MAJOR ARTICLE

Culture of Percutaneous Bone Biopsy Specimens for Diagnosis of Diabetic Foot Osteomyelitis: Concordance with Ulcer Swab Cultures

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(See the editorial commentary by Embil and Trepman on pages 63–5)

Background. We assessed the diagnostic value of swab cultures by comparing them with corresponding cultures of percutaneous bone biopsy specimens for patients with diabetic foot osteomyelitis.

Methods. The medical charts of patients with foot osteomyelitis who underwent a surgical percutaneous bone biopsy between January 1996 and June 2004 in a single diabetic foot clinic were reviewed. Seventy-six patients with 81 episodes of foot osteomyelitis who had positive results of culture of bone biopsy specimens and who had received no antibiotic therapy for at least 4 weeks before biopsy constituted the study population.

Results. Pathogens isolated from bone samples were predominantly staphylococci (52%) and gram-negative bacilli (18.4%). The distributions of microorganisms in bone and swab cultures were similar, except for coagulase-negative staphylococci, which were more prevalent in bone samples ($P < .001$). The results for cultures of concomitant foot ulcer swabs were available for 69 of 76 patients. The results of bone and swab cultures were identical for 12 (17.4%) of 69 patients, and bone bacteria were isolated from the corresponding swab culture in 21 (30.4%) of 69 patients. The concordance between the results of cultures of swab and of bone biopsy specimens was 42.8% for *Staphylococcus aureus,* 28.5% for gram-negative bacilli, and 25.8% for streptococci. The overall concordance for all isolates was 22.5%. No adverse events—such as worsening peripheral vascular disease, fracture, or biopsy-induced bone infection—were observed, but 1 patient experienced an episode of acute Charcot osteoarthropathy 4 weeks after bone biopsy was performed.

Conclusions. These results suggest that superficial swab cultures do not reliably identify bone bacteria. Percutaneous bone biopsy seems to be safe for patients with diabetic foot osteomyelitis.

Sustained eradication of chronic osteomyelitis is difficult to achieve for several reasons, including the low levels of most antibiotic agents in chronically infected bone; the decreased metabolism of the pathogens, which are usually incorporated into a relatively impermeable glycocalix biofilm; and the particular characteristics of the osseous environment as regards pH level, partial pressure of oxygen, and protein concentrations [1]. These characteristics, which impair the efficacy of most antibiotic agents, have usually led physicians to consider that a nonsurgical approach to chronic osteomyelitis could not be effective. Recently, however, several authors have reported satisfactory outcomes for patients with diabetic foot osteomyelitis managed by conservative treatment, chiefly consisting of antibiotic therapy with little or no surgery [2, 3]. The antibiotics used in these studies were fluoroquinolones, rifampin, and clindamycin, all of which reached high concentrations in bone and exhibited activity against bacteria in the stationary growth phase [4]. Given the high potential of these agents for selecting naturally resistant mutants among the initial bacterial population, a combined drug regimen is strongly recommended (especially with rifampin), comprising 2 components active against pathogens [4–6]. This aspect of the management of infection is a matter of concern, given the present worldwide spread of bacterial resistance and the decrease in the product-

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ion of new antimicrobial agents [7]. The definition of what constitutes reliable microbiological documentation of diabetic foot osteomyelitis is still controversial [8]. Because wound cultures may be contaminated by colonizing flora, a percutaneous bone biopsy sample obtained without traversal of an open wound is considered to be the gold standard method of guidance for antibiotic therapy [8]. However, bone biopsy is rarely performed in routine practice because of the expense involved and the possible adverse events, and it is usually replaced by cultures of ulcer swabs or by deep samples taken during surgical interventions, such as amputation or debridement of foot lesions [2, 9–11]. Studies comparing the results of foot ulcer cultures with those of reliable underlying bone biopsy specimens for patients with diabetes are therefore lacking. In this study, we report the findings of a retrospective cross-sectional observational analysis of patients with diabetes with confirmed episodes of foot osteomyelitis who had cultures of bone samples performed. The main objective was to establish to what extent the microbiological findings for swab specimens were concordant with those of the diagnostic gold standard (i.e., cultures of percutaneous bone specimens).

