MAJOR ARTICLE

A Randomized Clinical Trial to Compare Fleroxacin-Rifampicin with Flucloxacillin or Vancomycin for the Treatment of Staphylococcal Infection

Jacques Schrenzel,[1] Stephan Harbarth,[1] Gérard Schockmel,[1] Daniel Genné,[1] Thomas Bregenzer,[2] Ursula Flueckiger,[2] Christiane Petignat,[3] Frédérique Jacobs,[4] Patrick Francioli,[3] Werner Zimmerli,[2] Daniel P. Lew,[1] and the Swiss Staphylococcal Study Group[a]

[1]Geneva University Hospitals, Geneva, [2]Kantonsspital, Basel, and [3]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; and [4]Hôpital Erasme, Brussels, Belgium

Background. Oral combination therapy with fluoroquinolones plus rifampicin is a promising alternative to standard parenteral therapy for staphylococcal infections.

Methods. In a multicenter, randomized trial, we compared the efficacy, safety, and length of hospital stay for patients with staphylococcal infections treated either with an oral combination of a fluoroquinolone (fleroxacin) plus rifampicin or with standard parenteral treatment (flucloxacillin or vancomycin). Patients were included if cultures showed the presence of bacteremia or deep-seated infections with *Staphylococcus aureus* (104 patients) or catheter-related bacteremia due to drug-susceptible, coagulase-negative staphylococci (23 patients).

Results. The cure rate in the intention-to-treat analysis was 78% for the fleroxacin-rifampicin group (68 patients) and 75% for the standard therapy group (59 patients; 47 received flucloxacillin, and 12 received vancomycin); in the population of clinically evaluable patients ($n = 119$), the cure rate was 82% and 80%, respectively; and in the population of microbiologically evaluable patients ($n = 103$), the cure rate was 86% and 84%, respectively. Clinical and bacteriological failures after *S. aureus* infections were documented in similar proportions of patients. The median length of hospital stay after study entry was 12 days in the fleroxacin-rifampicin group, compared with 23 days in the standard treatment group ($P = .006$). More adverse events probably related to the study drug were reported in the fleroxacin-rifampicin group than in the standard therapy group (15 of 68 vs. 5 of 59 patients; $P = .05$).

Conclusions. This study suggests that an oral regimen containing a fluoroquinolone plus rifampicin may be effective for treating staphylococcal infections, allowing earlier discharge from the hospital.

Staphylococcal infections are common and represent an important therapeutic problem, because bacterial complications frequently arise [1]. Therefore, such infections require adequate management and highly effective anti-infective treatment [2]. The treatment currently recommended is a prolonged course of a parenteral, semisynthetic penicillin or vancomycin. However, this treatment entails a risk of complications and increased costs because of prolonged hospital stay and adverse events associated with the use of intravenous catheters.

Previous studies have demonstrated the efficacy of oral antibiotic treatment with rifampicin and ciprofloxacin in the treatment of staphylococcal infections of implanted foreign bodies [3] and of right-sided endocarditis in injection drug abusers [4, 5]. Although it has become common practice to use oral treatment combinations of fluoroquinolones with rifampicin for staphylococcal infections, only a few randomized trials have assessed the efficacy of this treatment regimen for other patient populations [6].

Experimental studies have shown that newer fluoroquinolones have equivalent or even better anti-staph-

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[a] Study group members are listed at the end of the text.

Reprints or correspondence: Dr. Jacques Schrenzel, Div. of Infectious Diseases, Geneva University Hospitals, 24, rue Micheli-du-Crest, CH-1211 Geneva, Switzerland (jacques.schrenzel@hcuge.ch).

