SUPPLEMENT ARTICLE

# Emerging Importance of Multidrug-Resistant *Acinetobacter* Species and *Stenotrophomonas maltophilia* as Pathogens in Seriously Ill Patients: Geographic Patterns, Epidemiological Features, and Trends in the SENTRY Antimicrobial Surveillance Program (1997–1999)

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**As part of the SENTRY Antimicrobial Surveillance Program, a total of 1078 *Acinetobacter* species and 842 *Stenotrophomonas maltophilia* isolates were collected between January 1997 and December 1999 from 5 geographic regions (Canada, the United States, Latin America, Europe, and the Asia-Pacific). The frequency of infections (by geographic region and body site), including those due to imipenem-resistant *Acinetobacter* species and trimethoprim-sulfamethoxazole (TMP-SMZ)–resistant *S. maltophilia*, was evaluated. The possibility of seasonal variations in bloodstream infections caused by *Acinetobacter* species was studied, as was the activity of several therapeutic antimicrobials against all strains. *Acinetobacter* species and *S. maltophilia* were most frequently associated with pulmonary infections, independent of the region evaluated. In contrast, patterns of antimicrobial resistance markedly varied among distinct geographic regions, especially for nosocomial isolates. Although the carbapenems were the most active antimicrobials against *Acinetobacter* species, nearly 11.0% of the nosocomial isolates were resistant to this drug group in both regions. TMP-SMZ, ticarcillin–clavulanic acid, gatifloxacin, and trovafloxacin were the only agents with consistent therapeutic activity against *S. maltophilia* isolates. Rates of resistance to TMP-SMZ ranged from 2% in Canada and Latin America to 10% in Europe. The geographic differences in resistance patterns among *Acinetobacter* species and *S. maltophilia* isolates observed in this study emphasize the importance of local surveillance in determining the most adequate therapy for acinetobacter and *S. maltophilia* infections and the possible clonal, epidemic nature of occurrence.**

*Acinetobacter* species are ubiquitous organisms widely distributed in nature. These gram-negative bacilli are usually commensal, but in the past few decades they have emerged as important opportunistic pathogens, especially in the nosocomial setting [1]. They are capable of causing a range of nosocomial infections, including pneumonia, bacteremia, secondary meningitis, urinary tract infections, and surgical wound infections. In the United States, data collected by hospitals par-

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ticipating in the National Nosocomial Infection Surveillance (NNIS) system during 1992–1997 showed that *Acinetobacter* species caused 1% of nosocomial bloodstream infections (BSIs) and 3% of pneumonia cases in the coronary care unit [2].

*Acinetobacter* was also reported as the seventh most common genus of pathogens recovered from intensive care unit patients in the European Prevalence of Infections in Intensive Care study, accounting for 8% and 10% of all cases of BSI and pneumonia, respectively [3]. *Acinetobacter* species isolates have unique characteristics among nosocomial gram-negative bacteria that favor their persistence in the hospital environment. They usually are resistant to the action of many antimicrobials, spread easily from patient to patient, and are resistant to desiccation, thus persisting in the environment for many days. This factor could explain their propensity for causing extended epidemic outbreaks. Species other than *Acinetobacter baumannii* are involved less frequently as causes of nosocomial infection and generally are more susceptible to antimicrobials [1, 4–6].

Previous studies have reported that acinetobacter infections are more prevalent in tropical countries and during the late summer [7, 8]. Community-acquired acinetobacter infections are relatively uncommon, although Anstey and colleagues reported that 10.0% of cases of community-acquired pneumonia in the Northern Territory of Australia were caused by *Acinetobacter* species [9]. In recent years, the increasing incidence of carbapenem (imipenem, meropenem)–resistant *Acinetobacter* strains has been noticed in several hospitals [10–14]. Therapy for infections caused by such organisms is often problematic, and usually the only antimicrobial agents available for therapy are polymyxins and ampicillin/sulbactam.

*Stenotrophomonas maltophilia*, previously known as *Pseudomonas maltophilia* and then *Xanthomonas maltophilia*, is a common commensal that is readily isolated from water, soil, and sewage [15–18]. However, it has also emerged as an important opportunistic pathogen in immunocompromised hosts such as patients undergoing transplantation or patients with cancer [19]. *S. maltophilia* generally causes hospital-acquired infections, but community-acquired infections have also been reported. Although *S. maltophilia* isolates may cause a wide spectrum of human diseases [20–27], the respiratory tract is the most common site of *S. maltophilia* infection, especially in patients with cystic fibrosis and others with compromised lung function [28–30]. It has been suggested that the increase in the incidence of *S. maltophilia* infections might be consequent to selective pressure caused by overuse of broad-spectrum $\beta$-lactams in the hospital environment or by individual patients [31–33].

Like other nonfermentative species, *S. maltophilia* isolates are intrinsically resistant to many commonly used antimicrobial agents. They produce diverse drug-hydrolyzing enzymes such as L1, a zinc-dependent metalloenzyme, and L2, a cephalosporinase, which are able to destroy important classes of $\beta$-lactams such as carbapenems and cephalosporins, respectively [34–36]. *S. maltophilia* isolates also quickly develop resistance to fluoroquinolones by mutations in outer-membrane proteins. Recently, Zhang and colleagues demonstrated the involvement of efflux mechanisms in acquired multidrug resistance in *S. maltophilia* [37]. Trimethoprim-sulfamethoxazole (TMP-SMZ) has been the drug of choice for treatment of *S. maltophilia* infections. Although TMP-SMZ has been shown to be the most potent antimicrobial against this pathogen, resistance has emerged [19, 24, 38–41].

