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Resistance to Cefotaxime and Seven Other β-Lactams in Members of the Family *Enterobacteriaceae*: a 3-Year Survey in France

D. L. SIROT,[1]* F. W. GOLDSTEIN,[2] C. J. SOUSSY,[3] A. L. COURTIEU,[4] M. O. HUSSON,[5] J. LEMOZY,[6] M. MEYRAN,[7] C. MOREL,[8] R. PEREZ,[9] C. QUENTIN-NOURY,[10] M. E. REVERDY,[11] J. M. SCHEFTEL,[12] M. ROSEMBAUM,[13] AND Y. REZVANI[13]

Laboratoire de Bactériologie, Faculté de Médecine, 28 Place Henri-Dunant, 63003 Clermont-Ferrand Cédex,[1] Hôpital Saint-Joseph, 75674 Paris Cédex 14,[2] Hôpital H. Mondor, 94010 Créteil Cédex,[3] Faculté de Médecine, 44035 Nantes Cédex 01,[4] Centre Hospitalier Universitaire, 59045 Lille Cédex,[5] Hôpital Purpan, 31059 Toulouse,[6] Hôpital Bégin, 94160 Saint-Mandé,[7] Centre Hospitalier Universitaire, 14033 Caen Cédex,[8] Hôpital de la Timone, 13385 Marseille,[9] Groupe Hospitalier Pellegrin Tripode, 33076 Bordeaux,[10] Hôpital E. Herriot, 69437 Lyon Cédex 3,[11] Institut de Bactériologie, 67000 Strasbourg,[12] and Laboratoires Roussel-France, 75279 Paris Cédex 06,[13] France

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During the second quarter each of 1988, 1989, and 1990, a French collaborative study group, including 12 university hospital laboratories, surveyed the resistance to β-lactams of clinical isolates from hospitalized patients: consecutively, 10,641, 10,692, and 9,382 isolates were tested. The distribution of bacterial species over time was similar in each laboratory. The susceptibilities of microorganisms to amoxicillin, ticarcillin, cephalothin, cefoxitin, cefotaxime (CTX), ceftazidime (CAZ), aztreonam (ATM), and imipenem (IPM) were measured by the disk diffusion method in accordance with the recommendations of the Antibiogram Committee of the French Society for Microbiology. Five reference strains were included for quality control. Extended-spectrum β-lactamases were detected by the synergistic effect of the combination of clavulanic acid-amoxicillin with CTX, CAZ, and ATM in the double-diffusion test. A synergistic effect with CTX, CAZ, and ATM was detected for 1.5% of all strains, mainly those of *Klebsiella pneumoniae* (13.3%). For this species, the synergy test enabled the detection of roughly 50% of the resistant strains misclassified as susceptible on the basis of interpretative standards. Extended-spectrum β-lactamases disseminated in 1990 in most enterobacterial species but at a low frequency. Important variations in the percentages of resistant strains were observed in terms of bacterial species, hospitals, and wards. However, when the total number of strains was considered, the percentages of resistance to newer β-lactams remained low.

Transferable resistance to extended-spectrum cephalosporins and aztreonam (ATM) in members of the family *Enterobacteriaceae* has emerged in France since 1984 and spread to many hospitals (4, 14, 16, 21, 25). Preliminary reports have shown striking differences in the spread of this resistance (3, 6).

The aim of this multicenter study was to monitor the evolution of resistance to newer β-lactams, with special reference to cefotaxime (CTX), during a 3-year period in 12 university hospital laboratories. CTX is by far the most commonly used extended-spectrum cephalosporin in French hospitals. Thus, it is a convenient drug for use in a survey of the development of resistance to newer β-lactams.

MATERIALS AND METHODS

During the second quarter each of 1988, 1989, and 1990, a French collaborative study group, including 12 university hospital laboratories, surveyed the resistance to β-lactams of clinical isolates of the family *Enterobacteriaceae* from hospitalized patients.

