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Cross Resistance to Ciprofloxacin and Other Antimicrobial Agents among Clinical Isolates of *Acinetobacter calcoaceticus* Biovar Anitratus

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Using an agar dilution assay, for 66 of 104 (63.5%) clinical isolates of *Acinetobacter calcoaceticus* biovar anitratus, the MIC of ciprofloxacin was ≥1.0 μg/ml. Cross resistance was demonstrable to ciprofloxacin and gentamicin ($P < 0.001$), amikacin ($P < 0.01$), cefotaxime ($P < 0.001$), azlocillin ($P < 0.001$), ceftazidime ($P < 0.001$), trimethoprim-sulfamethoxazole ($P < 0.001$), and minocycline ($P < 0.05$). The mean MIC of ciprofloxacin for drug-susceptible isolates was consistently lower than that for resistant isolates; however, these differences were significant only for amikacin ($P = 0.036$).

Acinetobacter calcoaceticus biovar anitratus has emerged in recent years as an important cause of nosocomial infection. Most isolates are resistant to multiple antimicrobial drugs, including newer β-lactam antibiotics (3, 7, 8). Several reports indicate that multiply resistant isolates are susceptible to carboxyquinolones (1, 5, 8).

In the present study, we determined the antimicrobial susceptibility of *Acinetobacter* strains isolated in two 500-bed general hospitals during the years 1986 and 1987. MICs were determined by agar dilution and disk diffusion methods, and these data were correlated with susceptibility to eight antimicrobial agents commonly employed for the treatment of nosocomial infection.

A total of 104 isolates of *A. calcoaceticus* biovar anitratus (one isolate from each patient) were obtained from blood, cerebrospinal fluid, urine, sputum, and wounds. Bacteria were identified by standard methods (9). The ciprofloxacin MIC was determined by an agar dilution method employing a multipoint inoculator (Cathra International, St. Paul, Minn.) and inocula of 10^4 CFU per spot. Ciprofloxacin powder (Bayer AG, Leverkusen, Federal Republic of Germany) was prepared in stock solution according to the instructions of the manufacturer. Pour plates consisted of Mueller-Hinton agar (Difco Laboratories, Detroit, Mich.) containing serial twofold dilutions of ciprofloxacin (16 to 0.03 μg/ml). Disk susceptibility tests were performed by the method of Bauer et al. (2). Agar dilution and disk diffusion plates were interpreted after incubation at 36°C for 24 h.

The disk diffusion susceptibility of each *Acinetobacter* isolate was further tested by using the following commercially available disks: gentamicin (10 μg), tobramycin (10 μg), amikacin (30 μg), cefotaxime (30 μg), ceftazidime (30 μg), azlocillin (75 μg), trimethoprim-sulfamethoxazole (1.25/23.75 μg), and minocycline (30 μg). Resistance among *Acinetobacter* strains to each of the above antimicrobial agents was compared with resistance to ciprofloxacin, and data were analyzed by the chi-square test with Yates' correction. The Student *t* test was used for comparison of ciprofloxacin MICs for antibiotic-resistant and -susceptible isolates.

The MICs of ciprofloxacin against 104 *Acinetobacter* isolates ranged from 0.6 to 16.0 μg/ml. The MICs for 50% of the strains tested and for 90% of the strains tested were 0.5 to 1.0 and 2 μg/ml, respectively. Of 104 strains, 38 (36.5%) were susceptible to ciprofloxacin concentrations of below 1.0 μg/ml. The mean MIC of ciprofloxacin for drug-susceptible isolates was consistently lower than that for resistant isolates (Fig. 1); however, the difference between susceptible and resistant strains was significant only for amikacin ($P = 0.036$).

Correlations between susceptibility of *Acinetobacter* isolates to ciprofloxacin and eight other antimicrobial agents are further analyzed in Table 1. Resistance to aminoglycosides, β-lactams, and trimethoprim-sulfamethoxazole was significantly more common among isolates for which the MIC of ciprofloxacin was ≥1 μg/ml. This trend was still demonstrable ($P < 0.05$) for ceftazidime, cefotaxime, amikacin, and sulfamethoxazole-trimethoprim when data were analyzed for strains for which the MIC of ciprofloxacin was ≥2 μg/ml.