The purpose of the present report is to establish the frequency of occurrence of *Acinetobacter* species and *S. maltophilia* infections by geographic region and body site of infection at the participating institutions of the SENTRY Antimicrobial Surveillance Program [42]. Comparative antimicrobial activity of numerous antimicrobial agents against *Acinetobacter* species and *S. maltophilia* isolates was evaluated, including an analysis of imipenem-resistant *Acinetobacter* species and TMP-SMZ–resistant *S. maltophilia* isolates. Seasonal variation in the occurrence of acinetobacter BSIs was also assessed.

## MATERIALS AND METHODS

***Study design.*** The SENTRY Antimicrobial Surveillance Program has monitored the predominant pathogens and antimicrobial resistance patterns in nosocomial and community-acquired infections via a broad network of sentinel hospitals in 5 geographic regions: the Asia-Pacific, Europe, Latin America, Canada, and the United States [42]. The monitored infections include BSIs (objective A), outpatient respiratory tract infections due to specific fastidious organisms (objective B), pneumonia in hospitalized patients (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 reference antimicrobial susceptibility testing. Since most of the isolates are collected from nonsterile body sites, the participating medical centers are encouraged to send only clinically significant isolates. Just 1 isolate per patient per site of infection was included in this study. A summary of demographic data such as each patient's age, sex, and ward, hospitalization in the intensive care unit, and whether the infection was nosocomial or community acquired was also obtained.

***Participating medical centers.*** The number of participating medical centers varied from 66 in 1997 to 81 in 1998. The number varied slightly 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. The number of sites remained the same in the Asia-Pacific region (17 sites) and Latin America

**Table 1. Total number of strains isolated and percentage of *Acinetobacter* species strains observed, by site of infection, as reported in the SENTRY Antimicrobial Surveillance Program by participating medical centers between January 1997 and December 1999.**

| | Occurrence by site of infection | | | |
|---|---|---|---|---|
| Country or region | Blood | Respiratory | Wound | Urine |
| Canada | | | | |
| Total no. of isolates | 3840 | 1659 | 633 | 651 |
| *Acinetobacter;* % (range) | 0.7 (0.5–1.0) | 2.0 (1.4–3.9) | 2.2 (2.0–2.4) | 0.2 (0.0–0.4) |
| United States | | | | |
| Total no. of isolates | 17,399 | 6711 | 2191 | 2569 |
| *Acinetobacter;* % (range) | 1.4 (0.9–1.7) | 2.5 (2.3–2.8) | 2.1 (2.0–2.2) | 1.0 (0.9–1.0) |
| Latin America | | | | |
| Total no. of isolates | 5295 | 1914 | 1353 | 1430 |
| *Acinetobacter;* % (range) | 4.6 (3.2–5.3) | 9.7 (7.1–11.6) | 4.7 (3.5–5.5) | 2.2 (0.9–3.2) |

**NOTE.** A total of 70,067 strains (1078 *Acinetobacter* species isolates) were analyzed over the 3 study years. Ranges indicate occurrence rates over the 3 years monitored.

(10 sites). Three reference laboratories, with use of common reagents and methodologies, evaluated the respective isolates: University of Iowa College of Medicine (Iowa City, IA; isolates from Canada, the United States, and Latin America for 1997–1999 and Europe for 1999); Women's and Children's Hospital (Adelaide, Australia; isolates from the Asia-Pacific region for 1998–1999); and Utrecht University (Utrecht, The Netherlands; 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 in association with objective B. Isolates collected from urinary tract and skin/soft-tissue infections in Canada, Europe, and the United States during 1999 were not included because of a change in the protocol design that affected prevalence data. During the study period, 1078 *Acinetobacter* species isolates and 842 *S. maltophilia* isolates were observed. In this study, only *Acinetobacter* species isolates collected from Canada, Latin America, and the United States were studied. The *Acinetobacter* data from the Asian-Pacific and European regions will be further analyzed.

***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 and purity. Confirmation of species identification was performed with the Vitek system (bioMérieux Vitek) or conventional methods as required.

***Susceptibility testing.*** At the monitoring laboratory, antimicrobial susceptibility testing was performed with use of the reference broth microdilution method, as described by the National Committee for Clinical Laboratory Standards (NCCLS) [43]. The MICs were defined as the lowest antimicrobial concentrations able to totally inhibit bacterial growth. Antimicrobial agents were obtained from the respective manufacturers. These agents included piperacillin, piperacillin-tazobactam, ticarcillin, ticarcillin–clavulanic acid, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, levofloxacin, gatifloxacin, trovafloxacin, amikacin, gentamicin, tobramycin, tetracycline, and TMP-SMZ. Numerous other compounds were tested but were not described here because of limited potency. Quality control was performed by testing *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212. All quality-control findings among reported data were within ranges published by the NCCLS [43].

