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Ciprofloxacin Therapy for Methicillin-Resistant *Staphylococcus aureus* Infections or Colonizations

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Thirty patients were treated for colonization or for skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus*. Three treatment regimens were evaluated, each progressively more aggressive. One regimen was 750 mg of ciprofloxacin twice daily for 5 days, the second regimen was 750 mg of ciprofloxacin twice daily for 10 to 14 days, and the final regimen was 750 mg of ciprofloxacin twice daily plus 300 mg of rifampin twice daily for 21 days. It appears that ciprofloxacin alone produced an initial eradication rate in at least one site in 50% of the patients, regardless of whether the treatment was for 5 or up to 14 days. All of the patients with eradication became recolonized within 1 week posttherapy. When rifampin was combined with ciprofloxacin, the eradication rate was 100% when the isolates were susceptible to both agents, and these patients remained free of methicillin-resistant *S. aureus* at 1-week and 1-month follow-ups.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has recently emerged as both a colonizing organism and a pathogen among many hospitalized patients. The therapy of infections caused by this organism or the eradication of colonization is particularly difficult. None of the beta-lactam antibiotics appears to be clinically effective; chloramphenicol has not proven effective for the treatment of staphylococcal infection in the past; erythromycin therapy produced rapid emergence of resistance and treatment failures; and finally, the use of aminoglycosides has resulted in the rapid emergence of resistant small-colony variants. Bacitracin, although active against this organism, cannot be applied to the upper nares comfortably to enable eradication of the carrier state. Although vancomcyin has proven effective for treating staphylococcal infections in many body sites, this therapy is expensive. Furthermore, vancomcyin is ineffective for those body sites in which vancomycin does not penetrate well, such as the nares.

With the availability of the newer quinolone compounds, many of which show adequate to good in vitro activity against both methicillin-susceptible and methicillin-resistant staphylococci (9, 10), enthusiasm for use of the quinolones for treatment of infection or colonization by MRSA seems justified. We therefore evaluated the effectiveness of ciprofloxacin for treatment of skin and soft tissue infections and for eradication of MRSA carriage.

MATERIALS AND METHODS

Patient population. Patients identified by the primary care physicians or infection control staff as infected or colonized with MRSA as the primary or sole pathogen were evaluated for entrance into the study. All patients were interviewed and clinically reevaluated by the principal investigator (R.H.K.E.) and informed consent was obtained prior to enrollment. Cultures of the skin structures were obtained by aspiration from the leading edge of the infection. Cultures of groin and perirectal areas were obtained by using saline-soaked cotton-tipped swabs over an area of at least 10 cm^2. Cultures of the nares were obtained by one investigator by inserting the saline-soaked cotton-tipped swabs into the nostrils for at least 3 cm and drawing them outward in a rotating motion against the walls of each nostril. Nares cultures were obtained for all patients as part of ongoing hospital surveillance and were noted when positive.

Treatment protocol. Patients were entered into one of the therapeutic regimens. Patients in the study had not received topical bacteriostatic or bactericidal agents for 48 h prior to receiving ciprofloxacin and did not for the remainder of the ciprofloxacin course and follow-up period. The patients entered early in the trials were treated orally twice daily with 750 mg of ciprofloxacin for 5 days. Cultures of sites which were initially positive were repeated on the last day of therapy and at 7 days posttherapy. When this regimen proved inadequate, newly enrolled patients were treated for a minimum of 10 days and a maximum of 14 days with 750 mg of ciprofloxacin twice daily. Cultures were obtained again at the end of therapy and at 7 days posttherapy. After the second regimen proved inadequate, a final regimen was used in which the patients were treated orally with 750 mg of ciprofloxacin plus 300 mg of rifampin twice daily. The treatment period was extended to 21 days. Cultures were at the end of therapy, at 7 days posttherapy, and at 30 days posttherapy. A body site which was culture positive for MRSA was considered infected if erythema, pain, or swelling was present at or surrounded the site or if profuse drainage was present. In the absence of these signs, the site was considered colonized by MRSA. Patients were seen twice weekly during therapy to be monitored for adverse reactions. A safety profile which included complete blood count and analyses of serum creatinine, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, bilirubin, and urine levels was performed weekly during therapy.

Bacteriology. The specimens were heavily inoculated onto mannitol-salt, MacConkey, and tryptic soy-sheep blood agars (BBL Microbiology Systems, Cockeysville, Md.). Plates were incubated at 35°C. After 24 and 48 h of incubation, colonies of appropriate morphologies were further studied by microscopic examination and coagulase test (4- and 24-h tube tests). When more than five colonies of *S.*

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aureus were found on a specimen, a minimum of five colonies was tested for susceptibility. Bauer-Kirby disk diffusion tests were initially performed with penicillin, oxacillin, nafcillin, rifampin, and ciprofloxacin. The zone sizes of inhibition for ciprofloxacin were recorded. The isolates were later tested by the broth microdilution technique in Mueller-Hinton broth (3). Susceptibility or resistance was interpreted according to National Committee for Clinical Laboratory Standards guidelines (6).

