Antimicrobial Activity of Alternative Broad-Spectrum Agents Against Imipenem-Non-Susceptible Gram-Negative Bacilli: Report from the USA MYSTIC Programme, 1999 - 2004

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

ABSTRACT

Background: Increasing antimicrobial resistance (R) rates in Enterobacteriaceae (ENT) and non-fermentative Gram-negative bacilli (NFB), including to the carbapenems, severely limits the therapeutic options for treating serious infections caused by these pathogens. We evaluated the susceptibility (S) rates of alternative broad-spectrum agents tested against strains non-S to imipenem (IMP).

Methods: 10,308 Gram-negative clinical isolates were collected from 10-15 medical centers as part of the annual MYSTIC Programme (1999 and 2004). Isolates were tested for S by CLSI M7-A6 broth microdilution methods and interpreted using M100-S15 criteria.

Results: During this 6-year period, 482 (4.7%) isolates were non-S to IMP (MIC, ≥ 8 μg/ml). The majority were *P. aeruginosa* ([PSA] 333; 69.1%) followed by *Acinetobacter* spp. (ACB; 70; 14.5%), other NFB (59; 12.2%) and ENT (20; 4.1%). The activities of six antimicrobial agents are summarized in the table:

	MIC (μg/ml)				
Antimicrobial agent	50%	90%	Range	% S	% R
Meropenem	16	32	0.12->32	22.6	55.4
Ciprofloxacin (CIP)	>2	>2	≤0.25->2	32.0	60.0
Ceftazidime (CTZ)	16	>16	≤0.12->16	45.2	44.8
Cefepime (CPM)	16	>16	≤0.12->16	40.2	38.2
Tobramycin	2	>8	≤1->8	59.1	37.6
Piperacillin/Tazobactam (P/T)	64	>128	≤1->128	52.9	44.0

Against IMP-non-S PSA isolates, aminoglycosides demonstrated the greatest S rates (52.9 - 85.7%) followed by P/T (64.0%) and CTZ (51.7%). An escalation in IMP-non-S ACB (32.9% of total) was noted in 2004 where tobramycin was the most active agent with 45.7% S. Gentamicin, CIP and CPM were the most active agents (45.0 - 50.0% S) against the IMP-non-S ENT isolates.

Conclusions: Multidrug-R, including IMP non-S, is much more prevalent in NFB than ENT. Continued surveillance of these Gram-negative pathogens will be necessary to monitor increasing antimicrobial R to carbapenems and promote the development of new agents.

INTRODUCTION

Increasing resistance rates among many bacterial species to multiple antimicrobial agents have been reported over the past decade. Recently, new options for treating Gram-positive pathogens causing serious infections have been developed with novel classes including quinupristin/dalfopristin, linezolid and daptomycin. Unfortunately, less attention has been placed on the development of agents with activity against Gram-negative pathogens.

The emergence of resistance among *Pseudomonas aeruginosa, Acinetobacter baumannii*, other non-fermentative Gram-negative bacilli and Enterobacteriaceae to commonly used broad spectrum agents has occurred worldwide, and involves a number of resistances targeting ß-lactams (including carbapenems), aminoglycosides and fluoroquinolones, among others. The presence of resistance mechanisms highly amenable to horizontal transfer via mobile genetic elements (extended-spectrum ß-lactamases, metallo-ß-lactamases, cephalosporinases, aminoglycoside inactivating enzymes) is being documented regularly and has become especially worrisome.

Because of the high prevalence of co-resistance among and between antimicrobial classes in these bacterial species, resistance studies are especially important in identifying potentially usable agents. In certain locales, high resistance rates have dictated the return to older compounds such as polymyxin B and colistin (polymyxin E).

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Programme for the United States (USA) was initiated in 1999 to monitor the antimicrobial activity of meropenem and compare the results with those for other broad-spectrum antimicrobial agents. In this study the susceptibility rates of 11 alternative broad-spectrum antimicrobial agents were tested against all imipenem non-susceptible isolates identified between the years 1999 and 2004.

MATERIALS AND METHODS

Organism collection. A total of 10,308 Gram-negative, non-duplicate, clinical isolates were collected from up to 15 North American medical centers participating in the MYSTIC Programme during a six-year period (1999 - 2004). The species and number of strains non-susceptible to imipenem (MIC, ≥ 8 μg/ml) included *P. aeruginosa* (333 strains; 3.2% of all strains tested) followed by *Acinetobacter* spp. (70 strains; 0.7%), other non-fermentative bacilli (59 strains; 0.6%) and Enterobacteriaceae (20 strains; 0.2%).

