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Evaluation of Current Activities of Fluoroquinolones against Gram-Negative Bacilli Using Centralized In Vitro Testing and Electronic Surveillance

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Given the propensity for *Enterobacteriaceae* and clinically significant nonfermentative gram-negative bacilli to acquire antimicrobial resistance, consistent surveillance of the activities of agents commonly prescribed to treat infections arising from these organisms is imperative. This study determined the activities of two fluoroquinolones, levofloxacin and ciprofloxacin, and seven comparative agents against recent clinical isolates of *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* using two surveillance strategies: 1) centralized in vitro susceptibility testing of isolates collected from 27 hospital laboratories across the United States and 2) analysis of data from The Surveillance Network Database-USA, an electronic surveillance network comprising more than 200 laboratories nationwide. Regardless of the surveillance method, *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* demonstrated similar rates of susceptibility to levofloxacin and ciprofloxacin. Susceptibilities to the fluoroquinolones approached or exceeded 90% for all *Enterobacteriaceae* except *Providencia* spp. (≤65%). Approximately 70% of *P. aeruginosa* and 50% of *A. baumanii* isolates were susceptible to both fluoroquinolones. Among *S. maltophilia* isolates, 50% more isolates were susceptible to levofloxacin than to ciprofloxacin. Overall, the rate of ceftazidime nonsusceptibility among *Enterobacteriaceae* was 8.7%, with fluoroquinolone resistance rates notably higher among ceftazidime-nonsusceptible isolates than ceftazidime-susceptible ones. Multidrug-resistant isolates were present among all species tested but were most prevalent for *Klebsiella pneumoniae* and *Enterobacter cloacae*. No gram-negative isolates resistant only to a fluoroquinolone were encountered, regardless of species. Thus, while levofloxacin and ciprofloxacin have maintained potent activity against *Enterobacteriaceae*, the potential for fluoroquinolone resistance, the apparent association between fluoroquinolone and cephalosporin resistance, and the presence of multidrug resistance in every species examined emphasize the need to maintain active surveillance of resistance patterns among gram-negative bacilli.

The potent activity of fluoroquinolones (FQs) against a myriad of gram-negative and gram-positive bacterial pathogens has fostered a decade of frequent and continued clinical use. Recently, levofloxacin has broadened the range of indications for FQs to include community-acquired respiratory tract infections attributable to penicillin-resistant *Streptococcus pneumoniae*. In spite of their success, concern remains regarding the development and increasing prevalence of resistance to FQs among human pathogens and colonizing bacterial species (12, 23, 24, 25).

A decline in the activity of FQs would be especially problematic in view of the ability of gram-negative bacilli to acquire resistance to all other classes of antimicrobials (4, 5, 10, 11, 14, 15, 17, 20, 22, 29, 30). This ability underscores the need to closely monitor FQ activity in the United States and to do so in a timely manner. Recent surveillance studies examining FQ resistance among gram-negative bacilli in the United States have been limited, with published reports focusing largely on bloodstream isolates (7, 18).

To investigate the current status of FQ activity against prominent gram-negative species, as well as any associations with cephalosporin resistance and multidrug resistance, two surveillance strategies were employed. The first was a centralized in vitro study using isolates collected from across the United States and tested at a central reference laboratory. The second strategy utilized The Surveillance Network (TSN) Database-USA, an electronic surveillance network that collects antimicrobial susceptibility data from more than 200 laboratories nationwide. The results from these two strategies were then analyzed and compared.

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MATERIALS AND METHODS

Centralized in vitro surveillance study. Between 1 January and 31 March 1999, fresh, prospective clinical isolates of gram-negative bacilli were collected from 27 hospital laboratories geographically distributed throughout the United States. Laboratories were requested to provide defined quotas of a specific species or group of organisms. Isolates were limited to one per patient and were accepted regardless of specimen source, inpatient or outpatient status, or other patient demographic parameters. Upon receipt at the central laboratory, all isolates were subcultured to sheep blood agar, and their identifications were confirmed using the RapID ONE System (Remel, Lenexa, Kans.) for oxidase-negative fermentative gram-negative species and the RapID NF Plus System (Remel) for nonfermentative gram-negative species. In total, 2,684 *Enterobacteriaceae*

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isolates, comprised of 204 *Citrobacter* spp., 183 *Enterobacter aerogenes*, 323 *Enterobacter cloacae*, 709 *Escherichia coli*, 584 *Klebsiella pneumoniae*, 413 *Proteus mirabilis*, 72 *Providencia* spp., and 196 *Serratia marcescens* isolates, and 684 non-*Enterobacteriaceae* isolates, including 464 *Pseudomonas aeruginosa*, 97 *Acinetobacter baumannii*, and 123 *Stenotrophomonas maltophilia* isolates, were collected.

Broth microdilution testing of all isolates was performed according to the recommended procedures of the National Committee for Clinical Laboratory Standards (NCCLS) (16). Briefly, colonies taken from overnight growth on 5% sheep blood agar (16 to 20 h at 35°C) were resuspended in cation-adjusted Mueller-Hinton broth to a turbidity approximating a 0.5 McFarland standard. This suspension was used to inoculate broth microdilution plates (TREK Diagnostics, Westlake, Ohio) to obtain a final organism concentration of 5×10^5 CFU/ml. Plates were incubated at 35°C for 16 to 20 h in ambient air prior to reading.

