Trends in β-Lactam Resistance Among Enterobacteriaceae

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β-Lactam resistance among Enterobacteriaceae is related primarily to the emergence of novel β-lactamases. The class A extended-spectrum β-lactamases hydrolyze extended-spectrum β-lactams and are inhibited by clavulanic acid. These β-lactamases are divided in two groups: TEM and SHV derivatives and non-TEM and non-SHV extended-spectrum β-lactamases (CTX-M1, CTX-M2, M-1, PER-1, PER-2, TOHO-1, and VEB-1). The plasmid-mediated cephalosporinases (MIR-1, FOX-1, MOX-1, BIL-1, CMY-1, CMY-2, and LAT-1) hydrolyze extended-spectrum cephalosporins and cephamycins and are not inhibited by clavulanic acid. They have been reported in Europe and in the United States. The 15 inhibitor-resistant penicillinases are TEM derivatives (except for SHV-10) and plasmid mediated, and they are mainly from Escherichia coli isolates. The carbapenemases noted among Enterobacteriaceae are either the chromosomally located penicillinases (Sme-1, NmcA, IMI-1) found in rare Enterobacter cloacae or Serratia marcescens isolates or the plasmid-mediated metalloenzyme IMP-1 that is widespread in Japan. The incidence of resistance among Enterobacteriaceae related to the other more common β-lactam-resistance mechanisms has continued to rise worldwide.

Within the last 10 years, several antibiotic resistance mechanisms have emerged among gram-negative bacteria, especially related to the β-lactam antibiotic class. Therefore, we focus on some of the β-lactam-resistant phenotypes that have emerged recently and that are interesting either for their novel genetic background or for their epidemiological features (see table 1).

TEM- and SHV-Derived Extended-Spectrum β-Lactamases

Although several biochemical mechanisms may explain β-lactam resistance among gram-negative organisms, β-lactamase biosynthesis is the most important. From 1984 to 1995 in Germany and in France, and later in Europe and the rest of the world, several extended-spectrum β-lactamases (ESBLs) were identified [1, 2]. These are the Ambler class A penicillinases that possess an extended hydrolysis spectrum directed toward third-generation cephalosporins (cefotaxime, ceftazidime, and ceftriaxone) and aztreonam. Some authors [3] have classified such enzymes according to their major resistance phenotype for third-generation cephalosporins such as the so-called cefotaximases or ceftazidimases. Most of the ESBLs confer moderate- or high-level resistance to ceftazidime and aztreonam, but the level of resistance to cefotaxime may be low. Like restricted-spectrum penicillinases, the activity of ESBLs is inhibited by β-lactam inhibitors such as clavulanic acid and tazobactam.

Many of the extended-spectrum penicillinase genes have been sequenced. They are derived mainly from TEM-1/TEM-2 and SHV-1 restricted-spectrum β-lactamases. SHV-2 to SHV-9 and TEM-3 to TEM-29, TEM-42, TEM-43, and TEM-51 have point mutations, unlike their ancestors, and this may explain their extended catalytic activity [4, 5]. Along the overall 280 amino-acid length of the protein, there are some limited amino-acid changes that are contained within the catalytic sites and these may be the basis for extended hydrolytic properties of these β-lactamases [6]. The evolution of the ESBLs involving multiple amino-acid changes appears to reflect the successive accumulation of random mutations [7, 8].

Epidemiological studies concerning the spread of ESBLs are numerous [4, 9]. ESBLs are widespread and have been identified in the United Kingdom, Spain, Portugal, Italy, Greece, the United States, North Africa, South America, and China [9]. The predominant types vary geographically. In Germany, SHV-2 and SHV-5 seem to be the most predominant, whereas in France SHV-3, SHV-4, and TEM-3 are more common [6]. In the United States, however, these ESBLs were detected 5 years later, and TEM-10, 12, and 26 are the ESBLs predominantly isolated (8% of Klebsiella pneumoniae strains, 1989). SHV-2 is widespread internationally [9].

