

AmpC β -Lactamases

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INTRODUCTION

The first bacterial enzyme reported to destroy penicillin was the AmpC β -lactamase of *Escherichia coli*, although it had not been so named in 1940 (1). Swedish investigators began a systematic study of the genetics of penicillin resistance in *E. coli* in 1965. Mutations with stepwise-enhanced resistance were termed *ampA* and *ampB* (84, 85). A mutation in an *ampA* strain that resulted in reduced resistance was then designated *ampC*. *ampA* strains overproduced β -lactamase, suggesting a regulatory role for the *ampA* gene (180). *ampB* turned out not to be a single locus, and such strains were found to have an altered cell envelope (236). *ampC* strains made little if any β -lactamase, suggesting that *ampC* was the structural gene for the enzyme (46). Most of the *amp* nomenclature has changed over the years, but the designation *ampC* has persisted. The sequence of the *ampC* gene from *E. coli* was reported in 1981 (144). It differed from the sequence of penicillinase-type β -lactamases such as TEM-1 but, like them, had serine at its active site (161). In the Ambler structural classification of β -lactamases (7), AmpC enzymes belong to class C, while in the functional classification scheme of Bush et al. (47), they were assigned to group 1.

DISTRIBUTION

When the functional classification scheme was published in 1995, chromosomally determined AmpC β -lactamases in *Enterobacteriaceae* and also in a few other families were known (47). Since then, the number of sequenced bacterial genes and genomes has grown enormously. In GenBank, *ampC* genes are included in COG 1680, where COG stands

for cluster of orthologous groups. COG 1680 comprises other penicillin binding proteins as well as class C β -lactamases and includes proteins from archaea as well as bacteria, gram-positive as well as gram-negative organisms, strict anaerobes along with facultative ones, and soil and water denizens as well as human pathogens, such as species of *Legionella* and *Mycobacterium*. Sequence alone is insufficient to differentiate an AmpC β -lactamase from ubiquitous low-molecular-weight penicillin binding proteins involved in cell wall biosynthesis, such as D-peptidase (D-alanyl-D-alanine carboxypeptidase/transpeptidase). Both have the same general structure and share conserved sequence motifs near an active-site serine (149, 162). *E. coli* even produces a β -lactam binding protein, AmpH, which is related to AmpC structurally but lacks β -lactamase activity (121). The AmpC name is not trustworthy since several enzymes so labeled in the literature actually belong to class A (177, 337). Cephalosporinase activity is not reliable either, since some β -lactamases with predominant activity on cephalosporins belong to class A (97, 205, 278, 298). Accordingly, the conservative listing of AmpC β -lactamases in Table 1 includes proteins with the requisite structure from organisms that have been demonstrated to possess appropriate AmpC-type β -lactamase activity. It is undoubtedly incomplete. For example, organisms not yet shown to produce a functional AmpC-type enzyme but with identified *ampC* genes include such diverse bacteria as *Agrobacterium tumefaciens* (110), *Coxiella burnetii* (GenBank accession number YP_001424134), *Legionella pneumophila* (56), *Rickettsia felis* (239), and *Sinorhizobium meliloti* (127). For other organisms, supportive MIC or enzymatic but not structural data are available for the presence of AmpC β -lactamase, including *Enterobacter sakazakii* (258), *Ewingella americana* (311), *Providencia rettgeri* (207), and several species of *Serratia* (306, 307) and *Yersinia* (215, 288, 313). The phylum *Proteobacteria* contains the largest number, but at least one acid-fast actinobacte-

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TABLE 1. Taxonomy of bacteria expressing chromosomally determined AmpC β -lactamases

Phylum, class, and order	Genus and species	GenBank protein accession no.	Reference(s)
<i>Actinobacteria</i>	<i>Mycobacterium smegmatis</i>	YP_888266	92
<i>Proteobacteria</i>			
<i>Alphaproteobacteria</i>	<i>Ochrobactrum anthropi</i>	CAC04522	127, 226
	<i>Rhodobacter sphaeroides</i>	YP_355256	24
	<i>Chromobacterium violaceum</i>	NP_900980	87
<i>Betaproteobacteria</i>			
<i>Neisseriales</i>	<i>Laribacter hongkongensis</i>	AAT46346	167
<i>Gammaproteobacteria</i>			
<i>Aeromonadales</i>	<i>Aeromonas caviae</i>	AAM46773	95
	<i>Aeromonas hydrophila</i>	YP_857635	11, 334
	<i>Aeromonas jandaei</i> ^a	AAA83416	272
	<i>Aeromonas salmonicida</i>	ABO89301	120
	<i>Aeromonas veronii</i> bv. <i>sobria</i>	CAA56561	333, 334
<i>Enterobacteriales</i>	<i>Buttiauxella agrestis</i>	AAN17791	90
	<i>Citrobacter braakii</i>	AAM11668	223
	<i>Citrobacter freundii</i>	AAM93471	178
	<i>Citrobacter murlinae</i>	AAM11664	12, 223
	<i>Citrobacter youngae</i>	CAD32304	12
	<i>Citrobacter werkmanii</i>	AAM11670	223
	<i>Edwardsiella tarda</i>	ABO48510	312
	<i>Enterobacter aerogenes</i>	AAO16528	266
	<i>Enterobacter asburiae</i>	CAC85157	279
	<i>Enterobacter cancerogenus</i>	AAM11666	223
	<i>Enterobacter cloacae</i>	P05364	101
	<i>Enterobacter dissolvens</i>	CAC85359	279
	<i>Enterobacter hormaechei</i>	CAC85357	279
	<i>Enterobacter intermedius</i> ^b	CAC85358	279
	<i>Erwinia rhapontici</i>	AAP40275	225
	<i>Escherichia albertii</i>	EDS93081	310
	<i>Escherichia fergusonii</i>	AAM11671	223
	<i>Escherichia coli</i>	NP_418574	144
	<i>Hafnia alvei</i>	AAF86691	107, 320
	<i>Morganella morganii</i>	AAC68582	260, 264
	<i>Providencia stuartii</i>	CAA76739	68
	<i>Serratia marcescens</i>	AAK64454	148
	<i>Shigella boydii</i>	YP_410551	291
	<i>Shigella dysenteriae</i> ^c	YP_405772	291
	<i>Shigella flexneri</i> ^c	YP_691594	291
	<i>Shigella sonnei</i>	YP_313059	291
	<i>Yersinia enterocolitica</i>	YP_001006653	293, 294, 296
	<i>Yersinia mollaretii</i>	ZP_00826692	309
	<i>Yersinia ruckeri</i>	ABA70720	198, 288
<i>Oceanospirillales</i>	<i>Chromohalobacter</i>	BAD16740	321
<i>Pseudomonadale</i>	<i>Acinetobacter baumannii</i>	CAB77444	39
	<i>Acinetobacter baylyi</i>	CAL25116	26
	<i>Pseudomonas aeruginosa</i>	NP_252799	281
	<i>Pseudomonas fluorescens</i>	YP_349452	209
	<i>Psychrobacter immobilis</i>	CAA58569	88
<i>Xanthomonadales</i>	<i>Lysobacter lactamgenus</i>	CAA39987	159

^a Originally named *Aeromonas sobria*.

^b Alternate name, *Kluyvera intermedia*.

^c *Shigella* strains with enhanced virulence and a 190-kb chromosomal deletion that includes *bla*_{AmpC} have been described (208).

rium also produces AmpC β -lactamase. Sequence variation occurs within each type. For example, more than 25 varieties of AmpC β -lactamase that share $\geq 94\%$ protein sequence identity have been described for *Acinetobacter* spp. (137; G. Bou et al., personal communication), and GenBank contains similar multiple listings for *E. coli*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and other organisms. Some frequently encountered *Enterobacteriaceae* are conspicuous by their absence. *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, and *Salmonella* spp. (31) lack a chromosomal

*bla*_{AmpC} gene, as do *Citrobacter amalonaticus* (328), *Citrobacter farmeri*, *Citrobacter gilleni* (224), *Citrobacter koseri* (formerly *Citrobacter diversus* and *Levinea malonatica*), *Citrobacter rodentium*, *Citrobacter sedlakii* (252), *Edwardsiella hoshinae*, *Edwardsiella ictaluri* (312), *Kluyvera ascorbata* (138, 305), *Kluyvera cryocrescens* (72), *Plesiomonas shigelloides* (9), *Proteus penneri* (175), *Proteus vulgaris* (60), *Rahnella aquatilis* (30, 308), *Yersinia pestis*, and *Yersinia pseudotuberculosis* (313) as well as, probably, *Escherichia hermannii* (91), *Francisella tularensis* (27), *Shewanella algae* (123),

TABLE 2. Physical and kinetic parameters

Enzyme class	Source	Location ^a	Molecular mass (kDa)	pI	Relative k_{cat}							Reference(s)
					Benzylpenicillin	Ampicillin	Cefazolin	Cephaloridine	Cefoxitin	Cefotaxime	Imipenem ^c	
C	<i>E. cloacae</i>	Chr	39.2	8.4	100	5	21,400	5,000	0.43	0.11	0.02	99, 100, 211
	<i>C. freundii</i>	Chr	39.9		100	21	16,100	2,260	1	0.05	0.05	99, 100, 287
	<i>E. coli</i> K-12	Chr	39.6	8.7	100	9	333	289	0.44	0.38	0.02	99, 100, 144, 212
	<i>S. marcescens</i>	Chr	37	9.5	100	0.6	1,730	1,470	0.02	2.3	0.001	99, 100, 148
	<i>P. aeruginosa</i>	Chr	34	8.4	100	6	— ^b	145	0.015	0.20	0.03	99, 100, 102, 221
	ACT-1	P	39.4	9.0	100	1.8	1,020	>455	0.67	0.09	0.02	25, 41
	MIR-1	P	39.2	8.4	100	3.9	— ^b	1,540	4.6	19.3	0.09	25, 248
	CMY-1	P	39.9	8.0	100	3.5	2,500	1,190	0.38	0.08	0.02	20, 25
	CMY-2	P	38.8	9.0	100	3.9	— ^b	1,536	1.64	0.29	0.24	22, 25
A	TEM-2	P	22.0	5.4	100	95	34	315				204
	<i>B. licheniformis</i>	Chr	29.5		100	68	14	29				204
D	OXA-29	Chr	28.5	>9	100	164	17			0.26	NH	96

^a Chr, chromosomal; P, plasmid.

^b Biphasic kinetics.

^c NH, no hydrolysis detected.

and *Stenotrophomonas maltophilia* (111). However, since *bla*_{AmpC} genes occur on transmissible plasmids, the clinical microbiologist needs to consider this resistance mechanism whatever the identification of an organism.

PHYSICAL AND ENZYMATIC PROPERTIES

AmpC enzymes typically have molecular masses of 34 to 40 kDa and isoelectric points of >8.0, although the isoelectric points of plasmid-mediated FOX enzymes are lower (6.7 to 7.2) (254), and an AmpC enzyme from *Morganella morganii* has an isoelectric point of 6.6 (264). The enzymes are located in the bacterial periplasm, with the exception of the AmpC β -lactamase of *Psychrobacter immobilis*, which is secreted mainly into the external medium (88). They are active on penicillins but even more active on cephalosporins and can hydrolyze cephamycins such as cefoxitin and cefotetan; oxyiminocephalosporins such as ceftazidime, cefotaxime, and ceftriaxone; and monobactams such as aztreo-

nam but at a rate <1% of that of benzylpenicillin (Table 2, which also shows data for class A and D β -lactamases for comparison). Although the hydrolysis rate for such substrates is low due to slow deacylation (99), the enzyme affinity, as reflected by a low K_m , is high (Table 3), a factor that becomes important at low substrate concentrations. The hydrolysis rates for cefepime, ceftipime, and carbapenems are also very low, and the estimated K_m values for cefepime and ceftipime are high, reflecting lower enzyme affinity (283).

With preferred cephalosporin substrates, the turnover rate of the *E. cloacae* P99 β -lactamase is diffusion limited rather than catalysis limited, implying that AmpC enzymes have evolved to maximal efficiency (45). Such data also suggest that AmpC β -lactamase evolved to deal with cephalosporins rather than for some other cellular function, although there is some evidence to suggest that these enzymes play a morphological role (121).

TABLE 3. Enzyme kinetics

Enzyme class	Source	K_m (μ M)							Reference(s)	
		Benzylpenicillin	Ampicillin	Cefazolin	Cephaloridine	Cefoxitin	Cefotaxime	Aztreonam		Imipenem ^b
C	<i>E. cloacae</i>	0.6	0.4	1,500	70	0.024	0.01	0.0012	0.04	99, 100
	<i>C. freundii</i>	0.4	0.2	600	35	0.250	0.005	0.0014	0.085	99, 100
	<i>E. coli</i> K-12	4.4	3.5	400	170	0.650	1.7	0.0012	0.8	99, 100
	<i>S. marcescens</i>	1.7	0.01	540	275	0.3	12	0.058	0.06	99, 100, 148
	<i>P. aeruginosa</i>	1.7	0.5	— ^a	20	0.05	0.2	0.050	0.026	99, 100
	ACT-1	2.1	1.7	430	>200	0.5	0.07	0.012	0.37	25
	MIR-1	0.4	0.16	— ^a	93	0.75	4	0.004	0.15	25
	CMY-1	1	2.2	54	110	0.055	0.015	0.01	0.05	25
	CMY-2	0.4	0.16	— ^a	93	0.07	0.0012	<0.003	ND	25
	A	TEM-2	15–20	22	680	2,100		3,000		
<i>B. licheniformis</i>		76	143	12	135		205			204
D	OXA-29	10	16	30			128	210	NH	96

^a Biphasic kinetics.

^b ND, not determined; NH, no hydrolysis detected.

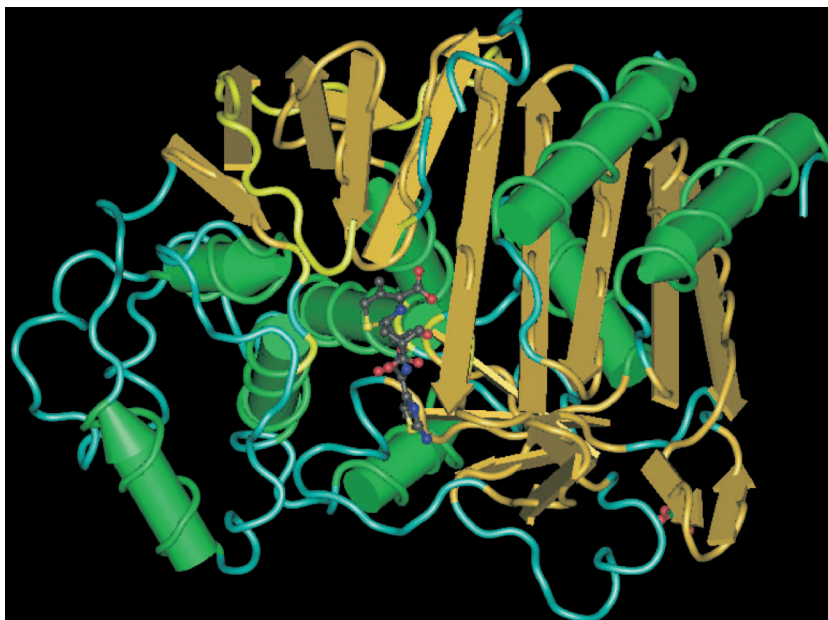


FIG. 1. Diagram of AmpC from *E. coli* complexed with acylated ceftazidime (PDB accession number 1IEL) (265) created with Cn3CD, version 4.1 (available at <http://www.ncbi.nlm.nih.gov>). The R2 loop at the top of the molecule and conserved residues S64, K67, Y150, N152, K315, and A318 are shown in yellow. β -Strands are gold, and α -helices are green.

Inhibitors of class A enzymes such as clavulanic acid, sulbactam, and tazobactam have much less effect on AmpC β -lactamases, although some are inhibited by tazobactam or sulbactam (48, 157, 218). AmpC β -lactamases are poorly inhibited by *p*-chloromercuribenzoate and not at all by EDTA. Cloxacillin, oxacillin, and aztreonam, however, are good inhibitors (47).

STRUCTURE AND ESSENTIAL SITES

The known three-dimensional structures of AmpC enzymes are very similar (Fig. 1). There is an α -helical domain on one side of the molecule (Fig. 1, left) and an α/β domain on the other (Fig 1, right). The active site lies in the center of the enzyme at the left edge of the five-stranded β -sheet with the

reactive serine residue at the amino terminus of the central α -helix (162, 190). The active site can be further subdivided into an R1 site, accommodating the R1 side chain of the β -lactam nucleus, and an R2 site for the R2 side chain (Fig. 2). The R1 site is bounded by the Ω -loop, while the R2 site is enclosed by the R2 loop containing the H-10 and H-11 helices. Overall, the AmpC structure is similar to that of class A β -lactamases (and DD-peptidase) except that the binding site is more open in class C enzymes, reflecting their greater ability to accommodate the bulkier side chains of cephalosporins. Key catalytic residues in addition to Ser64 for AmpC enzymes include Lys67, Tyr150, Asn152, Lys315, and Ala318, with substitutions at these sites lowering enzymatic activity dramatically (54). In the folded protein, most of these essential residues are

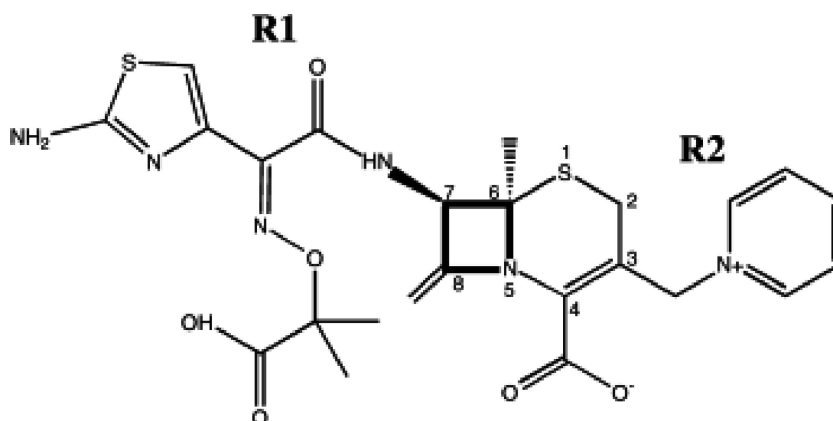


FIG. 2. Schematic representation of ceftazidime with the R1 side chain at C7 and the R2 side chain at C3. (Adapted from reference 158 with permission from Blackwell Publishing Ltd.)

found at the active site, with Lys67 hydrogen bonded to Ser64 and Tyr150 acting as a transient catalytic base (79).

REGULATION

In many *Enterobacteriaceae*, AmpC expression is low but inducible in response to β -lactam exposure. The induction mechanism is complex (118, 139, 140). The disruption of murein biosynthesis by a β -lactam agent leads to an accumulation of *N*-acetylglucosamine-1,6-anhydro-*N*-acetylmuramic acid oligopeptides. The *N*-acetylglucosamine moiety is removed to produce a series of 1,6-anhydro-*N*-acetylmuramic acid tri-, tetra-, and pentapeptides. These oligopeptides compete with oligopeptides of UDP-*N*-acetylmuramic acid for a binding site on AmpR, a member of the LysR transcriptional regulator family. Displacement of the UDP-*N*-acetylmuramic acid peptides signals a conformational change in AmpR, which activates the transcription of *ampC*. In addition, the cell has an enzyme, AmpD, a cytoplasmic *N*-acetyl-muramyl-L-alanine amidase, that removes stem peptides from the 1,6-anhydro-*N*-acetylmuramic acid and *N*-acetylglucosamine-1,6-anhydro-*N*-acetylmuramic acid oligopeptide derivatives, thus reducing their concentrations and preventing the overexpression of AmpC.

The most common cause of AmpC overexpression in clinical isolates is a mutation in *ampD* leading to AmpC hyperinducibility or constitutive hyperproduction (289). AmpR mutations are less common but can also result in high-constitutive or hyperinducible phenotypes (118, 153, 165). Least common are mutations in AmpG, which result in constitutive low-level expression. AmpG is an inner membrane permease that transports the oligopeptides involved in cell wall recycling and AmpC regulation into the cytosol (179).

Different organisms add additional features to AmpC regulation. *E. coli* lacks an *ampR* gene (129). Consequently, AmpC in *E. coli* is noninducible but is regulated by promoter and attenuator mechanisms (145), as is AmpC production in *Shigella* (33). *Acinetobacter baumannii* also lacks an *ampR* gene so that its AmpC β -lactamase is noninducible (39). AmpC in *Serratia marcescens* is regulated by *ampR*, but the *ampC* transcript has an unusual untranslated region of 126 bases forming a stem-loop structure that influences the transcript half-life (191). *P. aeruginosa* PAO1 has three *ampD* genes, explaining the stepwise upregulation of AmpC production seen in this organism with the successive inactivation of each *ampD* gene (151). The multiple *ampD* loci contribute to virulence since a *P. aeruginosa* strain partially derepressed by the inactivation of one *ampD* allele remains fully virulent, while double or triple *ampD* mutants lose the ability to compete in a mouse model of systemic infection (219). Other aspects of AmpC regulation in *P. aeruginosa* are also more complex than that in the *Enterobacteriaceae*. AmpR is involved in the regulation of other genes besides AmpC (164), an *ampE* gene encoding a cytoplasmic membrane protein acting as a sensory transducer has a role in *ampC* expression as part of an *ampDE* operon (150), and the CreBCD system as well as *dacB*, encoding a nonessential penicillin binding protein, are involved in AmpC hyperproduction as well (219a).

