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Successful Therapy of Experimental Chronic Foreign-Body Infection due to Methicillin-Resistant *Staphylococcus aureus* by Antimicrobial Combinations

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We compared the efficacy of a long-duration (3-week) therapy of vancomycin, fleroxacin, fleroxacin plus rifampin, and vancomycin plus fleroxacin and rifampin in a recently developed rat model of chronic staphylococcal foreign-body infection. Subcutaneous tissue cages containing polymethylmethacrylate coverslips were infected with 1×10^5 to 5×10^5 CFU of methicillin-resistant *Staphylococcus aureus*. Three weeks later, a quantitative culturing of the fluid that had accumulated in the cages was done (mean, 6.72 $\log_{10}$ CFU/ml; $n = 110$) and treatment was initiated after randomization. The CFUs in the cage fluid were counted on days 11 and 22 and 1 week after the termination of treatment; in addition, a final culture of coverslips (surface-bound microorganisms) was performed. The three-drug therapy was significantly superior to the other treatments on day 11 (a 5.16 $\log_{10}$ decrease of bacterial counts versus a 2.12 $\log_{10}$ to 2.94 $\log_{10}$ decrease for vancomycin, fleroxacin, and fleroxacin plus rifampin; $P < 0.01$). On day 22, count decreases were 4.16 $\log_{10}$ for vancomycin, 4.91 $\log_{10}$ for fleroxacin (vancomycin versus fleroxacin, not significant), 6.14 $\log_{10}$ for two-drug therapy, and 6.34 $\log_{10}$ for three-drug therapy (vancomycin-fleroxacin-rifampin versus fleroxacin-rifampin, not significant; fleroxacin-rifampin versus monotherapies, $P < 0.01$); the numbers of CFU in most cage fluids were under the detection limit (20 CFU/ml) in combination groups. One week after the end of treatment, 92% of fluids and coverslips (detection limit, 1 CFU) were culture negative with tritherapy, 88% of fluids and 41% of coverslips were negative with bitherapy, and less than 12% of fluids and coverslips were negative with single drugs (for coverslips, P was <0.01 for vancomycin-fleroxacin-rifampin versus fleroxacin-rifampin and P was <0.001 for fleroxacin-rifampin versus the monotherapies). No mutants resistant to rifampin or fleroxacin were detected. In conclusion, antimicrobial combinations were highly effective and superior to single drugs in treating a chronic staphylococcal foreign-body infection for 3 weeks. The three-drug therapy decreased bacterial counts more rapidly than the two-drug therapy under study and appeared to be curative in most cases.

Infection of implanted prosthetic devices is a major concern in modern medicine and surgery. *Staphylococcus aureus* is a frequent pathogen of such infections (18, 25), and methicillin-resistant strains, encountered with increasing frequency (1, 27), raise important therapeutic problems. Standard antibiotic regimens, such as vancomycin alone or in combination with rifampin (11, 13), are rarely able to cure patients without removal of the foreign implant (3, 5, 21), and rifampin-resistant mutants may emerge even under combination therapy (2, 8, 10, 17, 34).

In a rat model of chronic staphylococcal subcutaneous foreign-body infection, we recently showed that a combined regimen of fleroxacin and rifampin administered for 6 days had the same efficacy as vancomycin plus rifampin and did not lead to the emergence of resistant variants of *S. aureus* (24). Although combination therapy appeared clearly superior to monotherapy, none of these regimens led to the cure of infection.

The purpose of the present study was to define improved therapeutic regimens for established foreign-body infections. First, the duration of treatment of experimental infections was prolonged from 1 to 3 weeks. Thus, the in vivo efficacy of antibiotics could be evaluated in more realistic conditions. Second, a nonconventional multiple therapy combining three antibiotics, namely, vancomycin, fleroxacin, and rifampin, was studied in comparison with treatments using one or two drugs. Finally, this long-term therapeutic regimen was also suitable to evaluate with increased relevance the potential emergence of rifampin- and fleroxacin-resistant mutants.

