228
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Spectrum of Activity for Antimicrobials Tested Against Non-Fermentative Gram-Negative Bacilli (18,569 Strains) Isolated in the SENTRY Antimicrobial Surveillance Program (1997-2001)

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ABSTRACT

Background: Systemic infections due to non-fermentative gram-negative bacilli (NFB) are usually difficult to treat because of limited therapeutic choices. The objective of this study was to establish the occurrence and the antimicrobial susceptibility (S) of contemporary NFB pathogens collected during the first five years (1997-2001) of the SENTRY Program worldwide.

Methods: A total of 18,569 NFB strains were consecutively collected and tested by the broth microdilution method in three monitoring laboratories using common reagents and reference procedures. The most frequently isolated pathogen was *P. aeruginosa* (PA; 11,968 isolates; 64.5%) followed by *Acinetobacter* spp. (AS; 3,468 isolates; 18.7%) and *Stenotrophomonas maltophilia* (SM; 1,488 isolates; 8.0%).

Results: Among PA, the lowest resistance (R) rates were documented for amikacin (AMK; 8%), meropenem (MEM; 10%) and cefepime (CPM; 10%), and all fluoroquinolones (FQ) tested showed similar R rates (22-24%; no statistical advantage of ciprofloxacin [CIP]). The most active drugs against AS were the carbapenems, imipenem (IMP; 11% R) and MEM (12% R), followed by CPM (31% R) and gatifloxacin (GATI; 32% R). Few compounds showed reasonable activity against SM, with the most active agents being trimethoprim/sulfamethoxazole, GATI and levofloxacin (5-6% R). The overall spectrum analysis (18,569 NFB strains) showed that MEM had the lowest R and the highest S rates (17 and 79%, respectively). Other compounds with low R rates included CPM = IMP (18%) > AMK (20%). Piperacillin/tazobactam had the second highest S rate (78%), but had a relatively high R rate (22%). The FQ with the lowest R rate (23%) and highest S rate (68%) was GATI.

Conclusions: Despite a large number of contemporary antimicrobial classes available, the therapeutic options to treat NFB infections have become limited. Continued surveillance among NFB remains necessary to guide empiric antimicrobial therapy, especially for these less frequently isolated and difficult to test pathogens. Newer FQs and carbapenems appear best for current therapy.

INTRODUCTION

Non-fermentative Gram-negative bacilli (NFB) are primarily opportunists, causing infections mainly in seriously ill hospitalized patients, immunocompromised hosts, and patients with cystic fibrosis. NFBs can be isolated from the environment, are intrinsically resistant to many commonly used antimicrobial agents and can cause indwelling device-related infections. Most of these organisms have the potential to spread horizontally on fomites or on the hands of medical personal, and recent exposure to broad spectrum antimicrobial agents represents an important risk factor for acquisition of these organisms.

Pseudomonas aeruginosa is a leading cause of nosocomial infection, especially among patient hospitalized in intensive care units. This organism is the second most common cause of nosocomial pneumonia and the third most common cause of urinary tract infections in United States hospitals. *Acinetobacter* spp. has also become an important cause of nosocomial infection, especially pneumonia, in the last years and the prevalence of *Acinetobacter* spp. infections shows intriguing regional and seasonal variations. All other NFB are less frequently isolated, but the prevalence of infections caused by these pathogens has been constantly increasing. In addition, susceptibility testing methodologies are not completely standardized for most of these organisms, especially routine tests used in clinical microbiology laboratories. Thus, the knowledge of their epidemiology and antimicrobial susceptibility patterns are necessary in order to allow the development of therapeutic strategies.

The objective of the present report was to establish the frequency of occurrence and the antimicrobial susceptibility of contemporary NFB species collected during the first five years (1997-2001) of the SENTRY Antimicrobial Surveillance Program worldwide.

MATERIALS AND METHODS

The SENTRY 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 program was started in January 1997 and the primary monitored infections have been blood stream infections, outpatient respiratory tract infections due to specific fastidious organisms, pneumonia in hospitalized patients, skin and soft-tissue infections, and urinary tract infections. Consecutive isolates (approximately 540 strains/year per participant center) were forwarded to the regional monitors for confirmation of organism identification and reference antimicrobial susceptibility testing. Since some of the isolates are collected from nonsterile body sites, the participating medical centers are encouraged to send only clinically significant isolates. Only one isolate per patient per site of infection was included in this study.

