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Long-Term Follow-Up Trial of Oral Rifampin-Cotrimoxazole Combination versus Intravenous Cloxacillin in Treatment of Chronic Staphylococcal Osteomyelitis▽

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Oral therapies alternative to fluoroquinolones against staphylococcal chronic osteomyelitis have not been evaluated in comparative studies. Consecutive nonaxial *Staphylococcus aureus* chronic osteomyelitis cases were included in a comparative trial after debridement. Fifty patients were randomized: group A ($n = 22$) was treated with cloxacillin for 6 weeks intravenously plus 2 weeks orally (p.o.), and group B ($n = 28$) was treated with rifampin-cotrimoxazole for 8 weeks p.o. During follow-up (10 years), five relapses occurred: two (10%) in group A and three (11%) in group B. Foreign-body maintenance was associated with relapse ($P = 0.016$). Oral rifampin-cotrimoxazole treatment showed outcomes comparable to those for intravenous cloxacillin treatment.

Chronic osteomyelitis is difficult to eradicate (12, 21). *Staphylococcus aureus*, the main etiologic agent, adheres strongly to bone and to any associated foreign body (FB) (12, 16, 21), generating the biofilm that confers phenotypic antibiotic resistance (2, 19, 23).

Today, experts consider a combination of surgical debridement and antibiotics the best approach for this disease, but the choice of the drug and the route and duration of therapy remain controversial issues (14). Most of the recent successful studies with oral therapies (6, 8, 9, 13, 18, 20, 24, 26) have used fluoroquinolones alone or in combinations with rifampin. However, in light of the emergence of resistant *S. aureus* strains, there is an increasing interest in combinations of rifampin with drugs other than fluoroquinolones.

We present the results of a randomized study of a series of patients with chronic osteomyelitis due to *S. aureus* followed up for a long time to detect late relapses. A classical 6-week parenteral (plus 2-week oral) treatment with cloxacillin is compared to a full 8-week course of oral treatment with a rifampin-cotrimoxazole combination.

(These data were reported partially at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 2007 [L-1147].)

This randomized clinical trial was performed in the orthopedic infection ward of a 900-bed tertiary teaching hospital in Barcelona, Spain, with the approval of the hospital's ethical committee. Eligible subjects were patients who had undergone surgery for chronic nonaxial osteomyelitis due to *S. aureus*, with or without associated FBs (1991 to 1996). The diagnostic criteria included inflammatory signs and/or sinus drainage for ≥10 days, compatible X-ray results, and the presence of necrotic bone (14). Patients with prosthetic joint infections, polymicrobial infections, or infections with cloxacillin-, cotrimoxazole-, or rifampin-resistant isolates were excluded.

Surgery included extensive debridement of bone and soft tissues and removal of foreign material when possible. Osteomyelitis affecting long bones was complemented with closed suction irrigation or muscular flap, when indicated.

Surgical bone samples were cultured in 5% horse blood, chocolate, and MacConkey agar plates and in thioglycolate medium. *S. aureus* was identified using conventional methods. MICs were determined according to the CLSI guidelines (3), with a microdilution method.

When surgical sample culture results were available, consecutive cases meeting the inclusion criteria were randomized by a computer-generated randomization list and the empirical therapy was changed to the protocol treatment: intravenous (i.v.) cloxacillin treatment (2 g every 4 h [q4h]) for 6 weeks plus oral cloxacillin treatment (500 mg q6h) for 2 weeks (group A) or oral rifampin-cotrimoxazole treatment (600 mg rifampin q24h plus 7 to 8 mg/kg of body weight/day of the trimethoprim component, equivalent to three 80/400-mg tablets q12h) for 8 weeks (group B). Additional folinic acid was given in group B at the physician's discretion. Treatment compliance was considered unsatisfactory if <4 weeks of i.v. cloxacillin (group A) or oral rifampin-cotrimoxazole (group B) treatment was completed (14).

The follow-up period was defined as the time following the end of the antibiotic therapy. The patients were periodically visited until April 2007 to collect clinical, laboratory, and radiological data in order to identify relapses. If no recent clinical data were available, the patients or their closest relatives were contacted by telephone. Those who did not complete 1 year of follow-up were considered lost (14).

The primary outcome was the cure rate, defined as the remission of symptoms and the absence of failure during follow-up. Treatment failure was reported when a clinical relapse

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was detected (appearance or recurrence of local inflammatory signs or sinus tract drainage, with or without microbiological confirmation of *S. aureus* in local samples). The secondary outcomes were treatment tolerability and length of hospital stay.

