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MINIREVIEW

More Extended-Spectrum β-Lactamases

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INTRODUCTION

Extended-spectrum β-lactamases are plasmid-mediated enzymes that confer resistance to oxyimino-β-lactams such as cefotaxime, ceftazidime, and aztreonam, antibiotics that were designed to be effective against strains producing known plasmid-determined β-lactamases. Extended-spectrum β-lactamases were first recognized in Europe, have become increasingly prevalent there, and are being reported around the world, including many sites in the United States. Since this topic was reviewed in 1989 (68), many more TEM-related extended-spectrum β-lactamases have been described, as have plasmid-mediated β-lactamases which are unrelated to those in the TEM family and which confer resistance to cefoxitin and other cephamycins or to imipenem and other carbapenems, antibiotics that retained activity against strains producing the first extended-spectrum enzymes to be discovered. Treatment of infections caused by strains producing these enzymes remains problematic.

β-LACTAMASE VARIETY

Table 1 lists the extended-spectrum β-lactamases related to TEM-1, TEM-2, or TEM-13, a variant identical to TEM-2 in isoelectric point (pI) and resistance phenotype (44). The 16 extended-spectrum enzymes designated TEM-3 through TEM-19 have been proven to be unique by gene sequencing or oligotyping (44). Such information is not yet available for the second group of 21 TEM-related β-lactamases, which consequently may contain enzymes which duplicate each other or those in the first group. The pIs of extended-spectrum β-lactamases in the TEM family range between 5.1 and 6.5, with considerable clustering at 5.4, 5.55, 5.9, and 6.3. Clearly, isoelectric focusing alone cannot differentiate all the TEM varieties. Inhibition profiles have proven to be a useful adjunct to isoelectric focusing in discriminating the various extended-spectrum β-lactamases (56).

The enzymes vary considerably in the level of resistance conferred to cefotaxime, ceftazidime, or aztreonam. With few exceptions (TEM-3, TEM-4, TEM-20, and TEM-21), the MIC for *Escherichia coli* producing one of these enzymes is much higher with ceftazidime than with cefotaxime. Indeed, some of the enzymes do not increase the cefotaxime MIC at all with a conventional bacterial inoculum (TEM-11, TEM-12, CAZ-3, CAZ-hi, TEM-E1, TEM-E2, and several not yet named). Reported aztreonam resistance also varies from negligible to an MIC above 100 μg/ml. In such cases, aztreonam or cefotaxime MICs are at most equal to that of ceftazidime but never greater.

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Sixteen more extended-spectrum β-lactamases known or believed not to be in the TEM family are listed in Table 2. In view of the diversity of TEM-related enzymes, it is surprising that only four extended-spectrum β-lactamases have been reported as yet in the SHV family. They have pIs ranging from 7.0 to 8.2 and are all potent extended-spectrum enzymes producing MICs for *E. coli* of at least 32 μg/ml with cefotaxime, ceftazidime, or aztreonam. New on the scene are plasmid-mediated β-lactamases, found in *Klebsiella pneumoniae* and *E. coli*, that confer high-level resistance to cefoxitin and other 7-α-methoxy-β-lactams as well as to oxyimino-β-lactams. To date, such extended-spectrum enzymes have been found in isolates from South Korea, Greece, and Providence, R.I. The MIR-1 enzyme has been most extensively studied (50, 57). Its pI of 8.4, resistance to inhibition by clavulanate, and predominant cephalosporinase activity resemble the properties of chromosomally mediated AmpC-type β-lactamases which, when produced constitutively in organisms such as *Enterobacter cloacae*, are responsible for similar extended-spectrum β-lactam resistance (76). A partial sequence of the MIR-1 gene is, in fact, 90% identical to the sequence of an *ampC* gene from *E. cloacae* (57). CMY-1 and CMY-2 also have pIs similar to those of AmpC-type β-lactamases but are more readily inhibited than MIR-1 by clavulanate or sulbactam (8, 9). Whether they have a derivation similar to that of MIR-1 remains to be established.

An even more disturbing plasmid-mediated β-lactamase has been found in a *Pseudomonas aeruginosa* isolate from Japan (90). This enzyme confers resistance to imipenem and meropenem as well as to carbenicillin, ceftazidime, and moxalactam. It is a clavulanate-resistant metalloenzyme with an exceptionally broad substrate spectrum that includes carbapenems, oxyiminocephalosporins, and 7-α-methoxy-β-lactams and thus belongs in the same family as chromosomally mediated imipenem-hydrolyzing enzymes from *Xanthomonas maltophilia* or *Bacteroides fragilis*. Its spread will be watched with interest.

Several of the other extended-spectrum enzymes listed in Table 2 have properties that suggest derivation from an AmpC-type source. BIL-1 (pI 8.8), FEC-1 (pI 8.2), and MEN-1 (pI 8.4) are also predominantly cephalosporinases. BIL-1 is resistant as well to clavulanate inhibition, yet none of these enzymes is reported to confer cephamycin resistance. The molecular mass of FEC-1 (48 kDa) is also atypical for an AmpC-type β-lactamase. FUR was so named for its ability to hydrolyze and confer resistance to cefuroxime. Its pI (7.5) suggests a relationship to the SHV enzymes, which also confer high-level cefuroxime resistance (30), but FUR-related MICs are otherwise unlike those related to SHV-type extended-spectrum β-lactamases. DNA sequencing will be necessary to settle phylogeny in this heterogeneous group