β -Lactams differ in their inducing abilities (184, 189, 285, 302). Benzylpenicillin, ampicillin, amoxicillin, and cephalospo-

TABLE 4. Susceptibility of inducible and stably derepressed clinical isolates^a

Antimicrobial agent	Geometric mean MIC (μ g/ml)				
	<i>E. cloacae</i>		<i>P. aeruginosa</i>		
	Inducible	Fully derepressed	Inducible	Partially derepressed	Fully derepressed
Cefotaxime	0.31	215	19.5	132	>323
Ceftazidime	0.23	64	1.3	3.3	25.4
Ceftriaxone	0.44	430	4.3	313	>323
Aztreonam	0.06	38	4.3	5.6	50.8
Cefoxitin	256	304			
Imipenem	0.56	0.71	1.3	2.5	2.5

^a Adapted from reference 184 with kind permission from Springer Science and Business Media.

rins such as cefazolin and cephalothin are strong inducers and good substrates for AmpC β -lactamase. Cefoxitin and imipenem are also strong inducers but are much more stable for hydrolysis (Table 4). Cefotaxime, ceftriaxone, ceftazidime, cefepime, cefuroxime, piperacillin, and aztreonam are weak inducers and weak substrates but can be hydrolyzed if enough enzyme is made. Consequently, MICs of weakly inducing oxymino- β -lactams are dramatically increased with AmpC hyperproduction. Conversely, MICs of agents that are strong inducers show little change with regulatory mutations because the level of induced *ampC* expression is already high (Table 4). β -Lactamase inhibitors are also inducers, especially clavulanate, which has little inhibitory effect on AmpC β -lactamase activity (336) but can paradoxically appear to increase AmpC-mediated resistance in an inducible organism (160). The inducing effect of clavulanate is especially important for *P. aeruginosa*, where clinically achieved concentrations of clavulanate by inducing AmpC expression have been shown to antagonize the antibacterial activity of ticarcillin (181).

The AmpC enzyme in *Aeromonas* spp. is controlled, along with two other chromosomally encoded β -lactamases, not by an AmpR-type system but by a two-component regulator, termed *brlAB* in *Aeromonas hydrophila* (5, 234). BrIB is a histidine sensor kinase, the regulated β -lactamase genes are preceded by a short sequence tag (TTCAC), and an inner membrane protein is also involved in regulation, but the chemical signal for induction is not yet known (10). *E. coli* has a homologous regulatory system, and there is some evidence that two-component regulators also play a role in the expression of *E. coli ampC* (128).

PUMPS AND PORINS

In addition to the amount and intrinsic activity of β -lactamase, the rate at which the substrate is delivered to the enzyme is an important determinant of the resistance spectrum. The concentration of β -lactam substrate in the periplasm is a function of the permeability of the cell's outer membrane, in particular the presence of porin channels through which β -lactams penetrate and of efflux pumps, which transport them out of the cell. At one time, the binding of substrate to AmpC β -lactamase was entertained as a mechanism to explain resistance to β -lactams that appeared to be poorly hydrolyzed (316). Vu and Nikaido pointed out, however, that at the concentration of

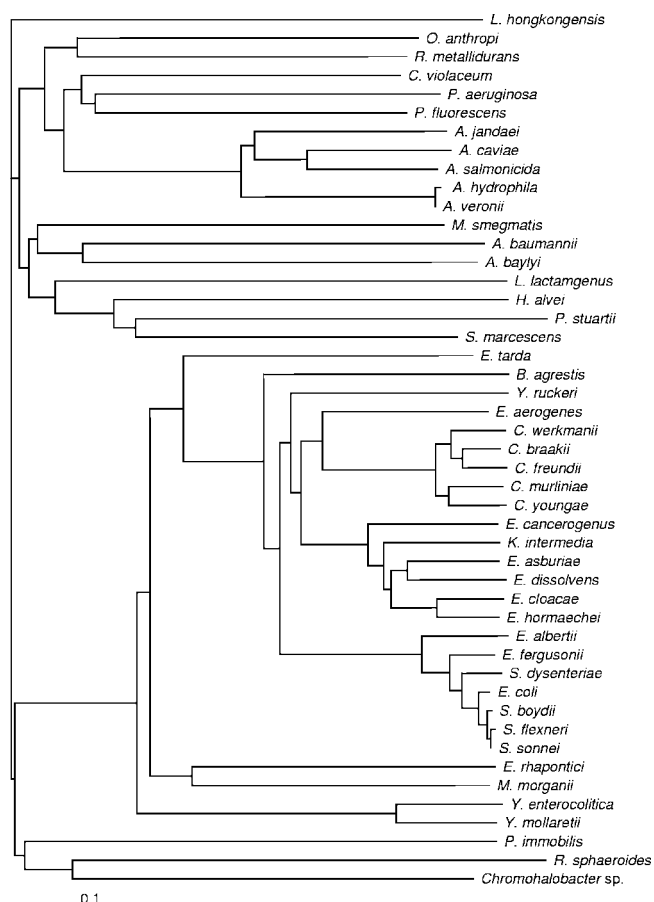


FIG. 3. Phylogram of AmpC enzymes listed in Table 1 constructed with ClustalX (available at <http://bips.u-strasbg.fr/fr/Documentation/ClustalX/>).

β -lactams in the periplasm needed to inhibit target penicillin binding proteins, AmpC β -lactamases can hydrolyze cephalosporins despite a low V_{\max} if the substrate also has a low K_m (330). Decreasing the number of porin entry channels or increasing efflux pump expression can lower influx and further augment enzyme efficiency. Thus, carbapenem resistance in clinical isolates of *P. aeruginosa* involves various combinations of overproduction of AmpC β -lactamase, decreased production of the OprD porin channel for imipenem entry, and activation of MexAB-OprM and other efflux systems (114, 163,

185, 268). Also, cephalosporins with both positive and negative charges (i.e., zwitterionic molecules) such as cefepime and ceftipime have the advantage of penetrating the outer bacterial membrane more rapidly than those with a net positive charge, such as cefotaxime and ceftriaxone, thus more easily reaching their lethal targets without β -lactamase inactivation (233).

PHYLOGENY

The serine β -lactamases are ancient enzymes estimated to have originated more than 2 billion years ago. A structure-based phylogeny indicates that the divergence of AmpC-type enzymes predated the divergence of class A and class D β -lactamases from a common ancestor (116). Figure 3 provides an overview of the phylogenetic relationship between the enzymes listed in Table 1. As would be expected, AmpC enzymes from organisms belonging to the same genus cluster together, while the AmpC β -lactamases of *Enterobacteriaceae*, *Pseudomonas*, and *Acinetobacter* are more distantly related.

PLASMID-MEDIATED AmpC β -LACTAMASES

Plasmid-encoded AmpC genes have been known since 1989 (Table 5) (254, 335). They have been found around the world in nosocomial and nonnosocomial isolates, having been most easily detected in those enterobacteria not expected to produce an AmpC β -lactamase. Minor differences in amino acid sequence have given rise to families. Forty-three CMY alleles are currently known (<http://www.lahey.org/Studies/>), and in GenBank, sequence data can be found (some of it unpublished) for seven varieties of FOX; four varieties of ACC, LAT, and MIR; three varieties of ACT and MOX; and two varieties of DHA. Some of these varieties are determined by chromosomal genes and represent possible progenitors for the plasmid-determined enzymes.

As indicated in Table 5, the plasmid-determined enzymes are related, sometimes very closely, to chromosomally determined AmpC β -lactamases. CMY is represented twice since it has two quite different origins. Six current varieties (CMY-1, -8, -9, -10, -11, and -19) are related to chromosomally determined AmpC enzymes in *Aeromonas* spp., while the remainder (including CMY-2, the most common plasmid-mediated AmpC β -lactamase worldwide) are related to AmpC β -lactamases of *Citrobacter freundii*. The LAT enzymes have a similar origin, but of the four original LAT enzymes, improved se-

TABLE 5. Chronology and homology of plasmid-mediated AmpC β -lactamases

AmpC β -lactamase	Country of origin	Publication yr	Species of first isolate	Likely source of AmpC gene	Similarity (%)	Reference(s)
CMY-1	South Korea	1989	<i>K. pneumoniae</i>	<i>A. hydrophila</i>	82	20, 23
CMY-2	Greece	1996	<i>K. pneumoniae</i>	<i>C. freundii</i>	96	22
MIR-1	United States	1990	<i>K. pneumoniae</i>	<i>E. cloacae</i>	99	142, 248
MOX-1	Japan	1993	<i>K. pneumoniae</i>	<i>A. hydrophila</i>	80	134
LAT-1	Greece	1993	<i>K. pneumoniae</i>	<i>C. freundii</i>	95	326
FOX-1	Argentina	1994	<i>K. pneumoniae</i>	<i>A. caviae</i>	99	95, 109
DHA-1	Saudi Arabia	1997	<i>S. enteritidis</i>	<i>M. morgani</i>	99	98
ACT-1	United States	1997	<i>K. pneumoniae</i>	<i>E. asburiae</i>	98	41, 279
ACC-1	Germany	1999	<i>K. pneumoniae</i>	<i>H. alvei</i>	99	21, 106
CFE-1	Japan	2004	<i>E. coli</i>	<i>C. freundii</i>	99	229

TABLE 6. In vitro susceptibilities of *E. coli* derivatives producing plasmid-encoded AmpC β -lactamases

Antimicrobial agent	MIC (μ g/ml) for derivatives producing:									
	ACC-1 ^a	ACT-1 ^b	CMY-1 ^c	CMY-2 ^d	CFE-1 ^e	DHA-1 ^f	FOX-1 ^g	LAT-1 ^h	MIR-1 ⁱ	MOX-1 ^j
Ampicillin			2,048			>512		>128	1,000	>512
Piperacillin	32	32	128	64	>256	128				
Temocillin	4		8	8					64	
Cephalothin			2,048		>256		128			>512
Cefotaxime	8	≤ 2	64	16	256	64	2	128	64	16
Ceftazidime	32	4	4	128	>256	64	8	>128	128	
Cefoxitin	4	>256	256	256		128	128	64	≥ 256	
Cefotetan	2	16	256	64			32	128	≥ 64	>512
Cefmetazole			128	64	256		4		≥ 64	512
Moxalactam	1		8	2		0.5	1		64	>512
Aztreonam	1	4	16	64	64	16	1	64	128	16
Cefepime	0.25	≤ 0.06	0.25	0.5	1	0.125			1	
Cefpirome	1		2	0.5					1	
Imipenem	0.13	1	0.25	0.5	0.5	≤ 0.125		2	1	0.5
Meropenem	0.03		0.06	0.06					0.125	

^a See reference 21.

^b See reference 41.

^c See reference 23.

^d See reference 22.

^e See reference 229.

^f See reference 98.

^g See reference 109.

^h See reference 326.

ⁱ See reference 248.

^j See reference 134.

quencing disclosed that LAT-2 was identical to CMY-2, LAT-3 was identical to CMY-6, and LAT-4 was identical to LAT-1, which is the only one remaining unique (15).

Like the chromosomally determined AmpC β -lactamases, the plasmid-mediated enzymes confer resistance to a broad spectrum of β -lactams (Table 6) including penicillins, oxymino- β -cephalosporins, cephamycins, and (variably) aztreonam. Susceptibility to cefepime, cefpirome, and carbapenems is little, if at all, affected. Note that ACC-1 is exceptional in not conferring resistance to cephamycins and is actually cefoxitin inhibited (21, 106).

The genes for ACT-1, DHA-1, DHA-2, and CMY-13 are linked to *ampR* genes and are inducible (16, 93, 214, 274), while other plasmid-mediated AmpC genes are not, including other CMY alleles and apparently CFE-1 despite its linkage to an *ampR* gene (142, 229). Nonetheless, the level of expression of both inducible ACT-1 and noninducible MIR-1 is 33- to 95-fold higher than the level of expression of the chromosomally determined AmpC gene of *E. cloacae* thanks to a higher gene copy number for the plasmid-determined enzymes (2 copies for *bla*_{ACT-1} and 12 copies for *bla*_{MIR-1}) and greater promoter strength for the plasmid genes (8-fold increased from the hybrid MIR-1 promoter and 17-fold increased because of a single base change relative to the wild type in the ACT-1 promoter) (275, 276). AmpC plasmids lack *ampD* genes, but the level of ACT-1 expression is increased with the loss of chromosomal AmpD function (276).

An AmpD-deficient *E. coli* strain producing ACT-1 remains susceptible to imipenem (MIC, 2 μ g/ml) (276), but imipenem MICs of ≥ 16 μ g/ml have been found in clinical isolates of *K. pneumoniae* carrying ACT-1 plasmids associated with a loss of outer membrane porins (41). In a porin-deficient *K. pneumoniae* isolate, other plasmid-mediated AmpC enzymes also

provide imipenem, ertapenem, and meropenem resistance (141). Such strains generally remain susceptible to cefepime but are otherwise also resistant to oxymino- β -cephalosporins.

Plasmids carrying genes for AmpC β -lactamases often carry multiple other resistances including genes for resistance to aminoglycosides, chloramphenicol, quinolones, sulfonamide, tetracycline, and trimethoprim as well as genes for other β -lactamases such as TEM-1, PSE-1 (6), CTX-M-3 (55), SHV varieties (119), and VIM-1 (214). The AmpC gene is usually part of an integron but is not incorporated into a gene cassette with an affiliated 59-base element (273). Note that the same *bla*_{AmpC} gene can be incorporated into different backbones on different plasmids (50).

A variety of genetic elements have been implicated in the mobilization of AmpC genes onto plasmids (Fig. 4). The insertion sequence *ISEcp1* (or truncated versions thereof) is associated with many CMY alleles including CMY-2 (105, 115, 155), CMY-4 (228), CMY-5 (343), CMY-7 (135), CMY-12 (182), CMY-14 (182), CMY-15 (182), CMY-16 (69), CMY-21 (133), CMY-31 (GenBank accession number EU331425), and CMY-36 (GenBank accession number EU331426) as well as the β -lactamases ACC-1 (78, 249) and ACC-4 (247). *ISEcp1* plays a dual role. It is involved in the transposition of adjacent genes (261) and has been shown able to mobilize a chromosomal *bla* gene onto a plasmid (166), and it also can supply an efficient promoter for the high-level expression of neighboring genes. The transcription of at least CMY-7 has been shown to start within the *ISEcp1* element and takes place at a much higher level than the expression of the corresponding AmpC gene in *C. freundii* (135).

Other *bla*_{AmpC} genes are found adjacent to an insertion sequence common region (*ISCR1*) involved in gene mobilization into (typically) complex class 1 integrons (322). Genes for

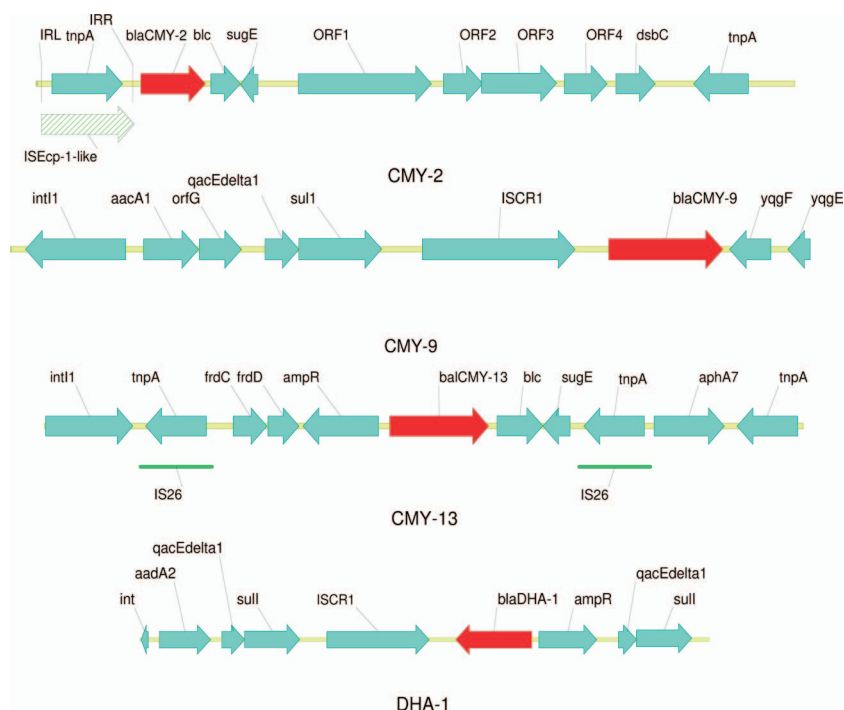


FIG. 4. Genetic environment of representative AmpC genes: CMY-3 (GenBank accession number DQ164214), CMY-9 (accession number AB061794), CMY-13 (accession number AY339625), and DHA-1 (accession number SEN237702).

several CMY varieties (CMY-1, -8, -9, -10, -11, and -19), DHA-1, and MOX-1 are so linked (322, 332). On the other hand, the gene for CMY-13 and its attendant *ampR* gene are bounded by directly repeated IS26 elements made up of a transposase gene (*tnpA*) with flanking inverted terminal repeat segments (214). Other elements are associated with and may have been involved in capturing the genes for FOX-5 (269), MIR-1 (142), and MOX-2 (271).

ONGOING EVOLUTION: EXTENDED-SPECTRUM CEPHALOSPORINASES

Just as amino acid alterations in TEM and SHV β -lactamase have given rise to extended-spectrum enzymes with broader substrate specificities, amino acid insertions, deletions, and substitutions have been described for AmpC β -lactamases that enhance catalytic efficiency toward oxymino- β -lactam substrates (235). Such changes in both plasmid-determined and chromosomally mediated AmpC enzymes have been described. Their properties are shown in Table 7. The alterations occur either in the Ω -loop, making the enzyme more accessible for substrates with bulky R1 side chains, or at or near the R2 loop, widening the R2 binding site. At both locations, the amino acid alterations can have opposite effects on enzyme kinetics. Generally, the catalytic constant for ceftazidime increased along with the K_m , or the K_m decreased (reflecting greater affinity), but the k_{cat} decreased as well. In either case, the k_{cat}/K_m ratio or catalytic efficiency for ceftazidime and related substrates increased compared to that of the wild-type enzyme with the result that the ceftazidime MICs for a strain carrying such enzymes were in the resistance range (MIC \geq 32 μ g/ml), while the MICs for cefotaxime and cefepime usually

reflected only reduced susceptibility, such as a cefepime MIC of 8 μ g/ml for *E. coli* with the AmpC enzymes from *E. cloacae* CHE or *Enterobacter aerogenes* Ear2. The enzyme from *S. marcescens* HD, however, when expressed in *E. coli*, conferred a cefepime MIC of 512 μ g/ml (196), and those from *E. coli* strains EC14, EC18, and BER were associated with cefepime MICs of 16 μ g/ml (197, 199). MICs for aztreonam and imipenem were usually little affected except that an aztreonam MIC of 128 μ g/ml was produced by CMY-10 (172). Structural gene mutations were often accompanied by promoter mutations that increased the level of expression of the mutant gene (193). Modifications at additional enzyme sites in laboratory mutant have been described (14). Interestingly, the AmpC variant from *E. coli* HKY28 became more susceptible to inhibition by clavulanic acid, sulbactam, and tazobactam, a curious phenotype previously described for a few other AmpC variants (13, 341).

CLINICAL RELEVANCE

Chromosomal AmpC Enzymes

For enteric organisms with the potential for high-level AmpC β -lactamase production by mutation, the development of resistance upon therapy is a concern. In a landmark study of 129 patients with bacteremia due to *Enterobacter* spp., Chow et al. identified 6 out of 31 patients treated with broad-spectrum cephalosporins who developed decreased susceptibility (cephalosporin MIC posttherapy of >16 μ g/ml) and augmented β -lactamase production after treatment with cefotaxime, ceftazidime, or ceftizoxime, a much higher frequency (19%) than that for the emergence of resistance to aminoglycosides or

TABLE 7. Properties of extended-spectrum cephalosporinases

Organism	Alteration ^a	Kinetic effect ^b						MIC effect ^c	Reference(s)
		Ceftazidime		Cefepime		Imipenem			
		k_{cat}	K_m	k_{cat}	K_m	k_{cat}	K_m		
<i>E. cloacae</i> GC1	3-aa insertion in Ω -loop	↑	↑					↑ CAZ, ↑ ATM	67, 237
<i>S. marcescens</i> SRT-1	E219K in Ω -loop		↑	↑				↑ CAZ	206
<i>S. marcescens</i> ES46	E219K in Ω -loop							↑ CAZ	348
<i>S. marcescens</i> SMSA	S220Y in Ω -loop	↑	↑	↑	↓			↑ CAZ	126
<i>E. coli</i> HKY28	3-aa deletion in H-9 helix	↓		↑				↑ CAZ, ↑ FEP	77
<i>E. coli</i> ECB33	1-aa insertion in H-9 helix							↑ CAZ	193
<i>E. coli</i> EC16	S287C in R2 loop							↑ CAZ	197
<i>E. coli</i> EC18	S287N in R2 loop							↑ CAZ, ↑ FEP, ↑ ATM	197
<i>E. aerogenes</i> Ear2	L293P in R2 loop		↓	NC	↓			↑ CAZ, ↑ FEP	17
<i>E. coli</i> EC15	H296P in R2 loop							↑ CAZ	197
<i>E. coli</i> EC14	V298L in R2 loop							↑ CAZ, ↑ FEP	197
<i>E. coli</i> KL	14-aa substitutions	NC	↓	NC	↓			↑ CAZ	194
<i>E. coli</i> BER	2-aa insertion in R2 loop	↓	↓		↓	↓	↓	↑ CAZ, ↑ FEP	199, 299
<i>E. cloacae</i> CHE	6-aa deletion in R2 loop		↓	↑	↓			↑ CAZ, ↑ FEP	18
<i>S. marcescens</i> HD	4-aa deletion in R2 loop	↑	↓	NC	↓	NC		↑ CAZ, ↑ FEP	196
CMY-10	3-aa deletion in R2 loop	↑	↑			↑	↑	↑ CAZ, ↑ ATM	158, 172
CMY-19	I292S in R2 loop	↓	↓		↓			↑ CAZ	332
CMY-37	L316I in R2 loop							↑ CAZ, ↑ FEP	4

^a Positioned according to data in references 173 and 299. aa, amino acid.

^b NC, no change.

