Stable Antimicrobial Susceptibility Rates for Clinical Isolates of *Pseudomonas aeruginosa* from the 2001–2003 Tracking Resistance in the United States Today Surveillance Studies

James A. Karlowsky,[1] Mark E. Jones,[1] Clyde Thornsberry,[1] Alan T. Evangelista,[2] Y. Cheung Yee,[2] and Daniel F. Sahm[1]

[1]Focus Bio-Inova, Herndon, Virginia; [2]Ortho-McNeil Pharmaceutical, Raritan, New Jersey

From 2001 to 2003, rates of susceptibility to piperacillin-tazobactam (86%), ceftazidime (80%), ciprofloxacin (68%), and levofloxacin (67%) did not decrease or decreased by <1.5%, whereas the rate of susceptibility to gentamicin decreased by 3.2% (from 75.5% to 72.3%) and the rate of susceptibility to imipenem decreased by 5.6% (from 84.4% to 78.8%), for 2394 clinical isolates of *Pseudomonas aeruginosa* collected in the Tracking Resistance in the United States Today surveillance studies. Rates of multidrug resistance (i.e., resistance to ⩾3 antimicrobial agents) increased from 7.2% in 2001 to 9.9% in 2003 and were significantly higher for isolates from the East North Central and Mid-Atlantic regions of the United States than for isolates from other regions. Analysis of minimum inhibitory concentrations (MICs) suggested that combining an antipseudomonal β-lactam with ciprofloxacin or levofloxacin would yield a 3.4%–7.1% increase in the percentage of isolates susceptible to the combination, compared with the β-lactam alone. Ratios of the area under the serum concentration–time curve values for free drug to modal MICs for ciprofloxacin and levofloxacin were similar and were >125 (target ratio), whereas those ratios for gatifloxacin and moxifloxacin were significantly lower. Ongoing surveillance of *P. aeruginosa* is essential.

Pseudomonas aeruginosa is a ubiquitous organism, an opportunistic pathogen, and one of the most common gram-negative bacterial species isolated from respiratory-tract specimens obtained from hospitalized patients [1, 2]. Human infections caused by *P. aeruginosa* can range from superficial skin infections to fulminant sepsis. *P. aeruginosa* is frequently the etiologic agent of nosocomial pneumonia, which is the leading cause of death (mortality rate, up to 50%) among hospitalized patients with infections [1, 2]. Infection with *P. aeruginosa* is of greatest concern for patients who are critically ill and immunocompromised (e.g., patients with cystic fibrosis, cancer, or disrupted anatomical barriers); it rarely causes serious infections in otherwise healthy persons and is infrequently identified as normal microbial flora in healthy individuals [1, 2]. Rates of colonization with *P. aeruginosa* increase in hospitalized patients coincident with the length of their hospital stay, especially with their stay in the intensive care unit (ICU), and in patients who have received broad-spectrum antimicrobial therapy or chemotherapy for cancer [1, 2].

Empirical therapy for a patient with a serious infection for which the suspected etiologic agent is *P. aeruginosa* generally consists of an antipseudomonal β-lactam (e.g., carbapenem, ceftazidime, cefepime, piperacillin, or piperacillin-tazobactam) as monotherapy or the combination of an antipseudomonal β-lactam with an aminoglycoside or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin). Antimicrobial resistance among clinical isolates of *P. aeruginosa* may complicate the treatment of infections and can adversely affect clinical outcomes and costs of treating patients [3, 4]. Mul-

Reprints or correspondence: Dr. Mark E. Jones, Focus Bio-Inova, 13665 Dulles Technology Dr., Ste. 200, Herndon, VA 20171-4603 (mjones@focusbioinova.com) or Dr. Alan T. Evangelista, Ortho-McNeil Pharmaceutical, 1000 Rte. 202, Rm. 3046, Raritan, NJ 08869-0602 (aevange2@ompus.jnj.com).

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tidrug-resistant (MDR) isolates are sometimes encountered, further complicating and limiting therapeutic choices. New antimicrobial agents with activity against *P. aeruginosa* will not be available in the near future, making ongoing surveillance of the activities of currently available agents critical. To evaluate the continued effectiveness of available antipseudomonal antimicrobial agents, the current report presents data from the Tracking Resistance in the United States Today (TRUST) surveillance studies of 2001, 2002, and 2003. Specifically, this report describes data on the in vitro activities of commonly tested and prescribed antipseudomonal agents, trends in multidrug resistance among *P. aeruginosa,* the correlation of resistance with isolate and patient demographic parameters, and a comparison of pharmacodynamic (PD) ratios as predictors of successful clinical and microbiological outcomes associated with the use of fluoroquinolones.

MATERIALS AND METHODS

Bacterial isolates studied. From January through May 2001, 514 clinical isolates of *P. aeruginosa* were prospectively collected from 27 hospital laboratories distributed throughout the United States; 3 laboratories in each of the 9 US Bureau of the Census regions participated. Isolates of *P. aeruginosa* were also collected from January through May 2002 ($n = 998$ isolates) and from January through May 2003 ($n = 882$ isolates) from 36 hospital laboratories distributed throughout the United States; in 2002 and 2003, 4 laboratories in each of the 9 US Bureau of the Census regions participated. Sixteen laboratories participated in all 3 years of the study. All isolates of *P. aeruginosa* were deemed to be potential etiologic agents of infection by use of algorithms in place at the participating laboratories. Isolates were limited to 1 per patient, and were accepted regardless of inpatient or outpatient status, specimen source, or patients' demographic parameters. Participating laboratories were asked to submit 25–30 consecutive, nonduplicate isolates of *P. aeruginosa* each year. Isolates were transported to a central laboratory (Focus Bio-Inova; Herndon, VA), where they were subcultured onto blood agar and their identities were confirmed by use of standard clinical laboratory methods [1]. Specimen source, geographic region, and patients' demographic information (i.e., age, sex, and inpatient or outpatient status) were submitted to the central laboratory along with each isolate.