TABLE 1. Extended-spectrum β-lactamases in the TEM family

β-Lactamase	Species	Country of origin	Yr of first isolation (I) or report (R)	pI	MIC[a] of:			Reference(s)
					Cefotaxime	Ceftazidime	Aztreonam	
Parental types								
TEM-1	*E. coli*	Greece	1963 (I)	5.4	0.125	0.25	0.125	23
TEM-2	*P. aeruginosa*	England	1969 (I)	5.6	0.125	0.5	0.25	43
TEM-13	*M. morganii*	[b]	1990 (R)	5.6				44
Proven unique								
TEM-3 (CTX-1)	*K. pneumoniae*	France	1984 (I)	6.3	32	64	16	14, 79
TEM-4	*E. coli*	France	1986 (I)	5.9	32	32	16	58
TEM-5 (CAZ-1)	*K. pneumoniae*	France	1987 (I)	5.55	4	128	8	66
TEM-6	*E. coli*	Germany	1987 (R)	5.9	1	128	64	8
TEM-7	*Citrobacter freundii*	France	1988 (R)	5.41	0.5	64	2	27
TEM-8	*K. pneumoniae*		1989 (R)	5.9				44
TEM-9 (RHH-1)	*K. pneumoniae*	England	1987 (R)	5.5	2	128	128	84
TEM-10	*K. pneumoniae*	United States	1989 (R)	5.57	1	64	32	72
TEM-11 (CAZ-lo)	*K. pneumoniae*	Belgium	1989 (R)	5.7	0.06	4	0.25	89
TEM-12	*E. coli*	United States	1987 (R)	5.25	0.06	4	0.25	91
TEM-14	*K. pneumoniae*	[b]	1990 (R)	6.3				44
TEM-15	*K. pneumoniae*	[b]	1990 (R)	6.0				44
TEM-16	*K. pneumoniae*	[b]	1990 (R)	6.3				44
TEM-17	*K. pneumoniae*	[b]	1990 (R)	5.9				44
TEM-18	*K. pneumoniae*	[b]	1990 (R)	6.3				44
TEM-19	*E. coli*	[b]	1990 (R)	5.4				44
Not yet proven unique								
CAZ-2	*K. pneumoniae*	France	1987 (I)	6.0	2	128	16	78
CAZ-3	*K. pneumoniae*	France	1987 (I)	5.3	0.12	16	1	78
CAZ-6	*K. pneumoniae*	France	1988 (I)	6.5	8	512	128	19
CAZ-7	*K. pneumoniae*	France	1988 (I)	6.3	4	256	64	19
CAZ-hi	*K. pneumoniae*	Belgium	1989 (R)	6.5	0.25	32	8	89
MGH-1	*K. pneumoniae*	United States	1988 (I)	5.55	2	512	64	31
MRH-1	*K. pneumoniae*	United States	1990 (R)	5.44	S	R	S	71
TEM-20	*K. pneumoniae*	Tunisia	1990 (R)	5.4	4	2	1	11
TEM-21	*K. pneumoniae*	Tunisia	1990 (R)	6.4	8	8	4	11
TEM-E1	*E. coli*	Belgium	1987 (I)	5.41	0.13	32	0.13	62
TEM-E2[c]	*Klebsiella oxytoca*	England	1982 (I)	5.3	0.25	32	1	63
TEM-E3[d]	*E. coli*	England	1989 (R)	5.55	1	125	32	60
TEM-E4	[e]	Belgium	[e]	5.61	<1	16		59
YOU-1	*K. pneumoniae*	United States	1988 (I)	5.57	1	256	32	73
YOU-2	*K. pneumoniae*	United States	1988 (I)	5.2	0.5	64	8	73
Not named	*K. pneumoniae*	United States	1988 (I)	5.25	≤0.5	>64	>64	80
Not named	*E. cloacae*	England	1986 (I)	5.7–5.9	<0.5	16		22
Not named	*E. coli*	United States	1988 (I)	5.2	S	R	S	49
Not named	*K. pneumoniae*	United States	1987 (I)	[f]	S	R	S	49
Not named	*K. pneumoniae*	United States	1988 (I)	5.35	S	R	S	49
Not named	*K. pneumoniae*	United States	1988 (I)	5.1	S	R	S	49

[a] MICs are generally given for *E. coli* transconjugants producing the given β-lactamase. Some were determined in a uniform genetic background (30), but most were determined by a variety of techniques that may make them not closely comparable. When no values are given, data are not available. R, resistant, level unspecified; S, susceptible.

[b] Strains producing these enzymes originated in France, Belgium, England, Chile, and Germany, but the exact country of origin for each has not yet been reported (44).

[c] Reported to be identical to CAZ-3 (59).

[d] Reported to be identical to TEM-10 (59).

[e] Not specified.

[f] No β-lactamase bands were visualized on isoelectric focusing.

and to establish whether some of these enzymes are derived from the many other known plasmid-determined β-lactamases (48).

MOLECULAR BASIS OF THE EXTENDED SPECTRUM

TEM-1 differs from TEM-2 by a functionally silent Gln→Lys substitution at position 37 which serves to differentiate between the extended-spectrum enzymes derived from TEM-1 and the less prevalent TEM-2. The recently recognized variant TEM-13 has an additional Thr→Met change at position 261 which also does not affect the substrate spectrum (44). The amino acid alterations in TEM-3 to TEM-19 are shown in Table 3 and involve substitutions at five other sites. TEM-4 and TEM-9 also have a silent Leu→Phe alteration in the leader peptide at position 19 which is excised in processing the mature enzymes.

The amino acid sequences of 10 enzymes in the SHV family have been determined or can be deduced from nucleotide sequencing. A Thr-Ala at positions 117 and 118 (numbered as in TEM for consistency) was initially proposed for SHV-1 from plasmid p453 (4), but the order of this pair is

TABLE 2. Extended-spectrum β-lactamases not related to TEM

β-Lactamase	Species	Country of origin	Yr of first isolation (I) or report (R)	pI	MIC[a] of:					Inhibition by clavulanate	Reference(s)
					Cefotaxime	Ceftazidime	Aztreonam	Cefoxitin	Imipenem		
SHV derivatives											
SHV-1	*E. coli*	Switzerland	1974 (R)	7.6	0.125	1	0.5	16	0.5	+	47
SHV-2	*K. ozaenae*	Germany	1983 (I)	7.6	64	32	32	16	0.5	+	37
SHV-3	*K. pneumoniae*	France	1986 (I)	7.0	64	32	32	16	0.25	+	69
SHV-4 (CAZ-5)	*K. pneumoniae*	France	1987 (I)	7.75	128	128	256	16	0.25	+	15
SHV-5 (CAZ-4)	*K. pneumoniae*	Chile	1987 (I)	8.2	64	128	256	8	0.25	+	26
Responsible for cephamycin resistance											
CMY-1	*K. pneumoniae*	South Korea	1989 (R)	8.0	64	4	16	256	0.25	±	6
CMY-2	*K. pneumoniae*	Greece	1990 (R)	8.1	32	128	64	256	0.25	±	9
MIR-1	*K. pneumoniae* *E. coli*	United States	1988 (I)	8.4	64	128	128	≥256	1	−	50, 57
Responsible for carbapenem resistance											
Not named	*P. aeruginosa*	Japan	1988 (I)	9.0	NR	400	3	NR	12.5	−	90
Not further differentiated											
BIL-1	*E. coli*	Pakistan	1989 (I)	8.8	16	64	NR	NR	NR	−	59, 92
CTX-M	*E. coli*	Germany	1989 (I)	8.9	16	2	8	4	NR	+	7
DJP-1	*K. pneumoniae*	India	1988 (I)	7.9	NR	NR	NR	NR	NR	+	59, 61
FEC-1	*E. coli*	Japan	1988 (R)	8.2	200	12.5	25	2	0.8	+	46
FUR	*K. pneumoniae*	Belgium	1989 (R)	7.5	1	2	16	2	0.25	+	89
MEN-1	*E. coli*	France	1990 (R)	8.4	R	NR	NR	S	S	+	12
Not named	*K. pneumoniae*	United States	1988 (I)	7.65	S	R	R	S	S	+	49
Not named	*K. pneumoniae*	United States	1988 (I)	7.0, 7.8[b]	S[c]	S	S	S	S	+	49

