Outcome of Diabetic Foot Osteomyelitis Treated Nonsurgically

A retrospective cohort study

Eric Senneville, md[1]
Audrey Lombart, md[1]
Eric Beltrand, md[2]
Michel Valette, md[1]
Laurence Legout, md[1]
Marie Cazaubiel, md[1]
Yazdan Yazdanpanah, md, phd[1]
Pierre Fontaine, md, phd[3]

OBJECTIVE — The purpose of this article was to identify criteria predictive of remission in nonsurgical treatment of diabetic foot osteomyelitis.

RESEARCH DESIGN AND METHODS — Diabetic patients who were initially treated without orthopedic surgery for osteomyelitis of the toe or metatarsal head of a nonischemic foot between June 2002 and June 2003 in nine French diabetic foot centers were identified, and their medical records were reviewed. Remission was defined as the absence of any sign of infection at the initial or contiguous site assessed at least 1 year after the end of treatment. A total of 24 demographic, clinical, and therapeutic variables including bone versus swab culture–based antibiotic therapy were analyzed.

RESULTS — Fifty consecutive patients aged 62.2 ± 11.1 years (mean ± SD) with diabetes duration of 16 ± 10.9 years were included. The mean duration of antibiotic treatment was 11.5 ± 4.21 weeks. Bone biopsy was routinely available in four of the nine centers. Overall patient management was similar in the different centers except for the use of rifampin, which was recorded more frequently in patients from centers in which a bone biopsy was available. At the end of a 12.8-month posttreatment mean follow-up, 32 patients (64%) were in remission. Bone culture–based antibiotic therapy was the only variable associated with remission, as determined by both univariate (18 of 32 [56.3%] vs. 4 of 18 [22.2%], $P = 0.02$) and multivariate analyses (odds ratio 4.78 [95% CI 1.0–22.7], $P = 0.04$).

CONCLUSIONS — Bone culture–based antibiotic therapy is a factor predictive of success in diabetic patients treated nonsurgically for osteomyelitis of the foot.

Diabetes Care **31:637–642, 2008**

The question of surgical versus nonsurgical treatment for diabetic patients with osteomyelitis of the foot remains subject to debate (1). It was traditionally thought that these infections could not be treated without resecting the infected bone (2). However, the option to treat such patients without surgery may be decided on the basis of other "real-life" reasons, such as the unavailability of a surgeon, refusal of the patient to undergo operation, or the surgeon's refusal to operate. As surgical treatment of osteomyelitis may lead to biomechanical deterioration, some authors have tried to treat these patients with little or no bone surgery, and apparently satisfactory results have been reported in several recent studies (3–7). Patients were mainly given fluoroquinolones, clindamycin, and rifampin, which reach high concentrations in bone, penetrate into white blood cells, and exhibit activity toward bacterial strains with reduced metabolism, as described in biofilm-related infections (8–11). Except for one series reported by our group (3), antibiotic therapy for these patients was based on culture of nonbone specimens such as wound tissues or deep samples taken during debridement of foot lesions (4–7).

The factors associated with success in diabetic patients treated for osteomyelitis of the foot have been assessed in several studies (5,7,12,13). Bamberger et al. (12) found that success was associated with intravenous therapy given for at least 4 weeks or with a combination of intravenous and oral therapy administered for at least 10 weeks. Bacteremia, gangrene, and open versus closed wounds were identified by Peterson et al. (13) as risk factors in failure. More recently, Embil et al. (7) did not find any difference in the outcome of patients treated with bone versus nonbone debridement nor in those treated with oral versus oral plus intravenous therapy. The respective roles of an increase in serum creatinine levels and of a fever, identified by Pittet et al. (5) as independent predictive factors of failure in such patients, cannot be applied to bone infections, as deep tissue infection and osteomyelitis were not evaluated separately in their study. Appropriate antimicrobial therapy is obviously of major importance in nonsurgical treatment, together with other components of patient care, such as optimal wound nursing and suitable offloading. Recently, the French consensus on the management of diabetic foot infections proposed antibiotic regimens based on the results of bone culture for patients with osteomyelitis of the foot (14). However, no study has dealt with the benefits of reliable microbiological documentation of the infected bone in terms of patient outcome.