Among the Enterobacteriaceae, these ESBLs are most prevalent in K. pneumoniae; K. pneumoniae is one of the few Enterobacteriaceae encountered frequently as a nosocomial pathogen, and it does not possess any genes for cephalosporinase induction or derepression. Therefore, wild-type K. pneumoniae may become resistant to third-generation cephalosporins, on the basis of either selection for porin deficiency or acquisition of a plasmid-mediated β-lactamase, in contrast to other Enterobacteriaceae such as Enterobacter species, Serratia species, Morganella morgani, and Citrobacter species. The predilection of ESBL for K. pneumoniae partly reflects the fact that these bacteria may survive longer than others on skin and surfaces.
b-lactam Resistance Among Enterobacteriaceae

Table 1. Classification of and features of b-lactamases.

<table>
<thead>
<tr>
<th>Ambler genetic classification</th>
<th>Type of enzymes</th>
<th>Most important hydrolysis-spectrum features</th>
<th>Organisms</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Restricted-spectrum b-lactamases: TEM-1, TEM-2, and SHV-1</td>
<td>Aminopenicillins and carboxypenicillins, clavulanic acid susceptible</td>
<td>Enterobacteriaceae, Pseudomonas aeruginosa (+)</td>
<td>Plasmid and chromosomally mediated (Klebsiella pneumoniae, SHV-1)</td>
</tr>
<tr>
<td>A</td>
<td>Extended-spectrum b-lactamases: TEM-3 to TEM-29, TEM-42, TEM-43, TEM-51, SHV-2 to SHV-9, PER-1, PER-2, CTX-M1, CTX-M2, M-1, VEB-1, and TOHO-1</td>
<td>Extended-spectrum b-lactams, clavulanic acid susceptible</td>
<td>Enterobacteriaceae, (K pneumoniae ++), P. aeruginosa (+)</td>
<td>Plasmid mediated</td>
</tr>
<tr>
<td>A</td>
<td>Inhibitor resistant b-lactamases: TEM-30 to TEM-41, TEM-44, and TEM-45</td>
<td>Aminopenicillins and carboxypenicillins, clavulanic acid resistant</td>
<td>Enterobacteriaceae (Escherichia coli +++)</td>
<td>Plasmid mediated</td>
</tr>
<tr>
<td>A</td>
<td>Inhibitor resistant and extended-spectrum b-lactamases: SHV 10, unnamed TEM series (TEM-33 and TEM-15)</td>
<td>Extended-spectrum b-lactams (low-level), clavulanic acid resistant</td>
<td>Escherichia coli</td>
<td>Plasmid mediated</td>
</tr>
<tr>
<td>A</td>
<td>Carbapenemases: NmcA, Sme-1, IMI-1</td>
<td>Carbapenems, aztreonam, clavulanic acid susceptible</td>
<td>Enterobacter cloacae Serratia marcescens</td>
<td>Chromosomal</td>
</tr>
<tr>
<td>B</td>
<td>Carbapenemase: IMP-1</td>
<td>Extended-spectrum b-lactams, carbapenems, clavulanic acid resistant</td>
<td>Enterobacteriaceae, P. aeruginosa</td>
<td>Plasmid and chromosomally mediated</td>
</tr>
<tr>
<td>C</td>
<td>Plasmid-mediated cephalosporinases: MIR-1, MOX-1, CMY-1, CMY-2, LAT-1, BIL-1, FOX-1, ACT-1</td>
<td>Cephamycins, oximinocephalosporins, and aztreonam, clavulanic acid resistant (except MOX-1)</td>
<td>Enterobacteriaceae, (K pneumoniae ++)</td>
<td>Plasmid mediated</td>
</tr>
</tbody>
</table>

NOTE. ++ = frequent; + = rare.