Two FQs, levofloxacin and ciprofloxacin, were studied. Other agents were also tested to ascertain the prevalence of multidrug resistance and to examine any association between cephalosporin resistance and FQ resistance. These other agents included ampicillin, piperacillin-tazobactam, ceftazidime, ceftriaxone, imipenem-cilastatin, gentamicin, and trimethoprim-sulfamethoxazole (SXT).

Electronic surveillance study. The electronic surveillance study was accomplished using TSN Database-USA. TSN has been operating since 1994 and has been previously described (21; K. M. Tomfohrde, A. V. Mendes, M. L. Hickey, C. Thornsberry, and D. F. Sahm, Progr. Abstr. Int. Conf. Emerg. Infect. Dis., abstr. P-10.7, p. 109, 1998). TSN Database-USA is a repository of quantitative and qualitative antimicrobial susceptibility test results collected from 229 clinical microbiology laboratories throughout the United States. All participant laboratories use commercial or standard susceptibility testing methods. After passing several internal quality control and processing filters, the data is analyzed using a variety of query applications.

To include the most recent TSN data that was contemporary with the data from the centralized in vitro study, data from 1 January 1998 to 31 March 1999 were compiled. All interpretative result data from TSN for each species was included in susceptibility comparisons, regardless of the number of concurrent antimicrobials tested.

Data analysis. Isolates were assessed as susceptible, intermediate, or resistant to each agent tested as defined by NCCLS breakpoint criteria (16). To examine any associated resistance between FQs and extended-spectrum cephalosporins, isolates were also analyzed for ceftazidime susceptibility. The prevalence of multidrug resistance was also investigated. For *E. coli* and *P. mirabilis*, a multidrug-resistant (MDR) phenotype was defined as resistance to three or more of the following agents: ampicillin, gentamicin, SXT, and levofloxacin. For all other species of *Enterobacteriaceae*, resistance to three or more of ceftazidime, gentamicin, SXT, and levofloxacin defined an MDR phenotype. For *P. aeruginosa*, multidrug resistance included resistance to three or more of ceftazidime, gentamicin, imipenem, and levofloxacin. In all definitions of multidrug resistance, levofloxacin was arbitrarily chosen as the marker drug for FQ resistance. In determining rates of concurrent resistance to FQs and ceftazidime and of multidrug resistance among isolates from TSN, only data from isolates tested against all antimicrobial agents included in the centralized in vitro study were included. This was done to facilitate a balanced comparison of data by the two surveillance methods.

RESULTS

The activities of all antimicrobials tested against *Enterobacteriaceae*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, as determined by centralized in vitro testing and TSN, are shown in Table 1. *Enterobacteriaceae* other than *E. coli* and *P. mirabilis* demonstrated ampicillin resistance rates approximately 15 to 30% higher by TSN than by centralized in vitro testing. It is likely that this difference reflects the reporting practices of clinical laboratories, which commonly report isolates of *Enterobacteriaceae*, excluding *E. coli* and *P. mirabilis*, as resistant to ampicillin regardless of susceptibility results. The overriding of susceptibility results by clinical laboratories is done to discourage the clinical use of ampicillin, as current susceptibility testing methods do not readily detect inducible β-lactamases, such as AmpC, that are pervasive among certain clinically relevant *Enterobacteriaceae*. In our centralized in vitro surveillance study we did not alter data in this manner.

According to the centralized in vitro data, the activities of the two FQs studied were comparable for each species of *Enterobacteriaceae* studied. In most instances, >90% of the isolates were susceptible to both FQs. Exceptions were *E. cloacae* (88.2% susceptible to ciprofloxacin) and *S. marcescens* (89.3% susceptible to ciprofloxacin). Regardless of the FQ examined, susceptibility among *Providencia* spp. did not exceed approximately 65%.

The TSN data revealed similar FQ activities for the *Enterobacteriaceae* studied (Table 1). The percent susceptible, intermediate, and resistant results provided by the two methods were usually within 2 to 4% of each other. A notable exception was the *Providencia* spp., for which the percent susceptible results were approximately 10% lower by TSN data than by the centralized in vitro approach.

By centralized in vitro testing, the activities of levofloxacin (71.3% susceptible isolates) and ciprofloxacin (71.1% susceptible isolates) were nearly identical against *P. aeruginosa*, and these findings were mirrored by those obtained by TSN for levofloxacin (68.8% susceptible isolates) and ciprofloxacin (71.5% susceptible isolates) (Table 1). Similarly, centralized in vitro and TSN results showed *A. baumannii* at about 50% susceptibility to either of the two agents. However, for levofloxacin the percentage of resistant isolates was notably higher (44.0%) by TSN results than by centralized in vitro testing (32.0%) due to the higher percentage of intermediate isolates by centralized in vitro testing than by TSN (14.4% versus 2.8%). For *S. maltophilia*, the activity of levofloxacin (88.6% susceptible) was substantially higher than that of ciprofloxacin (34.1% susceptible). The higher activity of levofloxacin than ciprofloxacin was also noted in TSN data, with 78.2 and 28.9% of the isolates being susceptible, respectively (Table 1).

Figure 1 depicts FQ MIC distributions for isolates of *P. aeruginosa* collected by the centralized in vitro study. The data indicate that at the intermediate breakpoints, levofloxacin (4 μg/ml) and ciprofloxacin (2 μg/ml) inhibited 78.5 and 76.3% of *P. aeruginosa* isolates, respectively. It was also observed that isolation rates of *P. aeruginosa* with ciprofloxacin (4.7%) and levofloxacin (5.1%) MICs of >32 μg/ml were similar.