In northern France, for the last 10 years, nine centers have been working together as referral centers for diabetic patients with foot infections, applying the same treatment protocols, except for bone biopsy, which has been routinely available only in four centers. The objective of the present retrospective study was therefore to examine the impact of demographic and therapeutic parameters, including bone culture–based antibiotic

From the [1]Diabetic Foot Clinic, Dron Hospital, Tourcoing, France; the [2]Department of Orthopedic Surgery, Dron Hospital, Tourcoing, France; and the [3]Department of Diabetology, Centre Hospitalier Régional Universitaire of Lille, Lille, France.

Address correspondence and reprint requests to Eric Senneville, Infectious Diseases Department, Dron Hospital, 135 rue du Pr Coty 59200 Tourcoing, France. E-mail: esenneville@ch-tourcoing.fr.

Received for publication 4 September 2007 and accepted in revised form 2 January 2007.

Published ahead of print at http://care.diabetesjournals.org on 9 January 2008. DOI: 10.2337/dc07-1744.

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*.

therapy, on the outcome of diabetic patients with osteomyelitis of the foot treated nonsurgically.

RESEARCH DESIGN AND METHODS

— We conducted a retrospective study in which medical records were examined for diabetic patients with osteomyelitis of the foot (i.e., below the ankle) treated nonsurgically in nine referral centers in northern France (Béthune, Boulogne sur Mer, Douai, Dunkerque, Lens, Lille, Roubaix, Tourcoing, and Valenciennes). (A complete list of the participating centers and investigators can be found in the APPENDIX.) Treatment was defined as nonsurgical if no surgical intervention involving the bone was performed during the 10 days after the initiation of antimicrobial therapy.

Inclusion criteria

The 2.5-year study period, including follow-up, lasted from June 2002 to December 2004. Patients aged ≥18 years were included if they had type 2 diabetes and osteomyelitis of a nonischemic foot, which was defined as the absence of any pedal pulse. Patients with suspected osteomyelitis of the foot had at least two of the following clinical criteria: a wound lasting ≥2 weeks over an underlying bony prominence, with an ulcer surface >2 cm^2 or depth >3 mm, associated with probing to bone and/or abnormalities consistent with the diagnosis of osteomyelitis on plain radiographs, bone scans (coupled gallium [^{67}Ga-citrate]-technetium [^{99m}Tc-diphosphonate] radionuclide or Leukoscan [sulesomab scintigraphy using an antigranulocyte antibody Fab′ fragment labeled with ^{99m}Tc]), or magnetic resonance imaging. Patients with a definitive diagnosis of osteomyelitis of the foot met the same diagnostic criteria associated with a positive bone culture. In addition, data concerning patient follow-up for at least 12 months after the end of treatment had to be available. Patients who had gangrene or required bone resection or amputation when osteomyelitis of the foot was diagnosed were excluded.

Specimen collection

Nonbone specimens were swabs only taken from the soft tissues of the wound after brief cleansing with sterile saline solution by passing a sterile compress over the ulcer surface. Bone lesion samples were collected by an orthopedist in the operating room under fluoroscopic guidance using an 11-gauge biopsy needle (Becton Dickinson, Franklin Lakes, NJ) inserted through a 5- to 10-mm skin incision at least 20 mm from the ulcer periphery, in accordance with the procedure described by our group previously (15).

Treatment

Patients were treated using a nonsurgical approach if there were no signs of bone fragmentation on plain radiographs of the foot. Swab culture results were used to select antibiotic treatment in patients who did not have a bone biopsy or those with a negative result. In patients with a positive bone biopsy, antibiotic regimens were tailored to cover the microorganisms isolated from the bone with no reference to the swab culture results. The use of rifampin was discouraged in centers that did not do bone biopsies and in patients with no positive bone culture results. Antibiotics were selected in accordance with the patient's comorbidities and prescribed at doses adapted from those proposed by Lew et al. (16). Antibiotics were administered either orally for the entire treatment period or intravenously for a short period (<7 days) followed by a long course of oral antimicrobial therapy. Patients who had a negative bone biopsy were evaluated together with the group of patients treated with swab culture–based antibiotic therapy.

