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Factors Associated with Relative Rates of Antibiotic Resistance in *Pseudomonas aeruginosa* Isolates Tested in Clinical Laboratories in the United States from 1999 to 2002

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For the period from 1999 to 2002 in the United States, the in vitro susceptibilities of 52,637 *Pseudomonas aeruginosa* isolates to 10 antimicrobial agents were evaluated. The isolates were from 29 laboratories, 11 of which participated in The Surveillance Network for four consecutive years. Isolates were collected from adult patients (≥18 years of age) in intensive care units (ICU), non-ICU inpatients, nursing home patients, and outpatients; data were analyzed to evaluate factors, such as year of isolation, patient age group, isolate specimen source, and patient type (hospitalized patients [ICU, non-ICU, or nursing home] or outpatients). Rates of resistance for the 4-year period were highest for isolates from patients in ICU and 18- to 39-year-old patients and for isolates from the lower respiratory tract. Resistance decreased with age. Resistance was lowest in isolates from outpatients, in isolates from ≥70-year-old patients, and from specimens from the upper respiratory tract. Multidrug resistance (MDR) (resistance to three or more antimicrobial agents) accounted for 24.9% of all isolates. The MDR rate was highest in isolates from patients in nursing homes (29.9%) and ICU (29.5%).

Infection with *Pseudomonas aeruginosa* is a serious problem affecting hospitalized patients, particularly those who are critically ill and immunocompromised, such as patients with cystic fibrosis, neutropenia, iatrogenic immunosuppression, or disrupted anatomical barriers (3, 8). *P. aeruginosa* only occasionally causes serious infections in otherwise healthy persons and is infrequently identified as normal microbial flora in healthy individuals (8). Rates of colonization with *P. aeruginosa* increase in hospitalized patients, particularly in those who have been hospitalized for extended periods of time and/or have received broad-spectrum antimicrobial therapy or cancer chemotherapy. These increasing resistance rates have greatly limited the number of therapeutic choices (9, 10, 11).

P. aeruginosa is a common human saprophyte that is able to adapt to a multitude of physical and nutritional environments and survive in large numbers in close proximity to its host. For these reasons, it is found in a broad range of infections. Infections caused by *P. aeruginosa* range from superficial skin infections to more serious infections, such as meningitis, endocarditis, and osteomyelitis, to fulminant sepsis (15). Antimicrobial resistance among clinical isolates of *P. aeruginosa* may complicate the treatment of infections and can adversely affect clinical outcomes and patient treatment costs (1, 5). 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 of critical importance.

Although several surveillance studies have reported on the relative in vitro activities of various antimicrobial agents (4, 6, 7, 13, 16), an extensive comparative statistical analysis of resistance to antimicrobial agents relative to factors associated with resistance has not been performed. Such analysis is important to more completely elucidate the status of antimicrobial resistance among *P. aeruginosa* isolates and to attempt to understand and predict the direction and chronology of future resistance trends. In this study, data from the The Surveillance Network (TSN) Database-USA from 1999 to 2002 were analyzed to evaluate the activities of several antipseudomonal agents based on factors, such as year of isolation, patient age group, isolate specimen source, and patient type.

MATERIALS AND METHODS

TSN Database-USA (Focus Technologies, Herndon, Va.) was used as the source of antimicrobial susceptibility testing results for this study. TSN electronically assimilates antimicrobial susceptibility testing and patient demographic data from a network of hospitals in the United States (17). Laboratories are included in TSN on the basis of factors, such as the number of beds in the hospital, patient population, geographic location, and antimicrobial susceptibility testing methods used (17). Susceptibility testing of patient isolates is conducted on-site by each participating laboratory as a part of their routine diagnostic testing. Only data generated using Food and Drug Administration-approved testing methods with MIC results interpreted according to National Committee for Clinical Laboratory Standards (NCCLS) recommendations (12) are included in TSN. To guarantee the integrity of the data, a series of proprietary quality control filters (i.e., critical rule sets) are used to screen susceptibility test results for patterns indicative of testing errors; suspect results are removed from the analyzable data set until they are confirmed by the reporting laboratory.

