Emergence of monomicrobial methicillin-resistant *Staphylococcus aureus* infections in diabetic foot osteomyelitis
Retrospective study of 48 cases

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Summary

Objective > Describe the clinical appearance, microorganisms involved, and prognosis of diabetic foot osteomyelitis.

Method > Retrospective study of 48 patients seen in 2004 for presumed osteomyelitis (exposed bone or suggestive radiographic or clinical picture). Specimens for culture came from swabs of wound discharge, needle aspiration and bone biopsy.

Results > Forty-eight patients with diabetes and contiguous osteomyelitis of the foot were followed for a year. The principal microorganisms isolated were *Staphylococcus aureus* (58%) and Gram-negative bacilli (29%). 58% of the infections were monomicrobial, 31% of the microorganisms multidrug-resistant, and 85% of the patients were hospitalized, for a median duration of 30 days. Healing occurred in 40 patients, although 15 required amputation first, and 18 had a new infection at a different site (11 involving osteomyelitis) in the year after antibiotic treatment ended.

Perspectives > Diabetic foot osteomyelitis is a serious disease in view of its site and the microorganisms involved, which are often multidrug-resistant. There is a clear predominance of *S. aureus*. Medical treatment has an increasingly important role in its management and requires that samples be properly collected for bacteriological testing. The prognosis for these infections, which remains grim in view of the amputation rate and the high risk of new infection, could be improved by reinforcing prevention measures.
Ulceration of the foot is frequent in diabetes. It is promoted by a combination of neurological, arterial and infectious complications and provoked by repeated microtrauma. These lesions can be serious and require amputation [1]: the risk of amputation among French diabetes patients is 14 times higher than in the general population [2]. Twenty percent of hospitalization days for diabetes are due to foot conditions [3], which account for 6,000-15,000 admissions annually in France. The cost of management of patients with diabetes with chronic foot wounds and those requiring amputations is estimated at 570 million euros a year [4]. Regardless of their specific cause or origin, these foot wounds are easily complicated by osteomyelitis [5]: 50-60% of severe cutaneous infections (grade 3 and 4) are so complicated and 10-20% of grade 2 infections [6-8]. Osteomyelitis is especially difficult to diagnose and treat. The diagnostic difficulty comes from the fact that it cannot always be identified by clinical examination and radiologic signs may be delayed or related to a noninfectious osteoarthropathy [9]. It is hard to treat because treatment failure and recurrence occur in more than 30% of cases with bone damage, even though medical treatment can successfully treat 80-90% of chronic diabetic foot infections [10]. Despite its frequency and potential seriousness, diabetic foot osteomyelitis remains little studied and is the object more often of guidelines than of original studies. To improve our understanding of its clinical aspects, the microorganisms involved, and the prognosis, we conducted a retrospective study of diabetes patients with osteomyelitis of the lower extremities followed at Clermont-Ferrand University Hospital Center.

Methods

Patients

We retrospectively reviewed the records of patients meeting the following criteria:
- patients with diabetes;
- followed at the multidisciplinary diabetic foot consultation at Gabriel Montpied Hospital in Clermont-Ferrand or at the orthopedic clinic of the department of infectious diseases at Hôtel-Dieu, Clermont-Ferrand;

Osteomyelitis was presumed when there was exposed bone during exploration of the wound [5, 11] or a suggestive radiologic image with signs of local infection (pus or inflammation) without initial or subsequent evidence of Charcot disease. We excluded from the study patients with a foot infection without underlying osteomyelitis and patients followed in 2004 for osteomyelitis diagnosed before 2003. The variables studied were demographic data, type of diabetes and complications (for this study, peripheral arterial disease of the lower limbs was defined by the absence of a distal pulse on examination), site and appearance of the wound, laboratory and imaging examinations, types of specimens used for bacteriological testing, microorganisms identified, and treatment (hospitalization, antibiotic therapy, and surgery).

Management

All patients were managed by a team that included an infectious disease specialist and a diabetologist, working in close contact with orthopedic and vascular surgeons. Initial off-loading generally involved Barouk® or Sanital® shoes; once healing occurred, a rheumatologist on the multidisciplinary team prescribed orthopedic shoes.

