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Emergence of Ciprofloxacin Resistance in Nosocomial Methicillin-Resistant *Staphylococcus aureus* Isolates

Resistance During Ciprofloxacin Plus Rifampin Therapy for Methicillin-Resistant *S aureus* Colonization

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• We initiated a randomized, single-blinded trial of ciprofloxacin plus rifampin vs sulfamethoxazole and trimethoprim plus rifampin in the therapy for patients who underwent colonization with methicillin-resistant *Staphylococcus aureus* (MRSA). Patients who were colonized with MRSA received 2 weeks of either regimen. The study was terminated after the enrollment of 21 subjects due to the recognition of ciprofloxacin resistance in 10 of 21 new MRSA isolates during the last 2 months of the study. Five of the 10 patients with ciprofloxacin-resistant MRSA isolates had never received ciprofloxacin. Long-term (6-month) eradication had been achieved in only three of 11 ciprofloxacin plus rifampin and four of 10 sulfamethoxazole and trimethoprim plus rifampin recipients. The use of this new fluoroquinolone for the eradication of MRSA colonization is usually not effective and may risk the development of ciprofloxacin resistance in MRSA within the hospital environment.

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The emergence and persistence of methicillin-resistant *Staphylococcus aureus* (MRSA) is a major health care problem, both in terms of morbidity and mortality, as well as in terms of cost to the health care system.[1,2] Larger hospitals are more likely to be at risk for the acquisition of endemic MRSA strains, and a recent survey demonstrated that the interrelated Veterans Administration Medical Center system is experiencing an increasing incidence of MRSA infection and colonization on a national basis.[3]

The eradication of MRSA colonization has been attempted by using several approaches, including whole-body bathing with specified agents, as well as therapy with selected systemic and topical antimicrobial agents.[4] Long-term (defined as ≥6 months) eradication of MRSA has generally not been achieved with any of these methods.[5-10] To our knowledge, no pharmaceutical agent has yet received Food and Drug Administration approval for use in this treatment.

The development and early investigations with new fluoroquinolones, particularly ciprofloxacin, demonstrated their in vitro activity against both methicillin-susceptible *S aureus* and MRSA.[11] The interest in using these agents as a new approach to the control of MRSA colonization was also supported by the findings from an initial investigation.[8] While some resistance developed in MRSA when patients were treated with this compound as a single agent,[8] the early results reported with the fluoroquinolones suggested that combination therapy may prove to be even more efficacious.[2] One preliminary report that used ciprofloxacin combined with rifampin in five subjects suggested the utility of this approach.[12] More recently, several reports have appeared regarding the potential for the development of ciprofloxacin resistance in MRSA when ciprofloxacin is administered, especially as a single agent.[13-19]

The purpose of this report is to (1) describe the results of a single-blinded, prospective evaluation of ciprofloxacin plus rifampin vs sulfamethoxazole and trimethoprim plus rifampin in the eradication of MRSA colonization and (2) to describe the development and apparent spread of ciprofloxacin resistance in MRSA during the first year of the study.

MATERIALS AND METHODS

The Veterans Administration Medical Center, Minneapolis, Minn, is an 845-bed acute-care and referral hospital that serves in excess of 16 000 inpatients and 40 000 outpatients annually. The isolate from our index case of endemic MRSA (phage type 54) was recognized at our medical center in 1984. More than 60 new cases were recognized each in 1987 and 1988. This study, designed to control the spread of this pathogen, was approved by the institutional review board of the medical center, and written informed consent was obtained from all enrollees.

