Ciprofloxacin-Resistant Methicillin-Resistant \textit{Staphylococcus aureus} in an Acute-Care Hospital

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Use of ciprofloxacin as an alternative to vancomycin for treatment of methicillin-resistant \textit{Staphylococcus aureus} infection has been paralleled by the emergence of resistant strains. This phenomenon has also been noticed in our hospital. To confirm our observation, methicillin and ciprofloxacin susceptibilities were tested by disk diffusion and broth microdilution techniques. We studied 83 methicillin-resistant \textit{Staphylococcus aureus} isolates obtained from various sources over a 4-month period. Ciprofloxacin resistance (MIC, >2 \textmu g/ml) was detected in 69 isolates (83%). Prior use of ciprofloxacin was reported for 24 of 69 patients with ciprofloxacin-resistant strains and 0 of 14 patients with ciprofloxacin-susceptible strains. The day of detection during the hospital stay and the location of the source patient were not significantly different between resistant and susceptible strains. Bacteriophage typing showed a higher occurrence of nontypeable strains among ciprofloxacin-resistant strains (54%). Review of our microbiology register showed a progressive increase in the rate of resistance to ciprofloxacin during the first year of use, with initial rates being about 10% and recent rates being higher than 80%. On the other hand, methicillin-susceptible \textit{S. aureus} remained uniformly susceptible to ciprofloxacin (98.4%). We conclude that prior use of ciprofloxacin is an important factor for the selection of ciprofloxacin-resistant strains and that ciprofloxacin has limited usefulness against methicillin-resistant \textit{S. aureus}.

Infections produced by strains of methicillin-resistant \textit{Staphylococcus aureus} (MRSA) are a frequent occurrence in both community and nosocomial settings (1, 3, 4, 25). This is due, at least in part, to the capability of \textit{S. aureus} to colonize sites like nares or skin and, subsequently, spread to cause disease (25). MRSA remains universally susceptible to vancomycin (1, 4, 14). However, the facts that this antibiotic can be administered only intravenously and that it carries a relative risk of toxicity have caused an intense search for other agents that are active against MRSA. Among them, quinolones, and particularly ciprofloxacin, have been examined as alternatives to vancomycin (27, 28), although most investigators believe that their clinical role remains to be defined (1, 2, 7, 14).

Initial studies have shown that the resistance rate of MRSA isolates to ciprofloxacin is generally quite low (11, 15, 26), and successful treatment of experimental MRSA endocarditis has been reported (5, 10). More recently, reports have revealed an increasing resistance of MRSA to ciprofloxacin (8, 16, 19, 22, 24); H. M. Blumberg, D. Rimland, and I. K. Wachsmuth, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 7, 1989; M. S. Gelfand, K. E. Aldridge, B. P. Simmons, and N. L. Barg, 29th ICAA, abstr. no. 1256, 1989; L. J. Strausbaugh, C. M. Jacobson, D. L. Sewell, and T. T. Ward, 29th ICAA, abstr. no. 1257, 1989). In some of them, a very high percentage of MRSA isolates was found to be resistant (24; Blumberg et al., 29th ICAA; Gelfand et al., 29th ICAA; Strausbaugh et al., 29th ICAA).

In our hospital, we observed ciprofloxacin resistance in 130 of 171 isolates (76%) in the first 9 months of 1989. This finding prompted a prospective study to confirm the observation.

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\textbf{MATERIALS AND METHODS}

\textbf{Setting.} Cabrini Medical Center is an acute-care teaching hospital that serves a diverse patient population, including frequently hospitalized individuals such as patients with acquired immunodeficiency syndrome and nursing home residents.

\textbf{Bacterial isolates.} We studied 102 consecutive different isolates of MRSA from hospitalized patients between 1 October 1989 and 8 February 1990.

If, during the same hospitalization, a culture of more than one specimen from the same source in a patient contained MRSA, only the first specimen was included in the study.

\textbf{Data collection.} The following data were collected from patients whose specimens contained MRSA: demographic characteristics, hospital location at the time of specimen collection, day during the hospital stay of specimen collection, prior use of ciprofloxacin during the previous 1 year, day of previous hospitalization if MRSA was isolated in the first 3 days from the time of admission, and main clinical diagnosis.

