β-Lactam MICs Correlate Poorly with Mutant Prevention Concentrations for Clinical Isolates of *Acinetobacter* spp. and *Pseudomonas aeruginosa*

To reduce the emergence of acquired bacterial resistance, an antimutant dosing strategy using the mutant prevention concentration (MPC) has been advocated (7, 8). Recently, Drlica and collaborators showed that there was a low correlation between MIC and MPC when *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* were tested against several fluoroquinolones (4). A poor correlation was also found when *S. pneumoniae* was tested against macrolides. The use of MPC as a dosing threshold could also be applied to β-lactam agents, since the hyperproduction of AmpC β-lactamase, which is chromosomally encoded, is the principal mechanism of resistance to broad-spectrum cephalosporins among nonfermentative gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. This mechanism coupled with alteration in the outer membrane protein has also been responsible for conferring carbapenem resistance. Thus, the measurement of the MPC could identify the β-lactams less likely to favor the growth of resistant subpopulations. Since *P. aeruginosa* and *Acinetobacter* spp. constitute important nosocomial pathogens in Brazilian hospitals, we have evaluated the correlation between MIC and MPC for β-lactams and fluoroquinolones against *P. aeruginosa* and *Acinetobacter* spp. isolates by use of a linear regression model (r^2). Our results are shown in Table 1. Among *Acinetobacter* spp., the r^2 values were very low (≤ 0.2) for all antimicrobial agents tested. Against *P. aeruginosa*, no correlation between MIC and MPC was observed for cefepime and meropenem ($r^2 = 0.0$). A poor correlation between MIC and MPC was also found for imipenem and ceftazidime. Although levofloxacin ($r^2 = 0.17$) and gatifloxacin ($r^2 = 0.25$) MICs and MPCs displayed correlations lower than that for

ciprofloxacin MIC and MPC ($r^2 = 0.51$) against *P. aeruginosa* isolates, a weak correlation between MIC and MPC was found for all of the fluoroquinolones tested. To determine the MIC, a low inoculum (10^4 to 10^5 CFU/ml) has been recommended by the Clinical Laboratory Standards Institute (CLSI) and other antimicrobial susceptibility committees (1, 2). When the suggested inoculum is used, the MIC measurement for a determined antimicrobial agent does not take into consideration subpopulations of resistant bacteria that naturally occur. For example, bacterial isolates possessing single mutations on the quinolone resistance-determining region of the *gyrA* or *parC* gene are usually categorized as susceptible to fluoroquinolones (3, 5, 6, 9). However, treatment failure due to the acquisition of additional mutations has been reported when fluoroquinolones were prescribed for treatment of infections caused by such isolates. Our results are in accordance with those published recently by Drlica and collaborators (4). Both studies confirm the poor correlation between MIC and MPC, which is independent of the antimicrobial agent and species evaluated. These results also emphasize the importance of measuring the MPC to select the most favorable dose regimen for treatment.

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TABLE 1. Relationship between MIC and MPC for several antimicrobial agents against *Acinetobacter* spp. and *Pseudomonas aeruginosa*

Bacterial species (no. of isolates tested)	Antimicrobial agent	r^2 for MPC/MIC
<i>Acinetobacter</i> spp. (20)	Ceftazidime	0.01
	Cefepime	0.01
	Imipenem	0.04
	Meropenem	0.09
	Ciprofloxacin	0.15
	Levofloxacin	0.20
	Gatifloxacin	0.19
<i>P. aeruginosa</i> (20)	Ceftazidime	0.13
	Cefepime	0.0
	Imipenem	0.24
	Meropenem	0.0
	Ciprofloxacin	0.51
	Levofloxacin	0.17
	Gatifloxacin	0.25

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