## RESULTS AND DISCUSSION

**Acinetobacter *species distribution and infection sites.*** Despite the limitation of commercial systems for identification of the genus *Acinetobacter* at the species level, *A. baumannii* was the most commonly reported species in the 3 geographic regions evaluated in this report. Among Latin American isolates, the 3 most frequent species isolated were *A. baumannii* (75.0%), *Acinetobacter anitratus* (8.2%), and *Acinetobacter* species (7.4%), whereas in Canada and the United States the most frequently isolated were *A. baumannii* (54.6%), *A. anitratus* (14.8%), and *A. calcoaceticus* (14.6%). These data agree with those from previous studies [6, 44], which showed *A. baumannii* as the most frequent species. Among the nosocomial isolates, the 3 most frequent species were *A. baumannii* > *A. anitratus* > *A. calcoaceticus* in both regions. However, among the community-acquired isolates, *A. lwoffii* was the second and third most frequent species in Canada/United States and Latin America, respectively.

The distribution of *Acinetobacter* isolates by body site is

**Table 2. Distribution by age and sex of patients in Latin America, Canada, and the United States with infections caused by *Acinetobacter* species, as reported in the SENTRY Antimicrobial Surveillance Program by participating medical centers between January 1997 and December 1999.**

| Age, years | No. (%) of patients infected | | | |
|---|---|---|---|---|
| | Latin America | | Canada and United States | |
| | Female | Male | Female | Male |
| <1 | 6 (3.3) | 11 (3.6) | 8 (3.7) | 19 (5.6) |
| 1–10 | 9 (5.0) | 10 (3.3) | 21 (9.6) | 20 (5.9) |
| 11–20 | 4 (2.2) | 12 (3.9) | 15 (6.9) | 23 (6.8) |
| 21–30 | 17 (9.5) | 25 (8.2) | 17 (7.8) | 35 (10.3) |
| 31–40 | 13 (7.3) | 33 (10.8) | 21 (9.6) | 45 (13.3) |
| 41–50 | 23 (12.8) | 36 (11.8) | 28 (12.8) | 41 (12.2) |
| 51–60 | 25 (14.0) | 52 (17.1) | 22 (10.0) | 51 (15.1) |
| 61–70 | 31 (17.3) | 46 (15.1) | 37 (17.0) | 45 (13.3) |
| 71–80 | 34 (19.0) | 55 (18.1) | 31 (14.2) | 44 (13.0) |
| >80 | 17 (9.5) | 24 (7.9) | 18 (8.2) | 14 (4.1) |
| Total | 179 | 304 | 218 | 337 |

shown in table 1. The statistics for Canada and the United States show that *Acinetobacter* isolates were frequently recovered from wounds (2.0%–2.4%) and respiratory tract infections (1.4%–3.9%), whereas in Latin America the respiratory tract was clearly the most common body site of infections (7.1%–11.6%). In Latin America, respiratory *Acinetobacter* species isolates were 2-fold more frequent than wound isolates ($P < .001$). The greater frequency of acinetobacter infections in Latin America than in all other SENTRY regions was highly significant ($P < .001$; isolated 2–10 times more often). Percentages of *Acinetobacter* species isolates causing BSIs were similar to those previously reported from the SENTRY and Surveillance and Control of Pathogens of Epidemiologic Importance programs [42, 44], in which these microorganisms accounted for ≤1.6% of all BSIs in Canada/United States and for 5.3% in Latin America.

***Patient and hospital demographics of acinetobacter infections.*** The number of acinetobacter infections increased linearly with age from 11 to 80 years for both sexes and in the geographic locations monitored. A higher prevalence rate was noted from birth to age 10 years (6.9%–13.3%), especially among infants <1 year of age (3.3%–5.6% of all cases), regardless of sex or geographic area (table 2). In contrast, a decline in the number of infections among patients >81 years of age was observed. Approximately 61.0% and 63.0% of acinetobacter infections were in male patients in Canada/United States and Latin America, respectively ($P < .0001$).

The distribution of acinetobacter infections by medical service is shown in table 3. Most cases occurred in the internal medicine service in both regions. In Canada/United States, surgical units were the second most frequent contributors of *Acinetobacter* species isolates. However, the percentage of acinetobacter infections was higher in intensive care units than in surgery services in Latin America. This finding might indicate the presence of endemic clones in intensive care units [45]. Recently, Wisplingghoff and colleagues reported that *A. baumannii* BSIs occurred more frequently in intensive care units [44]. No differences in the distribution of isolates of *Pseudomonas aeruginosa* (another nonfermentative pathogen) by medical service were noted between Latin America and Canada/United States in the SENTRY program (data not shown).

Among the acinetobacter infections in Latin America, nearly 60.0% were nosocomial. This trend was not observed in the Canada/United States region, where *Acinetobacter* strains were equally distributed among nosocomial and community-acquired infections. However, the mode of acquisition of acinetobacter infections was unknown in 44.0% of cases in this geographic region.

***Antimicrobial susceptibility of* Acinetobacter *species isolates.*** Tables 4 and 5 list the activity of 15 selected antimicrobial agents tested against all *Acinetobacter* strains. Generally, isolates from Canada/United States (table 4) were more susceptible to all recorded drugs than were those from Latin America (table 5). Some of the most notable differences between these respective regions in terms of susceptibility to the antimicrobials tested were as follows: ceftazidime, 67.0% vs. 25.9%; piperacillin/tazobactam, 68.5% vs. 25.0%; ciprofloxacin, 69.6% vs. 29.7%; amikacin, 87.5% vs. 32.2%; and tetracycline, 70.7% vs. 57.1%. Only the carbapenems remained highly active in both areas (89.0% and 95.5% susceptibility, respectively).

