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Global Assessment of the Polymyxin B Antimicrobial Activity against 55,151 Clinical Strains of Gram-Negative Bacilli: Report from the SENTRY Antimicrobial Surveillance Program (2001-2004)



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AMENDED ABSTRACT

Background. The emergence of multidrug-resistant (MDR) *P. aeruginosa* (PSA) and *Acinetobacter* spp. (ASP) isolates causing lifethreatening infections has restored the potential therapeutic indication for the parenteral use of the polymyxins. **Methods.** 55,151 Gram-negative bacilli isolated from diverse sites of infection were tested for susceptibility (S) against polymyxin B (PB) and > 30 drugs by CLSI broth microdilution method and the results were interpreted according to the 2005 CLSI M100-S15 document (PB S breakpoint of \leq 2 µg/ml). The isolates were collected in the Asia-Pacific region (APAC; 17 medical centers [MC]), Europe (EU; 30 MC), Latin America (LA; 12 MC), and North America (NA; 43 MC) in 2001 - 2004. Isolates resistant (R) to all other antimicrobials tested were considered MDR.

Results. PB showed excellent potency and spectrum against PSA (8,705 strains, MIC_{50/90}, \leq 1/2 μg/ml; 98.7% S) and ASP (2,621 strains, MIC_{50/90}, \leq 1/2 μg/ml; 97.9% S). PB R rates were slightly higher for carbapenem-R PSA (1,398 strains, 2.4% R) and ASP (495 strains, 2.8% R) or MDR PSA (209, 3.3% R) and ASP (231, 3.2% R) when compared to the entire group. PB-R PSA varied from 2.9% in APAC to 1.1% in EU, LA and NA; while PB-R ASP varied from 2.7% in EU to 1.7% in NA and LA. PB also showed excellent activity against *Citrobacter* spp. (MIC₉₀, \leq 1 μg/ml; 99.1% S), *E. coli* (MIC₉₀, \leq 1 μg/ml; 99.5% S) and *Klebsiella* spp. (MIC₉₀, \leq 1 μg/ml; 98.2% S). PB activity was variable against *Enterobacter* (MIC₅₀, \leq 1 μg/ml; 83.3% S) and *S. maltophilia* (MIC₅₀, 1 μg/ml; 72.4% S), and very limited (MIC₅₀, > 8 μg/ml) against *B. cepacia* (11.8% S), *Serratia* spp. (5.4% S), indole-positive *Proteus* (1.3% S) and *P. mirabilis* (0.7% S).

Conclusions: PB was highly active against PSA and ASP, including MDR strains. The emergence of acquired R to PB is of great concern since these agents are typically regarded as agents of last resort with no therapeutic option left behind.

INTRODUCTION

The polymyxins were discovered in 1947 and introduced into clinical practice in the 1950's. The exact mechanism of action of polymyxins is not completely known but these agents have surfactant activity, which disrupts the bacterial outer and cytoplasmic membranes. Only polymyxins B and E (colistin) were considered clinically safe and used extensively for the treatment of Gramnegative infections until the 1970's when the development of better-tolerated antipseudomonal agents occurred. The emergence of multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp. has restored the current systemic use of polymyxins.

The polymyxins have activity against a wide variety of Gram-negative bacilli and resistance is associated with two mechanisms: mutation or adaptation through a change in the bacterium's outer membrane which prevent the drug from reaching the inner cytoplasmic membrane. Although resistance to polymyxins has been rarely documented, it could impose serious consequences since no antimicrobial agent would be available for the treatment of infections caused by some multidrug-resistant *P. aeruginosa* and *Acinetobacter* spp. strains.

The main objective of this study was to assess the contemporary activity and spectrum of polymyxin B against a worldwide Gram-negative bacilli collection isolated through the SENTRY Antimicrobial Surveillance Program (2001 - 2004).