Thereby facilitating cross-infection [10]. Emergence of such ESBL-producing organisms has been correlated in several cases with the use of third-generation cephalosporins, especially ceftazidime [7, 8].

Among patients in intensive care units (ICUs), ESBL-producing K. pneumoniae are isolated primarily from those with urinary tract infections (50% of cases) and more rarely from those with bloodstream infections (15% of cases) [3, 11]. In a study conducted in Assistance Publique-Hôpitaux de Paris (Paris), ~16% of K. pneumoniae strains were found to produce such ESBLs in 1992 (P. Nordmann, unpublished data). Because of the detection and isolation of colonized patients and improved hygiene measures, this rate decreased to ~10% in 1996 (Assistance Publique-Hôpitaux de Paris, P. Nordmann, unpublished data). The spread of ESBLs may therefore be attributable mainly to patient-to-patient transfer, rather than to direct selection of point-mutation derivatives.

Such ESBLs have been described for almost all Enterobacteriaceae: Escherichia coli, Enterobacter species, Serratia species, M. morganii, Salmonella species, and Proteus species, but less frequently than for K. pneumoniae [11]. As is true for other Enterobacteriaceae, the best way to detect these b-lactamases is to determine antibiotic susceptibility by use of diffusion on a solid medium and by placement of a clavulanic acid–containing disk 3 cm from a disk containing a third-generation cephalosporin (the best is ceftazidime) or aztreonam and to look for synergy [12, 13]. The presence of synergy implies that the strain tested has a resistance mechanism that affects most cephalosporins; cephamycins are not affected by these enzymes. In Proteus mirabilis, expression of such resistance is often at a low level [14]; therefore, careful attention is necessary to detect in vitro synergy in this species.

Epidemiological studies clearly indicate that these enzymes are disseminated by the spread of either plasmids or strains [15]. Some studies [16, 17] have suggested that SHV- or TEM-derived genes are located on transposons. Identical ESBLs have evolved de novo in different places at different times, and occasionally single isolates have carried multiple ESBLs. Evidence of intrahospital transmission of such ESBL-possessing strains is numerous [18, 19]. It is interesting that TEM-42 [20] and SHV-2 (P. Nordmann, unpublished data), as well as OXA-18 [21], a novel class D extended-spectrum derivative, have also been found in Pseudomonas aeruginosa. These findings suggest that the ESBL reservoir is not restricted to Enterobacteriaceae. The location of the ESBL genes on plasmids may also explain the problem of coresistance, given that such plasmids often also carry aminoglycoside resistance genes, most often AAC(6'), as well as chloramphenicol or trimethoprimsulfamethoxazole (TMP-SMZ) resistance genes [22–24]. This leads to difficulties in treatment of infections, given that
most of the *K. pneumoniae* strains that possess ESBLs are also fluoroquinolone resistant (P. Nordmann, unpublished data).

Although the ESBL activity is inhibited by clavulanic acid, the only infections that may be treated safely with a β-lactam/β-lactam inhibitor combination are those involving the urinary tract. In this instance, β-lactam inhibitor concentrations are high enough to counteract the hydrolytic activity of ESBLs in an antibiotic combination such as clavulanic acid and amoxicillin. Clinical evidence of the efficacy of such antibiotic combinations for treating bloodstream-based infections is still lacking [25, 26]. However, some reports claim that piperacillin/tazobactam (or even third-generation cephalosporins, depending on the dosage) is efficacious for treating tissue infections in a rat experimental model [27–30]. Therefore, antibiotic choice in these cases is often restricted to carbapenems or cephemycins such as moxalactam, cefoxitin, or cefotetan. However, cephemycins are known to select for porin-deficient mutants.