The isolates of *P. aeruginosa* collected from adult patients (≥18 years of age) included in the current analysis (n = 52,637) were concurrently tested against amikacin, cefepime, ceftazidime, ciprofloxacin, gentamicin, imipenem, piperacillin, piperacillin-tazobactam, ticarcillin-clavulanate, and tobramycin. The isolate results were from 29 U.S. laboratories, 11 of which participated in TSN for the four consecutive years of this analysis and were collected from 1999 to 2002. Isolate results were from intensive care unit (ICU) patients, non-ICU inpatients, outpatients, and nursing home patients. Laboratories were included in the study if a total of 100 or more isolates were tested over the 4-year period. Isolates were

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TABLE 1. In vitro susceptibilities to 10 antimicrobial agents for clinical isolates of *P. aeruginosa* collected from 1999 to 2002[a]

Antimicrobial agent(s)	Yr	% Susceptible					% Intermediate					% Resistant				
		Non-ICU	ICU	NH	OP	Combined	Non-ICU	ICU	NH	OP	Combined	Non-ICU	ICU	NH	OP	Combined
Amikacin	1999	86.0	91.3	93.4	88.6	87.7	3.9	4.8	5.3	4.3	4.1	10.1	3.9	1.3	7.1	8.2
	2000	88.9	87.9	92.3	83.8	86.8	4.6	7.0	3.1	6.6	5.7	6.4	5.1	4.6	9.6	7.5
	2001	91.8	89.5	95.2	82.1	88.7	3.8	3.4	3.1	5.8	4.3	4.4	7.2	1.7	12.1	6.9
	2002	92.1	89.6	93.0	88.5	90.8	3.4	4.5	4.8	4.5	4.0	4.5	5.9	2.2	7.0	5.2
	1999–2002	90.6	89.4	94.0	85.4	89.0	3.8	4.8	4.0	5.4	4.4	5.5	5.7	2.0	9.2	6.6
Cefepime	1999	75.6	79.5	81.6	82.7	78.4	13.3	13.5	17.1	11.7	12.9	11.1	7.0	1.3	5.6	8.8
	2000	75.3	66.9	76.9	78.5	75.3	13.1	17.3	15.4	12.4	13.5	11.6	15.7	7.7	9.1	11.2
	2001	77.3	73.4	73.1	78.8	77.0	13.5	14.9	19.3	12.6	13.8	9.2	11.7	7.6	8.6	9.2
	2002	75.7	64.2	72.9	83.4	76.4	14.9	19.0	18.4	10.6	14.3	9.4	16.8	8.7	6.0	9.2
	1999–2002	76.1	69.6	73.3	80.7	76.6	13.9	16.7	18.7	11.8	13.8	10.0	13.7	7.9	7.5	9.5
Ceftazidime	1999	77.9	83.2	92.1	86.9	81.5	5.2	4.5	3.9	4.7	4.9	17.0	12.4	3.9	8.4	13.6
	2000	76.9	72.9	84.6	86.1	79.9	7.7	8.1	3.1	4.7	6.6	15.4	19.0	12.3	9.2	13.5
	2001	75.2	72.2	57.0	83.5	76.2	11.1	9.6	26.3	6.3	10.6	13.6	18.2	16.7	10.2	13.2
	2002	75.0	65.0	64.0	85.8	76.3	11.9	13.5	22.6	7.2	11.4	13.1	21.6	13.4	6.9	12.3
	1999–2002	75.8	71.5	62.1	85.3	77.6	10.0	9.8	23.3	6.1	9.4	14.2	18.7	14.6	8.7	13.0
Ciprofloxacin	1999	61.6	74.4	60.5	62.3	63.8	10.5	6.9	6.6	10.1	9.8	27.9	18.8	32.9	27.6	26.5
	2000	62.4	66.6	69.2	66.6	64.7	6.7	4.5	1.5	7.7	6.7	30.9	28.9	29.2	25.7	28.6