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ylococcal efficacy when given in combination with rifampicin, compared with fluoroquinolone monotherapy [7]. The pharmacokinetics of oral fleroxacin is particularly well understood, with regard both to the bioavailability in bacteremic subjects (reaching almost 100%) and the interaction with rifampicin in healthy volunteers [8, 9]. In addition, its long half-life (10 h) allows once-daily oral administration [10]. Fleroxacin is eliminated primarily by renal clearance, with ~60%–70% of a dose being recovered unchanged in the urine within 96 h [11]. This randomized trial compared the efficacy, safety, and length of hospital stay for patients with staphylococcal infections treated either with oral fleroxacin-rifampicin or with standard parenteral therapy (flucloxacillin or vancomycin).

METHODS

Study design. This was a prospective, randomized, open-label, multicenter trial comparing mainly oral fleroxacin-rifampicin with parenteral flucloxacillin for the treatment of staphylococcal infections. Patients randomized to receive flucloxacillin who were allergic to penicillin, or in whom the infection was due to methicillin-resistant *Staphylococcus aureus* (MRSA) or to methicillin-resistant coagulase-negative staphylococci (CoNS) susceptible to fleroxacin and rifampicin, received intravenous vancomycin as alternative therapy. Patients were stratified prospectively into 2 study arms, according to the presence or absence of catheter-related staphylococcal bacteremia.

In each center, consecutive patients who fulfilled the inclusion criteria were randomly assigned by sealed, numbered envelopes to 1 of the 2 treatment groups. Each study center had its own block numbers for randomization so that numbers were allocated sequentially in the order in which the patients were enrolled.

The trial included 5 tertiary care centers in Switzerland (Geneva, Basel, Lausanne, Fribourg, and Bern) and 1 hospital in Brussels, Belgium. The investigators obtained approval for the study by the human research ethics committee at each participating center.

Study population. Adult patients (age, ⩾18 years old) with staphylococcal infections were eligible for this study provided that they had given informed consent and that pure bacteriologic cultures showed the presence of bacteremia and/or deep-seated infection with *S. aureus* or the presence of catheter-related bacteremia due to CoNS that was susceptible to fleroxacin, rifampicin, and flucloxacillin (or to vancomycin, in the case of methicillin resistance or allergy). At study entry, patients were to have at least 1 of the following types of staphylococcal infection requiring anti-infective treatment: lower respiratory tract infection (e.g., pneumonia), infection of a serous membrane (e.g., empyema), acute bone and joint infection (e.g., osteomyelitis and/or arthritis), chronic bone infection (provided that surgical debridement was done and that any foreign material was removed), complicated urinary tract infection (e.g., prostatitis), other deep-seated abscess, right-sided endocarditis, or catheter-related bacteremia. Catheter-related bacteremia had to fulfill 1 of the following criteria: pus at the insertion site and isolation of the same organism from pus and the bloodstream; a positive result of a semiquantitative or quantitative culture of the distal tip with concomitant isolation of *S. aureus* or CoNS from the bloodstream; or differential quantitative cultures of blood, with a ⩾10-fold colony count of organisms concomitantly isolated from blood drawn through a central venous catheter and from cultures of peripheral blood specimens.

Exclusion criteria. Chronic bone infections without surgical debridement were excluded, as were nonbacteremic infections of the skin, because the latter vary in severity and therefore involve an excessively heterogeneous patient population [12]. Infections associated with foreign bodies that were kept in place were included in another study [3]. Left-sided endocarditis was excluded because of a high excess mortality, ruling out an early switch to oral treatment [13].

Pregnant and lactating women were excluded, as was any subject with hypersensitivity or staphylococci resistant to fluoroquinolones or rifampicin. Other exclusion criteria included any of the following: refusal to substitute oral contraception for another form during treatment (for women), significant impairment of hepatic function, concomitant infections at other sites requiring broad-spectrum antibiotics, and treatment with other antimicrobials for >72 h.

