SUPPLEMENT ARTICLE

Characterization of *Pseudomonas aeruginosa* Isolates: Occurrence Rates, Antimicrobial Susceptibility Patterns, and Molecular Typing in the Global SENTRY Antimicrobial Surveillance Program, 1997–1999

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During 1997–1999, a total of 70,067 isolates (6631 *Pseudomonas aeruginosa* isolates) were analyzed in the SENTRY program by geographic region and body site of infection. The respiratory tract was the most common source of *P. aeruginosa*. *P. aeruginosa* isolation rates increased during the study interval. Europe was the only region to show a significant decline in β-lactam and aminoglycoside susceptibility rates. There was a reduction in the rates of susceptibility of Canadian isolates to imipenem and of Latin American isolates to meropenem. A total of 218 multidrug-resistant *P. aeruginosa* isolates (MDR-PSA; resistant to piperacillin, ceftazidime, imipenem, and gentamicin) were observed; MDR-PSA occurrence rates (percentages of all isolates) ranged from 8.2% (Latin America) to 0.9% (Canada). No antimicrobial inhibited >50% of MDR-PSA strains. Molecular characterization of selected, generally resistant strains was performed. Isolates showing unique ribogroups were found in Europe, Latin America, and the United States, but clonal spread was documented in several medical centers.

Pseudomonas aeruginosa is a cosmopolitan gram-negative aerobic bacillus [1] isolated from soil, water, plants, and animals, including humans. It is occasionally pathogenic for plants as well as animals. The minimal nutritional requirements of *P. aeruginosa*, its tolerance of a wide variety of physical conditions, and its relative resistance to antimicrobial agents contribute to its ecologic success and to its role as an effective opportunistic pathogen. It rarely causes disease in healthy persons, although it is a common human saprophyte. In most cases the disease process begins with some alteration of normal host defenses. This may involve a disruption in the integrity of physical barriers to bacterial invasion, such as intravenous lines, urinary catheters, or endotracheal tubes. In other instances, there is an underlying dysfunction of specific host-defense mechanisms, such as neutropenia or iatrogenic immunosuppression [2, 3].

The existence of multiple pathogenic mechanisms in such diverse diseases caused by *P. aeruginosa* must be assumed [2]. Cellular injury caused by endotracheal intubation may also play a role in the initial attachment of *P. aeruginosa* to epithelial cells in the respiratory tract [4]. In addition to factors involved in the virulence of *P. aeruginosa*, its resistance to antimicrobials contributes to its role as an effective opportunistic pathogen. Resistance to antipseudomonal β-lactams has been well described, and resistance to recent-generation cepha-

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losporins, monobactams, and carbapenems is becoming a disturbing clinical problem.

β-Lactam resistance is due to a variety of mechanisms; AmpC β-lactamase production [5–7], extended-spectrum β-lactamases [8], including carbapenemases [9–12], a barrier to diffusion at the outer membrane, and efflux mechanisms are among those described [13–24]. Loss of permeability [25] and active antimicrobial efflux may affect other types of drugs such as aminoglycosides or quinolones [26, 27]. This may be complemented with alterations in DNA gyrase [28] and the presence of aminoglycoside-modifying enzymes, leading to the emergence of multidrug-resistant *P. aeruginosa* (MDR-PSA) [13, 18, 29–39] against which there are very few therapeutic options, such as polymyxins [30, 40–42].

P. aeruginosa is primarily a nosocomial pathogen [43]. The frequency with which it causes disease is reliably estimated from annual surveillance data collected by the National Nosocomial Infection Surveillance (NNIS) system of the Centers for Disease Control and Prevention (CDC). According to these data, collected between 1986 and 1998, *P. aeruginosa* was the second most common cause of nosocomial pneumonia (14% of isolates), the third most common cause of urinary tract infection (7%), the fourth most common cause of surgical site infection (8%), the seventh most frequently isolated pathogen from the bloodstream (2%), and the fifth most common isolate (9%) overall from all sites [14]. Patients with cystic fibrosis, neutropenia, or multiple devices are at the greatest risk of *P. aeruginosa* infection [10, 17, 18, 33, 37, 44–55].

Because of the prevalence of *P. aeruginosa* in the hospital environment, epidemiological investigation for discrete outbreaks is facilitated by the use of markers that discriminate among strains [32]. The most specific and sensitive epidemiological tool identified to date is molecular characterization of the strains [25, 45, 52, 56–61].