PATIENTS AND METHODS

Population. The medical charts were reviewed for patients with suspected foot osteomyelitis who attended our diabetic foot clinic, established in a 360-bed general hospital (Dron Hospital, Tourcoing, France). These patients had undergone surgical percutaneous bone biopsy but had not received either local or systemic antibiotic therapy for at least 4 weeks before biopsy. Foot osteomyelitis was strongly suspected if at least 2 of the following clinical criteria were present: wound ulcer lasting $\geqslant$2 weeks, underlying bony prominence, and ulcer with a surface area >2 cm^2 or a depth >3 mm; and if the presence of such criteria was associated with probing to bone and/or other abnormal findings consistent with the diagnosis of osteitis on radiographic imaging (plain radiography, tomodensitometry, or nuclear magnetic resonance) or on bone scan (coupled gallium [^{67}Ga-citrate]–technetium [^{99m}Tc-diphosphonate] radionuclide or Leukoscan [Sulesomab scintigraphy using an antigranulocyte antibody Fab' fragment labeled with ^{99m}Tc; Immunomedics GmbH]). Prospectively collected data were analyzed retrospectively, including age, sex, details about and duration of diabetes, glycated hemoglobin level, presence of peripheral vascular disease, ulcer duration, grade in Wagner's classification, and antibiotic use before consultation or hospitalization. The vascular status of the foot was evaluated according to the presence or absence of dorsal-pedal and posterior-tibial pulses; transcutaneous oxygen pressure was measured for patients with symptomatic ischemia of the foot. Percutaneous bone biopsy was contraindicated when the transcutaneous oxygen pressure was <30 mm Hg.

Specimen collection. Swab samples were obtained after brief cleansing of the ulcer with sterile physiologic glucose solution by means of a sterile compress passed over the ulcer surface to reduce the amount of contaminating bacteria. Swab samples were obtained from the bottom of the ulcer by vigorous rotation of the swab. Ulcer cultures were only included in the analysis if they had been obtained within 3 days before bone biopsy. All of the patients in the study underwent percutaneous bone biopsies, performed in the surgical room by an orthopedist using an 11-gauge biopsy needle (Becton Dickinson) inserted through a 5–10-mm skin incision at least 20 mm from the ulcer periphery, to avoid contamination by the colonizing flora. This minimum distance was reduced when osteomyelitis was diagnosed and bone on the toes was biopsied. Percutaneous bone samples were obtained under fluoroscopic guidance. For patients who underwent multiple bone biopsies, a new needle set was used for each biopsy site. In case of plantar ulcer, bone biopsy was performed via a dorsal route. When the severity of infection required debridement, percutaneous bone biopsy was performed before opening the foot. All bone biopsies were performed with peroperative sterile precautions and with local or general anesthesia. In case of severe peripheral neuropathy resulting in superficial and deep anesthesia, no additional anesthesia was performed. Two bone fragments were obtained for each biopsy; one was inoculated into Rosenow broth (Biorad), and the other was placed in a standard transport system (Port-a-germ; Biomérieux). Both fragments were immediately brought to the microbiology laboratory, where aerobic and anaerobic cultures were maintained for 5 days and 2 weeks, respectively.