The study was designed to demonstrate the possible noninferiority of the oral schedule relative to the standard i.v. schedule, though since limited data were available about the outcomes of chronic staphylococcal osteomyelitis treated with oral therapies, a defined sample size was not initially established. Baseline characteristics and prognostic factors were identified and compared between groups. Continuous variables are expressed as medians (ranges or interquartile ranges [IQR]) or means ± standard deviations and compared using the Mann-Whitney U test or the Student *t* test. For categorical variables, the Chi-square or Fisher exact test was applied. Analysis was by intention to treat or per protocol, as indicated in the results. Survival was defined as the interval from the end of the antibiotic therapy to the relapse. All patients who had not relapsed by the date of the last analysis were censored. Kaplan-Meier survival curves were calculated for each prognostic factor. A Cox regression model was used for the multivariate analysis: variables with *P* values of <0.20 in the survival analysis and those considered theoretically relevant were included by the backward conditional method. *P* values of <0.05 were considered statistically significant. Statistical analyses were performed with SPSS software version 15.0 (SPSS, Inc., Chicago, IL).

During the recruitment period, 55 patients were considered for inclusion. Five patients were excluded before starting the protocol treatment for not meeting the inclusion criteria (three had been randomized to group A and two to group B). Finally, 50 patients were included; 38 (76%) were male (mean age, 44 ± 20 years), and 14 (28%) had some underlying condition (4 with diabetes mellitus, 2 with cirrhosis, 2 with human immunodeficiency virus infection, and 6 with other conditions). The pathogenesis and localization of osteomyelitis are summarized in Table 1. Most patients (40 [80%]) described pain and demonstrated soft tissue signs of inflammation, 30 (60%) had purulent discharge, and 10 (20%) presented with temperatures of ≥38°C. Blood cultures were performed for eight (17%) patients, but only one bacteremia was demonstrated (group A).

All *S. aureus* strains were susceptible to oxacillin (MIC ≤ 1 mg/liter), cotrimoxazole (MIC ≤ 2/38 mg/liter), and rifampin (MIC ≤ 1 mg/liter).

All patients underwent surgical debridement, with a median of one debridement per patient (range, one to three debridements), and 14 (28%) patients required more than one. Twenty (40%) patients were carrying a FB, and 18 (90%) had the FB removed. A muscular flap was performed for five (10%) patients. Further closed suction irrigation was indicated for 11 (22%) patients, with good results except for 1 patient, who was superinfected with gram-negative bacilli.

Twenty-two patients were randomized to group A (44%) and 28 to group B (56%). No significant differences were found between groups in terms of baseline characteristics or surgical treatment (Tables 1 and 2). Median hospital stay was significantly shorter in group B than in group A (31 versus 51 days; $P = 0.002$) (Table 2).

For six patients, treatment compliance was not satisfactory: three in group A (because of i.v. access problems) and three in group B (two developed an allergy [one bronchospasm and one skin rash], and one completed 3 weeks correctly but took a lower cotrimoxazole dose after discharge because of a misunderstanding). Another three patients in group B developed side effects, but treatment could be continued: one had mild gastrointestinal effects (nausea and vomiting) that responded to antiemetics, and two had pruritus and a rash, requiring antihistaminics. Therefore, the side effects per group were as follows: in group A, three (13.6%) had phlebitis, and in group B, three (10.7%) had a skin rash, one (3.6%) had a bronchospasm, and one (3.6%) had vomiting (Table 2). No patient in group B developed leucopenia below the normal range. The overall median follow-up was 10 years (IQR, 4 to 13). Two patients (4%), one from each group, were considered lost (with last evaluations 4 and 6 months after therapy), and seven (15%) died of nonrelated causes during follow-up. With losses to follow-up excluded, the overall cure rate was 89.6% (43/48) (per protocol, 92.9% [39/42]), without significant differences between groups (Table 2); the cure rate difference between groups was 1.6% (95% confidence interval [CI], −15.7 to 33.3%).

Overall, five relapses occurred (10%): two in group A (2/21 [10%]) and three in group B (3/27 [11%]) (Table 3). One patient from each group had not completed the planned therapy, so per protocol, three relapses occurred: one in group A (1/18 [6%]) and two in group B (2/24 [8%]). The overall median time for relapse was 9 months (range, 4 to 39 months). Two of the patients with relapses, both from group B, were still carrying an FB.