[a] NR, not reported; R, resistant; S, susceptible.
[b] Which β-lactamase is responsible for resistance has not been established.
[c] Although testing susceptible with a zone size of 23 mm around a ceftazidime disk, the zone diameter was 35 mm in the presence of 10 μg of clavulanate per ml, indicating the presence of a weak extended-spectrum β-lactamase.

reversed in all subsequently determined sequences. With this correction, the amino acid sequences of SHV-2 from *E. coli* A2302 (2), *K. pneumoniae* 5214773 (41), and *Klebsiella ozaenae* 2180 (29) are identical and differ from that of SHV-1 by a Gly→Ser substitution at position 236. Similarly, the sequences of SHV-3 (53), SHV-4 (64), and SHV-5 (13) differ from this common SHV-2 sequence only at the positions shown in Table 3. However, the sequence of SHV-2 from *Salmonella typhimurium* 122 has a Leu→Gln at position 31 (25), and another sequence of SHV-2 from *K. ozaenae* 2180 has a silent Leu→Trp change at position 17 in the leader peptide (70). Finally, the reported sequence of SHV-1 from *Klebsiella* sp. plasmid R974 has 6 amino acid differences from the sequences of the other SHV enzymes (51).

Assuming that the amino acid changes at positions 102, 162, 203, 235, 236, and 237 modify enzyme function, TEM-7, TEM-12, TEM-17, TEM-18, TEM-19, and SHV-2 have undergone a single amino acid alteration. TEM-3, TEM-4, TEM-6, TEM-9, TEM-10, TEM-11, TEM-14, TEM-15, TEM-16, SHV-3, and SHV-5 have two substitutions, and TEM-5, TEM-8, and SHV-4 have three changes (44). Although these modifications occur far from the critical serine residue at position 68 (position 66 for SHV-type β-lactamases), if the known three-dimensional structure of the class A β-lactamase of *Staphylococcus aureus* is used as a model (28), then the amino acid alterations in the TEM- and SHV-type extended-spectrum β-lactamases are located in the walls of a crevice with serine 68 at its base (82). More efficient substrate binding can be pictured as the result of new hydrogen bonding and electrostatic interactions allowed by the lysine and serine substitutions or changes in the conformation of the hydrophobic cleft in the active site (38, 40, 83). Whether the AmpC-type extended-spectrum β-lactamases also have undergone substitutions to increase their efficiency with certain substrates remains to be established.

The TEM- and SHV-type β-lactamases pay a price, however, for their extended spectrum in terms of activity. Kinetic analysis indicates that the native TEM enzyme has evolved to near-optimum efficiency (20). Compared with the parental types, extended-spectrum β-lactamases have considerably lower activities either in crude cell extracts (30) or after partial purification (16).

EPIDEMIOLOGY OF RESISTANCE

Extended-spectrum enzymes were first recognized in Europe in 1983 but have since been reported in many countries (Table 4). Undoubtedly, where they have been found largely reflects where they have been looked for. Despite the great variety discovered in France (Table 1), outside France a much more limited group has been detected. SHV-2 (10 locales), SHV-5 (6 locales), TEM-12 or enzymes compatible with TEM-12 (5 locales), and TEM-10 or compatible en-

TABLE 3. Molecular basis of extended-spectrum activity

β-Lactamase	Amino acid at position[a]:								Reference
	37	102	162	203	235	236	237	261	
TEM-1	Gln	Glu	Arg	Gln	Ala	Gly	Glu	Thr	85
TEM-2	Lys								3
TEM-13	Lys							Met	44
TEM-3	Lys	Lys				Ser			81
TEM-4		Lys				Ser		Met	44
TEM-5			Ser		Thr		Lys		82
TEM-6		Lys	His						44
TEM-7	Lys		Ser						21
TEM-8	Lys	Lys	Ser			Ser			44
TEM-9		Lys	Ser					Met	44
TEM-10			Ser				Lys		39
TEM-11	Lys		His			[b]			44
TEM-12			Ser						44
TEM-14	Lys	Lys				Ser		Met	44
TEM-15		Lys				Ser			44
TEM-16	Lys	Lys	His						44
TEM-17		Lys							44
TEM-18	Lys	Lys							44
TEM-19						Ser			44
SHV-1	Gln	Asp	Arg	Arg	Ala	Gly	Glu	Leu	4
SHV-2						Ser			2
SHV-3				Leu		Ser			53
SHV-4				Leu		Ser	Lys		64
SHV-5						Ser	Lys		13

[a] Amino acid residues are numbered as described by Sutcliffe for TEM-1 (85) and should be numbered two less for SHV-1. The residue at position 37 for TEM enzymes defines which are derived from TEM-1 and which are derived from TEM-2. For SHV-1, all the amino acid residues analogous to those shown for TEM-1 are given. For other sequences, only amino acids which differ from those of TEM-1 or SHV-1 are indicated.

[b] Substitution not yet known.

zymes (4 locales) lead the list in frequency. The distribution of particular β-lactamases suggests pockets of local dissemination with limited wide-range spread. For example, the TEM-related extended-spectrum enzymes first recognized in France have yet to be reported in North America, while TEM-10, TEM-12, and related enzymes, which have been found in several cities in the United States, have been rare or absent in continental Europe.