To examine the association between FQ resistance and resistance to β-lactam agents, the activities of levofloxacin and ciprofloxacin were assessed in relation to the ceftazidime susceptibility status of the isolates. For the centralized in vitro study, the percent susceptibility to the FQs was lower in the ceftazidime-nonsusceptible group than in the ceftazidime-susceptible group for every organism group (Table 2). In general, the decrease in percent susceptibility was comparable for both FQs. The most apparent anomaly for this generalization appeared among the eight isolates of ceftazidime-nonsusceptible *S. marcescens*; however, the number of isolates available in this instance was too small to establish a definitive correlation.

The extent of the decrease in FQ activities among ceftazidime-nonsusceptible groups did vary notably between certain bacterial species. For example, among *K. pneumoniae* isolates, FQ susceptibility dropped by approximately 40% or more among ceftazidime-nonsusceptible isolates, whereas among *E. cloacae* isolates, the decrease was only between 10% (for levofloxacin) and 20% (for ciprofloxacin). As noted with

TABLE 1. Comparison of antimicrobial activities determined by centralized in vitro[a] and electronic (TSN)[b] surveillance

Organism	Antimicrobial agent	In vitro surveillance results				TSN surveillance results			
		n	% S[c]	% I	% R	*n*	% S	% I	% R
E. coli	Ampicillin	709	60.1	1.1	38.8	208,129	60.4	0.8	38.8
	Ceftazidime	709	98.3	0.7	1.0	89,128	98.5	0.3	1.2
	Ceftriaxone	709	98.7	0.8	0.4	120,545	99.4	0.3	0.3
	Imipenem	709	100.0	0.0	0.0	77,221	100.0	0.0	0.0
	Piperacillin-tazobactam	709	98.7	0.3	1.0	38,568	95.8	2.6	1.6
	Gentamicin	709	96.3	0.3	3.4	194,687	97.4	0.3	2.4
	SXT	709	80.4	0.0	19.6	206,601	82.2	0.1	17.7
	Ciprofloxacin	709	94.8	0.0	5.2	175,660	97.4	0.1	2.5
	Levofloxacin	709	95.1	0.1	4.8	47,564	96.5	0.2	3.4
K. pneumoniae	Ampicillin	584	8.0	29.8	62.2	49,832	1.4	4.1	94.5
	Ceftazidime	584	93.3	0.5	6.2	27,034	91.5	1.7	6.8
	Ceftriaxone	584	96.2	2.7	1.0	31,270	95.5	2.3	2.3
	Imipenem	584	100.0	0.0	0.0	25,565	100.0	0.0	0.0
	Piperacillin-tazobactam	584	94.3	3.3	2.4	11,963	90.0	5.0	5.0
	Gentamicin	584	94.3	1.4	4.3	49,366	94.3	0.9	4.8
	SXT	584	88.7	0.0	11.3	50,717	87.6	0.2	12.2
	Ciprofloxacin	584	93.5	1.4	5.1	43,551	93.4	1.1	5.6
	Levofloxacin	584	95.0	2.1	2.9	13,600	92.2	2.0	5.8
P. mirabilis	Ampicillin	413	85.5	1.9	12.6	28,439	86.3	0.9	12.8
	Ceftazidime	413	99.3	0.2	0.5	12,710	99.3	0.3	0.5
	Ceftriaxone	413	100.0	0.0	0.0	18,365	99.6	0.2	0.2
	Imipenem	413	100.0	0.0	0.0	12,805	100.0	0.0	0.0
	Piperacillin-tazobactam	413	99.8	0.0	0.2	6,161	98.1	1.2	0.8
	Gentamicin	413	92.3	1.2	6.5	27,274	93.4	1.4	5.2
	SXT	413	90.6	0.0	9.4	28,311	88.2	0.0	11.8
	Ciprofloxacin	413	91.3	2.2	6.5	23,665	93.0	4.7	6.1
	Levofloxacin	413	94.7	1.5	3.9	7,585	90.4	6.3	7.4
E. cloacae	Ampicillin	323	12.1	14.9	73.1	18,053	2.8	2.9	94.3
	Ceftazidime	323	71.8	3.7	24.5	13,204	67.1	2.1	30.8
	Ceftriaxone	323	71.8	8.7	19.5	12,648	70.7	7.2	22.1
	Imipenem	323	100.0	0.0	0.0	11,945	100.0	0.0	0.0
	Piperacillin-tazobactam	323	76.8	12.4	10.8	4,986	71.4	10.1	18.5
	Gentamicin	323	92.0	1.5	6.5	18,376	90.8	0.8	8.4
	SXT	323	88.2	0.0	11.8	18,301	87.3	0.2	12.5
	Ciprofloxacin	323	88.2	4.0	7.7	15,671	90.4	2.0	7.7
	Levofloxacin	323	94.4	1.2	4.3	5,248	93.7	2.0	4.3
Citrobacter spp.	Ampicillin	204	15.7	16.2	68.1	13,444	6.9	4.4	88.7
	Ceftazidime	204	77.9	3.4	18.6	8,225	79.3	2.0	18.8
	Ceftriaxone	204	79.4	14.2	6.4	9,633	82.2	5.9	11.9
	Imipenem	204	100.0	0.0	0.0	7,501	100.0	0.0	0.0
	Piperacillin-tazobactam	204	91.2	7.4	1.5	3,284	81.5	10.2	8.4
	Gentamicin	204	92.2	2.9	4.9	13,969	93.1	0.9	6.0
	SXT	204	87.3	0.0	12.7	14,400	84.3	0.1	15.7
	Ciprofloxacin	204	91.7	2.5	5.9	12,261	90.9	1.3	7.9
	Levofloxacin	204	94.6	3.4	2.0	3,848	90.4	1.5	8.1
S. marcescens	Ampicillin	196	6.1	16.8	77.0	10,385	4.5	4.4	91.2
	Ceftazidime	196	95.9	1.5	2.6	7,512	91.1	1.4	7.5
	Ceftriaxone	196	96.9	1.5	1.5	7,482	94.2	3.2	2.6
	Imipenem	196	100.0	0.0	0.0	6,967	100.0	0.0	0.0
	Piperacillin-tazobactam	196	94.9	4.1	1.0	3,254	90.3	5.6	4.1
	Gentamicin	196	95.9	1.0	3.1	10,360	95.9	0.7	3.3
	SXT	196	94.4	0.0	5.6	10,357	95.1	0.3	4.6
	Ciprofloxacin	196	89.3	2.0	8.7	9,032	90.8	2.8	6.4
	Levofloxacin	196	94.9	1.0	4.1	3,162	94.2	1.9	3.9
E. aerogenes	Ampicillin	183	8.2	10.9	80.9	9,346	2.1	2.4	95.5
	Ceftazidime	183	81.4	2.2	16.4	6,209	69.5	3.3	27.2
	Ceftriaxone	183	85.2	10.4	4.4	6,510	80.0	14.4	5.7
	Imipenem	183	100.0	0.0	0.0	5,760	100.0	0.0	0.0
	Piperacillin-tazobactam	183	83.6	15.3	1.1	2,271	76.3	14.4	9.3
	Gentamicin	183	99.5	0.5	0.0	9,377	95.2	0.5	4.3
	SXT	183	96.7	0.0	3.3	9,508	94.0	0.1	5.9
	Ciprofloxacin	183	94.5	1.1	4.4	8,197	92.3	1.0	6.7
	Levofloxacin	183	96.2	1.6	2.2	2,521	93.9	1.6	4.6

