ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1989, p. 593–594
0066-4804/89/040593-02$02.00/0

Vol. 33, No. 4

Widespread Quinolone Resistance among Methicillin-Resistant *Staphylococcus aureus* Isolates in a General Hospital

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Received 17 October 1988/Accepted 24 January 1989

Ofloxacin and ciprofloxacin resistance (MIC, >4 μg/ml) was encountered in 45 of 50 clinical isolates of methicillin-resistant *Staphylococcus aureus*. None of 20 methicillin-susceptible strains was resistant to the quinolones ($P < 10^{-6}$). Quinolone-susceptible and -resistant isolates did not differ with respect to culture source or bacteriophage type. The future usefulness of quinolones for *S. aureus* infection may be limited.

Staphylococcus aureus continues to be a major cause of nosocomial infection, despite the advent of a wide variety of new antibiotics and antibiotic classes. Initial studies have found the new quinolones to be active against both methicillin-susceptible and methicillin-resistant staphylococci.

Ofloxacin, ciprofloxacin, and pefloxacin have been used in our hospital since January 1987. Following the introduction of routine tests for quinolone susceptibility in August 1987, we noted that most clinical isolates of *S. aureus* recovered in the microbiology laboratory were resistant to both methicillin and quinolones. An investigation was undertaken to further define this phenomenon.

Seventy isolates of *Staphylococcus aureus* were recovered in a 500-bed tertiary hospital between October and December 1987. Clinical sources included surgical wounds (57%), sputum (16%), blood (14%), intravenous catheters (4%), otic discharge (4%), and other sources (5%). Specimens originated from nine hospital wards; the ratio of methicillin-susceptible to -resistant isolates did not vary significantly among the wards. None of the patients had been transferred from other medical institutions.

Bacteria were identified by standard methods and characterized as methicillin susceptible or methicillin resistant by using a disk diffusion method (2) which used 5-μg methicillin disks (Difco Laboratories) and Mueller-Hinton agar plates (Difco) incubated at 30°C.

The MICs of methicillin, ciprofloxacin, ofloxacin, vancomycin, and rifampin were determined as follows. Serial twofold dilutions of laboratory-grade powders were prepared in duplicate plates of Mueller-Hinton agar (Difco). Fresh plates were seeded with inocula of 1,000 CFU by using a multipoint replicator (Cathra) and incubated for 24 h at 35°C. Incubation at 30°C was used in studies of methicillin susceptibility. The presence or absence of growth was determined for all inoculation points by a technician who used a single-blind technique. Bacteriophage typing was performed by the National Reference Laboratory.

Fifty isolates of *S. aureus* were found to be resistant to methicillin (MIC, >8 μg/ml) (Table 1). Of these, 45 (90%) were resistant to both ofloxacin and ciprofloxacin at concentrations of >4 μg/ml. Twenty isolates of methicillin-susceptible *S. aureus* were susceptible to the quinolones (MIC, ≤0.5 μg/ml). The difference in quinolone susceptibility between the two groups of staphylococci was highly significant ($P < 10^{-6}$). All isolates were susceptible to vancomycin

TABLE 1. Antibiotic susceptibility of methicillin-resistant and methicillin-susceptible *S. aureus*

Antibiotic and strain[a]	Cumulative % of strains inhibited by concn (μg/ml):													
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Methicillin														
MRSA													0	100
MSSA							0	45	90	100				
Vancomycin														
MRSA						0	98	100						
MSSA					0	10	100							
Ofloxacin														
MRSA				0	4	8	8	8	8	10	78	100		
MSSA				0	70	100								
Ciprofloxacin														
MRSA				0	4	8	8	8	10	100				
MSSA				0	65	100								
Rifampin														
MRSA	88	88	88	90	90	90	90	94	98	98	100			
MSSA	100													

[a] MRSA, Methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

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(MIC, ≤1.0 μg/ml). Three strains of methicillin-resistant *S. aureus* were resistant to rifampin (MIC, >2 μg/ml).

The methicillin-resistant/methicillin-susceptible and quinolone-resistant/quinolone-susceptible *S. aureus* ratios during each of the three study months were similar. Epidemiologic investigations did not reveal a common source for infection. In no instance was a quinolone-resistant organism isolated from a patient following quinolone therapy. No bacteriophage type was identified among 20% of methicillin-resistant and 55% of methicillin-susceptible strains. The remaining organisms were classified into 27 phage patterns (methicillin-resistant, 18; methicillin-susceptible, 9).

Many in vitro and clinical studies have suggested that the quinolone antibiotics are useful for the therapy of staphylococcal infection, including those caused by methicillin-resistant strains (1, 3–5, 7–11). Isolates of methicillin-resistant, quinolone-resistant *S. aureus* have been described previously (6). Such strains have appeared during the administration of quinolones (8) or were selected in vitro through serial exposure of staphylococci to increasing concentrations of ciprofloxacin (6). In one hospital, the prevalence of quinolone resistance increased from 15 to 48% among *S. aureus* isolates during a 6-month period (R. D. Isaacs, P. J. Kunke, R. L. Cohen, and J. W. Smith, Letter, Lancet **ii**:843, 1988).

Our data raise concern as to the future usefulness of quinolones for *S. aureus* infection. The fact that a majority of clinical isolates of *S. aureus* in our hospital are resistant to both methicillin and quinolone antibiotics is of particular concern. Failure to identify a single bacteriophage type or nosocomial source suggests that we are not dealing with an isolated mutant or epidemiological aberration.

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