A Latin American “Point de Vue” on the Epidemiology, Control, and Treatment Options of Infections Caused by Extended-spectrum Beta-lactamase Producers

José Maria Casellas and Mirta G. Quinteros

Abstract
Soon after the introduction of the third-generation cefalosporins (3GC) in the 1980s, plasmidic beta-lactamases derived from the so-called broad-spectrum beta-lactamases (BSBLs, which are able to hydrolyze first- and some second-generation cephalosporins, amino-, ureido- and carboxy-penicillins) such as TEM-1, SHV-1 and others, appeared and were shown to be capable of hydrolyzing monobactams, beta-lactam/beta-lactamase inhibitor combinations and in some instances fourth-generation cephalosporins (4GC) as well. These new enzymes were denominated extended-spectrum beta lactamases (ESBLs) and they are derived from BSBLs. Three ESBLs families are predominant: TEM-derived (Europe and the US); SHV-derived (worldwide), and CTX-M, which were first detected in Argentina and later on in Eastern Europe and are nowadays globally extended. While TEM-derived ESBLs hydrolyze preferentially ceftazidime, SHV-type hydrolyze both ceftazidime and cefotaxime; CTX-M preferentially hydrolyze cefotaxime and 4GC. ESBLs are frequently present in megaplasmids and carry several genes determining resistance to other antibiotics. Difficulties in screening for ESBLs lasted a decade and were due to the fact that NCCLS was reluctant to recommend phenotypic methods including cefotaxime, and also considered that investigation of ESBLs should only be performed in Escherichia coli and Klebsiella spp. isolates. Latin America is presently the region showing the higher incidence of ESBLs. Low income level and other social issues, crowded hospitals, prolonged hospital stay, as well as the increasing use of invasive devices are factors increasing the risk for ESBL-producer infections. Previous use of 3GC, 4GC, fluoroquinolones, and aminoglycosides are also important factors. Perhaps even high inocula in infections such as abscesses could also be responsible for the selection of ESBL-producing organisms causing difficulties in clinical treatments. ESBL producers are only uniformly susceptible, in human infections, to carbapenems and tigecycline.

Introduction
Many bacteria possess enzymatic mechanisms that allow them to inactivate different antibacterial drugs (i.e., aminoglycoside inactivating enzymes, chloramphenicol acetyltransferases, beta-lactamas (BLAs), etc.) Most of these enzymes are produced by the same bacterial species which synthesize the antibacterial compounds themselves. BLAs are the most common and widely distributed among an-
tibacterial inactivating enzymes. Although first discovered in a Gram-positive species (the staphylococcal penicillinases), BLAs constitute the major defense of Gram-negative bacteria against beta-lactam antibiotics (Jacoby and Muñoz-Price, 2005). Most BLAs are ancient enzymes, and it was soon observed that at least two of them have a separate heritage (Garau et al., 2004). One group is the so-called serine enzymes which have a serine residue at the active site, just as penicillin binding proteins (PBPs); it is supposed that these BLA probably evolved from the PBPs over the past 2 billion years (Medeiros, 1997). The other ancient BLA group are the metallo-enzymes which use a metallic ion, preferentially zinc, as a cofactor (Livermore, 1995).

After the introduction of beta-lactam antibiotics for clinical human and veterinary usage, new BLAs appeared in the late 1950s in common, clinically relevant Gram-negative bacilli such as Escherichia coli, Klebsiella spp. and other enteric bacteria (Livermore, 1995; Medeiros, 1997; Jacoby and Muñoz-Price, 2005). These enzymes hydrolyzed efficiently ampicillin and in some cases first-generation cephalosporins. Their hydrolytic spectrum was enlarged compared with those of penicillinases and were therefore denoted “broad-spectrum beta lactamases” (BSBLs) (Casellas and Goldberg, 1989; Livermore, 1995; Bush et al., 1995). Later on, in the 1970s, BSBLs spread to bacterial species that previously did not produce any BLA such as Haemophilus spp. and Neisseria gonorrhoeae. During the 1980s a plethora of new antibiotics were introduced, particularly new, “third-generation” cephalosporins (3GCs) having an extended spectrum and activity to treat infections caused by enteric bacteria (Enterobacter spp., Serratia spp., etc.) or non-fermentative Gram-negative bacilli (as Pseudomonas spp.). Soon after, BLAs capable of hydrolyzing 3GCs were discovered; they were named “extended-spectrum beta-lactamases” (ESBLs). The properties, origins, epidemiology, laboratory detection of ESBLs as well as recommendations for treating the infections to which they are associated are the topic of this review. Other BLAs, such as AmpC, or metallo-beta-lactamases will not be considered. The genotypic characterization of beta-lactamases by molecular methods are also out of the scope of this chapter.

Rationale of the classification of BLAs

Even dealing exclusively with ESBLs, a brief review of the classification of BLAs is mandatory in order to understand their origin and relation with other beta-lactamases. A list of all the different BLAs that have been described up to this date is an almost impossible task. A functional classification arrangement of BLAs has been provided by Bush et al. (1995). Hundreds of BLAs have been added to that arrangement and as the amino acid sequencing of BLAs is nowadays readily available, the list is increasing permanently. A website allows specialists to be aware about information related to the new BLAs (www.lahey.org/studies/wbt.stm), particularly their amino acid sequences. Fortunately, a simpler and rational classification is available due to Ambler et al. (1992); it is called “molecular classification” since it is based on the molecular weight of the BLA and the amino acid residue present at the active site. Based on Ambler’s scheme and including the inhibitory activity of clavulanic acid, Jacoby and Muñoz-Price (2005) published recently a simple classification using the “familiar names” used by infectious diseases physicians as well as clinical microbiologists. We added here the common codification site of the enzymes (plas-
### Table 5.1 Beta-lactamases from Gram-negative bacteria