In Canada/United States, nosocomial isolates were significantly more resistant to $\beta$-lactams than were community-acquired isolates (data not shown) or all isolates tested ($P < .001$). In contrast, in Latin America the resistance rates of nosocomial and all isolates were very similar for all drug classes.

**Table 3. Number and percentage of *Acinetobacter* species strain isolations, by medical service, as reported in the SENTRY Antimicrobial Surveillance Program by participating medical centers between January 1997 and December 1999.**

| Service | No. (%) of isolates | |
|---|---|---|
| | Latin America | Canada and United States |
| Internal medicine | 302 (73.5) | 179 (50.0) |
| Surgery | 30 (7.3) | 74 (20.7) |
| Intensive care unit | 38 (9.2) | 53 (14.8) |
| Pediatrics | 31 (7.5) | 29 (8.1) |
| Gynecology and obstetrics | 2 (0.5) | 2 (0.5) |
| Emergency | 5 (1.2) | 17 (4.7) |
| Transplantation | 3 (0.7) | 4 (1.1) |

**Table 4. Activity of 15 selected antimicrobial agents tested against nosocomial and all *Acinetobacter* species strains isolated in the SENTRY Antimicrobial Surveillance Program in the United States and Canada between January 1997 and December 1999.**

| | Nosocomial isolates ($n$ = 150) | | | | All reported isolates ($n$ = 552)[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | MIC; μg/mL[b] | | Test result; %[c] | | MIC; μg/mL[b] | | Test result; %[c] | |
| Antimicrobial agent | $MIC_{50}$ | $MIC_{90}$ | Susceptible | Resistant | $MIC_{50}$ | $MIC_{90}$ | Susceptible | Resistant |
| Ticarcillin | 16 | >128 | 54.7 | 28.7 | 16 | >128 | 62.3 | 15.3 |
| Ticarcillin–clavulanic acid | 16 | >128 | 62.7 | 18.0 | 16 | 128 | 69.1 | 12.5 |
| Piperacillin | 32 | >128 | 45.3 | 28.0 | 16 | >128 | 50.9 | 23.0 |
| Piperacillin/tazobactam | 16 | >64 | 62.7 | 20.7 | 8 | >64 | 68.5 | 15.7 |
| Ceftazidime | >16 | >16 | 65.3 | 24.0 | 8 | >16 | 67.0 | 19.8 |
| Cefepime | 16 | >16 | 67.3 | 19.3 | 4 | >16 | 67.5 | 18.8 |
| Imipenem | 0.25 | 8 | 88.0 | 8.0 | 0.25 | >8 | 95.5 | 3.0 |
| Meropenem | 0.5 | >8 | 87.3 | 10.7 | 0.5 | >8 | 94.1 | 4.1 |
| Ciprofloxacin | 0.25 | >2 | 70.0 | 28.0 | 0.25 | >2 | 69.6 | 27.1 |
| Gatifloxacin[b] | 0.12 | >4 | 76.0 | 20.0 | 0.12 | >4 | 75.0 | 21.3 |
| Trovafloxacin | ⩽0.03 | >4 | 78.7 | 12.0 | ⩽0.03 | >4 | 75.4 | 22.7 |
| Amikacin | 4 | 16 | 91.3 | 4.0 | 4 | 32 | 87.5 | 8.2 |
| Gentamicin | ⩽1 | >8 | 71.3 | 25.3 | 2 | >8 | 70.9 | 26.2 |
| Tobramycin | 1 | 16 | 85.3 | 12.0 | 1 | >8 | 79.6 | 16.4 |
| Tetracycline | ⩽4 | >8 | 70.7 | 20.7 | ⩽4 | >8 | 70.7 | 22.3 |

[a] Includes only 151 strains of community-acquired *Acinetobacter* species.
[b] MICs determined by broth microdilution, as described by the National Committee for Clinical Laboratory Standards (2000 guidelines).
[c] Percentages of susceptibility and resistance determined by NCCLS interpretive criteria (2000 guidelines) or as follows: gatifloxacin, susceptible at ⩽2 μg/mL and resistant at ⩾8 μg/mL (product package insert).

Therefore, the rank order for resistance among *Acinetobacter* isolates was as follows: Latin America nosocomial isolates = Latin America total isolates > North America nosocomial isolates > North America total isolates or community-acquired isolates.

The best drugs for therapy in North America were imipenem (88.0%–95.5% susceptible) and meropenem (87.3%–94.1% susceptible) among the β-lactams, gatifloxacin (75.0%–76.0% susceptible) among the clinically usable fluoroquinolones, amikacin (87.5%–91.3% susceptible) among the aminoglycosides, and tetracyclines (70.7% susceptible). In Latin America (table 5), only the carbapenems inhibited >80% of strains. Tetracycline showed the second highest susceptibility rate, inhibiting 57.1%–58.8% at ⩽4 μg/mL. Although tobramycin was more active than amikacin against *Acinetobacter* species isolated in Latin America, only 42.1%–46.6% were susceptible at its limits of susceptibility. The newer fluoroquinolones, gatifloxacin and trovafloxacin, were slightly superior to ciprofloxacin in the spectrum of potential clinical uses against *Acinetobacter*. Comparison of these results with those previously published revealed a trend toward increasing incidence of antimicrobial resistance among *Acinetobacter* isolates [42, 46, 47].

