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Inverse correlation of *Acinetobacter* spp. resistance rate and ciprofloxacin utilization

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Several studies tried to investigate the relation between utilization rate of antibiotics and resistance, but only some of them found that increased utilization had been associated with increase in resistance to antibiotics.[1,2] Other studies either did not find a correlation or found a very weak one.[3–5] In order to clarify the issue further, we have evaluated the impact of antibiotic consumption on resistance rate of multidrug-resistant bacteria (*Pseudomonas aeruginosa* and *Acinetobacter* spp.) to antibiotics among inpatients from intensive care unit of a tertiary care university hospital 'Clinical Center of Kragujevac', during a 5-year period (2007–2011). Antibiotic utilization rate was expressed in DDDs (defined daily doses) per 100 BDs (bed days), and resistance of isolated bacteria to antibiotics was tested by disk-diffusion method. There was between 600 and 700 isolates per year and 200 of them were randomly selected for each study year; from the 1000 selected isolates, only those of *P. aeruginosa* (314 isolates) and *Acinetobacter* spp. (140 isolates) were taken into account (according to the sample size calculation, we needed 141 isolates for establishing resistance rate of *P. aeruginosa* (confidence level 95%, confidence interval ±7.5% and resistance rate to ciprofloxacin from previous studies 29%) and 96 isolates for establishing resistance rate of *Acinetobacter* spp. (confidence level 95%, confidence interval ±10% and resistance rate to ciprofloxacin from previous studies 66%).[6,7] Within each of the two bacterial species, all isolates were of the same serological phenotype, implying the same clonal ancestry. The origin of the isolates were as following: 26.5% were isolated from infected operative wounds, 24.9% from urine and 19.4% from tracheal aspirates.

For *P. aeruginosa*, only resistance to piperacillin/tazobactam significantly correlated with utilization rate of this antibiotic ($r=0.952$, $P=0.013$) as shown in Table 1. The resistance rate ranged from 5.1% to 13.4%, and utilization of piperacillin/tazobactam ranged from 0.12 to 0.34 DDDs per 100 BDs. Resistance rates of *Acinetobacter* spp. to piperacillin/tazobactam, ciprofloxacin and ceftazidime correlated well with utilization rates of these antibiotics ($r=0.882$, $P=0.048$; $r=-0.913$, $P=0.030$; $r=-0.991$, $P=0.009$, respectively; Table 1), although in opposite directions: for piperacillin/tazobactam the correlation was direct, whereas for the other two antibiotics the correlation was inverse. The resistance rate of *Acinetobacter* spp. ranged from 8% to 94% for piperacillin/tazobactam, from 73% to 100% for ciprofloxacin and from 91.3% to 100% for ceftazidime, whereas the utilization rate ranged from 4.15 to 5.68 DDDs per 100 BDs for ciprofloxacin and from 0.9 to 2.08 DDDs per 100 BDs for ceftazidime (Table 1).

It was found in some studies that high-utilization rate of β-lactams increased prevalence of β-lactam-resistant *P. aeruginosa*, and that decreasing β-lactam utilization was an efficient method to increase susceptibility of *P. aeruginosa*, *Acinetobacter* spp. and other pathogens to β-lactam antibiotics.[8–10] In our study, the same conclusion was confirmed

Table 1 Correlation between antibiotic utilization rates (DDDs per 100 BDs) and resistance rates of *P. aeruginosa* and *Acinetobacter* spp. (%); annual antibiotic utilization rates (DDDs per 100 BDs) and pathogen resistance rates (%)

	Piperacillin/tazobactam		*Ciprofloxacin*		*Ceftazidime*	
	r	P-*value*	r	P-*value*	r	P-*value*
P. aeruginosa	0.952	0.013	−0.375	0.534	0.448	0.449
Acinetobacter spp.	0.882	0.048	−0.913	0.03	−0.991	0.009

Year	P. aeruginosa *resistance rates*	Acinetobacter *spp. resistance rates*	*Utilization rates*	P. aeruginosa *resistance rates*	Acinetobacter *spp. resistance rates*	*Utilization rates*	P. aeruginosa *resistance rates*	Acinetobacter *spp. resistance rates*	*Utilization rates*
2007	6.5	8	0.12	73.6	100	4.15	65.9	100	0.9
2008	5.1	13.6	0.16	62.2	88.1	5.14	46.9	100	1.39
2009	10.2	49.8	0.27	56.6	80	5.68	50.9	100	1.46
2010	12.8	53.4	0.34	77.8	73.3	5.48	76.0	91.3	2.08
2011	13.4	94	0.32	68.8	73	5.53	67.4	92.9	1.88

Abbreviations: 100BDs, 100 bed days; DDD, defined daily doses; *r*, Pearson's correlation coefficient.

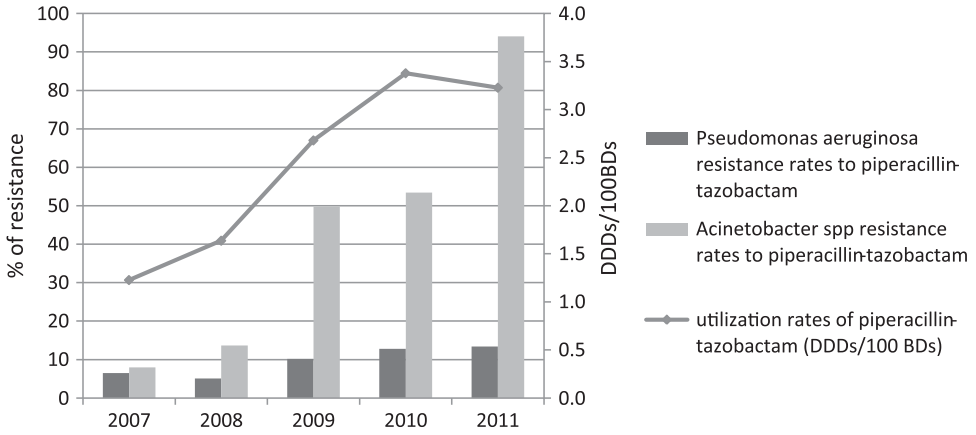

Figure 1 Association between piperacillin/tazobactam utilization rates and resistance rates of *P. aeruginosa* and *Acinetobacter* spp.