Continued on following page

TABLE 1—*Continued*

Organism	Antimicrobial agent	In vitro surveillance results				TSN surveillance results			
		n	% S[c]	% I	% R	*n*	% S	% I	% R
Providencia spp.	Ampicillin	72	30.6	18.1	51.4	2,760	19.3	6.1	74.6
	Ceftazidime	72	97.2	0.0	2.8	1,627	92.2	1.5	6.3
	Ceftriaxone	72	100.0	0.0	0.0	2,003	98.5	1.0	0.5
	Imipenem	72	100.0	0.0	0.0	1,481	99.5	0.5	0.0
	Piperacillin-tazobactam	72	98.6	1.4	0.0	680	91.6	6.5	1.9
	Gentamicin	72	81.9	12.5	5.6	2,775	74.1	8.2	17.7
	SXT	72	77.8	0.0	22.2	2,769	71.9	0.6	27.5
	Ciprofloxacin	72	62.5	2.8	34.7	2,344	53.2	3.6	43.2
	Levofloxacin	72	65.3	13.9	20.8	806	55.0	5.8	39.2
P. aeruginosa	Ampicillin	464	—[d]	—	—	—	—	—	—
	Ceftazidime	464	81.3	5.6	13.1	63,556	86.6	5.0	8.5
	Ceftriaxone	464	21.6	36.2	42.2	26,849	27.4	37.4	35.2
	Imipenem	464	85.6	8.6	5.8	54,052	83.3	3.2	13.5
	Piperacillin-tazobactam	464	78.2	10.3	11.4	22,054	90.0	0.0	10.0
	Gentamicin	464	82.8	7.3	9.9	67,037	77.3	7.4	15.3
	SXT	464	14.7	0.0	85.3	37,638	4.9	0.2	94.9
	Ciprofloxacin	464	71.1	5.2	23.7	64,971	71.5	4.7	23.8
	Levofloxacin	464	71.3	7.1	21.6	21,199	68.8	6.3	24.9
A. baumannii	Ampicillin	97	6.2	22.7	71.1	—	—	—	—
	Ceftazidime	97	56.7	18.6	24.7	5,118	53.9	13.9	32.2
	Ceftriaxone	97	27.8	34.0	38.1	3,210	42.5	17.3	40.3
	Imipenem	97	94.8	0.0	5.2	4,596	91.7	3.0	5.3
	Piperacillin-tazobactam	97	66.0	20.6	13.4	1,619	64.3	18.3	17.4
	Gentamicin	97	59.8	6.2	34.0	5,678	51.8	4.1	44.1
	SXT	97	56.7	0.0	43.3	5,116	53.1	0.1	46.8
	Ciprofloxacin	97	50.5	1.0	48.5	5,328	47.5	1.5	51.0
	Levofloxacin	97	53.6	14.4	32.0	1,835	53.2	2.8	44.0
S. maltophilia	Ampicillin	123	0.8	4.1	95.1	—	—	—	—
	Ceftazidime	123	64.2	13.0	22.8	3,326	43.5	13.1	43.4
	Ceftriaxone	123	2.4	7.3	90.2	1,776	2.3	6.5	91.2
	Imipenem	123	0.8	1.6	97.6	2,613	0.0	0.7	99.3
	Piperacillin-tazobactam	123	31.7	46.3	22.0	682	55.7	17.9	26.4
	Gentamicin	123	18.7	13.8	67.5	2,995	16.1	9.1	74.8
	SXT	123	94.3	0.0	5.7	3,825	98.7	0	1.3
	Ciprofloxacin	123	34.1	30.9	35.0	3,268	28.9	26.9	44.3
	Levofloxacin	123	88.6	5.7	5.7	1,211	78.2	9.4	12.4

[a] Organisms collected between 1 January and 31 March 1999.
[b] Data collected from 1 January 1998 to 31 March 1999.
[c] S, susceptible; I, intermediate; R, resistant.
[d] —, no data collected.

the *Enterobacteriaceae*, a marked reduction in FQ susceptibility also occurred among *P. aeruginosa* isolates that were not susceptible to either ceftazidime or imipenem. These isolates exhibited a 30 to 40% decrease in susceptibility to both FQs (Table 2).