All physicians adopted the same approach to wound care, which included the use of alginates, hydrocolloids, or hydrogels. Patients were not treated with any topical antimicrobials or other adjunctive therapies. A recommendation was also made to remove pressure from the infected wound using a suitable device.

Evaluation of outcome

Remission was defined as the absence of any sign of infection at the initial or a contiguous site evaluated at least 1 year after the end of antibiotic treatment, with neither a new infectious episode nor the need for orthopedic surgery of the foot at either of these sites during the treatment and follow-up period. Failure was defined as any other outcome.

Statistical analysis

In the initial analysis of the data, all variables were stratified according to the patient outcome of success or failure, and variables regarding treatment were stratified into centers with and without the availability of bone biopsy. Next, we performed a comparison of continuous variables, e.g., patient's age at enrollment, with a two-sample *t* test, and categorical variables such as sex, by use of a two-tailed Fisher's exact test. The significance level was set at $P < 0.05$. Variables in univariate analysis that had a *P* value of <0.05 were included in the regression analysis model. Statistical analyses were conducted using Stata software version 7.0.

RESULTS

Patient and episode characteristics

During the study period, we identified 59 consecutive patients with diabetes and osteomyelitis of a nonischemic foot; 3 of them died of noninfectious causes, and 6 were lost to follow-up. The study population consisted of 50 patients (sex ratio 32 men to 18 women, aged 62.2 ± 11.1 years [mean ± SD]), among whom 16 (32%) had already been treated for osteomyelitis of the foot; 14 of these underwent amputations for worsening infection 1–5 years before they were enrolled in the present study. Twenty-seven patients (54%) had been followed at a diabetic foot clinic before diagnosis of osteomyelitis of the foot. Osteomyelitis was located on a metatarsal head in 35 patients (70%), on the proximal phalanx in 13 patients (26%), and on the distal phalanx in 2 patients (4%). Mean duration of the foot wound was 20.2 ± 23.2 weeks, and mean diabetes duration was 16 ± 10.9 years. At enrollment, mean values for C-reactive protein, glycated hemoglobin, and creatinine clearance were 32.1 ± 57.3 mg/l, 8.09 ± 1.89%, and 66.5 ± 11.8 ml/min, respectively. At inclusion, all patients had at least one imaging examination showing abnormalities suggestive of osteomyelitis. Eleven patients had normal plain radiographs of the foot, with 10 having a positive bone scan and 1 a positive magnetic resonance imaging scan.

The swab and bone culture results are shown in Table 1. *Staphylococcus aureus* was the predominant organism cultured from both types of samples, and Gram-negative bacilli accounted for approximately one-third of the total amount of pathogens. Polymicrobial infections were identified in 22 (44%) cultures, including 7 of 22 (31.8%) positive bone biopsies and 15 of 28 (53.6%) swabs ($P = 0.17$). The prevalence of multiresistant strains, including methicillin-resistant *S. au-*

Table 1—*Distribution of pathogens cultured from 22 bone biopsies and 28 swabs from 50 diabetic patients with osteomyelitis of the foot*

Pathogens	Bone biopsies	Swabs
n	22	28
Staphylococci	21 (58.3)	13 (43.3)
MSSA	7 (19.4)	7 (23.3)
MRSA	4 (11.1)	3 (10)
MSCoNS	9 (25)	2 (6.7)
MRCoNS	1 (2.8)	1 (3.3)
Streptococci	2 (5.6)	6 (20)
Group B	0	5 (16.7)
Group C	0	0
Group G	0	1 (3.3)
Streptococcus viridans	2 (5.6)	0
Enterococci	3 (8.3)	1 (3.3)
Gram-negative bacilli	10 (27.8)	10 (33.3)
Escherichia coli	1 (2.8)	0
Proteus spp.	2 (5.6)	2 (6.7)
Pseudomonas aeruginosa	4 (11.1)	2 (6.7)
Other	3 (8.3)	6 (20)
Polymicrobial	7 (31.8)	15 (53.6)*