	2001	60.5	67.5	43.0	64.4	61.1	5.8	5.1	8.6	8.4	6.8	33.6	27.3	48.4	27.3	32.1
	2002	59.6	57.9	44.1	66.5	60.4	5.4	4.3	10.4	6.4	5.9	35.0	37.8	45.5	27.1	33.7
	1999–2002	60.7	65.0	44.7	65.4	61.9	6.4	5.0	9.2	7.7	6.8	32.9	30.1	46.0	26.9	31.3
Gentamicin	1999	71.9	73.0	69.7	70.9	71.8	9.9	10.3	18.4	10.3	10.2	18.2	16.7	11.8	18.8	18.0
	2000	69.3	63.3	83.1	67.5	67.8	9.0	9.3	4.6	10.5	9.6	21.7	27.4	12.3	21.9	22.6
	2001	74.9	75.3	68.4	67.1	72.0	8.3	6.1	13.2	10.0	9.0	16.8	18.6	18.4	23.0	19.0
	2002	72.9	69.4	65.2	76.0	72.9	10.8	8.4	16.4	9.2	10.4	16.3	22.1	18.4	14.8	16.7
	1999–2002	72.8	70.1	67.2	70.7	71.5	9.6	8.3	14.7	9.9	9.8	17.6	21.6	18.1	19.5	18.7
Imipenem	1999	76.7	80.4	85.5	83.6	79.4	6.0	3.9	3.9	6.8	5.9	17.3	15.7	10.5	9.5	14.7
	2000	77.8	73.5	87.7	86.4	80.6	4.5	5.6	1.5	4.0	4.4	17.7	20.8	10.8	9.6	15.0
	2001	79.0	75.8	70.1	84.5	79.7	7.4	5.1	18.4	4.7	7.1	13.7	19.2	11.5	10.8	13.1
	2002	76.7	68.2	71.0	86.6	78.2	7.7	5.0	18.2	5.1	7.4	15.6	26.8	10.8	8.3	14.4
	1999–2002	77.6	73.3	71.4	85.5	79.3	6.8	5.0	17.5	4.9	6.5	15.6	21.7	11.1	9.5	14.2
Piperacillin	1999	81.1	85.6	94.7	90.1	84.6	–[b]	–	–	–	–	18.9	14.4	5.3	9.9	15.4
	2000	80.8	77.0	84.6	88.4	83.2	–	–	–	–	–	19.2	23.0	15.4	11.6	16.8
	2001	83.5	77.2	82.2	87.1	83.9	–	–	–	–	–	16.5	22.8	17.8	12.9	16.1
	2002	83.5	73.5	82.9	91.1	84.5	–	–	–	–	–	16.5	26.5	17.1	8.9	15.5
	1999–2002	82.7	77.1	83.0	89.1	84.1	–	–	–	–	–	17.3	22.9	17.0	10.9	15.9
Piperacillin-tazobactam	1999	83.2	88.8	98.7	92.7	87.0	–	–	–	–	–	16.8	11.2	1.3	7.3	13.0
	2000	85.3	84.5	92.3	91.2	87.5	–	–	–	–	–	14.7	15.5	7.7	8.8	12.5
	2001	89.3	85.9	88.9	90.9	89.4	–	–	–	–	–	10.7	14.1	11.1	9.1	10.6
	2002	89.3	85.1	89.6	94.3	90.3	–	–	–	–	–	10.7	14.9	10.4	5.7	9.7
	1999–2002	87.8	85.7	89.6	92.3	89.1	–	–	–	–	–	12.2	14.3	10.4	7.7	10.9
Ticarcillin-clavulanate	1999	70.3	72.1	88.2	76.7	72.6	–	–	–	–	–	29.7	27.9	11.8	23.3	27.4
	2000	68.9	65.1	78.5	79.6	72.5	–	–	–	–	–	31.1	34.9	21.5	20.4	27.5
	2001	65.8	65.6	44.5	77.7	68.0	–	–	–	–	–	34.2	34.4	55.5	22.3	32.0
	2002	65.8	56.9	50.7	80.1	67.9	–	–	–	–	–	34.2	43.1	49.3	19.9	32.1
	1999–2002	66.9	63.4	49.7	78.8	69.4	–	–	–	–	–	33.1	36.6	50.3	21.2	30.6
Tobramycin	1999	87.6	88.1	94.7	85.6	87.2	2.0	1.5	1.3	2.8	2.1	10.4	10.5	3.9	11.6	10.7
	2000	84.2	79.2	90.8	84.9	83.8	2.4	1.4	1.5	3.0	2.5	13.4	19.5	7.7	12.1	13.8
	2001	85.8	84.7	80.4	81.5	83.9	2.0	0.7	5.1	3.3	2.5	12.2	14.6	14.4	15.2	13.5
	2002	86.4	82.4	83.8	89.0	86.5	1.5	1.0	2.4	1.9	1.7	12.1	16.6	13.9	9.1	11.8
	1999–2002	86.0	83.1	82.7	85.3	85.3	1.9	1.1	3.6	2.7	2.1	12.1	15.8	13.7	12.0	12.6