Participating laboratories. The participating laboratories (consultants in charge of the laboratories) were as follows: Hôpital Saint-Joseph, Paris (J. F. Acar); Groupe Hospitalier Pellegrin Tripode, Bordeaux (C. Bebear); Hôpital H. Mondor, Créteil (J. Duval); Hôpital E. Herriot, Lyon (J. Fleurette); Institut de Bactériologie, Strasbourg (H. Monteil); Hôpital de la Timone, Marseille (D. Raoult); Hôpital Bégin, Saint-Mandé (A. Thabaut); Faculté de Médecine, Clermont-Ferrand (R. A. Cluzel and J. L. Sirot); Faculté de Médecine, Nantes (A. L. Courtieu); Centre Hospitalier Universitaire, Lille (H. Leclerc); Hôpital Purpan, Toulouse (H. Dabernat); and Centre Hospitalier Universitaire, Caen (C. Morel).

Strains. A total of 30,715 nonduplicate strains (only one strain of each species per patient) were collected consecutively: 10,641 in 1988, 10,692 in 1989, and 9,382 in 1990. They included all species of the family *Enterobacteriaceae* isolated from clinical specimens (*n*): *Escherichia coli* (16,870), *Proteus mirabilis* (3,624), *Klebsiella* spp. (3,671), *Enterobacter* spp. (2,214), *Serratia* spp. (1,327), *Proteus* spp. (indole positive) and *Providencia* spp. (2,013), *Citrobacter* spp. (611), *Salmonella* spp. (279), *Citrobacter diversus* (43), *Shigella* spp. (20), and *Yersinia* spp. (9).

Susceptibility testing and tests for extended-spectrum β-lactamases. The susceptibilities of the microorganisms were determined by the disk diffusion method with Mueller-Hinton agar (7). Eight β-lactams were tested: amoxicillin

* Corresponding author.

TABLE 1. Percentage of strains of each species resistant[a] to β-lactams in 1988, 1989, and 1990

Antibiotic	*E. coli*				*P. mirabilis*				*K. pneumoniae*				*K. oxytoca*			
	1988 (5,746)	1989 (5,890)	1990 (5,234)	*P*	1988 (1,215)	1989 (1,301)	1990 (1,108)	*P*	1988 (977)	1989 (918)	1990 (790)	*P*	1988 (289)	1989 (303)	1990 (298)	*P*
AMX	40.7	40.3	41.0	NS	23.2	28.1	29.1	<0.01	98.5	98.8	97.2	NS	98.6	98.7	97.3	NS
TIC	35.8	36.3	37.6	NS	18.8	23.2	22.9	NS	95.1	97.2	95.9	NS	90.3	92.7	93.3	NS
CF	19.6	18.6	25.0	<0.001	9.4	11.5	12.9	<0.01	26.9	30.3	28.6	NS	15.3	18.2	20.5	NS
FOX	5.6	5.6	7.1	<0.01	3.5	6.3	7.5	<0.001	13.7	18.3	19.3	<0.01	4.5	6.1	7.1	NS
CTX	0.4	0.4	0.5	NS	0.1	0.7	0.3	NS	11.5	14.3	14.1	NS	1.7	6.3	3.4	NS
CAZ	1.0	1.1	1.3	NS	0.2	0.5	0.7	NS	12.6	15.8	15.8	NS	1.7	4.6	1.0	NS
ATM[b]	0.7	1.5	1.0	NS	0.0	0.5	0.8	NS	10.3	12.4	14.8		5.2	6.0	9.1	
IPM	0.1	0.4	0.2	NS	2.2	4.9	2.4	NS	0.2	0.8	0.3	NS	0.0	1.0	0.7	NS

[a] Data below years show percentages of resistant strains. Numbers in parentheses are numbers of strains tested. Strains classified as resistant included strains showing intermediate resistance, resistant strains, and strains giving a positive result in the synergy test with CTX, CAZ, and ATM. NS, not significant.
[b] Synergy tests were not performed in 1988 and 1989.