Data are *n* (%). *$P = 0.17$. MSSA, methicillin-susceptible *S. aureus*; MSCoNS, methicillin-susceptible coagulase-negative staphylococci; MRCoNS: methicillin-resistant coagulase-negative staphylococci.

reus (MRSA) and extended spectrum β-lactamase–producing Enterobacteriaceae, was similar among the bacteria cultured from bone (25%) and swab (22.7%) samples. Four of the 26 (15.4%) patients who had a bone biopsy with negative bone culture results were enrolled in the present study because of a strong suspicion of osteomyelitis of the foot attributable to a foot wound lasting for >2 weeks, which was associated with imaging abnormalities consistent with osteomyelitis at the bony site underlying the wound. In addition, bone lesions in these patients were located either on the toe or on the metatarsal head, neither of which is likely to be involved in diabetic neuro-osteoarthropathy (1).

Twenty-six (52%) and 24 (48%) patients were followed at centers with and without routinely available bone biopsy, respectively. Five patients followed at centers where bone biopsy was routinely available refused the biopsy, and one patient followed at a center where it was not routinely available had a bone biopsy nonetheless. Hospitalization was recorded in 28 (56%) patients, and this was decided according to the severity of the infection and the local hospital's capacity in terms of beds allocated for diabetic foot infection. The length of hospital stay was 15.1 ± 9.3 days, and the duration of antibiotic treatment was 11.5 ± 4.21 weeks. In all, 22 (44%) patients had bone culture–based therapy, and 28 (56%) patients had swab culture–based therapy. Three patients treated with bone culture–based therapy underwent surgery during the first week of therapy but were included because the intervention was only to drain a deep abscess and did not involve bone. Forty-one (82%) patients started antibiotic therapy after sample results were available, including 24 patients treated with swab culture–based therapy and 17 with bone culture–based therapy. The other 9 patients were treated empirically, with combinations of broad-spectrum β-lactams plus either aminoglycosides or glycopeptides because of concomitant cellulitis. Six of them (4 treated with swab culture–based therapy and 2 with bone culture–based therapy) had their antibiotic regimen subsequently adapted according to the sample culture results. In all, 16 (32%) patients were given intravenous antibiotic therapy for the first week of treatment. Fluoroquinolone/rifampin and fluoroquinolone/pristinamycin were the most frequently used antibiotic combinations, accounting for 32 and 18% of patients, respectively, followed by other fluoroquinolone or rifampin combinations (26%), fluoroquinolone/third- to fourth-generation cephalosporin (12%), and other combinations (12%). Overall patient management was comparable among the nine investigation centers except for rifampin usage, which was more frequent at the four centers where bone biopsy was available (Table 2).

Outcome

At the end of a 12.8-month mean follow-up after the end of treatment, 32 patients (64%) were in remission. Among the 18 patients not in remission, worsening foot infection occurred during the antibiotic treatment period in 3, requiring surgery consisting of deep tissue debridement in 1 and toe amputation in 2. During follow-up, 15 other patients experienced new infectious episodes of the foot. Nine of them required surgery, consisting of toe amputation in 2 and lim-

Table 2—*Detailed characteristics of study patients according to the referral diabetic foot center*

Diabetic foot center	1*	2†	3*	4†	5†	6*	7*	8†	9*	Total	Total no. patients*	Total no. patients†	*P* value
Enrolled patients	6	4	1	3	5	6	10	14	1	50 (100)	24(100)	26 (100)	—
Patients treated with BAT	0	4	0	2	5	0	0	10	1	22 (44)	1 (4.2)	21 (80.8)	<0.001
Patients with IV therapy	1	1	1	1	2	0	3	7	0	16 (32)	5 (20.8)	11 (42.3)	0.10
Duration of IV therapy (days)	5	5	5	4	5	0	4	5	0	5 (median)	5 (median)	5 (median)	—
Use of rifampin	1	2	1	3	3	0	2	10	1	23 (46)	5 (20.8)	18 (69.2)	0.006
Suitable wound off-loading	5	4	1	3	3	4	6	8	1	35 (70)	17 (70.8)	18 (69.2)	0.90
Patients with remission	5	3	0	1	5	3	5	10	0	32 (64)	13(54.1)	19 (73.1)	0.16

Data are *n* or *n* (%). *Centers at which bone biopsy was not performed routinely. †Centers at which bone biopsy was performed routinely. BAT, bone culture–based antibiotic therapy; IV, intravenous.