<table>
<thead>
<tr>
<th>Type of beta lactamases</th>
<th>Examples</th>
<th>Plasmidic (P) or chromosomal (C)</th>
<th>Resistance traits</th>
<th>Inhibition by clavulanate</th>
<th>Ambler class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Broad spectrum</strong></td>
<td><em>TEM 1; TEM2</em></td>
<td>P</td>
<td>Aminopenicillins, carboxypenicillins, ureidopenicillins, 1GC, 2GC</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>*SHV-1</td>
<td>P or C</td>
<td></td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>*OXA family</td>
<td>P</td>
<td></td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td><strong>Extended spectrum</strong></td>
<td>*TEM family</td>
<td>P</td>
<td>Same as BSBLs + 3GC and aztreonam</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>*SHV family</td>
<td>P</td>
<td></td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>*CTX-M family</td>
<td>P</td>
<td>Same plus cefepime (for most enzymes)</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>*Other†</td>
<td>P</td>
<td>Same as SHV and TEM family</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>*OXA family</td>
<td>P</td>
<td>Same as CTX-M</td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td><strong>amp C</strong></td>
<td>*Chromosomal amp C from <em>Enterobacter</em> spp., <em>Serratia</em> spp., <em>Citrobacter freundii</em>, etc.</td>
<td>C</td>
<td>1GC, 2GC, cephemycins. When derepressed C3G and aztreonam</td>
<td>No</td>
<td>C</td>
</tr>
<tr>
<td><strong>Plasmidic amp C</strong></td>
<td>*ACC-1; ACT-1; CFE-1; CMY family; DHA1–2; FOX family LAT family; MIR-1; MOX family</td>
<td>P</td>
<td>Same substrates as for ESBLs plus cephemycins</td>
<td>No</td>
<td>C</td>
</tr>
<tr>
<td><strong>Carbapenemases</strong></td>
<td>*IMP family; ViM family; GIM family; SPM-1 *KPC family *OXA family</td>
<td>P or C</td>
<td>Same substrates as for ESBLs plus cephemycins and carbapenems</td>
<td>No</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>*OXA family</td>
<td>P</td>
<td></td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td></td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td><strong>Inhibitor resistant (IRBL)</strong></td>
<td>*Variants of TEM or SHV</td>
<td></td>
<td>Same substrates as for BSBL but not affected by inhibitors</td>
<td>–</td>
<td>A</td>
</tr>
</tbody>
</table>

†BES-GES family; PER family; SFO-VEB family; TLA-1.
midic or chromosomic) and characteristic resistance traits (Table 5.1).

Origin and general properties of ESBLs

BLAs cleave the amide bond of the beta-lactam ring. Consequently, beta-lactams are not more able to bind to PBPs and can not block the synthesis of the cell wall, thus rendering beta-lactams harmless to bacteria. BSBLs are able to open the amide bond of penicillin, aminopenicillins and also, but not generally, of first-generation cephalosporins, carboxypenicillins, and ureidopenicillins. BLA inhibitors such as clavulanate, sulbactam or tazobactam are capable of preventing the activity of BSBLs by binding irreversibly to these enzymes. The structure of oxyminocephalosporins (3GCs), such as ceftazidime, cefotaxime, ceftriaxone and ceftizoxime, as well as monobactams, does not allow them to access BSBLs’ active site in a position that permits the enzyme’s serine and a water molecule to provoke the hydrolysis of the beta-lactam amide bond. However, if a positional change of the serine responsible for the cleavage of the cephalosporin amide bond occurs, then hydrolysis of the 3GC is possible. This was observed for the first time in 1983 at Prahmmod Shah’s laboratory at Frankfurt (Knothe et al., 1983). That enzyme was further studied in 1985 and proved to be derived from a BSBL, SHV-1, and named SHV-2 (Kliebe et al., 1985). The serine at position 238 in SHV-1 was found to be replaced by glycine in SHV-2, and that was found to be the cause of the enhanced activity against 3GCs (in fact, this reportedly first ESBL isolate was not really the first one: on 1981, in the laboratory of one of us (JMC) at Buenos Aires, we were participating in a study aimed to use amikacin as the sole aminoglycoside at the “Hospital del Docente” looking to reduce gentamicin resistance. Simultaneously, cefotaxime was being used in phase-III trials. One K. pneumoniae isolate resistant to amikacin proved to be resistant to cefotaxime as well, and resistance to both antibiotics showed to be transferable. That ESBL was later described as an SHV-5 ESBL (Casellas and Goldberg 1989; Casellas et al., 1990; Casellas, 1999; Paterson and Bonomo, 2005). Amikacin resistance was due to APH-3′ and AAC-6′ enzymes (G. Miller, unpublished data) that were encoded in the same megaplasmid, along with the SHV-5 gene).

With the exception of a few ESBLs of the OXA family which appertain to the Ambler class D, that are weakly inhibited by clavulanate, all other ESBLs belong to the Ambler class A and are strongly inhibited by clavulanate. They belong to the 2e group of the Bush et al. (1995) BLA classification, which includes plasmid-mediated enzymes. They can be classified on the basis of their hydrolytic activity against ceftazidime (ceftazidimases) or cefotaxime/ceftriaxone (cefotaximases), which in turn relates to the tertiary structure of the enzyme (Huang et al., 1996). Nonetheless, class A BLAs are a very heterogeneous molecular group, sharing a wide range of sequence identity (20 to 99%; Jacoby, 1994). ESBLs are widely distributed in a variety of Enterobacteriaceae, even among AmpC producers, as well as in non-fermentative Gram-negative bacilli, Vibrio spp. (Petroni et al., 2002), Aeromonas spp. (Quinteros et al., 2000), Capnocytophaga spp., etc. (Bradford, 2001).

ESBLs are frequently encoded by large, multicopy plasmids; the presence of highly active promoters is also common. In some circumstances, as in the case of K. pneumoniae isolates, decreased expression of outer membrane porins along with ESBL production, confer resistance to an-
tibiotics such as cefepime, which are not greatly affected by TEM- or SHV-derived ESBLs (Jacoby, 1994, Jacoby and Muñoz-Price, 2005, Bradford, 2001). The genes encoding ESBLs may also be located in the chromosome and may be carried by transposons (Jacoby, 1994), and other ESBL genes, as those encoding CTX-M enzymes, are often found in integrons (Jacoby and Muñoz-Price, 2005, Bradford, 2001).

**ESBL definition**

ESBLs are BLA enzymes able to hydrolyze penicillins, cephalosporins—in some cases including fourth-generation ones (4GC) such as cefepime or cefpirome—and monobactams. They are not able to hydrolyze cephemycins (e.g., cefoxitin, cefotetan) nor carbapenems. ESBLs characteristically hydrolyze 3GCs and monobactams and, in some cases, 4GCs, at rates that are at least 10% of that for benzylpenicillin. They are inhibited by clavulanate, thus distinguishing them from AmpC (group 1) BLAs produced by *Enterobacter cloacae*, *E. aerogenes*, *Citrobacter freundii* and *Serratia marcescens* (Bush et al., 1995) although it must be considered that some AmpC producers can harbor plasmids codifying for ESBLs as well.