***Occurrences of carbapenem-resistant* Acinetobacter *species.*** The distribution of carbapenem (imipenem)–non-susceptible *Acinetobacter* species (INSA) by geographic region and body site of infection is shown in table 6. The occurrence of these INSA isolates was higher in Latin America (11.4%) than in the United States (4.8%) or Canada (2.7%). Latin America contributed more INSA isolates than Canada/United States ($P < .0001$). Although the United States had more isolations than Canada, the difference was not statistically significant. In the United States and Canada, few sites (6%) regularly recovered INSA isolates, whereas in Latin America the majority of reporting medical centers isolated these resistant strains. It is notable that each of the medical centers in Canada contributed 1 isolate only. In the United States, the INSA strains were isolated in only 2 medical centers, located in New York. The 6 medical centers in Latin America were located in Argentina, Chile, Colombia, Mexico, Brazil, and Venezuela, and 3 sites had epidemic clusters (table 6); a single Brazilian institution contributed nearly one-half of the INSA isolates.

Nearly 70% of INSA isolates were *A. baumannii*. The distribution of these isolates by body site was the same in all regions evaluated, with respiratory isolates being slightly more frequent than BSI strains (difference not statistically significant). Seventy-four percent and 60% of INSA isolates were nosocomial in the United States and Latin America, respectively. Among infections caused by these isolated strains, 57%

and 52% required intensive care unit hospitalization in Latin America and the United States, respectively. In the United States, amikacin ($MIC_{50}$, 4 μg/mL) and tobramycin ($MIC_{50}$, 1 μg/mL) were the only drugs that had good in vitro activity against the INSA strains, inhibiting 95.7% and 69.6% of these isolates, respectively (data not shown). In contrast, in Latin America, no drug had acceptable activity. Although tetracycline and gatifloxacin were the best antimicrobials tested against such isolates, they inhibited <40% of the INSA isolates. Ampicillin/sulbactam and the polymyxins are the only possible options currently available for treatment of such infections.

The activities of polymyxin B and colistin were tested by broth microdilution against 60 bloodstream *Acinetobacter* isolates collected from diverse SENTRY Program medical sites in 1998. Approximately 20.0% of these samples were nonsusceptible to imipenem. Ninety percent of these strains were inhibited by very low concentrations of polymyxin B (≤2 μg/mL or 16 U) and colistin (≤2 μg/mL). In contrast to findings in other studies [10, 48], 3 *Acinetobacter* isolates with reduced susceptibility to polymyxins (MICs, ≥8 μg/mL) were detected. This indicates that polymyxins might not be completely active against *Acinetobacter* species.

***Seasonal characteristics of acinetobacter infections.*** Figure 1 shows the seasonal variation of *Acinetobacter* species infections. Only bloodstream isolates were included for this evaluation of acinetobacter infections since they were collected year round rather than during a specific period of time, as occurs for other SENTRY objectives. In Latin America (1997), the highest number of acinetobacter infections occurred during the summer. However, in 1998, the opposite seasonal occurrence

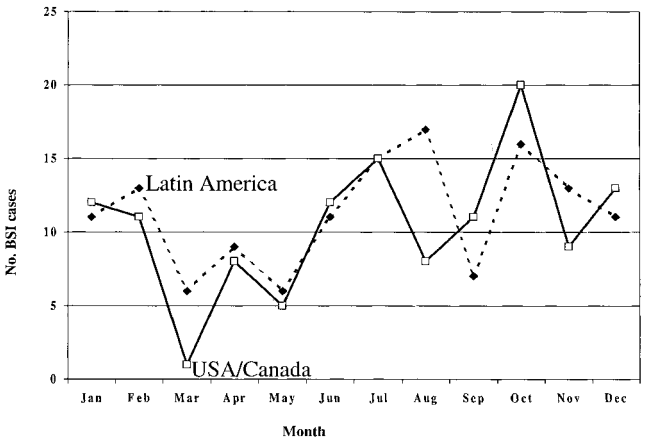


**Figure 1.** Occurrences of acinetobacter bloodstream infections (BSIs), by month of isolation of the organism in the SENTRY program (1997–1999) and by geographic region.