Specimens, samples and interpretations

Specimens for culture came from swabs of discharges, needle aspiration (10 mL syringe seeded on a blood culture flask after saline dilution), bone samples (percutaneous or intraoperative biopsies) or blood samples. The microorganism or microorganisms isolated from some samples were considered contaminants and not taken into account in the antibiotic treatment. The evidence leading to this decision is specified in these cases. Multidrug-resistance (MDR) was determined by antibiotic susceptibility testing and defined by results that were intermediate or resistant to ceftazidime for Gram-negative bacilli, resistant to meticillin for staphylococci, and resistant to vancomycin for enterococci.

What is already known

- Men with type 2 diabetes who are treated by insulin and have multiple complications are the population at highest risk of osteomyelitis of the foot.
- Diabetic foot osteomyelitis is difficult to diagnose: there may be no exposed bone and radiologic signs may occur late or be related to a noninfectious osteoarthropathy.
- The prognosis for the disease is poor and the amputation rate high.

What this article adds

- According to our study, diabetic foot osteomyelitis is most often a monomicrobial infection, and one third of the microorganisms are multidrug-resistant.
- Among the microorganisms involved, S. aureus is becoming predominant and anaerobic microorganisms appear much less often.
- Medical treatment has an increasingly important role in its management and requires that samples be properly collected for bacteriological testing.
- The rate of new episodes of infection after recovery from the initial episode is high. Preventive efforts are essential.
Course and prognosis

We assessed outcome for a year from the date of osteomyelitis diagnosis. Recovery was defined by the absence of radiographic development or the appearance of calcification with no local inflammatory signs during this period (one year). Treatment was considered to have failed for other patients. Of the patients whose wounds were healed, some had a new infectious episode (osteomyelitis or soft-tissue infection) during the follow-up period.

Statistical method

Comparison of qualitative variables used Pearson’s $\chi^2$ test. Quantitative variables such as age were compared by Mann–Whitney’s U test.

Results

Patients

In all, 52 patients met the inclusion criteria. Four were excluded because of missing data: the remaining 48 comprised the study population. They were seen for 59 distinct episodes of osteomyelitis: 11 patients had a second episode after the first was healed, at a separate site. Table I summarizes the characteristics of the study population.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Characteristics of the 48 cases of osteomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Frequency (n = 48)</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Mean age ± standard deviation (years)</td>
<td>64 ± 1</td>
</tr>
<tr>
<td>Sex ratio M/F</td>
<td>5/1</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>86 ± 3</td>
</tr>
<tr>
<td>Diabetes type 2 (%)</td>
<td>87.5</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>73</td>
</tr>
<tr>
<td>Oral antidiabetic agents</td>
<td>23</td>
</tr>
<tr>
<td>Diet only</td>
<td>4</td>
</tr>
<tr>
<td>Diabetic retinopathy (%)</td>
<td>67</td>
</tr>
<tr>
<td>Creatine clearance (Cockcroft formula) &lt; 60 mL/min (%)</td>
<td>42</td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>73</td>
</tr>
<tr>
<td>Arterial disease of lower limbs (%)</td>
<td>67</td>
</tr>
<tr>
<td><strong>Positive osteomyelitis diagnosis (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Exposed bone only</td>
<td>15</td>
</tr>
<tr>
<td>Radiology: signs of infection</td>
<td>39</td>
</tr>
<tr>
<td>Exposed bone + radiology</td>
<td>46</td>
</tr>
<tr>
<td><strong>Number of microorganisms considered pathogenic shown (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8</td>
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<tr>
<td>1</td>
<td>58</td>
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<tr>
<td>2</td>
<td>25</td>
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<td>3</td>
<td>4</td>
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<td>4</td>
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<td>6</td>
<td>2</td>
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</tbody>
</table>

Characteristics of the 48 cases of osteomyelitis (excluding recurrences)

During the initial consultation, all patients had contiguous osteomyelitis, that is with a wound serving as the portal of entry to the osteomyelitis site. The median duration of wound development before the initial consultation was 60 days (range: 2-1460 days). One quarter of the patients had already had swab specimens of the wound taken for bacteriological testing at private laboratories, on their general practitioners’ orders. More than half the patients (n = 27) had received antibiotic therapy in the 3 months before the first consultation, 11 of them a combination of 2 antibiotics (for 5, the combination was amoxicillin-clavulanic acid and quinolone).

Severe soft-tissue infection associated with osteomyelitis resulted in emergency hospitalization for 65% (n = 31). Moreover, 21% (n = 10) were hospitalized on a non-emergency basis to begin intravenous antibiotic therapy, stabilize their glycemic control, or for a vascular work-up.