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MATERIALS AND METHODS

Bacterial strain. The strain of *S. aureus* used, MRGR3, was a methicillin- and gentamicin-resistant bloodstream isolate from a patient with an intravenous catheter infection. As determined from previous studies (6, 24), the MICs and MBCs (28, 29) of vancomycin, fleroxacin, and rifampin for *S. aureus* MRGR3 were 1.0 and 2.0, 0.75 and 1.0, and 0.01 and 0.02 μg/ml, respectively.

Antimicrobial agents. Vancomycin (Lilly, Giessen, Germany), a standard powder for in vitro studies and a commercial product for the treatment of animals, was freshly solubilized and used within 72 h according to the instructions of the manufacturer. Fleroxacin was kindly provided by Hoffmann-La Roche (Basel, Switzerland) as a stable solution containing 4 mg/ml for in vitro tests and injections. Standard and commercial solutions of rifampin (CIBA-GEIGY, Basel,

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Switzerland) were prepared as recommended and stored at −70°C for a maximum of 1 week.

In vitro studies. Time-kill studies were performed with 5 μg of either vancomycin or fleroxacin per ml or with 0.5 μg of rifampin per ml and combinations of these antibiotics at similar concentrations to evaluate their mutual interactions in vitro. These antibiotic concentrations were chosen to approach the mean values found around the foreign body in our animal model; for rifampin, the concentration was lower in vitro than in vivo (0.5 instead of 5 μg/ml) to avoid carryover problems. Time-kill studies were also performed with a fixed multiple (fivefold) of the MIC for all single drugs and their combinations. Glass tubes containing 10 ml of Mueller-Hinton broth (Difco, Detroit, Mich.) were incubated with 10^6 CFU of exponential-growth-phase bacteria per ml in a shaking water bath at 37°C. The number of viable organisms was determined by subculturing 50 μl of 10-fold serially diluted portions of broth on Mueller-Hinton agar (Difco) after 0, 1, 3, 6, and 24 h of incubation. Bacteria were plated with a spiral plater (Spiral System, Cincinnati, Ohio), and colonies were counted with a laser colony counter (Spiral) after 24 h of incubation at 37°C. The sensitivity limits were 1.3 $\log_{10}$ CFU/ml with vancomycin and fleroxacin and 2.3 $\log_{10}$ CFU/ml with rifampin. No significant carryover of antibiotics was observed by using these experimental conditions, as previously stated (24, 36a). Antagonist activity was defined as a decrease in killing of ≥ 2 $\log_{10}$ at 24 h with the combination compared with that with the single most active drug. If the reduction in killing was <2 $\log_{10}$, the combination was considered indifferent (22).

Animal studies. Four polytetrafluoroethylene (Teflon) multiperforated tissue cages containing three polymethylmethacrylate (Plexiglas) coverslips (7 by 7 mm) were implanted subcutaneously in each Wistar rat as previously described (24, 38). At 3 weeks after implantation, the fluid that had accumulated in the cages (designated tissue cage fluid) was aspirated percutaneously, checked for sterility, and inoculated with 0.1 ml of saline containing 1×10^5 to 5×10^5 CFU of *S. aureus* MRGR3 in the stationary phase. Three weeks later, all tissue cages containing more than 10^5 CFU/ml of fluid were included in the therapeutic protocol.

Rats were randomized to receive (by the intraperitoneal route twice a day for 3 weeks) vancomycin (50 mg/kg), fleroxacin (50 mg/kg), or a combined regimen of either fleroxacin (50 mg/kg) and rifampin (25 mg/kg) or vancomycin (50 mg/kg) plus fleroxacin (50 mg/kg) and rifampin (25 mg/kg). Untreated control animals were tested in parallel.

According to a previous study (24), peak (4 h after injection) and trough antibiotic levels in the tissue cage fluid were found to be stable after day 4. They were, respectively, 14.6-fold (14.6 μg/ml) and 2.5-fold (2.5 μg/ml) the MIC of vancomycin, 13.9-fold (10.4 μg/ml) and 3.9-fold (2.9 μg/ml) that of fleroxacin, and 870-fold (8.7 μg/ml) and 580-fold (5.8 μg/ml) that of rifampin.