Study treatment. Hospitalized patients were randomized to receive either oral fleroxacin-rifampicin or standard parenteral treatment (flucloxacillin or vancomycin). Patients randomized to receive fleroxacin (400 mg q.d.) plus rifampicin (600 mg q.d.) received medication once daily; initially this could be administered intravenously for 24 h, but parenteral therapy was to be switched to the oral route as soon as possible. Flucloxacillin (2 g q.i.d.) and vancomycin (1 g b.i.d.; adapted to serum levels if necessary) were administered only by the intravenous route. Before study inclusion, patients in both treatment groups who required empirical coverage for gram-positive organisms until receipt of definitive results of susceptibility tests were allowed to receive antistaphylococcal agents for up to 72 h after the onset of infection. The recommended duration of anti-infective treatment was as follows: for bacteremia associated with skin-related infections or catheter-related bacteremia, 14 days; for bacteremia associated with deep-seated infections, 28 days; and for bacteremia with vertebral osteomyelitis, 42 days.

Evaluation and monitoring. Assessment of results of bacteriological analysis, clinical signs and symptoms of disease, and safety were made at baseline, during therapy (day 7 after the initiation of treatment), at the end of treatment, and 3 months

(±1 week) after the end of treatment. In cases of bacteremia, endocarditis and secondary septic foci had to be excluded by means of additional diagnostic testing during follow-up. In the event of a complicated clinical course (e.g., sustained bacteremia), complementary investigations with imaging tests were strongly recommended.

Antimicrobial susceptibility testing was done in accordance with NCCLS guidelines by use of disk diffusion techniques. Fleroxacin MICs were interpreted as follows: susceptible, ≤ 2 μg/mL; and resistant, ≥ 8 μg/mL.

All included patients were monitored for signs of drug toxicity and adverse events. Toxicity was reported to be probably related to antibiotics if it began when drugs were first administered, abated after discontinuation of drug use, and was not clearly attributable to other causes.

Analysis of efficacy. Three different patient populations were analyzed: the intention-to-treat (ITT) patient population, the clinically evaluable patient population, and the microbiologically evaluable patient population. The ITT population included all patients who received study medication for at least 24 h. Patients were considered to be clinically evaluable if they met the inclusion criteria and did not satisfy any exclusion criteria, received study drugs for at least 5 days, and did not receive effective antistaphylococcal therapy for >72 h prior to study inclusion. Patients were not clinically evaluable for reasons such as improper duration of therapy not related to adverse events or treatment failure, concomitant receipt of antistaphylococcal therapy after randomization, or inability to meet all predefined entry criteria. Microbiologically evaluable patients included all clinically evaluable patients who had undergone 3 months of follow-up with evaluation of bacterial eradication or relapse.

Primary efficacy variables were the clinical and microbiological outcomes, which were based on resolution of infection at the end of the follow-up period. Criteria for assessing clinical outcome were as follows: cure was defined as clinical signs and symptoms present at baseline that had resolved by the final clinical assessment, and failure was defined as no improvement or deterioration of the clinical condition that required change from the randomized treatment regimen. Bacteriologic cure was defined as eradication of the initially susceptible pathogen. Bacteriologic failure was defined as microbiologically documented persistence or relapse of the original pathogen. Secondary outcome variables evaluated were mortality and length of hospital stay after randomization.

Statistical analysis. A sample size of at least 130 evaluable patients per treatment group was initially required to show the equivalence of the treatments. The calculation was based on a clinical response rate of 70% under standard treatment, a Δ of 30%, a power of 80%, and a predetermined level of significance of .05 (2-sided test). An intermediate analysis done after 35 patients completed the study revealed higher response rates than were initially hypothesized. For this reason, and because of slow patient recruitment, the final analysis was done on the 2 pooled study arms with at least 50 patients per treatment group.

Categorical variables were compared by the χ^2 test or Fisher's exact test. For continuous variables, we used Student's t test or a nonparametric test when appropriate. Relative risks and 95% CIs were calculated for the difference in proportions between the 2 treatment groups.