**Different ESBL families**

**TEM-type ESBLs**

TEM-1 has been the most frequently encountered ESBL since its first report in 1965. The enzyme was found to be codified by a plasmid of an *Escherichia coli* clinical isolate resistant to ampicillin, sent from Athens, Greece, to Naomi Datta’s laboratory at London. The name of the patient was Temoniera, therefore the designation as TEM-1 (Datta and Kontomichelou, 1965; Paterson and Bonomo, 2005). At least 90% of *E. coli* isolates resistant to penicillins harbor this pI 5.4 enzyme. TEM-2 (pI 5.6) is very similar to TEM-1 but is less frequent. It is not surprising that single amino acid changes in both TEM-1 and TEM-2 BSBLs were the origin of the most frequent ESBLs found in Europe and the USA (Jacoby and Muñoz-Price, 2005) (an entirely different origin for TEM and SHV ESBLs is also briefly discussed in Chapter 7). TEM enzymes comprises nearly 140 different ESBLs (see website, above). One of the reasons for the expanded distribution of TEM ESBLs is that they seem to emerge quite easily by point mutations, as they are also easily created in the laboratory (Jacoby, 1994; Jacoby and Muñoz-Price, 2005). Modifications of the active site of the TEM enzymes facilitate access to oxymino-beta-lactams, as has been proved by crystallographic studies (Knox, 1995; Jacoby and Muñoz-Price, 2005). There are two TEM-ESBL families, one derived from TEM-1 and other derived from TEM-2.

Most of the TEM-derived ESBLs are more active against ceftazidime than against cefotaxime or ceftriaxone. Unfortunately, up to 1998, the National Committee for Clinical Laboratory Standards (NCCLS, now Clinical Laboratory Standards Institute, CLSI) recommended that the laboratory test for detecting ESBLs in the USA should be performed using ceftazidime as substrate; that is why many isolates producing cefotaximase ESBLs (CTX-family and some TEM-derived) were probably not detected (Jacoby 1994; Rossi et al., 1995; Bradford, 2001; Casellas et al., 2003; Quinteros et al., 2003; Paterson et al., 2003; Bonnet, 2004; Paterson and Bonomo, 2005). TEM-10 and TEM-26 are among the most common TEM-ESBLs in the USA and many European countries (Jacoby and Muñoz-Price, 2005). Jacoby and Muñoz-Price (2005)
recently stated that they are also frequent in South America. However, TEM derivatives are actually seldom found in South America (Casellas et al., 2003; Quinteros et al., 2003): a paper from Paterson et al. (2003) was cited by Jacoby addressing this point; Paterson et al. found TEM-10 and TEM-12 ESBLs in two isolates that one of us (J.M.C.) sent to them. When we read the paper we looked at the patients’ clinical history and found that both were recent flyers from Miami where both were hospitalized for 2–5 days. We still think that, whatever the reason, TEM-ESBL enzymes are uncommon in southern South America while frequent in the USA.

SHV-type ESBLs
As previously mentioned, SHV-type enzymes were the first discovered ESBLs (Knothe et al., 1983) and SHV-1 is the parental BSBL common in Klebsiella pneumoniae isolates. The enzyme was originally chromosomal but it has been presently found in plasmids (Jacoby and Muñoz-Price, 2005). SHV family ESBLs producers are all derived from SHV-1, by point mutations (one or two changed amino acids). SHV-5 and SHV-12 are prevalent in the USA while SHV-2 and SHV-5 are prevalent in Europe and Latin America (Casellas, 1999; Bradford, 2001; Casellas et al., 2003; Quinteros et al., 2003; Paterson et al., 2003; Jacoby and Muñoz-Price, 2005). More than 50 SHV ESBLs variants have been described so far (http://www.lahey.org/studies/webr.htm). Recently, outbreaks of SHV-producing Acinetobacter spp. and Pseudomonas aeruginosa isolates have been reported (Poirel et al., 2004; Paterson and Bonomo, 2005).

CTX-M type ESBLs
In the late 1980s, two reports of non-SHV, non-TEM ESBLs were published. In Japan, in 1986, a new ESBL was discovered and designated as FEC-1 (Bonnet, 2004), in a cefotaxime-resistant E. coli. However, the isolate was not obtained from human clinical specimens but instead from the feces of a laboratory animal, and the report was mostly ignored, although mentioned in the very complete review of the CTX-M family by Bonnet (2004). In 1990, Bauernfeind et al. (1992), from Munich University, reported an E. coli clinical isolate obtained in East Germany which produced a non-SHV, non-TEM ESBL which hydrolyzed cefotaxime but not ceftazidime, therefore the enzyme was denominated CTX-M-1 thus creating the “cefotaximase family” (CTX-M family).

During the period 1990–92 numerous reports were presented in Argentina quoting outbreaks due to invasive Salmonella enterica var. Typhimurium producing sepsis and meningitis, particularly in children (Casellas et al., 1990; Rossi et al., 1995). An isolate recovered in our laboratory (J.M.C.), showing a typical ESBL phenotype, was highly resistant to cefotaxime (MIC > 64 mg/L), but notably susceptible to ceftazidime (MIC 0.5 mg/L). The strain was inhibited by clavulanate and the pI of the enzyme was alkaline (8.2). The isolate was sent to A. Bauernfeind, who sequenced the encoding gene and proved it related to CTX M-1 and therefore was named as CTX M-2 (Bauernfeind, 1992; Casellas, 1999). The plasmid codifying CTX M-2 thereafter spread to other non-typhoid Salmonella, and Klebsiella (Casellas, 1999; Paterson et al., 2003; Bonnet, 2004). By now, CTX M-2 is by far the prevalent ESBL in Argentina (Radice et al., 2002; Casellas et al., 2003; Quinteros et al., 2003; Paterson et al., 2003; Rodriguez et al., 2005). By 1992, CTX M-2 producers accounted for up to 20–30% of Klebsiella pneumoniae cephalosporin resistance in
Argentina (Bradford, 2001; Radice et al., 2002; Quinteros et al., 2003; Rodríguez et al., 2005) and in 2005 up to 40%, 25% *E. coli*, 20% *P. mirabilis* and many other Enterobacteriaceae including AmpC producers. Most Salmonella spp. and Shigella spp. isolates that are ESBL producers, express CTX M-2 type enzymes (Radice et al., 2002; Quinteros et al., 2003; Rodríguez et al., 2005).