^c CAZ, ceftazidime; ATM, aztreonam; FEP, cefepime.

other β -lactams (58). A subsequent study of 477 patients with initially susceptible *Enterobacter* spp. also found that 19% of patients receiving broad-spectrum cephalosporins developed resistant *Enterobacter* isolates and that resistance was more likely to appear if the original isolate came from blood (156). A recent study evaluated 732 patients with infections due to *Enterobacter* spp., *S. marcescens*, *C. freundii*, or *M. morgani* (57). Resistance emerged in 11 of 218 patients (5%) treated with broad-spectrum cephalosporins, more often in *Enterobacter* spp. (10/121, or 8.3%) than in *C. freundii* (1/39 or 2.6%) and not at all in 37 infections with *S. marcescens* or 21 infections with *M. morgani*. A single patient died as a result. Biliary tract infection with malignant bile duct obstruction was identified as being a risk factor for resistance development. Combination therapy did not prevent resistance emergence. The clonal spread of AmpC-hyperproducing *E. cloacae* strains to other patients has been documented at some medical centers but seems not to be a widespread problem (253). Once selected, however, hyperproduction is stable so that 30 to 40% of *E. cloacae* isolates from inpatients in the United Kingdom (188) and 15 to 25% of North American isolates (147) currently have this mechanism of β -lactam resistance.

These studies did not address mortality, but in a study of 46 patients initially infected with cephalosporin-susceptible *Enterobacter* spp. that became resistant matched to 113 control patients with persistently susceptible isolates of the same organism, the patients were more likely to die as a result of the infection (26% versus 13%), had a longer hospital stay, and sustained higher attributable hospital charges (63).

Despite normally low-level expression of AmpC β -lactamase in *E. coli*, high-level producers have been identified in clinical specimens, typically as ceftazidime-resistant isolates with stronger AmpC promoters or mutations that destabilize the normal AmpC attenuator (32, 51, 52, 94, 241, 242, 297). For example, the screening of 29,323 clinical isolates of *E. coli* collected in

1999 to 2000 from 12 hospitals in Canada identified 232 strains that were resistant to ceftazidime, with 182 of them identified as being unique by pulsed-field gel electrophoresis (220). PCR and sequencing identified 51 different promoter or attenuator variants (323). In a few strains, the integration of an insertion element created a new and stronger *ampC* promoter (146, 220). Such strains are not only resistant to ceftazidime but also typically resistant to ampicillin, ticarcillin, cephalothin, and β -lactam combinations with clavulanic acid and have reduced susceptibility or are even resistant to expanded-spectrum cephalosporins. Some *E. coli* strains with up promoter mutations have alterations in *bla*_{AmpC} as well, expanding its resistance spectrum (193). An accompanying loss of outer membrane porins can augment the resistance phenotype further (195). These strains usually remain susceptible to cefepime and imipenem (201) but may become ertapenem resistant. At least for the *E. coli* strains isolated in France that overproduce chromosomal AmpC β -lactamase, most belong to phylogenetic group A, a group which fortunately lacks a number of virulence factors (62). *E. coli* strains overexpressing AmpC β -lactamase have also been isolated from calves with diarrhea (40), so such strains can be veterinary as well as human pathogens.

Acinetobacter spp. have a variety of acquired β -lactamases, but the oxyimino- β -lactam resistance seen increasingly in this opportunistic pathogen is often attributable to its AmpC enzyme (42). The enzyme is normally expressed at low levels and is not inducible, but overexpression occurs with the upstream insertion of an insertion element (*ISAbal*) common in *A. baumannii*, which provides an efficient promoter for the *bla*_{AmpC} gene (61, 122, 292). The overexpression of AmpC β -lactamase plays a role in the increasing resistance of *P. aeruginosa* as well, although acquired β -lactamases, pumps, and porins are also important (53, 186, 245). Because *P. aeruginosa* has at least three *ampD* genes (151, 290), enhanced AmpC production occurs in a stepwise fashion, producing resistance to anti-

pseudomonas penicillins, oxyiminocephalosporins, and, with full derepression, cefepime (151, 186).

Plasmid-Mediated AmpC Enzymes

Plasmid-mediated AmpC β -lactamases have been found worldwide but are less common than extended-spectrum β -lactamases (ESBLs), and in *E. coli*, they appear to be less often a cause of cefoxitin resistance than an increased production of chromosomal AmpC β -lactamase (Table 8). The β -lactamase CMY-2 has the broadest geographic spread and is an important cause of β -lactam resistance in nontyphoid *Salmonella* strains in many countries (81, 213). In the United States between 1996 and 1998, 13 ceftriaxone-resistant but otherwise unrelated *Salmonella* strains were isolated from symptomatic patients in eight states and were found to produce CMY-2 β -lactamase (50, 80). Such strains have been isolated from cats, cattle, chickens, dogs, horses, pigs, and turkeys (112, 340), and in one case, they were spread from infected calves to the farmer's 12-year-old son (89). Another small outbreak was traced to contaminated pet dog treats containing dried beef (259). In a survey of U.S. isolates from 2000, 44 of 1,378 (3.2%) nontyphoid *Salmonella* strains were positive for CMY β -lactamase by PCR, as were 7 *Shigella sonnei* and 4 *E. coli* O157:H7 strains (339). When treatment is indicated, fluoroquinolones are as effective as they are with pansusceptible *Salmonella* strains (74), but a few strains that are resistant to both fluoroquinolones and extended-spectrum cephalosporins have appeared (338). CMY-2-producing nontyphoid *Salmonella* strains have been isolated in other countries, as have *Salmonella* strains producing AmpC β -lactamases CMY-4, CMY-7, ACC-1, and DHA-1 (19, 135, 213, 314). CMY producers belong to several serogroups, with *Salmonella enterica* serovars Typhimurium and Newport (113) being the most common. CMY-2 has also been responsible for ceftriaxone resistance in a *Shigella sonnei* outbreak (136).

Most other strains with plasmid-mediated AmpC enzymes have been isolated from patients after several days of hospitalization, but recently, AmpC-producing isolates in cultures from long-term care facilities, rehabilitation centers, and outpatient clinics have been reported (117, 210). Risk factors for bloodstream infections caused by AmpC-producing strains of *K. pneumoniae* include long hospital stay, care in an intensive care unit (ICU), central venous catheterization, need for an indwelling urinary catheter, and prior administration of antibiotics, especially broad-spectrum cephalosporins and β -lactamase inhibitor combinations, and are thus similar to risk factors for infection by ESBL-producing *K. pneumoniae* strains (244, 347). Patients with leukemia (244, 303), cancer (134, 222, 244), and organ transplantation (222) have been affected. Outbreaks with MIR-1 (11 patients) (248), a BIL-1 (CMY-2)-like enzyme (5 patients) (222), CMY-16 (8 patients) (69), ACC-1 (13 patients [227] and 19 patients [240]), ACT-1 (17 patients) (41), and a LAT-type β -lactamase (6 patients) (103) have been reported. Sources of positive cultures included urine, blood, wounds, sputum, and stool. A CMY-2-producing *E. coli* isolate caused meningitis in a neonate (86). Often, the strain with a plasmid-mediated AmpC enzyme also produced other β -lactamases such as TEM-1 or an ESBL such as SHV-5, the presence of which may complicate detection of the AmpC phenotype.

AmpC DETECTION

There are presently no CLSI or other approved criteria for AmpC detection (76). Organisms producing enough AmpC β -lactamase will typically give a positive ESBL screening test but fail the confirmatory test involving increased sensitivity with clavulanic acid (29, 304). This phenotype is not, however, specific for an AmpC producer, since it can occur with certain complex TEM mutants (277), OXA-type ESBLs, and carbapenemases and in strains with high levels of TEM-1 β -lactamase. Except for non-lactose-fermenting gram-negative organisms intrinsically resistant to cephamycins, resistance to cefoxitin as well as oxyimino- β -lactams is suggestive of an AmpC enzyme, but it is not specific since cefoxitin resistance can also be produced by certain carbapenemases (262) and a few class A β -lactamases (331) and by decreased levels of production of outer membrane porins in both *K. pneumoniae* and *E. coli* (124, 125, 202, 203). Furthermore, some plasmid-mediated AmpC strains test susceptible to ceftriaxone, cefotaxime, and ceftazidime by current CLSI criteria and could easily be overlooked (315). Other confirmatory tests are needed (Table 9).

The three-dimensional test was designed to detect both AmpC and ESBL production. In the "indirect" form used for AmpC detection, a conventional disk diffusion susceptibility assay is carried out with a susceptible strain, such as *E. coli* ATCC 25922, as the lawn and a suspension of the test organism, which is added to a circular slit in the agar 3 mm from a disk containing cefoxitin or some other agent. Distortion of the zone of inhibition indicates a positive test, as cefoxitin is hydrolyzed by the presence of an AmpC enzyme (319). In subsequent modifications, a radial slit was employed, and rather than using intact cells, the test organisms were concentrated by centrifugation, and the pellet was freeze-thawed five to seven times to release β -lactamase (66, 200). Direct spot inoculation of the test organism 7 to 8 mm from the cefoxitin disk has also been used successfully (295), as has a heavy inoculum streaked radially from the cefoxitin disk on the agar surface without using a slit (169), although the latter procedure missed some CMY-2- and DHA-1-producing strains. In a further modification, the test organism has been applied to a filter paper disk containing Tris-EDTA to enhance membrane permeability, with the disk then placed onto a lawn of *E. coli* ATCC 25922 adjacent to a cefoxitin disk (35). In every case, the presence of an AmpC β -lactamase is indicated by a distortion of the inhibition zone around the cefoxitin disk. Organisms producing a carbapenemase can mimic an AmpC β -lactamase in cefoxitin inactivation, so reduced carbapenem susceptibility is important to exclude since otherwise, a carbapenem might be selected for therapy (35).

A variation on the three-dimensional test is to plate the sensitive indicator strain on agar containing 4 μ g/ml cefoxitin and add the freeze-thawed cell extract to a well in the plate. After incubation, growth around the well indicates the presence of a cefoxitin-hydrolyzing enzyme (230). This method is reported to be just as sensitive and specific as the three-dimensional test for AmpC detection, is easier to perform, and allows multiple samples per plate to be tested.

Another approach for AmpC detection is the use of an inhibitor for this β -lactamase class analogous to the use of

TABLE 8. Population studies of plasmid-mediated AmpC β -lactamases

Sample	Collection period (yr)	Location	Frequency of plasmid-mediated AmpC	AmpC type(s) ^a	Reference
63 cefoxitin-resistant <i>E. coli</i> strains from 2,133 strains screened	1996	10 hospitals in Greece	55 strains (87% of cefoxitin resistant strains) or 2.6% of total	LAT-3 (CMY-6), LAT-4 (LAT-1)	104
4,093 <i>Salmonella</i> isolates	1996–1998	17 U.S. state and community health departments	13 strains (0.32%)	CMY-2	80
408 nosocomial isolates of <i>K. pneumoniae</i> resistant to cephalosporins or carbapenem	1996–2000	24 U.S. hospitals in 18 states	54 strains (13.2%)	ACT-1, DHA-1, FOX-5, CMY-2	216
190 bloodstream isolates of <i>K. pneumoniae</i>	1995–1999	30 U.S. hospitals in 23 states	5 strains (2.6%)	ACT-1, FOX-5	65
752 cephalosporin-resistant <i>K. pneumoniae</i> , <i>K. oxytoca</i> , and <i>E. coli</i> strains	1992–2000	70 sites in 25 U.S. states and the District of Columbia	<i>K. pneumoniae</i> , 8.5%; <i>K. oxytoca</i> , 6.9%; <i>E. coli</i> , 4%	ACT-1, FOX-5, CMY-2, DHA-1	6
232 cefoxitin-resistant <i>E. coli</i> strains from a total of 29,323 screened	1999–2000	12 Canadian hospitals	25 of cefoxitin resistant strains (10.8%) or 0.09% of total	CMY-2	220
389 <i>K. pneumoniae</i> blood culture isolates	1998–2002	Seoul National University Hospital, Seoul, South Korea	65 isolates made ESBLs or AmpC enzymes; 28 of 61 strains characterized had AmpCs (7.2% of total)	DHA-1, CMY-1-like	244
99 cefoxitin- and extended-spectrum cephalosporin-resistant <i>K. pneumoniae</i> isolates	1999–2002	Teaching hospital, Taiwan	77 had AmpC enzymes (in 35 strains combined with ESBLs)	DHA-1, CMY-2, CMY-8	346
37 cefoxitin-resistant <i>E. coli</i> strains from 103 cephalosporin-resistant strains screened	1995–2003	Health Protection Agency, London, United Kingdom	25 cefoxitin-resistant strains (68%) or 24% of total	CMY-2, CMY-7, CMY-21	132
116 cefoxitin-resistant <i>E. coli</i> and 122 cefoxitin-resistant <i>K. pneumoniae</i> strains	2003	16 hospitals in South Korea	33% of <i>E. coli</i> strains made CMY-2-like enzymes, and 76% of <i>K. pneumoniae</i> strains made DHA-1	DHA-1, CMY-2-like, CMY-10-like, CMY-18	170
CLSI screening test-positive <i>E. coli</i> isolates (291 isolates) and <i>K. pneumoniae</i> isolates (282 isolates)	2003	7 medical centers in Taiwan	44% of <i>E. coli</i> and 15% of <i>K. pneumoniae</i> isolates had AmpC-like enzymes	CMY-2-like in <i>E. coli</i> ; DHA-1 and CMY-2-like in <i>K. pneumoniae</i>	345
1,429 <i>E. coli</i> isolates collected as part of a surveillance program	2004	30 North American medical centers	65 isolates were screen test positive for ESBLs; 26 were screen test-negative AmpC producers	13 CMY-2, 3 FOX-5, 1 DHA-1	73
1,122 cephalosporin-resistant <i>Enterobacteriaceae</i>	2004	16 hospitals in London and Southeast England	502 CTX-M ESBL producers, 149 other ESBL producers, and 190 (16.9%) high-level AmpC β -lactamase producers	<i>Enterobacter</i> spp. and <i>E. coli</i> mostly overproduced their chromosomal AmpC enzymes; the fewer plasmid-mediated AmpCs were of the <i>Citrobacter</i> type	263
746 screening test-positive gram-negative clinical isolates out of 6,421 evaluated	2000–2002	42 ICU and 21 non-ICU sites in the United States	ESBLs found in 4.9% of <i>Enterobacteriaceae</i> , and transferable AmpCs found in 3.3% of <i>K. pneumoniae</i> isolates and in 61% of isolates along with ESBLs; AmpCs also found in 3.6% of <i>K. oxytoca</i> and 1.4% of <i>P. mirabilis</i> isolates	FOX-5, DHA-like, ACT-1-like	217
359 cefoxitin-resistant <i>E. coli</i> strains from a total of 78,275 screened	2000–2003	Calgary Health Region, Canada	125 cefoxitin-resistant strains (35%) or 0.16% of total	CMY-2	257
123 enterobacterial isolates from 112 inpatients	2001	University Hospital, Rio de Janeiro, Brazil	35 isolates made ESBLs; 5 <i>E. coli</i> isolates also overproduced AmpC; no strains had a plasmid-mediated AmpC	None	70

Continued on following page

TABLE 8—Continued

Sample	Collection period (yr)	Location	Frequency of plasmid-mediated AmpC	AmpC type(s) ^a	Reference
327 cefoxitin-resistant isolates from 1,203 <i>E. coli</i> and 732 <i>Klebsiella</i> sp. isolates collected consecutively	2003–2005	Hospital, Shanghai, China	54 cefoxitin-resistant strains (17%) or 2.8% of total	41 DHA-1, 13 CMY-2	174
135 <i>E. coli</i> and 38 <i>Klebsiella</i> sp. isolates suspected of AmpC-mediated resistance	2004–2006	Health Protection Agency, London, United Kingdom	<i>E. coli</i> , 49%; <i>K. pneumoniae</i> , 55%	60 CIT type including CMY-23, 14 ACC type, 11 FOX type, 3 DHA type	342
124 cefoxitin-resistant strains from 3,217 <i>Enterobacteriaceae</i> normally lacking inducible chromosomal <i>ampC</i> genes	2006–2007	University Hospital, Basel, Switzerland	5 of 103 cefoxitin-resistant <i>E. coli</i> isolates had plasmid-mediated AmpCs; cause of cefoxitin resistance in 3 <i>K. oxytoca</i> and 18 <i>K. pneumoniae</i> isolates not identified	Not specified	2
2,388 isolates of <i>Enterobacteriaceae</i> from inpatients	2003–2004	13 hospitals in Poland	Plasmid-mediated AmpCs identified only in 71 <i>P. mirabilis</i> isolates (20.5% of all <i>P. mirabilis</i> isolates); ESBLs in 11.1% of all isolates	24 of 71 sequenced; 19 CMY-15, 4 CMY-12, 1 CMY-38 isolates	82
75 <i>E. coli</i> and 14 <i>Klebsiella</i> isolates out of 1,647 strains testing nonsusceptible to cefoxitin or cefpodoxime	2005	30 nursing homes, various outpatient clinics, and Creighton University Medical Center, United States	9 <i>E. coli</i> isolates and 1 <i>K. pneumoniae</i> isolate	All CMY-2	117
86 screening test-positive strains from 8,048 <i>Enterobacteriaceae</i> strains normally lacking or poorly expressing chromosomal <i>ampC</i> genes	1999–2007	Seattle Children's Hospital and Regional Medical Center, Seattle, Washington	36 had AmpC-type enzymes including 4 with class A β-lactamase as well; 47 had class A ESBLs alone, and 3 had carbapenemases	29 CMY-2-like and 6 DHA-types, and 1 uncharacterized	267
637 <i>K. pneumoniae</i> and 494 <i>E. coli</i> isolates	2005–2006	5 children's hospitals in China	207 were cefoxitin insusceptible, 128 were AmpC ⁺ by test with 3-aminophenylboronic acid, and 74 were AmpC ⁺ by multiplex PCR; occurrence rate of 10.1% in <i>K. pneumoniae</i> and 2.0% in <i>E. coli</i>	69 DHA-1, 4 CMY-2, 1 new CMY	75

^a Corrected enzyme designations after resequencing are shown in parentheses (15).

TABLE 9. Laboratory tests for AmpC detection

Assay	Reference(s)
Three dimensional.....	35, 66, 169, 200, 295, 319
Cefoxitin-agar.....	230
β-Lactam inhibitors	
Ro 48-1220.....	16, 37, 66
LN-2-128.....	37
Syn 2190.....	36, 65
Cloxacillin.....	38, 83, 280
Non-β-lactam inhibitors	
Boronic acid.....	300, 301
Phenylboronic acid.....	64, 315
Benzo(<i>b</i>)thiophene-2-boronic acid.....	44, 176
3-Aminophenylboronic acid.....	143, 344
PCR.....	251, 351

clavulanic acid in a confirmatory test for class A ESBLs. The β-lactams LN-2-128, Ro 48-1220, and Syn 2190 have been evaluated for this purpose, with the best results from the combination of Syn 2190 and cefotetan, which was 100% specific and 91% sensitive in AmpC β-lactamase detection (36, 37). Unfortunately, these inhibitors are not commercially available.

A double-disk test with a 500-μg cloxacillin disk placed between disks containing ceftazidime and cefotaxime on a lawn of the test organism has been explored using 15 AmpC-producing strains. All showed synergy. A central cefoxitin disk produced synergy with ceftazidime and cefotaxime only with ACC-1 β-lactamase and also revealed the inducibility of enzymes such as DHA-1 (280).

Etest strips with a gradient of cefotetan or cefoxitin on one half and the same combined with a constant concentration of cloxacillin on the other half have been evaluated for AmpC detection (38). Either a reduction in cephamycin MIC of at least three dilutions, deformation of the ellipse of inhibition, or a “phantom zone” was interpreted as a positive test. With

almost 500 test strains, the overall sensitivity and specificity were 88 to 93% (83).

Boronic acids have long been known as AmpC inhibitors (28). Various boronic acid derivatives have been either added to a blank disk placed near a β -lactam disk or added to the β -lactam disk for comparison with an unmodified β -lactam disk. For example, Yagi et al. found that a disk potentiation test utilizing a ≥ 5 -mm enhancement of the zone of inhibition around a ceftazidime or cefotaxime disk when 300 μg 3-aminophenylboronic acid was added reliably detected all AmpC varieties tested but was negative with strains producing ESBLs and carbapenemases (344), findings that have been confirmed with a different set of strains (143). Strains producing both a plasmid-mediated AmpC β -lactamase and an ESBL have been reliably detected (301), but such a test cannot differentiate between an AmpC enzyme encoded on a plasmid or on the chromosome. Specificity is also a concern since boronic acids also enhance the sensitivity of strains making a non-AmpC enzyme, class A KPC β -lactamase (250, 324).

Phenotypic tests cannot distinguish among the various families of plasmid-mediated AmpC enzymes and may also overlook chromosomally determined AmpC β -lactamases with an extended spectrum (193). For these purposes, and as the current "gold standard" for plasmid-mediated AmpC β -lactamase detection, multiplex PCR has been developed by utilizing six primer pairs (251) to which a seventh pair for CFE-1 β -lactamase (229) could be added. Chromosomal *bla*_{AmpC} did not interfere in testing strains of *K. pneumoniae*, *E. coli*, *P. mirabilis*, or *S. enterica* but could be a problem with *bla*_{AmpC} genes in one of the genera from which the plasmid-mediated enzymes are derived. (Table 5). A multiplex asymmetric PCR-based microarray method for detecting genes for both plasmid-mediated AmpC β -lactamases and mutations responsible for the ESBL phenotype in *bla*_{SHV} has been described (351). Perfection of a PCR array technology may ultimately allow the automation of AmpC β -lactamase detection for a suitably equipped clinical laboratory.

Is the recognition of plasmid-mediated AmpC enzymes necessary for the average laboratory? Therapeutic and infection control considerations argue that it is. AmpC-producing isolates may appear to be susceptible in vitro to some cephalosporins and aztreonam yet fail to respond if those agents are used so that a specific test for their presence is necessary (318). Compared to ESBL producers, isolates producing AmpC β -lactamase are resistant to additional β -lactams and insensitive to currently available β -lactamase inhibitors and have the potential for developing resistance to carbapenems. Furthermore, plasmid mediation of AmpC carries the threat of spread to other organisms within a hospital or geographic region. Time will tell whether these considerations will still apply if cephalosporin breakpoints are significantly lowered so that decisions about therapy become based only on low-MIC susceptibility.