Culture Methods

Swabs (Culturette II, Marion Laboratories Inc, Kansas City, Mo) of nares, rectum, and any open skin wounds were obtained on all patients before, during, and for a total of 6 months after treatment. All material was plated on sheep blood agar and mannitol salt agar that was incubated at 35°C in air for 48 hours. Any colonies suggestive of *S aureus* were confirmed by heat-stable nuclease testing. Susceptibility testing was performed by inoculation of the *S aureus* at a density of 1×10^5 colony-forming units per milliliter into microdilution panels that contained dilutions of oxacillin, rifampin, ciprofloxacin, and sulfamethoxozole and trimethoprim in divalent cation–supplemented Mueller-Hinton broth. The minimum inhibitory concentration was defined as the lowest concentration that showed no growth after overnight incubation in air at 35°C for all antibiotics other than oxacillin. Resistance to oxacillin was determined by the presence of growth in wells that contained greater than 4 mg/L of oxacillin after 48 hours of incubation. Resistance was confirmed by performing disk susceptibility testing, with resistance to oxacillin (methicillin) being defined as a zone (≤10 mm) of inhibition surrounding a 1-μg oxacillin disk after 16 to 18 hours of incubation at 35°C on Mueller-Hinton agar. Resistance to ciprofloxacin was defined as the presence of growth in wells that contained 2 mg/L or more of ciprofloxacin, to rifampin as growth in wells that contained 2 mg/L or more of rifampin, and to sulfamethoxazole and trimethoprim as growth in wells that contained 4 mg/L or more of trimethoprim and 76 mg/L of sulfamethoxazole.

Study Design

Infection control measures during the period of the study consisted of universal precautions for all patients at the medical center that required health care personnel to wear gloves whenever there was

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planned or likely contact with any patient's body fluid. Additionally, all patients, identified as being infected or colonized with MRSA, were placed in a private room under negative pressure with respect to the nursing unit.

All patients who were found to have MRSA in routine cultures submitted to the clinical microbiology laboratory and were colonized (no signs of active, acute infection were present) rather than infected with MRSA were eligible for study. Patients were excluded if they had a history of allergy to any of the study medications. Patients initially received therapy once MRSA was isolated. On enrollment, patients were randomized to receive either ciprofloxacin at a daily dose of 750 mg given orally every 12 hours plus rifampin administered at a dosage of 300 mg orally every 12 hours or sulfamethoxazole and trimethoprim at a daily dose of 320 mg/1600 mg given orally every 12 hours plus rifampin at the same dosage as in the ciprofloxacin regimen. Therapy was continued for 14 days unless terminated early for adverse effects. To evaluate efficacy, the colonizing *S aureus* needed to be susceptible, in vitro, to at least one of the study medications that the subject was receiving. Tests for hematologic, liver, and renal functions were monitored before, during, and after therapy. Cultures of positive sites of MRSA colonization were monitored weekly during therapy and at 1, 2 to 3 weeks, 3 and 6 months following completion of treatment. Once cultures were positive for the presence of MRSA at any site following completion of therapy, the patient was considered a treatment failure.

Serum concentrations of ciprofloxacin were monitored by high-pressure liquid chromatography in all patients who received ciprofloxacin as part of their therapeutic regimen.[20]

Epidemiologic Typing

The predominant nosocomial MRSA in our medical center has been previously analyzed by plasmid fingerprinting and found to consist of variants of a single plasmid pattern.[21] Isolates that had this plasmid pattern have been identified as phage type 54 by the Centers for Disease Control. Most have been sensitive only to phage 54, but occasionally have also been sensitive to other lytic phages, somewhat limiting the utility of this method of epidemiologic typing. Additional selected isolates were also phage typed at the Centers for Disease Control. Isolates of MRSA that were ciprofloxacin sensitive (minimum inhibitory concentration, ≤2.0 mg/L), as well as those that were ciprofloxacin resistant (minimum inhibitory concentration, >2.0 mg/L) were analyzed by both plasmid-pattern analysis[22] and by whole-cell (genomic) DNA restriction endonuclease analysis[23] in an attempt to determine if clonal differences were apparent between these two groups of isolates. Such an approach has recently been recommended for the epidemiological evaluation of staphylococci.[24]