Antimicrobial susceptibility testing. Antimicrobial susceptibility testing was performed in accordance with the recommended procedures of the NCCLS, with the use of freeze-dried broth microdilution panels prepared by TREK Diagnostics [5]. The MICs generated were interpreted as susceptible, intermediate, or resistant by use of NCCLS interpretative criteria [6]. The following antimicrobials were tested in all 3 study years: ceftazidime, ciprofloxacin, levofloxacin, gentamicin, imipenem, and piperacillin-tazobactam. In 2003, cefepime, meropenem, gatifloxacin, and moxifloxacin were added to the MIC testing panel. Slightly different antimicrobial concentration ranges were tested for certain agents in each year of the study.

Multidrug resistance analysis. Multidrug resistance was defined as resistance to $\geqslant 3$ of the following antimicrobial agents: ceftazidime (representative antipseudomonal cephalosporin), gentamicin, imipenem, and a fluoroquinolone (ciprofloxacin or levofloxacin).

Statistical analyses. Statistical analyses were performed by use of χ^2 testing with Epi Info Statcalc software (version 6.0; Centers for Disease Control and Prevention). Uncorrected $P < .05$ was considered to be statistically significant; $P < .001$ was considered to be highly statistically significant.

Analysis of antimicrobial agent combinations. To determine whether gentamicin or a fluoroquinolone could increase the susceptibilities of isolates to antipseudomonal β-lactams when used in combination, cumulative susceptibilities to β-lactams plus gentamicin and to β-lactams plus a fluoroquinolone (ciprofloxacin or levofloxacin) were calculated. Isolates that were susceptible to 1 of the 2 agents in a combination were considered to be susceptible to the combination.

PD parameters. The PD ratios of the area under the serum concentration–time curve (AUC) divided by the MIC are considered to be predictors of successful microbiological and clinical outcomes [7–10]. The PD ratios were calculated for ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin, on the basis of the AUC values from the respective prescribing information for each agent, by use of comparative dosages for the treatment of lower respiratory–tract infections or nosocomial pneumonia [11–14]. For the purpose of comparison of PDs within the fluoroquinolone class, gatifloxacin and moxifloxacin were included in the study, even though these 2 agents do not have Food and Drug Administration (FDA)–approved in vitro or clinical indications for *P. aeruginosa.* The modal MICs (i.e., the most frequently occurring MICs) were obtained from the TRUST surveillance data from 2003, for ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. The AUC values for free drug ($AUC_{0–24h\ free}$) were calculated assuming an approximation of 30% protein binding for ciprofloxacin and levofloxacin, 20% protein binding for gatifloxacin, and 50% protein binding for moxifloxacin, on the basis of their respective prescribing information [11–14]. The $AUC_{0–24h\ free}$ values were used in the present study, since it has been demonstrated that only the free, unbound fraction of the drug is the active moiety [15]; for studies of fluoroquinolones, the PD ratio $AUC_{0–24h\ free}$:MIC best associates with microbiological and clinical efficacy in an animal model [16].

RESULTS

During 2001–2003, the in vitro susceptibilities of all agents tested against *P. aeruginosa* were $\leqslant 87\%$, as shown in table 1.

Table 1. Summary of antimicrobial susceptibility testing results for clinical isolates of *Pseudomonas aeruginosa* collected from hospital microbiology laboratories across the United States, 2001–2003.

Antimicrobial, year[b]	MIC, μg/mL				MIC interpretation, % of isolates[a]		
	Range	Modal	MIC_{50}	MIC_{90}	Susceptible	Intermediate	Resistant
Cefepime, 2003	0.12 to >32	4	4	16	79.5	11.9	8.6
Ceftazidime							
2001	0.25 to >16	2	4	>16	80.5	5.4	14.0
2002	0.25 to >16	2	4	>16	79.7	5.1	15.2
2003	0.25 to >32	2	4	32	80.6	6.5	12.9
Ciprofloxacin							
2001	0.008 to >4	0.12	0.5	>4	66.5	6.6	26.8
2002	0.004 to >4	0.12	0.25	>4	67.4	5.3	27.3
2003	⩽0.002 to >128	0.12	0.25	32	68.8	5.9	25.3
Gatifloxacin, 2003	0.015 to >128	1	2	32	61.2	9.4	29.4
Gentamicin							
2001	⩽0.12 to >8	2	4	>8	75.5	11.1	13.4
2002	⩽0.12 to >8	2	4	>8	76.7	11.7	11.6
2003	⩽0.12 to >8	2	4	>8	72.3	13.7	13.9
Imipenem							
2001	0.06 to >8	1	1	8	84.4	6.8	8.8
2002	⩽0.03 to >8	1	2	>8	81.9	5.3	12.8
2003	0.06 to >8	2	2	>8	78.8	5.2	16.0
Levofloxacin							
2001	0.03 to >8	0.5	1	>8	66.0	7.0	27.0
2002	0.008 to >8	0.5	1	>8	67.7	5.9	26.4
2003	0.008 to >128	0.5	1	32	65.3	7.4	27.3
Meropenem, 2003	0.008 to >16	0.5	0.5	8	85.8	4.4	9.8
Moxifloxacin, 2003	0.03 to >128	2	4	128	…[c]	…	…
Piperacillin-tazobactam							
2001	⩽0.25 to >64	8	8	>64	85.6	…[d]	14.4
2002	⩽0.25 to >64	8	8	>64	85.8	…	14.2
2003	⩽0.25 to >64	8	8	>64	87.0	…	13.0

NOTE. Modal MIC, most frequently occurring MIC.

