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Escalating Resistance among Non-Fermentative Gram-negative Bacilli: Report from the North American SENTRY Antimicrobial Surveillance Program (1997-2006)

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SENTRY ANTIMICROBIAL SURVEILLANCE

ABSTRACT

Objective: Systemic infections due to non-fermentative Gram-negative bacilli (NFB) are often difficult to treat because of rising resistance rates and limited therapeutic options. We evaluated the occurrence and antimicrobial susceptibility profiles of NFB pathogens collected over 10 years of the SENTRY Antimicrobial Surveillance Program in North America.

Methods: Consecutive clinically significant and non-duplicate NFB strains (12,435 total) were submitted from medical centers in the USA (≥25) and Canada (5; 1997-2002 only) and susceptibility tested by broth microdilution using CLSI methods and interpretive criteria at a central laboratory (JMI Labs, North Liberty, Iowa). Specifically, changes in susceptibility rates were analyzed over time. Carbapenem-resistant *P. aeruginosa* (PSA) and *Acinetobacter* spp. (ASP) were screened for metallo-beta-lactamase (MBL) enzyme production by a disk approximation method or by Etest (AB BIODISK, Solna, Sweden).

Results: The most commonly recovered non-fermentative Gram-negative bacilli were PSA (68%), ASP (14%) and *S. maltophilia* (SM; 11%). Polymyxin B (tested 2001-2006) was very active against PSA and ASP (≥99% susceptible), but displayed more limited activity against other NFB. Tigecycline (2002-2006) exhibited good activity (MIC_{50} / % at ≤2 mg/L) against ASP (0.5/92) and SM (0.5/93), but limited potency against PSA. The activities of other antimicrobials are in the Table. Susceptibility patterns of PSA and SM remained very stable during the decade. In contrast, ASP susceptibility rates decreased for most agents, including (1997/2006 % susceptible): imipenem (94/78), amikacin (92/80), gentamicin (77/61) and ciprofloxacin (73/53). Many imipenem-non-susceptible ASP strains (77%) were from three medical centers in the New York City area, the remaining were from 13 centers and collected mainly in 2006 (61%). Imipenem-resistant PSA strains were widely distributed geographically. No MBL-producing strain was identified among ASP and PSA isolates.

Organism (no. tested)	MIC_{50} (mg/L)/% susceptible[a]				
	Amikacin	Ceftazidime	Imipenem	Levofloxacin	TMP/SMX
Acinetobacter spp. (1,779)	≤4/84	8/59	0.25/91	≤0.5/62	≤0.5/74
Aeromonas spp. (102)	≤4/97	≤1/95	0.5/97	≤0.5/99	≤0.5/87
A. xylosoxidans (118)	>32/14	4/86	2/92	2/57	≤0.5/90
B. cepacia (88)	>32/10	4/74	4/51	2/60	≤0.5/88
P. aeruginosa (8,420)	≤4/96	2/83	1/87	≤0.5/74	>2/46
P. fluorescens/putida (155)	≤4/96	4/90	1/87	≤0.5/85	2/52
S. maltophilia (1,309)	>32/13	8/54	>8/1	1/83	≤0.5/99

a. Based on CLSI breakpoints for *Acinetobacter* spp., *P. aeruginosa* and *S. maltophilia*. TMP/SMX = trimethoprim/sulfamethoxazole.

Conclusions: Therapeutic options to treat NFB infections are becoming increasingly limited secondary to progressively rising resistance rates. Continued NFB surveillance remains necessary to optimize empiric antimicrobial therapy, especially for the less frequently isolated and difficult to test species.

INTRODUCTION

The SENTRY Antimicrobial Surveillance Program is a surveillance study that monitors >100 medical centers worldwide. The Program began in 1997 and monitors the frequency of pathogen occurrence and antimicrobial susceptibility/resistance rates. Bacterial isolates have been collected from bloodstream, respiratory tract, skin and skin structure, urine, and gastrointestinal tract infections. Reports from this study have assisted clinicians when choosing empiric or directed therapy based on local, regional or national resistance patterns and suspected pathogen prevalence.