TREATMENT OF AmpC-PRODUCING ORGANISMS

Strains with *ampC* genes are often resistant to multiple agents, making the selection of an effective antibiotic difficult. β -Lactam/ β -lactamase inhibitor combinations and most ceph-

alosporins and penicillins should be avoided because of in vitro resistance, the potential for AmpC induction or selection of high-enzyme-level mutants, and documented poor clinical outcomes with ceftazidime, cefotaxime (244), and, in an animal model, piperacillin-tazobactam (329). Whether cefepime can be used is unsettled. Cefepime is a poor inducer of AmpC β -lactamase, rapidly penetrates through the outer cell membrane, and is little hydrolyzed by the enzyme (232, 283), so many AmpC-producing organisms test cefepime susceptible with a conventional inoculum (see Table 6 for examples). If a 100-fold-higher inoculum is used, however, cefepime MICs increase dramatically for some AmpC producers, suggesting caution in its use (154, 256), and some strains are frankly resistant (238). In a pneumonia model using guinea pigs, cefepime, imipenem, and meropenem were equally effective against a porin-deficient *K. pneumoniae* strain producing FOX-5 β -lactamase (255). Also, in a rat pneumonia model with a *K. pneumoniae* strain producing ACT-1, β -lactam therapy with imipenem, meropenem, ertapenem, or cefepime gave equivalent results, even if the test strain was porin deficient (243). However, in a mouse pneumonia model with a porin-deficient strain of *K. pneumoniae* producing CMY-2 β -lactamase, survival with cefepime therapy was no better than that without antibiotic and significantly inferior to that with imipenem treatment (256). Nonetheless, cefepime has cured infections due to multiply resistant *Enterobacter* spp. including those with reduced susceptibility to ceftazidime (286), and in a prospective, randomized study of ICU patients with nosocomial pneumonia having *P. aeruginosa* as the most common isolate, cefepime proved to be just as effective as imipenem (350). The jury is still out, but cefepime seems to be an exception to the recommendation to avoid all cephalosporin therapy even if an AmpC-producing isolate tests susceptible to an individual agent.

Temocillin, a 6- α -methoxy derivative of ticarcillin, is active in vitro against many AmpC-producing *Enterobacteriaceae* whether the enzyme is determined by chromosomal or plasmid genes and is also active against ESBL producers (108, 187), but clinical experience is limited, and it is available in only a few countries. Amdinocillin is also effective in vitro against AmpC-producing *E. coli* strains but shows a marked inoculum effect unless clavulanic acid is present (43) and is also not available in the United States.

Carbapenem therapy has usually been successful (244) but has also been followed by the emergence of carbapenem-resistant *K. pneumoniae* associated with ACT-1 β -lactamase production and outer membrane porin loss (3, 41, 152). Reduced imipenem susceptibility (MIC 8 to 32 $\mu\text{g}/\text{ml}$) has also been reported in porin-deficient clinical isolates of *K. pneumoniae* making AmpC enzymes ACC-1 (34), CMY-2 (171), CMY-4 (49), DHA-1 (171), or an uncharacterized AmpC-type enzyme (246). The same scenario has been described for clinical isolates of *E. aerogenes* (59, 71, 317, 325, 349), *E. cloacae* (168), and *C. freundii* (192) as well as laboratory mutants (131, 270, 327). In *E. coli*, reduced carbapenem susceptibility or frank resistance (imipenem MIC of 8 to 128 $\mu\text{g}/\text{ml}$) in porin-deficient clinical isolates producing CMY-2 (183) or CMY-4 (303) has been described, while a *Salmonella enterica* strain lacking a porin and making CMY-4 reached an imipenem MIC of 32 $\mu\text{g}/\text{ml}$ (8).

If the isolate is susceptible, fluoroquinolone therapy is an option especially for non-life-threatening infections such as urinary tract infection. Tigecycline is another option. It had good activity in vitro against 88% of AmpC-hyperproducing isolates of *E. coli*, *Enterobacter* spp., *Klebsiella* spp., and *Citrobacter* spp. from the United Kingdom (130), but few *P. aeruginosa* isolates (282) and, in some centers, only 22% of nosocomial *Acinetobacter* isolates (231) were tigecycline susceptible.

CONCLUDING REMARKS

AmpC β -lactamases are clinically important cephalosporinases encoded on the chromosome of many *Enterobacteriaceae* and a few other organisms where they mediate resistance to cephalothin, cefazolin, cefoxitin, most penicillins, and β -lactamase inhibitor/ β -lactam combinations. In many bacteria, AmpC enzymes are inducible and can be expressed at high levels by mutation. Overexpression confers resistance to broad-spectrum cephalosporins including cefotaxime, ceftazidime, and ceftriaxone and is a problem especially in infections due to *E. aerogenes* and *E. cloacae*, where an isolate initially susceptible to these agents may become resistant upon therapy. Transmissible plasmids have acquired genes for AmpC enzymes, which consequently can now appear in bacteria lacking or poorly expressing a chromosomal *bla*_{AmpC} gene, such as *E. coli*, *K. pneumoniae*, and *P. mirabilis*. Resistance due to plasmid-mediated AmpC enzymes is less common than ESBL production in most parts of the world but may be both harder to detect and broader in spectrum. AmpC enzymes encoded by both chromosomal and plasmid genes are also evolving to hydrolyze broad-spectrum cephalosporins more efficiently. Techniques to identify AmpC β -lactamase-producing isolates are available but are still evolving and are not yet optimized for the clinical laboratory, which probably now underestimates this resistance mechanism. Carbapenems can usually be used to treat infections due to AmpC-producing bacteria, but carbapenem resistance can arise in some organisms by mutations that reduce influx (outer membrane porin loss) or enhance efflux (efflux pump activation).

REFERENCES

- Abraham, E. P., and E. Chain. 1940. An enzyme from bacteria able to destroy penicillin. *Nature* **146**:837.
- Adler, H., L. Fenner, P. Walter, D. Hohler, E. Schultheiss, S. Oezcan, and R. Frei. 2008. Plasmid-mediated AmpC β -lactamases in Enterobacteriaceae lacking inducible chromosomal *ampC* genes: prevalence at a Swiss university hospital and occurrence of the different molecular types in Switzerland. *J. Antimicrob. Chemother.* **61**:457–458.
- Ahmad, M., C. Urban, N. Mariano, P. A. Bradford, E. Calcagni, S. J. Projan, K. Bush, and J. J. Rahal. 1999. Clinical characteristics and molecular epidemiology associated with imipenem-resistant *Klebsiella pneumoniae*. *Clin. Infect. Dis.* **29**:352–355.
- Ahmed, A. M., and T. Shimamoto. 2008. Emergence of a cefepime- and ceftiofame-resistant *Citrobacter freundii* clinical isolate harbouring a novel chromosomally encoded AmpC β -lactamase, CMY-37. *Int. J. Antimicrob. Agents* **32**:256–261.
- Alksne, L. E., and B. A. Rasmussen. 1997. Expression of the AsbA1, OXA-12, and AsbM1 β -lactamases in *Aeromonas jandaei* AER 14 is coordinated by a two-component regulon. *J. Bacteriol.* **179**:2006–2013.
- Alvarez, M., J. H. Tran, N. Chow, and G. A. Jacoby. 2004. Epidemiology of conjugative plasmid-mediated AmpC β -lactamases in the United States. *Antimicrob. Agents Chemother.* **48**:533–537.
- Ambler, R. P. 1980. The structure of β -lactamases. *Philos. Trans. R. Soc. Lond. B* **289**:321–331.
- Armand-Lefèvre, L., V. Leflon-Guibout, J. Bredin, F. Barguelli, A. Amor, J. M. Pagès, and M. H. Nicolas-Chanoine. 2003. Imipenem resistance in *Salmonella enterica* serovar Wien related to porin loss and CMY-4 β -lactamase production. *Antimicrob. Agents Chemother.* **47**:1165–1168.
- Avison, M. B., P. M. Bennett, and T. R. Walsh. 2000. β -Lactamase expression in *Pleiomonas shigelloides*. *J. Antimicrob. Chemother.* **45**:877–880.
- Avison, M. B., P. Niumsup, K. Nurmahomed, T. R. Walsh, and P. M. Bennett. 2004. Role of the 'cre/blr-tag' DNA sequence in regulation of gene expression by the *Aeromonas hydrophila* β -lactamase regulator, BlrA. *J. Antimicrob. Chemother.* **53**:197–202.
- Avison, M. B., P. Niumsup, T. R. Walsh, and P. M. Bennett. 2000. *Aeromonas hydrophila* AmpH and CepH β -lactamases: derepressed expression in mutants of *Escherichia coli* lacking *creB*. *J. Antimicrob. Chemother.* **46**:695–702.
- Avison, M. B., S. Underwood, A. Okazaki, T. R. Walsh, and P. M. Bennett. 2004. Analysis of AmpC β -lactamase expression and sequence in biochemically atypical ceftazidime-resistant Enterobacteriaceae from paediatric patients. *J. Antimicrob. Chemother.* **53**:584–591.
- Babini, G. S., F. Danel, S. D. Munro, P. A. Micklesen, and D. M. Livermore. 1998. Unusual tazobactam-sensitive AmpC β -lactamase from two *Escherichia coli* isolates. *J. Antimicrob. Chemother.* **41**:115–118.
- Barlow, M., and B. G. Hall. 2003. Experimental prediction of the evolution of cefepime resistance from the CMY-2 AmpC β -lactamase. *Genetics* **164**:23–29.
- Barlow, M., and B. G. Hall. 2002. Origin and evolution of the AmpC β -lactamases of *Citrobacter freundii*. *Antimicrob. Agents Chemother.* **46**:1190–1198.
- Barnaud, G., G. Arlet, C. Verdet, O. Gaillot, P. H. Lagrange, and A. Philippon. 1998. *Salmonella enteritidis*: AmpC plasmid-mediated inducible β -lactamase (DHA-1) with an *ampR* gene from *Morganella morganii*. *Antimicrob. Agents Chemother.* **42**:2352–2358.
- Barnaud, G., Y. Benzerara, J. Gravisse, L. Raskine, M. J. Sanson-Le Pors, R. Labia, and G. Arlet. 2004. Selection during cefepime treatment of a new cephalosporinase variant with extended-spectrum resistance to cefepime in an *Enterobacter aerogenes* clinical isolate. *Antimicrob. Agents Chemother.* **48**:1040–1042.
- Barnaud, G., R. Labia, L. Raskine, M. J. Sanson-Le Pors, A. Philippon, and G. Arlet. 2001. Extension of resistance to cefepime and ceftiofame associated to a six amino acid deletion in the H-10 helix of the cephalosporinase of an *Enterobacter cloacae* clinical isolate. *FEMS Microbiol. Lett.* **195**:185–190.
- Batchelor, M., K. L. Hopkins, E. J. Threlfall, F. A. Clifton-Hadley, A. D. Stallwood, R. H. Davies, and E. Liebana. 2005. Characterization of AmpC-mediated resistance in clinical *Salmonella* isolates recovered from humans during the period 1992 to 2003 in England and Wales. *J. Clin. Microbiol.* **43**:2261–2265.
- Bauernfeind, A., Y. Chong, and S. Schweighart. 1989. Extended broad spectrum β -lactamase in *Klebsiella pneumoniae* including resistance to cephamycins. *Infection* **17**:316–321.
- Bauernfeind, A., I. Schneider, R. Jungwirth, H. Sahly, and U. Ullmann. 1999. A novel type of AmpC β -lactamase, ACC-1, produced by a *Klebsiella pneumoniae* strain causing nosocomial pneumonia. *Antimicrob. Agents Chemother.* **43**:1924–1931.
- Bauernfeind, A., I. Stemplinger, R. Jungwirth, and H. Giamarellou. 1996. Characterization of the plasmidic β -lactamase CMY-2, which is responsible for cephamycin resistance. *Antimicrob. Agents Chemother.* **40**:221–224.
- Bauernfeind, A., I. Stemplinger, R. Jungwirth, R. Wilhelm, and Y. Chong. 1996. Comparative characterization of the cephamycinase *bla*_{CMY-1} gene and its relationship with other β -lactamase genes. *Antimicrob. Agents Chemother.* **40**:1926–1930.
- Baumann, M., H. Simon, K. H. Schneider, H. J. Danneel, U. Küster, and F. Giffhorn. 1989. Susceptibility of *Rhodobacter sphaeroides* to β -lactam antibiotics: isolation and characterization of a periplasmic β -lactamase (cephalosporinase). *J. Bacteriol.* **171**:308–313.
- Bauvois, C., A. S. Ibuka, A. Celso, J. Alba, Y. Ishii, J. M. Frère, and M. Galleni. 2005. Kinetic properties of four plasmid-mediated AmpC β -lactamases. *Antimicrob. Agents Chemother.* **49**:4240–4246.
- Beceiro, A., F. J. Pérez-Llarena, A. Pérez, M. Tomás, A. Fernández, S. Mallo, R. Villanueva, and G. Bou. 2007. Molecular characterization of the gene encoding a new AmpC β -lactamase in *Acinetobacter baylyi*. *J. Antimicrob. Chemother.* **59**:996–1000.
- Beckstrom-Sternberg, S. M., R. K. Auerbach, S. Godbole, J. V. Pearson, J. S. Beckstrom-Sternberg, Z. Deng, C. Munk, K. Kubota, Y. Zhou, D. Bruce, J. Noronha, R. H. Scheuermann, A. Wang, X. Wei, J. Wang, J. Hao, D. M. Wagner, T. S. Brettin, N. Brown, P. Gilna, and P. S. Keim. 2007. Complete genomic characterization of a pathogenic A.II strain of *Francisella tularensis* subspecies *tularensis*. *PLoS ONE* **2**:e947.
- Beesley, T., N. Gascayne, V. Knott-Hunziker, S. Petrusson, S. G. Waley, B. Jaurin, and T. Grundstrom. 1983. The inhibition of class C β -lactamases by boronic acids. *Biochem. J.* **209**:229–233.
- Bell, J. M., M. Chitsaz, J. D. Turnidge, M. Barton, L. J. Walters, and R. N. Jones. 2007. Prevalence and significance of a negative extended-spectrum β -lactamase (ESBL) confirmation test result after a positive ESBL screening test result for isolates of *Escherichia coli* and *Klebsiella pneumoniae*:

- results from the SENTRY Asia-Pacific surveillance program. *J. Clin. Microbiol.* **45**:1478–1482.
30. Bellais, S., L. Poirel, N. Fortineau, J. W. Decusser, and P. Nordmann. 2001. Biochemical-genetic characterization of the chromosomally encoded extended-spectrum class A β -lactamase from *Rahnella aquatilis*. *Antimicrob. Agents Chemother.* **45**:2965–2968.
 31. Bergström, S., F. P. Lindberg, O. Olsson, and S. Normark. 1983. Comparison of the overlapping *frd* and *ampC* operons of *Escherichia coli* with the corresponding DNA sequences in other gram-negative bacteria. *J. Bacteriol.* **155**:1297–1305.
 32. Bergstrom, S., and S. Normark. 1979. β -Lactam resistance in clinical isolates of *Escherichia coli* caused by elevated production of the *ampC*-mediated chromosomal β -lactamase. *Antimicrob. Agents Chemother.* **16**:427–433.
 33. Bergström, S., O. Olsson, and S. Normark. 1982. Common evolutionary origin of chromosomal beta-lactamase genes in enterobacteria. *J. Bacteriol.* **150**:528–534.
 34. Bidet, P., B. Burghoffer, V. Gautier, N. Brahimi, P. Mariani-Kurkdjian, A. El-Ghoneimi, E. Bingen, and G. Arlet. 2005. In vivo transfer of plasmid-encoded ACC-1 AmpC from *Klebsiella pneumoniae* to *Escherichia coli* in an infant and selection of impermeability to imipenem in *K. pneumoniae*. *Antimicrob. Agents Chemother.* **49**:3562–3565.
 35. Black, J. A., E. S. Moland, and K. S. Thomson. 2005. AmpC disk test for detection of plasmid-mediated AmpC β -lactamases in *Enterobacteriaceae* lacking chromosomal AmpC β -lactamases. *J. Clin. Microbiol.* **43**:3110–3113.
 36. Black, J. A., K. S. Thomson, J. D. Buynak, and J. D. Pitout. 2005. Evaluation of β -lactamase inhibitors in disk tests for detection of plasmid-mediated AmpC β -lactamases in well-characterized clinical strains of *Klebsiella* spp. *J. Clin. Microbiol.* **43**:4168–4171.
 37. Black, J. A., K. S. Thomson, and J. D. Pitout. 2004. Use of β -lactamase inhibitors in disk tests to detect plasmid-mediated AmpC β -lactamases. *J. Clin. Microbiol.* **42**:2203–2206.
 38. Bolmström, A., A. Engelhardt, L. Bylund, P. Ho, and Å. Karlsson. 2006. Evaluation of two new Etest strips for AmpC detection, abstr. D-0451. Abstr. 46th Intersci. Conf. Antimicrob. Agents Chemother.
 39. Bou, G., and J. Martínez-Beltran. 2000. Cloning, nucleotide sequencing, and analysis of the gene encoding an AmpC β -lactamase in *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* **44**:428–432.
 40. Bradford, P. A., P. J. Petersen, I. M. Fingerman, and D. G. White. 1999. Characterization of expanded-spectrum cephalosporin resistance in *E. coli* isolates associated with bovine calf diarrhoeal disease. *J. Antimicrob. Chemother.* **44**:607–610.
 41. Bradford, P. A., C. Urban, N. Mariano, S. J. Projan, J. J. Rahal, and K. Bush. 1997. Imipenem resistance in *Klebsiella pneumoniae* is associated with the combination of ACT-1, a plasmid-mediated AmpC β -lactamase, and the loss of an outer membrane protein. *Antimicrob. Agents Chemother.* **41**:563–569.
 42. Bratu, S., D. Landman, D. A. Martin, C. Georgescu, and J. Quale. 2008. Correlation of antimicrobial resistance with β -lactamases, the OmpA-like porin, and efflux pumps in clinical isolates of *Acinetobacter baumannii* endemic to New York City. *Antimicrob. Agents Chemother.* **52**:2999–3005.
 43. Brenwald, N. P., J. Andrews, and A. P. Fraiese. 2006. Activity of mecillinam against AmpC β -lactamase-producing *Escherichia coli*. *J. Antimicrob. Chemother.* **58**:223–224.
 44. Brenwald, N. P., G. Jevons, J. Andrews, L. Ang, and A. P. Fraiese. 2005. Disc methods for detecting AmpC β -lactamase-producing clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae*. *J. Antimicrob. Chemother.* **56**:600–601.
 45. Bulychev, A., and S. Mobashery. 1999. Class C β -lactamases operate at the diffusion limit for turnover of their preferred cephalosporin substrates. *Antimicrob. Agents Chemother.* **43**:1743–1746.
 46. Burman, L. G., J. T. Park, E. B. Lindström, and H. G. Boman. 1973. Resistance of *Escherichia coli* to penicillins: identification of the structural gene for the chromosomal penicillinase. *J. Bacteriol.* **116**:123–130.
 47. Bush, K., G. A. Jacoby, and A. A. Medeiros. 1995. A functional classification scheme for β -lactamases and its correlation with molecular structure. *Antimicrob. Agents Chemother.* **39**:1211–1233.
 48. Bush, K., C. Macalintal, B. A. Rasmussen, V. J. Lee, and Y. Yang. 1993. Kinetic interactions of tazobactam with β -lactamases from all major structural classes. *Antimicrob. Agents Chemother.* **37**:851–858.
 49. Cao, V. T., G. Arlet, B. M. Ericsson, A. Tammelin, P. Courvalin, and T. Lambert. 2000. Emergence of imipenem resistance in *Klebsiella pneumoniae* owing to combination of plasmid-mediated CMY-4 and permeability alteration. *J. Antimicrob. Chemother.* **46**:895–900.
 50. Carattoli, A., F. Tosini, W. P. Giles, M. E. Rupp, S. H. Hinrichs, F. J. Angulo, T. J. Barrett, and P. D. Fey. 2002. Characterization of plasmids carrying CMY-2 from expanded-spectrum cephalosporin-resistant *Salmonella* strains isolated in the United States between 1996 and 1998. *Antimicrob. Agents Chemother.* **46**:1269–1272.
 51. Caroff, N., E. Espaze, I. Berard, H. Richet, and A. Reynaud. 1999. Mutations in the *ampC* promoter of *Escherichia coli* isolates resistant to oxyiminocephalosporins without extended spectrum β -lactamase production. *FEMS Microbiol. Lett.* **173**:459–465.
 52. Caroff, N., E. Espaze, D. Gautreau, H. Richet, and A. Reynaud. 2000. Analysis of the effects of -42 and -32 *ampC* promoter mutations in clinical isolates of *Escherichia coli* hyperproducing ampC. *J. Antimicrob. Chemother.* **45**:783–788.
 53. Cavallo, J. D., R. Fabre, F. Leblanc, M. H. Nicolas-Chanoine, and A. Thabaut. 2000. Antibiotic susceptibility and mechanisms of β -lactam resistance in 1310 strains of *Pseudomonas aeruginosa*: a French multicentre study (1996). *J. Antimicrob. Chemother.* **46**:133–136.
 54. Chen, Y., G. Minasov, T. A. Roth, F. Prati, and B. K. Shoichet. 2006. The deacylation mechanism of AmpC β -lactamase at ultrahigh resolution. *J. Am. Chem. Soc.* **128**:2970–2976.
 55. Chen, Y. T., T. L. Lauderdale, T. L. Liao, Y. R. Shiau, H. Y. Shu, K. M. Wu, J. J. Yan, I. J. Su, and S. F. Tsai. 2007. Sequencing and comparative genomic analysis of pK29, a 269-kilobase conjugative plasmid encoding CMY-8 and CTX-M-3 β -lactamases in *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **51**:3004–3007.
 56. Chien, M., I. Morozova, S. Shi, H. Sheng, J. Chen, S. M. Gomez, G. Asamani, K. Hill, J. Nuara, M. Feder, J. Rineer, J. J. Greenberg, V. Steshenko, S. H. Park, B. Zhao, E. Tepitskaya, J. R. Edwards, S. Pampou, A. Georghiou, I. C. Chou, W. Iannuccilli, M. E. Ulz, D. H. Kim, A. Geringer-Sameth, C. Goldsberry, P. Morozov, S. G. Fischer, G. Segal, X. Qu, A. Rzhetsky, P. Zhang, E. Cayanis, P. J. De Jong, J. Ju, S. Kalachikov, H. A. Shuman, and J. J. Russo. 2004. The genomic sequence of the accidental pathogen *Legionella pneumophila*. *Science* **305**:1966–1968.
 57. Choi, S. H., J. E. Lee, S. J. Park, S. O. Lee, J. Y. Jeong, M. N. Kim, J. H. Woo, and Y. S. Kim. 2008. Emergence of antibiotic resistance during therapy for infections caused by *Enterobacteriaceae* producing AmpC β -lactamase: implications for antibiotic use. *Antimicrob. Agents Chemother.* **52**:995–1000.
 58. Chow, J. W., M. J. Fine, D. M. Shlaes, J. P. Quinn, D. C. Hooper, M. P. Johnson, R. Ramphal, M. M. Wagener, D. K. Miyashiro, and V. L. Yu. 1991. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann. Intern. Med.* **115**:585–590.
 59. Chow, J. W., and D. M. Shlaes. 1991. Imipenem resistance associated with the loss of a 40 kDa outer membrane protein in *Enterobacter aerogenes*. *J. Antimicrob. Chemother.* **28**:499–504.
 60. Cole, S. T. 1987. Nucleotide sequence and comparative analysis of the *frd* operon encoding the fumarate reductase of *Proteus vulgaris*. Extensive sequence divergence of the membrane anchors and absence of an *frd*-linked *ampC* cephalosporinase gene. *Eur. J. Biochem.* **167**:481–488.
 61. Corvec, S., N. Caroff, E. Espaze, C. Giraudeau, H. Drugeon, and A. Reynaud. 2003. AmpC cephalosporinase hyperproduction in *Acinetobacter baumannii* clinical strains. *J. Antimicrob. Chemother.* **52**:629–635.
 62. Corvec, S., A. Prodhomme, C. Giraudeau, S. Dauvergne, A. Reynaud, and N. Caroff. 2007. Most *Escherichia coli* strains overproducing chromosomal AmpC β -lactamase belong to phylogenetic group A. *J. Antimicrob. Chemother.* **60**:872–876.
 63. Cosgrove, S. E., K. S. Kaye, G. M. Eliopoulos, and Y. Carmeli. 2002. Health and economic outcomes of the emergence of third-generation cephalosporin resistance in *Enterobacter* species. *Arch. Intern. Med.* **162**:185–190.
 64. Coudron, P. E. 2005. Inhibitor-based methods for detection of plasmid-mediated AmpC β -lactamases in *Klebsiella* spp., *Escherichia coli*, and *Proteus mirabilis*. *J. Clin. Microbiol.* **43**:4163–4167.
 65. Coudron, P. E., N. D. Hanson, and M. W. Climo. 2003. Occurrence of extended-spectrum and AmpC beta-lactamases in bloodstream isolates of *Klebsiella pneumoniae*: isolates harbor plasmid-mediated FOX-5 and ACT-1 AmpC beta-lactamases. *J. Clin. Microbiol.* **41**:772–777.
 66. Coudron, P. E., E. S. Moland, and K. S. Thomson. 2000. Occurrence and detection of AmpC beta-lactamases among *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* isolates at a veterans medical center. *J. Clin. Microbiol.* **38**:1791–1796.
 67. Crichlow, G. V., A. P. Kuzin, M. Nukaga, K. Mayama, T. Sawai, and J. R. Knox. 1999. Structure of the extended-spectrum class C β -lactamase of *Enterobacter cloacae* GCl, a natural mutant with a tandem tripeptide insertion. *Biochemistry* **38**:10256–10261.
 68. Curtis, N. A. C., R. L. Eisenstadt, C. Rudd, and A. J. White. 1986. Inducible type I β -lactamases of gram-negative bacteria and resistance to β -lactam antibiotics. *J. Antimicrob. Chemother.* **17**:51–61.
 69. D'Andrea, M. M., E. Nucleo, F. Luzzaro, T. Giani, R. Migliavacca, F. Vailati, V. Kroumova, L. Pagani, and G. M. Rossolini. 2006. CMY-16, a novel acquired AmpC-type β -lactamase of the CMY/LAT lineage in multifocal monophyletic isolates of *Proteus mirabilis* from northern Italy. *Antimicrob. Agents Chemother.* **50**:618–624.
 70. da Silva Dias, R. C., A. A. Borges-Neto, G. I. D'Almeida Ferraiuoli, M. P. de-Oliveira, L. W. Riley, and B. M. Moreira. 2008. Prevalence of AmpC and other β -lactamases in enterobacteria at a large urban university hospital in Brazil. *Diagn. Microbiol. Infect. Dis.* **60**:79–87.
 71. de Champs, C., C. Henquell, D. Guelon, D. Siro, N. Gazuy, and J. Siro. 1993. Clinical and bacteriological study of nosocomial infections due to

