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Stable Polymyxin B Susceptibility to *Pseudomonas aeruginosa* and *Acinetobacter* spp. despite Persistent Recovery of These Organisms from Respiratory Secretions of Patients with Ventilator-Associated Pneumonia Treated with This Drug▽

In a recent article, Lee et al. (4) reported the occurrence of an increase in MICs for polymyxin B during therapy in 3 of 16 patients treated with this drug for carbapenem-resistant *Klebsiella pneumoniae* infections. This report is very important, since polymyxins, polymyxin B and colistin, are last-resort drugs for the treatment of multidrug-resistant gram-negative bacteria (7, 9) and rapid development of resistance occurring during exposure to polymyxins in in vitro infection models with simulated clinical dosage regimens have been reported (2, 6), including resistance to *K. pneumoniae* (5), but no in vivo demonstration of this phenomenon has been reported so far. The report of Lee et al. is of great concern, although no data about polymyxin B dosages were presented and, as acknowledged by the authors, it was not possible to definitively characterize whether there was the emergence of resistance in the same strain or patients were further infected by distinct strains resistant to polymyxin B during therapy.

In contrast to in vitro findings and to what the observations of Lee et al. might suggest, a preliminary prospective study aiming to assess microbiological outcomes in patients with *Pseudomonas aeruginosa* and *Acinetobacter* species ventilator-associated pneumonia (VAP) treated with polymyxin B found no decreased susceptibility to this drug during therapy despite the noneradication of *P. aeruginosa* from respiratory secretions of some patients.

A total of 11 patients with VAP due to *P. aeruginosa* ($n = 8$) or *Acinetobacter* spp. ($n = 3$), diagnosed according to criteria described elsewhere (1), with only those presenting $\geq 10^5$ CFU/ml in tracheal aspirate considered, were subjected to daily tracheal aspiration from the day before starting polymyxin B up to day 15 or death. The polymyxin B MIC was determined using the agar dilution method. *P. aeruginosa* ATCC 27853 was used as a quality control strain. The first and last isolates recovered from tracheal aspirates of each patient were subjected to molecular typing by pulsed-field gel electrophoresis, using the restriction endonuclease SpeI for *P. aeruginosa* and SmaI for *Acinetobacter* spp.

Baseline characteristics, treatment, and outcomes for each patient are shown in Table 1. During polymyxin B treatment, no patient presented an isolate with a MIC >2-fold higher than that for the initial isolate. In two patients, the MICs of the baseline *P. aeruginosa* isolates (before the initiation of therapy) were not available, but the isolates of both patients recovered after the second day of therapy presented an MIC of 1 μg/ml. The first and last recovered isolates of all patients were confirmed to be the same clonotype by pulsed-field gel electrophoresis. Although no isolate presented an MIC >2-fold higher than that of the corresponding initial isolate prior to intravenous polymyxin B treatment, it is unknown whether the population analysis profiles of the isolates changed after treatment with intravenous polymyxin B.

Of note, in a difference from the study of Lee et al., most of

TABLE 1. Baseline characteristics, treatments, and outcomes for patients with VAP treated with intravenous polymyxin B[a]

Case	Age (yr)/sex	ECC, ml/min	Bacterium; polymyxin B MIC (mg/ml)[b]	Treatment		Bacterial eradication[d]; time from initiation of polymyxin B to outcome, days	Clinical outcome; time from initiation of polymyxin B to outcome (death or ICU discharge), days[e]
				Dose (mg/kg)/dosing interval (h)[c]	Antibiotic coadministered		
1	80/F	<10	*P. aeruginosa*; NA	0.83/48	MEM (days 1–8)	No	Death; 8
2	52/M	83	*P. aeruginosa*; NA	1.25/12	LVX, VAN (after day 9)	No	Survival; 16
3	88/M	84	*P. aeruginosa*; 1	1.25/12	IPM (days 1–5)	No	Death; 5
4	42/M	98	*P. aeruginosa*; 2	1.0/12	CAZ (days 1 and 2), SXT (days 1–9), and CIP (days 3–9)	No	Death; 9
5	72/F	60	*P. aeruginosa*; 2	1.0/12	ATM (day 8–15)	No	Death; 64
6	49/M	<10	*Acinetobacter* spp.; 1	1.25/12	MEM (days 1–14)	Yes; 14	Survival; 40
7	86/F	34	*Acinetobacter* spp.; 1	1.0/12	None	Yes; 2	Survival; 21
8	76/M	66	*Acinetobacter* spp.; 1	1.0/12	ATM (days 1–14)	Yes; 2	Death; 15
9	72/M	26	*P. aeruginosa*; 1	1.5[f]/48	None	No	Death; 87
10	65/M	<10	*P. aeruginosa*; 0.5	0.5[g]/48	VAN (days 7–15)	No	Death; 30
11	48/F	246	*P. aeruginosa*; 1	1.0/12	SXT (days 1–14)	No	Survival; 42

[a] Abbreviations: M, male; F, female; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; SXT, trimethoprim-sulfamethoxazole; VAN, vancomycin; ECC, estimated creatinine clearance (estimated by the Cockcroft-Gault formula); NA, not available.