Plasmid DNA was amplified with chloramphenicol, and the cells were lysed by treatment with lysostaphin and sodium dodecyl sulfate. Plasmid DNA was separated, applied to agarose, and electrophoresed at 50 V for 16 hours. The gels were stained with ethidium bromide, and results were photographically recorded.[22] Restriction endonuclease analysis of chromosomal DNA was performed by a modification of the method of Matthews et al.[23] Cells were grown overnight in Luria broth that was supplemented with glucose and TRIS (20 mmol/L, pH 7.5) and washed twice with TRIS (10 mmol/L)–edetic acid (EDTA) (1.0 mmol/L, pH 7.9) buffer. The cells were then treated with lysostaphin and SDS, and after purification, the DNA was digested with 10 U of *Eco*RI restriction endonuclease (Bethesda Research Laboratories, Gaithersburg, Md). The restricted chromosomal DNA was electrophoresed in 0.7% agarose at 50 V for 16 hours. Finally, the gels were stained with ethidium bromide and photographed.

Statistical Analysis

The two-tailed Fisher's Exact Test was used to assess statistical significance between the therapeutic regimens under study. The initial size of the study was based on the postulate that past therapeutic protocols (sulfamethoxazole and trimethoprim plus rifampin) would yield a long-term (3-month) eradication rate of 30%, and the new regimen (ciprofloxacin plus rifampin) would yield a rate of 90%. Choosing a level of significance of .05, then a 90% chance for detecting this difference would require 35 patients enrolled in each arm of the study. The initial study design was open ended, with data analysis to occur after entry of each 30 patients.

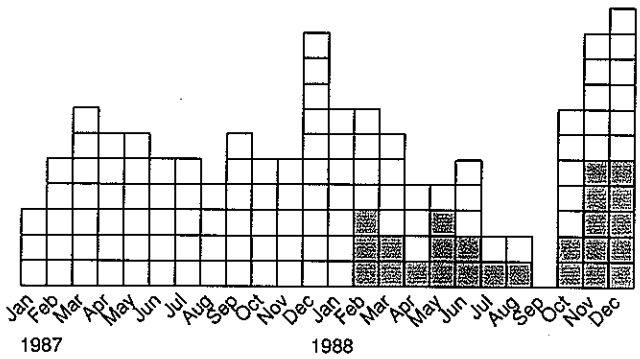

Fig 1.—Depiction of the number of new methicillin-resistant *Staphylococcus aureus* patient isolates seen each month during 1987 and 1988 at the Veterans Administration Medical Center, Minneapolis, Minn. Each box represents one new isolate; open boxes, one new case, ciprofloxacin sensitive; and shaded boxes, one new case, ciprofloxacin resistant.

RESULTS

Twenty-one subjects were enrolled into the colonization treatment study that began in February 1988. Eleven were entered into the group that received ciprofloxacin plus rifampin, and 10 were entered into the group that received sulfamethoxazole and trimethoprim plus rifampin. Figure 1 shows the recognition of new patients (both infection and colonization) with MRSA isolates at the medical center for the years 1987 and 1988. A retrospective chart review of all patients at our medical center with MRSA from 1988 revealed that 39% were patients who were colonized, 40% were infected with this organism, and the remaining 21% were indeterminant. Figure 1 also depicts the ciprofloxacin resistance of these isolates. As can be seen, there was no ciprofloxacin resistance until February 1988. During the last 2 months of 1988, 10 (48%) of 21 of all new MRSA isolates were ciprofloxacin resistant. Of these 10 patient isolates, five were obtained from patients who had not received any of the new fluoroquinolones. In December 1989, all 15 MRSA isolates, newly recognized in our medical center, were resistant to ciprofloxacin. During this same period (December 1987 through December 1989), greater than 95% of the 50 to 75 methicillin-susceptible *S aureus* strains that were seen each month have remained susceptible to ciprofloxacin. During the time of the study (1988), 36% of 115 MRSA strains were also resistant to rifampin, but by December 1989 (1 year after termination of the investigation), all new isolates (n=15) were susceptible to this agent. Resistance to rifampin did not appear to be linked to that of ciprofloxacin, and unlike our experience with ciprofloxacin, the resistance to rifampin virtually disappeared once the MRSA colonization treatment protocol was terminated. The study was terminated at the end of 1988, as a consequence of the development of quinolone resistance in our MRSA isolates, despite the fact that we had not enrolled sufficient patients to satisfy our initial statistical analysis.