Using TSN data to examine the association between FQ susceptibility and ceftazidime susceptibility allowed comparisons to be made using considerably larger numbers of isolates for each species (Table 3). However, the same pattern of lower FQ susceptibility among the ceftazidime-nonsusceptible groups was observed. Both levofloxacin and ciprofloxacin activities were comparably decreased among ceftazidime-nonsusceptible groups, and the extent of the decrease varied notably between certain species. For example, as was also evident from the centralized in vitro data in Table 2, FQ susceptibilities were more markedly reduced in the ceftazidime-nonsusceptible isolates of *K. pneumoniae* than of *E. cloacae*. Also, as observed with the centralized in vitro study analysis, a 30 to 40% reduction in susceptibility occurred with ceftazidime-nonsusceptible and imipenem-nonsusceptible *P. aeruginosa* relative to susceptible isolates.

The percentages of MDR isolates and the most prevalent MDR phenotypes encountered for each species, as reported by TSN and the centralized in vitro study, are presented in Table 4. For all *Enterobacteriaceae* considered together, TSN identified 2,655 (4.0%) of 67,016 isolates as MDR, while the centralized in vitro testing identified 86 (3.2%) of 2,684 isolates as MDR. With the exception of *E. coli*, *E. cloacae*, and *S. marcescens*, the percentage of MDR isolates was higher in TSN data than in the centralized in vitro study. According to TSN data, multidrug resistance among *Enterobacteriaceae* occurred most frequently among isolates of *K. pneumoniae* (7.3%), *Providencia* spp. (6.0%), and *E. cloacae* (5.9%). For *K. pneumoniae* and *E. cloacae*, the most prevalent MDR phenotype was resistance to ceftazidime, gentamicin, and SXT. For *Providencia* spp., the most prevalent MDR phenotype was resistance to gentamicin, SXT, and an FQ. Multidrug resistance was less frequently encountered among *S. marcescens* (0.6%),

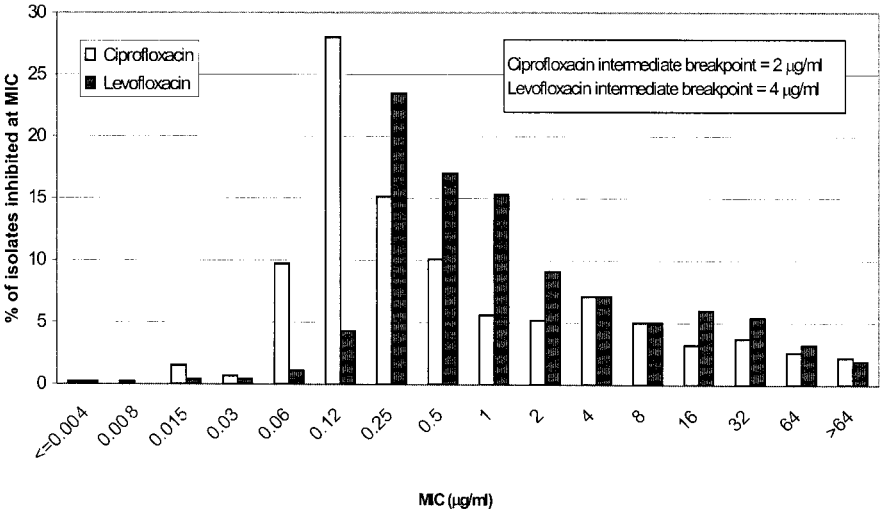

FIG. 1. Distribution of FQ MICs for 464 isolates of *P. aeruginosa* collected from across the United States during a 1999 centralized in vitro surveillance study.

E. aerogenes (2.5%), and *E. coli* (3.1%) isolates. Overall, FQ resistance was part of the most prevalent MDR phenotype for all species of *Enterobacteriaceae* studied except *K. pneumoniae* and *E. cloacae*.

The centralized in vitro study showed that multidrug resistance occurred most frequently with *E. cloacae* (6.5%) and *E. coli* (4.2%). The most frequent MDR phenotype for *E. cloacae* was resistance to ceftazidime, gentamicin, and SXT, which matched the most prevalent MDR profile found by TSN. For *E. coli*, the prominent MDR phenotype was resistance to ampicillin, SXT, and levofloxacin. Multidrug resistance was not encountered among isolates of *E. aerogenes* and was uncommon among *Citrobacter* spp. (0.5%) and *S. marcescens* (1.0%) isolates. In contrast to the TSN data, predominant MDR phe-

TABLE 2. Correlation between FQ and β-lactam susceptibilities using centralized in vitro surveillance data