Our findings indicate that multiply resistant *Acinetobacter* strains isolated from patients with nosocomial infections are generally susceptible to ciprofloxacin. Among the aminoglycosides, only amikacin may be considered as a suitable drug for empiric therapy (71.1% susceptible strains). Indeed, a prior study demonstrated that gentamicin-resistant strains of "*Acinetobacter anitratus*" have diminished susceptibility to norfloxacin and ciprofloxacin (11).

Minocycline also exhibited good in vitro activity (84.6% susceptible). Ceftazidime was the most active (61.5% susceptible) of the β-lactams tested, while cefotaxime and azlocillin were not effective. Others have found that transfer of *Acinetobacter* species in broth containing β-lactam antibiotics may promote quinolone resistance (6). Susceptibility to imipenem is diminished only slightly among transferred and quinolone-resistant isolates (6, 8, 11).

Previous studies have demonstrated an association between resistance of *Klebsiella* and *Serratia* isolates to trimethoprim, chloramphenicol, and nalidixic acid. Concomitant β-lactam and quinolone resistance in *Klebsiella pneumoniae* has been described (4). In such cases, outer membrane changes were demonstrated in resistant bacteria, suggesting the existence of a permeability barrier (10). Whether a similar mechanism may be operative for *A. calcoaceticus* biovar anitratus is unknown and warrants further investigation.

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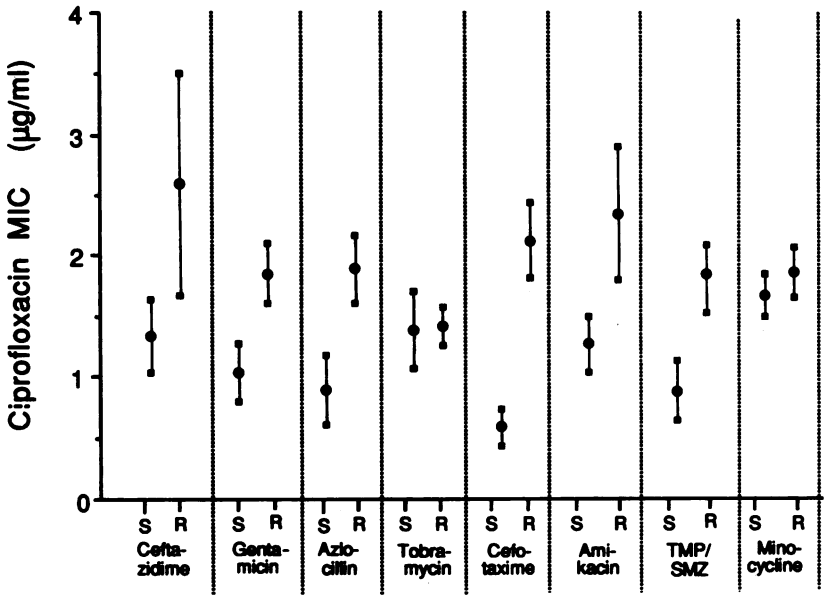

FIG. 1. MIC of ciprofloxacin for *A. calcoaceticus* biovar anitratus and correlation with antimicrobial susceptibility to eight other agents. Means ± standard errors are shown. S, Susceptible; R, resistant. Note that the mean MIC of ciprofloxacin with each of the other drugs is higher among resistant isolates than susceptible isolates. These differences are significant only for amikacin ($P = 0.036$).

TABLE 1. Correlation between susceptibilities of *Acinetobacter* isolates to ciprofloxacin and eight other antimicrobial agents

Drug	Susceptibility of isolates	No. tested	Ciprofloxacin MIC ≥1 μg/ml		P^a
			No.	%	
Gentamicin	Susceptible	25	9	36.0	<0.001
	Resistant	75	55	73.3	
Tobramycin	Susceptible	52	26	50.0	NS[b]
	Resistant	33	24	72.7	
Amikacin	Susceptible	74	40	54.1	<0.01
	Resistant	27	23	85.0	
Cefotaxime	Susceptible	8	3	37.5	<0.001
	Resistant	50	45	90.0	
Azlocillin	Susceptible	15	5	33.3	<0.001
	Resistant	83	61	73.4	
Ceftazidime	Susceptible	64	30	46.9	<0.001
	Resistant	16	15	93.8	
Trimethoprim-sulfamethoxazole	Susceptible	19	6	31.5	<0.001
	Resistant	84	60	71.4	
Minocycline	Susceptible	88	53	60.2	<0.04[c]
	Resistant	7	7	100.0	

[a] All P values were computed by the chi-square test.
[b] NS, $P > 0.05$.
[c] Fisher's exact test.

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