(AMX), ticarcillin (TIC), cephalothin (CF), cefoxitin (FOX), CTX, ceftazidime (CAZ), ATM, and imipenem (IPM).

Bacteria were classified as susceptible, intermediate in resistance, and resistant in accordance with the recommendations of the Antibiogram Committee of the French Society for Microbiology (1). The inhibition zone diameter and corresponding MIC breakpoints used for assessing susceptibility were respectively, as follows: AMX, ≥21 mm and ≤4 μg/ml; TIC, ≥22 mm and ≤16 μg/ml; CF, ≥18 mm and ≤8 μg/ml; FOX, ≥22 mm and ≤8 μg/ml; CTX and CAZ, ≥21 mm and ≤4 μg/ml; ATM, ≥23 mm and ≤4 μg/ml; and IPM, ≥22 mm and ≤4 μg/ml.

Extended-spectrum β-lactamases were presumptively detected by the synergistic effect of the combination of clavulanic acid-amoxicillin with CTX, CAZ, and ATM in the double-diffusion test. Synergy was detected by placing around a disk of Augmentin (20 μg of amoxicillin plus 10 μg of clavulanate; Diagnostics Pasteur, Paris, France) disks of CTX, CAZ, and ATM, 30 mm apart (center to center). A clear-cut extension of the edges of the CTX, and/or CAZ and/or ATM inhibition zones toward the disk containing clavulanate was interpreted as a positive synergy test (13, 20). This test detects extended-spectrum β-lactamases even with very low expression levels. The only limitation of this test is the presence of a high level of a cephalosporinase that prevents the expression of the synergistic effect but does not alter the categorization of the strains. Strains classified as not susceptible included strains showing intermediate resistance, resistant strains, and strains giving a positive result in the synergy test.

The statistical significance ($P < 0.01$) of the results was determined by application of the chi-square technique (2).

Controls. The variability within each center and between centers of the results of the agar disk diffusion test was studied by use of variance analysis. Five strains were included in this quality control analysis: UA200 (*E. coli* K-12 BM13 (producing a low level of a cephalosporinase), UA002 (an *E. coli* K-12 BM13 mutant hyperproducing a cephalosporinase), UA064 (*E. coli* K-12 BM13/RP4 producing TEM-2), *E. coli* K-12 BM13/pCFF04 producing CTX-1/TEM-3, and F201 (*Morganella morganii* producing a low level of a cephalosporinase). They were obtained from the National Reference Center for Antibiotics, Institut Pasteur, Paris, France. A significant variability in the inhibition zone diameters between centers was observed. However, the classification in the clinical categories susceptible, intermediate in resistance, and resistant remained valid. Standard deviations of diameters did not exceed 3 mm for each strain.

RESULTS

β-Lactam resistance among the major species of the family *Enterobacteriaceae* (*E. coli*, *P. mirabilis*, *K. pneumoniae*, *K. oxytoca*, *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., and indole-positive *Proteus* spp.) to the eight β-lactams tested is shown in Table 1. In 1990, the prevalences of resistance to aminopenicillins, TIC, and CF were, respectively, 41, 38, and 25% in *E. coli* and 29, 23, and 13% in *P. mirabilis*. In these species, the prevalences of resistance to extended-spectrum cephalosporins were, respectively, 1.3 and 0.8%. In other species of *Enterobacteriaceae* that are naturally resistant to aminopenicillins, the prevalences of resistance to extended-spectrum cephalosporins and ATM varied according to the species.

During the 3-year period (Table 2), the overall incidence of resistance to CTX increased from 4.7 to 5.7% and then decreased to 5.1%. Significant variations in the incidences of resistance to CTX were observed for three organisms (*Klebsiella*, *Enterobacter*, and *Serratia*), with maximal incidences in 1990 for *Serratia* spp. (38.7%) and in 1989 for *Enterobacter* spp. (28.5%) and *K. pneumoniae* (14.3%).