After isolating the first CTX-M ESBL producers in Argentina and East Europe, and as the existence of these plasmid enzymes with high plas was known, NCCLS decided to suggest that the phenotypic assay with clavulanate for ESBLs presumptive detection should be performed not only with ceftazidime but also with cefotaxime. Consequently, cefotaximase detection increased and CTX-M enzymes begun to be considered not so exotic ESBLs and were referenced globally later on (Bonnet et al., 2004; Paterson and Bonomo, 2005). CTX-M BLAs are by now exceeding 40 different types, and can be classified into five clusters based on their amino acid sequence relations (Bradford, 2001; Bonnet, 2004; Jacoby and Muñoz-Price 2005):

- group 1: CTX-M-1 cluster including plasmid-mediated CTX-M-1, 3, 10, 12, 15, 22, 23, 28, 30 and FEC-1;
- group 2: CTX-M-2 cluster including plasmid-mediated CTX-M-2, 4, 5, 6, 7, 20 and TOHO-1;
- group 3: CTX-M-8 group which includes plasmid-mediated CTX-M-8 alone;
- group 4: CTX-M-9 group including plasmid-mediated CTX-M-9, 13, 14, 16, 17, 19, 21, 27 and TOHO-2

CTX-M enzymes are derived from the mobilization of chromosomal enzymes of infrequently isolated species of Enterobacteriaceae of the genera *Kluyvera* to plasmids of other genera. The group of *Kluyvera* BLAs are designed KLU: KLU A from *K. ascorbata* (Oliver et al., 2001; Humeniuk et al., 2002; Poirel et al., 2002; Bonnet, 2004); KLU C from *K. georgiana* (Poirel et al., 2002); KLU C from *K. cryo-crescens* (Decousser et al., 2001). It has been shown that chromosomal KLU A found in CTX-M-3 is the possible origin of the first CTX-M enzyme that is CTX-M-1 (Bonnet, 2004). The homology between KLU G-1 and CTX-M-8 is remarkable since they share 99% amino acid identity. Of note, CTX-M enzymes share no more than 40% identity with TEM or SHV ESBLs (Paterson and Bonomo, 2005).

Strains expressing CTX-M type BLA, in addition to the general feature of their more rapid hydrolysis of cefotaxime and ceftriaxone, are better inhibited by tazobactam than by sulbactam or clavulanate (Bradford, 2001; Casellas et al., 2003; Quinteros et al., 2003; Bonnet, 2004; Paterson and Bonomo, 2005), which may explain the higher sensitivity of some CTX-M producers to piperacillin–tazobactam than to ceftazidime (Tzouvelekis et al., 2000; Yu et al., 2002; Casellas et al., 2003; Quinteros et al. 2003; Paterson et al., 2003).

CTX-M encoding genes have commonly been located on plasmids with varying sizes (7 to 160 kb). CTX-M-2, the most frequent in South America is generally encoded in megaplasmids (Bonnet, 2004; Jacoby and Muñoz-Price, 2005; Paterson and Bonomo, 2005). These plasmids carry genes for resistance to multiple other antibiotics including aminoglycosides, chloramphenicol, trimethoprim, sulfonamides...
and tetracyclines, and the clinical use of these antimicrobials can select for enterobacterial CTX-M producers (Casellas et al., 2003; Paterson et al., 2003; Paterson and Bonomo, 2005). CTX-M plasmids are frequently transmissible by conjugation in vitro, a fact that could explain the rapid dissemination of CTX-M harboring plasmids. In CTX-M-2, a class 1 integron located in a conjugative plasmid of Salmonella enterica serovar Typhimurium has been detected (Radice et al., 2002).

PER type ESBLs

PER enzymes share low homology (25–27%) with TEM, SHV, or CTX-M enzymes (Nordman et al., 1994; Bauernfeind et al., 1996; Paterson and Bonomo, 2005). These enzymes hydrolyze penicillins and cephalosporins and are inhibited by clavulanate (Bauernfeind et al., 1996). They efficiently hydrolyze cefotaxime and ceftriaxone as well as ceftazidime. Two PER enzymes are known at present from very different geographic areas. PER-1 was first detected in P. aeruginosa, Salmonella spp., and Acinetobacter spp. from Turkey (Nordman et al., 1994; Bauernfeind et al., 1996; Vahaboglu et al., 2001). PER-1 appears to be endemic in Turkey since as many as 11% of P. aeruginosa isolates were found to produce PER-1 in this country (Vahaboglu et al., 1995, 1998).

PER-2 was first detected from an isolate of S. enterica recovered in our laboratory (J.M.C.) at Buenos Aires (Bauernfeind et al., 1996). Later it was detected from several Enterobacteriaceae and even from Vibrio cholerae El Tor (Rossi et al., 1995; Petroni et al., 2002). PER-2 shows 86% homology with PER-1 (Vahaboglu et al., 1998; Bonnet, 2004; Paterson and Bonomo, 2005) but seems to be restricted to Argentina and border countries such as Chile, Paraguay, and Uruguay. We received isolates from Chile (from J. Labarca and J. Quinn) and Paraguay (from J.M. Casellas and J.M. Casellas Jr.) which were confirmed as PER-2 (M. Quinteros and J.M. Casellas, unpublished). PER-2-producing enteropathogenic E. coli were detected in isolates from Uruguay (Rodríguez et al., 2005) Interestingly and conversely with isolates harboring PER-1 enzymes, P. aeruginosa producing PER-2 have never been detected to our knowledge.

While PER-1 has expanded to countries distant from Turkey, such as France, Italy, Belgium and Korea (Paterson and Bonomo, 2005), PER-2 seems restricted to the southern cone of South America. CTX-M producers are frequently present in plasmids of typical Amp C producers. This has been observed for more than 20 years in Argentina (Quinteros et al., 2003).

Other ESBLs

A huge number of other ESBLs have been recently discovered particularly in Asia but they are still infrequent at the moment. They include VEB, GES, BES, TLA, SFO, and IBC (Poirel et al., 1999; Paterson and Bonomo, 2005). We will not consider these ESBLs in the present review.