In France, the prevalence of strains producing extended-spectrum β-lactamases is increasing (86). The frequencies of *K. pneumoniae* isolates with extended-spectrum β-lactamases were 0.75% in 1985, 8.4% in 1987, and 11% in 1988, and there has been a similar increase in the number of hospitals with such isolates. Nosocomial outbreaks due to strains producing such β-lactamases have been reported in Paris (58 patients) (1), Cambridge, Mass. (29 patients) (73), and Providence, R.I. (11 patients) (57).

K. pneumoniae is by far the most common species in which these enzymes have been recognized (Tables 1 and 2). Why this should be so is not yet clear. The level of resistance produced by extended-spectrum β-lactamases in *K. pneumoniae* is not conspicuously higher than that in *E. coli* or other gram-negative organisms (35).

Plasmids responsible for extended-spectrum β-lactamase production tend to be large (80 kb or more in size) and to carry resistance to several agents (32, 67, 80, 88), an important limitation in the design of treatment alternatives. Curiously, except for one brief report (33), none of these enzymes has been shown to be transposable (32). The usual transmissibility of the responsible plasmids, however, allows resistance to spread readily to other pathogens, so that

TABLE 4. Isolation of extended-spectrum β-lactamases related to TEM or SHV outside of France

Location	β-Lactamase	pI	Reference(s)
Africa			
Senegal	SHV-2	7.6	75
Tunisia	SHV-2	7.6	10
	TEM-3	6.3	10
	TEM-20	5.4	10
	TEM-21	6.4	10
Central America			
Caribbean	TEM-3	6.3	67
North America			
Boston, Mass.	MGH-1	5.55	31
	SHV-4	7.75	34
	TEM-12	5.2	33
Cambridge, Mass.	YOU-1	5.57	73
	YOU-2	5.2	73
Charleston, S.C.	Not named	7.65	49
	Not named	7.0, 7.7	49
Chicago, Ill.	MRH-1	5.44	71
	TEM-10	5.57	72
Cleveland, Ohio	Not named	5.2	49
	SHV-2	7.6	87
Cincinnati, Ohio	TEM-12	5.25	91
Fort Sam Houston, Tex.	Not named	5.25	80
Oklahoma City, Okla.	Not named	[a]	49
St. Louis, Mo.	Not named	5.35	49
	Not named	5.1	49
Toronto, Ontario, Canada	TEM-10	Not given	39
South America			
Argentina	Not named	6.0	18
	SHV-2	7.6	18
	SHV-5	8.2	42
Chile	SHV-2	7.6	31
	SHV-5	8.2	26
Australia, Perth	SHV-2	7.6	52
	SHV-5	8.2	52
Europe			
Belgium	CAZ-hi	6.5	89
	TEM-11	5.7	89
	TEM-E1	5.4	62
	TEM-E4	5.61	59
England	SHV-2[b]	7.6	77
	SHV-5[c]	8.2	77
	TEM-9	5.5	84
	TEM-10 (TEM-E3)	5.57	59, 60
	TEM-E2	5.3	63
	Not named	5.7–5.9	22
Germany	SHV-2	7.6	37
	TEM-6	5.9	8
Greece	SHV-2	7.6	31, 88
	SHV-5	8.2	55, 88
Spain	TEM-6	5.9	45
Far East			
China	SHV-2	7.6	31
Singapore	SHV-5	8.2	52

[a] No β-lactamase bands were visualized on isoelectric focusing.

[b] Isolated from a patient in Egypt.

[c] Isolated from a patient in Greece.

TABLE 5. Options for treatment of β-lactam-resistant strains

Enzyme or mechanism	Clinical isolates	β-Lactams affected	β-Lactams not affected[a]
Common plasmid-mediated β-lactamase	Many-gram-negative organisms	Ampicillin, azlocillin, carbenicillin, cefamandole, cephalothin, mezlocillin, piperacillin, ticarcillin	Cefotetan, cefoxitin, extended-spectrum cephalosporins, moxalactam, carbapenems, monobactams
Plasmid-mediated extended-spectrum β-lactamase in TEM or SHV family	*K. pneumoniae*, *E. coli*, *C. freundii*, *S. marcescens*, *E. cloacae*	Above-listed drugs plus aztreonam, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime	Cefmetazole, cefotetan, cefoxitin, imipenem, moxalactam
Constitutive production of chromosomal β-lactamase	*E. cloacae*, *C. freundii*, *P. aeruginosa*, *S. marcescens*	Above-listed drugs plus cefmetazole, cefotetan, cefoxitin, moxalactam	Imipenem
Plasmid-mediated extended-spectrum β-lactamase related to AmpC	*K. pneumoniae*, *E. coli*	Above-listed drugs	Imipenem
Carbapenem-hydrolyzing chromosomal β-lactamase	*X. maltophilia*, *B. fragilis*, *S. marcescens*, *E. cloacae*	Imipenem	Variable
Plasmid-mediated β-lactamase conferring carbapenem resistance	*P. aeruginosa*	Above-listed drugs	Aztreonam, piperacillin

[a] Investigational drugs have not been included.

extended-spectrum enzymes have been found in *Enterobacter aerogenes*, *Levinea malonatica*, *Morganella morganii*, *Salmonella* spp., and *Serratia marcescens*, in addition to the species listed in Tables 1 and 2 (65, 67). Molecular analysis demonstrated that the spread of TEM-3 in France to a variety of host bacteria involved a single epidemic plasmid that in the course of time itself underwent minor modifications (65). In other outbreaks, related plasmids from isolates at a single hospital encoded different extended-spectrum enzymes (19, 73), as though sequential mutations were occurring in a common β-lactamase gene.

TREATMENT OF RESISTANT INFECTIONS

Some infections due to organisms testing resistant to ceftazidime but susceptible to cefotaxime or ceftriaxone have responded to treatment with these alternate cephalosporins (14, 72, 73, 80). However, the MICs of these agents rise dramatically as the inoculum is increased (17, 24, 74), and in animal model infections treatment with cefotaxime (74) or ceftriaxone (24) has failed despite serum antibiotic levels far in excess of the MIC at the conventional 10^5 organisms per ml. The addition of a β-lactamase inhibitor such as sulbactam lowers the MIC in vitro but has been of only marginal benefit in animal model infections (17, 24, 74). Furthermore, the MICs of currently available β-lactamase inhibitor–β-lactam combinations are quite high, especially for strains producing enzymes of the SHV family (5, 30). Strains making TEM- or SHV-related β-lactamases remain fully susceptible to cephamycins and to carbapenems, but the presence of a β-lactamase does not prevent other mechanisms of resistance from emerging. For example, cefoxitin treatment of a patient with pneumonia caused by a TEM-3-producing strain of *K. pneumoniae* failed when the strain became cefoxitin resistant, apparently by the loss of outer membrane porins mediating cefoxitin permeability (54).