In this study we determined the frequencies of occurrence of *P. aeruginosa* (including MDR-PSA) as a reported pathogen, by geographic region and body site; the antimicrobial profiles of isolates were also studied. The SENTRY Antimicrobial Surveillance Program is a longitudinal surveillance study designed to track antimicrobial resistance trends nationally and internationally over a 5- to 10-year period. This report also includes evaluations of the antimicrobial activity of diverse antimicrobials against MDR-PSA strains and the molecular characterizations of *P. aeruginosa* strains.

MATERIALS AND METHODS

Study design. The SENTRY Antimicrobial Surveillance Program monitored the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of sentinel hospitals in 4 major world regions: Asia-Pacific, Europe, Latin America, and the United States/Canada. The monitored infections include bloodstream infections (objective A), outpatient respiratory infections due to fastidious organisms (objective B), pneumonia (objective C), skin/soft-tissue infections (objective D), and urinary tract infections (objective E). Consecutive isolates (540 strains/year for all objectives per laboratory) were forwarded to the regional monitors for confirmation of organism identification and susceptibility testing. Since most of the isolates are collected from nonsterile body sites, the participating medical centers are encouraged to send clinically significant isolates. Just 1 isolate per patient was included in this study. A summary description of demographic data such as each patient's age, sex, ward, hospitalization in the intensive care unit, and type of infection (nosocomial or community-acquired) was also obtained.

Participating medical centers. The number of participating medical centers ranged from 66 laboratories in 1997 to a high of 81 sites in 1998. The participants varied slightly in number by year in the following regions: 5–8 sites in Canada, 26–28 in the United States, and 12–23 in Europe, Israel, and Turkey combined. The number of sites remained constant in the Asia-Pacific region (17 sites) and Latin America (10 sites). Technicians at 3 reference laboratories, using common reagents and methodologies, evaluated the respective isolates. These laboratories were located at the University of Iowa College of Medicine, in Iowa City, Iowa (for isolates from Canada, the United States, and Latin America for 1997–1999 and Europe for 1999); Women's and Children's Hospital, in Adelaide, Australia (for isolates from the Asia-Pacific region for 1998–1999); and Utrecht University, in Utrecht, the Netherlands (for isolates from Europe for 1997–1998).

Bacterial strains. A total of 70,067 bacterial isolates were collected between January 1997 and December 1999. This number did not include isolates collected from objective B. Isolates collected from urinary tact and skin/soft-tissue infections in Canada, Europe, and the United States during 1999 also were not included because of a change in the protocol. During the study period, 6631 *P. aeruginosa* isolates were collected. The distribution of isolates by region was as follows: Asia-Pacific, 757; Canada, 580; Europe, 1659; Latin America, 1132; and the United States, 2498. Isolates for which MICs were high (piperacillin, >64 μg/mL; ceftazidime, >16 μg/mL; imipenem, >8 μg/mL; and gentamicin, >8 μg/mL) were classified as multidrug-resistant (MDR) isolates.

Organism identification. All isolates were identified at the participating institution by the routine methodology in use at each laboratory. Upon receipt at the monitoring laboratory, isolates were subcultured onto blood agar to ensure viability

Table 1. Geographic variation in the occurrence of infections caused by *Pseudomonas aeruginosa* in the SENTRY Antimicrobial Surveillance Program (1997–1999).

Country or region	Occurrence by site of infection: total no. of isolates, % *P. aeruginosa* (range[a])			
	Blood	Respiratory	Wound	Urine
Asia-Pacific	3162	1704	791	959
	4.5 (4.4–4.7)	23.4 (22.1–26.0)	13.8 (10.8–14.8)	11.0 (10.0–12.9)
Canada	3840	1659	633	651
	4.3 (3.6–4.9)	17.6 (16.3–18.8)	12.0 (11.8–12.1)	7.5 (7.3–7.6)
Europe	10,815	2572	2305	2135
	5.6 (5.3–6.3)	22.2 (20.4–26.8)	14.0 (13.3–14.7)	7.3 (6.2–8.5)
Latin America	5295	1914	1353	1430
	6.5 (5.6–7.7)	25.0 (21.6–26.9)	11.5 (9.4–12.4)	8.0 (7.4–9.1)
United States	17,399	6711	2191	2569
	4.4 (4.2–4.6)	19.3 (18.2–20.4)	11.9 (10.9–12.9)	6.7 (5.8–7.5)

NOTE. A total of 70,067 strains (6631 *P. aeruginosa* isolates) were analyzed over the 3-year study period.