Organism	β-Lactam susceptibility[a]	*n*	No. (%) of susceptible isolates	
			Levofloxacin	Ciprofloxacin
E. coli	CAZ-S	697	672 (96.4)	670 (96.1)
	CAZ-NS	12	2 (16.7)	2 (16.7)
K. pneumoniae	CAZ-S	545	532 (97.6)	528 (96.9)
	CAZ-NS	39	23 (59.0)	18 (46.2)
P. mirabilis	CAZ-S	410	390 (95.1)	376 (91.7)
	CAZ-NS	3	1 (33.3)	1 (33.3)
E. cloacae	CAZ-S	232	225 (97.0)	219 (94.4)
	CAZ-NS	91	80 (87.9)	66 (72.5)
Citrobacter spp.	CAZ-S	159	151 (95.0)	147 (92.5)
	CAZ-NS	45	42 (93.3)	40 (88.9)
S. marcescens	CAZ-S	188	182 (96.8)	175 (93.1)
	CAZ-NS	8	4 (50.0)	0 (0.0)
E. aerogenes	CAZ-S	149	147 (98.7)	146 (98.0)
	CAZ-NS	34	29 (85.3)	27 (79.4)
Providencia spp.	CAZ-S	70	46 (65.7)	44 (62.9)
	CAZ-NS	2	1 (50.0)	1 (50.0)
P. aeruginosa	CAZ-S	377	294 (78.0)	294 (78.0)
	CAZ-NS	87	37 (42.5)	36 (41.4)
	IPM-S	397	307 (77.3)	307 (77.3)
	IPM-NS	67	24 (35.8)	23 (34.3)

[a] β-Lactam susceptibility (S) based on ceftazidime (CAZ) for *Enterobacteriaceae* and CAZ and imipenem (IPM) for *P. aeruginosa*. NS, nonsusceptible (includes intermediate and resistant strains [16]).

TABLE 3. Correlation between FQ and β-lactam susceptibilities using electronic (TSN) surveillance data

Organism	β-Lactam susceptibility[a]	Levofloxacin		Ciprofloxacin	
		n	No. (%) susceptible	*n*	No. (%) susceptible
E. coli	CAZ-S	24,827	24,125 (97.2)	79,089	76,959 (97.3)
	CAZ-NS	301	120 (39.9)	908	356 (39.2)
K. pneumoniae	CAZ-S	6,735	6,518 (96.8)	22,213	21,371 (96.2)
	CAZ-NS	670	311 (46.4)	1,664	659 (39.6)
P. mirabilis	CAZ-S	3,855	3,661 (95.0)	11,080	10,402 (93.9)
	CAZ-NS	18	13 (72.2)	53	38 (71.7)
E. cloacae	CAZ-S	2,328	2,276 (97.8)	7,529	7,322 (97.3)
	CAZ-NS	335	280 (83.6)	3,237	2,373 (73.3)
Citrobacter spp.	CAZ-S	1,782	1,700 (95.4)	5,696	5,346 (93.9)
	CAZ-NS	400	276 (69.0)	1,303	919 (70.5)
S. marcescens	CAZ-S	1,866	1,781 (95.4)	5,742	5,364 (93.4)
	CAZ-NS	167	157 (94.0)	454	316 (69.6)
E. aerogenes	CAZ-S	1,196	1,166 (97.5)	3,708	3,612 (97.4)
	CAZ-NS	335	280 (83.6)	1,364	1,042 (76.4)
Providencia spp.	CAZ-S	418	228 (54.6)	1,299	678 (52.2)
	CAZ-NS	37	18 (48.7)	80	37 (46.3)
P. aeruginosa	CAZ-S	15,300	11,347 (74.2)	52,369	40,246 (76.9)
	CAZ-NS	1,608	607 (37.8)	4,960	1,861 (37.5)
	IPM-S	13,655	10,229 (74.9)	43,651	33,997 (77.9)
	IPM-NS	2,457	863 (35.1)	8,571	3,331 (38.9)

[a] β-Lactam susceptibility (S) based on ceftazidime (CAZ) for *Enterobacteriaceae* and CAZ and imipenem (IPM) for *P. aeruginosa*. NS, nonsusceptible (includes intermediate and resistant strains [16]).

TABLE 4. Prevalence of MDR isolates and predominant MDR phenotypes in centralized in vitro[a] and TSN Database-USA[b] surveillance data

Organism	In vitro surveillance results			TSN surveillance results		
	n	No. (%) of MDR isolates	Predominant MDR phenotype (%)[c]	*n*	No. (%) of MDR isolates	Predominant MDR phenotype (%)[c]
E. coli	709	30 (4.2)	AMP, SXT, FQ (46.7)	43,085	1,341 (3.1)	AMP, SXT, FQ (39.9)
K. pneumoniae	584	20 (3.4)	CAZ, GEN, SXT (45.0)	7,485	550 (7.3)	CAZ, GEN, SXT (42.2)
P. mirabilis	413	10 (2.4)	AMP, GEN, SXT (70.0)	6,938	378 (5.4)	AMP, SXT, FQ (40.0)
E. cloacae	323	21 (6.5)	CAZ, GEN, SXT (52.4)	3,311	196 (5.9)	CAZ, GEN, SXT (53.6)
Citrobacter spp.	204	1 (0.5)	CAZ, GEN, SXT (100.0)	2,155	112 (5.2)	CAZ, GEN, SXT, FQ (42.9)
S. marcescens	196	2 (1.0)	CAZ, GEN, SXT (50.0)	2,035	12 (0.6)	CAZ, GEN, SXT, FQ (41.7)
E. aerogenes	183	0 (0.0)		1,559	39 (2.5)	CAZ, SXT, FQ (35.9)
Providencia spp.	72	2 (2.8)	CAZ, SXT, FQ (50.0)	448	27 (6.0)	GEN, SXT, FQ (77.8)
Enterobacteriaceae	2,684	86 (3.2)		67,016	2,655 (4.0)	
P. aeruginosa	464	17 (3.7)	CAZ, GEN, IPM, FQ (58.8)	15,171	959 (6.3)	GEN, IPM, FQ (28.3)