Microbiological assessment. Bacterial isolates were identified at the species level with the use of API strips (Biomérieux). Each of the strains cultured from both bone samples and swab samples was identified and assessed for antibiotic susceptibility in accordance with the protocol instituted in our diabetic foot clinic in 1996 for sampling ulcer and bone specimens from all patients with diabetic foot osteomyelitis [3]. Semiquantitative analysis of the number of colony-forming units per culture was performed by means of a counting frame for swab and bone biopsy cultures. Bacteria recovered only in broth media were considered to be contaminants and were not included in the analysis. A microorganism belonging to the skin flora (coagulase-negative staphylococci and corynebacteria) isolated in bone samples was considered to be pathogenic only if the same strain (according to the susceptibility profile) had been cultured from Rosenow broth and the correspondent standard transport system.

Statistical analyses. Fisher's exact test was used to compare

the microbiological results. The statistical significance level was set at $P < .05$.

RESULTS

Population. Between January 1996 and June 2004, a total of 214 consecutive bone biopsies of the foot were performed for 190 patients, of whom 88 consecutive patients with diabetes met the study criteria. Seventy-six (86.4%) of these patients (5 of whom had 2 separate osteomyelitic areas, for a total of 81 episodes of osteomyelitis) had a positive bone culture result, and these patients constituted the study population. Of the 12 remaining patients, 10 had a sterile bone culture, had not received any antibiotic treatment prior to bone biopsy, and had not received a diagnosis of osteomyelitis at the same site at their clinical and radiological check-up at the diabetic foot clinic during a period of at least 1 year after bone biopsy. The mean age (±SD) of the patients was 61.9 ± 10.9 years, and the mean duration of diabetes (±SD) was 11.9 ± 2.7 years; all but 2 patients had type 2 diabetes mellitus, and the mean glycated hemoglobin level (±SD) for all patients was 7.13% ± 1.83% (range, 5%–12.6%). Of the 81 foot lesions, 65 (80.2%) were Wagner grade III, and the other 16 were Wagner grade IV, with gangrene as a consequence of infection in 11 of the 16 cases. Peripheral vascular disease was present in 22 (28.9%) of 76 patients. Bone biopsies were performed on a metatarsal head in 33 cases (40.7%), on the proximal phalanx in 29 (35.8%), and on the distal phalanx in 19 (23.5%). Eleven patients (14.4%) required surgical debridement.

Microbiological assessment. The distribution of the pathogens identified in 81 cultures of bone samples and 69 cultures of superficial swab samples is shown in table 1. Swabs could not be applied in 7 cases, because the foot lesion was dry, and swabs samples were not obtained concomitantly with bone biopsy in 5 other cases. The mean number of isolates per swab sample was 1.58 (range, 1–4). Of the 109 isolates cultured from swab samples, 78 (71.5%) were aerobic gram-positive bacteria, 28 (25.7%) were gram-negative bacilli, and 3 (2.8%) were strict anaerobes. In all, 125 isolates were cultured from bone biopsy samples (mean number of isolates per specimen, 1.54; range, 1–3), including 96 aerobic gram-positive bacteria (76.8% of isolates), 23 gram-negative bacilli (18.4%), and 6 strict anaerobes (4.8%). Overall, pathogens were equally represented in cultures of bone specimens and swab samples, except for staphylococci (52.0% vs. 37.6%, in bone specimens and swab samples, respectively; $P < .05$) and coagulase-negative staphylococci (25.6% vs. 4.6%, in bone specimens and swab samples, respectively; $P < .001$). Methicillin-resistant *Staphylococcus aureus* strains were identified in 11 (15.9%) of 69 swab samples and in 12 (14.8%) of 81 bone samples.

Semiquantitative analysis of the number of colony-forming units showed that the proportion of cultures resulting in a small number of colony-forming units was higher for bone biopsy cultures than for swab sample cultures (89.9% vs. 30.2%, respectively; table 2). The percentage of cultures resulting in a small number of colony-forming units was not significantly different for *S. aureus* and coagulase-negative staphylococci when the results were examined separately for swab sample and bone biopsy cultures (22.2% vs. 20% and 84.8% vs. 100%, respectively; table 2).

