493

Differences in Potency and Categorical Agreement between Colistin and Polymyxin B when Testing 15,377 Strains Collected Worldwide

HS SADER, PR RHOMBERG, DJ FARRELL

JMI Laboratories, North Liberty, Iowa, USA

IDWEEK 2014

JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

ABSTRACT

Background: Two polymyxin agents, colistin (COL) and polymyxin B (PB), are available for clinical use worldwide and clinical laboratories may not be able to susceptibility test both compounds appropriately. We evaluated the correlation between COL and PB MIC values on a large collection of Gram-negative bacilli (GNB) within the spectrum of the polymyxins.

Methods: 15,377 clinical GNB, including *P. aeruginosa* (PSA; 3,821), *Acinetobacter* spp. (ASP; 1,068), *Klebsiella* spp. (KSP; 4,177) and *E. coil* (EC; 6,311) were tested for susceptibility against COL and PB by CLSI broth microdilution methods using commercial (Sensitrite®) dry-form panels. The isolates were collected worldwide in 2013.

Results: Percentages of strains inhibited at ≤2 µg/ml of COL/PB were 99.8/99.8% for PSA, 97.2/97.9% for ASP, 95.8/95.9% for KSP and 99.6/99.6% for EC. Among PSA and ASP, COL and PB MIC values were within +/- one doubling dilution for >99.0% of strains, and identical MIC values were observed for 85.4% of PSA and 75.1% of ASP. When CLSI breakpoints were applied, categorical agreement (CA) was 99.8% for PSA and 98.9% for ASP (**Table 1**). Among KSP and EC, 55.0 and 53.2% of strains displayed a COL MIC one dilution lower than PB. However, differences in potency varied according to the degree of polymyxin susceptibility. Among KSP, percentages of strains with COL MIC ≥1 dilution lower/identical/≥1 dilution higher compared to PB were 58.5/39.9/1.6% for isolates with COL MIC ≤2 µg/ml, and 2.9/72.9/24.1% for isolates with COL MIC ≥4 µg/ml, respectively. If a susceptible/resistant breakpoint of ≤2/≥4 µg/ml were applied for both COL and PB (similar to ASP), CA would be 99.8% for KSP and >99.9% for EC.

Conclusions: There was a good correlation between COL and PB MIC values and ≥98.9% CA when testing PSA and ASP. Against KSP and EC, COL exhibited slightly greater potency than PB against isolates with lower MIC values (≤2 µg/ml) for both compounds, while PB was slightly more potent than COL against strains with decreased susceptibility (MIC, ≥4 µg/ml) to the polymyxins.

INTRODUCTION

The polymyxins are polypeptides with a basic structure that consists of a fatty acid side chain attached to a polycationic peptide ring composed of 8 to 10 amino acids. These antimicrobials are cationic detergents that disrupt bacterial cytoplasmic membranes, causing leakage of cytoplasmic contents. The polymyxins have activity against a wide variety of Gram-negative bacilli, including many Enterobacteriaceae and non-fermentative species; however, Gram-positive organisms and some Gram-negative species are intrinsically resistant to the polymyxins.

The emergence of multidrug-resistant (MDR) *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Klebsiella pneumoniae* has required the expanded systemic use of these antimicrobial agents. The polymyxins have constituted the drugs of choice for treatment of serious infections caused by carbapenem-resistant *P. aeruginosa* and *Acinetobacter* spp. isolates. In addition, polymyxins have also become one of the valuable therapeutic options against *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* infections. As polymyxins (colistin and polymyxin B) usage increases, the development of polymyxin resistance becomes a clinical concern. Thus, there is a need for standardization of an accurate susceptibility testing method for these compounds. We evaluated the correlation between colistin and polymyxin B MIC values on a large collection of Gram-negative bacilli within the spectrum of the polymyxins.

MATERIALS AND METHODS

Organism Collection: A total of 15,377 clinical isolates of Gram-negative bacilli were included in this investigation, including 3,821 *P. aeruginosa*, 1,068 *Acinetobacter* spp., 4,177 *Klebsiella* spp. and 6,311 *E. coil* were tested for susceptibility against colistin and polymyxin B by CLSI broth microdilution methods. The isolates were collected worldwide through the SENTRY Antimicrobial Surveillance Program from January to December 2013.