Susceptibility tests. MIC tests were performed according to the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution methods (M7-A6, 2003) in commercially prepared and validated dry-form panels (TREK Diagnostics, Cleveland, OH, USA). The tested broad-spectrum agents included imipenem, meropenem, aztreonam, ceftazidime, ceftriaxone, cefepime, piperacillin/tazobactam, amikacin, gentamicin, tobramycin ciprofloxacin and levofloxacin.

Categorical interpretations of susceptibility/resistance were based on CLSI interpretive criteria as published in M100-S15 (2005. Quality control was performed weekly using *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853.

RESULTS

- A total of 482 imipenem non-susceptible (intermediate and resistant; MIC ≥ 8 μg/ml) isolates were recovered through the MYSTIC Programme between 1999 and 2004, including *P. aeruginosa* (333; 69.1%), *Acinetobacter* spp. (70; 14.5%), other non-fermentors (59; 12.2%) and Enterobacteriaceae (20; 4.1%; Table 1).
- Percentages of *P. aeruginosa* that were non-susceptible to imipenem varied between the years 1999 and 2004, ranging from 11.5 to 21.8%; for *Acinetobacter* spp., 8.1 to 19.6%; for other non-fermentative bacilli, 7.8 to 31.9%; and for Enterobacteriaceae, 0.1 to 0.9% (Table 1). Lowest susceptibility rates among all groups were observed in the initial years, 1999 and 2000.
- Overall, imipenem non-susceptibility among non-fermentative Gram-negative bacilli (15.0%) was far greater than that seen with the Enterobacteriaceae (0.3%).
- Among the *P. aeruginosa* isolates tested, the aminoglycosides demonstrated the highest susceptibility rates and greatest potency with amikacin (85.7% susceptible; MIC_{50}, 4 μg/ml) > tobramycin (68.2%; MIC_{50}, ≤ 1 μg/ml) > gentamicin (52.9%; MIC_{50}, ≤ 4 μg/ml; Table 2).
- Other ß-lactams showed only modest activity against the *P. aeruginosa* population tested, with piperacillin/tazobactam (64.0%), ceftazidime (51.7%) and cefepime (47.7%) providing the best overall levels of susceptibility.

RESULTS CONTINUED

- Tobramycin (45.7% susceptible) provided the broadest coverage against *Acinetobacter* spp. followed by amikacin (39.1%), levofloxacin (15.6%) and gentamicin (11.4%). All remaining agents were lacking in coverage with less than 8% susceptibility (Table 2).
- Among other non-fermentative bacilli, susceptibility rates to the antimicrobial agents tested varied from only 20.3% (ceftriaxone) to 57.6% (ceftazidime); amikacin and piperacillin/tazobactam also provided ≥ 50.0% coverage.
- Modest activity against the imipenem non-susceptible Enterobacteriaceae was displayed by gentamicin (50.0% susceptible; MIC_{50}, 4 μg/ml) and ciprofloxacin (45.0%; MIC_{50}, 2 μg/ml); other agents were less effective with aztreonam being the least active agent (25.0% susceptible).
- Among the imipenem non-susceptible isolates tested, 24.6% of *P. aeruginosa*, 32.2% of other non-fermentative bacilli and 30.0% of Enterobacteriaceae remained susceptible to meropenem, although potency of the two carbapenem agents (MIC_{50} and MIC_{90} values) remained very similar.

Table 1. Rates of imipenem non-susceptible (N-S) isolates tested within the MYSTIC Programme (1999 - 2004).

