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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)
Actinobacteria	*Mycobacterium smegmatis*	YP_888266	92
Proteobacteria			
Alphaproteobacteria	*Ochrobactrum anthropi*	CAC04522	127, 226
	Rhodobacter sphaeroides	YP_355256	24
	Chromobacterium violaceum	NP_900980	87
Betaproteobacteria			
Neisseriales	*Laribacter hongkongensis*	AAT46346	167
Gammaproteobacteria			
Aeromonadales	*Aeromonas caviae*	AAM46773	95
	Aeromonas hydrophila	YP_857635	11, 334
	Aeromonas jandaei[a]	AAA83416	272
	Aeromonas salmonicida	ABO89301	120
	Aeromonas veronii bv. sobria	CAA56561	333, 334
Enterobacteriales	*Buttiauxella agrestis*	AAN17791	90
	Citrobacter braakii	AAM11668	223
	Citrobacter freundii	AAM93471	178
	Citrobacter murliniae	AAM11664	12, 223
	Citrobacter youngae	CAD32304	12
	Citrobacter werkmanii	AAM11670	223
	Edwardsiella tarda	ABO48510	312
	Enterobacter aerogenes	AAO16528	266
	Enterobacter asburiae	CAC85157	279
	Enterobacter cancerogenus	AAM11666	223
	Enterobacter cloacae	P05364	101
	Enterobacter dissolvens	CAC85359	279
	Enterobacter hormaechei	CAC85357	279
	Enterobacter intermedius[b]	CAC85358	279
	Erwinia rhapontici	AAP40275	225
	Escherichia albertii	EDS93081	310
	Escherichia fergusonii	AAM11671	223
	Escherichia coli	NP_418574	144
	Hafnia alvei	AAF86691	107, 320
	Morganella morganii	AAC68582	260, 264
	Providencia stuartii	CAA76739	68
	Serratia marcescens	AAK64454	148
	Shigella boydii	YP_410551	291
	Shigella dysenteriae[c]	YP_405772	291
	Shigella flexneri[c]	YP_691594	291
	Shigella sonnei	YP_313059	291
	Yersinia enterocolitica	YP_001006653	293, 294, 296
	Yersinia mollaretii	ZP_00826692	309
	Yersinia ruckeri	ABA70720	198, 288
Oceanospirillales	*Chromohalobacter*	BAD16740	321
Pseudomonadale	*Acinetobacter baumannii*	CAB77444	39
	Acinetobacter baylyi	CAL25116	26
	Pseudomonas aeruginosa	NP_252799	281
	Pseudomonas fluorescens	YP_349452	209
	Psychrobacter immobilis	CAA58569	88
Xanthomonadales	*Lysobacter lactamgenus*	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 ≥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 gillenii* (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	*E. cloacae*	Chr	39.2	8.4	100	5	21,400	5,000	0.43	0.11	0.02	99, 100, 211
	C. freundii	Chr	39.9		100	21	16,100	2,260	1	0.05	0.05	99, 100, 287
	E. coli K-12	Chr	39.6	8.7	100	9	333	289	0.44	0.38	0.02	99, 100, 144, 212
	S. marcescens	Chr	37	9.5	100	0.6	1,730	1,470	0.02	2.3	0.001	99, 100, 148
	P. aeruginosa	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
	B. licheniformis	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 aztreonam 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, cefpirome, and carbapenems are also very low, and the estimated K_m values for cefepime and cefpirome 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 (μM)								Reference(s)
		Benzylpenicillin	Ampicillin	Cefazolin	Cephaloridine	Cefoxitin	Cefotaxime	Aztreonam	Imipenem[b]	
C	*E. cloacae*	0.6	0.4	1,500	70	0.024	0.01	0.0012	0.04	99, 100
	C. freundii	0.4	0.2	600	35	0.250	0.005	0.0014	0.085	99, 100
	E. coli K-12	4.4	3.5	400	170	0.650	1.7	0.0012	0.8	99, 100
	S. marcescens	1.7	0.01	540	275	0.3	12	0.058	0.06	99, 100, 148
	P. aeruginosa	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			204
	B. licheniformis	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-helixes 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