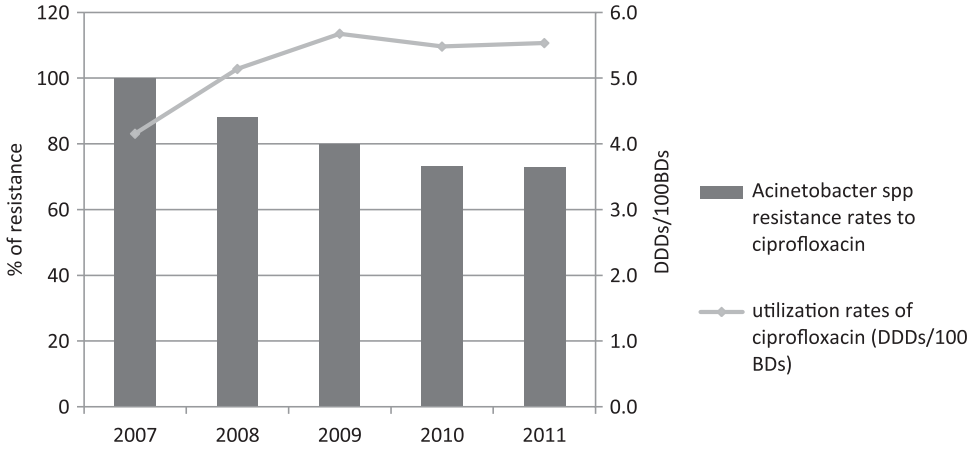

Figure 2 Association between ciprofloxacin utilization rates and resistance rates of *Acinetobacter* spp.

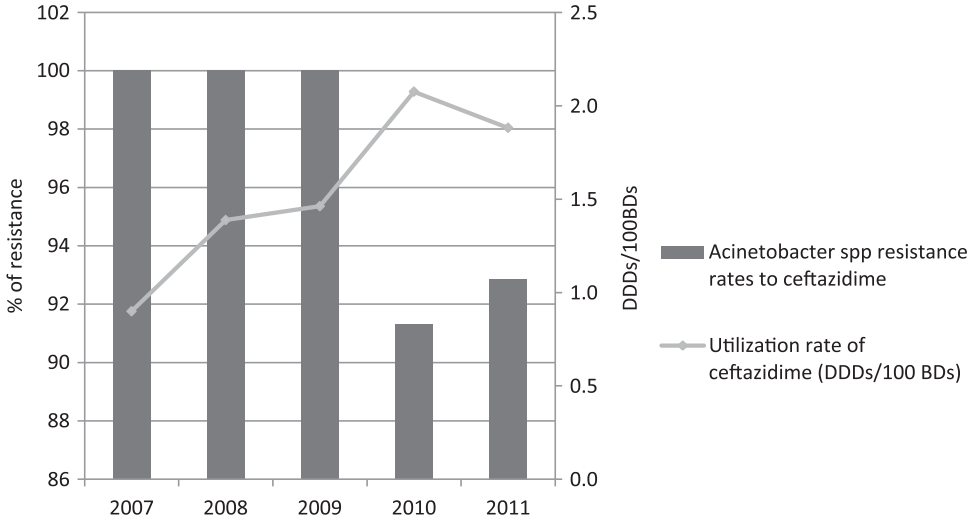

Figure 3 Association between ceftazidime utilization rates and resistance rates of *Acinetobacter spp.*

for piperacillin/tazobactam (Figure 1), but the opposite phenomenon was observed with ciprofloxacin, a non-β-lactam drug (Figure 2), and with ceftazidime (Figure 3), the β-lactam drug from cephalosporin subgroup. Although direct correlation between *P. aeruginosa* resistance rate and utilization of fluoroquinolones was found previously,[2] the same was never shown for *Acinetobacter* spp. and this group of antibiotics.[4]

One of the most important adaptive mechanisms of bacterial resistance to antibiotics is efflux pumps, which could be either overexpressed or inhibited by specific compounds with similar chemical structure as antibiotics.[11,12] Whereas gradually increasing utilization of antibiotics, which are administered as monotherapy (like piperacillin/tazobactam in our study), progressively selects resistant strains with overexpressed efflux pumps and increases overall rate of resistance to antibiotics, constant high-utilization rate of antibiotics, which are part of combination regimens (like ciprofloxacin and ceftazidime), could saturate the efflux pumps and make the bacteria more susceptible for the antibiotics concomitantly given to the patient. Ciprofloxacin and ceftazidime were never given as monotherapy in our intensive care unit: ceftazidime was usually combined with aminoglycosides, whereas ciprofloxacin frequently accompanied third-generation cephalosporins.

Although our data are limited, and are not fully supportive of our hypothesis, it is clear that both extent and pattern of antibiotic utilization are important determinants of antibiotic resistance. Many circumstances, including number, type, dosage and duration of antibiotic therapy could influence development of bacterial resistance, which could even decrease in spite of high overall antibiotics utilization figures.

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