RESULTS

Study population. Of the 130 patients enrolled, 69 were randomized to receive fleroxacin-rifampicin, and 61 were randomized to receive flucloxacillin or vancomycin. All patients (except 3) who received study medication for <24 h were included in the ITT analysis. In the ITT population, 68 patients were assigned to receive fleroxacin-rifampicin, 47 received flucloxacillin, and 12 received vancomycin (7 patients had a penicillin allergy, 4 had methicillin-resistant CoNS, and 1 had MRSA). The study groups and reasons for nonevaluability are shown in figure 1. Baseline clinical and demographic characteristics of the ITT population were similar for both treatment groups (table 1).

Infection sites and microbiology. The proportional frequency of infection-related diagnoses and causative microorganisms was similar in the 2 groups (table 1). Leading sources of infection were catheter-related bacteremia (in 55 patients) and acute bone and joint infection (in 35 patients). Secondary bacteremia unrelated to catheters was present in 40 patients. Eight patients (12%) in the fleroxacin-rifampicin group and 7 patients (12%) in the standard treatment group had signs of severe sepsis with ≥ 2 organ dysfunctions ($P = .9$). Organisms identified were *S. aureus* (in 104 patients) and CoNS (in 23 patients) in cases of catheter-related bacteremia. In each study arm, 1 case of MRSA infection and 4 cases of methicillin-resistant CoNS infection were included.

Antibiotic treatment. In the ITT patient population, the mean duration (±SD) of antibiotic treatment was 21 ± 16 days in the fleroxacin-rifampicin group and 19 ± 11 days in the standard parenteral treatment group ($P = .41$). The switch to the oral regimen in the fleroxacin-rifampicin group was done after a median of 1 day of intravenous therapy (interquartile range, 1–3 days). In both treatment groups, the same proportion of patients (93%) received empirical antistaphylococcal therapy for up to 72 h before study inclusion. The most commonly administered antistaphylococcal agents before randomization were amoxicillin–clavulanic acid (to 40 patients), flucloxacillin (to 30), and vancomycin (to 20).

The proportions of patients who discontinued therapy prematurely were similar between treatment groups. Overall, 15