The results of the treatment trial are in given the Table. This Table includes the results for all those patients entered

Eradication of MRSA Colonization Following Therapy for MRSA Colonization*

Regimen	No. (%) of Patients With Negative Cultures for MRSA			
	1 wk†	2-3 wk	3 mo	6mo
All patients				
Sulfamethoxazole and trimethoprim plus rifampin (n=10)	6 (60)	5 (50)	5 (50)	4 (40)‡
Ciprofloxacin plus rifampin (n=11)	7 (64)	4 (37)	3 (27)	3 (27)‡
Patients with isolates susceptible to all study agents				
Sulfamethoxazole and trimethoprim plus rifampin (n=9)	6 (67)	5 (56)	5 (56)	4 (44)‡
Ciprofloxacin plus rifampin (n=8)	6 (75)	3 (38)	2 (25)	2 (25)‡

*MRSA indicates methicillin-resistant *Staphylococcus aureus*.
†Time after completion of 2 weeks of therapy for MRSA colonization.
‡Difference between eradication rates at any of the time points is not significant at $P>.1$.

into the study, as well as those patients whose isolate was susceptible to all the study drugs. At the end of the 6-month follow-up period, only 40% of the total group that received sulfamethoxazole and trimethoprim plus rifampin therapy and 27% of the ciprofloxacin plus rifampin treatment groups remained free of MRSA once therapy was completed. These differences are not significant ($P>.1$), but the numbers of patients treated are not large enough to demonstrate statistical equivalence. Four subjects who received ciprofloxacin plus rifampin treatment and three subjects who received sulfamethoxazole and trimethoprim plus rifampin treatment did not clear their colonization during the 2-week treatment period. One additional patient who was treated with sulfamethoxazole and trimethoprim plus rifampin relapsed at 1 week after therapy. Three isolates developed resistance to ciprofloxacin, four developed resistance to rifampin, and two developed resistance to sulfamethoxazole and trimethoprim at the end of the study period. Two of the patients in whom resistance developed to rifampin had initial isolates that were sensitive to both ciprofloxacin and rifampin, and resistance developed to both of these study drugs that they received. The same was true of one patient who received sulfamethoxazole and trimethoprim plus rifampin therapy. The fourth patient whose isolate developed resistance to rifampin was colonized with an isolate that was initially resistant to sulfamethoxazole and trimethoprim, and resistance to rifampin developed during treatment in the sulfamethoxazole and trimethoprim plus rifampin therapy study arm. Three patients enrolled in the ciprofloxacin plus rifampin therapy arm had isolates that were initially resistant to ciprofloxacin; one of these patients was also resistant to rifampin. One patient whose isolate was only resistant to ciprofloxacin became a long-term (>6 months) eradication success; the other two were two of the patients who never cleared their colonization status. The one patient given sulfamethoxazole and trimethoprim plus rifampin therapy who had an isolate that was resistant to sulfamethoxazole and trimethoprim was also one who never cleared his colonization status. Of the patients who had negative cultures during therapy and later were found to have positive cultures for MRSA, all but one subject's culture became positive (relapsed) after discharge from the hospital.

Adverse effects were common in both study arms. While all subjects completed at least 5 days of therapy, nausea and/or vomiting that required early (<14 days) cessation of therapy occurred in one patient who received ciprofloxacin plus rifampin therapy and in two who received sulfamethoxazole and trimethoprim plus rifampin therapy. One subject who received ciprofloxacin plus rifampin therapy experienced threefold elevations in liver function test results that resolved when rifampin was discontinued (ciprofloxacin continued), and one subject who received ciprofloxacin plus rifampin therapy had diarrhea that resolved once the 14 days of therapy was completed. Two subjects who received sulfamethoxazole and trimethoprim plus rifampin therapy experienced elevations in liver function test results that resolved once therapy was completed. Serum concentrations of ciprofloxacin were similar to those in our previous evaluation of this fluoroquinolone (trough concentration = 0.6 ± 0.86 mg/L [mean ± 1 SD]; peak concentration = 1.8 ± 1.2 mg/L [mean ± 1 SD]).[25]