[a] MICs were interpreted, by use of NCCLS break points, as susceptible, intermediate, and resistant [5].

[b] There were 514 isolates from 2001, 998 isolates from 2002, and 882 isolates from 2003. Cefepime, gatifloxacin, meropenem, and moxifloxacin were tested in 2003. The concentration ranges used in testing varied slightly from year to year for some antimicrobial agents.

[c] NCCLS MIC interpretative break points are not defined for moxifloxacin tested against *P. aeruginosa* and other non-*Enterobacteriaceae* species [5].

[d] NCCLS intermediate MIC interpretative break points are not defined for piperacillin-tazobactam tested against *P. aeruginosa* and other non-*Enterobacteriaceae* species [5].

The cumulative percentages of these isolates that were susceptible were as follows: 86% were susceptible to piperacillin-tazobactam, 80% were susceptible to ceftazidime, 68% were susceptible to ciprofloxacin, and 67% were susceptible to levofloxacin. From 2001 to 2003, the percentage of susceptibility to these 4 antimicrobial agents either did not decrease or decreased by <1.5%. In contrast, from 2001 to 2003, the susceptibility of *P. aeruginosa* isolates to gentamicin decreased by 3.2% (from 75.5% to 72.3%), and that to imipenem decreased by 5.6% (from 84.4% to 78.8%). Meropenem and piperacillin-tazobactam were the most active compounds tested, followed by cefepime, ceftazidime, and imipenem. Ciprofloxacin and levofloxacin, although slightly less active, were more active than gatifloxacin, which was more active than moxifloxacin. The test results from 2003 showed that levofloxacin (modal MIC, 0.5 μg/mL; MIC_{50}, 1 μg/mL) was 2-fold more active than gatifloxacin (modal MIC, 1 μg/mL; MIC_{50}, 2 μg/mL) and 4-fold more active than moxifloxacin (modal MIC, 2 μg/mL; MIC_{50}, 4 μg/mL), whereas ciprofloxacin (modal MIC, 0.12 μg/mL; MIC_{50}, 0.25 μg/mL) was 4-fold more active than levofloxacin. Modal MICs of antimicrobial agents tested against P. aeruginosa were lowest for ciprofloxacin (0.12 μg/mL), levofloxacin (0.5 μg/mL), and meropenem (0.5 μg/mL) and were highest for piperacillin-tazobactam (8 μg/mL) and cefepime (4 μg/mL).

Table 2 depicts relative associations between resistance to a representative antipseudomonal cephalosporin (ceftazidime), a carbapenem (imipenem), an aminoglycoside (gentamicin), and a fluoroquinolone (levofloxacin). Significant differences ($P < .05$) in the percentages of resistant isolates were observed according to the age of the patient (for imipenem, gentamicin, and levofloxacin), the sex of the patient (for ceftazidime and levofloxacin), specimen source (for ceftazidime, imipenem, gentamicin, and levofloxacin), the inpatient or outpatient status of the patient (for ceftazidime, imipenem, and gentamicin), and US geographic region (for ceftazidime, imipenem, gentamicin, and levofloxacin). Resistance to each of the 4 agents was higher among patients aged 18–64 years than among older or younger patients, among inpatients than among outpatients, and among isolates from patients in the East North Central and Mid-Atlantic regions than among the other 7 regions.

Of the 2394 *P. aeruginosa* isolates studied from 2001 to 2003, 50.5% were pansusceptible to ceftazidime, imipenem, gentamicin, and a fluoroquinolone (ciprofloxacin or levofloxacin), as indicated in table 3. MDR isolates accounted for 8.9% ($n = 212$) of the 2394 isolates. Most MDR isolates ($n = 149$ [70.3%]) were resistant to 3 antimicrobial classes and accounted for 6.2% of all isolates. Isolates were also identified that were resistant to 4 antimicrobial classes ($n = 63$ [29.7% of MDR isolates; 2.6%

Table 2. Relative associations between 2394 isolates of *Pseudomonas aeruginosa* resistant to 4 antimicrobial agents and the risk factors of age, sex, and hospitalization status of the patient, source of the isolate specimen, and US geographic region (cumulative data, 2001–2003).