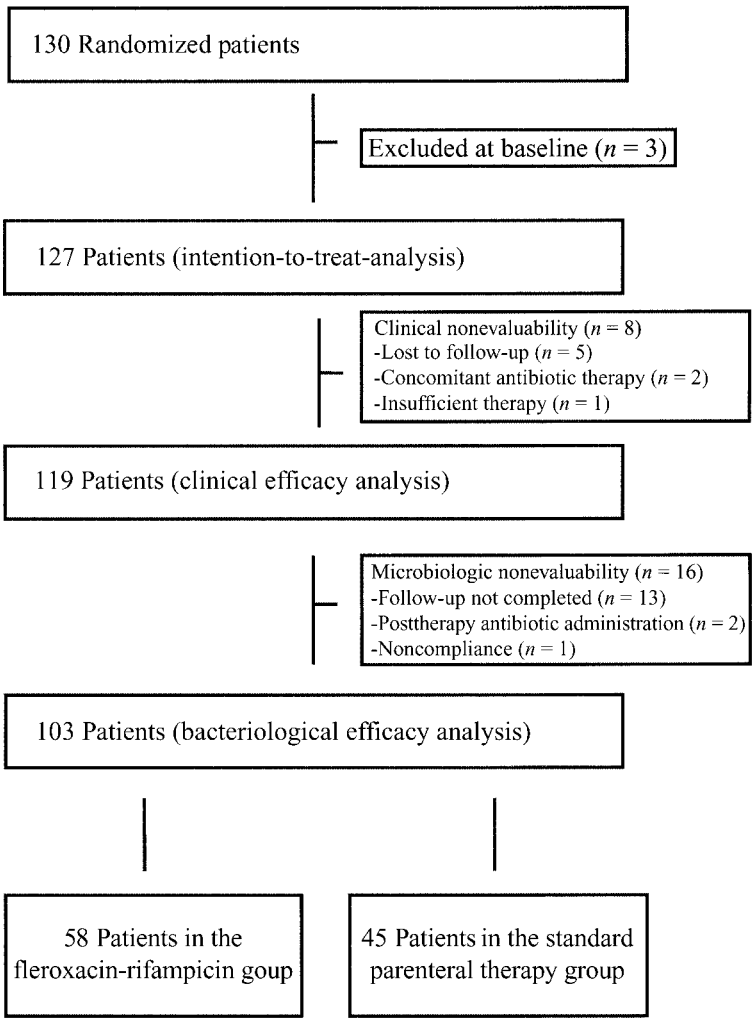

Figure 1. Trial profile and flow diagram of patient enrollment status in each stage of the study, including reasons for nonevaluability

patients (22%) in the fleroxacin-rifampicin group and 14 (24%) in the standard parenteral treatment group discontinued the assigned study medication ($P = .78$). Reasons for discontinuation of study treatment were drug toxicity ($n = 10$; 6 patients in the fleroxacin-rifampicin group and 4 in the standard treatment group), lack of efficacy ($n = 6$; 4 in the fleroxacin-rifampicin group and 2 in the standard treatment group), protocol violation ($n = 8$; 3 in the fleroxacin-rifampicin group and 5 in the standard treatment group) or death ($n = 5$; 2 in the fleroxacin-rifampicin group and 3 in the standard treatment group).

Efficacy. Analysis of response rates in the ITT population, the clinically evaluable population, and the microbiologically evaluable population demonstrated that fleroxacin-rifampicin produced a success rate equivalent to that of standard parenteral treatment (table 2). The overall cure rate in the ITT population ($n = 127$) was 78% and 75% in the fleroxacin-rifampicin and standard parenteral therapy groups, respectively. In the population of clinically evaluable patients ($n = 119$), the overall cure rate was 82% and 80%, respectively, and among the microbiologically evaluable patients ($n = 103$) with complete follow-up data, it was 86% and 84%, respectively. Bacteriological failure was documented in 15 patients (8 in the fleroxacin-rifampicin group and 7 in the standard treatment group). Among these 15 patients, we noted 6 cases of catheter-related bacteremia (including 1 due to CoNS), 6 osteoarticular infections, 2 deep-seated abscesses, and 1 case of primary bacteremia. No development of resistance was noted during fleroxacin-rifampicin treatment.

Similar proportions of clinical and bacteriologic failures after *S. aureus* infections were documented in each group (table 3). In particular, the proportions of microbiologically documented failure after catheter-related or primary *S. aureus* bacteremia (4 [14%] of 29 patients in the fleroxacin-rifampicin group vs. 2 [13%] of 15 patients in the standard treatment group; $P = 1.0$) and osteoarticular infection (2 [11%] of 18 in the flerox-

Table 1. Demographic and baseline clinical characteristics of 127 patients in the intention-to-treat population in a study comparing fleroxacin-rifampicin with standard parenteral therapy (flucloxacillin or vancomycin) for staphylococcal infection.