[a] Organisms collected between 1 January and 31 March 1999.
[b] Data collected from 1 January 1998 to 31 March 1999.
[c] AMP, ampicillin; CAZ, ceftazidime; GEN, gentamicin; IPM, imipenem.

notypes that included an FQ occurred for only two species: *E. coli* and *Providencia* spp. Resistance only to levofloxacin was not encountered in any of the *Enterobacteriaceae* isolates studied by either TSN or the centralized in vitro method.

For *P. aeruginosa*, multidrug resistance was identified in 6.3% of isolates from TSN and 3.7% of isolates from the centralized in vitro study (Table 4). In TSN data, the most prevalent MDR phenotype was resistance to gentamicin, imipenem, and an FQ (28.3% of MDR isolates) but was followed closely by an MDR phenotype (25.2% of MDR isolates) that included resistance to ceftazidime, gentamicin, imipenem, and an FQ. This MDR phenotype was also the most prevalent among *P. aeruginosa* isolates tested in the centralized in vitro study. Resistance to an FQ alone was not encountered among isolates of *P. aeruginosa* by either TSN or centralized in vitro surveillance.

DISCUSSION

The ability of clinically relevant gram-negative bacilli to develop resistance to FQs and the potential for this resistance to increase in prevalence underscore the need to monitor resistance trends (2, 5, 8, 9, 10, 19, 27, 29, 30). However, in recent years representative surveillance studies examining FQ resistance among gram-negative bacteria in the United States have been infrequent (7, 13, 18). In the current study, two different surveillance strategies, electronic surveillance using TSN and centralized in vitro testing, were used to examine the current status of FQ activity against commonly encountered species of *Enterobacteriaceae* and nonfermentative gram-negative bacilli.

The findings of this study are noteworthy from several perspectives. First, for *Enterobacteriaceae*, both surveillance approaches yielded results that were largely similar, with susceptibility to levofloxacin and ciprofloxacin at approximately 90% or greater for most of the species studied. Second, the results of both approaches were also similar for the nonfermentative gram-negative species studied. The activities of both FQs against *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* were substantially lower than the activities against the *Enterobacteriaceae*. Third, regardless of the surveillance method used, FQ resistance was notably higher among ceftazidime-resistant *Enterobacteriaceae* and ceftazidime- and imipenem-resistant *P. aeruginosa*. Also, multidrug resistance was evident in every species of enteric bacilli and in *P. aeruginosa*, but the percentage of strains exhibiting multidrug resistance varied among species, as did the most prevalent MDR phenotypes. Finally, resistance to levofloxacin in the absence of resistance to other antibiotics was not encountered among either *Enterobacteriaceae* or *P. aeruginosa*.

By both TSN and the centralized in vitro study, *Enterobacteriaceae* exhibited greater than 90% susceptibility to levofloxacin and ciprofloxacin, and the activities of the two agents were comparable. These findings are consistent with other recent reports that have primarily focused on blood culture isolates collected during 1997 (7, 13, 18). For example, in previous studies *E. coli* susceptibility to levofloxacin and ciprofloxacin exhibited a narrow range, from 97.2 to 97.6% (7, 13, 18). In the present study, *E. coli* susceptibilities were slightly lower but still demonstrated a narrow range, from 94.8% (ciprofloxacin) to 95.1% (levofloxacin) by centralized in vitro surveillance and from 96.5% (levofloxacin) to 97.4% (ciprofloxacin) according to TSN (Table 1). The susceptibility rates of other species, such as *K. pneumoniae*, *Enterobacter* spp., *Citrobacter* spp., and *S. marcescens*, found by TSN and the centralized in vitro study were also consistent with those of earlier studies, with percentages usually ranging from 90 to 96% susceptible (7, 8, 13, 18).

Interestingly, the current overall activities of these FQs against the species of *Enterobacteriaceae* included in the present study are not substantially different from those reported for ciprofloxacin in a report by Thornsberry and coworkers that included isolates from 1990 and 1991 (23). In that study, ciprofloxacin susceptibility ranged from 91.9 to 99.5%. Therefore, even though FQ resistance can vary between institutions, and certainly among different countries, the findings of this study indicate that in the United States the overall activity of these agents against *Enterobacteriaceae* has remained consistently high during the 1990s (2, 9, 11, 19, 26, 27). The exception to this finding is the abated activity that levofloxacin and ciprofloxacin demonstrated against *Providencia* spp. Although the reason for the reduced activity against this particular group of organisms is unknown, it has been reported in other studies and may be related to intrinsic permeability or mutational idiosyncrasies in this genus (3, 6, 19, 23, 28, 29, 30).