Non-fermentative Gram-negative bacilli are ubiquitous, widely distributed that have emerged as important causes of nosocomial infections. *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas maltophilia* are the most commonly observed non-fermentors in the clinical setting. These pathogens are intrinsically more resistant to most antimicrobial agents and can acquire additional resistance mechanisms, making the empiric selection antimicrobial therapy difficult.

Here we evaluated the frequency of occurrence of non-fermentative Gram-negative bacilli and their antimicrobial susceptibility patterns, recovered between 1997 and 2006 from patients in North American medical centers that participated in the SENTRY Program.

MATERIALS AND METHODS

Bacterial Strain Collection. A total of 12,435 non-duplicate predominatly non-fermentative Gram-negative bacilli isolates were submitted each year from ≥25 medical centers located in North America (1997-2006) and 5 in Canada (1997-2002 only) as part of the international SENTRY Program. All isolates were collected from bloodstream, lower respiratory tract, skin and skin structure, urine, or gastrointestinal tract sites and determined to be significant by local criteria as the probable cause of infection. The distribution of ranking species are listed in Table 1.

Susceptibility Test Methods. All strains were tested by the Clinical and Laboratory Standards Institute (CLSI M7-A7, 2006) microdilution method in Mueller-Hinton broth using validated panels (TREK Diagnostics, Cleveland, OH) against a variety of antimicrobial agents representing the most common classes and agents used in the empiric or directed treatment of non-fermentative pathogens. Categorical interpretation of MIC results was in accordance with CLSI M100-S18 criteria. Quality control studies utilized the following strains; *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 29213, with all QC results within CLSI specified ranges. *Acinetobacter* spp. and *P. aeruginosa* isolates with elevated MIC values for ceftazidime (>16 mg/L) and the carbapenems imipenem and meropenem (>8 mg/L) were further tested for the production of metallo-ß-lactamases.

RESULTS

- The most frequently observed non-fermentative Gram-negative bacilli recovered from North American patients between 1997 and 2006 included: *P. aeruginosa* (8,420 isolates; 67.7%) > *Acinetobacter* spp. (1,779 isolates; 14.3%) > *S. maltophilia* (1,309 isolates; 10.5%) > *Pseudomonas* spp. (non-*aeruginosa*; 329 isolates; 2.6%) > *Alcaligenes* spp. (157 isolates; 1.3%; Table 1).

Table 1. Frequency of occurrence of non-fermentative Gram-negative bacilli species/genera tested in the SENTRY Program in North America (1997-2006).

Rank	Species/genus group	No. tested (%)
1	*P. aeruginosa*	8,420 (67.7)
2	*Acinetobacter* spp.	1,779 (14.3)
3	*S. maltophilia*	1,309 (10.5)
4	*Pseudomonas* spp.	329 (2.6)
5	*Alcaligenes* spp.	157 (1.3)
6	*Aeromonas* spp.	102 (0.8)
7	*Burkholderia cepacia*	88 (0.7)
8	*Pasteurella* spp.	66 (0.5)
9	*Chryseobacterium* spp.	25 (0.2)
10	*Achromobacter* spp.	18 (0.1)
11	*Agrobacterium* spp.	16 (0.1)
12	*Ochrobacterium anthropi*	15 (0.1)
13	Other Non-fermentors	97 (0.8)

- Polymyxin B was tested against all strains collected in 2001 – 2006 and was the most active agent against *P. aeruginosa* and *Acinetobacter* spp. (>98.6% susceptible), but was less active against other non-fermentative species (70.3-86.3% susceptibility; Table 2).
- Tigecycline (tested from 2002 – 2006) exhibited activity against *Acinetobacter* spp. and *S. maltophilia* (MIC_{50}, 0.5 mg/L and MIC_{90}, 2 mg/L; Table 2), but showed limited activity against *P. aeruginosa* (data not shown).
- Trimethoprim/sulfamethoxazole was the most active agent tested against *S. maltophilia* (MIC_{90}, ≤0.5 mg/L; 98.9% susceptible); followed by tigecycline (MIC_{90}, 2 mg/L) and levofloxacin (MIC_{90}, 4 mg/L; 82.7% susceptible).
- Imipenem-resistant *P. aeruginosa* (7.5% of total) were widely distributed, while 77% of imipenem non-susceptible *Acinetobacter* spp. strains were isolated from three medical centers located in the New York City area.
- No metallo-ß-lactamase producing isolates were identified among *P. aeruginosa* and *Acinetobacter* spp. isolates collected from participating North American medical centers.