- Enterobacter aerogenes* resistant to imipenem. J. Clin. Microbiol. 31:123–127.
72. Decousser, J. W., L. Poirel, and P. Nordmann. 2001. Characterization of a chromosomally encoded extended-spectrum class A β -lactamase from *Kluyvera cryocrescens*. Antimicrob. Agents Chemother. 45:3595–3598.
 73. Deshpande, L. M., R. N. Jones, T. R. Fritsche, and H. S. Sader. 2006. Occurrence of plasmidic AmpC type β -lactamase-mediated resistance in *Escherichia coli*: report from the SENTRY Antimicrobial Surveillance Program (North America, 2004). Int. J. Antimicrob. Agents 28:578–581.
 74. Devasia, R. A., J. K. Varma, J. Whichard, S. Gettner, A. B. Cronquist, S. Hurd, S. Segler, K. Smith, D. Hoefler, B. Shiferaw, F. J. Angulo, and T. F. Jones. 2005. Antimicrobial use and outcomes in patients with multidrug-resistant and pansusceptible *Salmonella* Newport infections, 2002–2003. Microb. Drug Resist. 11:371–377.
 75. Ding, H., Y. Yang, Q. Lu, Y. Wang, Y. Chen, L. Deng, A. Wang, Q. Deng, H. Zhang, C. Wang, L. Liu, X. Xu, L. Wang, and X. Shen. 2008. The prevalence of plasmid-mediated AmpC β -lactamases among clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* from five children's hospitals in China. Eur. J. Clin. Microbiol. Infect. Dis. 27:915–921.
 76. Doi, Y., and D. L. Paterson. 2007. Detection of plasmid-mediated class C β -lactamases. Int. J. Infect. Dis. 11:191–197.
 77. Doi, Y., J. Wachino, M. Ishiguro, H. Kurokawa, K. Yamane, N. Shibata, K. Shibayama, K. Yokoyama, H. Kato, T. Yagi, and Y. Arakawa. 2004. Inhibitor-sensitive AmpC β -lactamase variant produced by an *Escherichia coli* clinical isolate resistant to oxyminocephalosporins and cephamycins. Antimicrob. Agents Chemother. 48:2652–2658.
 78. Doloy, A., C. Verdet, V. Gautier, D. Decre, E. Ronco, A. Hammami, A. Philippon, and G. Arlet. 2006. Genetic environment of acquired *bla*_{ACC-1} β -lactamase gene in *Enterobacteriaceae* isolates. Antimicrob. Agents Chemother. 50:4177–4181.
 79. Dubus, A., P. Ledent, J. Lamotte-Brasseur, and J. M. Frère. 1996. The roles of residues Tyr150, Glu272, and His314 in class C β -lactamases. Proteins 25:473–485.
 80. Dunne, E. F., P. D. Fey, P. Kludt, R. Reporter, F. Mostashari, P. Shillam, J. Wicklund, C. Miller, B. Holland, K. Stamey, T. J. Barrett, J. K. Rasheed, F. C. Tenover, E. M. Ribot, and F. J. Angulo. 2000. Emergence of domestically acquired ceftriaxone-resistant *Salmonella* infections associated with AmpC β -lactamase. JAMA 284:3151–3156.
 81. Egorova, S., M. Timinouni, M. Demartin, S. A. Granier, J. M. Whichard, V. Sangal, L. Fabre, A. Delauné, M. Pardos, Y. Millemann, E. Espié, M. Achtman, P. A. Grimont, and F. X. Weill. 2008. Ceftriaxone-resistant *Salmonella enterica* serotype Newport, France. Emerg. Infect. Dis. 14:954–957.
 82. Empel, J., A. Baraniak, E. Literacka, A. Mrowka, J. Fiett, E. Sadowy, W. Hryniewicz, and M. Gniadkowski. 2008. Molecular survey of β -lactamases conferring resistance to newer β -lactams in *Enterobacteriaceae* isolates from Polish hospitals. Antimicrob. Agents Chemother. 52:2449–2454.
 83. Engelhardt, A., A. Yusof, P. Ho, K. Sjöström, and C. Johansson. 2008. Evaluation of a new Etest strip for AmpC detection using a large collection of genotypically characterized strains, abstr. D-280. Abstr. 48th Intersci. Conf. Antimicrob. Agents Chemother.
 84. Eriksson-Grennberg, K. G. 1968. Resistance of *Escherichia coli* to penicillins. II. An improved mapping of the *ampA* gene. Genet. Res. 12:147–156.
 85. Eriksson-Grennberg, K. G., H. G. Boman, J. A. Jansson, and S. Thorén. 1965. Resistance of *Escherichia coli* to penicillins. I. Genetic study of some ampicillin-resistant mutants. J. Bacteriol. 90:54–62.
 86. Fakioglu, E., A. M. Queenan, K. Bush, S. G. Jenkins, and B. C. Herold. 2006. AmpC β -lactamase-producing *Escherichia coli* in neonatal meningitis: diagnostic and therapeutic challenge. J. Perinatol. 26:515–517.
 87. Farrar, W. E., Jr., and N. M. O'Dell. 1976. β -Lactamase activity in *Chromobacterium violaceum*. J. Infect. Dis. 134:290–293.
 88. Feller, G., Z. Zekhnini, J. Lamotte-Brasseur, and C. Gerday. 1997. Enzymes from cold-adapted microorganisms. The class C β -lactamase from the antarctic psychrophile *Psychrobacter immobilis* A5. Eur. J. Biochem. 244:186–191.
 89. Fey, P. D., T. J. Safranek, M. E. Rupp, E. F. Dunne, E. Ribot, I. P. C., P. A. Bradford, F. J. Angulo, and S. H. Hinrichs. 2000. Ceftriaxone-resistant *Salmonella* infection acquired by a child from cattle. N. Engl. J. Med. 342:1242–1249.
 90. Fihman, V., M. Rottman, Y. Benzerara, F. Delisle, R. Labia, A. Philippon, and G. Arlet. 2002. BUT-1: a new member in the chromosomal inducible class C β -lactamases family from a clinical isolate of *Buttiauxella* sp. FEMS Microbiol. Lett. 213:103–111.
 91. Fitoussi, F., G. Arlet, P. A. Grimont, P. Lagrange, and A. Philippon. 1995. *Escherichia hermannii*: susceptibility pattern to β -lactams and production of β -lactamase. J. Antimicrob. Chemother. 36:537–543.
 92. Flores, A. R., L. M. Parsons, and M. S. Pavelka, Jr. 2005. Genetic analysis of the β -lactamases of *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* and susceptibility to β -lactam antibiotics. Microbiology 151:521–532.
 93. Fortineau, N., L. Poirel, and P. Nordmann. 2001. Plasmid-mediated and inducible cephalosporinase *DHA-2* from *Klebsiella pneumoniae*. J. Antimicrob. Chemother. 47:207–210.
 94. Forward, K. R., B. M. Willey, D. E. Low, A. McGeer, M. A. Kapala, M. M. Kapala, and L. L. Burrows. 2001. Molecular mechanisms of cefoxitin resistance in *Escherichia coli* from the Toronto area hospitals. Diagn. Microbiol. Infect. Dis. 41:57–63.
 95. Fosse, T., C. Giraud-Morin, I. Madinier, and R. Labia. 2003. Sequence analysis and biochemical characterization of chromosomal CAV-1 (*Aeromonas caviae*), the parental cephalosporinase of plasmid-mediated AmpC 'FOX' cluster. FEMS Microbiol. Lett. 222:93–98.
 96. Franceschini, N., L. Boschi, S. Pollini, R. Herman, M. Perilli, M. Galleni, J. M. Frère, G. Amicosante, and G. M. Rossolini. 2001. Characterization of OXA-29 from *Legionella (Fluoribacter) gormanii*: molecular class D β -lactamase with unusual properties. Antimicrob. Agents Chemother. 45:3509–3516.
 97. Franceschini, N., M. Galleni, J. M. Frère, A. Oratore, and G. Amicosante. 1993. A class-A β -lactamase from *Pseudomonas stutzeri* that is highly active against monobactams and cefotaxime. Biochem. J. 292:697–700.
 98. Gaillot, O., C. Clement, M. Simonet, and A. Philippon. 1997. Novel transferable β -lactam resistance with cephalosporinase characteristics in *Salmonella enteritidis*. J. Antimicrob. Chemother. 39:85–87.
 99. Galleni, M., G. Amicosante, and J. M. Frère. 1988. A survey of the kinetic parameters of class C β -lactamases. Cephalosporins and other β -lactam compounds. Biochem. J. 255:123–129.
 100. Galleni, M., and J. M. Frère. 1988. A survey of the kinetic parameters of class C β -lactamases. Penicillins. Biochem. J. 255:119–122.
 101. Galleni, M., F. Lindberg, S. Normark, S. Cole, N. Honore, B. Joris, and J. M. Frere. 1988. Sequence and comparative analysis of three *Enterobacter cloacae ampC* β -lactamase genes and their products. Biochem. J. 250:753–760.
 102. Gates, M. L., C. C. Sanders, R. V. Goering, and W. E. Sanders, Jr. 1986. Evidence for multiple forms of type I chromosomal β -lactamase in *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother. 30:453–457.
 103. Gazouli, M., M. E. Kaufmann, E. Tzelepi, H. Dimopoulou, O. Paniara, and L. S. Tzouveleakis. 1997. Study of an outbreak of cefoxitin-resistant *Klebsiella pneumoniae* in a general hospital. J. Clin. Microbiol. 35:508–510.
 104. Gazouli, M., L. S. Tzouveleakis, A. C. Vatopoulos, and E. Tzelepi. 1998. Transferable class C β -lactamases in *Escherichia coli* strains isolated in Greek hospitals and characterization of two enzyme variants (LAT-3 and LAT-4) closely related to *Citrobacter freundii ampC* β -lactamase. J. Antimicrob. Chemother. 42:419–425.
 105. Giles, W. P., A. K. Benson, M. E. Olson, R. W. Hutkins, J. M. Whichard, P. L. Winokur, and P. D. Fey. 2004. DNA sequence analysis of regions surrounding *bla*_{CMY-2} from multiple *Salmonella* plasmid backbones. Antimicrob. Agents Chemother. 48:2845–2852.
 106. Girlich, D., T. Naas, S. Bellais, L. Poirel, A. Karim, and P. Nordmann. 2000. Biochemical-genetic characterization and regulation of expression of an ACC-1-like chromosome-borne cephalosporinase from *Hafnia alvei*. Antimicrob. Agents Chemother. 44:1470–1478.
 107. Girlich, D., T. Naas, S. Bellais, L. Poirel, A. Karim, and P. Nordmann. 2000. Heterogeneity of AmpC cephalosporinases of *Hafnia alvei* clinical isolates expressing inducible or constitutive ceftazidime resistance phenotypes. Antimicrob. Agents Chemother. 44:3220–3223.
 108. Glupczynski, Y., T. D. Huang, C. Berhin, G. Claeys, M. Delmée, L. Ide, G. Ieven, D. Pierard, H. Rodriguez-Villalobos, M. Struelens, and J. Vaneldere. 2007. In vitro activity of temocillin against prevalent extended-spectrum beta-lactamases producing *Enterobacteriaceae* from Belgian intensive care units. Eur. J. Clin. Microbiol. Infect. Dis. 26:777–783.
 109. Gonzalez Leiza, M., J. C. Perez-Diaz, J. Ayala, J. M. Casellas, J. Martinez-Beltran, K. Bush, and F. Baquero. 1994. Gene sequence and biochemical characterization of FOX-1 from *Klebsiella pneumoniae*, a new AmpC-type plasmid-mediated β -lactamase with two molecular variants. Antimicrob. Agents Chemother. 38:2150–2157.
 110. Goodner, B., G. Hinkle, S. Gattung, N. Miller, M. Blanchard, B. Qurollo, B. S. Goldman, Y. Cao, M. Askenazi, C. Halling, L. Mullin, K. Houmiel, J. Gordon, M. Vaudin, O. Iartchouk, A. Epp, F. Liu, C. Wollam, M. Allinger, D. Doughty, C. Scott, C. Lappas, B. Markelz, C. Flanagan, C. Crowell, J. Gurson, C. Lomo, C. Sear, G. Strub, C. Cielzo, and S. Slater. 2001. Genome sequence of the plant pathogen and biotechnology agent *Agrobacterium tumefaciens* C58. Science 294:2323–2328.
 111. Gould, V. C., A. Okazaki, and M. B. Avison. 2006. β -Lactam resistance and β -lactamase expression in clinical *Stenotrophomonas maltophilia* isolates having defined phylogenetic relationships. J. Antimicrob. Chemother. 57:199–203.
 112. Gray, J. T., L. L. Hungerford, P. J. Fedorka-Cray, and M. L. Headrick. 2004. Extended-spectrum-cephalosporin resistance in *Salmonella enterica* isolates of animal origin. Antimicrob. Agents Chemother. 48:3179–3181.
 113. Gupta, A., J. Fontana, C. Crowe, B. Bolstorff, A. Stout, S. Van Duyn, M. P. Hoekstra, J. M. Whichard, T. J. Barrett, and F. J. Angulo. 2003. Emergence of multidrug-resistant *Salmonella enterica* serotype Newport infections resistant to expanded-spectrum cephalosporins in the United States. J. Infect. Dis. 188:1707–1716.
 114. Gutiérrez, O., C. Juan, E. Cercenado, F. Navarro, E. Bouza, P. Coll, J. L. Pérez, and A. Oliver. 2007. Molecular epidemiology and mechanisms of