**Table 5. Activity of 15 selected antimicrobial agents tested against nosocomial and all *Acinetobacter* species strains isolated in the SENTRY Antimicrobial Surveillance Program in Latin America between January 1997 and December 1999.**

| | Nosocomial isolates ($n$ = 311) | | | | All isolates ($n$ = 526)[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | MIC; μg/mL[b] | | Test result; %[c] | | MIC; μg/mL[b] | | Test result; %[c] | |
| Antimicrobial agent | $MIC_{50}$ | $MIC_{90}$ | Susceptible | Resistant | $MIC_{50}$ | $MIC_{90}$ | Susceptible | Resistant |
| Ticarcillin | >128 | >128 | 19.9 | 70.8 | >128 | >128 | 19.8 | 70.8 |
| Ticarcillin–clavulanic acid | >128 | >128 | 24.1 | 61.4 | >128 | >128 | 24.0 | 60.5 |
| Piperacillin | >128 | >128 | 17.0 | 72.9 | >128 | >128 | 17.1 | 73.9 |
| Piperacillin/tazobactam | 64 | >64 | 25.7 | 49.8 | >64 | >64 | 25.0 | 51.2 |
| Ceftazidime | >16 | >16 | 24.1 | 65.6 | >16 | >16 | 25.9 | 63.6 |
| Cefepime | 16 | >16 | 35.4 | 45.7 | 16 | >16 | 34.3 | 43.8 |
| Imipenem | 1 | >8 | 88.4 | 10.3 | 1 | 8 | 88.6 | 9.9 |
| Meropenem | 1 | >8 | 88.7 | 10.6 | 1 | 8 | 89.0 | 9.7 |
| Ciprofloxacin | >2 | >2 | 30.9 | 68.5 | >2 | >2 | 29.7 | 69.9 |
| Gatifloxacin[b] | 4 | >4 | 36.0 | 45.0 | 4 | >4 | 34.3 | 46.5 |
| Trovafloxacin | >4 | >4 | 38.4 | 60.6 | >4 | >4 | 36.7 | 62.2 |
| Amikacin | >32 | >32 | 31.5 | 64.8 | >32 | >32 | 32.2 | 62.5 |
| Gentamicin | >8 | >8 | 34.7 | 58.1 | >8 | >8 | 33.5 | 60.6 |
| Tobramycin | 8 | >16 | 46.6 | 48.1 | 16 | >16 | 42.1 | 52.9 |
| Tetracycline | ≤4 | >8 | 58.8 | 20.9 | ≤4 | >8 | 57.1 | 22.1 |

[a] Includes only 63 strains of community-acquired *Acinetobacter* species.
[b] MICs determined by broth microdilution, as described by the National Committee for Clinical Laboratory Standards (2000 guidelines).
[c] Percentages of susceptibility and resistance determined by NCCLS interpretive criteria (2000 guidelines) or as follows: gatifloxacin, susceptible at ≤2 μg/mL and resistant at ≥8 μg/mL (product package insert).

**Table 6. Distribution of imipenem-nonsusceptible *Acinetobacter* species strains, by geographic location and body site of infection, in the SENTRY Antimicrobial Surveillance Program, 1997–1999.**

| Region | No. of medical centers reporting imipenem-nonsusceptible isolates | Site of infection, no. of isolates | | | |
|---|---|---|---|---|---|
| | | Blood | Respiratory | Wound | Urine |
| Canada | 2 | 1 | 1 | 0 | 0 |
| Latin America | 6[a] | 24 | 26 | 9 | 0 |
| United States | 2[b] | 9 | 9 | 5 | 0 |

[a] Epidemic clusters detected in 3 medical centers, in Argentina, Brazil, and Venezuela.
[b] Epidemic clusters detected in 2 medical centers.

was observed, with many cases detected during the winter. In 1999 the highest number of cases involving *Acinetobacter* species was observed during the winter, heavily influenced by an outbreak in one of the Brazilian medical centers. In the Canada/United States during 1997, the highest number of cases occurred in the winter. In 1998, 2 peaks of high isolation rates occurred, 1 in the summer and the other during the fall. Nearly 50% of the cases reported during the fall were at 3 different hospitals and represent small epidemic clusters. In 1999 the highest percentage of cases occurred during the summer, representing a seasonal increase in the incidence of acinetobacter infection that has been previously reported [7, 8].

McDonald et al. [8] analyzed acinetobacter infection rates reported to the NNIS system from 1987 through 1996 and found a persistent seasonal increase during the late summer months. The reasons for this phenomenon are unclear, but they may be related to increased ambient humidity favorable for this organism's growth. Many reasons could account for the lack of this pattern in Latin America, such as the persistence of endemic strains in some medical centers, allowing the occurrence of clustered epidemic acinetobacter infections throughout the year, or an insufficient number of strains collected monthly in the SENTRY program to clarify seasonal prevalence.

***Occurrence of* S. maltophilia *infections.*** Table 7 lists the frequency of occurrence of *S. maltophilia* isolates by geographic region, site of infection, and year of isolation. In the SENTRY program, the respiratory tract was the most commonly reported *S. maltophilia* infection site in all geographic regions. Pneumonia-causing *S. maltophilia* isolates were 4-fold more prevalent than BSI isolates (3.3% of all isolates). The SENTRY rates by geographic area per year for isolations of *S. maltophilia* in cases of pneumonia varied from 1.2% to 4.8%. The highest rates were detected in Canada (4.7%, 4.8%, and 6.1% in 1997, 1998, and 1999, respectively), and these values were associated with epidemic occurrences in some of the monitored institutions. The prevalence of *S. maltophilia* in BSIs was only 0.4%–1.3% of cases among all SENTRY program geographic regions and years (average, 0.8% of cases overall). The highest BSI occurrences were seen in Asia-Pacific (1.3% in 1998) and Europe (1.0% and 1.1% in 1999 and 1997, respectively). In a previous report on this study [42], *S. maltophilia* accounted for 0.6%–0.9% of all BSIs reported from the United States, Canada, and Latin America. Wound and urinary tract infections caused by *S. maltophilia* remain more rare (≤1.1%).