Before (day 1), in the middle (day 11), and at the end (day 22) of the treatment period, as well as 1 week later (day 28), quantitative cultures of tissue cage fluid were performed on Mueller-Hinton agar. Possible bacterial clumps were disrupted by sonication for 1 min at 60 W (Branson 2200; Branson Ultrasonics, Danbury, Conn.) before plating. Colonies were counted after 48 h of incubation at 37°C. To prevent antibiotic carryover, cultures were performed with 0.1-ml portions of at least 10-fold-diluted tissue cage fluid; thus, the sensitivity limit was 2 $\log_{10}$ CFU/ml. Since rifampin trough levels exceeded by >100-fold the MIC for *S. aureus* MRGR3, a time interval of 24 h was left between the last dose of this antibiotic, now reduced to 10 mg/kg, and the culture of tissue cage fluid; the rifampin concentration was 0.28 ± 0.13 μg/ml (mean ± standard deviation; $n = 15$) at the time of numeration. With vancomycin and fleroxacin, the culture sampling was done 12 h after the last dose. To increase the sensitivity and still avoid a significant carryover of antibiotics, we also performed cultures of 0.05 ml of undiluted cage fluid in a large volume (70 ml) of medium, by using commercial blood culture bottles (Liquoid; Hoffmann-La Roche). This allowed us to detect 1.3 $\log_{10}$ (i.e., 20) CFU/ml.

One week after the end of therapy, the three coverslips were removed aseptically from explanted tissue cages and directly cultured in 5 ml of Mueller-Hinton broth at 37°C for 7 days. A brief sonication (60 W, 1 min) was performed to disrupt the biofilm and phagocytic cells in order to optimize the yield of viable bacteria. The detection limit was 1 CFU per three coverslips. Tissue cages were not cultivated because they were subject to possible contamination during the removal procedure.

Resistance to antimicrobial agents. Bacteria recovered from cage fluids on days 22 and 28 and from coverslips on day 28 were screened for the emergence of resistance to rifampin or fleroxacin: 100-μl samples of the 10-fold-diluted cage fluid were plated on Mueller-Hinton agar containing a 4-fold MIC of fleroxacin or a 100-fold MIC of rifampin. Plates were incubated for 48 h at 37°C. Positive broth cultures of coverslips were analyzed for resistant mutants by the same methodology. The detection limits were 2 $\log_{10}$ CFU/ml for cage fluid and 1 CFU for coverslips.

Statistics. Comparisons of bacterial counts were made by a nested analysis of variance, with Bonferroni's correction for multiple comparisons. Relative frequencies of culture-positive and -negative specimens 1 week after the end of therapy were compared by a chi-square test with Yates' correction or a two-tailed Fisher's exact test when indicated. Data were considered significant when P was <0.05.

RESULTS

In vitro studies. Time-kill studies showed that rifampin antagonized fleroxacin by reducing its bactericidal activity by 2.16 and 2.29 $\log_{10}$ CFU/ml at 1 and 3 h, respectively; the combination was indifferent at 6 and 24 h, but the killing effect of fleroxacin alone was underestimated at these later times as the detection limit of 1.3 $\log_{10}$ CFU/ml was reached and culture-negative tubes were referred to as containing 1.3 $\log_{10}$ CFU/ml. The combined bactericidal activity of fleroxacin plus rifampin was reduced by the addition of vancomycin; however, this reduction was less than 2 $\log_{10}$ CFU/ml at any time (Fig. 1). Similar results were obtained when a fixed multiple (fivefold) of the MIC was used for single drugs and their combinations (data not shown).