- carbapenem resistance in *Pseudomonas aeruginosa* isolates from Spanish hospitals. *Antimicrob. Agents Chemother.* **51**:4329–4335.
115. Haldorsen, B., B. Aasnaes, K. H. Dahl, A. M. Hanssen, G. S. Simonsen, T. R. Walsh, A. Sundsfjord, and E. W. Lundblad. 2008. The AmpC phenotype in Norwegian clinical isolates of *Escherichia coli* is associated with an acquired *ISEcp1*-like *ampC* element or hyperproduction of the endogenous AmpC. *J. Antimicrob. Chemother.* **62**:694–702.
 116. Hall, B. G., and M. Barlow. 2004. Evolution of the serine β -lactamases: past, present and future. *Drug Resist. Updates* **7**:111–123.
 117. Hanson, N. D., E. S. Moland, S. G. Hong, K. Propst, D. J. Novak, and S. J. Cavalieri. 2008. Surveillance of community-based reservoirs reveals the presence of CTX-M, imported AmpC, and OXA-30 β -lactamases in urine isolates of *Klebsiella pneumoniae* and *Escherichia coli* in a U.S. community. *Antimicrob. Agents Chemother.* **52**:3814–3816.
 118. Hanson, N. D., and C. C. Sanders. 1999. Regulation of inducible AmpC β -lactamase expression among Enterobacteriaceae. *Curr. Pharm. Des.* **5**:881–894.
 119. Hanson, N. D., K. S. Thomson, E. S. Moland, C. C. Sanders, G. Berthold, and R. G. Penn. 1999. Molecular characterization of a multiply resistant *Klebsiella pneumoniae* encoding ESBLs and a plasmid-mediated AmpC. *J. Antimicrob. Chemother.* **44**:377–380.
 120. Hayes, M. V., C. J. Thomson, and S. G. Amyes. 1994. Three beta-lactamases isolated from *Aeromonas salmonicida*, including a carbapenemase not detectable by conventional methods. *Eur. J. Clin. Microbiol. Infect. Dis.* **13**:805–811.
 121. Henderson, T. A., K. D. Young, S. A. Denome, and P. K. Elf. 1997. AmpC and AmpH, proteins related to the class C β -lactamases, bind penicillin and contribute to the normal morphology of *Escherichia coli*. *J. Bacteriol.* **179**:6112–6121.
 122. Héritier, C., L. Poirel, and P. Nordmann. 2006. Cephalosporinase overexpression resulting from insertion of *ISAba1* in *Acinetobacter baumannii*. *Clin. Microbiol. Infect.* **12**:123–130.
 123. Héritier, C., L. Poirel, and P. Nordmann. 2004. Genetic and biochemical characterization of a chromosome-encoded carbapenem-hydrolyzing Ambler class D β -lactamase from *Shewanella algae*. *Antimicrob. Agents Chemother.* **48**:1670–1675.
 124. Hernández-Allés, S., V. J. Benedí, L. Martínez-Martínez, A. Pascual, A. Aguilar, J. M. Tomás, and S. Albertí. 1999. Development of resistance during antimicrobial therapy caused by insertion sequence interruption of porin genes. *Antimicrob. Agents Chemother.* **43**:937–939.
 125. Hernández-Allés, S., M. Conejo, A. Pascual, J. M. Tomás, V. J. Benedí, and L. Martínez-Martínez. 2000. Relationship between outer membrane alterations and susceptibility to antimicrobial agents in isogenic strains of *Klebsiella pneumoniae*. *J. Antimicrob. Chemother.* **46**:273–277.
 126. Hidri, N., G. Barnaud, D. Decré, C. Cerceau, V. Lalande, J. C. Petit, R. Labia, and G. Arlet. 2005. Resistance to ceftazidime is associated with a S220Y substitution in the omega loop of the AmpC β -lactamase of a *Serratia marcescens* clinical isolate. *J. Antimicrob. Chemother.* **55**:496–499.
 127. Higgins, C. S., M. B. Avison, L. Jamieson, A. M. Simm, P. M. Bennett, and T. R. Walsh. 2001. Characterization, cloning and sequence analysis of the inducible *Ochrobactrum anthropi* AmpC β -lactamase. *J. Antimicrob. Chemother.* **47**:745–754.
 128. Hirakawa, H., K. Nishino, J. Yamada, T. Hirata, and A. Yamaguchi. 2003. β -Lactam resistance modulated by the overexpression of response regulators of two-component signal transduction systems in *Escherichia coli*. *J. Antimicrob. Chemother.* **52**:576–582.
 129. Honoré, N., M. H. Nicolas, and S. T. Cole. 1986. Inducible cephalosporinase production in clinical isolates of *Enterobacter cloacae* is controlled by a regulatory gene that has been deleted from *Escherichia coli*. *EMBO J.* **5**:3709–3714.
 130. Hope, R., M. Warner, N. A. Potz, E. J. Fagan, D. James, and D. M. Livermore. 2006. Activity of tigecycline against ESBL-producing and AmpC-hyperproducing Enterobacteriaceae from south-east England. *J. Antimicrob. Chemother.* **58**:1312–1314.
 131. Hopkins, J. M., and K. J. Townner. 1990. Enhanced resistance to cefotaxime and imipenem associated with outer membrane protein alterations in *Enterobacter aerogenes*. *J. Antimicrob. Chemother.* **25**:49–55.
 132. Hopkins, K. L., M. J. Batchelor, E. Liebana, A. P. Deheer-Graham, and E. J. Threlfall. 2006. Characterisation of CTX-M and *ampC* genes in human isolates of *Escherichia coli* identified between 1995 and 2003 in England and Wales. *Int. J. Antimicrob. Agents* **28**:180–192.
 133. Hopkins, K. L., A. Deheer-Graham, E. Karisik, M. J. Batchelor, E. Liebana, and E. J. Threlfall. 2006. New plasmid-mediated AmpC β -lactamase (CMY-21) in *Escherichia coli* isolated in the UK. *Int. J. Antimicrob. Agents* **28**:80–82.
 134. Horii, T., Y. Arakawa, M. Ohta, S. Ichiyama, R. Wacharotayankun, and N. Kato. 1993. Plasmid-mediated AmpC-type β -lactamase isolated from *Klebsiella pneumoniae* confers resistance to broad-spectrum β -lactams, including moxalactam. *Antimicrob. Agents Chemother.* **37**:984–990.
 135. Hossain, A., M. D. Reishig, and N. D. Hanson. 2004. Plasmid-encoded functions compensate for the biological cost of AmpC overexpression in a clinical isolate of *Salmonella typhimurium*. *J. Antimicrob. Chemother.* **53**:964–970.
 136. Huang, I. F., C. H. Chiu, M. H. Wang, C. Y. Wu, K. S. Hsieh, and C. C. Chiou. 2005. Outbreak of dysentery associated with ceftriaxone-resistant *Shigella sonnei*: first report of plasmid-mediated CMY-2-type AmpC β -lactamase resistance in *S. sonnei*. *J. Clin. Microbiol.* **43**:2608–2612.
 137. Hujer, K. M., N. S. Hamza, A. M. Hujer, F. Perez, M. S. Helfand, C. R. Bethel, J. M. Thomson, V. E. Anderson, M. Barlow, L. B. Rice, F. C. Tenover, and R. A. Bonomo. 2005. Identification of a new allelic variant of the *Acinetobacter baumannii* cephalosporinase, ADC-7 β -lactamase: defining a unique family of class C enzymes. *Antimicrob. Agents Chemother.* **49**:2941–2948.
 138. Humeniuk, C., G. Arlet, V. Gautier, P. Grimont, R. Labia, and A. Philippon. 2002. β -Lactamases of *Kluyvera ascorbata*, probable progenitors of some plasmid-encoded CTX-M types. *Antimicrob. Agents Chemother.* **46**:3045–3049.
 139. Jacobs, C., J. M. Frère, and S. Normark. 1997. Cytosolic intermediates for cell wall biosynthesis and degradation control inducible β -lactam resistance in gram-negative bacteria. *Cell* **88**:823–832.
 140. Jacobs, C., L. Huang, E. Bartowsky, S. Normark, and J. T. Park. 1994. Bacterial cell wall recycling provides cytosolic muropeptides as effector for β -lactamase induction. *EMBO J.* **13**:4684–4694.
 141. Jacoby, G. A., D. M. Mills, and N. Chow. 2004. Role of β -lactamases and porins in resistance to ertapenem and other β -lactams in *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **48**:3203–3206.
 142. Jacoby, G. A., and J. Tran. 1999. Sequence of the MIR-1 β -lactamase gene. *Antimicrob. Agents Chemother.* **43**:1759–1760.
 143. Jacoby, G. A., K. E. Walsh, and V. J. Walker. 2006. Identification of extended-spectrum, AmpC, and carbapenem-hydrolyzing β -lactamases in *Escherichia coli* and *Klebsiella pneumoniae* by disk tests. *J. Clin. Microbiol.* **44**:1971–1976.
 144. Jaurin, B., and T. Grundström. 1981. *ampC* cephalosporinase of *Escherichia coli* K-12 has a different evolutionary origin from that of β -lactamases of the penicillinase type. *Proc. Natl. Acad. Sci. USA* **78**:4897–4901.
 145. Jaurin, B., T. Grundström, T. Edlund, and S. Normark. 1981. The *E. coli* β -lactamase attenuator mediates growth rate-dependent regulation. *Nature* **290**:221–225.
 146. Jaurin, B., and S. Normark. 1983. Insertion of IS2 creates a novel *ampC* promoter in *Escherichia coli*. *Cell* **32**:809–816.
 147. Jones, R. N., J. T. Kirby, and P. R. Rhomberg. 2008. Comparative activity of meropenem in US medical centers (2007): initiating the 2nd decade of MYSTIC program surveillance. *Diagn. Microbiol. Infect. Dis.* **61**:203–213.
 148. Joris, B., F. De Meester, M. Galleni, S. Masson, J. Dusart, J. M. Frère, J. Van Beumen, K. Bush, and R. Sykes. 1986. Properties of a class C β -lactamase from *Serratia marcescens*. *Biochem. J.* **239**:581–586.
 149. Joris, B., P. Ledent, O. Dideberg, E. Fonze, J. Lamotte-Brasseur, J. A. Kelly, J. M. Ghuysen, and J. M. Frère. 1991. Comparison of the sequences of class A β -lactamases and of the secondary structure elements of penicillin-recognizing proteins. *Antimicrob. Agents Chemother.* **35**:2294–2301.
 150. Juan, C., M. D. Macia, O. Gutierrez, C. Vidal, J. L. Perez, and A. Oliver. 2005. Molecular mechanisms of β -lactam resistance mediated by AmpC hyperproduction in *Pseudomonas aeruginosa* clinical strains. *Antimicrob. Agents Chemother.* **49**:4733–4738.
 151. Juan, C., B. Moyá, J. L. Pérez, and A. Oliver. 2006. Stepwise upregulation of the *Pseudomonas aeruginosa* chromosomal cephalosporinase conferring high-level β -lactam resistance involves three AmpD homologues. *Antimicrob. Agents Chemother.* **50**:1780–1787.
 152. Kaczmarek, F. M., F. Dib-Hajj, W. Shang, and T. D. Gootz. 2006. High-level carbapenem resistance in a *Klebsiella pneumoniae* clinical isolate is due to the combination of *bla*_{ACT-1} β -lactamase production, porin *OmpK35/36* insertional inactivation, and down-regulation of the phosphate transport porin *PhoE*. *Antimicrob. Agents Chemother.* **50**:3396–3406.
 153. Kaneko, K., R. Okamoto, R. Nakano, S. Kawakami, and M. Inoue. 2005. Gene mutations responsible for overexpression of AmpC β -lactamase in some clinical isolates of *Enterobacter cloacae*. *J. Clin. Microbiol.* **43**:2955–2958.
 154. Kang, C. I., H. Pai, S. H. Kim, H. B. Kim, E. C. Kim, M. D. Oh, and K. W. Choe. 2004. Cefepime and the inoculum effect in tests with *Klebsiella pneumoniae* producing plasmid-mediated AmpC-type β -lactamase. *J. Antimicrob. Chemother.* **54**:1130–1133.
 155. Kang, M. S., T. E. Besser, and D. R. Call. 2006. Variability in the region downstream of the *bla*_{CMY-2} β -lactamase gene in *Escherichia coli* and *Salmonella enterica* plasmids. *Antimicrob. Agents Chemother.* **50**:1590–1593.
 156. Kaye, K. S., S. Cosgrove, A. Harris, G. M. Eliopoulos, and Y. Carmeli. 2001. Risk factors for emergence of resistance to broad-spectrum cephalosporins among *Enterobacter* spp. *Antimicrob. Agents Chemother.* **45**:2628–2630.
 157. Kazmierczak, A., X. Cordin, J. M. Duez, E. Siebor, A. Pechinot, and J. Sirot. 1990. Differences between clavulanic acid and sulbactam in induction and inhibition of cephalosporinases in enterobacteria. *J. Int. Med. Res.* **18**(Suppl. 4):67D–77D.
 158. Kim, J. Y., H. I. Jung, Y. J. An, J. H. Lee, S. J. Kim, S. H. Jeong, K. J. Lee, P. G. Suh, H. S. Lee, S. H. Lee, and S. S. Cha. 2006. Structural basis for the

- extended substrate spectrum of CMY-10, a plasmid-encoded class C β -lactamase. *Mol. Microbiol.* **60**:907–916.
159. Kimura, H., M. Izawa, and Y. Sumino. 1996. Molecular analysis of the gene cluster involved in cephalosporin biosynthesis from *Lyso bacter lactamgenus* YK90. *Appl. Microbiol. Biotechnol.* **44**:589–596.
 160. Kitzis, M. D., B. Ferre, A. Coutrot, J. F. Acar, and L. Gutmann. 1989. In vitro activity of combinations of beta-lactam antibiotics with beta-lactamase inhibitors against cephalosporinase-producing bacteria. *Eur. J. Clin. Microbiol. Infect. Dis.* **8**:783–788.
 161. Knott-Hunziker, V., S. Petursson, G. S. Jayatilake, S. G. Waley, B. Jaurin, and T. Grundström. 1982. Active sites of β -lactamases. *Biochem. J.* **201**:621–627.
 162. Knox, J. R., P. C. Moews, and J. M. Frere. 1996. Molecular evolution of bacterial β -lactam resistance. *Chem. Biol.* **3**:937–947.
 163. Kohler, T., M. Michea-Hamzehpour, S. F. Epp, and J. C. Pechere. 1999. Carbapenem activities against *Pseudomonas aeruginosa*: respective contributions of OprD and efflux systems. *Antimicrob. Agents Chemother.* **43**:424–427.
 164. Kong, K. F., S. R. Jayawardena, S. D. Indulkar, A. Del Puerto, C. L. Koh, N. Hoiby, and K. Mathee. 2005. *Pseudomonas aeruginosa* AmpR is a global transcriptional factor that regulates expression of AmpC and PoxB β -lactamases, proteases, quorum sensing, and other virulence factors. *Antimicrob. Agents Chemother.* **49**:4567–4575.
 165. Kuga, A., R. Okamoto, and M. Inoue. 2000. *ampR* gene mutations that greatly increase class C β -lactamase activity in *Enterobacter cloacae*. *Antimicrob. Agents Chemother.* **44**:561–567.
 166. Lartigue, M. F., L. Poirel, D. Aubert, and P. Nordmann. 2006. In vitro analysis of ISEcp1B-mediated mobilization of naturally occurring β -lactamase gene *bla*_{CTX-M} of *Kluyvera ascorbata*. *Antimicrob. Agents Chemother.* **50**:1282–1286.
 167. Lau, S. K., P. L. Ho, M. W. Li, H. W. Tsoi, R. W. Yung, P. C. Woo, and K. Y. Yuen. 2005. Cloning and characterization of a chromosomal class C β -lactamase and its regulatory gene in *Laribacter hongkongensis*. *Antimicrob. Agents Chemother.* **49**:1957–1964.
 168. Lee, E. H., M. H. Nicolas, M. D. Kitzis, G. Pialoux, E. Collatz, and L. Gutmann. 1991. Association of two resistance mechanisms in a clinical isolate of *Enterobacter cloacae* with high-level resistance to imipenem. *Antimicrob. Agents Chemother.* **35**:1093–1098.
 169. Lee, K., S. G. Hong, Y. J. Park, H. S. Lee, W. Song, J. Jeong, D. Yong, and Y. Chong. 2005. Evaluation of phenotypic screening methods for detecting plasmid-mediated AmpC β -lactamases-producing isolates of *Escherichia coli* and *Klebsiella pneumoniae*. *Diagn. Microbiol. Infect. Dis.* **53**:319–323.
 170. Lee, K., M. Lee, J. H. Shin, M. H. Lee, S. H. Kang, A. J. Park, D. Yong, and Y. Chong. 2006. Prevalence of plasmid-mediated AmpC β -lactamases in *Escherichia coli* and *Klebsiella pneumoniae* in Korea. *Microb. Drug Resist.* **12**:44–49.
 171. Lee, K., D. Yong, Y. S. Choi, J. H. Yum, J. M. Kim, N. Woodford, D. M. Livermore, and Y. Chong. 2007. Reduced imipenem susceptibility in *Klebsiella pneumoniae* clinical isolates with plasmid-mediated CMY-2 and DHA-1 β -lactamases co-mediated by porin loss. *Int. J. Antimicrob. Agents* **29**:201–206.
 172. Lee, S. H., S. H. Jeong, and Y. M. Park. 2003. Characterization of *bla*_{CMY-10} a novel, plasmid-encoded AmpC-type β -lactamase gene in a clinical isolate of *Enterobacter aerogenes*. *J. Appl. Microbiol.* **95**:744–752.
 173. Lee, S. H., J. H. Lee, M. J. Heo, I. K. Bae, S. H. Jeong, and S. S. Cha. 2007. Exact location of the region responsible for the extended substrate spectrum in class C β -lactamases. *Antimicrob. Agents Chemother.* **51**:3778–3779.
 174. Li, Y., Q. Li, Y. Du, X. Jiang, J. Tang, J. Wang, G. Li, and Y. Jiang. 2008. Prevalence of plasmid-mediated AmpC β -lactamases in a Chinese university hospital from 2003 to 2005: first report of CMY-2-type AmpC β -lactamase resistance in China. *J. Clin. Microbiol.* **46**:1317–1321.
 175. Liassine, N., S. Madec, B. Ninet, C. Metral, M. Fouchereau-Peron, R. Labia, and R. Auckenthaler. 2002. Postneurosurgical meningitis due to *Proteus penneri* with selection of a ceftriaxone-resistant isolate: analysis of chromosomal class A β -lactamase HugA and its LysR-type regulatory protein HugR. *Antimicrob. Agents Chemother.* **46**:216–219.
 176. Liebana, E., M. Gibbs, C. Clouting, L. Barker, F. A. Clifton-Hadley, E. Pleydell, B. Abdalhamid, N. D. Hanson, L. Martin, C. Poppe, and R. H. Davies. 2004. Characterization of β -lactamases responsible for resistance to extended-spectrum cephalosporins in *Escherichia coli* and *Salmonella enterica* strains from food-producing animals in the United Kingdom. *Microb. Drug Resist.* **10**:1–9.
 177. Lin, J. W., S. F. Weng, Y. F. Chao, and Y. T. Chung. 2005. Characteristic analysis of the *ampC* gene encoding β -lactamase from *Photobacterium phosphoreum*. *Biochem. Biophys. Res. Commun.* **326**:539–547.
 178. Linberg, F., and S. Normark. 1986. Sequence of the *Citrobacter freundii* OS60 chromosomal *ampC* β -lactamase gene. *Eur. J. Biochem.* **156**:441–445.
 179. Lindquist, S., K. Weston-Hafer, H. Schmidt, C. Pul, G. Korfmann, J. Erickson, C. Sanders, H. H. Martin, and S. Normark. 1993. AmpG, a signal transducer in chromosomal β -lactamase induction. *Mol. Microbiol.* **9**:703–715.
 180. Linström, E. B., H. G. Boman, and B. B. Steele. 1970. Resistance of *Escherichia coli* to penicillins. VI. Purification and characterization of the chromosomally mediated penicillinase present in *ampA*-containing strains. *J. Bacteriol.* **101**:218–231.
 181. Lister, P. D., V. M. Gardner, and C. C. Sanders. 1999. Clavulanate induces expression of the *Pseudomonas aeruginosa* AmpC cephalosporinase at physiologically relevant concentrations and antagonizes the antibacterial activity of ticarcillin. *Antimicrob. Agents Chemother.* **43**:882–889.
 182. Literacka, E., J. Empel, A. Baraniak, E. Sadowy, W. Hryniewicz, and M. Gniadkowski. 2004. Four variants of the *Citrobacter freundii* AmpC-type cephalosporinases, including novel enzymes CMY-14 and CMY-15, in a *Proteus mirabilis* clone widespread in Poland. *Antimicrob. Agents Chemother.* **48**:4136–4143.
 183. Liu, Y. F., J. J. Yan, W. C. Ko, S. H. Tsai, and J. J. Wu. 2008. Characterization of carbapenem-non-susceptible *Escherichia coli* isolates from a university hospital in Taiwan. *J. Antimicrob. Chemother.* **61**:1020–1023.
 184. Livermore, D. M. 1987. Clinical significance of beta-lactamase induction and stable derepression in gram-negative rods. *Eur. J. Clin. Microbiol.* **6**:439–445.
 185. Livermore, D. M. 1992. Interplay of impermeability and chromosomal β -lactamase activity in imipenem-resistant *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **36**:2046–2048.
 186. Livermore, D. M. 2002. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? *Clin. Infect. Dis.* **34**:634–640.
 187. Livermore, D. M., R. Hope, E. J. Fagan, M. Warner, N. Woodford, and N. Potz. 2006. Activity of temocillin against prevalent ESBL- and AmpC-producing Enterobacteriaceae from south-east England. *J. Antimicrob. Chemother.* **57**:1012–1014.
 188. Livermore, D. M., and N. Woodford. 2006. The β -lactamase threat in Enterobacteriaceae, *Pseudomonas* and *Acinetobacter*. *Trends Microbiol.* **14**:413–420.
 189. Livermore, D. M., and Y. J. Yang. 1987. β -Lactamase lability and inducer power of newer β -lactam antibiotics in relation to their activity against β -lactamase-inducibility mutants of *Pseudomonas aeruginosa*. *J. Infect. Dis.* **155**:775–782.
 190. Lobkovsky, E., P. C. Moews, H. Liu, H. Zhao, J. M. Frere, and J. R. Knox. 1993. Evolution of an enzyme activity: crystallographic structure at 2-Å resolution of cephalosporinase from the *ampC* gene of *Enterobacter cloacae* P99 and comparison with a class A penicillinase. *Proc. Natl. Acad. Sci. USA* **90**:11257–11261.
 191. Mahlen, S. D., S. S. Morrow, B. Abdalhamid, and N. D. Hanson. 2003. Analyses of *ampC* gene expression in *Serratia marcescens* reveal new regulatory properties. *J. Antimicrob. Chemother.* **51**:791–802.
 192. Mainardi, J. L., P. Mugnier, A. Coutrot, A. Buu-Hoi, E. Collatz, and L. Gutmann. 1997. Carbapenem resistance in a clinical isolate of *Citrobacter freundii*. *Antimicrob. Agents Chemother.* **41**:2352–2354.
 193. Mammeri, H., F. Eb, A. Berkani, and P. Nordmann. 2008. Molecular characterization of AmpC-producing *Escherichia coli* clinical isolates recovered in a French hospital. *J. Antimicrob. Chemother.* **61**:498–503.
 194. Mammeri, H., H. Nazik, T. Naas, L. Poirel, S. Leotard, and P. Nordmann. 2004. AmpC β -lactamase in an *Escherichia coli* clinical isolate confers resistance to expanded-spectrum cephalosporins. *Antimicrob. Agents Chemother.* **48**:4050–4053.
 195. Mammeri, H., P. Nordmann, A. Berkani, and F. Eb. 2008. Contribution of extended-spectrum AmpC (ESAC) β -lactamases to carbapenem resistance in *Escherichia coli*. *FEMS Microbiol. Lett.* **282**:238–240.
 196. Mammeri, H., L. Poirel, P. Bemer, H. Drugeon, and P. Nordmann. 2004. Resistance to cefepime and ceftipime due to a 4-amino-acid deletion in the chromosome-encoded AmpC β -lactamase of a *Serratia marcescens* clinical isolate. *Antimicrob. Agents Chemother.* **48**:716–720.
 197. Mammeri, H., L. Poirel, N. Fortineau, and P. Nordmann. 2006. Naturally occurring extended-spectrum cephalosporinases in *Escherichia coli*. *Antimicrob. Agents Chemother.* **50**:2573–2576.
 198. Mammeri, H., L. Poirel, H. Nazik, and P. Nordmann. 2006. Cloning and functional characterization of the Ambler class C β -lactamase of *Yersinia ruckeri*. *FEMS Microbiol. Lett.* **257**:57–62.
 199. Mammeri, H., L. Poirel, and P. Nordmann. 2007. Extension of the hydrolysis spectrum of AmpC β -lactamase of *Escherichia coli* due to amino acid insertion in the H-10 helix. *J. Antimicrob. Chemother.* **60**:490–494.
 200. Manchanda, V., and N. P. Singh. 2003. Occurrence and detection of AmpC β -lactamases among gram-negative clinical isolates using a modified three-dimensional test at Guru Tegh Bahadur Hospital, Delhi, India. *J. Antimicrob. Chemother.* **51**:415–418.
 201. Martínez-Martínez, L., M. C. Conejo, A. Pascual, S. Hernández-Allés, S. Ballesta, E. Ramírez De Arellano-Ramos, V. J. Benedit, and E. J. Perea. 2000. Activities of imipenem and cephalosporins against clonally related strains of *Escherichia coli* hyperproducing chromosomal β -lactamase and showing altered porin profiles. *Antimicrob. Agents Chemother.* **44**:2534–2536.