Overall, there were only seven subjects in each treatment group who were (1) able to complete a full course of therapy and (2) whose initial isolate was sensitive to both study medications. Two of those patients (29%) who received the ciprofloxacin plus rifampin regimen and four (57%) who received the sulfamethoxazole and trimethoprim plus rifampin regimen remained free of MRSA for 6 months after treatment.

Figure 2 demonstrates the whole-cell DNA restriction endonuclease analysis and plasmid-profile pattern for two MRSA isolates that were ciprofloxacin sensitive and two that were ciprofloxacin resistant. There were no demonstrable pattern differences in this group of isolates that could be recognized by chromosomal restriction endonuclease analysis. The only change was a shift in plasmid bands in one of the two ciprofloxacin-resistant isolates. All isolates in Fig 2 were susceptible to phage type 54; however, their susceptibility to other lytic phages was variable. Four of the five subjects (from November and December 1988) with ciprofloxacin-resistant MRSA who had not received ciprofloxacin had their isolates evaluated by chromosomal analysis and phage typing. Three of four isolates had similar restriction endonuclease types and were susceptible to phage 54. In total, nine colonized patients had their isolates typed by genomic restriction endonuclease analysis, and three of these also had their subsequent (relapse) organisms typed. All but one isolate was of the same type (identical to that lysed by phage 54). During this period, 16 patients who were infected with MRSA had their isolates typed by the same method, and 14 were of the identical type as the 8 patients with colonization. Three of these isolates from the patients with colonization and two from the infected patients were resistant to rifampin. The isolates were highly resistant to most antimicrobials. Of the 28 total isolates evaluated by genomic typing, 43% were fully susceptible to ciprofloxacin, 36% to tetracycline, 29% to gentamicin, 50% to sulfamethoxazole and trimethoprim, 54% to amikacin, 96% to netilmicin, and 100% to vancomycin. They were uniformly resistant to all other antimicrobials tested.

The MRSA isolates that were resistant to ciprofloxacin appeared to be highly resistant. Seven isolates were tested with higher ciprofloxacin concentrations than we had used previously, and all were found to be resistant to 256 mg/L of ciprofloxacin. No new patients were enrolled in the study during January 1989, and the investigation was permanently