Non-TEM and Non-SHV EBSLs

Non-TEM and non-SHV derived ESBLs have been identified recently. All of these ESBLs are class A β-lactamases and can therefore be classified as penicillinases. Unlike TEM and SHV ESBL derivatives, the corresponding restricted-spectrum non-SHV and non-TEM β-lactamases have never been isolated. Therefore, no specific antibiotic treatment can be related to the selection of such enzymes as described for cefotaxime or ceftazidime use in relation to SHV and TEM ESBL isolation [31]. MEN-1 from *E. coli* and *K. pneumoniae* isolates was reported in France in 1992 [32, 33], and this penicillinase has only 38% homology with TEM derivatives. In addition, MEN-1 has been reported in Argentina and called CTX-M1. CTX-M2, reported in 1992 in Germany, possesses 84% amino-acid homology with MEN-1 [34]. Both of these enzymes may be classified within a novel ESBL group.

PER-1 was first reported in France in *P. aeruginosa* from a patient from Turkey who had just landed in Paris [35]. Subsequently, PER-1 was isolated from Turkish *Salmonella typhi*- strain as well as other Enterobacteriaceae, its gene being located on four different plasmids [36, 37]. It shares only 35% amino-acid homology with TEM-derived β-lactamases. As described previously for TEM and SHV derivatives, PER-1 is another example of genetic exchange between Enterobacteriaceae and *Pseudomonas* species. PER-2, reported more recently from isolates in Germany, was found in *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *S. typhimurium* [38], and it shares 86% amino-acid homology with PER-1. TOHO-1, isolated in Japan in 1994, shares only 60% homology with TEM derivatives [39]. VEB-1, isolated recently in France from a patient from Vietnam, shares only 40% homology with the closest β-lactamase, PER-1 [40]. Like SHV and TEM derivatives, these unusual ESBLs have spread worldwide. An analysis of the proteins of these unusual ESBLs, when compared with that of TEM and SHV ESBLs, does not suggest immediate structural similarities, as did their extended hydrolysis spectra. Dendrograms show that these ESBLs can be separated into five groups: TEM and SHV derivatives, MEN-1 (CTX-M1) and CTX-M2, PER-1 and PER-2, TOHO-1, and VEB-1 ([40] and P. Nordmann, unpublished data). Other than for PER-1, reports of such enzymes are limited, and they are therefore not considered as significant epidemiologically. Similarly, reports of oxacillinase derivatives among Enterobacteriaceae that have a slight extended spectrum toward cefotaxime or ceftriaxone are rare [41].

Plasmid-Mediated Cephalosporinases

Along with ESBLs, the emergence of plasmid-mediated cephalosporinases has occurred recently. These enzymes are class C cephalosporinases as opposed to class A ESBLs. They are related to AmpC chromosomally located cephalosporinases (mainly *Citrobacter freundii* AmpC). The first, MIR-1, was described among *K. pneumoniae* isolates in Providence, RI [42]. These β-lactamases mediate resistance to cefoxitin, oxyiminocephalosporins, and aztreonam. Unlike ESBLs, their activity is not inhibited by clavulanic acid or tazobactam (except for MOX-1), and unlike the AmpC cephalosporinases, such as those from *Enterobacter* species, *Serratia* species, *C. freundii*, or *P. aeruginosa*, they are expressed constitutively. These enzymes may be classified into three groups: the first group is represented by MOX-1, described in *K. pneumoniae* in Japan [43] and FOX-1 in *K. pneumoniae* in Argentina [44]. They share 66% amino-acid homology and are related most closely to AmpC cephalosporinase from *P. aeruginosa* (40% amino-acid homology). The second group is represented by CMY-1 isolated from *K. pneumoniae* in South Korea [45], CMY-2 from *K. pneumoniae* in Greece [46], LAT-1 from *K. pneumoniae* in Greece [47], and BIL-1 from *E. coli* in Pakistan [48]. These enzymes are related to each other (94% amino-acid homology) and to AmpC from *C. freundii* (98% amino-acid homology). The last group is represented only by MIR-1, which is related very distantly to the other plasmid-mediated cephalosporinases.