We tested all \textit{S. aureus} isolates that were detected during the study period for ciprofloxacin susceptibility.

Finally, we reviewed the rate of ciprofloxacin resistance, as initially determined by disk susceptibility, in all MRSA isolates starting September 1988 (in our hospital, ciprofloxacin became a formulary drug at the end of September 1988) until September 1989 (the study was initiated in October 1989).

\textbf{Bacteriologic methods.} Catalase-positive, gram-positive cocci were recovered from a variety of clinical sources. Prior to testing, we isolated each isolate on a Trypticase soy agar (BBL Microbiology Systems, Cockeysville, Md.) plate supplemented with 5% sheep blood and incubated the plates at 35°C with 5% CO\textsubscript{2} for 18 to 24 h. Isolates that coagulated plasma by the tube test (13) and that were positive by a rapid latex agglutination assay (Staphaurex; Wellcome Diagnos-
tics, Research Triangle Park, N.C.) were identified as \textit{S. aureus}.

Portions of five well-isolated colonies which were morphologically similar were touched with a sterile nichrome loop and inoculated into a tube containing 5 ml of Trypticase soy broth. The broth was incubated at 35°C, and then the turbidity was adjusted to a no. 0.5 McFarland standard. A sterile cotton swab on a wooden stick was dipped into the broth; excess inoculum was removed by rotating the swab against the wall of the tube above the fluid level. The Mueller-Hinton agar plate (150 by 15 mm; BBL) was evenly streaked in three directions. Within 15 min after the surface of the agar was inoculated, antimicrobial disks were applied with a self-tapping dispenser (BBL) (17). The antimicrobial disks tested included penicillin, oxacillin, vancomycin, erythromycin, clindamycin, tetracycline, chloramphenicol, cephalothin, trimethoprim-sulfamethoxazole, and ciprofloxacin. The plates were inverted and incubated at 35°C for 24 h within 30 min of inoculation. The diameter of each zone of inhibition was measured to the nearest millimeter through the underside of the plate by using a caliper.

\textit{S. aureus} isolates were determined to be methicillin resistant when the zone diameter of inhibition around a 1-μg oxacillin disk was equal to or less than 10 mm; the isolates were considered to be susceptible to oxacillin when the zone diameter of inhibition was greater than or equal to 13 mm (17). Isolates were considered to be resistant to ciprofloxacin when the zone diameter of inhibition around a 5-μg ciprofloxacin disk was less than or equal to 15 mm; when zone diameters of inhibition were greater than or equal to 21 mm, isolates were considered to be susceptible (17).

Those isolates proven to be resistant to oxacillin were tested on the MicroScan Gram Positive MIC dry microdilution panel (MicroScan Division, Baxter Healthcare Corp., West Sacramento, Calif.) by using the Autoscan-4 automated panel reader and computerized data management system. The isolates were restreaked onto Trypticase soy agar-5% sheep blood and incubated at 35°C in 5% CO₂ for 18 h. Bacterial suspensions of three well-isolated colonies with similar morphologies were prepared by using the Prompt inoculation system-D (3M Corp., St. Paul, Minn.) (6). Following the test procedure recommended by the manufacturer, we prepared the microtiter MIC test panels by using the MicroScan RENOK rehydrator-inoculator system (Baxter). The inoculated MIC microtiter test panels were then covered and incubated at 35°C for 24 h.

The MicroScan computer customization program for antimicrobial testing uses the interpretations of the National Committee for Clinical Laboratory Standards (18). For oxacillin-resistant \textit{S. aureus} isolates, MICs were considered to be greater than or equal to 4 μg/ml, and for oxacillin-susceptible \textit{S. aureus} isolates, MICs were considered to be less than or equal to 2 μg/ml (18). For ciprofloxacin-resistant \textit{S. aureus} isolates, MICs were considered to be greater than 2 μg/ml (the automated reader reports values greater than 2 μg/ml; thus, the next dilution of 4 μg/ml is typical for organisms considered to be resistant according to present standards), and for ciprofloxacin-susceptible \textit{S. aureus}, MICs were considered to be less than 1 μg/ml (18). Isolates for which the MIC was 2 μg/ml were considered to be moderately susceptible and were included among the susceptible isolates in the statistical analysis.