[a] Range indicates occurrence rates over the 3 study years.

and purity. Species identifications were confirmed with the Vitek system (bioMérieux Vitek) or conventional methods as required [1].

Susceptibility testing. At the monitoring laboratory, antimicrobial susceptibility testing was performed with the reference broth microdilution method, as described by the National Committee for Clinical Laboratory Standards [62]. The MICs were defined as the lowest antibiotic concentrations able to inhibit bacterial growth. Antimicrobial agents were obtained from the respective manufacturers. They included aztreonam, piperacillin, piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, levofloxacin, gatifloxacin, trovafloxacin, amikacin, gentamicin, tobramycin, tetracycline, and trimethoprim-sulfamethoxazole. Quality control was performed by testing *Escherichia coli* American Type Culture Collection (ATCC) 25922, *Staphylococcus aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212, *Haemophilus influenzae* ATCC 49247, and *Streptococcus pneumoniae* ATCC 49619.

Molecular study. The *P. aeruginosa* isolates were selected for typing by ribotypes if they were recovered during a short period of time at a single center and had similar antibiograms. Ribotyping was performed with the RiboPrinter Microbial Characterization system (E.I. duPont de Nemours) according to the manufacturer's instructions. In brief, colonies were picked from individual culture plates and streaked for growth on brain-heart infusion plates. Cells were suspended in lysis buffer, lysing enzymes were added, and the tubes were placed in the RiboPrinter. Within the RiboPrinter, bacterial cells were lysed, the DNA was digested with Pvu II, and the restriction fragments were separated by electrophoresis and transferred to nylon membranes. A chemiluminescent-labeled DNA probe containing the rRNA operon (*rrn*B) from *E. coli* was hybridized to the DNA on the membrane. The patterns were electronically imaged, stored, and compared. Pattern comparisons were based on both position and signal intensity. Isolates with coefficients of similarity >0.9 were considered to have the same ribotype profile [52].

RESULTS

Frequency of occurrence of* P. aeruginosa *as a reported pathogen, by geographic region and body site. During the 3-year period (1997–1999), SENTRY participants reported a total of 70,067 strains, of which 6631 were *P. aeruginosa*. Table 1 lists the geographic distribution of infections caused by *P. aeruginosa*, classified by site of infection. There was considerable geographic variation in the rates of isolation of *P. aeruginosa*, and the highest figures across all sites of infection were recorded in the Asia-Pacific region and Latin America (11.4%; data not shown), followed by Europe (9.3% of isolates), the United States (8.7%), and Canada (8.6%). The difference was statistically significant for *P. aeruginosa* isolations in Latin America or the Asia-Pacific region versus those in Europe or North America ($P < .001$). However, the difference found between the rates in Europe and Canada or the United States was not statistically significant ($P = .092$).

The distribution or rank order of *P. aeruginosa* isolates by body site was generally the same for all regions evaluated: the respiratory tract was the most frequent source of *P. aeruginosa* isolates, followed by wounds, urine, and bloodstream. However, some regions contributed more *P. aeruginosa* isolates from a specific site than other geographic areas. As an example, Latin America and Europe showed the highest proportion of *P. aeru-*

Table 2. Trends in antimicrobial susceptibility of all *Pseudomonas aeruginosa* isolates according to monitored region, during 1997, 1998, and 1999 (SENTRY Antimicrobial Surveillance Program).