TABLE 2. Prevalence of resistance to CTX from 1988 to 1990 (all laboratories)

Species	% of strains showing the indicated resistance[a] in:					
	1988		1989		1990	
	R + I	R + I + SYN	R + I	R + I + SYN	R + I	R + I + SYN
E. coli	0.2	0.4	0.4	0.5	0.5	0.5
P. mirabilis		0.1	0.5	0.7	0.3	0.3
Enterobacter	19.5	19.6	28.0	28.5	20.2	21.2
Citrobacter	18.2	18.2	16.4	16.9	19.1	19.1
Serratia	26.5	26.7	28.1	28.1	38.1	38.7
Indole-positive *Proteus*	3.6	4.0	3.6	4.4	4.4	4.4
M. morganii	5.1	5.1	6.4	6.4	5.9	5.9
P. vulgaris	0.7	2.0		1.8	1.9	1.9
Klebsiella[b]	4.5	8.9	5.9	12.2	7.2	11.4
K. pneumoniae	5.9	11.5	7.1	14.3	9.1	14.1
K. oxytoca	0.3	1.7	2.3	6.3	1.0	3.4
Others	0.3	0.3	1.2	1.2	1.2	1.6
Total	4.0	4.7	4.8	5.7	4.6	5.1

[a] R, resistance; I, intermediate resistance; SYN, susceptible on the basis of the breakpoints used for assessing susceptibility but synergy test positive.
[b] All *Klebsiella* species.

TABLE 1—*Continued*

Enterobacter spp.				*Citrobacter* spp.				*Serratia* spp.				Indole-positive *Proteus* spp.			
1988 (820)	1989 (782)	1990 (645)	*P*	1988 (198)	1989 (219)	1990 (194)	*P*	1988 (524)	1989 (467)	1990 (336)	*P*	1988 (476)	1989 (551)	1990 (545)	*P*
93.5	95.4	94.3	NS	93.4	94.5	94.3	NS	93.3	94.6	95.5	NS	92.4	87.3	91.0	NS
33.0	37.0	33.0	NS	57.6	58.0	59.8	NS	67.6	67.5	70.5	NS	13.9	21.1	20.7	<0.01
91.8	94.4	94.1	NS	74.6	78.1	72.9	NS	99.2	100.0	99.7	NS	88.2	84.2	88.7	NS
85.3	90.3	85.9	NS	74.1	75.6	68.3	NS	83.6	80.8	85.9	NS	42.8	44.8	54.7	<0.001
19.6	28.5	21.2	NS	18.2	16.9	19.1	NS	26.7	28.1	38.7	<0.001	4.0	4.4	4.4	NS
21.4	28.8	22.0	NS	20.2	21.0	22.7	NS	3.6	3.9	7.7	<0.01	7.1	8.5	8.6	NS
18.1	25.0	18.4	NS	18.7	16.6	19.1	NS	8.1	4.3	12.2	NS	1.3	2.9	2.2	NS
1.1	3.3	1.4	NS	1.0	0.5	2.1	NS	0.6	0.9	0.6	NS	9.8	10.1	6.1	NS

The prevalence of resistance to CTX in *K. pneumoniae* varied from 0 to 47.6% in terms of the different hospitals (Table 3). The prevalence was the highest (30.6%) in intensive-care units (Table 4).

Table 5 shows the incidence of resistance to CTX in terms of the origins of the specimens; the incidence was lower in isolates recovered from urine specimens (9.4 to 13.6%) than from blood cultures (11.1 to 23.5%) or respiratory tract specimens (14.3 to 27.2%).

Table 6 shows the percentages of enterobacterial species giving positive results in the synergy test.

DISCUSSION

Extended-spectrum cephalosporins are often used as primary agents for the treatment of severe and/or nosocomial infections (10).