RESULTS

Clinical response. All of the 30 patients infected with MRSA clinically responded, regardless of the therapeutic regimen used. In the case of skin ulcers, the exudates became less, the erythema decreased, and the sizes of the ulcers frequently decreased. In cases of wound infections, all responded with healing and crusting by day 5 of therapy. In the four patients with MRSA colonization in the sputum, no noticeable changes in the clinical respiratory status of the patients were noted. Similarly, those patients with MRSA colonization at other sites showed no clinical change at the colonization sites during therapy.

Bacteriological response. Results of the three therapeutic regimens are shown in Table 1. Despite the consistently good clinical outcome obtained, ciprofloxacin was able to eradicate MRSA in at least one site from only 50% of the patients. This 50% eradication occurred regardless of whether the patient was treated for 5 days or for longer periods of up to 14 days. In the 16 patients treated with ciprofloxacin alone for 5 days, 7 of 14 (50%) infected sites showed eradication of MRSA and 0 of 3 (0%) of the nares colonization sites showed eradication of this organism. In the eight patients treated with ciprofloxacin alone for 10 to 14 days, three of six (50%) of the infected sites showed eradication and zero of three nares colonization sites showed eradication of MRSA. All sites in which MRSA had been eradicated became culture positive within 1 week after termination of therapy. However, more-dramatic results were seen in the patients treated with ciprofloxacin plus rifampin. In all five (100%) patients who had isolates susceptible to both agents, MRSA strains were eradicated. Unlike the patients treated with ciprofloxacin, these patients (100%) remained culture negative at 1-month follow-up. One patient in the group given ciprofloxacin plus rifampin had an initial isolate resistant to rifampin. In this patient, the isolate was not eradicated by ciprofloxacin, which corresponds to data for the first two regimens. Additional pathogens isolated included *Providencia stuartii* (ulcer), *Klebsiella pneumoniae* (ulcer), *Pseudomonas aeruginosa* (wound), *P. aeruginosa* plus *Proteus mirabilis* (wound), coagulase-negative staphylococci plus *Proteus mirabilis* (stye), and *Enterococcus* sp. (wound). All of these isolates were susceptible to ciprofloxacin and were not recovered after termination of therapy. In five of these six patients, MRSA was eradicated during therapy.

A summary of the efficacy of the three therapeutic regimens is shown in Table 2. Data are divided into infected sites versus colonized sites. For the ciprofloxacin regimens of 5 and 10 to 14 days, ciprofloxacin was more effective in eradicating MRSA from infected (50%) than colonized (25%) sites. Persistent eradication was not obtained even in the 10- to 14-day regimen. A marked improvement in both initial (100%) and persistent (100%) eradication was seen when the combination of ciprofloxacin plus rifampin was used for both infected and colonized sites.

TABLE 1. Summary of treatment results

Patient no. and regimen	Site(s) of infection or colonization	Eradication of MRSA during therapy	Recolonization post-therapy
Ciprofloxacin (5 days)			
1	Heel cellulitis and ulcer infection	No	
2	Thigh ulcer infection	Yes	Yes
3	Hip ulcer infection	Yes	Yes
4	Hip ulcer infection	Yes	Yes
5	Foot cellulitis	Yes	Yes
6	Foot ulcer infection	Yes	Yes
7	Leg wound infection	No	
8	Leg wound infection	Yes	Yes
9	Thigh wound infection	No	
10	Leg ulcer infection	No	
11	Foot ulcer infection	No	
12	Cystostomy wound infection	No	
13	Nares colonization	No	
14	Nares colonization	No	
	Sputum colonization	Yes	Yes
15	Foot ulcer infection	No	
16	Nares colonization	No	
	Tracheostomy wound infection	Yes	Yes
Ciprofloxacin (10–14 days)			
1	Buttock skin infection	Yes	Yes
2	Thigh skin ulcer infection	No	
3	Leg skin ulcer infection	Yes	Yes
4	Nares colonization	No	
	Sputum colonization	Yes	Yes
5	Stye	Yes	Yes
	Nares colonization	No	
6	Leg skin ulcer infection	No	
7	Toe skin ulcer infection	No	
8	Perirectal colonization	No	
Ciprofloxacin plus rifampin (21 days)			
1	Leg skin ulcer infection	Yes	No
	Nares colonization	Yes	No
2	Leg wound infection	Yes	No
	Groin colonization	Yes	No
	Nares colonization	Yes	No
3	Leg skin ulcer infection	Yes	No
	Nares colonization	Yes	No
4	Scalp wound infection	No[a]	
	Nares colonization	No[a]	
5	Sputum colonization	Yes	No
	Tracheostomy wound infection	Yes	No
6	Sputum colonization	Yes	No
	Tracheostomy wound infection	Yes	No

[a] Initial isolate of MRSA resistant to rifampin.