β-Lactams that can still be used for therapy despite the presence of various kinds of β-lactamases are listed in Table 5, which omits investigational drugs, some of which are effective in vitro against organisms making particular extended-spectrum β-lactamases (30, 36). Future drug development will need to take these enzymes in all their variety into account.

REFERENCES

1. **Arlet, G., M. J. Sanson-le Pors, M. Rouveau, G. Fournier, O. Marie, B. Schlemmer, and A. Philippon.** 1990. Outbreak of nosocomial infections due to *Klebsiella pneumoniae* producing SHV-4 beta-lactamase. Eur. J. Clin. Microbiol. Infect. Dis. **9**:797–803.
2. **Barthélémy, M., J. Péduzzi, H. Ben Yaghlane, and R. Labia.** 1988. Single amino acid substitution between SHV-1 β-lactamase and cefotaxime-hydrolyzing SHV-2 enzyme. FEBS Lett. **231**:217–220.
3. **Barthélémy, M., J. Peduzzi, and R. Labia.** 1985. Distinction entre les structures primaires des β-lactamases TEM-1 et TEM-2. Ann. Inst. Pasteur Microbiol. **136A**:311–321.
4. **Barthélémy, M., J. Peduzzi, and R. Labia.** 1988. Complete amino acid sequence of p453-plasmid-mediated PIT-2 β-lactamase (SHV-1). Biochem. J. **251**:73–79.
5. **Bauernfeind, A.** 1990. Perspectives of beta-lactamases inhibitors in therapy of infections caused by *Escherichia coli* or *Klebsiella* with plasmidic resistance to third generation cephalosporins. Infection **18**:48–52.
6. **Bauernfeind, A., Y. Chong, and S. Schweighart.** 1989. Extended broad spectrum β-lactamase in *Klebsiella pneumoniae* including resistance to cephamycins. Infection **17**:316–321.
7. **Bauernfeind, A., H. Grimm, and S. Schweighart.** 1990. A new plasmidic cefotaximase in a clinical isolate of *Escherichia coli*. Infection **18**:294–298.
8. **Bauernfeind, A., and G. Hörl.** 1987. Novel R-factor borne β-lactamase of *Escherichia coli* conferring resistance to cephalosporins. Infection **15**:257–259.
9. **Bauernfeind, A., S. Schweighart, K. Dornbusch, and H. Giamarellou.** 1990. A transferable cephamycinase (CMY-ase) in *Klebsiella pneumoniae* (*K.pn.*). Program Abstr. 30th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 190.
10. **Ben Hassen, A., G. Fournier, A. Kechrid, C. Fendri, S. Ben Redjeb, and A. Philippon.** 1990. Résistance enzymatique au

céfotaxime chez cinquante-six souches de *Klebsiella* spp., *Escherichia coli* et *Salmonella* spp. dans un hôpital tunisien (1984–1988). Pathol. Biol. **38**:464–469.