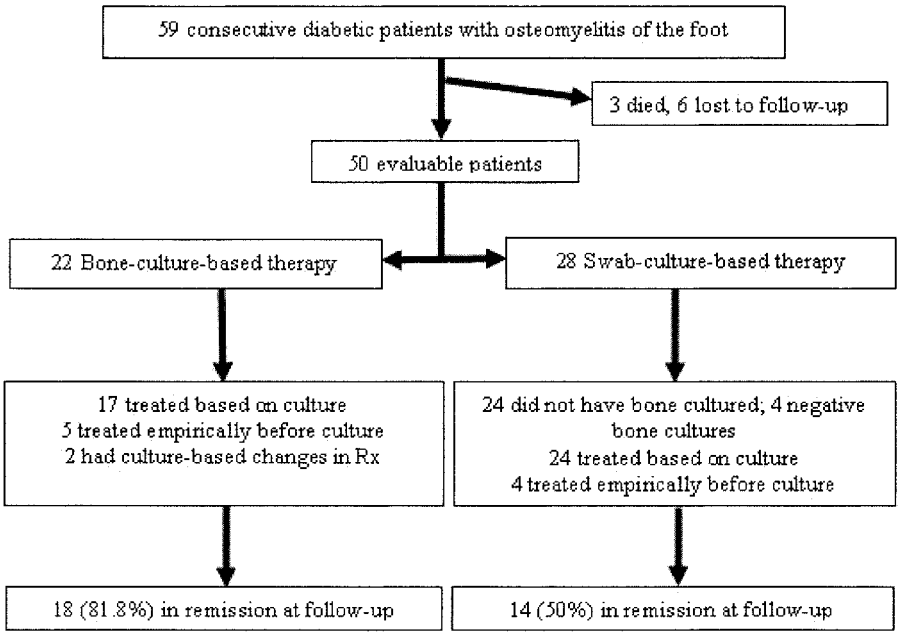

Figure 1—*Summarized data for patients' outcome.*

ited bone resection in 7. Eighteen (81.8%) and 14 (50%) diabetic patients treated with bone culture– and swab culture–based therapy, respectively, were in remission at the end of follow-up (P = 0.02). Three bacterial strains resistant to the initial antibiotic treatment (two MRSA and one methicillin-resistant coagulase-negative staphylococci) were isolated from bone samples of the 9 patients who required surgery. These bacteria were isolated in 3 patients who had been treated with swab culture–based fluoroquinolone, rifampin, or fusidic acid combinations. Data regarding the patients' outcomes are summarized in Fig. 1.

Criteria predictive of remission

Patients' characteristics associated with or without remission are shown in Table 3. Bone culture–based antibiotic therapy was the only variable associated with remission, as determined by both univariate (18 of 32 [56.3%] vs. 4 of 18 [22.2%], $P = 0.02$) and multivariate analyses (odds ratio 4.78 [95% CI 1.0–22.7], $P = 0.04$).

Table 3—*Characteristics associated with remission of nonsurgical treatment in 50 diabetic patients with osteomyelitis of the foot*