Epidemiology and geographic distributions of ESBLs

As mentioned previously, the first reports of ESBLs came from Europe. French investigators were particularly concerned with studying the clinical epidemiology and spread of ESBLs. Several reports from that country, especially by Brun-Buisson et al. (1987, 1989) describe outbreaks in different intensive care units. The number of patients infected and the rate of dissemination to different units and cities that occurred in the late 1980s was impressive.
Probably the same problem occurred in other countries as the USA but unfortunately the low interest in the detection of ESBLs in that country at that moment accounted for the huge differences in the incidence of ESBLs isolates between France and the USA.

Undoubtedly, the spread of infections due to ESBLs producers is higher in countries with lower economic resources. This is very clear when comparing incidence data from Sweden (3%) with those from Greece, Turkey or Portugal (> 25%) (Ilanberge et al., 1992; Paterson and Bonomo, 2005) or South America (> 30%) (Casellas, 1999; Quinteros et al., 2003). Notably, a survey from Turkey related to the incidence of Klebsiella spp. from intensive care units revealed that 58% of 193 isolates harbored ESBLs (Paterson and Bonomo, 2005).

As stated, few clinicians were interested in ESBLs in the USA. However, investigators such as Bush, Bradford, Medeiros, Jacoby, Paterson, Yu, Sanders, Thomson, Quinn, Peterson, Rahal and others described outbreaks and set an alert about the spread of ESBLs in the USA (Quinn et al., 1989; Thomson and Sanders, 1992; Medeiros, 1997; Bush et al., 1995; Rahal et al., 1998; Bradford, 2001; Paterson et al., 2003; Paterson and Bonomo, 2005). At the moment CTX-M type ESBLs have been described in the USA and Canada and by no doubts these enzymes will further spread (Casellas, 1999; Paterson and Bonomo, 2005).

The most impressive increase in ESBL infections, as well as detection of new enzymes, occurs in South America and Asia, particularly from China (Chang et al., 2001). Among K. pneumoniae Chinese isolates, 25–38% proved to be ESBLs producers, particularly of SHV group enzymes. Similar problems appear now in Korea. It is difficult to estimate how big is the ESBLs distribution in Asia since data from many crowded countries with low economic resources are missing (India, Thailand, Iraq, Iran, Mongolia) and, coincidentally, the imprudent use of antibacterial drugs in those countries appears to be the rule. As an example, CTX-M enzymes are by now spreading in Japan, India, China, Taiwan, and Korea (Cheng et al., 1994; Karim et al., 2001; Komatsu et al., 2001; Pai et al., 2001; Bell et al., 2002; Du et al., 2002; Yu et al., 2002; Wang et al., 2003). This seems coincident with the increasing use of generic ceftriaxone as happened in South America and East Europe (Casellas, 1999). In Australia the incidence of ESBLs is less than 5% and most of them belong to the SHV family (Paterson and Bonomo, 2005).

The problem in Latin America

Probably the highest incidence of infections due to ESBL-producing organisms is found in Latin America. Several reasons account for that, in addition to the poor social and economic conditions, and the high incidence of malnutrition, particularly among children: (1) crowded hospitals with frequently high patient/nurse ratios; (2) infrequent surveillance of antibiotic use; (3) self-prescription of antibiotics, as these drugs are sold over the counter in the whole region (except for Chile, Costa Rica, Cuba and, very recently, Venezuela); (4) deficient hospital hygiene, resulting in a high rate of Klebsiella spp. infections as well as colonization. This last one is a very important issue, as Klebsiella has the particular ability to acquire plasmids determining ESBL production. ESBL have been found in 30–60% of Klebsiella isolates from intensive care units in Argentina, Brazil, Colombia, and Venezuela (Casellas and Goldberg, 1989; Casellas et al., 1990;
As stated before, the first ESBLs detected in Latin America were SHV types, in Chile and Argentina (Guzmán Blanco et al., 2000; Bonnet et al., 2000a). No TEM ESBLs were first reported in humans in Argentina (Bauernfeind et al., 1992). Presently, CTX-M ESBLs are widely distributed in South American countries. PER-2 is restricted to the south cone of South America and particularly in Argentina (Rossi et al., 1995; Quinteros et al., 2003; Bonnet, 2004). Other CTX-M types (CTX-M-8, CTX-M-9, and CTX-M-16) have been detected in Brazil (Guzmán Blanco et al., 2000; Bonnet et al., 2000a, 2001; Poirel et al., 2000; Pessoa-Silva et al., 2004). Two non-TEM, non-SHV, non-CTX-M ESBLs have been recently reported from South America: GES-1 from Guiana (Mendes et al., 2000) and BES-1 from Brazil (Bonnet et al., 2000b). There are now more methods of assessing ESBL types and collaborative studies between Latin American laboratories are increasing, which means that laboratories are no longer dependent on sending isolates to Europe or the USA, as in the past (Pfaller et al 1999a,b; Diekema et al., 1999; Sader et al., 2000a,b; Otman et al., 2002). ESBLs have been reported also from Mexico, Central America and Caribbean countries (González Vértiz et al., 2001; Chernian et al., 1999; Otman et al., 2002). However, the genotype of the isolates has not frequently been determined.

**Methods utilized for the detection of ESBLs**

**Screening tests and phenotypic procedures**

Detection of ESBLs is not routinely performed in many countries and even in the USA and Europe not more than half of the clinical laboratories perform tests to detect ESBL production by Enterobacteriaceae (Casellas et al., 2003; Jacoby and Muñoz-Price, 2005; Paterson and Bonomo, 2005). Moreover, ESBL producers are frequently reported as cefotaxime-susceptible, as was observed by Babbini and Livermore (2000) in a survey of *Klebsiella* spp. isolates collected from intensive care units in Southern and Western Europe.

Difficulties in screening for ESBLs are mostly due to the huge differences in breakpoints for cefotaxime, ceftazidime and aztreonam among different countries. As an example, susceptibility to cefotaxime varies from ≤ 1 mg/L in Spain, to ≤ 8 mg/L in the USA. The CLSI breakpoints for both cephalosporins and aztreonam were established in the early 80s prior to the discovery of ESBLs, and unfortunately these breakpoints were never changed. As pointed out by Paterson *et al.* (2001) at that time, the clinical success against infections due to enteric bacteria with MICs of ≤ 8 mg/L was > 95%. The Argentinean Society for Clinical Bacteriology (SADEBAC) proposed, as early as 1998, a breakpoint of ≤ 2 mg/L for cefotaxime and ceftazidime as well as the equivalent diffusion breakpoints and suggested that isolates with MICs ≥ 2 mg/L for these cephalosporins should be assayed for ESBL production.