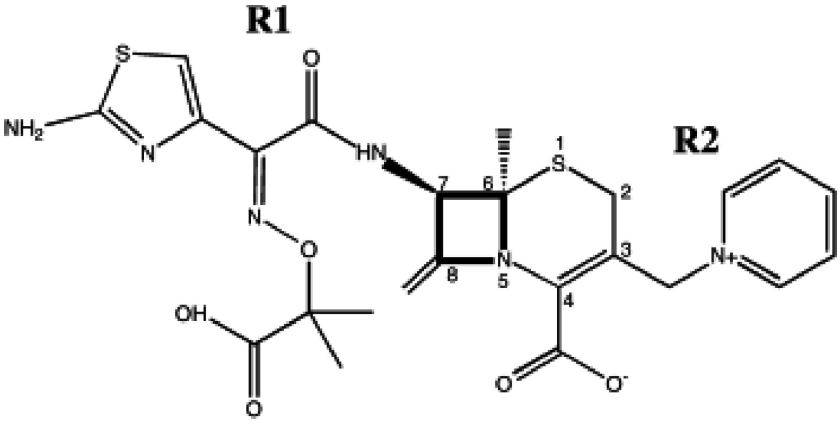

FIG. 2. Schematic representation of ceftazidime with the R1 side chain at C7 and the R2 side chain at C3. (Adapted from reference 158 with permission from Blackwell Publishing Ltd.)

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 cephalosporins 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 oxyimino-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).

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

Antimicrobial agent	Geometric mean MIC (μg/ml)				
	E. cloacae		*P. aeruginosa*		
	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.

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). BrlB 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

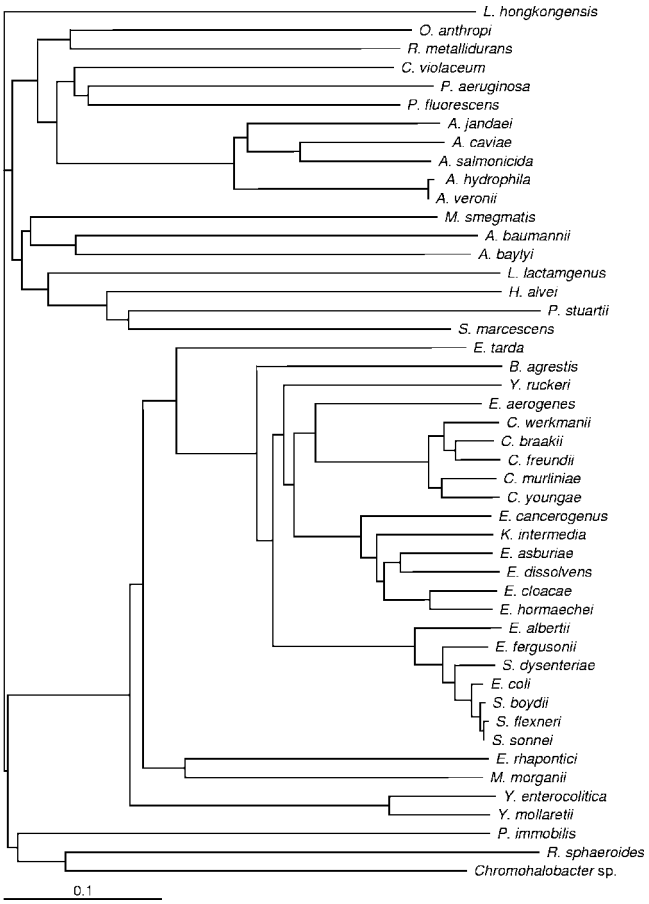

FIG. 3. Phylogram of AmpC enzymes listed in Table 1 constructed with ClustalX (available at http://bips.u-strasbg.fr/fr/Documentation/ClustalX/).

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 cefpirome 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	*K. pneumoniae*	*A. hydrophila*	82	20, 23
CMY-2	Greece	1996	*K. pneumoniae*	*C. freundii*	96	22
MIR-1	United States	1990	*K. pneumoniae*	*E. cloacae*	99	142, 248
MOX-1	Japan	1993	*K. pneumoniae*	*A. hydrophila*	80	134
LAT-1	Greece	1993	*K. pneumoniae*	*C. freundii*	95	326
FOX-1	Argentina	1994	*K. pneumoniae*	*A. caviae*	99	95, 109
DHA-1	Saudi Arabia	1997	*S. enteriditis*	*M. morganii*	99	98
ACT-1	United States	1997	*K. pneumoniae*	*E. asburiae*	98	41, 279
ACC-1	Germany	1999	*K. pneumoniae*	*H. alvei*	99	21, 106
CFE-1	Japan	2004	*E. coli*	*C. freundii*	99	229