**Table 7. Frequency of occurrence of *Stenotrophomonas maltophilia* isolates in the SENTRY Antimicrobial Surveillance Program, indexed by geographic region, site of infection, and year of isolation (1997–1999).**

| Region | Source of isolate | Occurrence by year, % of isolates | | | |
|---|---|---|---|---|---|
| | | 1997 | 1998 | 1999 | Overall |
| Asia-Pacific | Blood | NT | 1.3[a] | 0.4 | 0.9 |
| | Respiratory | NT | 2.9 | 2.7 | 2.8 |
| | Wound | NT | 0.2 | 0.0 | 0.1 |
| | Urine | NT | 0.3 | 0.0 | 0.2 |
| Canada | Blood | 0.6 | 0.5 | 0.6 | 0.6 |
| | Respiratory | 4.7[b] | 6.1[b] | 4.8[b] | 5.2[b] |
| | Wound | 1.8[c] | 0.4 | NT[d] | 1.1 |
| | Urine | 0.0 | 0.0 | NT | 0.0 |
| Europe | Blood | 1.1[a] | 0.7 | 1.0[a] | 0.9 |
| | Respiratory | 2.9 | 2.5 | 4.1 | 3.2 |
| | Wound | 0.7 | 0.5 | NT | 0.6 |
| | Urine | 0.1 | 0.2 | NT | 0.2 |
| Latin America | Blood | 0.9 | 0.8 | 0.7 | 0.8 |
| | Respiratory | 2.3 | 2.0 | 1.2 | 1.8 |
| | Wound | 0.9 | 0.2 | 0.0 | 0.4 |
| | Urine | 0.0 | 0.0 | 0.0 | 0.0 |
| United States | Blood | 0.7 | 0.7 | 0.6 | 0.7 |
| | Respiratory | 3.5 | 3.7 | 2.7 | 3.3 |
| | Wound | 0.7 | 1.4[c] | NT | 1.0 |
| | Urine | 0.5[d] | 0.1 | NT | 0.3 |

**NOTE.** NT, not tested in a prevalence study format.
[a] Highest rate of bloodstream infections, across all regions and time periods.
[b] Highest rates of *S. maltophilia* pneumonia were reported from Canada.
[c] Significantly higher rates of wound infection were associated with *S. maltophilia.*
[d] Urinary tract infection rate 5-fold greater than the overall SENTRY program rate of occurrence (<0.1%).

**Table 8. Antimicrobial activity of 10 selected compounds tested against *Stenotrophomonas maltophilia* strains from 5 continents ($n$ = 842) in the SENTRY Antimicrobial Surveillance Program, 1997–1999.**

| | Resistance, % of isolates (range for monitored years) | | | | |
|---|---|---|---|---|---|
| Antimicrobial agent | Asia-Pacific ($n$ = 80) | Canada ($n$ = 119) | Europe ($n$ = 192) | Latin America ($n$ = 83) | United States ($n$ = 368) |
| TMP-SMZ | 8 (4–11) | 2 (0–6) | 10 (3–19) | 2 (0–6) | 5 (0–9) |
| Ticarcillin–clavulanate | 29 (25–32) | 15 (12–18) | 14 (7–27) | 13 (9–21) | 10 (8–13) |
| Piperacillin/tazobactam | 73 (70–75) | 40 (30–53) | 43 (23–66) | 41 (9–63) | 47 (42–53) |
| Ceftazidime | 53 (48–58) | 40 (33–49) | 28 (10–49) | 25 (16–32) | 33 (33–34) |
| Amikacin | 81 (71–91) | 81 (67–92) | 45 (12–88) | 74 (66–88) | 79 (64–91) |
| Tobramycin | 87 (83–91) | 81 (67–89) | 53 (26–88) | 82 (66–91) | 85 (75–94) |
| Ciprofloxacin | 49 (43–54) | 53 (43–62) | 21 (10–42) | 43 (41–47) | 45 (37–50) |
| Gatifloxacin | 13 (4–21) | 15(6–24) | 2 (0–5) | 6 (5–6) | 7 (5–10) |
| Trovafloxacin | 13 (5–21) | 12 (6–16) | 2 (0–5) | 7 (5–9) | 10 (7–12) |
| Tetracycline | 75 (70–79) | 61 (41–73) | 49 (30–81) | 49 (38–58) | 55 (45–70) |

**NOTE.** TMP-SMZ, trimethoprim/sulfamethoxazole.

The antimicrobial activities of 10 selected compounds against 842 *S. maltophilia* strains collected from the 5 continents are shown in table 8. Against *S. maltophilia*, the activity and spectrum of few antimicrobial drugs are acceptable for treatment. Most of the isolates discovered in this study were susceptible to TMP-SMZ and ticarcillin–clavulanic acid. These data agree with those from previous studies [38, 40]. Overall, rates of resistance to the "drug of choice" (TMP-SMZ) ranged from 2% in Canada and Latin America to 10% in Europe (range during study period, 3%–19%). Several other investigators have reported resistance to TMP-SMZ [19, 24, 40, 41, 49]. Other drugs of potential therapeutic value also had high resistance rates: ticarcillin–clavulanic acid, 10%–29% resistance; gatifloxacin, 2%–15%; and trovafloxacin, 2%–13%.