Bacteriophage typing with the international set of typing phages and an additional set of experimental phages was performed on all MRSA test isolates by the Department of Health and Public Health Research Institute of the City of New York (23).

**Statistical analysis.** In the attempt to identify the factors responsible for ciprofloxacin resistance, data were analyzed by linear regression. The following were used as explanatory variables: prior use of ciprofloxacin by the source patient, day of hospitalization that a specimen was obtained from the source patient, location of the source patient in the hospital (intensive care units versus other units), and the presence of human immunodeficiency virus (HIV) disease in the source patient.

Data on the day of isolation were readjusted for statistical analysis. When detection occurred within 7 days of hospitalization, previous admission was considered. When admission was during the previous 30 days, the day of specimen isolation was calculated by adding the actual day of isolation to the days spent at the hospital during the previous admission and to those spent outside the hospital, as if the patient had been continuously hospitalized.

For the analysis of bacteriophage typing, significance of difference between groups was determined by the chi-square test. A \( P \) value of less than 0.05 was considered significant.

**RESULTS**

During the period from 1 October 1989 to 8 February 1990, cultures of 102 consecutive specimens from different sources grew MRSA, as detected by disk susceptibility. Of these 102 specimens, 92 were confirmed to contain MRSA isolates by using an automated panel reader (the remaining 10 specimens were identified as oxacillin susceptible and were thus excluded from analysis). Of 92 confirmed MRSA isolates, 9 were the second MRSA isolates obtained from the same patient and were excluded from analysis.

Eighty-three isolates obtained from different patients were studied for ciprofloxacin susceptibility.

All the patients were hospitalized in different wards or units for variable periods of time. There were 50 men and 33 women; the age range was 28 to 96 years (mean age, 63.5 years); they had multiple underlying diagnoses, including HIV-related conditions (20 patients).

**Sources of specimens.** Sources of specimens were as follows: respiratory secretions from 43 patients (including 6 bronchoalveolar lavages and 2 tracheal aspirates); wound or ulcer specimens from 19 patients; urine from 13 patients; stool from 3 patients, blood from 2 patients; and corneal, cerebrospinal fluid, and venous catheter tip specimens from 1 patient each.

**Ciprofloxacin susceptibility.** Ciprofloxacin resistance was detected by using an automated system in 69 (83.1%) of 83 MRSA isolates; the MIC for these isolates was greater than 2 μg/ml. For 3 isolates, the MIC was 2 μg/ml, and for 11 isolates, the MIC was less than 1 μg/ml; these 14 (16.9%) isolates were defined as moderately susceptible and susceptible, respectively.

Comparison with disk susceptibility testing confirmed ciprofloxacin susceptibility in 13 of 14 isolates, whereas 1 isolate was found to be resistant.

**Susceptibilities to other antimicrobial agents.** When tested for susceptibilities to other antimicrobial agents, the 83 isolates found to be 100% susceptible to vancomycin; susceptibility to trimethoprim-sulfamethoxazole was detected in 75 (90.3%) isolates; 21 (25.3%) isolates were found to be susceptible to chloramphenicol, and 12 (14.4%) isolates were found to be susceptible to clindamycin.

The ciprofloxacin-susceptible isolates were also suscep-
ble to vancomycin (100%), trimethoprim-sulfamethoxazole (85.7%), chloramphenicol (78.5%), and clindamycin (42.8%).

Factors influencing ciprofloxacin resistance. (i) Prior ciprofloxacin use. Prior ciprofloxacin use was reported for 24 patients. Ciprofloxacin-resistant MRSA isolates were isolated from all the patients; none of the patients who yielded ciprofloxacin-susceptible MRSA had used ciprofloxacin previously ($P = 0.006$).

The use of ciprofloxacin by the 24 patients with resistant strains varied between a single dose and an 82-day course of therapy, and ciprofloxacin therapy ended between 8 months prior to isolation and on the day of isolation. Three patients with HIV-related disease used ciprofloxacin for several months, and all the isolates from these three patients were resistant.