Susceptibility Testing: Antimicrobial susceptibility testing of isolates was performed by validated broth microdilution method using commercial (Sensitrite®) dry-form panels and following the Clinical and Laboratory Standards Institute (CLSI) recommendations. The results were interpreted according to the CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria, where available. Quality control was performed by testing *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853, with all results within published ranges.

RESULTS

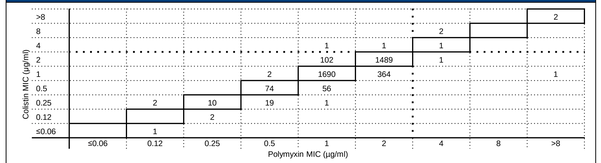
- Percentages of strains inhibited at ≤2 µg/ml of colistin/polymyxin B were 99.8/99.8% for *P. aeruginosa*, 97.2/97.9% for *Acinetobacter* spp., 95.8/95.9% for *Klebsiella* spp. and 99.6/99.6% for *E. coli* (data not shown).
- Among *P. aeruginosa* and *Acinetobacter* spp., colistin and polymyxin B MIC values were within +/- one doubling dilution for >99.0% of strains, and identical MIC values were observed for 85.4% of *P. aeruginosa* and 75.1% of *Acinetobacter* spp. (**Table 1**).
- When CLSI breakpoints were applied, i.e. susceptible at ≤2 µg/ml for both colistin and polymyxin B for *P. aeruginosa* and *Acinetobacter* spp., and resistant at ≥8 µg/ml for *P.* aeruginosa and ≥4 µg/ml for *Acinetobacter* spp., categorical agreement (CA) was 99.8% for *P. aeruginosa* and 98.9% for *Acinetobacter* spp. (**Table 1** and **Figures 1** and **2**).
- Among *Klebsiella* spp. and *E. coli*, 55.0 and 53.2% of strains displayed a colistin MIC one dilution lower than polymyxin B, respectively. However, differences in potency varied according to the degree of polymyxin susceptibility (**Table 1** and **Figures 3** and **4**).
- Among *Klebsiella* spp., percentages of strains with colistin MIC ≥1 dilution lower/identical/≥1 dilution higher compared to polymyxin B were 58.5/39.9/1.6% for isolates with colistin MIC ≤2 µg/ml, and 2.9/72.9/24.1% for isolates with colistin MIC ≥4 µg/ml, respectively (**Figure 3**).
- If a susceptible/resistant breakpoint of ≤2/≥4 µg/ml were applied for both colistin and polymyxin B (similar to *Acinetobacter* spp.), categorical agreement would be 99.8% for *Klebsiella* spp. and >99.9% for *E. coli* (**Figures 3** and **4**).

Table 1. Differences in potency (MIC value) between polymyxin B and colistin when testing 15,377 strains collected worldwide in 2013.

	Poly B more potent than colistin by (% of strains):				Colistin more potent than poly B by (% of strains):			
Organisms (no.)	≥3 dilutions	2 dilutions	1 dilution	**Same MIC value**	1 dilution	2 dilutions	≥3 dilutions	**Categorical agreement[a]**
P. aeruginosa (3,821)	-	<0.1	2.9	**85.4**	11.6	<0.1	<0.1	**99.8%**
Acinetobacter spp. (1,068)	-	0.8	18.8	**75.1**	5.1	<0.1	-	**98.9%**
Klebsiella spp. (4,177)	<0.1	<0.1	2.5	**41.2**	55.0	1.1	0.1	**NA[b]**
E. coli (6,311)	-	-	1.0	**44.8**	53.2	0.9	<0.1	**NA**
All (15,377)	<0.1	<0.1	3.1	**56.1**	40.0	0.7	<0.1	**NA**

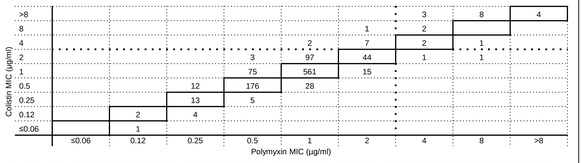
a. Categorical agreement between polymyxin B and colistin according to CLSI breakpoint criteria.
b. NA, not applicable due to the lack of breakpoint criteria for polymyxin B by either CLSI or EUCAST.