	Percentage of isolates susceptible[a]													
	Asia-Pacific		Canada			Europe			Latin America			United States		
Antimicrobial agent	1998	1999	1997	1998	1999	1997	1998	1999	1997	1998	1999	1997	1998	1999
β-Lactams														
Aztreonam	66.5	65.3	73.4	67.1	75.2	80.2	73.2	55.6[a]	55.5	45.0	48.2	67.0	64.7	62.3
Piperacillin	85.5	85.8	91.7	87.4	89.1	85.6	77.0	73.8[b]	71.9	66.7	67.5	87.9	87.3	83.7[c]
Piperacillin/tazobactam	90.2	87.5	93.2	90.4	95.6	90.1	77.0	73.8[b]	79.4	77.1	74.9	89.9	89.9	86.6[a]
Ceftazidime	76.1	83.7[d]	80.2	80.2	84.7	85.1	78.2	71.6[a]	66.6	64.4	66.9	79.5	81.2	78.1
Cefepime	81.6	85.8	80.2	84.4	91.2[c]	80.8	83.0	73.8[c]	66.2	67.9	66.3	77.7	85.8	83.1[b]
Imipenem	90.0	86.2	83.0	82.0	92.0[c]	89.3	79.0	71.6[a]	77.0	76.7	74.3	88.0	85.2	80.9
Meropenem	91.5	87.8	92.4	91.6	94.9	89.8	85.6	73.8[a]	83.0	79.7	76.6[b]	92.4	90.8	90.9
Aminoglycosides														
Amikacin	94.2	95.8	91.4	95.8	97.8[c]	89.0	86.8	78.9[c]	77.6	73.3	69.5[c]	95.0	94.8	96.6
Tobramycin	88.5	89.9	91.4	93.4	94.2	76.3	78.3	68.4[c]	68.1	64.9	64.2	91.1	92.7	92.2
Quinolones														
Ciprofloxacin	84.8	83.7	79.9	74.3	81.0	73.5	73.8	67.6	67.2	60.8	60.9	79.8	77.9	75.36
Levofloxacin	83.8	82.6	74.5	70.1	80.3	71.1	73.4	68.4	63.6	59.0	59.5	74.4	73.7	73.4
Gatifloxacin	80.1	77.5	66.2	64.1	74.5	72.0	72.2	64.0	60.9	57.1	56.8	69.1	69.0	67.2
Trovafloxacin	84.8	82.0	76.6	74.1	81.0	70.6	73.9	68.4	65.4	60.1	60.7	75.2	77.4	73.7
Tetracyclines	2.6	4.2	2.9	3.0	2.9	6.8	4.7	2.2[c]	1.2	1.7	1.8	2.7	2.3	3.5

NOTE. Susceptibility was determined with use of the National Committee for Clinical Laboratory Standards criteria published in 2000. The footnotes indicate statistical significance. $P < .5$ between values for the indicated years.

[a] Over the 3-year study period.
[b] Between 1997 and 1998 as well as 1997 and 1999.
[c] Between 1997 and 1999.
[d] Between 1998 and 1999.

ginosa strains among the consecutive blood isolates submitted. If the data from participating centers are representative of the national picture or are matched, this may indicate higher rates of *P. aeruginosa* bacteremia in these areas. Latin America, the Asia-Pacific region, and Europe had the highest rates of recovery among respiratory isolates; isolation rates in the United States were consistently below these except for urinary tract isolations. This may reflect greater use of indwelling urinary tract catheters in the United States, since this organism is rarely a primary urinary tract pathogen. The occurrence rates of *P. aeruginosa* over the 3 years were similar among different body sites in the United States and Canada. However, a higher variation in the ranges of respiratory isolations in the Asia-Pacific region, Latin America, and Europe was observed. These regions contributed more respiratory isolates in 1998 than in other years. Moreover, in the Asia-Pacific region, the number of wound isolates collected in 1998 was nearly 4 times higher than in 1999.

Trends in antimicrobial susceptibility patterns. The antimicrobial susceptibilities of *P. aeruginosa* isolates during the study period are shown in table 2. Several differences in antimicrobial susceptibilities, indexed by geographic regions, were observed. Overall, Latin American isolates showed the lowest susceptibility rate to all antimicrobial agents tested, followed by Asia-Pacific isolates (to β-lactams) and European strains (to the fluoroquinolones). Canada had the best global susceptibility testing results (low levels of resistance). Amikacin was the antimicrobial agent associated with the highest susceptibility rate, in all regions except Latin America. On the other hand, Europe was the only region in which there was a significant decline in the β-lactam and aminoglycoside susceptibility rates over the 3 monitored years. This fact cannot be explained by the later inclusion of Turkish sites, where MDR-PSA are present, since they replaced a Portuguese and an Italian site, where MDR-PSA were also frequently observed.

With respect to carbapenem susceptibility, 3 regions had increased resistance rates: there was a reduction in susceptibility of Canadian isolates to imipenem, of Latin American isolates to meropenem, and of European isolates to both imipenem and meropenem. Imipenem has probably acted as the selective agent (source of selective pressure), since in most countries meropenem has only recently become commercially available or its use has been severely restricted.

It is notable that Latin America had the lowest rates of sus-

Table 3. Occurrence of the 218 multidrug-resistant *Pseudomonas aeruginosa* (MDR-PSA) strains, by body site of isolation. Data were obtained from participant medical centers in the SENTRY Antimicrobial Surveillance Program.