MATERIALS AND METHODS

Study design. The SENTRY Program monitored the predominant pathogens and their antimicrobial resistance patterns via a broad network of sentinel hospitals in 4 major world regions: Asia-Pacific, Europe, Latin America, and North America (United States and Canada). Guided by common protocols, bacterial isolates from diverse body sites were forwarded to the regional monitors: JMI Laboratories in North Liberty, Iowa (for isolates from North America, Latin America and Europe), and Women's and Children's Hospital, in Adelaide, Australia (for isolates from the Asia-Pacific region) for confirmation of organism identification and susceptibility testing. Only a single isolate per patient could be referred to the monitoring center. Common reagents and methodologies were used in both reference laboratories.

Participating medical centers. The number of participating medical centers varied according to the geographic region: 5 sites in Canada, 37 in the United States among North American sites, 30 in Europe, 12 in Latin America, and 17 in the Asia-Pacific region.

Bacterial isolates. A total of 55,151 bacterial isolates were collected between January 2001 and December 2004. All isolates were identified at the participating institution by the routine methodology in use at each laboratory. Isolates exhibiting MIC \geq 16 µg/ml for imipenem or meropenem were considered resistant to carbapenems. Isolates exhibiting resistance to piperacillin/tazobactam, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, and amikacin were categorized as multidrug-resistant.

<u>Susceptibility testing</u>. Antimicrobial susceptibility testing was performed and interpreted according to the Clinical and Laboratory Standards Institute (CLSI, formerly the NCCLS) guidelines for broth microdilution methods. Dry-form (validated) microdilution panels and broth for inoculation were purchased from Trek Diagnostics Inc. (Cleveland, OH, USA). Testing of quality control strains *Escherichia coli* ATCC 25922 and 35218, and *Pseudomonas aeruginosa* ATCC 27853 were performed for quality assurance purposes.

RESULTS

- Only polymyxin B demonstrated reasonable potency and spectrum against *Acinetobacter* spp. (MIC_{50/90}, \leq 1/2 µg/ml; 97.9% susceptible) and *P. aeruginosa* (MIC_{50/90}, \leq 1/2 µg/ml; 98.7% susceptible). Susceptibility rates for other antimicrobial agents tested varied from 44.3% (ciprofloxacin) to 81.1% (imipenem) for *Acinetobacter* spp. and from 70.5% (ciprofloxacin) to 88.3% (amikacin) for *P. aeruginosa* (Table 1).
- Polymyxin B showed variable activity against some other non-fermentative Gram-negative bacilli such as *Pseudomonas* spp. other than *P. aeruginosa* (MIC_{50/90}, ≤ 1/4 µg/ml; 88.3% susceptible) and *S. maltophilia* (MIC_{50/90}, 1/8 µg/ml; 72.4% susceptible), and limited activity against *B. cepacia* MIC₅₀, >8 µg/ml; 11.8% susceptible; Table 1).
- Against Enterobacteriaceae, polymyxin B exhibited high activity against Citrobacter spp. (MIC₉₀, ≤ 1 μg/ml; 99.1% susceptible), E. coli (MIC₉₀, ≤ 1 μg/ml; 99.5% susceptible) and Klebsiella spp. (MIC₉₀, ≤ 1 μg/ml; 98.2% susceptible). However, it showed variable activity against Enterobacter spp. (MIC₅₀, ≤ 1 μg/ml; 83.3% susceptible) and limited activity (MIC₅₀, > 8 μg/ml) against Serratia spp., indole-positive Proteus and P. mirabilis (Table 2).
- Susceptibility rates varied according to the geographic region (Table 3).
 Among *P. aeruginosa*, the polymyxin resistance rates were 2.9% in the Asia-Pacific region and 1.1% in Europe, Latin America and North America.
 Against *Acinetobacter* spp., the polymyxin resistance rates were 2.7% in Europe > 1.9% in the Asia-Pacific region > 1.7% in Latin America and North America.
- A total of 495 *Acinetobacter* spp. and 1,398 *P. aeruginosa* isolates were resistant to carbapenems (imipenem or meropenem MIC, ≥ 16 μg/ml; Table 4) while 209 *P. aeruginosa* and 231 *Acinetobacter* spp. strains were considered multidrug-resistant strains. Polymyxin B resistance rates were slightly greater among carbapenem-resistant *P. aeruginosa* (2.4%) and *Acinetobacter* spp. (2.8%) or multidrug-resistant *P. aeruginosa* (3.3%) and *Acinetobacter* spp. (3.2%) when compared to the entire group of isolates by species.