		Ceftazidime		Imipenem		Gentamicin		Levofloxacin	
Risk factor	No. of isolates	No. (%) of resistant isolates	P[a]	No. (%) of resistant isolates	P	No. (%) of resistant isolates	P	No. (%) of resistant isolates	P
Any	2394	338 (14.1)	…	314 (13.1)	…	308 (12.9)	…	643 (26.9)	…
Age of patient[b]									
<18 years	196	23 (11.7)	.2	14 (7.1)	.001	14 (7.1)	.002	11 (5.6)	<.0001
18–64 years	1133	178 (15.7)	…	187 (16.5)	…	176 (15.5)	…	334 (29.5)	…
>64 years	1023	130 (12.7)	.05	111 (10.9)	.0002	116 (11.3)	.005	293 (28.6)	.7
Sex of patient[c]									
Female	1026	126 (12.3)	…	123 (12.0)	…	133 (13.0)	…	250 (24.4)	…
Male	1353	209 (15.4)	.03	190 (14.0)	.1	174 (12.9)	.94	390 (28.8)	.02
Specimen source[d]									
Respiratory tract[e]	959	169 (17.6)	…	163 (17.0)	…	149 (15.5)	…	254 (26.5)	…
Urine	725	81 (11.2)	.0002	81 (11.2)	.0008	91 (12.6)	.08	236 (32.6)	.007
Skin and soft tissue	548	67 (12.2)	.006	53 (9.7)	<.0001	47 (8.6)	.0001	117 (21.4)	.03
Hospitalization status of patient[f]									
Inpatient[g]	1558	239 (15.3)	…	234 (15.0)	…	222 (14.2)	…	440 (28.2)	…
Outpatient	817	94 (11.5)	.01	79 (9.7)	.0003	84 (10.3)	.006	200 (24.5)	.05
US geographic region[h]									
East North Central	275	53 (19.3)	.07	60 (21.8)	.0005	54 (19.6)	.01	100 (36.4)	.004
East South Central	281	28 (10.0)	.2	25 (8.9)	.5	23 (8.2)	.2	55 (19.6)	.2
Mid-Atlantic	292	63 (21.6)	.01	67 (22.9)	.0001	57 (19.5)	.01	126 (43.2)	<.0001
Mountain	267	39 (14.6)	.7	32 (12.0)	.6	41 (15.4)	.2	73 (27.3)	.5
New England	229	15 (6.6)	.01	23 (10.0)	.8	20 (8.7)	.3	48 (21.0)	.3
Pacific	262	44 (16.8)	.3	28 (10.7)	…	36 (13.7)	.5	63 (24.0)	.9
South Atlantic	255	34 (13.3)	…	24 (9.4)	.6	30 (11.8)	…	63 (24.7)	…
West North Central	268	27 (10.1)	.3	29 (10.8)	.96	17 (6.3)	.03	43 (16.0)	.01
West South Central	265	35 (13.2)	.97	26 (9.8)	.7	30 (11.3)	.9	72 (27.2)	.5

[a] $P < .05$ was considered to be statistically significant.
[b] Isolates from the 18–64 year age group were compared with those from patients in the <18 year and >64 year age groups. The patient's age was not known for 42 isolates.
[c] Isolates from female patients were compared with those from male patients. The patient's sex was not known for 15 isolates.
[d] Data for isolates from blood ($n = 84$), other sources ($n = 53$), and unknown specimen sources ($n = 25$) were not included in this analysis.
[e] Respiratory-tract isolates were compared with those recovered from urine and skin and soft tissue.
[f] The patient's hospitalization status was not known for 19 isolates.
[g] Isolates from inpatients were compared with those from outpatients.
[h] Isolates from the regions with the median rates of resistance to each of the 4 antimicrobial agents were compared with those from other regions: South Atlantic (ceftazidime, gentamicin, and levofloxacin) and Pacific (imipenem).

Table 3. Antimicrobial resistance phenotypes of 212 multidrug-resistant (MDR) *Pseudomonas aeruginosa* isolates (cumulative data, 2001–2003).

Antimicrobial resistance phenotype	No. of isolates	MDR isolates, %	Total isolate, %[a]
Ceftazidime, imipenem, gentamicin, and fluoroquinolone[b]	63	29.7	2.6
Ceftazidime, gentamicin, and fluoroquinolone	53	25.0	2.2
Ceftazidime, imipenem, and fluoroquinolone	49	23.1	2.0
Imipenem, gentamicin, and fluoroquinolone	38	17.9	1.6
Ceftazidime, imipenem, and gentamicin	9	4.2	0.4

[a] Of the 2394 *P. aeruginosa* isolates, 8.9% ($n = 212$) were MDR.
[b] Fluoroquinolones include ciprofloxacin and levofloxacin.

of all isolates]). The most common multidrug resistance phenotype was concurrent resistance to ceftazidime, imipenem, gentamicin, and a fluoroquinolone (ciprofloxacin or levofloxacin), and it accounted for 29.7% of MDR isolates (table 3); other multidrug resistance phenotypes were also common (resistance to ceftazidime, gentamicin, and a fluoroquinolone; resistance to ceftazidime, imipenem, and a fluoroquinolone; and resistance to imipenem, gentamicin, and a fluoroquinolone).

From 2001 to 2003, the percentages of *P. aeruginosa* isolates collected that were pansusceptible to ceftazidime, imipenem, gentamicin, and levofloxacin were constant (range, 49.1%–51.8% of isolates/year) (figure 1). The percentage of isolates that were single-drug resistant (SDR) decreased from 22.8% in 2001 to 18.4% in 2003, and the percentage of isolates that were MDR increased from 7.2% in 2001 to 9.9% in 2003. Pansusceptible isolates were significantly ($P < .05$) more common among patients <18 years old than among older patients; among male patients than among female patients; among urine and skin and soft-tissue isolates than among respiratory-tract isolates; among outpatients than among inpatients; and among isolates from patients in the West North Central region than among isolates from patients in the other 7 regions (table 4). Significantly lower rates of pansusceptibility among isolates from patients in the East North Central and Mid-Atlantic regions were also observed. SDR isolates were significantly more common among male patients than among female patients and were significantly less common among skin and soft tissue isolates than among respiratory-tract or urine isolates. MDR isolates were significantly more common among patients 18–64 years old than among younger and older patients and among patients in the East North Central and Mid-Atlantic regions than among patients in the other 7 regions. Significantly lower rates of multidrug resistance were observed in isolates from skin and soft tissue, those from outpatients, and those from patients in the Pacific region.