Characteristics	Failure (%)	Remission (%)	95% CI	*P* value
n	18 (36)	32 (64)	—	—
Age (years)	62.1 ± 11.7	62.2 ± 11.0	−7.05–6.80	0.97
Sex (male/female)	9/9	22/10	—	0.19
Diabetes duration (years)	16.5 ± 10.4	15.8 ± 11.4	−6.49–7.04	0.84
Wound duration (weeks)	23.6 ± 29.1	18.0 ± 18.4	−10.25–21.50	0.47
Previous episode of osteomyelitis of the foot	5 (27.8)	11 (34.4)	—	0.63
Previous episode of foot amputation	3 (16.7)	11 (34.4)	—	0.18
Follow-up at a diabetic foot clinic	8 (44.4)	19 (59.4)	—	0.31
Antibiotic therapy within a month*	3 (16.7)	9 (28.1)	—	0.10
Metatarsal head involvement	14 (77.8)	21 (65.6)	—	0.37
Pus discharge from the wound	5 (27.8)	7 (21.8)	—	0.64
Cellulitis surrounding the wound	3 (16.7)	11 (34.4)	—	0.18
Body temperature ≥38°C	2 (11.1)	1 (3.1)	—	0.25
S. aureus infection	7 (41.1)	11 (34.4)	—	0.75
Neutrophil count (g/l)	5,698 ± 2,582	5,185 ± 1,709	−1,297.91–322.31	0.56
C-reactive protein (mg/l)	48.1 ± 86.3	23.2 ± 30.8	13.60–63.30	0.19
Glycated hemoglobin (%)	8.09 ± 2.15	8.09 ± 1.78	−1.27–1.27	0.99
Creatinine clearance (ml/min)	61.0 ± 12.2	72.6 ± 11.2	−51.30–28.18	0.52
Results of plain radiographs:				
Normal	6 (33.5)	5 (15.6)	—	0.14
Osteolysis	10 (55.5)	21(65.6)	—	0.48
Cortical defect	1 (5.5)	5 (15.6)	—	0.29
Joint destruction	1 (5.5)	1 (3.2)	—	0.65
Bone culture–based antibiotic therapy	4 (22.2)	18 (56.3)	—	0.02
Use of rifampin	6 (33.3)	17(53.1)	—	0.18
Intravenous antibiotic therapy for the first week	4 (22.2)	12 (37.5)	—	0.27
Appropriate combination therapy†	11 (39.3)	21(65.6)	—	0.75
Duration of antibiotic therapy (weeks)	11 ± 4.16	12.4 ± 4.22	—	0.19
Suitable wound off-loading	11(61.1)	24 (75)	—	0.30

Data are *n* (%) or means ± SD unless indicated otherwise. *Before diagnosis of osteomyelitis of the foot. †Pathogens susceptible to the two agents of the antibiotic combination.

CONCLUSIONS — The results of the present retrospective study suggest that bone culture–based antibiotic therapy is an independent factor predictive of remission in diabetic patients with osteomyelitis of the foot treated nonsurgically. The present overall rate of clinical remission of 64% confirms the efficacy of nonsurgical treatment of diabetic foot osteomyelitis, even though it is slightly lower than the rate of 70–80% reported in previous studies (3–7). The fact that there was a period of at least 12 months between the end of antibiotic therapy and outcome assessment, as recommended by some authorities for chronic osteomyelitis, may explain this discrepancy compared with previous studies (16).

It has been suggested that empirical treatment with appropriate antibiotics may be the most effective strategy for patients with suspected osteomyelitis (17). However, the wide variety of bacteria potentially involved in osteomyelitis of the diabetic foot and current spread of resistant bacteria in most diabetic foot clinics, especially MRSA and extended spectrum β-lactamase–producing bacteria, render empirical therapy hazardous (18–20). In addition, empirical use of some antimicrobial agents such as fluoroquinolones or rifampin may result in additional bacterial resistance (21,22). Here, bacteria resistant to the initial antibiotic treatment were all cultured from patients who had been given swab culture–based rifampin, fluoroquinolones, and fusidic acid combinations. Diamantopoulos et al. (23) reported a series of 84 diabetic patients with severe foot infections, including 41 patients with osteomyelitis, who were treated with a combination of ciprofloxacin and clindamycin for 5 days and then with oral ciprofloxacin as single therapy, according to results of deep wound or debrided tissue cultures. They reported that 35% of the pathogens were resistant to clindamycin, and patients were therefore treated with ciprofloxacin alone. This may have led to the selection of bacteria with acquired resistance to ciprofloxacin, which was reported in 10.2% of their study patients. Both our results and those obtained by Diamantopoulos et al. highlight the possible negative effect of nonbone-based antibiotic therapy for osteomyelitis of the diabetic foot, even when suitable antibiotics such as clindamycin, fluoroquinolones, and rifampin are used to treat chronic osteomyelitis. In most diabetic foot clinics, treatment of osteomyelitis of the foot is either empirical or is based on microbiological documentation obtained by wound or deep tissue cultures (4–7,24). Some experts have stated that the use of nonbone specimens as a guide to antibiotic therapy in chronic osteomyelitis could cause an unacceptably high rate of therapeutic error because the microbiology of bone and nonbone is very different (16,25–28). Here, 18 of 22 (81.8%) and 14 of 28 (50%) diabetic patients with or without bone culture–based antibiotic therapy, respectively, were cured at the end of follow up ($P = 0.02$).