Fluoroquinolones have been considered a possible option for treatment [31, 41], although ciprofloxacin-resistant mutants of *S. maltophilia* can be easily selected in vitro. In this study, the activity of the newest fluoroquinolones was enhanced in comparison with that of ciprofloxacin, thus confirming results of previous studies [40, 50, 51]. The gatifloxacin resistance rate among all *S. maltophilia* isolates ranged from only 2% (Europe) to 15% (Canada). This study also confirms previous reports that ticarcillin–clavulanic acid is the most active $\beta$-lactam [40, 41].

Strains of *S. maltophilia* isolated in the Asia-Pacific region tended to be more resistant, especially to $\beta$-lactams and tetracycline. Aminoglycosides were most likely to be useful in Europe, but a wide variation between centers was noted. European isolates also had the lowest rates of fluoroquinolone resistance.

Table 9 summarizes various additional details concerning the 69 *S. maltophilia* strains that were resistant to TMP-SMZ. The majority (77%) of these strains were isolated in the United States and Europe from male patients (59%) with pneumonia or BSI. Marked genetic diversity was noted among the strains, which came from 43 contributing medical centers. Only 2 epidemic clusters, involving 5 strains from 1 site, were documented by ribotyping and pulsed-field gel electrophoresis. The average patient age ranged from 48 years in Europe to 80 years in Latin America.

## CONCLUSIONS

Nonfermentative gram-negative bacilli, especially *Acinetobacter* strains, represent a real problem in certain geographic regions such as Latin America, where these strains are routinely more resistant to antimicrobial agents. These elevated resistance rates may be consequent to the differences in antimicrobial usage, infection-control practices, and climate [52]. Previous resistance surveillance studies have also demonstrated geographic differences in the antimicrobial susceptibility patterns of *Acinetobacter* species isolates [42, 53]. With *Acinetobacter* species isolates rapidly developing resistance to currently available antimicrobials, the development of new agents is extremely important, as is seeking the best agents among older compounds. Since no novel antimicrobial drugs for use against gram-negative bacilli are available, polymyxins and sulbactam in many cases are the only therapeutic options for treatment of multidrug-resistant acinetobacter infections.

Epidemic clusters of carbapenem-resistant strains were detected in some participating centers in the SENTRY program (3 in Latin America and 2 in the United States). This indicates that infection-control policies must be reviewed in the respective institutions and infection-control interventions must be initiated to decrease the number of serious acinetobacter infections.

**Table 9. Location and characteristics of trimethoprim/sulfamethoxazole-resistant *S. maltophilia* strains in the SENTRY Antimicrobial Surveillance Program, 1997–1999.**

| Region (no. of strains) | No. of medical centers | No. of isolations, by site of infection | | | | Average patient age, years | Male sex, % |
|---|---|---|---|---|---|---|---|
| | | Blood | Respiratory | Wound | Urine | | |
| Asia-Pacific ($n$ = 9) | 7 | 5 | 4 | 0 | 0 | 64 | 78 |
| Canada ($n$ = 4) | 3 | 0 | 4 | 0 | 0 | 74 | 100 |
| Europe ($n$ = 25) | 14 | 12 | 8 | 3 | 2 | 48 | 52 |
| Latin America ($n$ = 3) | 3 | 2 | 1 | 0 | 0 | 80 | 67 |
| United States ($n$ = 28) | 16[a] | 9 | 16 | 3 | 0 | 54 | 56 |
| Total ($n$ = 69) | 43 | 28 | 33 | 6 | 2 | 55 | 59 |

[a] Two epidemic clusters in 1 hospital (5 strains).

Over the past 15 years, infections due to multidrug-resistant *S. maltophilia* have also emerged as important nosocomial infections in many institutions. This fact is in part attributable to the increasing number of immunocompromised patients as well as the increasing use of broad-spectrum $\beta$-lactam agents and assisted-ventilation techniques. This report confirms that *S. maltophilia* remains highly resistant to various classes of antimicrobials and demonstrates that TMP-SMZ, ticarcillin–clavulanic acid, gatifloxacin, and trovafloxacin are among the only agents suitable for treatment of such infections, either alone or in combinations.

Epidemic occurrences of *S. maltophilia* and *Acinetobacter* species appear to be increasing. In the SENTRY program, epidemic clusters of pneumonia and BSI were detected in some of the participating medical centers. Also, an increasing trend in the incidence of respiratory tract infections due to *S. maltophilia* was observed in Europe (from 2.5% in 1998 to 4.1% in 1999) for this study interval. Unfortunately, the intrinsic resistance of this organism to many antimicrobials and the rapid selection of high-level multidrug-resistant isolates in clinical strains pose a continuing problem for treatment as well as infection control.

The SENTRY Antimicrobial Surveillance Program results have documented the wide variations in the prevalence and antimicrobial susceptibility of 2 important gram-negative nonenteric bacilli, *Acinetobacter* species and *S. maltophilia*. Because of the emerging complex resistance patterns found in these organisms and the difficulty of therapy, surveillance programs will be increasingly necessary to monitor the spread of resistant clones, to guide local interventions, and to be a testing arena for novel antimicrobial agents.

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