Animal studies. Eight of 118 cages (6.8%) with counts below 10^5 CFU/ml on the first day of therapy were excluded from the protocol. Bacterial counts (mean ± standard deviation) for cages containing more than 10^5 CFU/ml of cage fluid ($n = 110$) were 6.72 ± 0.96 $\log_{10}$ CFU/ml. There was no statistically significant difference in mean counts between groups at the beginning of therapy. From days 1 to 28, the numbers of cages spontaneously expelled were as follows: 3

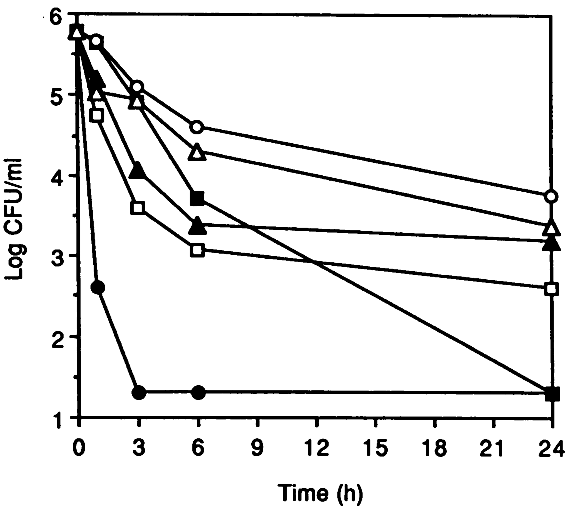

FIG. 1. In vitro bactericidal kinetics of vancomycin (5 μg/ml; ■), fleroxacin (5 μg/ml; ●), rifampin (0.5 μg/ml; ▲), fleroxacin (5 μg/ml) plus rifampin (0.5 μg/ml) (□), vancomycin (5 μg/ml) plus rifampin (0.5 μg/ml) (○), and vancomycin (5 μg/ml) plus fleroxacin (5 μg/ml) and rifampin (0.5 μg/ml) (△) on *S. aureus* MRGR3.

of 22 in the group receiving vancomycin, 3 of 20 in the group receiving fleroxacin, 2 of 19 of animals treated with two drugs, 1 of 23 in the group with three-drug therapy, and 2 of 26 in the control group. Bacterial counts could not be determined reliably after expulsion because cages were damaged and contaminated. One rat died in the untreated group, and two animals died in the group receiving triple therapy for unknown reasons. In this last group, the response to treatment had been good before the death of the animals. Rats receiving three antibiotics frequently had diarrhea and a slight tendency to lose weight (up to 15%).

From days 1 to 11, the decrease of viable counts was 5.16 ± 1.22 $\log_{10}$ CFU/ml and 67% of fluids were culture negative (<20 CFU/ml) in the group receiving the triple combination. The decrease of counts was less than 3 $\log_{10}$ CFU/ml in other groups (2.64 ± 1.08, 2.12 ± 1.50, and 2.94 ± 0.95 $\log_{10}$ CFU/ml with vancomycin, fleroxacin, and fleroxacin plus rifampin, respectively). There was a statistically significant difference ($P < 0.001$) when tritherapy was compared with bitherapy (Fig. 2A).

From days 1 to 22, bacterial counts decreased 4.16 ± 1.43 $\log_{10}$ CFU/ml in the group treated with vancomycin, 4.91 ± 1.13 $\log_{10}$ CFU/ml with fleroxacin, 6.14 ± 0.80 $\log_{10}$ CFU/ml with fleroxacin plus rifampin, and 6.34 ± 1.43 $\log_{10}$ CFU/ml with three drugs. Although fleroxacin seemed more active than vancomycin, this difference was not significant. No difference was demonstrable between groups with double and triple therapy; most cages were culture negative with these regimens. The combination of fleroxacin and rifampin was more effective than was vancomycin alone ($P < 0.01$), but the superiority of the double combination over fleroxacin alone was at the limit of significance ($P = 0.12$, with an analysis of variance and Bonferroni's correction; $P < 0.05$, with the Newman-Keuls' analysis, an equivalent method) (Fig. 2B).

The culture of tissue cage fluids on day 28, 1 week after the end of therapy, showed that only 5.6 and 11.8% of fluids were negative in groups treated with a monotherapy of vancomycin or fleroxacin, respectively. In contrast, 88.2 and 92.3% of fluids were culture negative in the double and triple therapy groups (P was <0.0001 for bitherapy versus monotherapy) (Fig. 3A). The culture of coverslips showed that none was negative in the group receiving vancomycin, 5.9% were negative with fleroxacin, 41.2% were negative with double therapy, and 92.3% were negative with the combination of three drugs. Thus, except for double therapy, results obtained with tissue cage fluid and coverslips were concordant. For coverslips, triple therapy was superior to double therapy ($P < 0.01$) and double therapy was more effective than treatment with a single drug ($P < 0.001$) (Fig. 3B).