Country or region, year (no. of isolates tested)	Occurrence by site of infection: no. of MDR-PSA isolates (no. of medical centers[a])			
	Blood	Respiratory	Wound	Urine
Asia-Pacific				
1997 (n = 8)	1 (1)	2 (2)	5 (3)	0
1998 (n = 7)	1 (1)	6 (1)	0	0
Canada				
1997 (n = 3)	0	3 (2)	0	0
1998 (n = 2)	0	1 (1)	0	1 (1)
1999 (n = 0)	0	0	0	1 (1)
Europe				
1997 (n = 6)	3 (2)	1 (1)	1 (1)	1 (1)
1998 (n = 48)	19 (8)	15 (5)	12 (4)	2 (2)
1999 (n = 24)	5 (4)	16 (5)	2 (1)	1 (1)
Latin America				
1997 (n = 23)	3 (3)	13 (5)	4 (2)	3 (2)
1998 (n = 31)	10 (4)	16 (4)	2 (2)	3 (3)
1999 (n = 36)	11 (3)	11 (5)	7 (3)	7 (2)
United States				
1997 (n = 12)	2 (2)	7 (4)	2 (1)	1 (1)
1998 (n = 8)	0	4 (4)	1 (1)	3 (2)
1999 (n = 10)	3 (3)	6 (4)	0	1 (1)

NOTE. *P. aeruginosa* isolates were defined as multiresistant (MDR-PSA) if they were resistant to piperacillin (MICs, >64 μg/mL), ceftazidime (>16 μg/mL), imipenem (>8 μg/mL), and gentamicin (>8 μg/mL).

[a] This indicates the number of medical centers contributing MDR-PSA in the respective region.

ceptibility to ceftazidime and cefepime and also the highest increase in susceptibility rate, when tazobactam was associated with piperacillin. This observation raises the hypothesis that extended-spectrum β-lactamase (ESBL) production could be one of the mechanisms of resistance shared by *P. aeruginosa* against broad-spectrum cephalosporins, since high rates of ESBL-producing *Klebsiella pneumoniae* strains have been noted in most of the participating Latin American centers. Increased cefepime susceptibility rates were observed in Canada and the United States, perhaps because overexpression of AmpC enzymes may be an important resistance mechanism in such isolates. In contrast, an elevation in the rate of susceptibility to ceftazidime, but not to cefepime, was seen in the Asia-Pacific region. Decreases in piperacillin and piperacillin/tazobactam susceptibility rates, at statistically significant levels, were observed only in Europe and the United States.

With regard to the resistance situation as a whole, a reduction in fluoroquinolone susceptibility rates was noted in the 3-year study, but a reduction in susceptibility at statistically significant levels was observed only in the United States. However, with ciprofloxacin being the most potent currently available agent, the 60.9% susceptibility rate in Latin America and the 67.6% rate in Europe denote major problems.

MDR-PSA. MDR-PSA isolates (218 strains), defined as being resistant to piperacillin, ceftazidime, imipenem, and gentamicin, were selected for analysis. Their distribution by geographic region and body site is shown in table 3. The respiratory tract was still the most frequent site of isolation (101 of 218 isolates; 46.1%), and the bloodstream was the second most frequent source of MDR-PSA isolates. Latin America was the region with the greatest number of MDR-PSA isolates (90). The rates of occurrence of MDR-PSA by geographic region were as follows: Latin America, 8.2%; Europe, 4.7%; United States, 1.2%; Asia-Pacific, 1.6%; and Canada, 0.9%. Approximately 56% of MDR-PSA strains isolated in Latin America were collected from just 1 Brazilian medical center. If this site were excluded, the frequency of occurrence of MDR-PSA in Latin America would be reduced to only 3.6%, i.e., less than the rate recorded for Europe.

Two medical centers in the Asia-Pacific region, 1 in China and another in the Philippines, contributed more MDR-PSA isolates than other sites, and an outbreak could not be excluded. A similar situation occurred in Europe, where a Portuguese facility and an Italian medical center isolated 20.0% and 16.4%, respectively, of the total number of MDR-PSA strains in 1998, and 2 Turkish sites each isolated 16.4% of the total number in 1999. In contrast, most of the MDR-PSA samples in Canada and the United States were isolated in diverse medical centers, and endemic strains were not discovered in the US or Canadian centers evaluated by SENTRY.