2001 - 2004).				
		MIC (μο		
Organism/antimicrobial agent (no. tested)	50%	90%	Range	% susceptible/resistant
Acinetobacter spp. (2,621)				
Polymyxin B	≤1	2	≤1 - >8	97.9/2.1
Ceftazidime	16	>16	≤1->16	44.6/48.3
Cefepime	16	>16	<0.12->16	47.7/37.3
Ampicillin/sulbactam	8	>32	_ <0.25->32	56.2/31.6
Imipenem	0.5	>8	_ <0.06->8	81.1/15.8
Meropenem	1	>8	_ 0.016->8	77.7/17.0
Ciprofloxacin	>2	>2	≤0.016->2	44.3/55.0
Amikacin	4	>32	<0.25->32	60.2/35.8
B. cepacia (153)	·	, 0_	_00 / 0_	
Polymyxin B	>8	>8	0.5->8	11.8/88.2
Ceftazidime	2	8	≤1->16	92.2/5.2
Cefepime	8	>16	<u>≤</u> 0.12->16	73.2/13.1
Piperacillin/tazobactam	4	64	<u>_</u> 0.12 > 10 ≤0.5->256	83.0/7.8
Imipenem	4	>8	_0.06->8	58.2/10.5
Meropenem	2	4	_0.06→0 ≤0.06->16	94.1/4.6
Ciprofloxacin	1	>4	<u>_</u> 0.016->4	54.9/28.8
Amikacin	>32	>32	<u>_</u> 0.010 > 1 ≤0.25->32	15.7/70.6
Trimethoprim/sulfamethoxazole	<i>≤</i> 0.5	>2	_0.20 > 02 ≤0.5->2	85.6/14.4
P. aeruginosa (8,705)	_		_	
Polymyxin B	≤1	2	≤1->8	98.7/1.3
Ceftazidime	4	>16	> 16 ≤1->16	76.6/18.7
Cefepime	4	>16	<u>_</u>	77.1/11.3
Piperacillin/tazobactam	8	>64	<u>_</u> 0.12→10 ≤0.12->64	82.8/17.2
Imipenem	1	>8	_0.06->8	79.3/12.5
Meropenem	0.5	>8	0.016->8	81.8/12.0
Ciprofloxacin	0.25	>4	≤0.016->4	70.5/25.3
Amikacin	4	32	≤0.25->32	88.3/8.9
Pseudomonas spp. (non-aeruginosa; 282) _p		_	
Polymyxin B	<i>–</i> ≤1	4	<1->8	88.3/11.7
Ceftazidime		>16	> 5 ≤1->16	83.0/13.1
Cefepime	2	16	<u>_</u> 1,7,13 ≤0.12->16	80.5/7.8
Piperacillin/tazobactam	8	>64	<u>_</u> 0.12 > 10 ≤0.5->64	77.7/12.1
Imipenem	1	8	<u>_</u> 0.0 > 0 + ≤0.06->8	85.1/8.2
Meropenem	1	>8	0.03->8	80.2/11.9
Ciprofloxacin	0.12	4	≤0.016->4	75.2/19.9
Amikacin	2	16	<0.25->32	90.1/7.1
Stenotrophomonas maltophilia (1,256)	<u>_</u>	10	_0.20 / 02	
Polymyxin B	1	8	≤1->8	72.4/27.6
Ceftazidime	8	>16	≤1->6 ≤1->16	52.4/34.7
	32			
Ticarcillin/clavulanate	3∠ 1	128	≤16->128 <0.03 > 4	47.6/17.4 86.0/5.8
Levofloxacin Trimethoprim/sulfamethoxazole	· · · · · · · · · · · · · · · · · · ·	4	≤0.03->4 ≤0.5->2	86.9/5.8 97.0/3.0