Table 2. Antimicrobial susceptibility profiles of the seven most frequently observed non-fermentative Gram-negative bacilli/groups tested in the SENTRY Program in North America (1997-2006).

Organism (no. tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	% susceptible[a]	% resistant[a]
P. aeruginosa (8,420)				
Ceftazidime	≤2	>16	82.7	12.5
Cefepime	4	16	84.3	6.1
Piperacillin/tazobactam	8	>64	89.1	10.9
Imipenem	1	8	86.5	7.5
Meropenem	0.5	8	89.9	5.4
Levofloxacin	≤0.5	>4	73.8	18.9
Amikacin	≤4	8	96.0	2.2
Gentamicin	≤2	8	85.6	9.4
Tobramycin	0.5	4	90.5	7.9
Polymyxin B	≤1	2	99.6	<0.1
Acinetobacter spp. (1,779)				
Ceftazidime	8	>16	59.2	31.6
Imipenem	0.25	4	91.3	4.8
Meropenem	0.5	8	87.0	9.3
Ampicillin/sulbactam	4	>16	69.2	21.3
Levofloxacin	≤0.5	>4	62.4	33.1
Amikacin	≤4	>32	84.3	10.8
Gentamicin	≤2	>8	63.8	32.5
Tobramycin	1	>16	77.1	19.4
Polymyxin B	≤1	2	98.6	1.4
Tigecycline	0.5	2	91.8[b]	0.4[b]
S. maltophilia (1,309)				
Ceftazidime	8	>16	54.1	33.7
Ticarcillin/clavulanate	16	128	56.0	14.3
Levofloxacin	1	4	82.7	8.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.9	1.1
Polymyxin B	≤1	>4	72.9[c]	14.5[c]
Tigecycline	0.5	2	93.4[b]	2.4[b]
Alcaligenes xylosoxidans (188)				
Ceftazidime	4	16	86.4	8.5
Cefepime	16	>16	14.5	45.3
Imipenem	2	4	92.4	0.0
Levofloxacin	2	>4	56.8	20.3
Amikacin	>32	>32	14.4	82.2
Gentamicin	>8	>8	9.3	85.6
Polymyxin B	2	4	70.3	7.8
Pseudomonas fluorescens/putida (155)				
Ceftazidime	4	16	89.7	6.5
Cefepime	2	8	91.0	4.5
Piperacillin/tazobactam	8	32	89.0	4.5
Imipenem	1	8	87.1	7.7
Meropenem	2	8	85.7	5.8
Ciprofloxacin	≤0.25	>2	85.8	10.3
Levofloxacin	≤0.5	4	85.2	9.0
Amikacin	≤4	8	95.5	2.6
Gentamicin	≤2	4	93.5	5.8
Tobramycin	≤0.25	1	95.5	3.2
Trimethoprim/sulfamethoxazole	2	>2	51.6	48.4
Polymyxin B	≤1	4	86.3	10.0
Aeromonas spp. (102)				
Ceftazidime	≤2	≤2	95.1	2.9
Cefepime	≤0.12	0.5	100.0	0.0
Imipenem	0.5	4	97.0	2.0
Levofloxacin	≤0.5	≤0.5	99.0	1.0
Amikacin	≤4	8	97.1	0.0
Gentamicin	≤2	≤2	98.0	0.0
Polymyxin B	≤1	>4	81.0	14.3
Burkholderia cepacia (88)				
Ceftazidime	4	>16	73.9	15.9
Meropenem	2	>8	75.0	13.6
Piperacillin/tazobactam	8	>64	67.0[c]	19.3[c]
Ticarcillin/clavulanate	>128	>128	13.6	80.5
Levofloxacin	2	>4	60.2	25.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	87.5	12.5

a Criteria as published by the CLSI [2008].
b. Criteria as published by USA-FDA for Enterobacteriaceae were used for comparison purposes only.
c. Susceptibility percentages were calculated using breakpoints established for Other Non-Enterobacteriaceae by the CLSI. These figures are for comparison purposes only.