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

Antimicrobial agent	MIC (μg/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, oxyimino-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 $bla_{\text{ACT-1}}$ and 12 copies for $bla_{\text{MIR-1}}$) 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 μg/ml) (276), but imipenem MICs of ≥16 μg/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 oxyimino-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 IS*Ecp1* (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). IS*Ecp1* 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 IS*Ecp1* 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 (IS*CR1*) involved in gene mobilization into (typically) complex class 1 integrons (322). Genes for

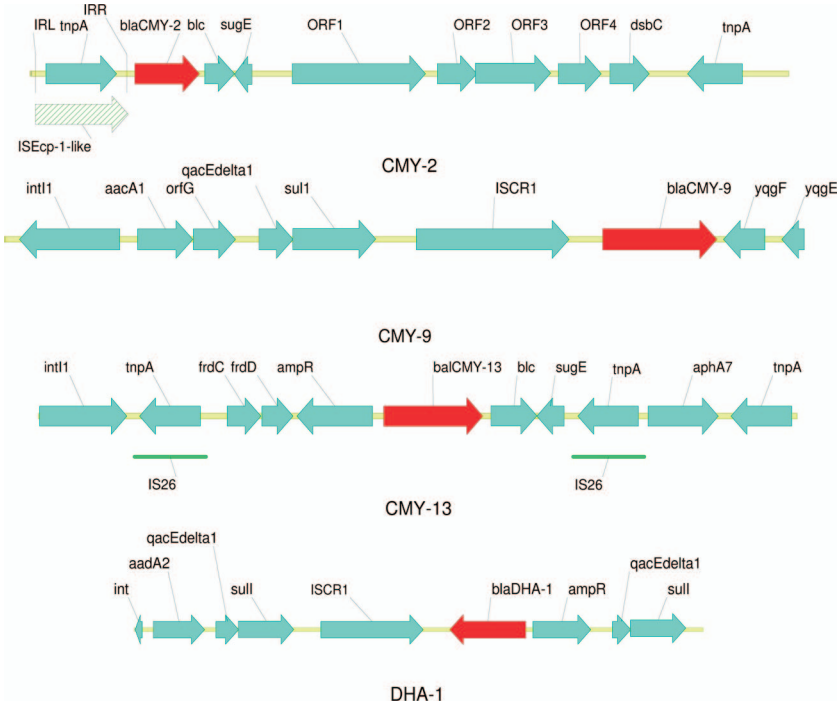

FIG. 4. Genetic environment of representative AmpC genes: CMY-3 (GenBank accession number DQ164214), CMY-9 (accession number AB061794), CMY-13 (accession number AY339625), and DHA-1 (accession number SEN237702).