Shortly after CTX was introduced in France (1981), the resistance of strains belonging to the species *Enterobacter*, *Citrobacter*, and *Serratia* was observed and was found due to the stable hyperproduction of a chromosomal cephalosporinase (derepressed mutants) (9, 17, 18, 22, 24). In 1984 in Clermont-Ferrand, France, resistance to CTX, CAZ, and ATM was observed for *K. pneumoniae* and thereafter for other enterobacterial species (19, 26). This resistance was found due to the production, mostly plasmid mediated, of an extended-spectrum β-lactamase. Very disquieting is the frequent association of this resistance with resistance to aminoglycosides, including amikacin (12, 27). For these reasons, regular surveys of resistance to extended-spectrum cephalosporins and ATM have been done in France since 1984 (3, 6).

Derepressed mutants usually display a high level of resistance (MIC, >64 mg/liter) to newer cephalosporins and ATM; in contrast, MICs in Mueller-Hinton agar for strains producing an extended-spectrum β-lactamase are usually 4 to 16 mg/liter (14). This low level of resistance is not always detected with standard methods and criteria. For this reason, a synergy test is routinely performed in all the laboratories. This detection method explains the differences observed, especially for *K. pneumoniae*, between the number of strains classified as resistant-intermediate in resistance and resistant-intermediate in resistance-positive in the synergy test, including strains apparently susceptible but producing an extended-spectrum β-lactamase.

With the exception of species of the family *Enterobacteriaceae* belonging to the *Klebsiella-Enterobacter-Serratia* group (Table 1), resistance to extended-spectrum cephalosporins and ATM is still very limited. This limited resistance is in strong contrast to the 40% prevalence of resistance to AMX or about 20% prevalence of resistance to older cephalosporins like CF in *E. coli*.

The evolution of resistance to extended-spectrum cephalosporins and ATM in *Enterobacter*, *Serratia*, and *Citrobacter* spp. is related to local epidemics and antibiotic usage: it has been clearly demonstrated that bacteria with an inducible cephalosporinase may be selected in patients treated

TABLE 3. Prevalence of resistance[a] to CTX among *K. pneumoniae* strains recovered from each university hospital laboratory

University hospital laboratory	1988			1989			1990		
	No. of strains tested	%		No. of strains tested	%		No. of strains tested	%	
		R + I	R + I + SYN		R + I	R + I + SYN		R + I	R + I +SYN
Paris	48	4.2	6.2	77	0	0	62	1.6	1.6
Bordeaux	13	0	0	55	0	0	38	5.3	13.2
Créteil	96	1.0	12.5	108	6.5	35.2	47	2.1	6.4
Lyon	164	1.8	3.7	133	6.8	8.3	123	2.4	2.4
Strasbourg	100	0	0	92	1.1	1.1	85	0	3.5
Marseille	86	11.6	14.0	105	23.8	36.2	91	14.3	29.7
Saint-Mandé	47	2.1	6.4	34	5.9	5.9	57	7.0	8.8
Clermont-Ferrand	55	27.3	50.9	38	23.7	36.8	42	38.1	47.6
Nantes	19	0	0						
Lille	137	13.9	22.6	105	11.4	22.9	119	26.1	35.3
Toulouse	105	6.7	16.2	74	0	1.4	68	1.5	2.9
Caen	107	0	0	97	0	2.1	58	0	0
Total	977	5.9	11.5	918	7.1	14.3	790	9.1	14.1

[a] See Table 2, footnote *a*.