Although bone biopsy is a safe procedure, it is rarely performed in diabetic patients with osteomyelitis of the foot (15). This may result in prescribing suboptimal antibiotic therapy in patients who are nonetheless at high risk of a poor outcome because of micro/macroangiopathy, peripheral neuropathy, and/or poor immunological responses (29).

Several methodological weaknesses may have affected the validity of our results. First, the absence of data regarding bone pathogens in patients treated with swab culture–based antibiotic therapy did not enable us to assess the role of inappropriate antibiotic therapy on the outcome of these patients. Second, given the retrospective design of the study, undetermined differences in global management of patients among the diabetic foot centers may have influenced the effect of bone culture– versus swab culture–based antibiotic therapy. Third, the presence of osteomyelitis could not be confirmed in patients who did not have a bone biopsy.

In summary, our results provide arguments for recommending the use of bone biopsy in diabetic patients treated nonsurgically for osteomyelitis of the foot.

Acknowledgments — We thank Katherine Flower for proofreading.

APPENDIX

Participating investigators and institutions are as follows: Fabrice Devemy, MD (General Hospital of Lens), Catherine Fermont, MD (Teaching Hospital of Lille), Vincent Legros, MD (General Hospital of Valenciennes), Christine Lemaire, MD (General Hospital of Béthune), Marc Lepeut, MD (General Hospital of Roubaix), Nordine Bouhous, MD (General Hospital of Dunkerque), Gaëtan Prévost, MD (General Hospital of Douai), and Dominique Tsirtsikolou, MD (General Hospital of Boulogne sur Mer).

References

1. Jeffcoate WJ, Lipsky BA: Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. *Clin Infect Dis* 39:115–122, 2004
2. Mader JT, Ortiz M, Calhoun JH: Update on the diagnosis and management of osteomyelitis. *Clin Podiatr Med Surg* 13:701–724, 1996
3. Senneville E, Yazdanpanah Y, Cazaubiel M, Cordonnier M, Valette M, Beltrand E, Khazarjian A, Maulin L, Alfandari S, Caillaux M, Dubreuil L, Mouton Y: Rifampin-ofloxacin oral regimen for the treatment of mild to moderate diabetic foot osteomyelitis. *J Antimicrob Chemother* 39:235–240, 2001
4. Venkatesan P, Lawn S, Macfarlane RM, Fletcher EM, Finch RG, Jeffcoate WJ: Conservative management of osteomyelitis in the feet of diabetic patients. *Diabet Med* 14:487–490, 1997
5. Pittet D, Wyssa B, Herter-Clavel C, Kursteiner K, Vaucher J, Lew DP: Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up. *Arch Intern Med* 159:851–856, 1999
6. Yadlapalli N, Vaishnar A, Sheehan P: Conservative management of diabetic foot ulcers complicated by osteomyelitis. *Wounds* 14:31–35, 2002
7. Embil JM, Rose G, Trepman E, Math MC, Duerksen F, Simonsen JN, Nicolle LE: Oral antimicrobial therapy for diabetic foot osteomyelitis. *Foot Ankle Int* 27:771–779, 2006
8. Norden CW: Lessons learned from animal models of osteomyelitis. *Rev Infect Dis* 10: 103–110, 1988
9. Norden CW, Shinners E, Niederitter K: Clindamycin treatment of experimental chronic osteomyelitis due to Staphylococcus aureus. *J Infect Dis* 153:956–959, 1986
10. Rissing JP: Antimicrobial therapy for chronic osteomyelitis in adults: role of the quinolones. *Clin Infect Dis* 25:1327–1333, 1997
11. Norden CW: Experimental chronic staphylococcal osteomyelitis in rabbits: treatment with rifampin alone and in combination with other antimicrobial agents. *Rev Infect Dis* 5 (Suppl 1): 491–494, 1983
12. Bamberger DM, Daus GP, Gerding DN: Osteomyelitis in the feet of diabetic patients: long-term results, prognostic factors, and the role of antimicrobial and surgical therapy. *Am J Med* 83:653–660, 1987
13. Peterson LR, Lissack LM, Canter K, Fasching CE, Clabots C, Gerding DN: Therapy of lower extremity infections with