Eleven antimicrobial agents were tested against MDR-PSA isolates (table 4). Overall susceptibility rates were very low, and aminoglycosides were the most active antimicrobial class, although they inhibited one-half of MDR-PSA strains only in the United States. MDR-PSA strains isolated in Europe were

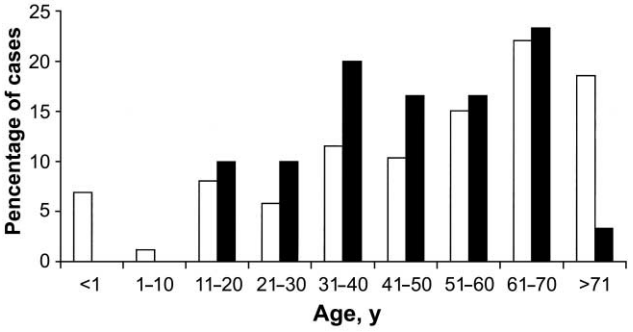

Figure 1. Distribution of multidrug-resistant *Pseudomonas aeruginosa* isolates, according to the ages of the patients from whom they were recovered, in Latin America *(white bars)* and the United States *(black bars)*.

Table 4. Antimicrobial activity of 11 antimicrobial agents tested against 218 multidrug-resistant *Pseudomonas aeruginosa* isolates in the SENTRY Antimicrobial Surveillance Program (1997–1999).

Agent tested	MIC_{50}, μg/mL (% of isolates susceptible)				
	Asia-Pacific (n = 15)[a]	Canada (n = 5)	Europe (n = 78)	Latin America (n = 90)	United States (n = 30)
β-Lactams					
Aztreonam	>16 (0)	>16 (20.0)	>16 (10.1)	>16 (0)	>16 (0)
Piperacillin/tazobactam	>64 (6.6)	>64 (0)	>64 (12.6)	>64 (7.8)	>64 (13.3)
Cefepime	>16 (0)	>16 (0)	>16 (1.3)	>16 (1.1)	>16 (13.3)
Meropenem	>8 (0)	8 (40.0)	>8 (0)	>8 (3.3)	>8 (0)
Aminoglycosides					
Amikacin	32 (33.3)	32 (20.0)	>32 (19.0)	>32 (12.2)	16 (50.0)
Tobramycin	16 (0)	8 (40.0)	>16 (3.8)	>16 (3.8)	>16 (20.0)
Quinolones					
Ciprofloxacin	>2 (13.3)	>2 (20.0)	>2 (2.5)	>2 (6.6)	>2 (3.3)
Gatifloxacin	>4 (13.3)	>4 (0)	>4 (3.8)	>4 (3.3)	>4 (6.6)
Levofloxacin	>4 (13.3)	>4 (0)	>4 (5.0)	4 (7.7)	>4 (10.0)
Trovafloxacin	>4 (13.3)	>4 (20.0)	>4 (3.8)	>4 (10.0)	>4 (6.6)
Tetracyclines	>8 (0)	>8 (0)	>8 (0)	>8 (0)	>8 (6.6)

NOTE. *P. aeruginosa* isolates were defined as multiresistant if they were resistant to piperacillin (MICs, ≥128 μg/mL), ceftazidime (>16 μg/mL), imipenem (>8 μg/mL), and gentamicin (>8 μg/mL). MICs were determined by broth microdilution. Susceptibility was determined with use of the National Committee for Clinical Laboratory Standards criteria published in 2000.

[a] *n*, no. tested.

less susceptible to fluoroquinolones than in other regions, and β-lactams had little activity against MDR-PSA in any region, as expected on the basis of the definition of MDR-PSA. It is remarkable that no therapeutic agent that was routinely tested inhibited >50% of MDR-PSA strains, since there are few options for treatment against such microbes. Eighty bloodstream *P. aeruginosa* isolates in 1998 were tested with polymyxin B and colistin (data not shown), and none of the strains were resistant; therefore, polymyxins may be an alternative for treatment against MDR-PSA, although these compounds are considerably toxic and have poor distribution profiles.

MDR-PSA demographic information. Figure 1 shows the distribution of MDR-PSA isolates according to age, in both Latin America and the United States. Most MDR-PSA strains (56%) occurred in patients >51 years of age in Latin America; 64% were males, and 90% of the infections were nosocomial. In the United States, 57% of MDR-PSA isolates were recovered from male patients, and 23% of isolations occurred between the ages of 61 and 70 years; a second peak occurred between 31 and 40 years of age (20% of isolates). In contrast to cases in Europe and Latin America, only 3.3% of cases occurred in patients >71 years of age. In Europe, 80% of the infections were nosocomial, and the greatest number of cases (50%) occurred in intensive care units, followed by internal medicine units (28%). More than 80% of patients in Europe needed intensive care during hospitalization. In contrast to the United States and Latin America, where infections in the very young were rare, 24% of the MDR-PSA infections in Europe occurred in patients <10 years old.