Figure 1. Correlation between polymyxin B and colistin MIC values when testing 3,821 *P. aeruginosa* collected worldwide in 2013[a].



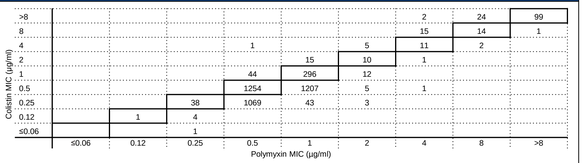
a. Boxes with solid lines indicate number of strains with the same MIC value for colistin and polymyxin B. Bold dashed lanes indicate susceptible breakpoints according to CLSI criteria (CLSI, 2014).

Figure 2. Correlation between polymyxin B and colistin MIC values when testing 1,068 *Acinetobacter* spp. collected worldwide in 2013[a].



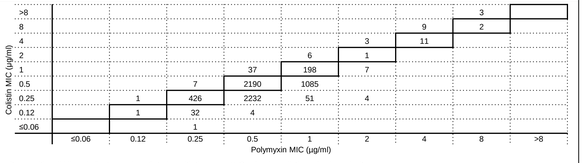
a. Boxes with solid lines indicate number of strains with the same MIC value for colistin and polymyxin B. Bold dashed lanes indicate susceptible breakpoints according to CLSI criteria (CLSI, 2014).

Figure 3. Correlation between polymyxin B and colistin MIC values when testing 4,177 *Klebsiella* spp. collected worldwide in 2013[a].



a. Boxes with solid lines indicate number of strains with the same MIC value for colistin and polymyxin B.

Figure 4. Correlation between polymyxin B and colistin MIC values when testing 6,311 *E. coli* collected worldwide in 2013[a].



a. Boxes with solid lines indicate number of strains with the same MIC value for colistin and polymyxin B.

CONCLUSIONS

- There was good correlation between colistin and polymyxin B MIC values and ≥98.9% categorical agreement when testing *P. aeruginosa* and *Acinetobacter* spp.
- Against *Klebsiella* spp. and *E. coli*, colistin exhibited slightly greater potency than polymyxin B against isolates with lower MIC values (≤2 µg/ml) for both compounds, while polymyxin B was slightly more potent than colistin against strains with decreased susceptibility (MIC, ≥4 µg/ml) to the polymyxins.
- Greater stickiness of polymyxin B to plastic compared to colistin could explain the higher MIC values for this compound among isolates more susceptible to colistin and/or polymyxin B; however, further studies are necessary to evaluate this hypothesis.

REFERENCES

1. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition*. Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2014). *M100-S24. Performance standards for antimicrobial susceptibility testing: 24th informational supplement.* Wayne, PA: CLSI.
3. EUCAST (2014). Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, January 2014. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2014.
4. Falagas ME, Rafailidis PI, Ioannidou E, Alexiou VG, Matthaiou DK, Karageorgopoulos DE, Kapaskelis A, Nikita D, Michalopoulos A (2010). Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. *Int J Antimicrob Agents* 35: 194-199.
5. Gales AC, Jones RN, Sader HS (2011). Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006-09). *J Antimicrob Chemother* 66: 2070-2074.
6. Sader HS, Farrell DJ, Jones RN (2011). Susceptibility of *Klebsiella* spp. to colistin and polymyxin B: Results from the SENTRY Antimicrobial Surveillance Program (2006-2009). *Int J Antimicrob Agents* 37: 174-175.
7. Zavascki AP, Goldani LZ, Li J, Nation RL (2007). Polymyxin B for the treatment of multidrug-resistant pathogens: A critical review. *J Antimicrob Chemother* 60: 1206-1215.