The epidemiology of the dissemination of these enzymes is not yet understood. In a recent survey conducted among 20 different hospitals in the United States, the prevalence of such AmpC-type plasmid-located enzymes was greater than that for the TEM-type EBSLs [49]. Another study performed in Greece revealed an outbreak of LAT-1 β-lactamase among patients hospitalized in ICUs [50]. The detection of these β-lactamases requires genetic transfer experiments, which are difficult to perform in routine testing. Moreover, naturally produced AmpC Enterobacteriaceae (*Enterobacter* species, *Serratia* species, *C. freundii*, and *Providencia stuartii*) cannot be differentiated from the chromosomally located enzymes except by co-transfer with other antibiotic resistance genes carried on the same plasmids. Emergence of these β-lactamases has not been described except among Enterobacteriaceae, but there are no reports of a search for such enzymes in other species.
**Inhibitor-Resistant Penicillinas**

Fourteen inhibitor-resistant mutants of TEM enzymes have been described thus far [5, 51]. These inhibitor-resistant TEM β-lactamases (IRBLs), previously known as IRT (Inhibitor Resistant TEM derivatives), are derived from restricted-spectrum β-lactamases TEM-1 or TEM-2 [5]. IRBL possessing strains are no longer susceptible to amoxicillin/clavulanic acid (or ampicillin/subactam). First identified in France [52] and then in Spain [53] in 1989 in *E. coli*, they have been identified subsequently in *K. pneumoniae* and *P. mirabilis* [54–56]. Recently, such enzymes have been reported in a *C. freundii* strain of animal origin.

These β-lactamases confer resistance to aminopenicillins and carboxypenicillins, but they are less active against narrow-spectrum cephalosporins (cefalothin) than are classical TEM-type enzymes. Amino-acid sequence analysis of these β-lactamases (TEM-30 to TEM-41, TEM-44, TEM-45) reveals that they all possess, at least, point mutations located at one or several positions among the following: 69, 165, 182, 244, 275, or 276 [5, 51]. These mutated amino acids are different from those involved in the TEM ESBLs. Some of these positions (69 and 244) are within or close to the catalytic site of TEM β-lactamases and may explain the resistance to inhibitors. Their genes are plasmid located. The extent of these novel β-lactamases in clinical practice is not well known; an epidemiological study performed in France in 1993 revealed that 5% of *E. coli* strains may possess such β-lactamases [57]. However, the most common genetic mechanism explaining inhibitor-resistant *E. coli* strains is overproduction of restricted-spectrum TEM-1/ TEM-2 or SHV-1 β-lactamases or oxacillinase gene presence, rather than inhibitor-resistant penicillinases. Very recently, a complex mutant of TEM-1 β-lactamase with mutations encountered in both IRBL TEM-33 β-lactamase and ESBL TEM-15 was identified in an *E. coli* strain in France [58]. This enzyme confers resistance to inhibitors at a very low level and to extended-spectrum cephalosporins at a low level. There is only one report of a clinical strain from Greece that possesses an inhibitor-resistant SHV derivative, SHV-10 [59]. It derives from the extended-spectrum SHV-5 β-lactamase (serine to glycine change at position 130). It confers resistance at a low level to inhibitors and to extended-spectrum cephalosporins.