**Screening tests**

CLSI proposed both disk diffusion and dilution methods in order to screen for ESBL production by *Klebsiella* spp. and *Escherichia coli*. In 2005, *Proteus mirabilis* was added to the group. For that purpose cefpodoxime, ceftazidime, cefotaxime or ceftriaxone, and aztreonam are used. Unfortunately, CLSI suggestions have several pitfalls from our point of view:
1. As suggested, any one of the aforementioned antibacterial drugs is equally useful for screening purposes; this is not the SADEBAC’s opinion: as mentioned by Paterson and Bonomo (2005), more than one (we would say at least three) of these antimicrobials should be used.

2. Moreover, we think that the use of cefepime is important since it is an excellent detector of most CTX-M ESBLs in AmpC producers.

3. Disks containing 10 µg of cefpodoxime have been recommended (Thomson and Sanders, 1992); however, a break point of ≤22 mm lacks specificity (Tenover et al., 2003), and CLSI is now recommending a break point ≤17 mm.

4. CLSI is reluctant to admit that Salmonella spp., Shigella spp. or other class A beta-lactamase producers should always be monitored for ESBL production; this is particularly important in countries where Salmonella spp. and Shigella spp. are endemic, as in Latin American countries; CTX-M enzymes started most of their endemic distribution from Salmonella spp. infections (Casellas, 1999).

5. The cefpodoxime dilution screening test should use a breakpoint of ≥8 mg/L since most TEM-1 E. coli hyperproducers are resistant to 2 or 4 mg/L.

6. It must be considered that many possibilities do exist for obtaining an MIC result of ≥2 mg/L for cefotaxime, ceftriaxone or ceftazidime which are unrelated to ESBL production, as happens with hyperproduction of TEM-1 or SHV-1 or a combination of these with permeability or efflux related resistance; therefore, it must be kept in mind that the CLSI recommended screening tests are not confirmatory of ESBL production.

Presumptive phenotypic tests for ESBL production

In our understanding, there is no specific phenotypic confirmatory test for the detection of ESBL production. Phenotypic methods can in most instances bring a very high suspicion of the presence of an ESBL enzyme in a bacterial isolate, but genotypic methods often prove that the phenotype-based suspicion is wrong. Probably the best and simpler phenotypic assay for the presumptive detection of ESBLs is the Jarlier test (Jarlier et al., 1998) which is based in the observation, by Masuda et al. (1976) of the phenomena of enhanced zones when clavulanate disks are close to cefotaxime disks, due to the inhibitory activity of clavulanate against most ESBLs. The simplest test is, in our opinion, the diffusion method placing a disk of clavulanate close (20 mm edge to edge) to cefotaxime, ceftriaxone, ceftazidime, cefepime and aztreonam disks. However, technical problems such as the adequate distance between disks are troublesome. Another method is based in comparing zones obtained with cefotaxime or ceftazidime 30 µg disks with similar disks soaked with 10 µg lithium clavulanate. This method was proposed by Casellas and Goldberg (1989): a difference of ≥4–5 mm for zones obtained with clavulanate combined disks as compared with zones of cephalosporins alone is considered as a phenotypic presumption of ESBL production (Casellas et al., 2000).

Our experience with broth microdilution assays by automated methods is unfortunate, since we observed failures due to TEM-1 or SHV-1 hyperproduction, as well as K. oxytoca K-1 hyperproduc-
tion, in strains lacking ESBLs as assessed by genotypic methods. Failures with these methods can be as high as 13% (Casellas et al., 2000; Paterson and Bonomo, 2005). Conversely, we agree with Helfand and Bonomo (2005) that the most effective method to suggest the presence of ESBLs phenotypically, is the E-test, given its simplicity and reliability. Unfortunately, AB Biodisk requires the purchase of 100 strips for each antimicrobial drug, which is generally unaffordable for most Latin American laboratories.

Is it important to detect ESBLs production or is the MIC the only important data for the choice of antibacterial treatment?
Enterobacterial ESBL producers show MIC values frequently high for 3GC, 4GC or aztreonam. The failure rate if patients infected with ESBL producers are treated with these drugs is high, near 100% in most cases (Meyer et al., 1993; Schiappa et al., 1996; Pai et al., 2001; Gupta et al., 2003; Paterson et al., 2004). Moreover, failures have also been observed when using 3GC or even 4GC to treat serious infections due to ESBL producers which MICs are in the “intermediate” or even in the higher end of the susceptible range (Jett et al., 1995; Medeiros and Crellin, 1997; Rice et al., 1991; Paterson et al., 2001). Nevertheless other investigators understood that if the MICs are sufficiently low (i.e., \( \leq 1 \) mg/L for cefotaxime or ceftriaxone, or \( \leq 4 \) mg/L for cefepime) 3GC as well as 4GC could be used safely (W. Craig, Colombian Congress for Infectious Diseases, 2005). However, the critical question is about the routine phenotypic detection of ESBLs: Do the mechanisms of resistance not really matter, and the efforts for detecting ESBLs in the clinical laboratories must be reduced? It must be considered that the benefits of determining MICs results rather than ESBLs detection has been showed in the murine thigh infection model, but not in humans (Andes and Craig, 2005).

The most controversial issue is the clinical relevance of the inoculum effect. In vitro, cephalosporins MICs increase as the inoculum also increases. This has been observed with different ESBLs producers (Rice et al., 1991; Jett et al., 1995; Medeiros and Crellin, 1997; Casellas et al., 2003; Song et al., 2005). The differences in MICs values for different inocula can be impressive. For example, a K. pneumoniae strain producing a TEM-26 ESBL showed a MIC of 0.25 mg/L at an inoculum of \( 10^6 \) CFU/mL, which rose to 64 mg/L when using an inoculum of \( 10^7 \) CFU/mL (Queenan et al., 1996). These differences are both dependent on the type of BLA and the drug. We showed differences as much of 4–6 dilutions in MICs against K. pneumoniae CTX-M-2 producers when, tested against cefepime comparing \( 10^6 \) to \( 10^8 \) CFU/mL inocula. We must consider that serious deep infections (e.g., intrabdominal, meningitis, lower respiratory tract) occurred with bacterial viable populations of \( 10^8 \) CFU. We believe that prescribing ceftriaxone or cefotaxime when MICs are borderline, represents a high risk for treatment failure as these antibiotics do not always show optimal tissue penetration (Paterson and Bonomo, 2005). Quennan et al. (1996) showed that when performing microdilution tests with ESBL producers lowering the inocula 0.5 log resulted in false negative results. The arguments of Craig et al. (2004), suggesting that the inoculum effect is “an artifact rather than a fact” since it is related to the length of incubation in vitro for MICs or
time killing curves determinations are not quite convincing to us.