202. Martínez-Martínez, L., S. Hernández-Allés, S. Albertí, J. M. Tomás, V. J. Benedí, and G. A. Jacoby. 1996. In vivo selection of porin-deficient mutants of *Klebsiella pneumoniae* with increased resistance to cefoxitin and expanded-spectrum cephalosporins. *Antimicrob. Agents Chemother.* **40**:342–348.
203. Martínez-Martínez, L., A. Pascual, S. Hernández-Allés, D. Alvarez-Díaz, A. I. Suárez, J. Tran, V. J. Benedí, and G. A. Jacoby. 1999. Roles of β -lactamases and porins in activities of carbapenems and cephalosporins against *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **43**:1669–1673.
204. Matagne, A., A. M. Misselyn-Bauduin, B. Joris, T. Erpicum, B. Granier, and J. M. Frère. 1990. The diversity of the catalytic properties of class A β -lactamases. *Biochem. J.* **265**:131–146.
205. Matsubara, N., A. Yotsuji, K. Kumano, M. Inoue, and S. Mitsuhashi. 1981. Purification and some properties of a cephalosporinase from *Proteus vulgaris*. *Antimicrob. Agents Chemother.* **19**:185–187.
206. Matsumura, N., S. Minami, and S. Mitsuhashi. 1998. Sequences of homologous β -lactamases from clinical isolates of *Serratia marcescens* with different substrate specificities. *Antimicrob. Agents Chemother.* **42**:176–179.
207. Matsuura, M., H. Nakazawa, M. Inoue, and S. Mitsuhashi. 1980. Purification and biochemical properties of β -lactamase produced by *Proteus rettgeri*. *Antimicrob. Agents Chemother.* **18**:687–690.
208. Maurelli, A. T., R. E. Fernandez, C. A. Bloch, C. K. Rode, and A. Fasano. 1998. “Black holes” and bacterial pathogenicity: a large genomic deletion that enhances the virulence of *Shigella* spp. and enteroinvasive *Escherichia coli*. *Proc. Natl. Acad. Sci. USA* **95**:3943–3948.
209. Michaux, C., J. Massant, F. Kerff, J. M. Frère, J. D. Docquier, I. Vandenberghe, B. Samyn, A. Pierrard, G. Feller, P. Charlier, J. Van Becumen, and J. Wouters. 2008. Crystal structure of a cold-adapted class C β -lactamase. *FEBS J.* **275**:1687–1697.
210. Migliavacca, R., E. Nucleo, M. M. D’Andrea, M. Spalla, T. Giani, and L. Pagani. 2007. Acquired AmpC type beta-lactamases: an emerging problem in Italian long-term care and rehabilitation facilities. *New Microbiol.* **30**:295–298.
211. Minami, S., M. Inoue, and S. Mitsuhashi. 1980. Purification and properties of a cephalosporinase from *Enterobacter cloacae*. *Antimicrob. Agents Chemother.* **18**:853–857.
212. Minami, S., M. Inoue, and S. Mitsuhashi. 1980. Purification and properties of cephalosporinase in *Escherichia coli*. *Antimicrob. Agents Chemother.* **18**:77–80.
213. Miriagou, V., P. T. Tassios, N. J. Legakis, and L. S. Tzouveleki. 2004. Expanded-spectrum cephalosporin resistance in non-typhoid *Salmonella*. *Int. J. Antimicrob. Agents* **23**:547–555.
214. Miriagou, V., L. S. Tzouveleki, L. Villa, E. Lebessi, A. C. Vatopoulos, A. Carattoli, and E. Tzelepi. 2004. CMY-13, a novel inducible cephalosporinase encoded by an *Escherichia coli* plasmid. *Antimicrob. Agents Chemother.* **48**:3172–3174.
215. Mittal, S., S. Mallik, S. Sharma, and J. S. Virdi. 2007. Characteristics of β -lactamases and their genes (*blaA* and *blaB*) in *Yersinia intermedia* and *Y. frederiksenii*. *BMC Microbiol.* **7**:25.
216. Moland, E. S., J. A. Black, J. Ourada, M. D. Reisbig, N. D. Hanson, and K. S. Thomson. 2002. Occurrence of newer β -lactamases in *Klebsiella pneumoniae* isolates from 24 U.S. hospitals. *Antimicrob. Agents Chemother.* **46**:3837–3842.
217. Moland, E. S., N. D. Hanson, J. A. Black, A. Hossain, W. Song, and K. S. Thomson. 2006. Prevalence of newer β -lactamases in gram-negative clinical isolates collected in the United States from 2001 to 2002. *J. Clin. Microbiol.* **44**:3318–3324.
218. Monnaie, D., and J. M. Frere. 1993. Interaction of clavulanate with class C β -lactamases. *FEBS Lett.* **334**:269–271.
219. Moya, B., C. Juan, S. Albertí, J. L. Pérez, and A. Oliver. 2008. Benefit of having multiple *ampD* genes for acquiring β -lactam resistance without losing fitness and virulence in *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **52**:3694–3700.
- 219a. Moya, B., C. Juan, J. Blazquez, L. Zamorano, J. L. Perez, A. Oliver, and H. Son Dureta. 2008. Abstr. 48th Intersci. Conf. Antimicrob. Agents Chemother., abstr. C1-3729.
220. Mulvey, M. R., E. Bryce, D. A. Boyd, M. Ofner-Agostini, A. M. Land, A. E. Simor, and S. Paton. 2005. Molecular characterization of cefoxitin-resistant *Escherichia coli* from Canadian hospitals. *Antimicrob. Agents Chemother.* **49**:358–365.
221. Murata, T., S. Minami, K. Yasuda, S. Iyobe, M. Inoue, and S. Mitsuhashi. 1981. Purification and properties of cephalosporinase from *Pseudomonas aeruginosa*. *J. Antibiot. (Tokyo)* **34**:1164–1170.
222. M’Zali, F. H., J. Heritage, D. M. Gascoyne-Binzi, M. Denton, N. J. Todd, and P. M. Hawkey. 1997. Transcontinental importation into the UK of *Escherichia coli* expressing a plasmid-mediated AmpC-type β -lactamase exposed during an outbreak of SHV-5 extended-spectrum β -lactamase in a Leeds hospital. *J. Antimicrob. Chemother.* **40**:823–831.
223. Naas, T., D. Aubert, N. Fortineau, and P. Nordmann. 2002. Cloning and sequencing of the β -lactamase gene and surrounding DNA sequences of *Citrobacter braakii*, *Citrobacter murlinae*, *Citrobacter werkmanii*, *Escherichia fergusonii* and *Enterobacter cancerogenus*. *FEMS Microbiol. Lett.* **215**:81–87.
224. Naas, T., D. Aubert, A. Özcan, and P. Nordmann. 2007. Chromosome-encoded narrow-spectrum Ambler class A β -lactamase GIL-1 from *Citrobacter gillenii*. *Antimicrob. Agents Chemother.* **51**:1365–1372.
225. Naas, T., D. Aubert, S. Vimont, and P. Nordmann. 2004. Identification of a chromosome-borne class C β -lactamase from *Erwinia rhapontici*. *J. Antimicrob. Chemother.* **54**:932–935.
226. Nadjar, D., R. Labia, C. Cerceau, C. Bizet, A. Philippon, and G. Arlet. 2001. Molecular characterization of chromosomal class C β -lactamase and its regulatory gene in *Ochrobactrum anthropi*. *Antimicrob. Agents Chemother.* **45**:2324–2330.
227. Nadjar, D., M. Rouveau, C. Verdet, J. Donay, J. Herrmann, P. H. Lagrange, A. Philippon, and G. Arlet. 2000. Outbreak of *Klebsiella pneumoniae* producing transferable AmpC-type β -lactamase (ACC-1) originating from *Hafnia alvei*. *FEMS Microbiol. Lett.* **187**:35–40.
228. Nakano, R., R. Okamoto, N. Nagano, and M. Inoue. 2007. Resistance to gram-negative organisms due to high-level expression of plasmid-encoded *ampC* β -lactamase *bla_{CMY-4}* promoted by insertion sequence *ISEcp1*. *J. Infect. Chemother.* **13**:18–23.
229. Nakano, R., R. Okamoto, Y. Nakano, K. Kaneko, N. Okitsu, Y. Hosaka, and M. Inoue. 2004. CFE-1, a novel plasmid-encoded AmpC β -lactamase with an *ampR* gene originating from *Citrobacter freundii*. *Antimicrob. Agents Chemother.* **48**:1151–1158.
230. Nasim, K., S. Elsayed, J. D. Pitout, J. Conly, D. L. Church, and D. B. Gregson. 2004. New method for laboratory detection of AmpC β -lactamases in *Escherichia coli* and *Klebsiella pneumoniae*. *J. Clin. Microbiol.* **42**:4799–4802.
231. Navon-Venezia, S., A. Leavitt, and Y. Carmeli. 2007. High tigecycline resistance in multidrug-resistant *Acinetobacter baumannii*. *J. Antimicrob. Chemother.* **59**:772–774.
232. Neu, H. C., N. X. Chin, K. Jules, and P. Labthavikul. 1986. The activity of BMY 28142 a new broad spectrum β -lactamase stable cephalosporin. *J. Antimicrob. Chemother.* **17**:441–452.
233. Nikaïdo, H., W. Liu, and E. Y. Rosenberg. 1990. Outer membrane permeability and β -lactamase stability of dipolar ionic cephalosporins containing methoxyimino substituents. *Antimicrob. Agents Chemother.* **34**:337–342.
234. Niumsup, P., A. M. Simm, K. Nurmahomed, T. R. Walsh, P. M. Bennett, and M. B. Avison. 2003. Genetic linkage of the penicillinase gene, *amp*, and *bla_{AB}*, encoding the regulator of β -lactamase expression in *Aeromonas* spp. *J. Antimicrob. Chemother.* **51**:1351–1358.
235. Nordmann, P., and H. Mammeri. 2007. Extended-spectrum cephalosporinases: structure, detection and epidemiology. *Future Microbiol.* **2**:297–307.
236. Nordström, K., L. G. Burman, and K. G. Eriksson-Grennberg. 1970. Resistance of *Escherichia coli* to penicillins. 8. Physiology of a class II ampicillin-resistant mutant. *J. Bacteriol.* **101**:659–668.
237. Nukaga, M., S. Haruta, K. Tanimoto, K. Kogure, K. Taniguchi, M. Tamaki, and T. Sawai. 1995. Molecular evolution of a class C β -lactamase extending its substrate specificity. *J. Biol. Chem.* **270**:5729–5735.
238. Odeh, R., S. Kelkar, A. M. Hujer, R. A. Bonomo, P. C. Schreckenberger, and J. P. Quinn. 2002. Broad resistance due to plasmid-mediated AmpC β -lactamases in clinical isolates of *Escherichia coli*. *Clin. Infect. Dis.* **35**:140–145.
239. Ogata, H., P. Renesto, S. Audic, C. Robert, G. Blanc, P. E. Fournier, H. Parinello, J. M. Claverie, and D. Raoult. 2005. The genome sequence of *Rickettsia felis* identifies the first putative conjugative plasmid in an obligate intracellular parasite. *PLoS Biol.* **3**:e248.
240. Ohana, S., V. Lefont, E. Ronco, M. Rottman, D. Guillemot, S. Lortat-Jacob, P. Denys, G. Loubert, M. H. Nicolas-Chanoine, J. L. Gaillard, and C. Lawrence. 2005. Spread of a *Klebsiella pneumoniae* strain producing a plasmid-mediated ACC-1 AmpC β -lactamase in a teaching hospital admitting disabled patients. *Antimicrob. Agents Chemother.* **49**:2095–2097.
241. Olsson, O., S. Bergström, F. P. Lindberg, and S. Normark. 1983. *ampC* β -lactamase hyperproduction in *Escherichia coli*: natural ampicillin resistance generated by horizontal chromosomal DNA transfer from *Shigella*. *Proc. Natl. Acad. Sci. USA* **80**:7556–7560.
242. Olsson, O., S. Bergström, and S. Normark. 1982. Identification of a novel *ampC* β -lactamase promoter in a clinical isolate of *Escherichia coli*. *EMBO J.* **1**:1411–1416.
243. Padilla, E., D. Alonso, A. Doménech-Sánchez, C. Gomez, J. L. Pérez, S. Albertí, and N. Borrell. 2006. Effect of porins and plasmid-mediated AmpC β -lactamases on the efficacy of β -lactams in rat pneumonia caused by *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **50**:2258–2260.
244. Pai, H., C. I. Kang, J. H. Byeon, K. D. Lee, W. B. Park, H. B. Kim, E. C. Kim, M. D. Oh, and K. W. Choe. 2004. Epidemiology and clinical features of bloodstream infections caused by AmpC-type- β -lactamase-producing *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **48**:3720–3728.
245. Pai, H., J. Kim, J. H. Lee, K. W. Choe, and N. Gotoh. 2001. Carbapenem resistance mechanisms in *Pseudomonas aeruginosa* clinical isolates. *Antimicrob. Agents Chemother.* **45**:480–484.
246. Palasubramaniam, S., R. Karunakaran, G. G. Gin, S. Muniandy, and N. Parasakthi. 2007. Imipenem-resistance in *Klebsiella pneumoniae* in Malaysia due to loss of *OmpK36* outer membrane protein coupled with AmpC hyperproduction. *Int. J. Infect. Dis.* **11**:472–474.

247. Papagiannitsis, C. C., L. S. Tzouveleki, E. Tzelepi, and V. Miriagou. 2007. Plasmid-encoded ACC-4, an extended-spectrum cephalosporinase variant from *Escherichia coli*. *Antimicrob. Agents Chemother.* **51**:3763–3767.
248. 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.
249. Partridge, S. R. 2007. Genetic environment of ISEcp1 and bla_{ACC-1}. *Antimicrob. Agents Chemother.* **51**:2658–2659.
250. Pasteran, F. G., L. Otaegui, L. Guerriero, G. Radice, R. Maggiora, M. Rapoport, D. Faccione, A. Di Martino, and M. Galas. 2008. *Klebsiella pneumoniae* carbapenemase-2, Buenos Aires, Argentina. *Emerg. Infect. Dis.* **14**:1178–1180.
251. Pérez-Pérez, F. J., and N. D. Hanson. 2002. Detection of plasmid-mediated AmpC β -lactamase genes in clinical isolates by using multiplex PCR. *J. Clin. Microbiol.* **40**:2153–2162.
252. Petrella, S., D. Clermont, I. Casin, V. Jarlier, and W. Sougakoff. 2001. Novel class A β -lactamase Sed-1 from *Citrobacter sedlakii*: genetic diversity of β -lactamases within the *Citrobacter* genus. *Antimicrob. Agents Chemother.* **45**:2287–2298.
253. Pfaller, M. A., R. N. Jones, S. A. Marshall, S. L. Coffman, R. J. Hollis, M. B. Edmond, and R. P. Wenzel. 1997. Inducible ampC β -lactamase producing gram-negative bacilli from blood stream infections: frequency, antimicrobial susceptibility, and molecular epidemiology in a national surveillance program (SCOPE). *Diagn. Microbiol. Infect. Dis.* **28**:211–219.
254. Philippon, A., G. Arlet, and G. A. Jacoby. 2002. Plasmid-determined AmpC-type β -lactamases. *Antimicrob. Agents Chemother.* **46**:1–11.
255. Pichardo, C., M. del Carmen Conejo, M. Bernabéu-Wittel, A. Pascual, M. E. Jiménez-Mejías, M. de Cueto, M. E. Pachón-Ibañez, I. García, J. Pachón, and L. Martínez-Martínez. 2005. Activity of cefepime and carbapenems in experimental pneumonia caused by porin-deficient *Klebsiella pneumoniae* producing FOX-5 β -lactamase. *Clin. Microbiol. Infect.* **11**: 31–38.
256. Pichardo, C., J. M. Rodríguez-Martínez, M. E. Pachón-Ibañez, C. Conejo, J. Ibañez-Martínez, L. Martínez-Martínez, J. Pachón, and A. Pascual. 2005. Efficacy of cefepime and imipenem in experimental murine pneumonia caused by porin-deficient *Klebsiella pneumoniae* producing CMY-2 β -lactamase. *Antimicrob. Agents Chemother.* **49**:3311–3316.
257. Pitout, J. D., D. B. Gregson, D. L. Church, and K. B. Laupland. 2007. Population-based laboratory surveillance for AmpC β -lactamase-producing *Escherichia coli*, Calgary, *Emerg. Infect. Dis.* **13**:443–448.
258. Pitout, J. D., E. S. Moland, C. C. Sanders, K. S. Thomson, and S. R. Fitzsimmons. 1997. β -Lactamases and detection of β -lactam resistance in *Enterobacter* spp. *Antimicrob. Agents Chemother.* **41**:35–39.
259. Pitout, J. D., M. D. Reisbig, M. Mulvey, L. Chui, M. Louie, L. Crowe, D. L. Church, S. Elsayed, D. Gregson, R. Ahmed, P. Tilley, and N. D. Hanson. 2013. Association between handling of pet treats and infection with *Salmonella enterica* serotype Newport expressing the AmpC β -lactamase, CMY-2. *J. Clin. Microbiol.* **41**:4578–4582.
260. Poirel, L., M. Guibert, D. Girlich, T. Naas, and P. Nordmann. 1999. Cloning, sequence analyses, expression, and distribution of ampC-ampR from *Morganella morganii* clinical isolates. *Antimicrob. Agents Chemother.* **43**: 769–776.
261. Poirel, L., M. F. Lartigue, J. W. Decousser, and P. Nordmann. 2005. ISEcp1B-mediated transposition of bla_{CTX-M} in *Escherichia coli*. *Antimicrob. Agents Chemother.* **49**:447–450.
262. Poirel, L., T. Naas, D. Nicolas, L. Collet, S. Bellais, J. D. Cavallo, and P. Nordmann. 2000. Characterization of VIM-2, a carbapenem-hydrolyzing metallo- β -lactamase and its plasmid- and integron-borne gene from a *Pseudomonas aeruginosa* clinical isolate in France. *Antimicrob. Agents Chemother.* **44**:891–897.
263. Potz, N. A., R. Hope, M. Warner, A. P. Johnson, and D. M. Livermore. 2006. Prevalence and mechanisms of cephalosporin resistance in Enterobacteriaceae in London and South-East England. *J. Antimicrob. Chemother.* **58**: 320–326.
264. Power, P., M. Galleni, J. A. Ayala, and G. Gutkind. 2006. Biochemical and molecular characterization of three new variants of AmpC β -lactamases from *Morganella morganii*. *Antimicrob. Agents Chemother.* **50**:962–967.
265. Powers, R. A., E. Caselli, P. J. Focia, F. Prati, and B. K. Shoichet. 2001. Structures of ceftazidime and its transition-state analogue in complex with AmpC β -lactamase: implications for resistance mutations and inhibitor design. *Biochemistry* **40**:9207–9214.
266. Preston, K. E., C. C. Radomski, and R. A. Venezia. 2000. Nucleotide sequence of the chromosomal ampC gene of *Enterobacter aerogenes*. *Antimicrob. Agents Chemother.* **44**:3158–3162.
267. Qin, X., D. M. Zerrt, S. J. Weissman, J. A. Englund, D. M. Denno, E. J. Klein, P. I. Tarr, J. Kwong, J. R. Stapp, L. G. Tulloch, and E. Galanakis. 2008. Prevalence and mechanisms of broad-spectrum β -lactam resistance in *Enterobacteriaceae*: a children's hospital experience. *Antimicrob. Agents Chemother.* **52**:3909–3914.
268. Quale, J., S. Bratu, J. Gupta, and D. Landman. 2006. Interplay of efflux system, ampC, and oprD expression in carbapenem resistance of *Pseudomonas aeruginosa* clinical isolates. *Antimicrob. Agents Chemother.* **50**:1633–1641.
269. Queenan, A. M., S. Jenkins, and K. Bush. 2001. Cloning and biochemical characterization of FOX-5, an AmpC-type plasmid-encoded β -lactamase from a New York City *Klebsiella pneumoniae* clinical isolate. *Antimicrob. Agents Chemother.* **45**:3189–3194.
270. Raimondi, A., A. Traverso, and H. Nikaido. 1991. Imipenem- and meropenem-resistant mutants of *Enterobacter cloacae* and *Proteus rettgeri* lack porins. *Antimicrob. Agents Chemother.* **35**:1174–1180.
271. Raskine, L., I. Borrel, G. Barnaud, S. Boyer, B. Hanau-Bercot, J. Gravis, R. Labia, G. Arlet, and M. J. Sanson-Le-Pors. 2002. Novel plasmid-encoded class C β -lactamase (MOX-2) in *Klebsiella pneumoniae* from Greece. *Antimicrob. Agents Chemother.* **46**:2262–2265.
272. Rasmussen, B. A., D. Keeney, Y. Yang, and K. Bush. 1994. Cloning and expression of a cloxacillin-hydrolyzing enzyme and a cephalosporinase from *Aeromonas sobria* AER 14M in *Escherichia coli*: requirement for an *E. coli* chromosomal mutation for efficient expression of the class D enzyme. *Antimicrob. Agents Chemother.* **38**:2078–2085.
273. Recchia, G. D., and R. M. Hall. 1995. Gene cassettes: a new class of mobile element. *Microbiology* **141**:3015–3027.
274. Reisbig, M. D., and N. D. Hanson. 2002. The ACT-1 plasmid-encoded AmpC β -lactamase is inducible: detection in a complex β -lactamase background. *J. Antimicrob. Chemother.* **49**:557–560.
275. Reisbig, M. D., and N. D. Hanson. 2004. Promoter sequences necessary for high-level expression of the plasmid-associated ampC β -lactamase gene bla_{MIR-1}. *Antimicrob. Agents Chemother.* **48**:4177–4182.
276. Reisbig, M. D., A. Hossain, and N. D. Hanson. 2003. Factors influencing gene expression and resistance for gram-negative organisms expressing plasmid-encoded ampC genes of *Enterobacter* origin. *J. Antimicrob. Chemother.* **51**:1141–1151.
277. Robin, F., J. Delmas, M. Archambaud, C. Schweitzer, C. Chanal, and R. Bonnet. 2006. CMT-type β -lactamase TEM-125, an emerging problem for extended-spectrum β -lactamase detection. *Antimicrob. Agents Chemother.* **50**:2403–2408.
278. Rogers, M. B., A. C. Parker, and C. J. Smith. 1993. Cloning and characterization of the endogenous cephalosporinase gene, cepA, from *Bacteroides fragilis* reveals a new subgroup of Ambler class A β -lactamases. *Antimicrob. Agents Chemother.* **37**:2391–2400.
279. Rottman, M., Y. Benzerara, B. Hanau-Bercot, C. Bizet, A. Philippon, and G. Arlet. 2002. Chromosomal ampC genes in *Enterobacter* species other than *Enterobacter cloacae*, and ancestral association of the ACT-1 plasmid-encoded cephalosporinase to *Enterobacter asburiae*. *FEMS Microbiol. Lett.* **210**:87–92.
280. Ruppé, E., P. Bidet, C. Verdet, G. Arlet, and E. Bingen. 2006. First detection of the Ambler class C 1 AmpC β -lactamase in *Citrobacter freundii* by a new, simple double-disk synergy test. *J. Clin. Microbiol.* **44**:4204–4207.
281. Sabath, L. D., M. Jago, and E. P. Abraham. 1965. Cephalosporinase and penicillinase activities of a β -lactamase from *Pseudomonas pyocyanea*. *Biochem. J.* **96**:739–752.
282. Sader, H. S., R. N. Jones, M. G. Stilwell, M. J. Dowzicky, and T. R. Fritsche. 2005. Tigecycline activity tested against 26,474 bloodstream infection isolates: a collection from 6 continents. *Diagn. Microbiol. Infect. Dis.* **52**:181–186.
283. Sanders, C. C. 1993. Cefepime: the next generation? *Clin. Infect. Dis.* **17**:369–379.
284. Reference deleted.
285. Sanders, C. C., and W. E. Sanders, Jr. 1986. Type I β -lactamases of gram-negative bacteria: interaction with β -lactam antibiotics. *J. Infect. Dis.* **154**:792–800.
286. Sanders, W. E., Jr., J. H. Tenney, and R. E. Kessler. 1996. Efficacy of cefepime in the treatment of infections due to multiply resistant *Enterobacter* species. *Clin. Infect. Dis.* **23**:454–461.
287. Sawai, T., A. Yamaguchi, and K. Tsukamoto. 1988. Amino acid sequence, active-site residue, and effect of suicide inhibitors on cephalosporinase of *Citrobacter freundii* GN346. *Rev. Infect. Dis.* **10**:721–725.
288. Schiefer, A. M., I. Wiegand, K. J. Sherwood, B. Wiedemann, and I. Stock. 2005. Biochemical and genetic characterization of the β -lactamases of *Y. aldovae*, *Y. bercovieri*, *Y. frederiksenii* and “*Y. ruckeri*” strains. *Int. J. Antimicrob. Agents* **25**:496–500.
289. Schmidtke, A. J., and N. D. Hanson. 2006. Model system to evaluate the effect of ampD mutations on AmpC-mediated β -lactam resistance. *Antimicrob. Agents Chemother.* **50**:2030–2037.
290. Schmidtke, A. J., and N. D. Hanson. 2008. Role of ampD homologs in overproduction of AmpC in clinical isolates of *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **52**:3922–3927.
291. Schumacher, H., M. Nir, B. Mansa, and A. Grassy. 1992. β -Lactamases in *Shigella*. *APMIS* **100**:954–956.
292. Segal, H., E. C. Nelson, and B. G. Elisha. 2004. Genetic environment and transcription of ampC in an *Acinetobacter baumannii* clinical isolate. *Antimicrob. Agents Chemother.* **48**:612–614.
293. Seoane, A., M. V. Francia, and J. M. Garcia Lobo. 1992. Nucleotide