Resistance to antimicrobial agents. No MRGR3 isolates resistant to either fleroxacin or rifampin were recovered from cage fluid or coverslips from animals treated with fleroxacin alone or combined regimens.

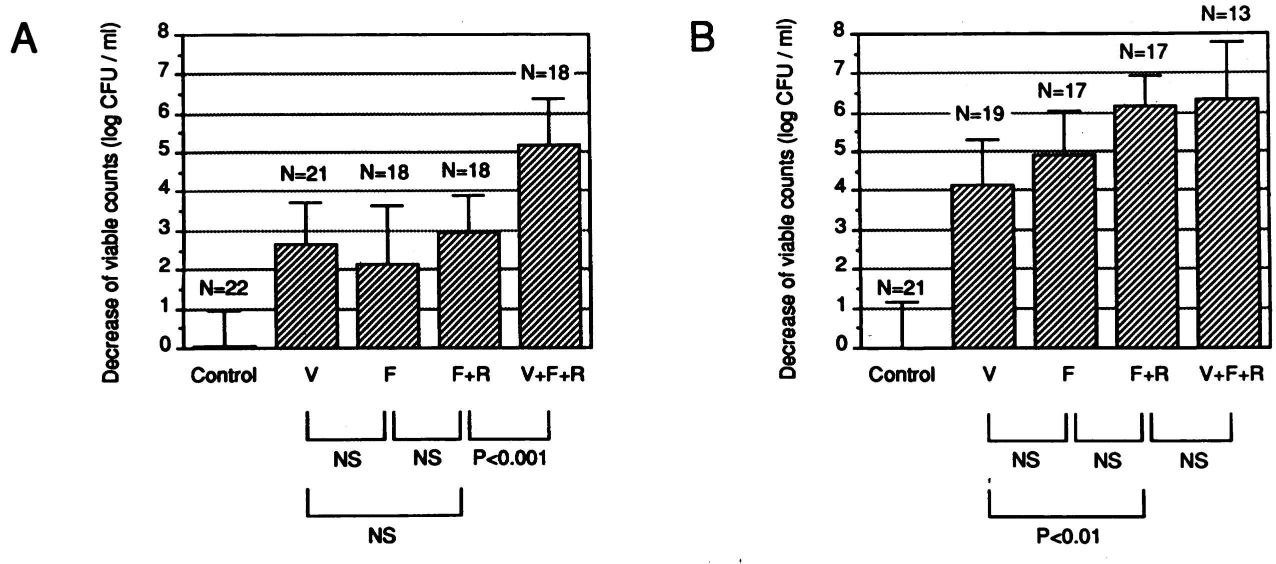

FIG. 2. Decrease of bacterial counts in tissue cage fluid during the first half of the treatment period (day 1 to day 11) (A) and between the beginning and the end of the treatment period (day 1 to day 22) (B). V, vancomycin; F, fleroxacin; R, rifampin; NS, not significant.