However, the most important argument in favor of continuous efforts in detecting ESBLs in human and veterinary medicine is, as stated by Paterson and Bonomo (2005) that the simple report of an MIC can not warn of an outbreak due to ESBLs producing organisms and the corresponding need for appropriate infection control interventions. We recently detected an outbreak in our institution by two clones of $K.\ pneumoniae$ which included more than 30 isolates and affected 15 patients (Casellas et al., 2005). Detection was possible by ESBL phenotypic assay, but not always by the 3GC MICs.

**Treatment and outcome of infections due to ESBLs producers**

There are no significant differences in mortality when comparing patients colonized or infected with ESBLs (De Champs et al., 1989, 1991; Piroth et al., 1998; Lautenbach et al., 2001; Gupta et al., 2003; Paterson et al., 2004). However, it must be considered that mortality is higher in bacteremic patients (Schiappa et al., 1996) as we also showed in a recent outbreak at our institution (Casellas et al., 2005). Mortality is obviously higher among patients who did not receive adequate antibiotic therapy.

As ESBLs are able to hydrolyze all available beta-lactam antibiotics, except for carbapenems and cephemycins, no beta-lactam drug other than carbapenems should be used even if it appears effective by sensitivity tests. Cephemycins must not be used in the treatment of infections caused by ESBL-producing organisms (Pangon et al., 1989; González Leiza et al., 1994; Bradford et al., 1997; Siu et al., 1999; Bradford, 2001; Casellas et al., 2003; Paterson and Bonomo, 2005). If not accompanied by an AmpC enzyme, ESBL-producing isolates of $Klebsiella$ spp., $E.\ coli$, $Proteus\ mirabilis$, salmonellae, etc. always appears susceptible to cephemycins; however, we observed failures of cefoxitin treatments against ESBL producer infections. In one case, this was due to the in vivo acquisition of a plasmid-mediated AmpC by the etiological $K.\ pneumoniae$, which also lead to the discovery of a FOX-1 BLA (González Leiza et al., 1994). In other occasions, resistance rapidly occurred due to the selection of permeability mutants (Paterson and Bonomo, 2005). We do not recommend the use of cephemycins against infections caused by ESBL producers, even if susceptibility is documented.

Another important point is that several resistance mechanisms can be found simultaneously in a single ESBL-producing isolate, such as other chromosome- or plasmid-mediated BLAs (AmpC, TEM-1, SHV-1 or metallo-beta-lactamases), as well as efflux pumps, permeability or PBP alterations. It must be also considered that $Klebsiella$ spp. often bear megaplasmids that mediate different drug resistance mechanisms. So, infections by ESBL producers can not be treated empirically with aminoglycosides, chloramphenicol, tetracyclines, trimethoprim, etc., which resistance determinants are commonly linked to ESBL genes. Resistance to fluoroquinolones is also important, particularly among CTX-M producers (Casellas et al., 2003; Bonnet, 2004; Paterson and Bonomo, 2005). Colistin and polymixin B are very active against $Klebsiella$ spp. and $E.\ coli$ but not against $Proteus$ spp. and importantly many infections caused by ESBL producers are located in the lower respiratory tract where colistin is not particularly effective (Casellas, 2004; Falagas and Kasiakou, 2005).
ESBL producers can be considered typically as multi-resistant bacteria; *K. pneumoniae* isolates are 12 times more likely to be multi-resistant as compared to *E. coli* isolates. This is important since 19 to 35% *K. pneumoniae* are ESBL producers (Bradford, 2001; Casellas et al., 2003; Jacoby and Muñoz-Price, 2005; Helfand and Bonomo, 2005; Livermore and Hawkey, 2005). Another cause of concern is the observation that hypermutable *E. coli* strains were found more frequently found among ESBL producers than in nonproducers (Baquero et al., 2005).

Considering results of phase III trials, the new drug tigecycline should be useful for the treatment of serious ESBL infections. We have tested 50 ESBL producers and were susceptible to tigecycline with very low MIC values (< 1 mg/L). However, care must be taken in the use of this new drug in intensive care units, since it is not active against *P. aeruginosa*.

**Risk factors for ESBL acquisition: colonization and infection**

It is very important to differentiate colonization from infection by ESBLs-producing bacteria. Data coming from bacteriological laboratories must be carefully analyzed by Infectious Diseases specialists, since many colonization cases end up considered as infections. As pointed by Paterson and Bonomo (2005), a plethora of studies used a case–control design to assess the risk factors for colonization and infection with ESBLs-producing organisms, and results are conflicting and frequently confusing. However, some generalizations related to the patient’s risk of developing colonization or infection due to ESBLs producers can be established (Paterson et al., 2000, 2001, 2003; Paterson, 2002) as follows:

1. Seriously ill patients with prolonged (> 15 days) hospital stay.
2. Extended urinary tract catheterizations.
3. Extended (more than 10 days) placement of endotracheal tubes, central venous lines or nasogastric tubes (Asensio et al., 2000).
4. Parenteral nutrition (Pena et al., 1997).
5. Hemodyalisis (D’Agata et al., 1998).
7. Excessive previous use of antibiotics, especially 3GC (Casellas et al., 1990; Fantin et al., 1990; Schiappa et al., 1996; Guzman Blanco et al., 2000; Bradford, 2001; Du et al., 2002; Bonnet et al., 2001; Paterson et al., 2001; Lautenbach et al., 2001; Eveillard et al., 2002; Kim et al., 2002a,b; Casellas et al., 2003; Paterson et al., 2003; Pessoa-Silva et al., 2004; Lee et al., 2004; Paterson et al., 2004; Paterson and Bonomo, 2005). Ceftriaxone has been particularly involved due to its high biliary excretion (Casellas et al., 1990; Casellas, 1999; Casellas et al., 2003). Also, from a survey at 15 USA hospitals, an association between aztreonam and cephalosporins use, and the emergence of ESBLs-producing organisms was found (Mavroidi et al., 2001).
8. There is a striking association between the prolonged use of ciprofloxacain and colonization/infection by ESBL producers, as shown in a collaborative study involving 5 continents (Paterson et al., 2000).
9. Nursing home stay, with some issues worth highlighting: (a) nursing homes are entirely different among countries; in the USA, Europe and other countries, they are like hotels, while in most Latin American countries (par-
ticularly Argentina) they resemble jails; (b) medical care and nursery also differs completely; in many of our geriatric institutions, patients suffer urinary catheterization just for nurses comfort; (c) in most LA nursing homes, antibiotics are given without medical prescription, ceftriaxone being favorite due to the possibility to use as an OD intramuscular dose, and at low cost; (d) patients coming from nursing homes may have not recently or never been hospitalized, but many of them circulate continuously from nursing homes to hospitals and vice versa. In a recent survey at Buenos Aires we found that 48% of patients from nursing homes were carriers of ESBL producers, as detected in urine or feces (unpublished).