	Year						
Organism	1999	2000	2001	2002	2003	2004	1999-2004
P. aeruginosa							
Total	193	299	298	321	454	689	2,254
Number IMP N-S[a]	42	57	43	37	70	84	333
Percent N-S	21.8	19.1	14.4	11.5	15.4	12.2	14.8
Acinetobacter spp.							
Total	32	56	79	69	111	142	489
Number IMP N-S[a]	6	11	13	8	9	23	70[b]
Percent N-S	18.8	19.6	16.5	11.6	8.1	16.2	14.3
Non-fermentative bacilli							
Total	22	47	48	61	56	103	337
Number IMP N-S[a]	7	15	6	12	11	8	59[c]
Percent N-S	31.8	31.9	12.5	19.7	19.6	7.8	17.5
Enterobacteriaceae							
Total	708	1,048	1,037	1,131	1,439	1,865	7,228
Number IMP N-S[a]	3	9	3	2	1	2	20[d]
Percent N-S	0.4	0.9	0.3	0.2	0.1	0.1	0.3

a. Imipenem non-susceptibility (MIC, ≥ 8 μg/ml) based on CLSI M100-S15 interpretative criteria.
b. Includes *Acinetobacter baumannii* (61 strains) and *Acinetobacter* spp. (nine strains).
c. Includes *Aeromonas* spp. (one strain), *Alcaligenes faecalis* (four strains), *A. xylosoxidans* (11 strains), *Alcaligenes* spp. (one strain), *Bordetella bronchiseptica* (one strain), *Burkholderia cepacia* (17 strains), *Chryseobacterium indologenes* (one strain), *Chromobacterium violaceum* (one strain), *Myroides odoratum* (one strain), *Ochrobactrum anthropi* (one strain), *Pseudomonas fluorescens* (six strains), *P. fluorescens/putida* (six strains), *P. putida* (two strains), *P. vesicularis* (one strain), *Pseudomonas* spp. (four strains) and unidentified non-fermentative GNR (one strain). *S. maltophilia* were not sampled in the MYSTIC Programme.
d. Includes *Enterobacter aerogenes* (one strain) *E. cloacae* (two strains), *E. gergoviae* (one strain), *Klebsiella oxytoca* (one strain), *K. pneumoniae* (six strains), *Proteus mirabilis* (six strains) and *Serratia marcescens* (three strains).

Table 2. Antimicrobial activity of 11 broad-spectrum agents tested against imipenem non-susceptible isolates within the USA MYSTIC Programme (1999 - 2004).

	MIC (μg/ml)			% Category[a]	
Organism/antimicrobial agent (no. tested)	50%	90%	Range	Susceptible	Resistant
P. aeruginosa (333)					
Imipenem	16	32	8->32	0.0	62.2
Meropenem	16	32	0.5->32	24.6	50.8
Aztreonam	>16	>16	≤1->16	28.8	52.9
Ceftriaxone	>32	>32	2->32	2.4	77.8
Ceftazidime	8	>16	1->16	51.7	36.3
Cefepime	16	>16	0.5->16	47.7	26.1
Piperacillin/Tazobactam	32	>128	≤1->128	64.0	36.0
Amikacin (84)[b]	≤4	32	≤4->32	85.7	8.3
Gentamicin	4	>8	≤2->8	52.9	34.8
Tobramycin	≤1	>8	≤1->8	68.2	28.8
Ciprofloxacin	>2	>2	≤0.25->2	37.2	54.4
Levofloxacin (154)[c]	>8	>8	0.25->8	22.1	61.7
Acinetobacter spp.[d] (70)					
Imipenem	16	32	8->32	0.0	55.7
Meropenem	32	>32	4->32	2.9	90.0
Aztreonam	>16	>16	>16	0.0	100.0
Ceftriaxone	>32	>32	16->32	0.0	91.4
Ceftazidime	>16	>16	2->16	7.1	90.0
Cefepime	>16	>16	2->16	4.3	82.9
Piperacillin/Tazobactam	>128	>128	4->128	2.9	87.1
Amikacin (23)[b]	>32	>32	≤4->32	39.1	52.2
Gentamicin	>8	>8	≤2->8	11.4	81.4
Tobramycin	8	>8	≤1->8	45.7	50.0
Ciprofloxacin	>2	>2	≤0.25->2	4.3	95.7
Levofloxacin (32)[c]	>8	>8	0.12->8	15.6	84.4
Other non-fermentors[e] (59)					
Imipenem	8	>32	8->32	0.0	47.5
Meropenem	8	>32	0.25->32	32.2	40.7
Aztreonam	>16	>16	≤0.12->16	22.0	69.5
Ceftriaxone	>32	>32	1->32	20.3	66.1
Ceftazidime	8	>16	0.25->16	57.6	35.6
Cefepime	16	>16	≤0.12->16	39.0	47.5
Piperacillin/Tazobactam	16	>128	≤1->128	55.9	32.2
Amikacin (8)[b]	≤4	>32	≤4->32	50.0	50.0
Gentamicin	>8	>8	≤2->8	32.2	64.4
Tobramycin	>8	>8	≤1->8	32.2	64.4
Ciprofloxacin	>2	>2	≤0.25->2	30.5	52.5
Levofloxacin (19)[c]	8	>8	0.12->8	36.8	52.6
Enterobacteriaceae[f] (20)					
Imipenem	16	>32	8->32	0.0	75.0
Meropenem	16	>32	0.12->32	30.0	55.0
Aztreonam	>16	>16	≤0.12->16	25.0	75.0
Ceftriaxone	32	>32	≤0.016->32	35.0	40.0
Ceftazidime	>16	>16	≤0.12->16	35.0	55.0
Cefepime	>16	>16	≤0.12->16	45.0	55.0
Piperacillin/Tazobactam	>128	>128	≤1->128	35.0	60.0
Gentamicin	4	>8	≤2->8	50.0	45.0
Tobramycin	>8	>8	≤1->8	35.0	60.0
Ciprofloxacin	2	>2	≤0.25->2	45.0	50.0