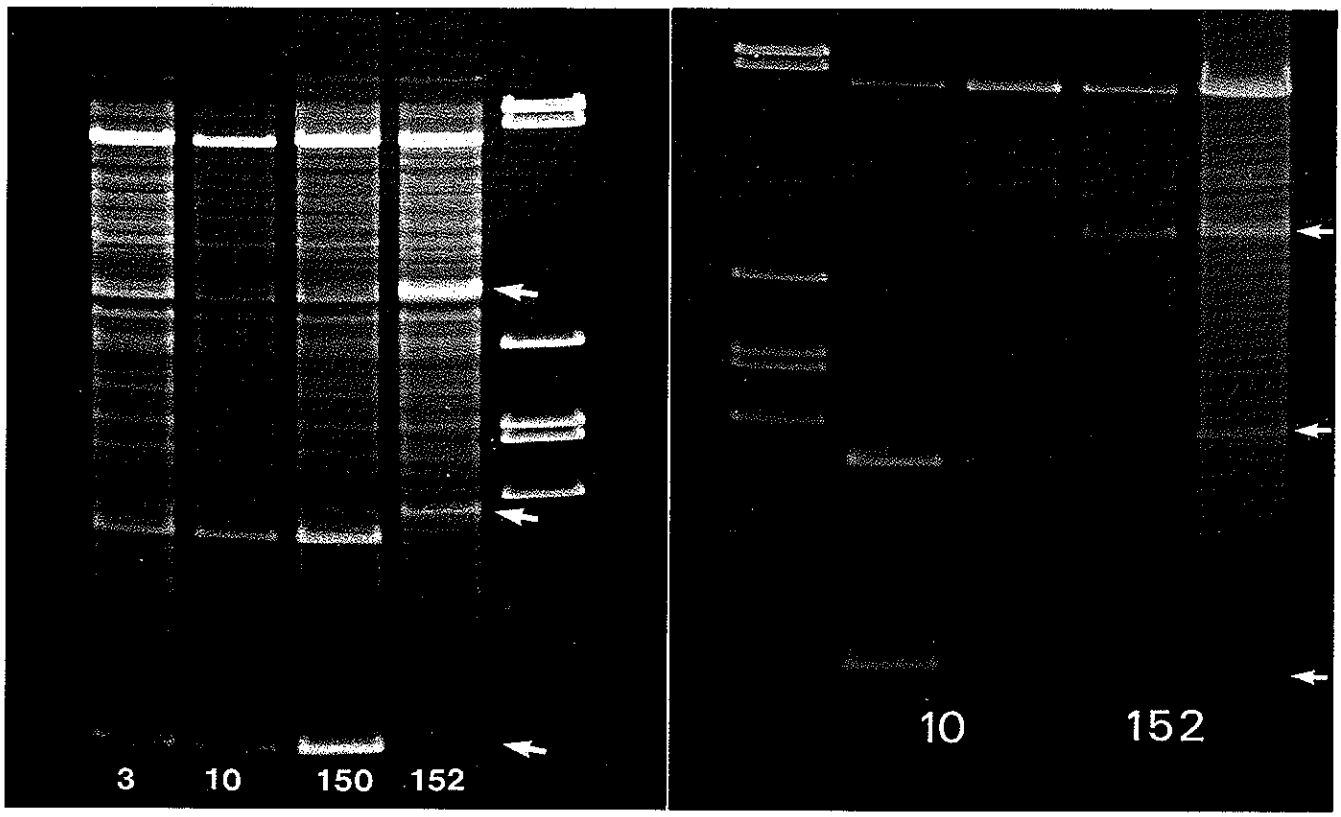

Fig 2.—Left, Restriction endonuclease analysis pattern of total DNA of two ciprofloxacin-sensitive (strains 3 and 10) and two ciprofloxacin-resistant (strains 150 and 152) isolates from four different patients. The first three isolates demonstrate the typical pattern of the endemic methicillin-resistant *Staphylococcus aureus* strain. No difference is seen between these sensitive and resistant strains. The fourth ciprofloxacin-resistant strain (No. 152) differs only by the pattern of plasmid bands (arrows) and has an identical chromosomal restriction pattern. λ-DNA (lane 5) accompanies the restriction endonuclease patterns. Right, Whole-cell DNA restriction endonuclease (lanes 3 and 4) and plasmid DNA pattern (lanes 2 and 5) of one ciprofloxacin-sensitive (strain 10) and one ciprofloxacin-resistant (strain 152) methicillin-resistant *S aureus* isolate. The only pattern difference between these paired isolates is in the plasmid-pattern profile (arrows). λ-DNA (lane 1) accompanies the restriction endonuclease and plasmid profiles.

interrupted on February 1, 1989 after a total of 21 enrollments.

COMMENT

The problem of MRSA in larger medical centers has been well documented, as is the difficulty in eradication of staphylococci from patients with colonization.[1-10] Studies that have followed up subjects for 1 or more months after treatment of staphylococcal colonization have only recorded permanent eradication rates that ranged from 10% to 50%.[5-8,15] This is not different than the loss of *S aureus* colonization reported by Yu et al[6] with no specific therapy. Only Bartzokas et al[4] have reported near-uniform eradication of MRSA from patients with colonization. They employed prolonged whole-body cleansing for several weeks with antiseptic soap and reported eradication of MRSA from 14 patients and staff on a surgical unit. Hill et al[26] also reported eradication of MRSA colonization through the use of nasal application of mupirocin and selective skin cleansing. This approach appeared to be useful for staff carriage, with up to 8 weeks of follow-up. Patients, many with sites other than the nares colonized, were not as successfully treated, and the follow-up data were limited. These last two studies suggested that more ambulatory patients, as well as medical staff, may respond more favorably to attempts at eradication of MRSA colonization. Those patients who require longer periods of institutionalization and have multiple sites colonized with MRSA appear to be most difficult to treat and may present bacteria with a great opportunity to develop resistance to antibiotics used in this therapeutic modality.