A total of 18,569 NFB were collected between January 1997 and December 2001. All isolates were identified at the participating institution by the routine methodology in use at each laboratory and referred to the monitoring laboratories. Technicians at the three reference laboratories, using common reagents and methodologies, evaluated the respective isolates. The laboratories included the Jones Group / JMI Laboratories, North Liberty, Iowa (for isolates from Canada, the United States, and Latin America); Women's and Children's Hospital, in Adelaide, Australia (for isolates from the Asia-Pacific region); and Utrecht University, in Utrecht, The Netherlands (for isolates from Europe). 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, Hazelwood, MO, USA) or conventional methods as required. Antimicrobial agents were obtained from the respective manufacturers and susceptibility testing was performed with use of the reference broth microdilution method, as described by the National Committee for Clinical Laboratory Standards (NCCLS). Quality control was performed by testing *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212. All quality control data were within ranges published by the NCCLS.

RESULTS

- Among the NFB (Table 1), *P. aeruginosa* was the most frequently isolated pathogen (11,968 isolates; 64.5%), followed by *Acinetobacter* spp. (3,468 isolates; 18.7%) and *S. maltophilia* (1,488 isolates; 8.0%). These three pathogens accounted for more than 90% of the isolates processed.
- The antimicrobial susceptibility patterns of *P. aeruginosa* (Table 2), *Acinetobacter* spp. (Table 3) and *S. maltophilia* (Table 4) are summarized. Since these pathogens generally present multiple resistance mechanisms and severe infections are usually treated with combination therapy, we analyzed the antimicrobial spectrum based on the percentage of resistant strains.
- The most active compound against *P. aeruginosa* was amikacin (MIC_{90}, 32 μg/ml; 89% susceptible [S]) with only 8% of isolates being resistant to this aminoglycoside (Table 2). Meropenem (MIC_{90}, 8 μg/ml; 86% S) and cefepime (MIC_{90}, 16 μg/ml; 78% S) showed the second lowest resistance rate of 10%.
- The fluoroquinolones evaluated (ciprofloxacin, gatifloxacin and levofloxacin) showed very similar potency (MIC_{50}, 0.25-1 μg/ml) and resistance rates (22-24%; p >0.05) against this worldwide collection of *P. aeruginosa* (Table 2).
- The carbapenems (imipenem and meropenem) were the most active compounds against *Acinetobacter* spp. (Table 3). The rank order by resistance rates among *Acinetobacter* spp. isolates was: imipenem (11%) < meropenem (12%) < cefepime (31%) < gatifloxacin (32%) < tobramycin (33%).
- Few drugs showed an acceptable potency or spectrum against *S. maltophilia*. Trimethoprim/sulfamethoxazole, the "drug-of-choice", was the most active compound (MIC_{90}, ≤0.5 μg/ml; 92% S) with only 5% of isolates being resistant. Resistance rates were also very low for the fluoroquinolones, gatifloxacin (5%) and levofloxacin (6%). On the other hand, only 32% of isolates were susceptible to ciprofloxacin.
- Meropenem showed the lowest resistance and the highest susceptibility rates (17% and 79%, respectively) against all 18,569 NFB evaluated (Table 5). Other compounds with low resistance rates include cefepime (18%), imipenem (18%) and amikacin (20%).

Table 1. Global occurrence rates for non-fermentative Gram-negative bacilli isolates from the SENTRY Antimicrobial Surveillance Program medical centers in 1997-2001 (18,569 strains).

Organism or group	No. of occurrences	% of all isolates
1. *P. aeruginosa*	11,968	64.5
2. *Acinetobacter* spp.[a]	3,468	18.7
3. *S. maltophilia*	1,488	8.0
4. Other *Pseudomonas* spp.[b]	523	2.8
5. *Aeromonas* spp.[c]	258	1.4
6. *Burkholderia* spp.[d]	197	1.1
7. *Alcaligenes* spp.[e]	184	1.0
8. *Campylobacter* spp.[f]	169	0.9
9. *Chryseobacterium* spp.[g]	56	0.3
10. *Pasteurella* spp.[h]	48	0.2
11. Other species[i]	210	1.1