[a] The percentages of susceptible, intermediate, and resistant isolates according to NCCLS breakpoints are shown. *P. aeruginosa* isolates were collected from non-ICU patients, ICU patients, nursing home (NH) patients, outpatients (OP), and all patients combined. The total numbers of isolates collected from non-ICU patients, ICU patients, NH patients, OP, and all patients from 1999 to 2002 follow: in 1999, 3,388, 963, 76, 1,847, and 6,274, respectively; in 2000, 4,442, 1,391, 65, 3,728, and 9,626, respectively; in 2001, 7,923, 1,577, 1,185, 4,975, and 15,660, respectively; in 2002, 9,896, 2,163, 1,269, 5,444, and 18,772, respectively. For all isolates collected in 1999 to 2002, the total numbers of isolates collected from non-ICU patients, ICU patients, NH patients, OP, and all patients combined were 25,649, 6,094, 2,595, 15,994, and 50,332, respectively.

[b] –, NCCLS breakpoints for the susceptible, intermediate, and resistant categories unavailable.

considered duplicates and excluded from the database if they were collected over any 5-day period from the same patient and were of the same bacterial species and had identical antibiograms. Identical isolates from different specimen sources collected within that same 5-day period were also excluded. The prevalence of multidrug resistance (MDR) was investigated among isolates of *P. aeruginosa*; for the purpose of this study, MDR isolates were defined as those resistant to 3 or more of the 10 antimicrobial agents. Analysis of variance was used to test for differences in the effects of drug and patient type (hospitalized patients [in ICU, non-ICU, or nursing home] or outpatients), drug versus age group, drug versus specimen source, and MDR by patient type, age, and specimen source.

RESULTS

Analysis of variance demonstrated that the effects of drug and patient type (hospitalized patients [in ICU, non-ICU, or nursing home] or outpatients) were significant ($P < 0.0001$) (Table 1). Resistance rates differed between drugs and between the patient types ($P < 0.0091$). From 1999 to 2002, *P. aeruginosa* isolates were most susceptible to piperacillin-tazobactam (89.1%) and amikacin (89.0%), followed by tobramycin (85.3%), piperacillin (84.1%), imipenem (79.3%), ceftazidime (77.6%), cefepime (76.6%), gentamicin (71.5%), ticarcillin-clavulanate (69.4%), and ciprofloxacin (61.9%) (Table 1). Resistance rates were highest for ciprofloxacin (31.3%) and ticarcillin-clavulanate (30.6%) ($P < 0.05$). Piperacillin-tazobactam, cefepime, and amikacin comprised a group not significantly different from each other but with the lowest resistance ($P < 0.05$). The remaining agents grouped together and were not significantly different from each other.

In ICU patients, an increase in resistance of 1.8 to 19.0% was observed from 1999 to 2002 for all agents; an increase in resistance of >6% was also observed among nursing home patients from 1999 to 2002 for all agents except amikacin (0.9%) and imipenem (0.3%). Increased resistance was observed for only ciprofloxacin (7.1%), ticarcillin-clavulanate (4.5%), and tobramycin (1.7%) from 1999 to 2002 in non-ICU inpatients. Among *P. aeruginosa* isolated from outpatients, an overall decrease in resistance rates of 0.2 to 3.3% was seen in all agents, except cefepime, ciprofloxacin, ticarcillin-clavulanate, and tobramycin (0.4, 7.2, 4.7, and 1.1% increases, respectively) during the 4-year analysis period; the highest resistance rates were observed during 2001 for most agents. From 1999 to 2002, resistance rates were highest in the ICU (19.2%) and lowest in the outpatient group (13.3%) ($P < 0.05$).