**Control of ESBL-related outbreaks**

Outbreak infections can be either monoclonal or polyclonal. When monoclonal, outbreaks are caused by patient-to-patient or patient-healthcare personnel–patient transmission. Oppositely, polyclonal nosocomial outbreaks are generally due to pitfalls in antibiotic use or control. Consequently, monoclonal infections require additional care of barrier measures, infection control and surveillance cultures, while polyclonal infections demands actions of the Antibiotic Use Committee in the hospital.

In the past, biotyping, antibiotyping, serotyping and even phagotyping, were used in order to determine the clonal type of an outbreak. These methods are no longer appropriate but for screening isolates to choose which ones to compare. In the case of antibiotyping, care must be taken with frozen isolates, as plasmid lose is not rare. Currently, molecular methods are preferred as epidemiological tools. Most are plasmid profile analysis; the simplest is to visualize plasmids using pulse-field gel electrophoresis (PFGE). PFGE of chromosomal DNA is however the preferred method and the gold standard for genotyping ESBL producers (Venazia et al., 1995; Prodinger et al., 1996; Rice et al., 1996; Ardanuy et al., 1998; Rahal et al., 1998; Siu et al., 1999; Stewart and Lessing, 1999; Paterson and Bonomo, 2005). If ribotyping is available, this is a very useful method for typing ESBLs as well as several PCR-derived methods. As it is not the purpose of this chapter to deal with molecular methods we refer the reader to the excellent reviews by Paterson and Bonomo (2005) as well as from Jacoby and Muñoz-Price (2005).

Once the outbreak is deemed monoclonal or polyclonal, the bacterial spread within the hospital must be addressed. *K. pneumoniae*, a common ESBL producer, is particularly able to survive in hospital fomites, and desiccation nor high humidity are an inconvenience for them, so they are frequently found in thermometers and bronchoscopes. Prevalence of *K. pneumoniae* in hospitals, especially Latin American ones, increases because of some peculiar practices: (a) bronchoscopes and urosopes are frequently sterilized in our hospitals with glutaraldehyde, but only for 15 minutes, which is not enough; pneumologists and urologists claim that both instruments are tarnished by a larger exposure; (b) sink basins are a frequent cause of permanence of *K. pneumoniae* in intensive care units; The reason seems to be the positive electric charges of the metallic basins, which attracts the negative charges of the external membrane (G. Tomé and J.M. Casellas, unpublished data); (c) cockroaches are also a frequent cause of transmission of acinetobacters, *P. aeruginosa* and *K. pneumoniae*; the three species are able
to use chitin as carbon source. Many Latin American hospitals, but especially those in the southern cone of South America, are full of cockroaches. In a hospital where one of us has worked since 2001 in San Isidro, Argentina, the same *Acinetobacter baumannii* clone isolated from cockroaches collected nearby the ICU was also cultured from the hands of health care personnel, infected patients, and fomites (Casellas J M., Gliosca L. and Tomé, unpublished data). This was also observed by Cotton et al. (2000); (d) *Klebsiella* spp. are highly resistant to soap, and soap is frequently re-utilized in some Latin American hospitals, this being also a cause of ESBL producer dissemination.

Undoubtedly the transient carriage of bacteria producing ESBLs in the hands of health personnel is the most important method of transfer of ESBL producers from patient to patient and has been fully documented (Eisen et al., 1995; Radice et al., 2001; Paterson and Bonomo, 2005; Casellas et al., 2005). Even though most Argentinean outbreaks of ESBLs start by intestinal transmission in the community (Bauernfeid et al., 1992), this does not seem to be an important cause of dissemination at the hospital (Paterson and Bonomo, 2005), although fecal transmission has been observed (Mhamd et al., 1999).

When an outbreak occurs we recommend to inoculate hands and feces swabs on MacConkey agar supplemented with 2 mg/L cefotaxime and 5 mg/L vancomycin. We do not use amphotericin B. This media is not in accordance with the one suggested by Green and Barbaroda (1998), who disregard the possibility of the isolation of CTX-M enzymes, as they use ceftazidime. Therefore we do not recommend ceftazidime media in countries where CTX-M ESBLs are prevalent.

Finally, to solve the problem of endemic colonization, the best approach is probably to review infection control measures and introduce piperacillin–tazobactam in the formulary. In nursery homes the use of ertapenem is also recommended even though the emergency of *P. aeruginosa* outbreaks should be carefully controlled; if CTX-M ESBLs are not prevalent, ceftazidime could be another choice.

**A new challenge: ESBLs in community-acquired infections**

Curiously, ESBLs in community-acquired (CA) infections appeared almost at the same time as CA-methicillin-resistant *Staphylococcus aureus*. Coincidence or not, it is a serious problem. Most community-acquired ESBLs in Latin America and in other developing countries are reported amongst *Salmonella* spp. and *Shigella* spp. isolates (Casellas and Goldberg, 1989; Bauernfeid et al., 1992; Bonnet et al., 2001; Fortineau et al., 2001; Aitmhand et al., 2002; Baraniak et al., 2002; Jacoby et al., 2003; Kruger et al., 2004). However, in the last years several reports of community acquired *E. coli* and *K. pneumoniae* not related to nursery homes or hospitals have been published. Reports came from Spain, France, Israel, UK and Canada (Mirelis et al., 2003; Colodner et al., 2004; Mundai et al., 2004; Rodriguez Bano et al., 2004; Blomberg et al., 2005; Brigante et al., 2005; Arpin et al., 2005). In the last year at least two or three community-acquired infections due to ESBLs producers are detected in our institution. Relation of these strains with foodstuff have been postulated (Paterson and Bonomo, 2005), but we also found pet carriage of these isolates (unpublished).
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