A summary of ciprofloxacin susceptibility results is shown in Table 3. The MICs for 50 and 90% of the strains tested did not differ for the initial and end-of-therapy isolates; however, the range did increase from 1.0 to 8.0 μg/ml. Two patients, one treated with ciprofloxacin for 14 days and one treated with ciprofloxacin plus rifampin for 21 days, had end-of-therapy isolates for which MICs were 4.0 and 8.0

TABLE 2. Efficacy of therapeutic regimens for eradication of MRSA

Regimen (days)	No. (%) of infected sites of eradication		No. (%) of colonized sites of eradication		Total no. (%) of sites of eradication	
	Initial	Persistent	Initial	Persistent	Initial	Persistent
Ciprofloxacin (5)	7/14 (50)	0/7 (0)	1/4 (25)	0/4 (0)	8/18 (44)	0/11 (0)
Ciprofloxacin (10–14)	3/6 (50)	0/3 (0)	1/4 (25)	0/1 (0)	4/10 (40)	0/4 (0)
Ciprofloxacin plus rifampin (21)[a]	5/5 (100)	5/5 (100)	5/5 (100)	5/5 (100)	10/10 (100)	10/10 (100)

[a] Rifampin-susceptible isolates only.

μg/ml, respectively. The patient treated with ciprofloxacin plus rifampin had an initial isolate resistant to rifampin and susceptible to ciprofloxacin (0.5 μg/ml). The range and MICs for 90% of the strains tested for the follow-up isolates reflect these isolates, while the MIC for 50% of the strains tested remained unchanged throughout the study.

Safety profile. All patients tolerated ciprofloxacin and rifampin well. One patient complained of a metallic taste in the mouth during therapy. No patients developed measurements of liver enzymes higher than twice normal during therapy with ciprofloxacin alone or combined with rifampin.

DISCUSSION

Ciprofloxacin is the first of the new quinolone antimicrobial agents which can be considered for treatment of skin and soft tissue infections because it maintains adequate levels in blood and tissue of most organs (1, 2). Because of its established in vitro activity for gram-positive organisms (11), it appeared logical to use this agent to treat infections caused by MRSA or to eradicate the carrier state involving MRSA.

All study patients responded clinically. Skin infections were either resolved or considerably reduced. The clinical responses seen in these patients is comparable to that reported by Self et al. (8) in which 21 of 22 patients having skin and skin structure infections involving *S. aureus* improved with ciprofloxacin therapy. In our study, MRSA was eradicated in only 50% of the cases when ciprofloxacin was used alone. This may suggest that in areas of good blood supply, tissue levels of ciprofloxacin were probably adequate to halt the infection. Indeed, concentrations as high as 4.0 μg/ml have been achieved with an oral 750-mg dose (4). However, as the infection resolves, the organisms residing on or colonizing the poorly vascularized epidermis remain uninhibited. An alternate explanation for the good clinical but only modest bacteriological response is that the staphylococcal infections may have resolved spontaneously and the salutary course was independent of the administered therapy.

Respiratory secretions containing MRSA were easily cleared of this organism, as demonstrated by eradication in all four cases, in one case with only 5 days of therapy. However, nares colonization with MRSA is notoriously difficult to treat, as the nasal secretions generally contain low concentrations of most antimicrobial agents. Perhaps as much as 1 μg of ciprofloxacin per ml may be found in the nasal secretions (Miles Laboratories, personal communication). This concentration may be adequate to eradicate very susceptible organisms, such as *Neisseria* sp. (7), but proved inadequate for the less susceptible organisms, such as MRSA. This is best illustrated clinically by an earlier study using ciprofloxacin to treat MRSA nasal colonization in which short courses of therapy were also inadequate and which reported that long courses possibly suppressed MRSA, although the potential for recolonization posttherapy was high (5).

The regimen of 21-day therapy with ciprofloxacin plus rifampin dramatically improved the bacteriological results. The improved eradication rate may be ascribed to the longer period of ciprofloxacin treatment, but extending therapy from 5 days to 10 to 14 days of ciprofloxacin alone did little to alter the eradication rate. More likely, the improved eradication rate was due to the addition of rifampin. Rifampin is known to penetrate well not only into the skin but also into the nasal secretions. Rifampin is extraordinarily active against staphylococci, with MICs and MBCs as low as 0.001 μg/ml. When combined with ciprofloxacin, it is likely that rifampin markedly increased the efficiency of MRSA eradication. One patient was treated with both ciprofloxacin and rifampin for 3 weeks, although the organism proved resistant to rifampin initially, and no eradication was achieved. When this case was excluded from analysis, the combination of ciprofloxacin plus rifampin achieved and maintained MRSA eradication in all five patients treated.

The combination of rifampin plus ciprofloxacin for susceptible isolates produced eradication rates superior to those for ciprofloxacin alone. Currently, this regimen appears useful in the management of patients colonized by or superficially infected with MRSA. Whether the development of rifampin resistance with widespread use of this regimen will vitiate its effectiveness remains to be seen.

TABLE 3. Summary of susceptibility results

MRSA isolates	Ciprofloxacin MIC (μg/ml)[a]		
	Range	50%	90%
Initial (n = 30)	0.125–1.0	0.5	0.5
End of therapy (n = 18)	0.125–8.0	0.5	0.5
Follow-up (n = 12)	0.25–8.0	0.5	8.0

[a] 50% and 90%, MIC for 50 and 90% of isolates, respectively.

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