Survival univariate analysis showed that the following factors

TABLE 1. Patient baseline characteristics

Baseline characteristic	Value for group[a]		*P*
	A (*n* = 22)	B (*n* = 28)	
Male sex	17 (77.3)	21 (75.0)	0.85
Age (yr) (mean ± SD)	47.7 ± 18.3	41.7 ± 21.1	0.29
Underlying conditions	8 (36.4)	6 (21.4)	0.34
Source of infection			0.27
Postsurgical	18 (81.8)	16 (57.1)	
Hematogenous	3 (13.6)	6 (21.4)	
Secondary to trauma	1 (4.5)	3 (10.7)	
Secondary to contiguous focus	0 (0)	3 (10.7)	
Localization of infection			0.41
Femur	9 (40.9)	8 (28.6)	
Tibia	7 (31.8)	9 (32.1)	
Humerus	3 (13.6)	2 (7.1)	
Small bones (hand, foot, or patella)	3 (13.6)	9 (32.1)	
Previous episodes	9 (47.4)	11 (42.3)	0.74
Median duration of symptoms (mo) (IQR)[b]	5 (2–16)	3 (1–10)	0.25
Temp of >38°C	6 (27.3)	4 (14.3)	0.43
Orthopedic implants (not prosthesis)	10 (45.2)	10 (35.7)	0.49

[a] All data are numbers (%) of patients except where otherwise indicated.
[b] The median (IQR) values by source of infection are as follows: for postsurgical infections, 3 (1–15); for hematogenous infections, 5 (2–84); for infections secondary to trauma, 6 (2–18); and for infections secondary to contiguous focus, 2 (1–2) ($P = 0.41$).

TABLE 2. Treatment and outcome data

Parameter	Value for group[a]		*P*
	A (n = 22)	B (n = 28)	
Treatment			
Median no. of surgeries (range)	1 (1–3)	1 (1–3)	0.78
Closed suction irrigation	6 (42.9)	5 (21.7)	0.27
No. with implants removed/no. with implants	10/10 (100.0)	8/10 (80.0)	0.47
Median no. of days in hospital stay (IQR)	51 (43–67)	31 (21–49)	0.002[b]
Median no. of days of prior empirical Ab[c] therapy (IQR)	3 (2–4)	5 (2–7)	0.10
Side effects or treatment complications	3 (13.6)	5 (17.9)	1.00
Nonfulfillment of protocol	3 (13.6)	3 (10.7)	1.00
Median duration of Ab therapy (wk) (IQR)			
By intention to treat	8.1 (7.6–9.0)	8.1 (7.1–9.0)	0.56
Per protocol (violations excluded)	8.1 (7.9–9.0)	8.1 (7.9–9.0)	0.69
Outcome			
Lost to follow-up	1 (5.0)	1 (4.0)	1.00
Cured			
By intention to treat[d]	19/21 (90.5)	24/27 (88.9)	1.00
Per protocol	17/18 (94.4)	22/24 (91.7)	1.00
Median duration of follow-up (yr) (IQR)	7.6 (3.7–12.0)	9.9 (3.8–13.0)	0.58

[a] All data are numbers (%) of patients except where otherwise indicated.
[b] Statistically significant.
[c] Ab, antibiotic (before protocol treatment).
[d] Losses to follow-up were excluded.

had no significant influence on relapse: sex, age, underlying condition, previous episode, fever, number of debridements, treatment group, treatment duration, closed suction irrigation, and length of hospital stay. FB maintenance ($P = 0.00001$) and nonfulfillment of the protocol treatment ($P = 0.046$) were significantly associated with relapse. Also, multivariate analysis identified two risk factors for relapse: FB maintenance (odds ratio, 51; 95% CI, 4 to 664) and nonfulfillment of protocol treatment (odds ratio, 28; 95% CI, 2 to 344).

This is, to our knowledge, the first study to compare a rifampin-cotrimoxazole combination therapy with i.v. therapy for treatment of chronic staphylococcal osteomyelitis. We suggest that an 8-week oral rifampin-cotrimoxazole treatment schedule may be as efficacious as i.v. cloxacillin treatment for 6 weeks (plus oral treatment for 2 weeks), classically considered the reference antistaphylococcal therapy. Treatment compliance was generally satisfactory. Though side effects were more frequent in the rifampin-cotrimoxazole group, the difference was not statistically significant. i.v. access problems were the cause of nonfulfillment of the protocol treatment in the cloxacillin group, while in the rifampin-cotrimoxazole group, allergy was the most frequent cause (one patient had gastrointestinal effects without causing treatment disruption). Treatment by the oral route allowed a shorter hospital stay in the rifampin-cotrimoxazole group, which was the main advantage in comparison to the cloxacillin group.