a. Includes *A. anitratus* (256 strains), *A. baumannii* (2,411 strains), *A. calcoaceticus* (243 strains), *A. haemolyticus* (eight strains), *A. junii* (11 strains), *A. lwoffii* (265 strains) and *Acinetobacter* spp., NOS (274 strains).
b. Includes *P. acidivoran* (two strains), *P. alcaligenes* (one strain), *P. diminuta* (one strain), *P. fluorescens* or *fluorescens/putida* (183 strains), *P. mendocina* (four strains), *P. stutzeri* (27 strains), *P. vesicularae* (three strains) and *Pseudomonas* spp., NOS (302 strains).
c. Includes *A. caviae* (40 strains), *A. hydrophila* (149 strains), *A. salmonicida* (one strain), *A. sobria* (nine strains), *A. veronii* (seven strains) and *Aeromonas* spp., NOS (52 strains).
d. Includes *B. cepacia* (189 strains), *B. gladioli* (three strains) and *B. pseudomallei* (five strains).
e. Includes *A. faecalis* (20 strains), *A. xylosoxidans* (144 strains) and *Alcaligenes* spp., NOS (20 strains).
f. Includes *C. coli* (three strains), *C. jejuni* (104 strains) and *Campylobacter* spp., NOS (62 strains).
g. Includes *C. gleum* (one strain), *C. indologenes* (19 strains), *C. meningosepticum* (23 strains), and *Chryseobacterium* spp., NOS (13 strains).
h. Includes *P. haemolytica* (three strains), *P. multocida* (42 strains), *P. pneumotropica* (one strain) and *Pasteurella* spp., NOS (two strains).
i. These strains include 210 isolates from 24 different species.

Table 2. Comparative activity of the 14 most active agents[a] tested against 11,968 strains of *P. aeruginosa* isolated in SENTRY Program hospitals worldwide (1997-2001).

	Cumulative % inhibited at MIC (μg/ml) of:												
Antimicrobial agent	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	% S/R[b]
Cefepime	-	<1	<1	3	14	42	62	78[c]	90	-	-	-	78/10
Ceftazidime	-	<1	<1	2	11	46	67	77	82	-	-	-	77/18
Piperacillin	-	-	-	-	3	9	36	57	69	76	81	87	81/19
Piperacillin/Tazobactam	-	-	-	2	4	12	42	61	72	79	85	-	85/15
Ticarcillin	-	-	-	-	2	3	4	8	30	60	72	84	72/28
Ticarcillin/Clavulanate	-	-	-	-	2	3	4	8	25	58	72	86	72/28
Imipenem	<1	<1	2	14	55	76	82	88	-	-	-	-	82/12
Meropenem	5	16	35	55	70	79	86	90	-	-	-	-	86/10
Amikacin	-	-	<1	2	6	34	68	83	89	92	-	-	89/8
Gentamicin	-	<1	<1	3	27	61	76	81	-	-	-	-	76/19
Tobramycin	-	2	11	52	75	81	82	83	85	-	-	-	82/17
Ciprofloxacin	-	-	58	67	73	78	-	-	-	-	-	-	73/22
Gatifloxacin	<1	2	10	36	56	68	76	-	-	-	-	-	68/24
Levofloxacin	-	-	-	51	63	71	77	-	-	-	-	-	71/23

a. Only agents with > 40% susceptibility rates were listed.
b. Interpretive criteria of the NCCLS. S = susceptible and R = resistant.
c. Underline indicates the breakpoint for susceptibility and - = untested MIC concentration.

Table 3. Comparative activity of the 16 most active agents[a] tested against 3,468 strains of *Acinetobacter* spp. isolated in SENTRY Program hospitals worldwide (1997-2001).