Characteristic	Fleroxacin-rifampicin group (n = 68)	Standard treatment group (n = 59)	P
Age, mean years ± SD	59.2 ± 17.9	57.1 ± 18.8	.52
Male sex/female sex	44/24	38/21	.97
Weight, mean kg ± SD	69 ± 14	73 ± 15	.16
Smoker	12 (18)	9 (15)	.81
Transfer from another hospital	5 (7)	4 (7)	.86
Prior hospitalization during the 5 years before randomization	36 (53)	32 (54)	.98
Length of hospital stay before randomization, median days (interquartile range)	7.5 (3.5–13.5)	9 (5–12)	.40
Surgery during the 6 months before randomization	8 (12)	10 (17)	.45
Infection during the 3 months before randomization	11 (16)	9 (15)	.89
Steroid therapy	5 (7)	6 (10)	.75
Degree of dependence			.61
Able to carry on normal activity	18 (26)	14 (24)	
Unable to work, needs assistance	23 (34)	25 (42)	
Full dependence on external care	27 (40)	20 (34)	
Underlying condition			
Cardiovascular disease	26 (38)	21 (36)	.85
Diabetes mellitus	16 (24)	10 (17)	.39
Cancer	20 (29)	19 (33)	.85
Neurological disease	9 (13)	12 (20)	.34
Renal disease	7 (10)	5 (8)	.77
Rheumatologic disease	7 (10)	4 (7)	.54
Respiratory disease	5 (7)	3 (5)	.72
Site of primary infection[a]			
Catheter-related bacteremia	30 (44)	25 (42)	.84
Primary bacteremia without identified focus	11 (16)	5 (8)	.28
Secondary bacteremia	23 (34)	17 (29)	.57
Acute bone and joint infection	18 (26)	17 (29)	.84
Chronic osteomyelitis	4 (6)	3 (5)	.99
Deep-seated abscess	7 (10)	8 (14)	.59
Other[b]	2 (3)	2 (3)	.99
Microorganism			
Staphylococcus aureus[c]	58 (85)	46 (78)	.36
Coagulase-negative staphylococci[d]	10 (15)	13 (22)	.36

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Five patients (4 in the fleroxacin-rifampicin group and 1 in the flucloxacillin group) had 2 sites of infection.

[b] Lower respiratory tract infection (in 2 patients) and complicated urinary tract infections (in 2 patients).

[c] In each study arm, there was 1 case of infection due to methicillin-resistant *S. aureus*.

[d] In each study arm, there were 4 cases of infection due to methicillin-resistant coagulase-negative staphylococci.

acin-rifampicin group vs. 4 [31%] of 13 in the standard treatment group; $P = .21$) were comparable between groups.

Secondary outcome variables. Three patients (4.4%) in the group receiving fleroxacin-rifampicin and 5 patients (8.5%) in the standard treatment group died (relative risk, 0.7; 95% CI, 0.3–1.8; $P = .48$). The median length of hospital stay after study inclusion was 12 days (interquartile range, 5–32 days) in the fleroxacin-rifampicin group and 23 days (interquartile range, 15–42 days) in the standard treatment group ($P = .006$).

Safety and tolerability. We recorded 58 adverse events in 39 patients (23 in the fleroxacin-rifampicin group and 16 in

Table 2. Assessment of efficacy in patients in the intention-to-treat, clinically evaluable, and microbiologically evaluable populations who were assigned to receive fleroxacin-rifampicin or standard parenteral therapy (flucloxacillin or vancomycin) for staphylococcal infection.

Population, outcome	Fleroxacin-rifampicin group	Standard treatment group	Relative risk (95% CI)	*P*
Intention-to-treat, cure	53/68 (78)	44/59 (75)	1.1 (0.7–1.6)	.66
Clinically evaluable			1.1 (0.7–1.6)	.79
Clinical success	53/65 (82)	43/54 (80)		
Clinical failure	12/65 (18)	11/54 (20)		
Microbiologically evaluable			1.1 (0.6–1.8)	.64
Eradication	50/58 (86)	38/45 (84)		
Bacteriologic failure	8/58 (14)	7/45 (16)		

NOTE. Data are no. of patients who achieved the outcome/no. of patients evaluated (%).

the standard therapy group; $P = .4$). More adverse events probably related to the study medication were reported from the group treated with fleroxacin-rifampicin (15 of 68 vs. 5 of 59 patients; $P = .05$). Seven patients (10%) in that group had mild adverse events that were probably related to the study medication (3 patients had gastrointestinal symptoms, 2 had increased transaminase levels, and 2 were photosensitive), compared with 1 patient (2%) in the standard treatment group, who had a temporarily decreased leukocyte count.