[b] Data for eight patients are reported elsewhere (8). MICs of isolates recovered before therapy are shown. All isolates were susceptible to polymyxin only, with the exception of the isolate from patient 4 (susceptible to ciprofloxacin and amikacin) and that from patient 5 (susceptible to amikacin). An isolate with a polymyxin B MIC of ≤2 μg/ml was considered susceptible (3).

[c] For eight patients, the polymyxin B dose and antibiotic coadministered are reported elsewhere (8).

[d] Bacterial eradication is defined as a tracheal aspirate that was negative for the infecting organism, followed by subsequent negative cultures.

[e] Except for those who died before the end of the treatment, patients received polymyxin B therapy for 14 days.

[f] First dose, 3.0 mg/kg of body weight.

[g] First dose, 2.0 mg/kg of body weight.

our patients received combination therapy, and although all but one isolate showed in vitro resistance to these second agents, it might have had some impact on microbiological outcomes. Additionally, our study included only patients with VAP due to *P. aeruginosa* and *Acinetobacter* spp. but none with *K. pneumoniae*.

Currently there is no human pharmacokinetic study assessing concentrations of polymyxins in lung epithelial lining fluids after administration intravenously or by inhalation (7, 9). Eight patients in our study had plasma polymyxin B concentrations measured, and unbound plasma concentrations of polymyxin B were in the vicinity of the pathogens' MICs or even lower (8). However, the fact that all *Acinetobacter* species isolates, which presented MICs similar to those of *P. aeruginosa* isolates, were eradicated from tracheal aspirate might suggest that polymyxin B reached inhibitory concentrations in the epithelial lining fluids, although the addition of meropenem and aztreonam to the therapy of two patients may have contributed to eradication, despite the finding of in vitro resistance to these agents by *Acinetobacter* species isolates.

In summary, our preliminary observations have neither confirmed in vitro findings nor in vivo emergence of resistance to polymyxin B therapy during treatment with this drug. However, considering previous in vitro studies and the recent report of Lee et al., we believe that further studies with a large number of patients are required to assess this phenomenon.

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REFERENCES

1. **American Thoracic Society; Infectious Diseases Society of America.** 2005. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am. J. Respir. Crit. Care Med. **171:**388–416.
2. **Bergen, P. J., J. Li, R. L. Nation, J. D. Turnidge, K. Coulthard, and R. W. Milne.** 2008. Comparison of once-, twice-, and thrice-daily dosing of colistin on antibacterial effect and emergence of resistance: studies with *Pseudomonas aeruginosa* and an in vitro pharmacodynamic model. J. Antimicrob. Chemother. **61:**636–642.
3. **Clinical and Laboratory Standards Institute.** 2008. Performance standards for antimicrobial susceptibility testing, 18th informational supplement. Document M100-S18. Clinical and Laboratory Standards Institute, Wayne, PA.
4. **Lee, J., G. Patel, S. Huprikar, D. P. Calfee, and S. G. Jenkins.** 2009. Decreased susceptibility to polymyxin B during treatment for carbapenem-resistant *Klebsiella pneumoniae* infection. J. Clin. Microbiol. **47:**1611–1612.
5. **Poudyal, A., B. P. Howden, J. M. Bell, W. Gao, R. J. Owen, J. D. Turnidge, R. L. Nation, and J. Li.** 2008. In vitro pharmacodynamics of colistin against multidrug-resistant *Klebsiella pneumoniae*. J. Antimicrob. Chemother. **62:** 1311–1318.
6. **Tan, C. H., J. Li, and R. L. Nation.** 2007. Activity of colistin against heteroresistant *Acinetobacter baumannii* and emergence of resistance in an in vitro pharmacokinetic/pharmcodynamic model. Antimicrob. Agents Chemother. **51:**3413–3415.
7. **Zavascki, A. P., and J. Li.** 2008. Intravenous colistimethate for multidrug-resistant Gram-negative bacteria. Lancet Infect. Dis. **8:**403–405.
8. **Zavascki, A. P., L. Z. Goldani, G. Cao, S. V. Superti, L. Lutz, A. L. Barth, F. Ramos, M. M. Boniatti, J. Li, and R. L. Nation.** 2008. Pharmacokinetics of intravenous polymyxin B in critically-ill patients. Clin. Infect. Dis. **47:**1298–1304.
9. **Zavascki, A. P., L. Z. Goldani, R. L. Nation, and J. Li.** 2007. Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. J. Antimicrob. Chemother. **60:**1206–1215.

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