**Carbapenem Resistance**

During the last 8 years, several novel carbapenemases have been reported in Enterobacteriaceae. Carbapenemases may be in the class A penicillinas or in the class B metalloenzyme groups. Among the class A β-lactamases, three different carbapenemase genes have been sequenced thus far: NmcA, Sme-1, and IMI-1 [4]. The NmcA gene is chromosomally located and was isolated from *Enterobacter cloacae* in Paris in 1990 [60]. It confers resistance to aminopenicillins and carboxypenicillins, aztreonam, and carbapenem (mainly imipenem and less so mero-
penem). Its activity is partially inhibited by clavulanic acid as is the case for the other common penicillinas. NmcA does not significantly hydrolyze any third-generation cephalosporin. Amino-acid sequence determination reveals that it represents a novel subclass of penicillinas, sharing only 50% homology with TEM or SHV derivatives and mostly related to MEN-1 ESBL [61]. Genetic analysis revealed that the *nmcA* gene is subject to positive regulation by a regulator, *nmcR*, in a mode similar to that for *ampR* regulation of the *ampC* in AmpC-expressing Enterobacteriaceae. Although determined lately, IMI-1 sequence is very close to NmcA (95% amino-acid identity) [62]. In 1986 IMI-1 was found in one *E. cloacae* isolate in California before the marketing of imipenem. Similarly, in 1982, Sme-1 was found in Great Britain in two *Serratia marcescens* isolates [63]. Sme-1 possesses a β-lactam hydrolytic profile similar to those of NmcA or IMI-1, but shares only 70% amino-acid homology with both enzymes [64]. As opposed to that of NmcA, the inducibility of Sme-1 is marginal. No transposon-like or integron-like structure has been found around either the carbapenemase structural gene or the regulator genes. These three enzymes remain limited to the original isolates in which they were found, unlike the class B carbapenemase IMP-1.

Not only does IMP-1 hydrolyze carbapenemases at a level much higher than do class A carbapenemases, but it also hydrolyzes third-generation cephalosporins [65]. IMP-1 activity is not inhibited by clavulanic acid (but by EDTA). This class B carbapenemase shares some homology with other metalloenzymes such as those from *Bacteroides fragilis*, *Aeromonas hydrophila*, and *Bacillus cereus* [65]. The IMP-1 gene was originally identified in a *S. marcescens* isolate (chromosomally located) and, thereafter, in multiple *S. marcescens* isolates (plasmid-, transposon-, and finally integron-located) [66]. Furthermore, some *P. aeruginosa* isolates carry and express the IMP-1 gene [67]. IMP-1 is a greater threat than class A carbapenemases because of its plasmid location and because it has been found in *Klebsiella* species that are notorious vectors of resistance. So far the gene is restricted to Japan (although no epidemiological studies have been performed elsewhere).

The most prevalent carbapenem resistance mechanism among Enterobacteriaceae remains, however, a combined mechanism resulting from decreased outer-membrane permeability associated with overexpression of naturally occurring cephalosporinas or with an ESBL presence [68–70]. In such circumstances, imipenem resistance is linked with resistance to aztreonam and third-generation cephalosporins. Such a carbapenem resistance mechanism has been found in many different Enterobacteriaceae but mainly in *Enterobacter* species, and the occurrence of this mechanism may result from treatment with moxalactam, cefoxitin, or cefotetan (very rarely with carbapenem), which are agents that are known to select outer-membrane antibiotic resistance phenotypes. Recent studies, [71, 72] indicate that, in addition to resistance to cephamycins, imipenem resistance may occur in *K. pneumoniae* when a high level of a plasmid-mediated AmpC-like β-lactamase or an ex-
tended-spectrum SHV derivative is present in combination with the loss of a major outer-membrane protein.