	% susceptible (no. of isolates)				
Organism/antimicrobial agent (no. tested)	APAC ^a	Europe	Latin America	North America	
Acinetobacter spp.	(411)	(851)	(664)	(695)	
Polymyxin B	98.1	97.3	98.3	98.3	
Ceftazidime	58.4	39.7	32.4	54.2	
Cefepime	58.4	43.9	36.4	56.8	
Ampicillin/sulbactam	59.2	48.4	51.8	70.5	
Imipenem	73.7	73.7	86.4	89.4	
Meropenem	73.0	70.4	83.6	83.7	
Ciprofloxacin	55.0	38.7	34.8	54.0	
Amikacin	64.0	55.0	40.4	83.2	
P. aeruginosa	(898)	(3,145)	(1,626)	(3,036)	
Polymyxin B	97.1	98.9	98.9	98.9	
Ceftazidime	81.6	74.9	60.9	85.4	
Cefepime	82.3	75.4	62.0	85.4	
Ampicillin/sulbactam	86.1	81.2	72.0	89.2	
Imipenem	82.2	78.1	66.1	86.9	
Meropenem	85.7	80.6	68.0	89.4	
Ciprofloxacin	81.2	70.1	57.3	74.9	
Amikacin	92.7	0.88	70.8	96.6	

b. Includes P. alcaligenes (three strains), P. fluorescens (52 strains), P. fluorescens/putida (18 strains). P. luteola (seven strains). P. mendocina

(six strains), P. oryzihabitans (24 strains), P. putida (39 strains), Pseudomonas spp. (117 strains) and P. stutzeri (16 strains).

		MIC (µg	g/ml)	
Organism/antimicrobial agent (no. tested)	50%	90%	Range	% susceptible/resistar
Citrobacter spp. (895)				
Polymyxin B	≤1	≤1	≤1->8	99.1/0.9
Ceftriaxone	≤0.25	32	≤0.25->32	83.9/6.6
Cefepime	≤0.12	1	≤0.12->16	98.1/1.6
Piperacillin/tazobactam	2	64	≤0.5 - >256	86.0/5.6
Imipenem	≤0.5	1	≤0.5->8	99.9/0.1
Ciprofloxacin	≤0.03	1	≤0.03->4	90.6/7.7
Gentamicin	≤2	≤2	≤2->8	91.5/7.4
Interobacter spp. (4,693)				
Polymyxin B	≤1	>8	≤1->8	83.3/16.7
Ceftriaxone	≤0.25	>32	≤0.25->32	76.1/13.8
Cefepime	≤0.12	4	≤0.12->16	95.5/2.9
Piperacillin/tazobactam	2	>64	≤0.12->64	77.4/10.2
Imipenem	≤0.5	1	≤0.5->8	99.4/0.3
Ciprofloxacin	≤0.03	>2	≤0.03 - >2	87.2/10.8
Gentamicin	≤2	>8	≤2->8	88.3/10.3
. coli (18,325)				
Polymyxin B	≤1	≤1	≤1->8	99.5/0.5
Ceftriaxone	≤0.25	≤0.25	≤0.25 - >32	96.2/3.0
Cefepime	≤0.12	≤0.12	≤0.12->16	97.6/1.9
Piperacillin/tazobactam	2	4	≤0.12->256	96.2/1.8
Imipenem	≤0.5	≤0.5	≤0.5->8	>99.9/<0.1
Ciprofloxacin	≤0.03	>4	≤0.03->4	85.5/14.4
Gentamicin	≤2	≤2	≤2->8	92.1/7.1
<u>(lebsiella spp. (8,188)</u>				
Polymyxin B	≤1	≤1	≤1->8	98.2/1.8
Ceftriaxone	≤0.25	32	≤0.25->32	85.5/9.7
Cefepime	≤0.12	4	≤0.12->16	92.4/5.9
Piperacillin/tazobactam	2	64	≤0.12->256	87.4/9.6
Imipenem	≤0.5	≤0.5	≤0.5->8	99.7/0.2
Ciprofloxacin	≤0.03	2	≤0.03->4	89.5/8.9
Gentamicin	≤2	>8	≤2->8	85.9/12.8
ndole-positive <i>Proteus</i> spp. (895)				
Polymyxin B	>8	>8	≤1->8	1.3/98.7
Ceftriaxone	≤0.25	2	≤0.25->32	95.6/2.6
Cefepime	≤0.12	0.25	≤0.12->16	97.7/1.5
Piperacillin/tazobactam	≤0.5	4	≤0.5->64	98.3/0.6
Imipenem	2	2	≤0.12->8	99.3/0.1
Ciprofloxacin	≤0.03	>4	≤0.03->4	81.1/16.6
Gentamicin	≤2	>8	≤2->8	85.8/11.6
<u>P. mirabilis (1,931)</u>				
Polymyxin B	>8	>8	≤1->8	0.7/99.3
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	94.7/3.3
Cefepime	≤0.12	0.25	≤0.12->16	96.2/2.9
Piperacillin/tazobactam	≤0.5	1	≤0.5->64	99.0/0.2
Imipenem	1	2	≤0.06-8	99.8/0.0
Ciprofloxacin	≤0.03	4	≤0.03->4	80.8/14.3
Gentamicin	≤2	>8	≤2->8	87.8/10.4
<u>Serratia spp. (1,919)</u>				
Polymyxin B	>8	>8	0.25->8	5.4/94.6
Ceftriaxone	≤0.25	8	≤0.25->32	90.0/5.2
Cefepime	≤0.12	1	≤0.12->16	95.5/3.4
Piperacillin/tazobactam	2	32	≤0.5->256	88.5/3.0
Imipenem	0.5	1	≤0.12->8	99.3/0.5
Ciprofloxacin	0.06	1	≤0.016->4	90.5/6.1
Gentamicin	≤2	8	≤2->8	88.3/9.7