Table 5 depicts the potential effect of combination therapy (β-lactams plus gentamicin or β-lactams plus a fluoroquinolone) on *P. aeruginosa* infections. All combinations improved the percentage of isolates susceptible to cefepime, ceftazidime, imipenem, or piperacillin-tazobactam alone (range, 3.4%–9.2% increase in susceptibility). Ciprofloxacin and levofloxacin provided very similar improvements in susceptibility when combined with an antipseudomonal β-lactam, whereas the highest increases in susceptibility were seen in association with the addition of gentamicin.

PD studies have previously demonstrated that a target AUC:MIC ratio of >125 is optimal for bactericidal activity and a successful clinical outcome for *P. aeruginosa* infection [7–10]. For ciprofloxacin and levofloxacin, achievement of target PD ratios against *P. aeruginosa* (AUC:MIC, >125) was examined on the basis of comparative dosing recommendations for the treatment of lower respiratory–tract infections and nosocomial pneumonia (table 6). The modal MICs (i.e., the most common MICs) obtained from the TRUST 2001–2003 studies were lower for ciprofloxacin (0.125 μg/mL) than for levofloxacin (0.5 μg/mL). When we compared the pharmacokinetic parameters that are given in the respective prescribing information for each antimicrobial agent, levofloxacin (750 mg q.d. iv) had a 3-fold higher maximum serum concentration (C_{max}) and a 3-fold higher AUC (total and free) than did ciprofloxacin (400 mg q8h iv). The resulting $AUC_{0-24h\,free}$:modal MIC ratios were sim-

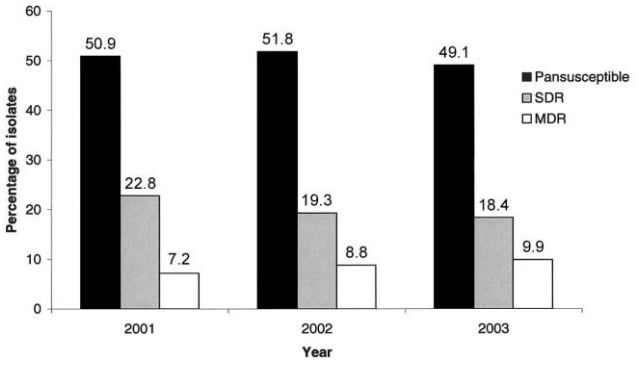

Figure 1. Prevalence of pansusceptibility, single-drug resistance (SDR), and multidrug resistance (MDR) phenotypes among clinical isolates of *Pseudomonas aeruginosa* collected from across the United States during 2001–2003.

Table 4. Prevalence of single-drug–resistant (SDR) and multidrug-resistant (MDR) clinical isolates of *Pseudomonas aeruginosa* and the relative associations between resistance phenotype and the risk factors of age, sex, and hospitalization status of the patient, source of the isolate specimen, and US geographic region (cumulative data, 2001–2003).

Risk factor	No. of isolates	Isolates susceptible to all agents tested[a]		SDR[b] isolates		MDR[c] isolates	
		No. (%)	*P*[d]	No. (%)	*P*	No. (%)	*P*
Any	2394	1210 (50.5)	…	472 (19.7)	…	212 (8.9)	…
Age of patient[e]							
<18 years	196	129 (65.8)	<.0001	29 (14.8)	.07	4 (2.0)	<.0001
18–64 years	1133	539 (47.6)	…	231 (20.4)	…	134 (11.8)	…
>64 years	1023	514 (50.2)	.2	207 (20.2)	.93	72 (7.0)	.0002
Sex of patient[f]							
Female	1026	491 (47.9)	…	170 (16.6)	…	85 (8.3)	…
Male	1353	728 (53.8)	.004	301 (22.2)	.0006	126 (9.3)	.4
Specimen source[g]							
Respiratory tract[h]	959	440 (45.9)	…	205 (21.4)	…	101 (10.5)	…
Urine	725	375 (51.7)	.003	146 (20.1)	.5	63 (8.7)	.2
Skin and Soft Tissue	548	314 (57.3)	<.0001	91 (16.6)	.03	36 (6.6)	.01
Hospitalization status of patient[i]							
Inpatient[j]	1558	756 (48.5)	…	312 (20.0)	…	153 (9.8)	…
Outpatient	817	445 (54.5)	.006	156 (19.1)	.6	58 (7.1)	.03
US geographic region[k]							
East North Central	275	112 (40.7)	.01	48 (17.5)	.5	36 (13.1)	.04
East South Central	281	144 (51.2)	…	57 (20.3)	.9	14 (5.0)	.2
Mid-Atlantic	292	121 (41.4)	.02	48 (16.4)	.3	58 (19.9)	<.0001
Mountain	267	131 (49.1)	.6	59 (22.1)	.5	29 (10.9)	.2
New England	229	128 (55.9)	.3	40 (17.5)	.5	9 (3.9)	.08
Pacific	262	136 (51.9)	.9	51 (19.5)	.96	20 (7.6)	…
South Atlantic	255	125 (49.0)	.6	62 (24.3)	.2	12 (4.7)	.2
West North Central	268	165 (61.6)	.02	55 (20.5)	.8	12 (4.5)	.1
West South Central	265	148 (55.8)	.3	52 (19.6)	…	22 (8.3)	.8