Some Epidemiological Aspects of More Common β-Lactam Resistance Mechanisms

Studies published in 1994 [57, 73] indicate a steady-state level of ampicillin or amoxicillin resistance in E. coli (mainly due to TEM-1/TEM-2 plasmid-mediated penicillinases). Overall among E. coli strains isolated from outpatients and hospitalized patients, this resistance level approaches ~40% in the United States and 40%–45% in the United Kingdom and in France, and the levels are higher in Spain (58%) and Israel (63%) [74]. The resistance level in E. coli for amoxicillin/clavulanic acid has been estimated at 5%–10% in Paris in 1994 and 5% in the United Kingdom [57, 75]. Despite the emergence of the inhibitor-resistant penicillinases, this resistance level has remained stable from 1990 to 1994. As discussed previously, amoxicillin/clavulanic acid resistance in E. coli may be due mainly to overexpression of classic TEM-1/TEM-2 or SHV-1 and restricted-spectrum oxacillinases rather than IRTs. In non-typhi Salmonella species, the levels of amoxicillin and amoxicillin-clavulanic acid resistance remained stable from 1988 to 1991, ~30% and 4%, respectively [76]. However, distribution of the resistance level varies greatly from one non-typhi Salmonella species to another. For example, between 1988 and 1991 the ampicillin resistance level increased from 30% to 65% in S. typhimurium and decreased from 29% to 16% in Salmonella enteritidis during the same period. A similar ampicillin resistance trend was observed between 1991 and 1994 in a study in Spain [77], where non-S. typhimurium infections are highly prevalent. Recently, an increase in the frequency of amoxicillin/clavulanate-resistant non-typhi Salmonella isolates has been found in central Europe [78] as well as in France (P. Nordmann, unpublished data).

Analysis of the pattern of nosocomial isolates in a United States hospital revealed that the prevalence of intrinsically β-lactam-susceptible bacteria decreased, whereas that of intrinsically β-lactam-resistant species increased [79]. For example, the isolation rate for E. coli decreased from 25.2% in 1986 to 18.2% in 1994 and for Proteus species from 5.3% to 2.6%. Remarkably, the frequency of Enterobacter isolates increased from 1.6% to 5.1% and that of Klebsiella species increased from 5.9% to 7.8%. It is of interest that the above phenomenon was paralleled by a significant increase in rates of acquired resistance to various antibiotics. For example, the ceftazidime resistance rate rose from 27% in 1986 to 43% in 1994. Similar results were obtained in studies of resistance patterns for ICU isolates from 1991 to 1994 ([80] and P. Nordmann, unpublished data).

The overall susceptibility rates depend on the type of specimen. For example, the overall susceptibility rate for blood isolates is greater than that for respiratory tract isolates, reflecting the difference in species distribution [80]. Finally, in an extensive study [81] conducted in the United States from 1990 to 1993 on 33,869 isolates, the ceftazidime resistance rate increased from 3.6% to 14.4% in K. pneumoniae and from 30.8% to 38.3% in Enterobacter species [81].

Conclusion

Among Enterobacteriaceae, problems of emerging β-lactam resistance remain limited to hospital-acquired strains. The prevalence of ESBLs seems to have decreased within the last 2 years, at least in countries where ESBLs are epidemic, such as France. However, among the problems of unknown incidence, one may find plasmid-mediated cephalosporinases and class B plasmid-mediated carbapenemases. In the near future, the role of other species reservoirs such as P. aeruginosa in the dissemination of novel ESBLs should be monitored.

The therapeutic problems resulting from novel β-lactam resistance mechanisms or extension of known β-lactam resistance mechanisms are related intimately to those problems stemming from resistance to other antibiotic classes. Most studies, as well as day-to-day analyses of clinical microbiology data, indicate that the bacterial strains among Enterobacteriaceae that are isolated in hospital settings and are resistant to some antibiotics usually cumulate resistance to more antibiotics of the same class or to different classes. E. coli strains that are amoxicillin susceptible are amoxicillin/clavulanate susceptible, given that the 25% of the E. coli that are amoxicillin/clavulanate-resistant are also amoxicillin resistant. Moreover, bacterial isolates that are resistant to extended-spectrum β-lactams usually cumulate resistance to aminoglycosides and fluoroquinolones. This is true particularly for K. pneumoniae and E. cloacae, which are among the most important nosocomial pathogens. The spread of such strains may explain dramatic increases in selected areas. Day-to-day analyses of the β-lactam resistance mechanisms may help to detect novel types before the analyses of their genetic background. From such studies, one might foresee measures to limit the spread of these novel resistance mechanisms.

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