11. **Ben Redjeb, S., G. Fournier, C. Mabilat, A. Ben Hassen, and A. Philippon.** 1990. Two novel transferable extended-spectrum β-lactamases from *Klebsiella pneumoniae* in Tunisia. FEMS Microbiol. Lett. **67**:33–38.
12. **Bernard, H., C. Tancrede, D. Sirot, A. Morand, and R. Labia.** 1990. A novel plasmid-mediated extended-spectrum beta-lactamase (ESBL) with an unusually high isolectric point. Kinetics of its interactions with 3rd generation cephalosporins (3GC). Program Abstr. 30th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 189.
13. **Billot-Klein, D., L. Gutmann, and E. Collatz.** 1990. Nucleotide sequence of the SHV-5 β-lactamase gene of a *Klebsiella pneumoniae* plasmid. Antimicrob. Agents Chemother. **34**:2439–2441.
14. **Brun-Buisson, C., P. Legrand, A. Philippon, F. Montravers, M. Ansquer, and J. Duval.** 1987. Transferable enzymatic resistance to third-generation cephalosporins during nosocomial outbreak of multiresistant *Klebsiella pneumoniae*. Lancet **ii**:302–306.
15. **Buré, A., P. Legrand, G. Arlet, V. Jarlier, G. Paul, and A. Philippon.** 1988. Dissemination in five French hospitals of *Klebsiella pneumoniae* serotype K25 harboring a new transferable enzymatic resistance to third generation cephalosporins and aztreonam. Eur. J. Clin. Microbiol. **7**:780–782.
16. **Bush, K., and S. B. Singer.** 1989. Biochemical characteristics of extended broad spectrum β-lactamases. Infection **17**:429–433.
17. **Caron, F., L. Gutmann, A. Bure, B. Pangon, J.-M. Vallois, A. Pechinot, and C. Carbon.** 1990. Ceftriaxone-sulbactam combination in rabbit endocarditis caused by a strain of *Klebsiella pneumoniae* producing extended-broad-spectrum TEM-3 β-lactamase. Antimicrob. Agents Chemother. **34**:2070–2074.
18. **Casellas, J. M., and M. Goldberg.** 1989. Incidence of strains producing extended spectrum β-lactamases in Argentina. Infection **17**:434–436.
19. **Chanal, C. M., D. L. Sirot, A. Petit, R. Labia, A. Morand, J. L. Sirot, and R. A. Cluzel.** 1989. Multiplicity of TEM-derived β-lactamases from *Klebsiella pneumoniae* strains isolated at the same hospital and relationships between the responsible plasmids. Antimicrob. Agents Chemother. **33**:1915–1920.
20. **Christensen, H., M. T. Martin, and S. G. Waley.** 1990. β-Lactamases as fully efficient enzymes. Biochem. J. **266**:853–861.
21. **Collatz, E., G. Tran Van Nhieu, D. Billot-Klein, R. Williamson, and L. Gutmann.** 1989. Substitution of serine for arginine in position 162 of TEM-type β-lactamases extends the substrate profile of mutant enzymes, TEM-7 and TEM-101, to ceftazidime and aztreonam. Gene **78**:349–354.
22. **Corkill, J. E., C. A. Hart, and P. Shears.** 1989. Plasmid mediated ceftazidime resistance associated with a β-lactamase giving a slow nitrocefin reaction. J. Antimicrob. Chemother. **24**:467–470.
23. **Datta, N., and P. Kontomichalou.** 1965. Penicillinase synthesis controlled by infectious *R* factors in Enterobacteriaceae. Nature (London) **208**:239–241.
24. **Fantin, B., B. Pangon, G. Potel, F. Caron, E. Vallée, J.-M. Vallois, J. Mohler, A. Buré, A. Philippon, and C. Carbon.** 1990. Activity of sulbactam in combination with ceftriaxone in vitro and in experimental endocarditis caused by *Escherichia coli* producing SHV-2-like β-lactamase. Antimicrob. Agents Chemother. **34**:581–586.
25. **Garbarg-Chenon, A., V. Godard, R. Labia, and J.-C. Nicolas.** 1990. Nucleotide sequence of SHV-2 β-lactamase gene. Antimicrob. Agents Chemother. **34**:1444–1446.
26. **Gutmann, L., B. Ferré, F. W. Goldstein, N. Rizk, E. Pinto-Schuster, J. F. Acar, and E. Collatz.** 1989. SHV-5, a novel SHV-type β-lactamase that hydrolyzes broad-spectrum cephalosporins and monobactams. Antimicrob. Agents Chemother. **33**:951–956.
27. **Gutmann, L., M. D. Kitzis, D. Billot-Klein, F. Goldstein, G. Tran Van Nhieu, T. Lu, J. Carlet, E. Collatz, and R. Williamson.** 1988. Plasmid-mediated β-lactamase (TEM-7) involved in resistance to ceftazidime and aztreonam. Rev. Infect. Dis. **10**:860–866.
28. **Herzberg, O., and J. Moult.** 1987. Bacterial resistance to β-lactam antibiotics: crystal structure of β-lactamase from *Staphylococcus aureus* PC1 at 2.5 Å resolution. Science **236**:694–701.
29. **Huletsky, A., F. Couture, and R. C. Levesque.** 1990. Nucleotide sequence and phylogeny of SHV-2 β-lactamase. Antimicrob. Agents Chemother. **34**:1725–1732.
30. **Jacoby, G. A., and I. Carreras.** 1990. Activities of β-lactam antibiotics against *Escherichia coli* strains producing extended-spectrum β-lactamases. Antimicrob. Agents Chemother. **34**: 858–862.
31. **Jacoby, G. A., A. A. Medeiros, T. F. O'Brien, M. E. Pinto, and H. Jiang.** 1988. Broad-spectrum, transmissible β-lactamases. N. Engl. J. Med. **319**:723–724.
32. **Jacoby, G. A., and L. Sutton.** 1991. Properties of plasmids responsible for extended-spectrum β-lactamase production. Antimicrob. Agents Chemother. **35**:164–169.
33. **Jiang, H., J. D. Hopkins, J. Zieg, A. A. Medeiros, and T. F. O'Brien.** 1990. Origin and transposition of a gene encoding a TEM12 β lactamase on pBWH102 and pBWH501 in ceftazidime resistant (CAZ^R) isolates of *Klebsiella pneumoniae* at one U.S. medical center. Program Abstr. 30th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 186.
34. **Jiang, H., T. F. O'Brien, and A. A. Medeiros.** Unpublished data.
35. **Katsanis, G., and G. A. Jacoby.** Unpublished data.
36. **Kitzis, M.-D., N. Liassine, B. Ferré, L. Gutmann, J. F. Acar, and F. Goldstein.** 1990. In vitro activities of 15 oral β-lactams against *Klebsiella pneumoniae* harboring new extended-spectrum β-lactamases. Antimicrob. Agents Chemother. **34**:1783–1786.
37. **Kliebe, C., B. A. Nies, J. F. Meyer, R. M. Tolxdorff-Neutzling, and B. Wiedemann.** 1985. Evolution of plasmid-coded resistance to broad-spectrum cephalosporins. Antimicrob. Agents Chemother. **28**:302–307.
38. **Labia, R., A. Morand, K. Tiwari, J. Sirot, D. Sirot, and A. Petit.** 1988. Interactions of new plasmid-mediated β-lactamases with third-generation cephalosporins. Rev. Infect. Dis. **10**:885–891.
39. **Lachapelle, J., J. P. Quinn, D. Miyashiro, S. Walmsley, K. Bush, J. L. Brunton, and R. C. Levesque.** 1990. Sequence of genes *blaT*-10 and *blaT*-11 which encode the extended-spectrum β-lactamases TEM-10 and TEM-11. Program Abstr. 30th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 187.
40. **Lee, K.-Y., J. D. Hopkins, T. F. O'Brien, and M. Syvanen.** 1991. Gly238Ser substitution changes the substrate specificity of the SHV class A β-lactamases. Proteins, in press.
41. **Lee, K.-Y., J. D. Hopkins, and M. Syvanen.** 1990. Direct involvement of IS*26* in an antibiotic resistance operon. J. Bacteriol. **172**:3229–3236.
42. **Lopardo, H. A., and A. A. Medeiros.** Unpublished data.
43. **Lowbury, E. J. L., A. Kidson, H. A. Lilly, G. A. J. Ayliffe, and R. J. Jones.** 1969. Sensitivity of *Pseudomonas aeruginosa* to antibiotics: emergence of strains highly resistant to carbenicillin. Lancet **ii**:448–452.
44. **Mabilat, C., and P. Courvalin.** 1990. Development of "oligotyping" for characterization and molecular epidemiology of TEM β-lactamases in members of the family *Enterobacteriaceae*. Antimicrob. Agents Chemother. **34**:2210–2216.
45. **Martinez-Beltran, J., C. Negri, M. Morosini, R. Canton, E. Loza, F. Baquero, G. Papanicolaou, and A. Medeiros.** 1990. Acquisition of a new plasmid-mediated β-lactalactamase in a intrahospitalary *Salmonella arizonae* outbreak. Program Abstr. 30th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 185.
46. **Matsumoto, Y., F. Ikeda, T. Kamimura, Y. Yokota, and Y. Mine.** 1988. Novel plasmid-mediated β-lactamase from *Escherichia coli* that inactivates oxyimino-cephalosporins. Antimicrob. Agents Chemother. **32**:1243–1246.
47. **Matthew, M., R. W. Hedges, and J. T. Smith.** 1979. Types of β-lactamase determined by plasmids in gram-negative bacteria. J. Bacteriol. **138**:657–662.
48. **Medeiros, A. A.** 1989. Plasmid-determined beta-lactamases, p. 101–127. *In* L. E. Bryan (ed.), Handbook of experimental pharmacology, vol. 91. Microbial resistance to drugs. Springer-Verlag, Berlin.
49. **Medeiros, A. A., A. Bauernfeind, G. Papanicolaou, R. S. Hare, E. Papa, and G. Miller.** 1989. Novel extended broad-spectrum