Table 3. Longitudinal susceptibility trends over a ten year period for the three most prevalent non-fermentative Gram-negative bacilli species/groups observed in the SENTRY Program in North America (1997-2006).

Organism/antimicrobial agent	Year (no. Isolates) % susceptible[a] 1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	All
P. aeruginosa	(1130)	(1099)	(1041)	(1107)	(815)	(1056)	(398)	(765)	(522)	(487)	(8420)
Amikacin	96.0	95.0	97.2	95.5	96.8	96.5	97.2	96.6	96.9	96.1	96.0
Gentamicin	85.6	86.6	86.7	83.4	85.2	86.0	90.5	88.4	88.1	89.7	85.6
Imipenem	86.8	84.7	88.4	87.7	86.7	86.5	89.4	86.4	83.7	83.0	86.5
Ciprofloxacin	79.8	77.3	76.1	73.8	75.8	73.3	75.4	76.2	76.6	80.1	76.3
Cefepime	78.3	85.6	84.5	84.4	85.0	85.2	88.4	84.7	83.9	87.2	84.3
Acinetobacter spp.	(223)	(215)	(149)	(180)	(207)	(160)	(135)	(194)	(145)	(171)	(1779)
Amikacin	92.4	83.3	85.9	86.1	87.0	86.3	82.2	77.3	80.0	80.1	84.3
Gentamicin	76.7	67.0	64.4	68.3	59.2	63.1	63.4	54.6	56.6	60.8	63.8
Imipenem	94.2	95.3	98.7	96.7	87.9	87.5	88.9	92.8	92.4	77.8	91.3
Ciprofloxacin	72.6	67.4	65.1	63.3	53.1	56.9	57.0	50.0	48.3	53.2	59.2
S. maltophilia	(177)	(173)	(136)	(146)	(178)	(161)	(54)	(111)	(85)	(88)	(1309)
Levofloxacin	77.4	73.4	87.5	87.0	88.2	84.5	83.3	78.4	88.2	81.8	82.7
Trimethoprim/sulfamethoxazole	92.1	96.0	100.0	97.9	97.2	98.1	100.0	98.2	100.0	95.5	98.9

a. Criteria as published by the CLSI M100-S18.

- *Aeromonas* spp. isolates as a group showed high susceptibility rates (≥95.1%) for all agents except polymyxin B, which inhibited only 81.0% at ≤2 mg/L.
- Susceptibility rates remained very stable among tested compounds against *P. aeruginosa* and *S. maltophilia* over the 10-year period (1997 – 2006).
- Susceptibility rates of *Acinetobacter* spp., during the course of the study, showed decreases for amikacin (92.4 to 80.1%; -12.3%), gentamicin (76.7 to 60.8%; -15.9%), imipenem (94.2 to 77.8%; -16.4) and ciprofloxacin (72.6 to 53.2; -19.4).

CONCLUSIONS

- *P. aeruginosa*, *Acinetobacter* spp. and *S. maltophilia* represented >92% of non-fermentative Gram-negative bacilli isolated in North American medical centers in the 1997-2006 period.
- Therapeutic options to treat infections caused by non-fermentative Gram-negative bacilli are becoming more limited due to rising antimicrobial resistance rates.
- Polymyxin B was the most active agent tested against *P. aeruginosa* and *Acinetobacter* spp. isolates; its use may be preferred in some geographic areas due to high prevalence of multidrug-resistant strains.
- Longitudinal comparisons of susceptibility data over the 10-year interval showed declining susceptibilities among multiple antimicrobial agents against *Acinetobacter* spp. but very stable susceptibility rates for *P. aeruginosa* and *S. maltophilia*.
- Continued surveillance among non-fermentative Gram-negative bacilli is warranted due to rapidity in resistance mechanism acquisition and potential for clonal spread.

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