TABLE 4. Prevalence of resistance[a] to CTX among *K. pneumoniae* strains recovered from different wards

Ward[b]	1988		1989		1990	
	No. of strains tested	% R + I + SYN	No. of strains tested	% R + I + SYN	No. of strains tested	% R + I + SYN
Outpatient	28	0	24	0	18	5.6
Burn unit	20	30.0	4	25.0	11	0
Surgery	224	14.7	157	17.2	144	17.4
Gynecology	44	0	35	0	41	0
Medicine	299	9.7	266	10.9	242	17.4
Pediatrics	64	0	75	9.3	72	13.9
Surgical ICU	68	19.1	60	23.3	36	30.6
Medical ICU	100	21.0	105	25.7	60	18.3
Oncology	41	14.6	28	14.3	27	3.7
Urology	0	0	58	13.8	50	6.0
Others	89	4.5	106	13.2	89	7.9

[a] See Table 2, footnote *a*.
[b] ICU, intensive-care unit.

TABLE 6. Strains presumptively harboring an extended-spectrum β-lactamase (synergy test positive) in 1990

Species (no. of strains tested)	No. of strains synergy test positive[a]
E. coli (5,324)	5
P. marabilis (1,108)	0
P. vulgaris (154)	0
M. morganii (354)	0
Providencia spp. (115)	0
K. pneumoniae (790)	105
K. oxytoca (298)	9
Enterobacter spp. (612)	15
Serratia spp. (336)	4
Citrobacter spp. (197)	1
Others (140)	
Total (9,382)	139 (1.5%)

[a] Synergistic effect observed with the combination of clavulanic acid-amoxicillin with CTX, CAZ, and ATM in the double-diffusion test.

with an extended-spectrum cephalosporin alone (12, 23, 28). In these bacteria, the prevalence of resistance to CTX varied from 20 to 40% during the 3-year study period (Tables 1 and 2).

The most important aspect of this study is the evolution of resistance to extended-spectrum cephalosporins and ATM in *K. pneumoniae* due to an extended-spectrum β-lactamase. This resistance varied from 11.5 to 15.2% during the 3-year study period. *K. pneumoniae* producing an extended-spectrum β-lactamase was isolated in nine hospitals in 1988, 11 hospitals in 1989, and 12 hospitals in 1990 (Table 3). For this species, the synergy test enabled the detection of roughly 50% of the resistant strains misclassified as susceptible on the basis of interpretative standards.

Resistant strains are mostly isolated from intensive-care units and surgical wards, but during the study period, all the medical and surgical wards, except for gynecology, were involved (Table 4). *K. pneumoniae* strains are mostly isolated from urinary tract infection specimens, but unexpectedly, the percentage of *K. pneumoniae* strains resistant to extended-spectrum cephalosporins and ATM was lower for urinary tract infections than for other infections, especially bacteremia and respiratory tract infections (Table 5).

Extended-spectrum β-lactamases disseminated in 1990 in most enterobacterial species but at a low frequency (Table 6).

Although CTX is widely used in French hospitals, the prevalence of resistance to newer β-lactams is low when the total number of isolates is considered. However, resistance to newer β-lactams due to extended-spectrum β-lactamases has emerged in recent years in most pathogens, but with considerable variations between hospitals. These variations could be related in part to local epidemiological factors, general preventive methods, and antibiotic policies, which are still much debated (5, 8, 11, 15). Better knowledge of the mechanism responsible for this resistance would allow the resistant strains to be detected and, together with coincidental preventive and curative methods, should limit the emergence and spread of the resistance.

TABLE 5. Prevalence of resistance[a] to CTX among *K. pneumoniae* strains recovered from different clinical specimens

Clinical specimens	1988		1989		1990	
	No. of strains tested	% R + I + SYN	No. of strains tested	% R + I + SYN	No. of strains tested	% R + I + SYN
Blood	59	13.6	45	11.1	34	23.5
Urine	489	9.4	523	13.6	438	10.7
Respiratory tract	140	14.3	111	15.3	92	27.2
Others	289	13.1	233	15.0	222	14.0

[a] See Table 2, footnote *a*.