[a] The agents tested were ceftazidime, imipenem, gentamicin, and levofloxacin.
[b] Single-drug resistance (SDR) is defined as resistance to only 1 of the following agents: ceftazidime, imipenem, gentamicin, or a fluoroquinolone (i.e., ciprofloxacin or levofloxacin).
[c] Multidrug resistance (MDR) is defined as resistance to ⩾3 of the following agents: ceftazidime, imipenem, gentamicin, or fluoroquinolone.
[d] $P < .05$ was considered to be statistically significant.
[e] Isolates from the 18–64 year age group were compared with those from patients in the <18 year and >64 year age groups. The patient's age was not know for 42 isolates.
[f] Isolates from female patients were compared with those from male patients. The patient's sex was not known for 15 isolates.
[g] Data for isolates from blood ($n = 84$), other sources ($n = 53$), and unknown specimen sources ($n = 25$) were not included in this analysis.
[h] Respiratory-tract isolates were compared with those from urine and skin and soft tissue.
[i] The patient's hospitalization status was not known for 19 isolates.
[j] Isolates from inpatients were compared with those from outpatients.
[k] Isolates from the regions with the median rates of pansusceptibility (East South Central), SDR (West South Central), and MDR (Pacific) were compared with those from other regions.

ilar and were greater than the target ratio of 125 for both ciprofloxacin and levofloxacin, whereas the PD ratios were considerably lower than the target ratio for gatifloxacin and moxifloxacin (28 and 10, respectively) (table 6).

DISCUSSION

The potential for antimicrobial resistance is an important concern for clinicians treating patients with confirmed or suspected *P. aeruginosa* infections. In the present study, from 2001 to 2003, the percentages of isolates susceptible to piperacillin-tazobactam (86%), ceftazidime (80%), ciprofloxacin (68%), and levofloxacin (66%) either did not decrease or decreased by <1.5%. However, during the same period, susceptibility of isolates to gentamicin decreased by 3.2% (from 75.5% to 72.3%), and that to imipenem decreased by 5.6% (from 84.4% to 78.8%). Surveillance studies of *P. aeruginosa* infection in the

Table 5. In vitro susceptibilities of *Pseudomonas aeruginosa* to individual antimicrobial agents and to antimicrobial agent combinations of a β-lactam (ceftazidime, cefepime, imipenem, or piperacillin-tazobactam) plus gentamicin or a fluoroquinolone, 2003.

Antimicrobial agent(s)[a]	Susceptible isolates, %[b,c]	Change in percentage of susceptible isolates[d]
Cefepime	79.5	…
Plus gentamicin	86.4	+6.9
Plus ciprofloxacin	85.0	+5.5
Plus levofloxacin	83.6	+4.1
Ceftazidime	80.6	
Plus gentamicin	89.4	+8.8
Plus ciprofloxacin	87.3	+6.7
Plus levofloxacin	86.8	+6.2
Imipenem	78.8	
Plus gentamicin	89.9	+11.1
Plus ciprofloxacin	86.9	+8.1
Plus levofloxacin	86.8	+8.0
Piperacillin-tazobactam	87.0	
Plus gentamicin	91.0	+4.0
Plus ciprofloxacin	89.8	+2.8
Plus levofloxacin	89.6	+2.6

NOTE. MICs were interpreted, by use of NCCLS break points, as susceptible, intermediate, or resistant [6].

[a] A total of 2394 isolates were tested against ceftazidime, ciprofloxacin, gentamicin, imipenem, levofloxacin and piperacillin-tazobactam; 882 isolates were tested against cefepime (tested in 2003 only).

[b] Percentage of isolates susceptible to at least 1 antimicrobial agent in the combination.

[c] In 2003, the percentages of isolates susceptible to gentamicin, ciprofloxacin, and levofloxacin were 72.3%, 68.8%, and 65.3%, respectively.

[d] Change in the percentage of isolates susceptible to the antimicrobial agent combination vs. the single agent alone.

United States, conducted across 2 or 3 consecutive years (1997–1999 and 1999–2000) and involving a consistent set of institutions, have generally shown no change or only minor decreases in susceptibilities to aminoglycosides, β-lactams, and fluoroquinolones over time [17–20]. When intervals >3 years are considered, the in vitro susceptibility of clinical isolates of *P. aeruginosa* to aminoglycosides, β-lactams, and fluoroquinolones appears to be decreasing in the United States [17–23]. The reasons for decreasing in vitro susceptibilities may include the nosocomial spread of MDR isolates due to the lack of adherence to approved infection-control policies in hospitals, increasing or cumulative antimicrobial use, and changes to the public health infrastructure [17, 20, 24–26]. Suggestions that susceptibility to fluoroquinolones appears to be decreasing at a faster rate than is susceptibility to other antimicrobial classes are not supported by the current data set (table 1) or by previous studies [17–20].