Molecular characterization. Molecular characterizations of isolates that were recovered within a short time at the same center and that had the same susceptibility patterns are shown in table 5. During the study period, 118 strains were selected for typing from the surveillance program. No isolates from the Asia-Pacific region were ribotyped. It is remarkable that isolates with unique ribotypes were found in Europe, Latin America, and the United States. On the other hand, ribogroup 566-6 was identified in samples collected from 3 SENTRY geographic regions: Europe, Latin America, and the United States. The samples were collected at 2 different sites in Argentina (3 and 4 isolates), 1 site in Colombia (1 isolate), 1 site in France (1 isolate), 1 site in Turkey (3 isolates), and 4 sites in the United States (6 isolates). All the European and US isolates belonging to this ribogroup (566-6) were collected from the respiratory tract.

Another common ribogroup, 798-3, was identified in Europe and the United States and also involved only respiratory isolates. The isolates were collected at 2 sites in Turkey and 2 in the United States. Just 1 ribogroup (560-7) was found in common among Canada, Latin America, and the United States, whereas Europe and Latin America shared 3 common ribogroups: 1033-3, at 2 sites in Argentina, 1 in Brazil, and 1 in

Table 5. Molecular characterization by automated ribotyping of *Pseudomonas aeruginosa* strains selected from the SENTRY Antimicrobial Surveillance Program between 1997 and 1999.

	No. of strains (no. of medical centers[a])							
Ribotype	Canada	Europe	Latin America	United States	Blood	Respiratory	Wound	Urine
559-4	0	0	17 (2)[b]	0	1 (1)	10 (2)	4 (1)	2 (1)
560-7	2 (1)	0	1 (1)	1 (1)	0	2 (1)	1 (1)	1 (1)
566-6	0	4 (2)[b]	8 (3)[b]	6 (4)	5 (2)	10 (6)	1 (1)	2 (2)
676-7	1 (1)	0	0	1 (1)	0	1 (1)	0	1 (1)
798-3	0	6 (2)[b]	0	4 (2)	0	10 (4)	0	0
1005-1	0	0	10 (2)[b]	0	2 (1)	7 (2)	1 (1)	0
1033-3	0	2 (1)	7 (3)	0	3 (1)	3 (1)	1 (1)	2 (1)
1034-5	0	2 (1)	1 (1)	0	1 (1)	2 (1)	0	0
1034-6	0	0	2 (1)	0	2 (1)	0	0	0
1161-1	0	3 (1)	1 (1)	0	1 (1)	3 (1)	0	0
1161-3	0	2 (1)	0	0	0	2 (1)	0	0
1163-4	0	0	0	2 (1)	2 (1)	0	0	0
1342-7	0	0	2 (1)	0	0	2 (1)	0	0
Unique	0							
Unique		6 (4)				5 (4)	1 (1)	
Unique			13 (5)		2 (2)	4 (3)	4 (4)	3 (3)
Unique				15 (7)	0	11 (4)	0	4 (3)

NOTE. The isolates were selected for typing only if they were recovered during a short period at a single center and displayed similar, usually resistant antibiograms.

[a] Number of centers that had MDR-PSA isolates with the respective ribotype number.

[b] Ribotype grouping clusters discovered at a single medical center.

Israel; 1034-5, at 1 site in Brazil and 1 in Turkey; and 1161-1, at 1 site in Argentina and 1 in Turkey. The isolates belonging to these ribogroups were recovered from diverse body sites.

Ribogroups 559-4 and 1005-1 were detected in 2 different Brazilian sites, but 1 of them contributed only 2 strains, 1 of each ribogroup. This situation clearly shows the presence of epidemic/endemic clones in 1 of the Brazilian sites. This respective site did not share ribogroups with any other facilities in Canada, Europe, or the United States. Further studies (pulsed-field gel electrophoresis) were performed and confirmed the dissemination of epidemic clones within medical centers in Europe (2 ribotypes; 2 sites each) and Latin America (3 ribotypes; 2 or 3 sites each [table 5]).