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REFERENCES

1. **Acar, J., E. Bergogne-Berezin, Y. Chabbert, R. Cluzel, A. Courtieu, P. Courvalin, H. Dabernat, H. Drugeon, J. Duval, J. P. Flandrois, J. Fleurette, F. Goldstein, M. Meyran, C. Morel, A. Philippon, J. Sirot, C. J. Soussy, A. Thabaut, and M. Veron.** 1990. Statement of the Antibiogram Committee of the French Society for Microbiology. Pathol. Biol. **38:**749–752.
2. **Armitage, P.** 1955. Tests for linear trends in proportions and frequencies. Biometrics **11:**375–386.
3. **Bebear, C., A. Bure, R. Cluzel, A. Courtieu, P. Courvalin, J. Duval, J. Fleurette, A. Goudeau, D. Izard, R. Perez, C. Suc, and A. Thabaut.** 1987. A multicenter Enterobacteriaceae surveillance study, abstr. 459. Abstr. 15th Int. Congr. Chemother.
4. **Brun-Buisson, C., P. Legrand, A. Philippon, F. Montravers, M. Ansquer, and J. Duval.** 1987. Transferable enzymatic resistance to third generation cephalosporins during nosocomial outbreak of multiresistant *Klebsiella pneumoniae*. Lancet **ii:**302–306.
5. **Brun-Buisson, C., P. Legrand, A. Rauss, C. Richard, F. Montravers, M. Besbes, et al.** 1989. Intestinal decontamination for control of nosocomial multi-resistant gram-negative bacilli. Ann. Intern. Med. **110:**873–881.
6. **Chanal, C. M., M. D. Kitzis, M. E. Reverdy, C. J. Soussy, C. Morel, and A. Thabaut.** 1989. Evolution de la resistance au cefotaxime chez les *Enterobacteries*: etude multicentrique française, abstr. 140P12. Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse, Paris.
7. **Comite OMS d'Experts de la Standardization Biologique.** 1977. 28e Rapport, p. 106–138. *In* Serie de rapports techniques no. 610. Organisation Mondiale de la Santé, Geneva, Switzerland.
8. **De Champs, C., D. Rouby, D. Guelon, J. Sirot, D. Sirot, D.**