Table 2. Antimicrobial activity of polymyxin B compared to other antimicrobial agents tested against

36,846 Enterobacteriaceae isolates (SENTRY Antimicrobial Surveillance Program, 2001 - 2004

Table 4.	Antimicrobial activity of Polymyxin B compared to other antimicrobial agents tested against
	carbapenem-resistant Acinetobacter spp. and P. aeruginosa isolates (SENTRY Antimicrobial
	Surveillance Program 2001-2004).

	μg/ml ^a				
Species (no.)/antimicrobial agent	MIC ₅₀	MIC ₉₀	% susceptible ^b	% resistant	
Acinetobacter spp. (495)					
Polymyxin B	≤1	2	97.2	2.8	
Ceftazidime	>16	>16	5.5	91.7	
Cefepime	>16	>16	5.3	71.9	
Ampicillin/Sulbactam	32	>32	8.4	66.6	
Ciprofloxacin	>2	>2	6.3	92.9	
Amikacin	>32	>32	22.8	77.2	
P. aeruginosa (1,398)					
Polymyxin B	≤1	2	97.6	2.4	
Ceftazidime	16	>16	33.4	59.4	
Cefepime	>16	>16	29.2	44.5	
Piperacillin/Tazobactam	>64	>64	45.4	54.6	
Ciprofloxacin	>2	>2	27.8	77.5	
Amikacin	16	>32	58.3	41.7	

Percentage of susceptibility and resistance calculated according to CLSI [2005].

• Polymyxin B remains very active against contemporary clinical isolates of *P. aeruginosa* and *Acinetobacter* spp. isolates including those resistant to carbapenems.

CONCLUSIONS

- In spite of the increasing use of polymyxin B in the recent years, no increase in the isolation of the polymyxin-resistant *Acinetobacter* spp. or *P. aeruginosa* was observed in the monitored 2001 2004 period for the SENTRY Program.
- The emergence of polymyxin-resistant *P. aeruginosa* and *Acinetobacter* spp. poses a serious therapeutic problem since no new antimicrobial agents are currently available for treatment of multidrug-resistant *P. aeruginosa* and *Acinetobacter* infections.
- Continued surveillance is critical to the assessment of polymyxin activity, especially against multidrug-resistant non-fermentative Gramnegative bacilli.

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