Analysis of variance showed that both drug and age group effects were significant ($P < 0.0001$) (Table 2). Resistance rates differed between drugs and between age groups ($P < 0.0001$). Resistance rates were highest in the 18- to 39-year-old patients and lowest in the ≥70-year-old patients, and this difference was statistically significant ($P < 0.05$). There was a trend of decreasing resistance observed as patient age increased, but the resistance rate for the 50- to 59-year-old patients was not significantly different from the patient age group with the highest resistance rate (18- to 39-year-old patients). The 50- to 59-year-old patients, however, were significantly different from the patient age groups with the lowest rates of resistance (i.e., the 60- to 69-year-old and ≥70-year-old patients) ($P < 0.05$) (Table 2). Three agents demonstrated >80% susceptibility across all age groups (18 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years old). These agents were piperacillin, piperacillin-tazobactam, and tobramycin (Table 2).

TABLE 2. Susceptibility of *P. aeruginosa* isolates to antimicrobial agents according to patient age (data from 1999 to 2002 combined)

Antimicrobial agent(s)	Patient age (yr)	Total no. of isolates	% S[a]	% I[a]	% R[a]
Amikacin	18–39	8,479	76.7	7.2	16.2
	40–49	5,113	90.7	3.9	5.4
	50–59	6,512	91.5	3.8	4.8
	60–69	7,086	92.4	3.8	3.8
	≥70	15,778	93.7	3.3	3.0
Cefepime	18–39	8,479	72.8	14.1	13.1
	40–49	5,113	76.1	14.0	9.8
	50–59	6,512	74.6	14.4	11.0
	60–69	7,086	74.8	15.1	10.0
	≥70	15,778	79.4	12.7	7.9
Ceftazidime	18–39	8,479	77.9	7.2	14.8
	40–49	5,113	77.5	8.4	14.1
	50–59	6,512	74.8	9.3	15.9
	60–69	7,086	75.4	10.0	14.6
	≥70	15,778	78.0	10.5	11.5
Ciprofloxacin	18–39	8,479	55.8	10.5	33.7
	40–49	5,113	59.7	7.3	33.0
	50–59	6,512	58.3	7.6	34.1
	60–69	7,086	61.7	5.6	32.7
	≥70	15,778	61.4	5.9	32.7
Gentamicin	18–39	8,479	61.2	11.1	27.7
	40–49	5,113	72.9	9.6	17.5
	50–59	6,512	73.1	8.1	18.8
	60–69	7,086	75.2	8.8	16.0
	≥70	15,778	75.2	10.1	14.6
Imipenem	18–39	8,479	77.9	6.0	16.1
	40–49	5,113	76.7	5.4	17.9
	50–59	6,512	76.5	7.0	16.5
	60–69	7,086	76.0	7.2	16.8
	≥70	15,778	81.1	6.9	11.9
Piperacillin	18–39	8,479	82.7	–[b]	17.3
	40–49	5,113	83.0	–	17.0
	50–59	6,512	80.7	–	19.3
	60–69	7,086	82.2	–	17.8
	≥70	15,778	85.6	–	14.4
Piperacillin-tazobactam	18–39	8,479	87.6	–	12.4
	40–49	5,113	88.1	–	11.9
	50–59	6,512	86.5	–	13.5
	60–69	7,086	87.0	–	13.0
	≥70	15,778	90.4	–	9.6
Ticarcillin-clavulanate	18–39	8,479	71.3	–	28.7
	40–49	5,113	68.2	–	31.8
	50–59	6,512	64.7	–	35.3
	60–69	7,086	65.7	–	34.3
	≥70	15,778	69.9	–	30.1
Tobramycin	18–39	8,479	80.0	4.0	16.0
	40–49	5,113	85.9	1.6	12.5
	50–59	6,512	84.3	1.6	14.1
	60–69	7,086	86.9	1.5	11.7
	≥70	15,778	87.6	1.6	10.7

[a] The percentages of susceptible (S), intermediate (I), and resistant (R) isolates according to NCCLS breakpoints are shown.
[b] –, NCCLS breakpoints for the intermediate category unavailable.