Eight patients had moderate or severe adverse events in the group treated with fleroxacin-rifampicin (4 patients had CNS symptoms with hallucinations and sleeplessness, 3 patients had hepatitis, and 1 had gastrointestinal symptoms). Six patients had to discontinue therapy because of toxicity. Four withdrawals were attributable to fleroxacin (CNS symptoms), and 2 were related to rifampicin (hepatitis). In the standard treatment group, 4 patients (3 with skin rash and 1 with nephritis) had to stop study medication because of toxicity.

DISCUSSION

This study compared the efficacy and safety of mainly oral fleroxacin-rifampicin therapy with that of standard parenteral therapy with flucloxacillin or vancomycin in the treatment of staphylococcal infection. In the 3 populations analyzed, we consistently observed that the efficacy of fleroxacin-rifampicin was similar to that of standard parenteral therapy. Moreover, the rate of cure of invasive *S. aureus* infections was similar. Although patients who received the fleroxacin-rifampicin regimen had a shorter length of hospital stay, we observed more adverse events that were probably related to study medication in this treatment group.

The few published studies of combination therapy with fluoroquinolones and rifampicin have reported mostly favorable outcomes among patients with right-sided endocarditis or osteoarticular infections [3–6, 14]. Senneville et al. [6] studied 17 patients with diabetic foot osteomyelitis treated with ofloxacin-rifampicin and observed a success rate of 77%, similar to that observed in our study. Moreover, fluoroquinolone-rifampicin combinations have been used successfully for treatment of other types of infections (e.g., leprosy, brucellosis, and peritonitis due to continuous ambulatory peritoneal dialysis) [15–17]. Finally, a ciprofloxacin-rifampicin combination was proposed for the prevention of infections in patients with neutropenia; however, this regimen did not improve the efficacy of antibacterial prophylaxis and increased the occurrence of side effects [18].

The incidence of drug toxicity was higher in the group receiving fleroxacin-rifampicin. Fleroxacin shares the phototoxic skin effects observed with other fluoroquinolones that produce comparable plasma levels, such as enoxacin and pefloxacin [19]. Neurotoxicity was another striking feature of the fleroxacin-containing regimen, limiting its use for several patients. In previous experiments, fleroxacin showed dose-dependent adverse effects on the CNS, leading to insomnia and nightmares [20]. More commonly prescribed, newer fluoroquinolones (e.g., moxifloxacin) with excellent antistaphylococcal activity have lower neurotoxicity and may be valuable alternatives [19, 21].

Fluoroquinolone overuse has become a major concern [22], because resistance rates to fluoroquinolones have increased in many countries [23]. Most nosocomial *S. aureus* strains are now resistant to fluoroquinolones, thus limiting their usefulness for clinical practice. However, most community-acquired MRSA strains are still susceptible to fluoroquinolone-rifampicin combinations; thus, these may be considered as alternatives to orally available agents such as clindamycin, trimethoprim-sulfamethoxazole, or linezolid [24]. Clearly, local and individual susceptibility patterns need to be considered before promoting combination therapies with fluoroquinolones for *S. aureus* infections. In Switzerland and other countries with a low incidence of multidrug-resistant staphylococci, a significant

Table 3. Cure rates among patients in the clinically ($n = 119$) and microbiologically ($n = 103$) evaluable populations assigned to receive fleroxacin-rifampicin or standard parenteral therapy (flucloxacillin or vancomycin) for staphylococcal infection, according to pathogen and infection site.