The results for cultures of concomitant foot ulcer swab samples were available for 69 episodes of osteomyelitis. Strictly identical

Table 1. Distribution of pathogens cultured from 69 swab samples and 81 percutaneous bone biopsy samples obtained from 76 patients with diabetes with suspected foot osteomyelitis.

Variable	Swab samples	Bone biopsy samples
No. of samples	69	76
No. of isolates	109	125
Mean no. of isolates per sample	1.58	1.54
No. (%) of isolates, by pathogen		
Staphylococci		
All	41 (37.6)	65 (52.0)[a]
Staphylococcus aureus		
All	36 (33.0)	33 (26.4)
MRSA	11 (10.1)	12 (9.6)
Coagulase-negative staphylococci	5 (4.6)	32 (25.6)[b]
Enterococci	5 (4.6)	10 (8.0)
Streptococci	22 (20.2)	15 (12.0)
Group A	1 (0.9)	1 (0.8)
Group B	12 (11.0)	10 (8.0)
Group C	2 (1.8)	1 (0.8)
Group D	1 (0.9)	0
Streptococcus viridans	4 (3.6)	1 (0.8)
Streptococcus pneumoniae	2 (1.8)	2 (1.6)
Other gram-positive cocci	2 (1.8)	3 (2.4)
Corynebacteria	8 (7.3)	3 (2.4)
Gram-negative bacilli	28 (25.7)	23 (18.4)
Escherichia coli	4 (3.6)	4 (3.2)
Klebsiella species	1 (0.9)	2 (1.6)
Proteus species	4 (3.6)	7 (5.6)
Acinetobacter species	2 (1.8)	3 (2.4)
Enterobacter species	4 (3.6)	2 (1.6)
Pseudomonas species	7 (6.4)	3 (2.4)
Others	6 (5.6)	2 (1.6)
Anaerobes	3 (2.8)	6 (4.8)
Bacteroides species	1 (0.9)	2 (1.6)
Peptococcus species	1 (0.9)	2 (1.6)
Propionibacterium acnes	1 (0.9)	1 (0.8)
Others	0	1 (0.8)

NOTE. MRSA, methicillin-resistant *S. aureus*.

[a] $P < .05$.

[b] $P < .001$.

Table 2. Semiquantitative analysis of cultures of swab and bone biopsy samples from 76 patients with diabetes with suspected foot osteomyelitis.

Pathogen, by sample type	No. of isolates	No. (%) of isolates, by no. of cfu per plate		
		1–50	51–200	>200
Swab	106	32 (30.2)	46 (43.4)	28 (26.4)
Staphylococcus aureus	36	8 (22.2)	14 (38.9)	14 (38.9)
CNS	5	1 (20)	4 (80)	…
Enterococci	5	5 (100)	…	…
Corynebacteria	8	4 (50)	…	4 (50)
Streptococci[a]	24	2 (8.3)	13 (54.2)	9 (37.5)
GNB	28	14 (50)	14 (50)	…
Bone biopsy	119	107 (89.9)	12 (10.1)	…
S. aureus	33	28 (84.8)	5 (15.2)	…
CNS	32	32 (100)	…	…
Enterococci	10	10 (100)	…	…
Corynebacteria	3	3 (100)	…	…
Streptococci[a]	18	8 (44.4)	10 (55.6)	…
GNB	23	20 (86.9)	3 (13.1)	…

NOTE. Data do not include anaerobes. CNS, coagulase-negative staphylococci; GNB, gram-negative bacilli.

[a] Includes group A, B, C, and D streptococci; *Streptococcus viridans; Streptococcus pneumoniae;* and other gram-positive cocci.

results for wound swab and bone specimen cultures were noted in 12 cases (17.4%), including 6 cases of infection due to *S. aureus*. In all of these cases, the *S. aureus* methicillin-susceptibility profile was concordant in the swab sample culture and in the corresponding bone specimen culture. Bone bacteria were grown on culture of the corresponding superficial swab sample in 21 (30.4%) of 69 cases. An estimate of the concordance between the results for swab sample and bone biopsy cultures was provided by the percentage of bone and swab samples that resulted in the identification of the same pathogen in a given patient. As shown in table 3, this concordance ranged from 0% to 42.8%, with an overall concordance of 22.5%. The best results were observed for *S. aureus* strains, whereas the most discordant results were those for coagulase-negative staphylococci, enterococci, corynebacteria, and anaerobes (table 3).