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 IS*26* 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 oxyimino-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 ≥ 32 μg/ml), while the MICs for cefotaxime and cefepime usually reflected only reduced susceptibility, such as a cefepime MIC of 8 μg/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 μg/ml (196), and those from *E. coli* strains EC14, EC18, and BER were associated with cefepime MICs of 16 μg/ml (197, 199). MICs for aztreonam and imipenem were usually little affected except that an aztreonam MIC of 128 μg/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 μg/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		
E. cloacae GC1	3-aa insertion in Ω-loop	↑	↑					↑ CAZ, ↑ ATM	67, 237
S. marcescens SRT-1	E219K in Ω-loop		↑	↑				↑ CAZ	206
S. marcescens ES46	E219K in Ω-loop							↑ CAZ	348
S. marcescens SMSA	S220Y in Ω-loop	↑	↑	↑	↑			↑ CAZ	126
E. coli HKY28	3-aa deletion in H-9 helix	↓	↓	↑	↓			↑ CAZ, ↑ FEP	77
E. coli ECB33	1-aa insertion in H-9 helix							↑ CAZ	193
E. coli EC16	S287C in R2 loop							↑ CAZ	197
E. coli EC18	S287N in R2 loop							↑ CAZ, ↑ FEP, ↑ ATM	197
E. aerogenes Ear2	L293P in R2 loop		↓	NC	↓			↑ CAZ, ↑ FEP	17
E. coli EC15	H296P in R2 loop							↑ CAZ	197
E. coli EC14	V298L in R2 loop							↑ CAZ, ↑ FEP	197
E. coli KL	14-aa substitutions	NC	↓	NC	↓			↑ CAZ	194
E. coli BER	2-aa insertion in R2 loop	↓	↓		↓	↓	↓	↑ CAZ, ↑ FEP	199, 299
E. cloacae CHE	6-aa deletion in R2 loop		↓	↑	↓			↑ CAZ, ↑ FEP	18
S. marcescens 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. morganii* (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. morganii*. 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 cefoxitin-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 cefoxitin, 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 cefoxitin 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 (IS*Aba1*) 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 μg/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 *E. coli* 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 *Salmonella* isolates	1996–1998	17 U.S. state and community health departments	13 strains (0.32%)	CMY-2	80
408 nosocomial isolates of *K. pneumoniae* 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 *K. pneumoniae*	1995–1999	30 U.S. hospitals in 23 states	5 strains (2.6%)	ACT-1, FOX-5	65
752 cephalosporin-resistant *K. pneumoniae*, *K. oxytoca*, and *E. coli* strains	1992–2000	70 sites in 25 U.S. states and the District of Columbia	*K. pneumoniae*, 8.5%; *K. oxytoca*, 6.9%; *E. coli*, 4%	ACT-1, FOX-5, CMY-2, DHA-1	6
232 cefoxitin-resistant *E. coli* 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 *K. pneumoniae* 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 *K. pneumoniae* 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 *E. coli* 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 *E. coli* and 122 cefoxitin-resistant *K. pneumoniae* strains	2003	16 hospitals in South Korea	33% of *E. coli* strains made CMY-2-like enzymes, and 76% of *K. pneumoniae* strains made DHA-1	DHA-1, CMY-2-like, CMY-10-like, CMY-18	170
CLSI screening test-positive *E. coli* isolates (291 isolates) and *K. pneumoniae* isolates (282 isolates)	2003	7 medical centers in Taiwan	44% of *E. coli* and 15% of *K. pneumoniae* isolates had AmpC-like enzymes	CMY-2-like in *E. coli*; DHA-1 and CMY-2-like in *K. pneumoniae*	345
1,429 *E. coli* 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 *Enterobacteriaceae*	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	*Enterobacter* spp. and *E. coli* mostly overproduced their chromosomal AmpC enzymes; the fewer plasmid-mediated AmpCs were of the *Citrobacter* 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 *Enterobacteriaceae*, and transferable AmpCs found in 3.3% of *K. pneumoniae* isolates and in 61% of isolates along with ESBLs; AmpCs also found in 3.6% of *K. oxytoca* and 1.4% of *P. mirabilis* isolates	FOX-5, DHA-like, ACT-1-like	217
359 cefoxitin-resistant *E. coli* 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 *E. coli* 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 *E. coli* and 732 *Klebsiella* 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 *E. coli* and 38 *Klebsiella* sp. isolates suspected of AmpC-mediated resistance	2004–2006	Health Protection Agency, London, United Kingdom	*E. coli*, 49%; *K. pneumoniae*, 55%	60 CIT type including CMY-23, 14 ACC type, 11 FOX type, 3 DHA type	342
124 cefoxitin-resistant strains from 3,217 *Enterobacteriaceae* normally lacking inducible chromosomal *ampC* genes	2006–2007	University Hospital, Basel, Switzerland	5 of 103 cefoxitin-resistant *E. coli* isolates had plasmid-mediated AmpCs; cause of cefoxitin resistance in 3 *K. oxytoca* and 18 *K. pneumoniae* isolates not identified	Not specified	2
2,388 isolates of *Enterobacteriaceae* from inpatients	2003–2004	13 hospitals in Poland	Plasmid-mediated AmpCs identified only in 71 *P. mirabilis* isolates (20.5% of all *P. mirabilis* isolates); ESBLs in 11.1% of all isolates	24 of 71 sequenced; 19 CMY-15, 4 CMY-12, 1 CMY-38 isolates	82
75 *E. coli* and 14 *Klebsiella* 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 *E. coli* isolates and 1 *K. pneumoniae* isolate	All CMY-2	117
86 screening test-positive strains from 8,048 *Enterobacteriaceae* strains normally lacking or poorly expressing chromosomal *ampC* 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 *K. pneumoniae* and 494 *E. coli* 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 *K. pneumoniae* and 2.0% in *E. coli*	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(*b*)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 insusceptible 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 cephalosporins 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 μg/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 μg/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 μg/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).

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