(ii) Day of isolation. The 14 susceptible MRSA isolates were detected between days 1 and 720 of hospitalization (mean, day 38.5). For four patients, detection occurred within 7 days of hospitalization, and data on prior admissions were available for all four patients; none of the patients had been hospitalized during the previous 30 days.

The 69 resistant isolates were detected between days 1 and 274 of hospitalization (mean, day 40.8). For 18 patients, detection occurred within 7 days of hospitalization, and data on prior admissions were available for all 18 patients; 3 patients had been hospitalized during the previous month, and the others 15 had been hospitalized in the more distant past.

The difference between the two groups was not significant.

(iii) Location of the source patient. We analyzed locations of source patients at the time of MRSA isolation to determine whether any particular epidemic was occurring in the hospital. Among 14 ciprofloxacin-susceptible MRSA isolates, the distribution was random on six medical wards, and one patient was hospitalized in the intensive care unit.

Among 69 ciprofloxacin-resistant MRSA isolates, the distribution was random on 11 different floors for 59 source patients, although 27 patients were located on two floors only; the remaining 10 patients were located in the intensive care unit.

No difference in the prevalence of ciprofloxacin-resistant MRSA was present between patients located in the intensive care unit and those in other locations.

(iv) HIV-related disease in source patients. We analyzed the impact of HIV-related disease on the emergence of ciprofloxacin-resistant MRSA; in fact, patients with HIV-related disease seemed to be prone to increased levels of infection and colonization with *S. aureus* (9, 20, 21), are frequently hospitalized, and often receive ciprofloxacin for treatment of *Mycobacterium avium-M. intracellulare* or other infections. Twenty patients with HIV-related conditions were identified among the source patients; 16 patients had ciprofloxacin-resistant MRSA, and 8 of them had used ciprofloxacin during the previous 1 year. Four patients had ciprofloxacin-susceptible MRSA, and none had used ciprofloxacin.

The presence of HIV infection did not explain ciprofloxacin resistance.

Bacteriophage pattern. Among 69 ciprofloxacin-resistant MRSA isolates, 10 different bacteriophage patterns were found in 17 isolates, results were not available or no test could be performed for 15 isolates, and 37 isolates were nontypeable with both international and experimental sets of typing phages.

Among 14 ciprofloxacin-susceptible MRSA isolates, seven different bacteriophage patterns were found in 7 isolates, results were not available or a test could not be done for 4 isolates, and 3 isolates were nontypeable.

Thus, nontypeable strains were significantly more common among ciprofloxacin-resistant MRSA isolates ($P < 0.05$).

Changing rate of ciprofloxacin resistance. We reviewed microbiology records to detect the appearance of ciprofloxacin resistance among MRSA isolates in our hospital.

Susceptibility to this agent was first studied by disk susceptibility in September 1988; at the end of that month, ciprofloxacin became a formulary drug.

The rate of resistance to ciprofloxacin was initially low, but it increased progressively starting in November 1988 and reached 92.3% in August 1989 (Fig. 1).

Ciprofloxacin susceptibility among methicillin-susceptible *S. aureus*. During the study period, 459 *S. aureus* isolates were detected in our laboratory. Ninety-two (20%) were MRSA, and 367 (80%) were methicillin-susceptible *S. aureus*.

Among the 367 methicillin-susceptible *S. aureus* isolates, 6 isolates (1.6%) were resistant to ciprofloxacin, while 361 (98.4%) were susceptible.

**DISCUSSION**

MRSA is an important nosocomial pathogen which emerged as a result of a chromosomal mutation shortly after methicillin became available (1, 2). This organism is essentially resistant to all beta-lactam antibiotics and a number of other agents (1). Thus, only a few valid alternatives to vancomycin exist: trimethoprim-sulfamethoxazole, telcoplalin, daptomycin, rifampin, and the quinolones (1, 7). Indeed,
the in vitro activities of the newer quinolones have generated initial enthusiasm for their use in clinical practice, and a few clinical data have confirmed their efficacy (16, 29).

However, recent reports have emphasized the in vitro selection of resistant mutants, predicting increased quinolone resistance as the use of these agents spreads, as well as serious limitations to their clinical usefulness as single agents (7, 27).

In Escherichia coli, the mechanism of resistance to quinolones is mediated by both alteration of the target enzyme DNA gyrase and decreased permeability (30). In S. aureus, resistance is probably the result of alteration of DNA gyrase only (28).