TABLE 3. Susceptibility of *P. aeruginosa* isolates to antimicrobial agents according to specimen source (data from 1999 to 2002 combined)

Antimicrobial agent(s)	Specimen source	Total no. of isolates	% S[a]	% I[a]	% R[a]
Amikacin	Blood or bone marrow	1,897	90.0	4.2	5.7
	Lower respiratory tract[b]	20,007	83.1	6.0	10.9
	Upper respiratory tract[c]	1,370	93.0	3.2	3.8
	Wound	12,111	94.1	2.6	3.3
Cefepime	Blood or bone marrow	1,897	76.5	12.3	11.1
	Lower respiratory tract	20,007	69.3	18.0	12.7
	Upper respiratory tract	1,370	91.2	6.0	2.8
	Wound	12,111	81.0	10.9	8.1
Ceftazidime	Blood or bone marrow	1,897	77.1	9.0	13.9
	Lower respiratory tract	20,007	71.5	11.4	17.1
	Upper respiratory tract	1,370	94.4	2.5	3.1
	Wound	12,111	79.7	8.2	12.1
Ciprofloxacin	Blood or bone marrow	1,897	68.7	4.7	26.6
	Lower respiratory tract	20,007	56.6	9.9	33.5
	Upper respiratory tract	1,370	85.2	5.1	9.7
	Wound	12,111	68.4	5.2	26.4
Gentamicin	Blood or bone marrow	1,897	74.6	7.7	17.6
	Lower respiratory tract	20,007	63.6	12.4	24.0
	Upper respiratory tract	1,370	85.1	6.8	8.1
	Wound	12,111	79.3	7.0	13.7
Imipenem	Blood or bone marrow	1,897	78.5	4.3	17.2
	Lower respiratory tract	20,007	72.4	8.4	19.2
	Upper respiratory tract	1,370	94.5	1.6	3.9
	Wound	12,111	83.0	5.2	11.8
Piperacillin	Blood or bone marrow	1,897	83.1	–[d]	16.9
	Lower respiratory tract	20,007	79.2	–	20.8
	Upper respiratory tract	1,370	96.4	–	3.6
	Wound	12,111	85.4	–	14.6
Piperacillin-tazobactam	Blood or bone marrow	1,897	88.8	–	11.2
	Lower respiratory tract	20,007	85.4	–	14.6
	Upper respiratory tract	1,370	97.5	–	2.5
	Wound	12,111	89.6	–	10.4
Ticarcillin-clavulanate	Blood or bone marrow	1,897	70.2	–	29.8
	Lower respiratory tract	20,007	64.0	–	36.0
	Upper respiratory tract	1,370	91.2	–	8.8
	Wound	12,111	71.9	–	28.1
Tobramycin	Blood or bone marrow	1,897	85.0	1.3	13.7
	Lower respiratory tract	20,007	81.5	3.1	15.4
	Upper respiratory tract	1,370	94.3	2.3	3.4
	Wound	12,111	88.7	1.4	9.9

[a] The percentages of susceptible (S), intermediate (I), and resistant (R) isolates according to NCCLS breakpoints are shown.
[b] Includes bronchus, brush biopsy, bronchus wash, sputum, tracheal aspirate, bronchoalveolar lavage, tracheostomy, transtracheal aspirate, lung, lung abscess, pleural biopsy, pleural fluid, and thoracentesis specimens.
[c] Includes sinus, ear, tonsil, tympanocentesis, oral, maxilla, and mandible specimens and nasopharynx, throat, or nose, specimens.
[d] –, NCCLS breakpoints for the intermediate category unavailable.

Analysis of variance demonstrated that both drug and specimen source effects were significant ($P < 0.0001$) (Table 3). Resistance rates differed between drugs and between specimen sources ($P < 0.0001$). The highest rates of resistance for all antimicrobial agents occurred with isolates from the lower respiratory tract ($P < 0.05$). The lowest rates of resistance occurred in specimens from the upper respiratory tract ($P < 0.05$). Only three agents demonstrated >80% susceptibility in each category of specimen source (Table 3). These agents were amikacin, piperacillin-tazobactam, and tobramycin. All agents demonstrated >80% susceptibility for upper respiratory tract isolates (Table 3).