The in vitro activity of ciprofloxacin suggested this agent as a possible therapy for MRSA infections, and while early results were not uniformly successful, the small study by Smith et al[12] seemed to suggest potent activity of ciprofloxacin combined with rifampin against MRSA.[8,11] Smith et al[12] attempted to use ciprofloxacin plus rifampin therapy in six patients with colonization. They were able to eradicate colonization in the five subjects who harbored isolates susceptible to both agents, but their follow-up was for less than 6 months. The use of quinolones combined with other agents has recently been suggested as a possible approach for management of MRSA infections[27]; however, the use of two agents given for 14 days did not improve the eradication of colonization in our current study and appeared to be associated with increased toxicity over what we had previously experienced when ciprofloxacin had been used as a single agent.[25] While the poor response to treatment in our study could have been due to reinfection by hospital strains rather than true relapse, this does not appear to be the case, as all but one patient either relapsed after discharge from the hospital or never cleared their colonization.

Two other new reports suggested that alterations in the

approach to past institutional infection control procedures may be needed to control the dissemination of MRSA within the hospital environment.[28,29] Our experience further suggests that this may need to be the case and that broad-spectrum antibiotic therapy should not be part of the approach to the eradication of MRSA from patients with colonization. Furthermore, Kaatz et al[30] have reported the efficacy of ciprofloxacin plus rifampin against *S aureus* to be unpredictable when studied in an experimental endocarditis model. This adds more support for a cautious approach when using the combination for the eradication of MRSA colonization.

The clonal dissemination of MRSA has been addressed by Rhinehart et al.[31] Their report described the dissemination of a unique isolate throughout the medical center environment, similar to what has occurred at our institution. Lacey,[32] in a review on the mechanisms of methicillin resistance, also describes the likely clonality of the spread of *S aureus*-containing resistance genes. The exact mechanism for the development of ciprofloxacin resistance in *S aureus* is currently unknown,[33] and the occurrence of resistance development during therapy has been described.[8,14,15] However, the abrupt onset of quinolone resistance has only been briefly mentioned in previous reports.[18,19,34] Ciprofloxacin resistance in MRSA developed at the time we began our trial (3 months after Food and Drug Administration approval of the agent) during subsequent use of ciprofloxacin in our medical center. This timing and the finding of ciprofloxacin-resistant MRSA in five patients who did not receive the drug combined with our current experience of near-uniform resistance in MRSA, and the fact that virtually all our isolates appeared to be of a single genomic type, raised concern that a clone that carried genes that coded for ciprofloxacin resistance may have spread within the hospital setting.

The data generated from this single-blinded, prospective study for the treatment of MRSA colonization suggest that (1) the oral regimen of ciprofloxacin plus rifampin is not superior to other regimens for this purpose and that rifampin therapy may lead to an increase in adverse effects over what would be expected from the use of ciprofloxacin alone, (2) ciprofloxacin resistance (perhaps clonal) can arise when there is use of this agent for the treatment of MRSA colonization and/or increased use of this agent in institutions with MRSA isolates, and (3) the use of this new agent for the therapy for colonization may negate its potential benefit for the treatment of staphylococcal infection should dissemination of resistance to ciprofloxacin in other staphylococci become widespread. Careful monitoring of the susceptibility of all *S aureus* to ciprofloxacin will be essential in any center by using this new fluoroquinolone in the therapy for MRSA colonization.

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