TRUST data show that the rates of susceptibility of *P. aeruginosa* to fluoroquinolones (ciprofloxacin and levofloxacin) have remained stable (in the mid-60% range) for 2001, 2002, and 2003 (table 1). The rates of susceptibility of *P. aeruginosa* to levofloxacin (66.0% in 2001; 67.7% in 2002; and 65.3% in 2003) and ciprofloxacin (66.5% in 2001; 67.4% in 2002; and 68.8% in 2003) were similar and were greater than the rate of susceptibility to gatifloxacin (61.2% in 2003). When we compared MIC_{90} values, we found that ciprofloxacin and levofloxacin (MIC_{90} for both agents, 32 μg/mL) were 4-fold more active than moxifloxacin (MIC_{90}, 128 μg/mL). It is important to note that gatifloxacin and moxifloxacin do not have FDA-approved clinical or in vitro indications for *P. aeruginosa.* Moreover, the use of gatifloxacin and moxifloxacin for susceptibility testing and reporting against *P. aeruginosa* is not recommended by the NCCLS [6]. In the present study, the percentage of isolates susceptible to levofloxacin and ciprofloxacin was similar, confirming data published elsewhere [17–20, 27, 28]. In the present study, modal MICs (the MICs most frequently encountered in clinical laboratories) were lowest for ciprofloxacin (0.125 μg/mL), levofloxacin (0.5 μg/mL), and meropenem (0.5 μg/mL), and they were highest for cefepime (4 μg/mL) and piperacillin-tazobactam (8 μg/mL). However, the efficacy and potency of antimicrobial agents, especially fluoroquinolones, should not be limited to comparisons of MICs alone but should also include comparisons of PD parameters (e.g., the AUC:MIC ratio) as predictors of patients' outcomes and the potential for emergence of resistance [29]. A comparison of fluoroquinolone AUC:MIC ratios with regard to *P. aeruginosa* will be addressed later in this section.

When either levofloxacin or ciprofloxacin is used to treat a patient with nosocomial pneumonia that is suspected or documented to be due to *P. aeruginosa,* the addition of an antipseudomonal β-lactam is recommended [14, 20]. The addition of levofloxacin, ciprofloxacin, or gentamicin in combination with an antipseudomonal β-lactam yielded higher susceptibilities against *P. aeruginosa* than did an antipseudomonal β-lactam alone (table 5). In vitro susceptibilities of *P. aeruginosa* isolates to the combination of either a β-lactam and gentamicin or a β-lactam and a fluoroquinolone were similar, generally differing by <3%. Ciprofloxacin and levofloxacin provided very similar improvements in susceptibility when combined with an antipseudomonal β-lactam (table 5). The β-lactam susceptibilities improved by 2.8%–8.1% with the addition of ciprofloxacin, by 2.6%–8.0% with the addition of levofloxacin, and by 4.0%–11.1% with the addition of gentamicin (table 5). The clinical significance of these differences is unknown.

Multidrug resistance phenotypes are slowly increasing in prevalence among *P. aeruginosa* isolates (figure 1) [30–33]; however, comparison between studies is often difficult, because definitions of multidrug resistance have not been uniform [17, 19, 31, 32]. It is important to document and track MDR isolates

Table 6. Similar pharmacodynamic ratios (area under the serum concentration–time curve [AUC]:MIC, >125) for the use of ciprofloxacin and levofloxacin against *Pseudomonas aeruginosa*.

Antimicrobial agent (iv dose at steady state)	Modal MIC, μg/mL[a]	C_{max}, μg/mL[b]	$AUC_{0-24h\ total}/AUC_{0-24h\ free}$, $\mu g \times h/mL$[b,c]	$AUC_{0-24h\ free}$: modal MIC
Ciprofloxacin (400 mg q12h)	0.125	4.1	25/18	144
Ciprofloxacin (400 mg q8h)	0.125	4.1	33/23	184
Levofloxacin (750 mg q24h)	0.5	12.1	108/76	152
Gatifloxacin (400 mg q24h)[d]	1	4.6	35/28	28
Moxifloxacin (400 mg q24h)[d]	2	4.2	38/19	10

NOTE. $AUC_{0-24\ free}$, area under the serum concentration–time curve values for free drug; C_{max}, maximum peak serum level; modal MIC, the most frequently occurring MIC; TRUST, Tracking Resistance in the United States Today.

[a] Modal MICs from TRUST 2001–2003 data from *P. aeruginosa* clinical isolates.

[b] C_{max} and AUC values were obtained from prescribing information for ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin.

[c] $AUC_{0-24h\ free}$ values were based on 30% protein binding for ciprofloxacin and levofloxacin, 20% protein binding for gatifloxacin, and 50% protein binding for moxifloxacin.

[d] Gatifloxacin and moxifloxacin do not have Food and Drug Administration–approved in vitro or clinical indications for *P. aeruginosa*.

because of their potential to be selected and spread by the use of any one of a number of agents; the use of one agent can increase resistance to all other agents included in a multidrug resistance phenotype. Outbreaks of infection due to MDR *P. aeruginosa,* both inside and outside ICUs, are an increasingly reported problem in hospitals [24, 34]. Data in the present study suggest that recent increases in MDR isolates were due to increases in resistance to imipenem and gentamicin; resistance to fluoroquinolones and resistance to ceftazidime were unchanged from 2001 to 2003. The slow emergence of MDR isolates appears to be the result of decreases in the percentages of SDR isolates, because the percentages of pansusceptible isolates were unchanged from 2001 to 2003 (figure 1). In addition, MDR isolates were not uniformly distributed among patients (table 4). They were significantly more common among patients 18–64 years old than among younger and older patients and among isolates from patients in the East North Central and Mid-Atlantic regions than among isolates from patients in the other 7 regions. Significantly lower rates of multidrug resistance were observed in isolates recovered from skin and soft tissue, from outpatients, and from patients in the Pacific region.