ciprofloxacin in patients with diabetes mellitus, peripheral vascular disease, or both. *Am J Med* 86:801–808, 1989
14. French Consensus on the management of diabetic foot infections. *Méd Mal Infect* 37: 14–25, 2007
15. Senneville E, Melliez H, Beltrand E, Legout L, Valette M, Cazaubiel M, Cordonnier M, Caillaux M, Yazdanpanah Y, Mouton Y: Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. *Clin Infect Dis* 42:57–62, 2006
16. Lew DP, Waldvogel FA: Osteomyelitis. *Lancet* 364:369–379, 2004
17. Eckman MH, Greenfield S, Mackey WC, Wong JB, Kaplan S, Sullivan L, Dukes K, Pauker SG: Foot infections in diabetic patients: decision and cost-effectiveness analyses. *JAMA* 273:712–720, 1995
18. Wheat LJ, Allen SD, Henry M, Kernek CB, Siders JA, Kuebler T, Fineberg N, Norton J: Diabetic foot infections: bacteriologic analysis. *Arch Intern Med* 146:1935–1940, 1986
19. Hartemann-Heurtier A, Robert J, Jacqueminet S, Ha Van G, Golmard JL, Jarlier V, Grimaldi A: Diabetic foot ulcer and multidrug-resistant organisms: risk factors and impact. *Diabet Med* 21:710–715, 2004
20. Tentolouris N, Petrikkos G, Vallianou N, Zachos C, Daikos GL, Tsapogas P, Markou G, Katsilambros N: Methicillin-resistant prevalence of methicillin-resistant *Staphylococcus aureus* in infected and uninfected diabetic foot ulcers. *Clin Microbiol Infect* 12:186–189, 2006
21. Wehrli W: Rifampin: mechanisms of action and resistance. *Rev Infect Dis* 5 (Suppl. 1):407–411, 1983
22. Zimmerli W, Trampuz A, Ochsner PE: Prosthetic joint infections. *N Engl J Med* 351:1645–1654, 2004
23. Diamantopoulos EJ, Haritos D, Yfandi G, Grigoriadou M, Margariti G, Paniara O, Raptis SA: Management and outcome of severe diabetic foot infections. *Exp Clin Endocrinol Diabetes* 106:346–352, 1998
24. Slater RA, Lazarovitch T, Boldur I, Ramot Y, Buchs A, Weiss M, Hindi A, Rapoport MJ: Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone. *Diabet Med* 21:705–709, 2004
25. Zuluaga AF, Galvis W, Jaimes F, Vespa O: Lack of microbiological concordance between bone and non-bone specimens in chronic osteomyelitis: an observational study. *BMC Infect Dis* 2:8, 2002
26. Khatri G, Wagner DK, Sohnle PG: Effect of bone biopsy in guiding antimicrobial therapy for osteomyelitis complicating open wounds. *Am J Med Sci* 321:367–371, 2001
27. Zuluaga AF, Galvis W, Saldarriaga JG, Agudelo M, Salazar BE, Vesga O: Etiologic diagnosis of chronic osteomyelitis: a prospective study. *Arch Intern Med* 166:95–100, 2006
28. Mackowiak PA, Jones SR, Smith JW: Diagnostic value of sinus-tract cultures in chronic osteomyelitis. *JAMA* 239:2772–2775, 1978
29. Lipsky BA: Osteomyelitis of the foot in diabetic patients. *Clin Infect Dis* 25:1318–1826, 1997