	Cumulative % inhibited at MIC (μg/ml) of:												
Antimicrobial agent	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	% S/R[b]
Cefepime	-	2	4	8	16	28	40	54[c]	69	-	-	-	53/31
Ceftazidime	-	<1	1	2	5	16	32	47	58	-	-	-	47/42
Piperacillin	-	-	-	-	1	3	8	19	34	45	50	55	50/50
Piperacillin/Tazobactam	-	-	-	17	20	24	30	37	47	55	64	-	64/36
Ticarcillin	-	-	-	-	2	6	12	24	39	51	58	61	58/42
Ticarcillin/Clavulanate	-	-	-	-	9	12	19	31	44	54	62	68	62/38
Imipenem	5	18	42	59	74	84	87	89	-	-	-	-	87/11
Meropenem	5	11	27	43	62	79	85	88	-	-	-	-	85/12
Amikacin	-	-	2	5	14	34	49	56	60	64	-	-	60/36
Gentamicin	-	1	3	8	34	44	48	52	-	-	-	-	48/48
Tobramycin	-	2	7	23	44	56	62	67	74	-	-	-	62/33
Ciprofloxacin	-	-	39	45	48	50	-	-	-	-	-	-	48/50
Gatifloxacin	35	43	47	48	51	54	68	-	-	-	-	-	54/32
Levofloxacin	12	21	25	48	50	52	64	-	-	-	-	-	52/36
Tetracycline	-	-	-	-	-	-	53	64	-	-	-	-	53/36
Trim/Sulfa[d]	-	-	-	46	48	-	-	-	-	-	-	-	46/52

a. Only agents with > 40% susceptibility rates were listed.
b. Interpretive criteria of the NCCLS. S = susceptible and R = resistant.
c. Underline indicates the breakpoint for susceptibility and - = untested MIC concentration.
d. Trimethoprim/Sulfamethoxazole

Table 4. In vitro activity of five selected antimicrobials tested against 1,488 strains of *S. maltophilia* isolated in SENTRY Program hospitals in the Asia-Pacific, Europe and Americas (1997-2001).

	MIC (μg/ml)			% by category[b]	
Antimicrobial agent[a]	50%	90%	Range	Susceptible	Resistant
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	92	5
Gatifloxacin	1	4	≤0.5->4	86[c]	5
Levofloxacin	1	4	≤0.5->4	86[c]	6
Ticarcillin/Clavulanate	16	128	≤1->128	86	14
Ceftazidime	8	>16	≤0.12->16	54	34

a. Only agents with > 50% susceptibility were listed.
b. Susceptibility criteria for *P. aeruginosa* were applied.
c. Ciprofloxacin susceptibility rate was only 32%.

Table 5. Rank order of the tested antimicrobial agents versus all 18,569 non-fermentative Gram-negative bacilli isolated in the SENTRY Program worldwide (1997-2001).

	Ranking by % with category:[a]	
Rank	Susceptible (%)	Resistant (%)
1	Meropenem (79)	Meropenem (17)
2	Piperacillin/Tazobactam (78)	Cefepime (18)
3	Amikacin (76)	Imipenem (18)
4	Imipenem (76)	Amikacin (20)
5	Piperacillin (71)	Piperacillin/Tazobactam (22)
6	Ticarcillin/Clavulanate (71)	Ceftazidime (23)
7	Tobramycin (71)	Gatifloxacin (23)
8	Cefepime (69)	Levofloxacin (23)
9	Ceftazidime (69)	Tobramycin (26)
10	Gatifloxacin (68)	Ciprofloxacin (29)

a. Rank 1 = best agent and rank 10 = tenth best antimicrobial.

CONCLUSIONS

- Amikacin, meropenem and cefepime provided the best coverage against *P. aeruginosa* (8 - 10% resistance rates). These results are similar to those observed by other investigators and may help to assist physicians and hospital formulary groups to select the most appropriate empiric antimicrobial therapy for *P. aeruginosa* infections.
- The antimicrobial susceptibility patterns of *Acinetobacter* spp. may vary geographically, but the carbapenems (imipenem and meropenem) are usually the best alternatives for empiric therapy. Cefepime (31% resistance) and gatifloxacin (32% resistance) may be usable in some geographic areas.
- Our results confirmed the excellent in vitro activity of trimethoprim/sulfamethoxazole (5% resistance) against *S.maltophilia* worldwide. In addition, our results indicated that the newer fluoroquinolones (gatifloxacin [5% resistance] and levofloxacin [6% resistance]) represent excellent candidates to be evaluated in post-marketing, clinical studies.
- Comprehensive worldwide surveillance programs remain extremely important to guide empiric antimicrobial therapy for rarely isolated pathogens and also for pathogens that are not routinely tested due to the lack of susceptibility testing standardization.

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