beta-lactamases (EBS Blas) found in survey of enterobacteria from U.S. hospitals. Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 670.
50. **Medeiros, A. A., and G. A. Jacoby.** Unpublished data.
51. **Mercier, J., and R. C. Levesque.** 1990. Cloning of SHV-2, OHIO-1, and OXA-6 β-lactamases and cloning and sequencing of SHV-1 β-lactamase. Antimicrob. Agents Chemother. **34:** 1577–1583.
52. **Mulgrave, L.** 1990. Extended broad-spectrum β-lactamases in Australia. Med. J. Aust. **152:**444–445.
53. **Nicolas, M.-H., V. Jarlier, N. Honore, A. Philippon, and S. T. Cole.** 1989. Molecular characterization of the gene encoding SHV-3 β-lactamase responsible for transferable cefotaxime resistance in clinical isolates of *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. **33:**2096–2100.
54. **Pangon, B., C. Bizet, A. Buré, F. Pichon, A. Philippon, B. Regnier, and L. Gutmann.** 1989. In vivo selection of a cephamycin-resistant, porin-deficient mutant of *Klebsiella pneumoniae* producing a TEM-3 β-lactamase. J. Infect. Dis. **159:**1005–1006.
55. **Papafragos, E., G. A. Papanicolaou, T. F. O'Brien, and A. A. Medeiros.** Unpublished data.
56. **Papanicolaou, G. A., and A. A. Medeiros.** 1990. Discrimination of extended-spectrum β-lactamases by a novel nitrocefin competition assay. Antimicrob. Agents Chemother. **34:**2184–2192.
57. **Papanicolaou, G. A., A. A. Medeiros, and G. A. Jacoby.** 1990. Novel plasmid-mediated β-lactamase (MIR-1) conferring resistance to oxyimino- and α-methoxy β-lactams in clinical isolates of *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. **34:** 2200–2209.
58. **Paul, G. C., G. Gerbaud, A. Bure, A. M. Philippon, B. Pangon, and P. Courvalin.** 1989. TEM-4, a new plasmid-mediated β-lactamase that hydrolyzes broad-spectrum cephalosporins in a clinical isolate of *Escherichia coli*. Antimicrob. Agents Chemother. **33:**1958–1963.
59. **Payne, D. J., and S. G. B. Amyes.** 1991. Transferable resistance to extended-spectrum β-lactams: a major threat or a minor inconvenience? J. Antimicrob. Chemother. **27:**255–261.
60. **Payne, D. J., P. H. Blakemore, Y. J. Drabu, and S. G. B. Amyes.** 1989. Comparison of TEM-E3 and TEM-5 β-lactamases. J. Antimicrob. Chemother. **24:**615–617.
61. **Payne, D. J., J. Hood, M. S. Marriott, and S. G. B. Amyes.** 1990. Separation of plasmid-mediated extended spectrum β-lactamases by fast protein liquid chromotography (FPLC system). FEMS Microbiol. Lett. **69:**195–200.
62. **Payne, D. J., M. S. Marriott, and S. G. B. Amyes.** 1989. TEM-E1: a novel β-lactamase conferring resistance to ceftazidime. FEMS Microbiol. Lett. **59:**97–100.
63. **Payne, D. J., M. S. Marriott, and S. G. B. Amyes.** 1990. Characterisation of a unique ceftazidime-hydrolyzing β-lactamase, TEM-E2. J. Med. Microbiol. **32:**131–134.
64. **Péduzzi, J., M. Barthélémy, K. Tiwari, D. Mattioni, and R. Labia.** 1989. Structural features related to hydrolytic activity against ceftazidime of plasmid-mediated SHV-type CAZ-5 β-lactamase. Antimicrob. Agents Chemother. **33:**2160–2163.
65. **Petit, A., G. Gerbaud, D. Sirot, P. Courvalin, and J. Sirot.** 1990. Molecular epidemiology of TEM-3 (CTX-1) β-lactamase. Antimicrob. Agents Chemother. **34:**219–224.
66. **Petit, A., D. L. Sirot, C. M. Chanal, J. L. Sirot, R. Labia, G. Gerbaud, and R. A. Cluzel.** 1988. Novel plasmid-mediated β-lactamase in clinical isolates of *Klebsiella pneumoniae* more resistant to ceftazidime than to other broad-spectrum cephalosporins. Antimicrob. Agents Chemother. **32:**626–630.
67. **Philippon, A., S. Ben Redjeb, G. Fournier, and A. Ben Hassen.** 1989. Epidemiology of extended spectrum β-lactamases. Infection **17:**347–354.
68. **Philippon, A., R. Labia, and G. Jacoby.** 1989. Extended-spectrum β-lactamases. Antimicrob. Agents Chemother. **33:**1131–1136.
69. **Philippon, A., G. Paul, G. Vedel, and P. Névot.** 1988. Résistance plasmidique aux céphalosporines de 3^{e} generation. Presse Med. **17:**1883–1889.
70. **Podbielski, A., and B. Melzer.** 1990. Nucleotide sequence of the gene encoding the SHV-2 β-lactamase (bla_{SHV-2}) of *Klebsiella ozaenae*. Nucleic Acids Res. **18:**4916.
71. **Punyagupta, M., J. Quinn, D. Miyashiro, and K. Bush.** 1990. Novel extended-spectrum plasmid-mediated beta-lactamase hydrolyzing ceftazidime in *Klebsiella pneumoniae*. Program Abstr. 30th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 188.
72. **Quinn, J. P., D. Miyashiro, D. Sahm, R. Flamm, and K. Bush.** 1989. Novel plasmid-mediated β-lactamase (TEM-10) conferring selective resistance to ceftazidime and aztreonam in clinical isolates of *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. **33:**1451–1456.
73. **Rice, L. B., S. H. Willey, G. A. Papanicolaou, A. A. Medeiros, G. M. Eliopoulos, R. C. Moellering, Jr., and G. A. Jacoby.** 1990. Outbreak of ceftazidime resistance caused by extended-spectrum β-lactamases at a Massachusetts chronic-care facility. Antimicrob. Agents Chemother. **34:**2193–2199.
74. **Rice, L. B., J. D. C. Yao, K. Klimm, G. M. Eliopoulos, and R. C. Moellering, Jr.** 1991. Efficacy of different β-lactams against an extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* strain in the rat intra-abdominal abscess model. Antimicrob. Agents Chemother. **35:**1243–1244.
75. **Richard, C., A. Philippon, S. M'Boup, and J. F. Vieu.** 1989. Epidemiologie des infections pediatriques a *Klebsiella* dans deux hopitaux de Dakar. Production de β-lactamases a spectre elargi (1987–1988). Med. Mal. Infect. **19:**753–759.
76. **Sanders, C. C.** 1987. Chromosomal cephalosporinases responsible for multiple resistance to newer β-lactam antibiotics. Annu. Rev. Microbiol. **41:**573–593.
77. **Shannon, K. P., A. King, I. Phillips, M. H. Nicolas, and A. Philippon.** 1990. Importation of organisms producing broad-spectrum SHV-group β-lactamases into the United Kingdom. J. Antimicrob. Chemother. **25:**343–351.
78. **Sirot, D., C. Chanal, R. Labia, M. Meyran, J. Sirot, and R. Cluzel.** 1989. Comparative study of five plasmid-mediated ceftazidimases isolated in *Klebsiella pneumoniae*. J. Antimicrob. Chemother. **24:**509–521.
79. **Sirot, D., J. Sirot, R. Labia, A. Morand, P. Courvalin, A. Darfeuille-Michaud, R. Perroux, and R. Cluzel.** 1987. Transferable resistance to third-generation cephalosporins in clinical isolates of *Klebsiella pneumoniae*: identification of CTX-1, a novel β-lactamase. J. Antimicrob. Chemother. **20:**323–334.
80. **Smith, C. E., B. S. Tillman, A. W. Howell, R. N. Longfield, and J. H. Jorgensen.** 1990. Failure of ceftazidime-amikacin therapy for bacteremia and meningitis due to *Klebsiella pneumoniae* producing an extended-spectrum β-lactamase. Antimicrob. Agents Chemother. **34:**1290–1293.
81. **Sougakoff, W., S. Goussard, and P. Courvalin.** 1988. The TEM-3 β-lactamase, which hydrolyzes broad-spectrum cephalosporins, is derived from the TEM-2 penicillinase by two amino acid substitutions. FEMS Microbiol. Lett. **56:**343–348.
82. **Sougakoff, W., A. Petit, S. Goussard, D. Sirot, A. Bure, and P. Courvalin.** 1989. Characterization of the plasmid genes *blaT-4* and *blaT-5* which encode the broad-spectrum β-lactamases TEM-4 and TEM-5 in Enterobacteriaceae. Gene **78:**339–348.
83. **Sowek, J. A., S. B. Singer, S. Ohringer, M. F. Malley, T. J. Dougherty, J. Z. Gougoutas, and K. Bush.** 1991. Substitution of lysine at position 104 or 240 of TEM-1_{pTZ18R} β-lactamase enhances the effect of serine-164 substitution on hydrolysis or affinity for cephalosporins and the monobactam aztreonam. Biochemistry **30:**3179–3188.
84. **Spencer, R. C., P. F. Wheat, T. G. Winstanley, D. M. Cox, and S. J. Plested.** 1987. Novel β-lactamase in a clinical of *Klebsiella pneumoniae* conferring unusual resistance to β-lactam antibiotics. J. Antimicrob. Chemother. **20:**919–921.
85. **Sutcliffe, J. G.** 1978. Nucleotide sequence of the ampicillin resistance gene of *Escherichia coli* plasmid pBR322. Proc. Natl. Acad. Sci. USA **75:**3737–3741.
86. **Thabaut, A., J. Acar, P. Allouch, G. Arlet, L. Berardi-Grassias, E. Bergogne-Bérézin, Y. Brun, Y. Buisson, G. Chabanon, R. Cluzel, A. Courtieu, H. Dabernat, J. Duval, J. Fleurette, V. Jarlier, M. Meyran, H. Monteil, P. Nevot, J. C. Petithory, A. Philippon, M. E. Reverdy, A. Reynaud, A. Sedallian, J. Sirot,**