High-level resistance to quinolones in several unrelated MRSA isolates was recently reported in New York (22). At the Atlanta Veterans Administration Medical Center, development of ciprofloxacin-resistant MRSA occurred within 3 months of clinical use of ciprofloxacin (Blumberg et al., 29th ICACC). A similar progressive phenomenon was reported in Memphis, Tenn. In that study, all MRSA isolates were cross resistant to other quinolones, like ofloxacin, fleroxacin, enoxacin, and norfloxacin (Gelfand et al., 29th ICACC). Furthermore, in 40 nursing home patients in Kentucky and California who were colonized with MRSA, use of ciprofloxacin alone or in combination with rifampin was partially successful in eradicating colonization. However, relapses occurred in 60% of the patients, and resistance to ciprofloxacin emerged in both groups (J. A. Korwick, J. Meek, and M. Mulligan, 29th ICACC, abstr. no. 646, 1989). Similarly, in Minneapolis, Minn., an attempt to eliminate MRSA colonization with a combination of ciprofloxacin and rifampin was paralleled by the rapid emergence of ciprofloxacin-resistant MRSA (L. Peterson, J. Quick, B. Jensen, S. Homann, S. Johnson, J. Tenquist, C. Shanholitzer, and D. Gerdng, 29th ICACC, abstr. no. 1255, 1989).

We used the MicroScan dilution method to determine susceptibilities of organisms to antibiotics in our patient population. This method yielded results comparable to those of the agar screen method, provided that an adequate inoculum size was ensured and incubation was for 24 h (31). Our finding of the rapid development of ciprofloxacin resistance in MRSA strains after a few months of clinical use is consistent with the observations of other investigators. In our hospital, ciprofloxacin can now be used only occasionally in the treatment of MRSA infections, as the rate of resistance is higher than 80%. Thus, trimethoprim-sulfamethoxazole remains the only valid alternative to vancomycin, as ciprofloxacin-resistant MRSA is 90% susceptible in vitro, whereas low susceptibility to other agents, like chloramphenicol and clindamycin, precludes their empirical use. It should be noted that ciprofloxacin-susceptible isolates have remained reasonably susceptible to chloramphenicol and clindamycin. This suggests that impaired permeability may play a role in determining resistance to different agents.

We tried to identify factors that are responsible for the selection of ciprofloxacin-resistant strains. Prior use of ciprofloxacin was detected only in patients who yielded ciprofloxacin-resistant isolates. This significant association indicates that widespread use of this agent is accompanied by an increase in the selection of resistant mutants. However, it should be noted that the majority of our patients with ciprofloxacin-resistant MRSA had not received ciprofloxacin in the past year (and so probably never, since this agent has only recently become available). Therefore, we speculated that some other factor could be responsible for the increased frequency of isolation of resistant isolates, and we analyzed the impact of prolonged hospitalization. However, analysis of our data did not confirm the hypothesis that prolonged hospitalization has an impact on the emergence of resistant isolates. Nonetheless, it is conceivable that the hospital environment serves as an important reservoir of ciprofloxacin-resistant MRSA, and patients who had prolonged exposure to ciprofloxacin could become colonized. Colonization may then persist and be detected during subsequent hospitalization, as was probably the case for some of our patients.

When bacteriophage typing was performed, it was found that nontypeable strains were significantly more common among ciprofloxacin-resistant MRSA strains than among ciprofloxacin-susceptible MRSA strains. The significance of this observation is not entirely clear, but it indicates that nontypeable strains are increasingly common among highly resistant nosocomial staphylococci (12). Furthermore, autonomous selection of ciprofloxacin-resistant MRSA strains was apparent, as indicated by the presence of strains with various phage types; this suggests that resistance to ciprofloxacin is not the result of an isolated mutation but, rather, is a more disseminated problem. This could be due to the widespread use of this broad-spectrum agent, which may select for resistant strains.

In conclusion, our data, considered together with reports from several different cities in the United States and other countries, raise concern as to the usefulness of ciprofloxacin in the treatment of MRSA. Alternative agents should be used in those areas where ciprofloxacin resistance is highly prevalent.

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