Population, pathogen and site of infection	Fleroxacin-rifampicin group	Standard treatment group	Relative risk (95% CI)	*P*
Clinically evaluable				
Staphylococcus aureus	44/56 (79)	32/42 (76)	1.1 (0.7–1.6)	.81
Catheter-related bacteremia	15/19 (79)	10/11 (91)	0.8 (0.4–1.3)	.63
Bone and joint infection	18/22 (82)	11/17 (65)	1.6 (0.7–3.5)	.28
Primary bacteremia	10/11 (91)	4/5 (80)	1.4 (0.3–5.9)	.54
Other[a]	1/4 (25)	7/9 (78)	0.2 (0.0–1.5)	.22
Coagulase-negative staphylococci (catheter-related bacteremia)	9/9 (100)	11/12 (92)	Undefined	1.0
Microbiologically evaluable				
S. aureus	41/49 (84)	27/33 (82)	1.1 (0.6–1.7)	1.0
Catheter-related bacteremia	15/19 (79)	9/10 (90)	0.8 (0.5–1.3)	.63
Bone and joint infection	16/18 (89)	9/13 (69)	1.9 (0.6–6.2)	.21
Primary bacteremia	10/10 (100)	4/5 (80)	Undefined	.33
Other[a]	0/2	5/5 (100)	Undefined	.05
Coagulase-negative staphylococci (catheter-related bacteremia)	9/9 (100)	11/12 (92)	Undefined	1.0

NOTE. Data are no. of patients who achieved cure/no. of patients evaluated (%). "Undefined" denotes cells containing a 0 value.

[a] Patients with deep-seated abscess, lower respiratory tract infection, or complicated urinary tract infection.

proportion of patients with *S. aureus* infections may still benefit from this oral combination therapy [25]. In settings with a high prevalence of fluoroquinolone-resistant staphylococci, other rifampicin-containing combination therapies should be investigated in the future.

Several studies have demonstrated the propensity of *S. aureus* to develop resistance to fluoroquinolone monotherapy [26]. We noted the absence of the development of resistance during fleroxacin-rifampicin treatment. This observation is in agreement with that from an experimental study comparing pefloxacin alone with pefloxacin-rifampicin for the treatment of osteomyelitis due to *S. aureus* [27]. By contrast, ciprofloxacin resistance during treatment with ciprofloxacin-rifampicin for MRSA colonization has been reported [28]. In that study, however, 5 of the 10 patients with ciprofloxacin-resistant MRSA isolates had never received ciprofloxacin, indicating possible exogenous cross-transmission [28].

This study has several important strengths. First, to our knowledge, this is the largest clinical trial of an oral fluoroquinolone-rifampicin combination among patients with staphylococcal infections. Second, we included a heterogeneous patient population in our trial, representing the spectrum of staphylococcal infections that clinicians are likely to encounter in clinical practice. Finally, we performed an extended follow-up to exclude late bacterial complications. Nevertheless, 2 study limitations merit consideration. First, fleroxacin is not available for clinical use in several European countries and the United States. However, our data about the antistaphylococcal efficacy of fleroxacin-rifampicin are relevant and should be equally valid for newer fluoroquinolones, such as moxifloxacin or gatifloxacin [29, 30]. Second, the subgroup of patients with catheter-related bacteremia due to CoNS was too small to provide an adequate statistical assessment of the efficacy of fleroxacin-rifampicin treatment in this specific type of infection. Therefore, the overall assessment of efficacy was done on the pooled study arms.

In summary, this study suggests that an oral regimen containing fleroxacin-rifampicin may be effective for treating staphylococcal infections, although tolerance was a limiting factor for several patients. Patients receiving fleroxacin-rifampicin had a rapid switch from intravenous to oral dosing and were discharged earlier than were patients receiving standard parenteral treatment. Decisions guiding treatment of staphylococcal infections should consider not only the efficacy but also the toxicity, the health care costs, and the potential selection of antibiotic-resistant microorganisms.

STUDY GROUP MEMBERS

The Swiss Staphylococcal Study Group is comprised of the authors and the following investigators (location in Switzerland): Christian Chuard (Fribourg), Ferenc Follath (Zurich),

Jorge Garbino (Geneva), Bernard Hirschel (Geneva), Stéphane Hulliger (Geneva), Didier Pittet (Geneva), Claude Regamey (Fribourg), Christian Ruef (Zurich), Olivier Rutschmann (Geneva), Hugo Sax (Geneva), and Heinz Schaad (Bern).

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