Beytout, and J. M. Gourgand. 1991. A case-control study of an outbreak of infections caused by *Klebsiella pneumoniae* strains producing CTX-1 (TEM-3) beta-lactamase. J. Hosp. Infect. **18:**5–13.
9. **Gootz, T. D., D. B. Jackson, and J. C. Sherris.** 1984. Development of resistance to cephalosporins in clinical strains of *Citrobacter* spp. Antimicrob. Agents Chemother. **25:**591–595.
10. **Goulon, M., P. Gadjos, and J. Pilliot.** 1981. Traitement des septicémies à bacilles à gram négatif par le cefotaxime: 16 Observations. Presse Med. **10:**613–616.
11. **Heizmann, W. R.** 1990. SDD and the novel extended-broad-spectrum β-lactamases. J. Antimicrob. Chemother. **26:**295–296.
12. **Jacoby, G. A., and L. Sutton.** 1991. Properties of plasmids responsible for extended-spectrum β-lactamase production. Antimicrob. Agents Chemother. **35:**164–168.
13. **Jarlier, V., M. H. Nicolas, G. Fournier, and A. Philippon.** 1988. Extended broad-spectrum beta-lactamases conferring transferable resistance to newer beta-lactams in *Enterobacteriaceae*: hospital prevalence and susceptibility patterns. Rev. Infect. Dis. **10:**867–878.
14. **Kitzis, M. D., D. Billot-Klein, F. W. Goldstein, R. Williamson, E. Collatz, G. Tran Van Nhieu, J. Carlet, J. F. Acar, and L. Gutmann.** 1988. Dissemination of the novel plasmid-mediated β-lactamase CTX-1, which confers resistance to broad-spectrum cephalosporins, and its inhibition by β-lactamase inhibitors. Antimicrob. Agents Chemother. **32:**9–14.
15. **Ledingham, I. M., S. R. Alcock, A. T. Eastaway, J. C. McDonald, J. C. McKay, and G. Ramsay.** 1988. Triple regimen of selective decontamination of the digestive tract, systemic cefotaxime, and microbiological surveillance for prevention of acquired infection in intensive care. Lancet **i:**785–790.
16. **Legrand, P., G. Fournier, A. Bure, V. Jarlier, M. H. Nicolas, D. Decre, J. Duval, and A. Philippon.** 1989. Detection and distribution of extended broad-spectrum beta-lactamases in Enterobacteriaceae in four French hospitals. Eur. J. Clin. Microbiol. Infect. Dis. **8:**527–529.
17. **Livermore, D. M.** 1987. Clinical significance of beta-lactamase induction and stable derepression in gram-negative rods. Eur. J. Clin. Microbiol. **6:**439–445.
18. **Nauciel, C., A. Philippon, E. Ronco, J. Pilliot, M. Guenounou, G. Paul, D. Brunel, and H. D. Outin.** 1985. Septicémies à *Enterobacter cloacae* et *E. aerogenes*: émergence de variants résistants (céphalosporinase déréprimée) en cours de traitement par des céphalosporines de troisième génération. Presse Med. **14:**673–676.
19. **Philippon, A., S. Ben Redjeb, P. Fournier, and A. Ben Hassen.** 1989. Epidemiology of extended-spectrum β-lactamases. Infection **17:**347–354.
20. **Philippon, A., G. Fournier, G. Paul, G. Vedel, and P. Nevot.** 1988. Détection et distribution des β-lactamases à spectre élargi chez les entérobactéries. Med. Mal. Infect. **12:**869–876.
21. **Philippon, A., G. Paul, G. Vedel, and P. Nevot.** 1988. Résistance plasmidique aux céphalosporines de troisième génération. Presse Med. **17:**1883–1889.
22. **Sanders, C. C.** 1987. Chromosomal cephalosporinases responsible for multiple resistance to newer β-lactam antibiotics. Annu. Rev. Microbiol. **41:**573–593.
23. **Sanders, C. C., and W. E. Sanders, Jr.** 1983. Emergence of resistance during therapy with the newer β-lactam antibiotics: role of inducible β-lactamases and implications for the future. Rev. Infect. Dis. **5:**639–648.
24. **Seeberg, A. H., R. M. Tolsdorff-Neutralizing, and B. Wiedemann.** 1983. Chromosomal β-lactamases of *Enterobacter cloacae* are responsible for resistance to third-generation cephalosporins. Antimicrob. Agents Chemother. **23:**918–925.
25. **Sirot, D., J. Sirot, R. Labia, A. Morand, P. Courvalin, A. Darfeuille-Michaud, R. Perroux, and R. Cluzel.** 1987. Transferable resistance to third generation cephalosporins in clinical isolates of *Klebsiella pneumoniae*. Identification of CTX-1, a novel beta-lactamase. J. Antimicrob. Chemother. **20:**323–334.
26. **Sirot, J., C. Chanal, A. Petit, D. Sirot, R. Labia, and G. Gerbaud.** 1988. *Klebsiella pneumoniae* and other enterobacteriaceae producing novel plasmid-mediated beta-lactamases markedly active against third generation cephalosporins: epidemiologic studies. Rev. Infect. Dis. **10:**850–859.
27. **Smith, C. E., B. S. Tillman, A. W. Howell, R. N. Longfield, and J. H. Jorgensen.** 1990. Failure of ceftazidime-amikacin therapy for bacteremia and meningitis due to *Klebsiella pneumoniae* producing an extended-spectrum β-lactamase. Antimicrob. Agents Chemother. **34:**1290–1293.
28. **Vuthien, H., and M. Rolland.** 1986. Emergence in vivo d'un mutant resistant aux bêta-lactamines au cours d'un traitement par la ceftazidime. Presse Med. **15:**1241–1242.