Analysis of variance demonstrated that MDR (resistance to three or more antimicrobial classes) varied by site, age group, and specimen source ($P < 0.0001$) (Table 4). Overall, MDR was identified in 24.9% (13,117 of 52,637 isolates) of all isolates collected from 1999 to 2002. MDR was significantly higher for nursing home patients (29.9%) and ICU patients (29.5%) than for non-ICU patients and outpatients ($P < 0.05$). MDR was significantly higher in the 18- to 39-year-old patients

TABLE 4. Contribution of resistance to individual antimicrobial agents to MDR phenotypes in clinical isolates of *P. aeruginosa* collected from 1999 to 2002

Patient group, specimen source, or collection yr[a]	% Isolates (no.)[b] that had an MDR phenotype	% of MDR isolates resistant to:						
		Ceftazidime	Piperacillin-tazobactam	Ticarcillin-clavulanate	Gentamicin	Ciprofloxacin	Imipenem	Tobramycin
Patient type								
Non-ICU	25.4 (6,526)	52.8	47.7	83.3	58.6	77.9	44.7	45.4
ICU	29.5 (1,795)	59.7	48.0	85.6	60.3	71.5	55.9	50.0
OP	19.4 (3,103)	41.7	39.2	66.1	74.1	71.2	36.2	57.1
NH	29.9 (775)	45.3	34.3	89.3	54.8	79.7	26.3	44.2
All	24.2 (12,199)	50.5	44.7	79.6	62.6	75.4	43.0	49.0
Patient age (yr)								
≥18–39	29.0 (2,463)	49.6	42.5	68.5	76.0	71.9	42.1	53.2
40–49	25.2 (1,290)	52.9	46.7	80.5	58.5	74.8	50.8	46.4
50–59	27.2 (1,771)	55.0	49.5	84.3	58.9	78.3	45.2	50.0
60–69	26.6 (1,817)	54.2	49.9	86.2	54.0	76.8	48.9	43.0
>70	21.5 (3,389)	50.2	44.4	83.9	57.2	81.7	40.2	47.5
All	25.0 (10,730)	51.9	46.0	80.4	61.4	77.2	44.2	48.3
Specimen source								
Blood	23.4 (443)	54.6	47.2	82.4	65.5	78.3	55.1	56.2
LRT	31.3 (6,264)	51.9	46.3	77.9	61.6	70.4	45.4	46.4
URT	5.8 (80)	43.7	40.0	55.0	70.0	62.5	47.5	46.3
Wound	20.7 (2,434)	56.8	51.4	84.9	56.3	75.5	43.2	46.0
All	26.0 (9,221)	53.2	47.6	79.8	60.4	72.1	45.3	46.7
Yr sample collected								
1999	22.7 (1,462)	55.1	55.9	78.5	60.3	67.0	40.9	43.4
2000	24.9 (2,536)	51.6	50.3	76.5	69.8	71.1	46.2	53.1
2001	26.2 (4,366)	48.5	40.8	78.8	64.7	77.1	41.4	52.7
2002	24.5 (4,753)	47.2	39.5	82.0	59.6	80.8	46.0	47.6
All	24.9 (13,117)	49.4	43.9	79.5	63.4	76.2	43.9	49.9

[a] Abbreviations: OP, outpatients; NH, nursing home; LRT and URT, lower and upper respiratory tract, respectively.
[b] Total percentage and number of isolates associated with MDR (resistance to ≥3 of the 10 antimicrobial agents).

(29.0%) than in the other age groups, except for the 50- to 59-year-old patients (27.2%) ($P < 0.05$). Rates were highest among isolates from the lower respiratory tract (31.3%), followed by blood (23.4%), then wound (20.7%) and finally upper respiratory tract (5.8%) specimens ($P < 0.05$) (Table 4). The percentage of piperacillin-tazobactam-resistant isolates of MDR was lower than for the other agents for all categories observed, except for 60- to 69-year-old patients and isolates from wound specimens (Table 4). Ticarcillin-clavulanate resistance and ciprofloxacin resistance were the two most common drug resistance phenotypes found in MDR isolates for each category. The most common MDR phenotype was resistance to gentamicin, ciprofloxacin, and tobramycin (2.7% of MDR), followed by resistance to ceftazidime, imipenem, piperacillin, piperacillin-tazobactam, ticarcillin-clavulanate, gentamicin, ciprofloxacin, cefepime, and tobramycin (2.3% of MDR). There was a total of more than 1,900 phenotypic combinations, with the top 10 phenotypes consisting of only 17.2%. The overall change in MDR was significant between 1999 and 2002 but was not significant between 2000 and 2001 ($P < 0.05$).

