kenya, where the enzyme was found in an outbreak among six newborn babies in 2001 [34]. Peru and Bolivia have reported CTX-M-2, CTX-M-14, CTX-M-15, CTX-M-24 and, recently, a new CTX-M variant, CTX-M-56 [30,35].

**Pseudomonas Extended Resistance-type ESBLs**

*Pseudomonas* Extended Resistance (PER) enzymes represent a distinct A ESBL class, presently restricted to South America, Asia and Europe [6,36,37]. These enzymes share low sequence
homology (25–27%) with TEM, SHV or CTX-M enzymes [37]. PER-type ESBLs are among the most efficient β-lactamases against broad-spectrum cephalosporins [36,37]. Two PER enzymes from very different geographical areas are known at present. PER-1 was first detected in Pseudomonas aeruginosa, Salmonella spp. and Acinetobacter spp. from Turkey [37], and PER-2 was first detected in an isolate of Salmonella enterica recovered by Casellas et al. in Buenos Aires [38,39]. Later on, PER-2 was detected in several Enterobacteriaceae, and even in Vibrio cholerae [40].

Unlike PER-1, PER-2 has never been reported in P. aeruginosa. It seems to be restricted to Argentina and bordering countries such as Chile, Paraguay and Uruguay [4]. In Argentina, PER-2 is the second most prevalent ESBL after CTX-M-2 [41].

Other ESBLs

Two novel non-TEM non-SHV ESBLs have been reported from South America: the ceftazidime-hydrolysing Guiana Extended-Spectrum-1, isolated from K. pneumoniae from an infant previously hospitalised in French Guiana [42], and Brazil Extended-Spectrum-1 (BES), from an S. marcescens isolate collected in Rio de Janeiro in 1997 [42]. BES-1 exhibits greater catalytic activity against ceftazidime and aztreonam than do CTX-M enzymes and was the first ESBL shown to exhibit selective resistance to tazobactam [27,28].

A NEW CHALLENGE: ESBLs IN COMMUNITY-ACQUIRED INFECTIONS

Most community-acquired ESBL producers in Latin America and in other developing countries are Salmonella and Shigella spp. isolates [43,44]. However, several reports of community-acquired E. coli and K. pneumoniae infection not related to nursing homes or hospitals have been published in the past several years. These reports come from Spain, France, Israel, the UK and Canada, and mostly concern strains with the CTX-M-class enzymes. In the last year, at least two or three community-acquired infections due to ESBL producers have been detected in Argentina (J. M. Casellas, unpublished data). A recent report from Brazil showed a 1.48% prevalence of ESBLs among enterobacterial isolates collected from urine samples in ambulatory patients between 2000 and 2002. TEM-type enzymes were identified in 95.4% of the isolates, with SHV types being found in most of the remainder, although seven strains produced CTX-M-type enzymes. Pulsed-field gel electrophoresis showed several identical genotypes, indicating a common source of acquisition [45]. Surveys of over 3000 healthy children from low-resource settings in Bolivia and Peru revealed an increase in faecal carriage of ESBL-producing E. coli from 0.1% in 2002 to 1.7% in 2005 [30]. Of 50 ESBL-producing isolates collected in 2005, 44 harboured a CTX-M-type enzyme and six had SHV-type enzymes.

REFERENCES