During the past several years, PD parameters, such as the AUC:MIC ratio, have been identified as predictive of the performance of fluoroquinolones against a variety of pathogens. Studies have demonstrated that, for fluoroquinolones, a target AUC:MIC ratio of >125 was optimal for microbiological eradication, successful clinical outcome, and reduced emergence of resistance to *P. aeruginosa* [7–10]. For ciprofloxacin and levofloxacin, achievement of target PD ratios (AUC:MIC, >125) against *P. aeruginosa* was examined on the basis of comparative dosing recommendations for the treatment of lower respiratory–tract infections and nosocomial pneumonia (table 6). Whether an individual MIC is studied or a population of MICs is studied as an MIC_{90}, the AUC:MIC ratio is clinically predictive for fluoroquinolones [9]. The MIC_{90} values from the TRUST 2001–2003 studies were 32 μg/mL for ciprofloxacin, levofloxacin, and gatifloxacin and 128 μg/mL for moxifloxacin. The use of MIC_{90} values for the determination of PD ratios would result in very low PD ratios for all fluoroquinolones, with ciprofloxacin, gatifloxacin, and moxifloxacin having AUC:MIC ratios of <1, and with levofloxacin having an AUC:MIC ratio of 2, thereby preventing comparison among the fluoroquinolones. In contrast, the modal MICs were 0.125 μg/mL for ciprofloxacin, 0.5 μg/mL for levofloxacin, 1 μg/mL for gatifloxacin, and 2 μg/mL for moxifloxacin. Thus, in the present study, the modal MIC served as a better value for differentiating the fluoroquinolones.

As a predictor of both clinical and microbiological outcomes and the emergence of resistance, the AUC:MIC ratio also incorporates the pharmacokinetic parameter the AUC of the dosing regimen. In comparing the PD ratios of ciprofloxacin and levofloxacin, the lower modal MIC of ciprofloxacin was offset by the 3-fold higher AUC value of levofloxacin. The resulting PD ratios of $AUC_{0-24h\ free}$:modal MIC were similar and were greater than the target ratio of 125 for both ciprofloxacin and levofloxacin, whereas the PD ratios were considerably lower for gatifloxacin and moxifloxacin (28 and 10, respectively) (table 6). In a recent report of a Monte Carlo simulation involving 10,000 subjects, the target percentage of attainment of an AUC:MIC ratio of 157 against *P. aeruginosa* was similar for levofloxacin and ciprofloxacin, when comparable dosages for nosocomial pneumonia were used [35]. The report also stated that, among all the currently available fluoroquinolones, only levofloxacin and ciprofloxacin would attain this target ratio at approved doses [35]. The potential for suboptimal coverage of *P. aeruginosa* by moxifloxacin was recently detailed in a report

from the Mayo Clinic describing breakthrough *P. aeruginosa* bacteremia in patients treated with moxifloxacin, among isolates that were susceptible to ciprofloxacin and levofloxacin [36]. Although there are no current publications detailing breakthrough bacteremia due to gatifloxacin, the low PD ratios of gatifloxacin against *P. aeruginosa* would predict that gatifloxacin has a greater potential for breakthrough bacteremia than does ciprofloxacin or levofloxacin. Another implication of the PD ratios presented in the present study would be that the use of gatifloxacin and moxifloxacin for the treatment of *P. aeruginosa* infections could select for the emergence of increased resistance of *P. aeruginosa* to fluoroquinolones. Currently, neither gatifloxacin nor moxifloxacin has in vitro or clinical FDA-approved indications for *P. aeruginosa*.

The potential for the emergence of resistance to fluoroquinolones also has been reported for the more-active fluoroquinolone agents (ciprofloxacin and levofloxacin) against *P. aeruginosa.* In a study of in vitro resistance selection by Gillespie and Masterton [37], ciprofloxacin more readily selected resistant mutants, at concentrations of 1, 2, 4, and 8 times the MIC for 7 nonmucoid clinical isolates of *P. aeruginosa* (28/28 mutants selected), than did levofloxacin (11/28 mutants selected). The authors of that study concluded that levofloxacin was less likely than ciprofloxacin to allow the emergence of resistant mutants, even in isolates for which the original MIC of levofloxacin was twice that of ciprofloxacin. Additional data regarding trends in *P. aeruginosa* resistance, which were reported by Rapp et al. [38], showed that, with appropriate infection-control measures in place at baseline, the increased use of levofloxacin and the corresponding decrease in use of and exposure to ciprofloxacin in 2000 correlated with improved susceptibility to fluoroquinolones, which continued through 2001, when levofloxacin replaced ciprofloxacin as the sole fluoroquinolone used.

In conclusion, the susceptibility of clinical isolates of *P. aeruginosa* to piperacillin-tazobactam, ceftazidime, and fluoroquinolones (ciprofloxacin and levofloxacin) remained stable from 2001 to 2003 in the United States. Previously reported decreases in the susceptibilities of *P. aeruginosa* to ciprofloxacin and levofloxacin appear to have stabilized at a mean ($\pm$SD) percentage of 66% $\pm$ 1% during this 3-year period. Isolates of *P. aeruginosa* with multidrug resistance phenotypes are slowly becoming increasingly prevalent at the expense of a decrease in the prevalence of isolates with single-drug resistance phenotypes. Appreciable decreases in the percentages of pansusceptible isolates of *P. aeruginosa* were not observed from 2001 to 2003 in the United States. Given that new antimicrobial agents with activity against *P. aeruginosa* will not be available in the near future, ongoing surveillance of the activities of currently available agents is critical. The ongoing surveillance is also critical for monitoring potential increased resistance of *P. aeruginosa* to fluoroquinolones resulting from the use of agents such as gatifloxacin and moxifloxacin, which have considerably lower PD AUC:MIC ratios than do ciprofloxacin or levofloxacin.

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