and B. Werneburg. 1990. Fréquence et distribution des bêtalactamases chez 1 792 souches de *Klebsiella pneumoniae* isolées en France entre 1985 et 1988. Pathol. Biol. **38**:459–463.

87. **Thomson, K. S., C. C. Sanders, and J. A. Washington II.** 1991. High-level resistance to cefotaxime and ceftazidime in *Klebsiella pneumoniae* isolates from Cleveland, Ohio. Antimicrob. Agents Chemother. **35**:1001–1003.
88. **Vatopoulos, A. C., A. Philippon, L. S. Tzouvelekis, Z. Komninou, and N. J. Legakis.** 1990. Prevalence of transferable SHV-5 type β-lactamase in clinical isolates of *Klebsiella pneumoniae* and *Escherichia coli* in Greece. J. Antimicrob. Chemother. **26**:635–648.
89. **Vuye, A., G. Verschraegen, and G. Claeys.** 1989. Plasmid-mediated β-lactamases in clinical isolates of *Klebsiella pneumoniae* and *Escherichia coli* resistant to ceftazidime. Antimicrob. Agents Chemother. **33**:757–761.
90. **Watanabe, M., S. Iyobe, M. Inoue, and S. Mitsuhashi.** 1991. Transferable imipenem resistance in *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother. **35**:147–151.
91. **Webber, D. A., C. C. Sanders, J. S. Bakken, and J. P. Quinn.** 1990. A novel chromosomal TEM derivative and alterations in outer membrane proteins together mediate selective ceftazidime resistance in *Escherichia coli*. J. Infect. Dis. **162**:460–465.
92. **Woodford, N., D. J. Payne, A. P. Johnson, M. J. Weinbren, R. M. Perinpanayagam, R. C. George, B. D. Cookson, and S. G. B. Amyes.** 1990. Transferable cephalosporin resistance not inhibited by clavulanate in *Escherichia coli*. Lancet **336**:253.