The overall cure rate, around 90%, was high compared to those in other studies, perhaps because our series included relatively young, healthy patients. FB maintenance was the main risk factor associated with failure. As it is usually done in clinical practice, the optimal management of these cases would include removal of the device, but this is not always possible. Some authors have reported acceptable cure rates for osteosynthesis device-related staphylococcal infections with rifampin combinations administered for several months (5, 6, 24). Here, we chose an 8-week schedule, comparable to the standard i.v. schedule used for most patients with staphylococcal osteomyelitis.

The rifampin dose (600 mg daily) was in the lower range compared to other series (600 to 900 mg/day) (5, 6, 17, 24, 26). There is no agreement at present on the ideal dose of rifampin in combination schedules.

Trimethoprim is known to act synergistically with rifampin against a wide range of bacteria, and these two drugs are

TABLE 3. Description of failures

Patient no.	Localization of infection	FB	Group	FB removal	Protocol violation	Duration of antibiotic therapy (mo)	Time to relapse (mo)	Microbiological confirmation
7	Femur	None	A		No	6[a]	5	Yes[b]
10	Hand	None	B		Yes (allergy)	8	4	No
22	Patella	Band fixation	A	Yes	Yes (i.v. access)	4	39	No
34	Femur	Plate	B	No	No	10	9	Yes[b]
40	Femur	Ender nailing	B	No	No	8	28	No

[a] Treatment was by the i.v. route.
[b] Cotrimoxazole- and rifampin-susceptible *S. aureus* strain.

compatible pharmacologically (11). The role of cotrimoxazole and the best dose for staphylococcal infections are difficult to determine with the information currently available. Classically, cotrimoxazole was not recommended for intravascular infections (4, 15). In contrast, successful results were found in an experimental and clinical study of *S. aureus* osteomyelitis, using cotrimoxazole alone with a high trimethoprim dose (10 mg/kg/day) (25). Doses of 7 mg/kg/day, similar to those given here, were used in combination with rifampin in a noncontrolled prospective clinical osteomyelitis study after 2 weeks of i.v. cloxacillin treatment, with a good outcome (17). The cotrimoxazole dose that we used may be appropriate when given in combination with rifampin, helping to achieve better tolerance and compliance, which we believe are essential factors in prolonged oral treatment.

The increasing epidemic of community-acquired methicillin-resistant *S. aureus* infections worldwide has renewed the interest in the possible contribution of cotrimoxazole in the treatment of staphylococcal infections. Classical data (7) and a recent report highlight its excellent in vitro bactericidal activity, which is even better than that of rifampin, suggesting that cotrimoxazole may be a good alternative in soft-tissue infections (10).

A limitation of the study was the difficulty of obtaining a sufficiently large number of patients to achieve statistically significant results. According to the standard noninferiority design (20% beta error and 5% delta), with the cure rates that we observed, we would have needed about 500 patients per group to achieve statistical significance. With the characteristics of the disease, this number was not affordable for a single-center study, but the advantage of obtaining a homogeneous series was a decisive factor; therefore, after 1996, the study continued only for patient follow-up.

The long-term follow-up design is a strength of the study. The IDSA guidelines (14) specify that "eradication" should be considered after 1 asymptomatic year following the end of antimicrobial therapy. Most authors have used this follow-up period. However, it is well known that relapses in chronic staphylococcal osteomyelitis may occur after 50 years without symptoms (1, 12, 21, 22). Interestingly, it was observed that the cure rate decreased from 80% to 50% when the follow-up was prolonged from 1 to 5 years (G. Rodriguez-Gomez and L. O. Gentry, presented at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1995). In our series, while most relapses appeared soon after the end of therapy, the long-term follow-up allowed us to identify two additional relapses (at 29 and 39 months).

Our data suggest that oral rifampin-cotrimoxazole therapy is a good alternative in the treatment of chronic staphylococcal osteomyelitis after surgical debridement. This combination may be especially useful against infections caused by emerging quinolone-resistant strains. Our experience corroborates the notion that, as the literature reports, surgical debridement of this kind of infection should include FB removal when possible.

None of the authors have any conflicts of interest.

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