Adverse events. No adverse events due to bone biopsy (e.g., worsening peripheral vascular disease, fracture, or bone infection) were observed in the patient population. One patient experienced an acute episode of Charcot osteoarthropathy 4 weeks after bone biopsy was performed.

DISCUSSION

This study was undertaken to compare the results of bone biopsy cultures with those of corresponding cultures of superficial swab samples for patients with diabetic foot osteomyelitis. To our knowledge, the present series is the largest population studied that comprises consecutive patients with diabetic foot osteomyelitis who underwent surgical percutaneous bone biopsy with adequate precautions to avoid contamination by colonizing flora.

Most of the pathogens cultured from bone specimens were gram-positive cocci (staphylococci, in particular), and there were comparable distributions of *S. aureus* and coagulase-negative staphylococci. As reported elsewhere, the mildness of foot lesions in the study population may explain the small number of isolates per case [12] and the small number of anaerobes cultured from bone specimens, although the samples were directly inoculated into Rosenow broth, which is designed for anaerobic culture. The smaller number of CFU in bone specimen cultures than in swab sample cultures was probably due to differences in the pathophysiological process, environment, and bacterial metabolism involved in skin and soft-tissue infections, on the one hand, and chronic bone infections, on the other [1]. Culture of bone specimens is considered to be the gold standard for conclusive microbiological diagnosis [13–15]. However, bone biopsy is not well accepted by the medical community, because it is an invasive technique that is believed to worsen peripheral vascular disease and/or neuropathy, although this has not been clearly demonstrated [16]. Except for 1 episode of acute Charcot osteoarthropathy that occurred in the month after bone biopsy was performed, no adverse events were reported for the present patients. This may be because bone biopsy was performed percutaneously under satisfactory conditions, because most patients only had mild-to-moderate foot infections. In addition, the expense and effort, as well as concern about spreading infection to an uninfected bone and the possibility of fracture, are usually cited as negative factors [8]. Consequently, there are currently very few studies whose authors used data derived from analysis of bone biopsy samples obtained in the manner we describe. In most studies describing series of patients with diabetic foot osteomyelitis, the bacterial documentation is not reliable, because it is based on the results of cultures of superficial samples, and bone biopsy is not usually performed [2, 9–11]. When results of bone biopsy culture are reported, they usually concern deep-tissue samples taken during debridement, rather than true biopsy specimens, and the patients studied constitute the majority of the series selected for the study and are not consecutive [10, 11]. In our patients, the absence of ongoing antibiotic treatment at the time of bone culture constitutes another significant difference from previous studies, in which the antibiotic-free interval before culture samples are obtained is not usually mentioned [10, 11, 15]. False-negative results of bone culture may indeed result from the prolonged release of antibiotics from bone, as shown by Witso et al. [17] in an in vitro model. The observance of a prolonged antibiotic-free period before biopsy may explain the high proportion of positive bone culture results for our patients.

Bone pathogens were identified from the corresponding cul-

Table 3. Proportion of pathogens isolated from cultures of bone biopsy and/or swab samples obtained from 69 patients with diabetes with suspected foot osteomyelitis.