DISCUSSION

The potential for encountering antimicrobial resistance is an important concern for clinicians treating patients with confirmed or suspected *P. aeruginosa* infections. Resistance in *P. aeruginosa* has been shown to lead to increased morbidity and mortality (1, 5). Multiple drug resistance caused by a variety of resistance mechanisms means that there are very few therapeutic alternatives for some patients (9, 11). The trend of increasing resistance in this gram-negative organism is even more disturbing, as most of the current new experimental antibacterial efforts are directed toward gram-positive pathogens.

Rates of antibiotic resistance differed depending on patient type, age, or specimen source. Rates were highest for isolates from patients in ICU, followed by patients in non-ICU hospital wards, then nursing homes, and finally outpatients. Resistance was inversely related to age. The youngest age group in this study, 18- to 39-year-old patients, demonstrated the highest level of resistance, and the oldest age group (≥70 years old) exhibited the lowest level. The 50- to 59-year-old patients were anomalous in that they were not significantly different from the 18- to 39-year-old patients. Resistance rates varied by specimen source, with the highest rate of resistance occurring in isolates from the lower respiratory tract and the lowest rate found in isolates from the upper respiratory tract. There have been a number of centralized in vitro studies conducted in the United States from 1997 to 2002 that have studied the susceptibility of *P. aeruginosa* (4, 6, 7, 13, 17). For the fluoroquinolones, it appears that susceptibility among *P. aeruginosa* isolates is decreasing in the United States (2, 4, 6, 7, 13, 14, 16), perhaps because of increasing or cumulative fluoroquinolone use, the lack of adherence to approved infection control prac-

tices by hospitals, or changes to the public health infrastructure (6). Ciprofloxacin and ticarcillin-clavulanate as assessed in this study demonstrated the highest levels of resistance. Piperacillin-tazobactam, cefepime, and amikacin demonstrated the greatest level of susceptibility regardless of patient age, specimen source, or patient type. Rates of resistance were only slightly increased in ICU patients for piperacillin-tazobactam and were lower in the outpatients and decreased in the non-ICU patients. Resistance rates for ticarcillin-clavulanate increased in the ICU, non-ICU, and nursing home patients but decreased in outpatients.

MDR (resistance to three or more antimicrobial agents) accounted for 24.9% of all isolates in this study. MDR was significantly higher for nursing home patients (29.9%) and ICU patients (29.5%) than for non-ICU patients and outpatients ($P < 0.05$). MDR was highest in the 18- to 39-year-old patients (29.0%; $P < 0.05$) and in isolates from the lower respiratory tract (31.3%; $P < 0.05$), with the lowest rate occurring in isolates from the upper respiratory tract (5.8%; $P < 0.05$). The agent that showed the lowest level of resistance among MDR isolates was piperacillin-tazobactam, except for isolates from 60- to 69-year-old patients and wound isolates. Ticarcillin-clavulanate resistance and ciprofloxacin resistance were the two most common drug resistance phenotypes found in MDR. The two most common MDR phenotypes were resistance to gentamicin, ciprofloxacin, and tobramycin (2.7% of MDR), followed by resistance to ceftazidime, imipenem, piperacillin, piperacillin-tazobactam, ticarcillin-clavulanate, gentamicin, ciprofloxacin, cefepime, and tobramycin (2.3% of MDR); the top 10 phenotypes consisted of only 17.2% of all MDR. The overall change in MDR was significant between 1999 and 2002 but was not significant between 2000 and 2001 ($P < 0.05$).

In summary, antimicrobial resistance is an ongoing concern for isolates of *P. aeruginosa* from patients whether they were patients in hospitals or nursing homes or outpatients. Resistance rates vary by patient type, age, and specimen source. Rates of susceptibility over time continue to decrease, leaving a limited number of therapeutic options available. Regardless of patient age, specimen source, or patient type, piperacillin-tazobactam, cefepime, and amikacin were the most active drugs. The development of newer therapeutic alternatives to address the problem of MDR gram-negative rods is needed.

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