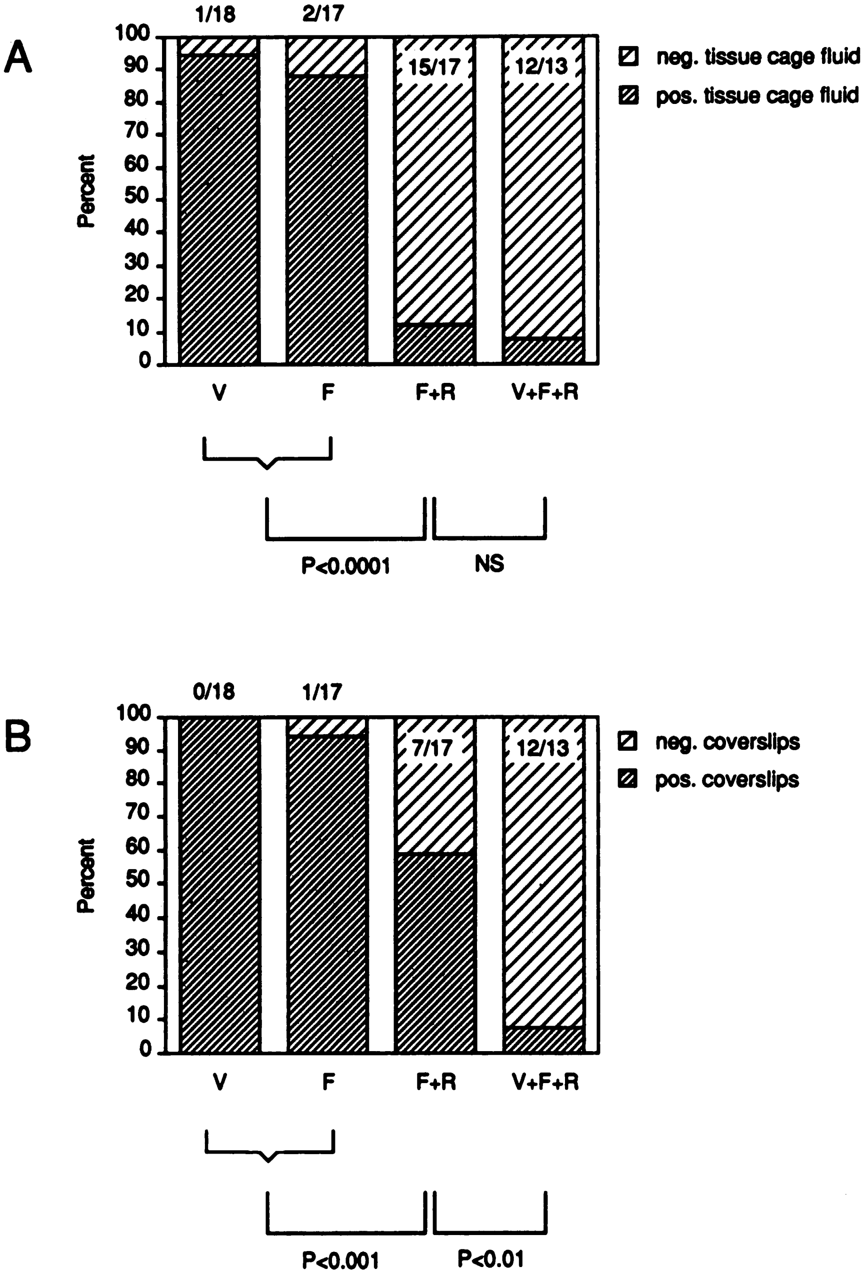

FIG. 3. Proportions of culture-positive and negative tissue cage fluids (A) and coverslips (B) 1 week after the termination of treatment (day 28). V, vancomycin; F, fleroxacin; R, rifampin; NS, not significant.

DISCUSSION

We have shown in this study that an antimicrobial therapy combining two or three drugs (fleroxacin plus rifampin or vancomycin plus fleroxacin and rifampin) was superior to single-agent regimens (vancomycin or fleroxacin) for treating a chronic foreign-body infection due to methicillin-resistant *S. aureus* for 3 weeks in rats. The combination of three antibiotics was the most effective regimen: it decreased the bacterial counts in the fluid surrounding the foreign body more rapidly than other treatments and appeared to cure infections more frequently (in 92% of the cases compared with 41% with fleroxacin plus rifampin and less than 6% with monotherapy). The cure was established by directly culturing the foreign body 1 week after the end of therapy; this procedure is highly sensitive, allowing theoretically for the detection of a single surviving bacterium. None of the antibiotic regimens led to the emergence of resistant mutants to either fleroxacin or rifampin.