DISCUSSION

P. aeruginosa is a leading cause of nosocomial infections, ranking second among the gram-negative pathogens reported to the NNIS [2, 14, 63]. There are a limited number of antimicrobial agents with reliable activity against *P. aeruginosa*, including antipseudomonal penicillins and cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones. Resistance to antimicrobials is an increasing clinical problem and is a recognized public health threat [64]. *P. aeruginosa* shows a particular propensity for the development of resistance, and this situation is associated with increased rates of mortality and morbidity and higher costs [65]. We conducted this study to assess the occurrence of *P. aeruginosa* infections in relation to body sites and geographic regions. We also studied resistance arising over a 3-year period in each geographic region.

A large number of isolates were contributed by several centers in different geographic areas. As expected, a decrease in the susceptibility of *P. aeruginosa* was seen over the 3-year period in all the geographic regions studied. This decrease was more evident for β-lactams in Europe, for piperacillin (alone or with tazobactam) in the United States, for aminoglycosides in Europe and Latin America, and for ciprofloxacin in the United States. The rates of occurrence of MDR-PSA between 3.6% and 7.7% were similar to those obtained in other series [14–16, 49, 53, 54, 66–70]. Rates of occurrence in bloodstream infections in Canada and the United States in 1999 were slightly higher than in previous studies that ended in 1998; this agrees with the increasing trend described above. Our rates of resistant isolates were greater than those described earlier [71], perhaps because in our study isolates from sites other than the bloodstream, which are more resistant, were included.

It is clear that surveillance programs are necessary to identify changes in the spectrum of pathogens causing serious infections and to monitor trends in antimicrobial susceptibility patterns. The information obtained from such studies is necessary to

design empirical approaches to therapy for infections and to guide formulary practices.

It is remarkable that there are considerable differences among isolates in different geographic regions. The reasons for these differences in antimicrobial susceptibility are generally unclear but may be due to differences in antimicrobial utilization practices and the quality of infection control practices or public health infrastructures.

One important finding of this study is that no single empirical therapy ensures a successful microbiological outcome against >90% of *P. aeruginosa* infections worldwide. In the Asia-Pacific region only aminoglycosides reach this target number (>90%) in empirical therapy; in Canada, several β-lactams and aminoglycosides reach this level. Europe and Latin America show the most disturbing trends in the efficacy of empirical therapy: no agent inhibits 80% of the strains. Resistance in the United States is similar to that seen in the Asia-Pacific region for most agents. Ciprofloxacin, the most potent agent available in oral form for treatment of *P. aeruginosa* infections, is in particular jeopardy: in Europe, the United States, and Latin America, rates of susceptibility to the drug are between 60% and 75%. The eventual loss of this agent may mean that the treatment of all *Pseudomonas* infections will require injectable therapy and possibly hospitalization, a clear example of the increased costs associated with resistance [65].

Independent of the controversy that concerns the need for monotherapy versus combination therapy for *P. aeruginosa* infections, antimicrobial resistance of *P. aeruginosa* has reached a level in most regions of the world such that empirical therapy against this organism may require the initial use of 2 or more agents, until susceptibility testing results are known. Resistance levels will continue to increase unless measures are taken to curtail this rise. Combinations will suffice only for empirical therapy; they have not been shown to definitively reduce the development of resistance against modern β-lactams, and there is a risk that this approach could encourage resistance to both agents. Moreover, MDR-PSA are increasingly being isolated [17, 72–75], and against some isolates the only therapeutic option is polymyxins, which have poor pharmacokinetic profiles and considerable toxicity [30, 40, 56, 76].

No new classes of antimicrobials active against *P. aeruginosa* will be available for therapy within the next 5–7 years. Most new quinolones in development are likely to show some degree of cross-resistance to ciprofloxacin. Much attention has been paid to increasing resistance among Enterobacteriaceae or gram-positive cocci against β-lactams, but these investigations suggest that resistance of *P. aeruginosa* may be a greater threat for hospitalized patients, especially since this organism is thought to be associated with the highest attributable mortality among gram-negative bacteria.

In conclusion, ongoing surveillance of microbial pathogens and their resistance profiles is important [74, 77] to guide future antimicrobial chemotherapy and the development of antimicrobial agents. The SENTRY program will continue its surveillance of both nosocomial and community-acquired serious infections. The findings of these surveillance studies will enhance our knowledge regarding the problem of antimicrobial resistance and will serve as a basis for future policies and practice styles.

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