a. Criteria as published by the CLSI, 2005.
b. Amikacin was tested against 2004 isolates only.
c. Levofloxacin was tested against 2003 and 2004 isolates only.
d. Includes *Acinetobacter baumannii* (61 strains) and *Acinetobacter* spp. (nine strains).
e. Includes *Aeromonas* spp. (one strain), *Alcaligenes faecalis* (four strains), *A. xylosoxidans* (11 strains), *Alcaligenes* spp. (one strain), *Bordetella bronchiseptica* (one strain), *Burkholderia cepacia* (17 strains), *Chryseobacterium indologenes* (one strain), *Chromobacterium violaceum* (one strain), *Myroides odoratum* (one strain), *Ochrobactrum anthropi* (one strain), *Pseudomonas fluorescens* (six strains), *P. fluorescens/putida* (six strains), *P. putida* (two strains), *P. vesicularis* (one strain), *Pseudomonas* spp. (four strains) and unidentified non-fermentative GNR (one strain).
f. Includes *Enterobacter aerogenes* (one strain), *E. cloacae* (two strains), ENG (one strain), *Klebsiella oxytoca* (one strain), *K. pneumoniae* (six strains), *Proteus mirabilis* (six strains) and *Serratia marcescens* (three strains).

Table 3. Antimicrobial activity of 11 antimicrobial agents for all imipenem non-susceptible isolates within the USA MYSTIC Programme.

	MIC (μg/ml)			% Category[a]	
Organism/antimicrobial agent (no. tested)	50%	90%	Range	Susceptible	Resistant
All isolates (482)					
Imipenem	16	32	8->32	0.0	60.0
Meropenem	16	32	0.12->32	22.6	55.4
Aztreonam	>16	>16	≤1->16	23.7	62.7
Ceftriaxone	>32	>32	≤0.016->32	5.6	76.8
Ceftazidime	16	>16	≤0.12->16	45.2	44.8
Cefepime	16	>16	≤0.12->16	40.2	38.2
Piperacillin/Tazobactam	64	>128	≤1->128	52.9	44.0
Amikacin (117)[b]	8	>32	≤4->32	74.4	19.7
Gentamicin	8	>8	≤2->8	44.2	45.6
Tobramycin	2	>8	≤1->8	59.1	37.6
Ciprofloxacin	>2	>2	≤0.25->2	32.0	60.0
Levofloxacin (208)[c]	>8	>8	0.12->8	22.6	64.4

a. Criteria as published by the CLSI, 2005.
b. Amikacin was tested against 2004 isolates only.
c. Levofloxacin was tested against 2003 and 2004 isolates.

CONCLUSIONS

- Multidrug-resistance, including non-susceptibility to imipenem, is more prevalent in non-fermentative Gram-negative bacilli (most notably *P. aeruginosa*) than in Enterobacteriaceae as monitored within the MYSTIC Programme (1999 to 2004).
- Against all 482 imipenem non-susceptible isolates tested, the rank order of susceptibilities to the tested antimicrobial agents was: amikacin > tobramycin > piperacillin/tazobactam > ceftazidime > gentamicin > cefepime (Table 3).
- Continued surveillance of these pathogen populations is encouraged to monitor emergence of resistance to carbapenems and other antimicrobial classes, and to promote the development of urgently needed therapeutic agents.

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