With regard to the nonfermentative gram-negative species, the activities of levofloxacin and ciprofloxacin against *P. aerugi-*

nosa were nearly identical in the TSN and centralized in vitro studies (Table 1). However, the percentage of susceptible isolates (approximately 70% for both FQs) was substantially lower than those reported in previous studies conducted in 1997, in which susceptibilities were 85% for levofloxacin and 89% for ciprofloxacin (7, 18). The lower percent susceptibility found in this study may reflect increasing FQ resistance among *P. aeruginosa* isolates in the United States. However, other factors, such as the geographic source of the isolates and the fact that the studies reported by Pfaller et al. (18) and Diekema et al. (7) involved only blood isolates, may also have contributed to these differences. In the centralized in vitro study, it was also observed that even though ciprofloxacin tended to be one doubling dilution more potent than levofloxacin at lower concentrations (MICs of $\leq$2 μg/ml), the prevalence of *P. aeruginosa* isolates with ciprofloxacin and levofloxacin MICs of >32 μg/ml was similar, at 4.7 and 5.1%, respectively (Fig. 1). This implies that the cumulative impact of GyrA and ParC mutations, as well as decreases in cellular permeability, conferred similar levels of resistance to both FQs.

The surveillance data presented in this study showed that levofloxacin and ciprofloxacin activities against *Acinetobacter* spp. were limited, with approximately 50% of the isolates being susceptible to either FQ. These susceptibilities are considerably lower than the 70 to 80% reported in previous studies (7, 13).

Of the gram-negative species included in this study, only *S. maltophilia* demonstrated marked differences in susceptibility between the FQs. While the percent susceptibility to levofloxacin was well above 70%, ciprofloxacin susceptibility was at least 50% less (Table 1). The poor activity of ciprofloxacin against *S. maltophilia* has also been documented in previous studies (7, 8, 23).

MDR organisms can present substantial therapeutic challenges, and as such may pose greater public health problems than highly prevalent isolates that exhibit resistance to a single agent. The potential for commonly encountered gram-negative bacilli to acquire cross-resistance to several antimicrobial agents has been well documented (1, 11, 17, 30). For these reasons, and because multidrug resistance has not been commonly addressed in surveillance studies, we investigated the activities of the FQs stratified by ceftazidime susceptibility status (Tables 2 and 3) and also determined the frequencies of MDR phenotypes (Table 4).

Both TSN and centralized in vitro surveillance data demonstrated lower susceptibilities to levofloxacin and ciprofloxacin among ceftazidime-nonsusceptible isolates than among ceftazidime-susceptible ones. Both FQs were comparably affected by concurrent ceftazidime nonsusceptibility. Similar observations were noted for every species examined and were consistent with reports that have evaluated isolates from individual institutions (7, 11, 14, 20, 30). Reductions in FQ activity against ceftazidime-nonsusceptible isolates were most common among *K. pneumoniae* and *E. coli* isolates and likely represent clonal spread among these species but may also be due to multifocal emergence. The apparent correlation between FQ resistance and resistance to extended-spectrum cephalosporins is a phenomenon that requires careful monitoring, as such resistant profiles seriously limit the therapeutic options available to treat infections caused by these organisms.

The association between cephalosporin and FQ resistance was also evident when multidrug resistance was investigated (Table 4). Of interest, the percentage of MDR isolates was higher for most species by TSN data than by centralized in vitro study data. Every species exhibited some percentages of isolates that were MDR. The reasons for the differences in multidrug resistance prevalence observed between TSN and centralized in vitro surveillance are uncertain but may include differences in the number of isolates examined, their geographic distribution, or the number of participating institutions. Regardless, multidrug resistance has permeated every one of the most common species of *Enterobacteriaceae*. Based on reports from individual institutions and from different countries, the prevalence and diversity of MDR phenotypes can substantially expand and become problematic (11, 27); therefore, continued monitoring in the United States is warranted.

Of the MDR phenotypes encountered with the two surveillance approaches, resistance to ceftazidime, gentamicin, and SXT was the most prominent phenotype among isolates of *K. pneumoniae* and *E. cloacae*, the two species that had the highest percentage of MDR isolates. However, FQ resistance was part of the most prominent MDR phenotype for all other species studied by TSN. In contrast, FQ resistance was part of the most prominent MDR phenotype only for *E. coli* and *Providencia* spp. by the centralized in vitro study. The reasons for the differences between TSN and centralized in vitro surveillance are unclear but again may be a result of differences in the number of isolates examined, their geographic distribution, or the number of institutions participating in the studies.

TSN also reported a higher percentage of MDR isolates for *P. aeruginosa* than did the centralized in vitro study, and the prominent phenotype differed in that resistance to ceftazidime did not occur. However, in TSN data, ceftazidime resistance was a component of the second most prominent phenotype, which occurred among 25.2% of the MDR isolates.

Resistance only to an FQ was not encountered for any species tested in the study, regardless of surveillance method. While several speculative explanations could be put forth for this observation, it is interesting that resistance to FQs, which are relatively new agents, is most likely to be encountered among organisms resistant to other agents. That is, with the increased use of FQs in a variety of clinical settings, including empiric therapy for outpatients, one might expect resistance to FQs alone to be a phenotype encountered much more frequently than was found in this study.

In summary, both an electronic surveillance network, TSN, and a centralized in vitro study were used to provide comparable and current perspectives on the activities of FQs against several clinically relevant gram-negative bacilli. While this class of agents has maintained an excellent level of activity against clinically relevant *Enterobacteriaceae*, careful monitoring at local, national, and international levels is still required to provide continuous feedback regarding the resistance status of this important group of organisms. It is imperative to include monitoring the activities of FQs and other antimicrobial classes in the context of associated resistance and multidrug resistance as an important component of any surveillance initiative.

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