- sequence of the *ampC-ampR* region from the chromosome of *Yersinia enterocolitica*. *Antimicrob. Agents Chemother.* **36**:1049–1052.
294. **Seoane, A., and J. M. Garcia Lobo.** 1991. Cloning of chromosomal β -lactamase genes from *Yersinia enterocolitica*. *J. Gen. Microbiol.* **137**:141–146.
 295. **Shahid, M., A. Malik, M. Agrawal, and S. Singhal.** 2004. Phenotypic detection of extended-spectrum and AmpC β -lactamases by a new spot-inoculation method and modified three-dimensional extract test: comparison with the conventional three-dimensional extract test. *J. Antimicrob. Chemother.* **54**:684–687.
 296. **Sharma, S., P. Ramnani, and J. S. Virdi.** 2004. Detection and assay of β -lactamases in clinical and non-clinical strains of *Yersinia enterocolitica* biovar 1A. *J. Antimicrob. Chemother.* **54**:401–405.
 297. **Siu, L. K., P. L. Lu, J. Y. Chen, F. M. Lin, and S. C. Chang.** 2003. High-level expression of *ampC* β -lactamase due to insertion of nucleotides between –10 and –35 promoter sequences in *Escherichia coli* clinical isolates: cases not responsive to extended-spectrum-cephalosporin treatment. *Antimicrob. Agents Chemother.* **47**:2138–2144.
 298. **Smith, C. J., T. K. Bennett, and A. C. Parker.** 1994. Molecular and genetic analysis of the *Bacteroides uniformis* cephalosporinase gene, *cblA*, encoding the species-specific β -lactamase. *Antimicrob. Agents Chemother.* **38**:1711–1715.
 299. **Sohn, S. G., J. J. Lee, E. S. Sohn, L. W. Kang, and S. H. Lee.** 2008. Extension of the hydrolysis spectrum of AmpC β -lactamase of *Escherichia coli* due to amino acid insertion in the H-10 helix. *J. Antimicrob. Chemother.* **61**:965–966.
 300. **Song, W., I. K. Bae, Y. N. Lee, C. H. Lee, S. H. Lee, and S. H. Jeong.** 2007. Detection of extended-spectrum β -lactamases by using boronic acid as an AmpC β -lactamase inhibitor in clinical isolates of *Klebsiella* spp. and *Escherichia coli*. *J. Clin. Microbiol.* **45**:1180–1184.
 301. **Song, W., S. H. Jeong, J. S. Kim, H. S. Kim, D. H. Shin, K. H. Roh, and K. M. Lee.** 2007. Use of boronic acid disk methods to detect the combined expression of plasmid-mediated AmpC β -lactamases and extended-spectrum β -lactamases in clinical isolates of *Klebsiella* spp., *Salmonella* spp., and *Proteus mirabilis*. *Diagn. Microbiol. Infect. Dis.* **57**:315–318.
 302. **Stapleton, P., K. Shannon, and I. Phillips.** 1995. The ability of β -lactam antibiotics to select mutants with derepressed β -lactamase synthesis from *Citrobacter freundii*. *J. Antimicrob. Chemother.* **36**:483–496.
 303. **Stapleton, P. D., K. P. Shannon, and G. L. French.** 1999. Carbenem resistance in *Escherichia coli* associated with plasmid-determined CMY-4 β -lactamase production and loss of an outer membrane protein. *Antimicrob. Agents Chemother.* **43**:1206–1210.
 304. **Steward, C. D., J. K. Rasheed, S. K. Hubert, J. W. Biddle, P. M. Raney, G. J. Anderson, P. P. Williams, K. L. Brittain, A. Oliver, J. E. McGowan, Jr., and F. C. Tenover.** 2001. Characterization of clinical isolates of *Klebsiella pneumoniae* from 19 laboratories using the National Committee for Clinical Laboratory Standards extended-spectrum β -lactamase detection methods. *J. Clin. Microbiol.* **39**:2864–2872.
 305. **Stock, I.** 2005. Natural antimicrobial susceptibility patterns of *Kluyvera ascorbata* and *Kluyvera cryocrescens* strains and review of the clinical efficacy of antimicrobial agents used for the treatment of *Kluyvera* infections. *J. Chemother.* **17**:143–160.
 306. **Stock, I., S. Burak, K. J. Sherwood, T. Gruger, and B. Wiedemann.** 2003. Natural antimicrobial susceptibilities of strains of 'unusual' *Serratia* species: *S. ficaria*, *S. fonticola*, *S. odorifera*, *S. plymuthica* and *S. rubidaea*. *J. Antimicrob. Chemother.* **51**:865–885.
 307. **Stock, I., T. Grueger, and B. Wiedemann.** 2003. Natural antibiotic susceptibility of strains of *Serratia marcescens* and the *S. liquefaciens* complex: *S. liquefaciens* sensu stricto, *S. proteamaculans* and *S. grimesii*. *Int. J. Antimicrob. Agents* **22**:35–47.
 308. **Stock, I., T. Gruger, and B. Wiedemann.** 2000. Natural antibiotic susceptibility of *Rahnella aquatilis* and *R. aquatilis*-related strains. *J. Chemother.* **12**:30–39.
 309. **Stock, I., B. Henrichfreise, and B. Wiedemann.** 2002. Natural antibiotic susceptibility and biochemical profiles of *Yersinia enterocolitica*-like strains: *Y. bercovieri*, *Y. mollaretii*, *Y. aldovae* and 'Y. ruckeri.' *J. Med. Microbiol.* **51**:56–69.
 310. **Stock, I., M. Rahman, K. J. Sherwood, and B. Wiedemann.** 2005. Natural antimicrobial susceptibility patterns and biochemical identification of *Escherichia albertii* and *Hafnia alvei* strains. *Diagn. Microbiol. Infect. Dis.* **51**:151–163.
 311. **Stock, I., K. J. Sherwood, and B. Wiedemann.** 2003. Natural antibiotic susceptibility of *Ewingella americana* strains. *J. Chemother.* **15**:428–441.
 312. **Stock, I., and B. Wiedemann.** 2001. Natural antibiotic susceptibilities of *Edwardsiella tarda*, *E. ictaluri*, and *E. hoshinae*. *Antimicrob. Agents Chemother.* **45**:2245–2255.
 313. **Stock, I., and B. Wiedemann.** 2003. Natural antimicrobial susceptibilities and biochemical profiles of *Yersinia enterocolitica*-like strains: *Y. frederiksenii*, *Y. intermedia*, *Y. kristensenii* and *Y. rohdei*. *FEMS Immunol. Med. Microbiol.* **38**:139–152.
 314. **Su, L. H., T. L. Wu, J. H. Chia, C. Chu, A. J. Kuo, and C. H. Chiu.** 2005. Increasing ceftriaxone resistance in *Salmonella* isolates from a university hospital in Taiwan. *J. Antimicrob. Chemother.* **55**:846–852.
 315. **Tan, T. Y., S. Y. Ng, L. Teo, Y. Koh, and C. H. Teok.** 2008. Detection of plasmid-mediated AmpC in *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*. *J. Clin. Pathol.* **61**:642–644.
 316. **Then, R. L., and P. Angehrn.** 1982. Trapping of nonhydrolyzable cephalosporins by cephalosporinases in *Enterobacter cloacae* and *Pseudomonas aeruginosa* as a possible resistance mechanism. *Antimicrob. Agents Chemother.* **21**:711–717.
 317. **Thiolas, A., C. Bollet, B. La Scola, D. Raoult, and J. M. Pagès.** 2005. Successive emergence of *Enterobacter aerogenes* strains resistant to imipenem and colistin in a patient. *Antimicrob. Agents Chemother.* **49**:1354–1358.
 318. **Thomson, K. S.** 2001. Controversies about extended-spectrum and AmpC beta-lactamases. *Emerg. Infect. Dis.* **7**:333–336.
 319. **Thomson, K. S., and C. C. Sanders.** 1992. Detection of extended-spectrum β -lactamases in members of the family *Enterobacteriaceae*: comparison of the double-disk and three-dimensional tests. *Antimicrob. Agents Chemother.* **36**:1877–1882.
 320. **Thomson, K. S., C. C. Sanders, and J. A. Washington II.** 1993. Ceftazidime resistance in *Hafnia alvei*. *Antimicrob. Agents Chemother.* **37**:1375–1376.
 321. **Tokunaga, H., M. Ishibashi, T. Arakawa, and M. Tokunaga.** 2004. Highly efficient renaturation of β -lactamase isolated from moderately halophilic bacteria. *FEBS Lett.* **558**:7–12.
 322. **Toleman, M. A., P. M. Bennett, and T. R. Walsh.** 2006. ISCR elements: novel gene-capturing systems of the 21st century? *Microbiol. Mol. Biol. Rev.* **70**:296–316.
 323. **Tracz, D. M., D. A. Boyd, R. Hizon, E. Bryce, A. McGeer, M. Ofner-Agostini, A. E. Simor, S. Paton, and M. R. Mulvey.** 2007. *ampC* gene expression in promoter mutants of cefoxitin-resistant *Escherichia coli* clinical isolates. *FEMS Microbiol. Lett.* **270**:265–271.
 324. **Tsakris, A., I. Kristo, A. Poulou, F. Markou, A. Ikonomidis, and S. Pour-naras.** 2008. First occurrence of KPC-2-possessing *Klebsiella pneumoniae* in a Greek hospital and recommendation for detection with boronic acid disc tests. *J. Antimicrob. Chemother.* **62**:1257–1260.
 325. **Tzouveleakis, L. S., E. Tzelepi, M. E. Kaufmann, and A. F. Mentis.** 1994. Consecutive mutations leading to the emergence in vivo of imipenem resistance in a clinical strain of *Enterobacter aerogenes*. *J. Med. Microbiol.* **40**:403–407.
 326. **Tzouveleakis, L. S., E. Tzelepi, A. F. Mentis, and A. Tsakris.** 1993. Identification of a novel plasmid-mediated β -lactamase with chromosomal cephalosporinase characteristics from *Klebsiella pneumoniae*. *J. Antimicrob. Chemother.* **31**:645–654.
 327. **Tzouveleakis, L. S., E. Tzelepi, A. F. Mentis, A. C. Vatopoulos, and A. Tsakris.** 1992. Imipenem resistance in *Enterobacter aerogenes* is associated with derepression of chromosomal cephalosporinases and impaired permeability. *FEMS Microbiol. Lett.* **74**:195–199.
 328. **Underwood, S., and M. B. Avison.** 2004. *Citrobacter koseri* and *Citrobacter amalonaticus* isolates carry highly divergent β -lactamase genes despite having high levels of biochemical similarity and 16S rRNA sequence homology. *J. Antimicrob. Chemother.* **53**:1076–1080.
 329. **Vimont, S., D. Aubert, J. X. Mazaot, L. Poirel, and P. Nordmann.** 2007. Broad-spectrum β -lactams for treating experimental peritonitis in mice due to *Escherichia coli* producing plasmid-encoded cephalosporinases. *J. Antimicrob. Chemother.* **60**:1045–1050.
 330. **Vu, H., and H. Nikaïdo.** 1985. Role of β -lactam hydrolysis in the mechanism of resistance of a β -lactamase-constitutive *Enterobacter cloacae* strain to expanded-spectrum β -lactams. *Antimicrob. Agents Chemother.* **27**:393–398.
 331. **Wachino, J., Y. Doi, K. Yamane, N. Shibata, T. Yagi, T. Kubota, and Y. Arakawa.** 2004. Molecular characterization of a cephamycin-hydrolyzing and inhibitor-resistant class A β -lactamase, GES-4, possessing a single G170S substitution in the Ω -loop. *Antimicrob. Agents Chemother.* **48**:2905–2910.
 332. **Wachino, J., H. Kurokawa, S. Suzuki, K. Yamane, N. Shibata, K. Kimura, Y. Ike, and Y. Arakawa.** 2006. Horizontal transfer of *bla*_{CMY}-bearing plasmids among clinical *Escherichia coli* and *Klebsiella pneumoniae* isolates and emergence of cefepime-hydrolyzing CMY-19. *Antimicrob. Agents Chemother.* **50**:534–541.
 333. **Walsh, T. R., L. Hall, A. P. MacGowan, and P. M. Bennett.** 1995. Sequence analysis of two chromosomally mediated inducible β -lactamases from *Aeromonas sobria*, strain 163a, one a class D penicillinase, the other an AmpC cephalosporinase. *J. Antimicrob. Chemother.* **36**:41–52.
 334. **Walsh, T. R., R. A. Stunt, J. A. Nabi, A. P. MacGowan, and P. M. Bennett.** 1997. Distribution and expression of β -lactamase genes among *Aeromonas* spp. *J. Antimicrob. Chemother.* **40**:171–178.
 335. **Walther-Rasmussen, J., and N. Høiby.** 2002. Plasmid-borne AmpC β -lactamases. *Can. J. Microbiol.* **48**:479–493.
 336. **Weber, D. A., and C. C. Sanders.** 1990. Diverse potential of β -lactamase inhibitors to induce class I enzymes. *Antimicrob. Agents Chemother.* **34**:156–158.
 337. **Weng, S. F., Y. F. Chao, and J. W. Lin.** 2004. Identification and characteristic analysis of the *ampC* gene encoding β -lactamase from *Vibrio fischeri*. *Biochem. Biophys. Res. Commun.* **314**:838–843.

338. Whichard, J., K. Gay, J. E. Stevenson, K. Joyce, K. Cooper, M. Omondi, M. F., G. A. Jacoby, and T. J. Barrett. 2007. Human *Salmonella* and concurrent decreased susceptibility to quinolones and extended-spectrum cephalosporins. *Emerg. Infect. Dis.* **13**:1681–1688.
339. Whichard, J. M., K. Joyce, P. D. Fey, J. M. Nelson, F. J. Angulo, and T. J. Barrett. 2005. β -Lactam resistance and *Enterobacteriaceae*, United States. *Emerg. Infect. Dis.* **11**:1464–1466.
340. Winokur, P. L., A. Brueggemann, D. L. DeSalvo, L. Hoffmann, M. D. Apley, E. K. Uhlenhopp, M. A. Pfaller, and G. V. Doern. 2000. Animal and human multidrug-resistant, cephalosporin-resistant *Salmonella* isolates expressing a plasmid-mediated CMY-2 AmpC β -lactamase. *Antimicrob. Agents Chemother.* **44**:2777–2783.
341. Wong-Beringer, A., J. Hindler, M. Loeloff, A. M. Queenan, N. Lee, D. A. Pegues, J. P. Quinn, and K. Bush. 2002. Molecular correlation for the treatment outcomes in bloodstream infections caused by *Escherichia coli* and *Klebsiella pneumoniae* with reduced susceptibility to ceftazidime. *Clin. Infect. Dis.* **34**:135–146.
342. Woodford, N., S. Reddy, E. J. Fagan, R. L. Hill, K. L. Hopkins, M. E. Kaufmann, J. Kistler, M. F. Palepou, R. Pike, M. E. Ward, J. Cheesbrough, and D. M. Livermore. 2007. Wide geographic spread of diverse acquired AmpC β -lactamases among *Escherichia coli* and *Klebsiella* spp. in the UK and Ireland. *J. Antimicrob. Chemother.* **59**:102–105.
343. Wu, S. W., K. Dornbusch, G. Kronvall, and M. Norgren. 1999. Characterization and nucleotide sequence of a *Klebsiella oxytoca* cryptic plasmid encoding a CMY-type β -lactamase: confirmation that the plasmid-mediated cephamycinase originated from the *Citrobacter freundii* AmpC β -lactamase. *Antimicrob. Agents Chemother.* **43**:1350–1357.
344. Yagi, T., J. Wachino, H. Kurokawa, S. Suzuki, K. Yamane, Y. Doi, N. Shibata, H. Kato, K. Shibayama, and Y. Arakawa. 2005. Practical methods using boronic acid compounds for identification of class C β -lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*. *J. Clin. Microbiol.* **43**:2551–2558.
345. Yan, J. J., P. R. Hsueh, J. J. Lu, F. Y. Chang, J. M. Shyr, J. H. Wan, Y. C. Liu, Y. C. Chuang, Y. C. Yang, S. M. Tsao, H. H. Wu, L. S. Wang, T. P. Lin, H. M. Wu, H. M. Chen, and J. J. Wu. 2006. Extended-spectrum β -lactamases and plasmid-mediated AmpC enzymes among clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* from seven medical centers in Taiwan. *Antimicrob. Agents Chemother.* **50**:1861–1864.
346. Yan, J. J., W. C. Ko, H. M. Wu, S. H. Tsai, C. L. Chuang, and J. J. Wu. 2004. Complexity of *Klebsiella pneumoniae* isolates resistant to both cephamycins and extended-spectrum cephalosporins at a teaching hospital in Taiwan. *J. Clin. Microbiol.* **42**:5337–5340.
347. Yan, J. J., W. C. Ko, J. J. Wu, S. H. Tsai, and C. L. Chuang. 2004. Epidemiological investigation of bloodstream infections by extended spectrum cephalosporin-resistant *Escherichia coli* in a Taiwanese teaching hospital. *J. Clin. Microbiol.* **42**:3329–3332.
348. Yatsuyanagi, J., S. Saito, T. Konno, S. Harata, N. Suzuki, J. Kato, and K. Amano. 2006. Nosocomial outbreak of ceftazidime-resistant *Serratia marcescens* strains that produce a chromosomal AmpC variant with N235K substitution. *Jpn. J. Infect. Dis.* **59**:153–159.
349. Yigit, H., G. J. Anderson, J. W. Biddle, C. D. Steward, J. K. Rasheed, L. L. Valera, J. E. McGowan, Jr., and F. C. Tenover. 2002. Carbapenem resistance in a clinical isolate of *Enterobacter aerogenes* is associated with decreased expression of OmpF and OmpC porin analogs. *Antimicrob. Agents Chemother.* **46**:3817–3822.
350. Zanetti, G., F. Bally, G. Greub, J. Garbino, T. Kinge, D. Lew, J. A. Romand, J. Bille, D. Aymon, L. Stratchounski, L. Krawczyk, E. Rubinstein, M. D. Schaller, R. Chiolero, M. P. Glauser, and A. Cometta. 2003. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob. Agents Chemother.* **47**:3442–3447.
351. Zhu, L. X., Z. W. Zhang, D. Liang, D. Jiang, C. Wang, N. Du, Q. Zhang, K. Mitchelson, and J. Cheng. 2007. Multiplex asymmetric PCR-based oligonucleotide microarray for detection of drug resistance genes containing single mutations in *Enterobacteriaceae*. *Antimicrob. Agents Chemother.* **51**:3707–3713.