Although the superiority of the three-drug regimen was demonstrated only against the double combination of fleroxacin plus rifampin in the present study, it is doubtful that other double combinations, such as vancomycin plus rifampin and vancomycin plus fleroxacin, would have been more effective than fleroxacin plus rifampin. Indeed, a previous study using the same model showed that vancomycin combined with rifampin did not prevent rifampin-resistant mutants from emerging after only 6 days of treatment (24); these mutants would probably be encountered more frequently and in higher numbers after 3 weeks of therapy and lead to treatment failures. It was also previously demonstrated that vancomycin plus fleroxacin was less efficacious than combinations including rifampin (24).

The in vivo superiority of combined regimens over single-drug therapy was not predictable from tests performed in vitro. Time-kill studies showed, on the contrary, that the addition of rifampin to fleroxacin decreased the killing obtained with fleroxacin alone. The same phenomenon was observed with the addition of vancomycin to the combination of fleroxacin plus rifampin. Although there appears to be conflicting evidence regarding the interactions of quinolones and rifampin (30), indifference and antagonism have frequently been reported (12, 16). In contrast, this combination has yielded better results than quinolones alone in several animal models (8, 17, 24). A discrepancy between in vitro and in vivo results when rifampin was combined with other antibiotics, such as penicillinase-resistant penicillins (36, 37) and vancomycin (24), has also been observed. In fact, the efficacy of rifampin as a single drug is much higher in vivo (8, 17, 24) than in vitro compared with other antistaphylococcal agents. Its ability to penetrate phagocytes and to kill intracellularly (26, 35) could explain this phenomenon. In our model, infected tissue cage fluid contains a purulent exudate rich in polymorphonuclear cells, and the activity of antibiotics in polymorphonuclear cells is likely to play a role in the curing process. In combined regimens, rifampin is probably responsible for the major part of killing, whereas the second agent is mainly useful in preventing the emergence of resistant mutants to rifampin. The reasons why the results obtained with fleroxacin plus rifampin were markedly improved when we added vancomycin as the third antibiotic are not clear.

The use of currently available quinolones as single drugs in antistaphylococcal therapy has been criticized in light of the frequent emergence of resistance in clinical situations (4, 7, 15, 31, 32). We did not find any mutant resistant to fleroxacin when this drug was administered alone for as long as 3 weeks. This could be related to the particular conditions of our experimental model, especially the fact that we did not allow antibiotic concentrations in tissue cage fluid to fall under the MIC at any time. The in vitro selection or induction of resistance by multiple passages of bacteria on subinhibitory concentrations of quinolones is a well-described property of these antibiotics (14, 23). If such a mechanism can take place in vivo, the use of a quinolonelike fleroxacin with a long half-life should be an advantage. The relatively low number of bacteria in the cages at the beginning of therapy (10^7 CFU/ml, whereas in vitro spontaneous mutational resistance of *S. aureus* MRGR3 to fleroxacin occurs at a frequency $<10^{-10}$) is possibly also an explanation for the absence of the development of resistance in this model; in contrast, mutants resistant to quinolones have emerged in models of endocarditis (19, 20), with very high bacterial concentrations in vegetations (10^9 to more than 10^{10} CFU/g).

The combination of quinolones with rifampin has been proposed as a safer alternative for patients infected with methicillin-resistant *S. aureus* who need a prolonged peroral therapy. This regimen has yielded positive results in experimental models of chronic osteomyelitis (8, 17) and in recent pilot clinical studies on the treatment of chronic bone and joint infections with foreign material (7, 33), as well as in a trial on right-sided endocarditis (9). Some authors have, however, reported the possible emergence of resistance to ciprofloxacin even when this drug is combined with rifampin (20, 31, 35a). Our study supports the good in vivo activity of rifampin combined with a quinolone; we did not detect any mutants resistant to fleroxacin or rifampin with this treatment.

To our knowledge, there is no experience with a regimen combining vancomycin, a quinolone, and rifampin for treating infections due to *S. aureus*. Such a therapy is probably not useful in most staphylococcal diseases which respond rapidly and fully to a single agent. It could, however, be an interesting alternative in cases where conventional therapies are unsatisfactory, especially in infections of prosthetic devices and in chronic osteomyelitis. We think, therefore, that this antibiotic combination warrants further studies in animal models and possibly in humans.

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