Pathogen	No. of instances in which culture yielded the specified pathogen				
	Total	From bone biopsy sample only	From swab sample only	From both bone biopsy and swab samples	Concordance,[a] %
Staphylococcus aureus	49	13	15	21	42.8
CNS	35	30	4	1	2.8
Streptococci[b]	31	11	12	8	25.8
Enterococci	15	9	5	1	6.67
Corynebacteria	10	2	8	0	0
Gram-negative bacilli	42	12	18	12	28.5
Anaerobes	9	6	3	0	0
Total	191	79	65	43	22.5

NOTE. CNS, coagulase-negative staphylococci.

[a] Percentage of instances in which bone and swab samples yielded the same pathogen for a given patient.

[b] Includes group A, B, C, and D streptococci; *Streptococcus viridans; Streptococcus pneumoniae;* and other gram-positive cocci.

tures of superficial swab samples in only 21 (30.4%) of 69 cases, which confirms the poor reliability of cultures of swab samples for the microbiological diagnosis of foot osteomyelitis in patients with diabetes. Mackowiak et al. [18] established bone specimen cultures as the gold standard for microbiological diagnosis of chronic osteomyelitis in a well-conducted retrospective analysis of sinus tract and bone cultures from a series of patients with chronic osteomyelitis; this study, however, did not include diabetic foot infections. There are similarities and differences between the present study and the one by Mackowiak et al. [18]; the bone pathogen was isolated in 30.4% and 44% of the superficial swab sample cultures in each study, respectively, whereas the concordances for pathogens other than *S. aureus* were 0%–29.2% and 8%–29%, respectively. The concordance for *S. aureus* in the study by Mackowiak et al. [18] (78%) was significantly different from that in our study, which was much lower (42.8%). The greater variability of the composition of the colonizing flora of diabetic foot wounds, compared with the composition of fistula of chronic osteomyelitis, may explain this discrepancy [14]. To the best of our knowledge, no ongoing study involving patients with diabetic foot osteomyelitis has been designed to evaluate the concordance between cultures of superficial swab samples and percutaneous bone biopsy samples. Slater et al. [11] recently reported that the cultures of superficial swab samples and deep-tissue samples obtained during surgical debridement correlated in 65% of cases with bone involvement. In their study, however, deep-tissue samples were taken intraoperatively via the infected foot lesion, which may have resulted in their contamination by the surface bacteria, and thus, in the overestimation of the concordance between cultures of deep and superficial tissue samples.

Although the percutaneous bone biopsies analyzed in the present study were obtained under fluoroscopic guidance and only performed by specialized senior orthopedic surgeons, the use of an 11-gauge bone biopsy needle, rather than an open surgical biopsy, may have meant that the osteomyelitic area was missed, leading to the undertreatment of patients because of false-negative results. Another limitation of the present study was the absence of concurrent histological confirmation of osteomyelitis, which may have facilitated the interpretation of microbial results, especially those for coagulase-negative staphylococci and enterococci. However, histological examination would have required larger bone samples from the infected bone areas. Note that the finding of a higher proportion of coagulase-negative staphylococci isolates in bone biopsy samples, compared with swab samples, was independent of the findings of our microbiological laboratory, which identified all of the organisms cultured from both bone and swab samples (including bacteria from the skin flora) in accordance with the protocol established in 1996 in our diabetic foot clinic [3]. In addition, comparable results regarding the high proportion of coagulase-negative staphylococci cultured from reliable bone samples for patients with diabetic foot osteomyelitis have already been reported [14].

CONCLUSIONS

Our results confirm the poor reliability of cultures of superficial swab samples obtained from patients with diabetic foot oste-

omyelitis for identifying bone pathogens and the safety of surgical percutaneous bone biopsy. However, given the difficulty of organizing percutaneous bone biopsies for patients with diabetic foot osteomyelitis, it may be best to restrict such biopsies to diabetic centers where antibiotic agents with a potential for selecting bacterial resistance (especially fluoroquinolones and rifampin) are routinely prescribed. Additional studies are required to evaluate the concordance between the results of cultures of samples obtained by wound aspiration or curettage and cultures of samples obtained from percutaneous bone biopsies.

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