The osteomyelitis affected the first ray in 31% of cases, another metatarsal in 56%, and the calcaneum in 13%. Wound characteristics included: inflammation (62.5%), exposed bone (60%), purulent discharge (27%), moist necrosis (19%), nauseating odor (15%), and a visible joint (10%).

At admission 65% of patients had CRP (C reactive protein) > 10 mg/L and for 40% it exceeded 100 mg/L.

Microorganisms involved

Microorganisms considered pathogenic were found in the following types of samples: swabs only in 54% of cases (n = 26), needle aspiration samples 23% (n = 11), bone samples 17% (n = 8), and blood samples 6% (n = 3). Only one microorganism was found in 58% of cases (table I). The microorganisms found most often were S. aureus (58%) and Gram-negative bacilli (GNB) (29%) (figure 1). When only one organism was found (n = 28), it was most often S. aureus (75%, n = 21). Of the microorganisms found, 31% were considered resistant (figure 1). This resistance was not statistically associated with antibiotic administration in the 3 months preceding diagnosis nor with any particular antibiotic (data not shown).

Of 11 needle aspiration samples, 7 were monomicrobial — 5 S. aureus. Of the 8 bone samples, 5 were monomicrobial (4 S. aureus). All 3 blood samples were positive for S. aureus. Some of the microorganisms found for 4 patients were not considered to cause the infection and were not taken into account in prescribing antibiotic therapy. For one of them, poor clinical response to antibiotic treatment appropriate for the 2 microorganisms (one E. coli and one enterococcus) shown by the swab sample led us to take a needle sample that showed S. aureus. Retrospectively, therefore, we consider that the E. coli and enterococci were not pathogens.

In 5 patients, finally classified as healed, poor clinical response despite initially appropriate antibiotic therapy resulted in taking...
new samples. These 3 swabs, one needle and one biopsy, led us to identify microorganisms different from the initial samples (methicillin-resistant *S. aureus* [MRSA], *S. epidermidis*, *S. lugdunensis*, *E. coli* and a combination of MRSA and *E. faecalis*). Adjustment of the antibiotic therapy led to recovery in all 5 patients.

**Patient outcome**

*Figure 2* summarizes patient outcome. All patients were treated with antibiotic therapy, for a median duration of 95 days. Initial antibiotic treatment was intravenous for 60%. In all, 85% (n = 41) of patients were hospitalized for their osteoarticular infections, for a median duration of 30 days (range: 5-300 days).

**Recovery**

Forty patients (83%) recovered from the infection, 15 of them only after amputation; they accounted for 37% of the healed patients and 31% of the overall population. Ten had a first ray amputation, 8 of them metatarsal-phalangeal; 4 amputations were transmetatarsal, and one was of the leg. Eleven amputations were performed on an emergency basis for: vascular necrosis (n = 6), severe cellulitis (n = 4), and visible joint (n = 1). Two amputations followed failure of medical treatment and 2 more failed revascularization. Peripheral arterial disease was present in 53% of the amputated patients, including all with transmetatarsal or leg amputations. Factors associated with amputation were moist necrosis, which indicated severe arterial disease (p = 0.002), and CRP > 100 mg/L (p = 0.05). Moreover, 6% of the patients underwent debridement procedures and 17% revascularization. Of the 40 healed patients, 18 had a new infectious episode in a different site during the year of follow-up (*figure 2*).

**Treatment failure**

Of the 7 patients for whom treatment failed, 2 died from complications of *S. aureus* bacteremia, the portal of entry of which was osteomyelitis of the foot, and one died of a cardiac problem while under antibiotic treatment for calcaneal osteomyelitis. Among the deaths, 4 had calcaneal osteomyelitis, 5 had other risk factors of morbidity (4 had severe heart failure, one severe kidney failure, and one end-stage kidney failure) and all had peripheral arterial occlusive disease. Microorganisms and resistance profiles did not differ from those of other patients.
**New osteomyelitis episode**

Eleven patients (7 men and 4 women) developed a second osteomyelitis episode at a different site (figure 2). Nine of them had distal arterial disease, and 4 had had amputations for the preceding episode. Microorganisms considered pathogenic were found in the following types of samples: swabs alone in 5 patients, needle aspiration samples in 4, and bone samples for 2. Only one microorganism was found in 73% of cases, 2 microorganisms in 9%, and none in 18%. Of the microorganisms responsible for these second episodes, 30% were multidrug-resistant. The microorganism was *S. aureus* in 50% of cases (n = 5, including 3 MSSA and 2 MRSA), GNB in 40% (n = 4 including *P. aeruginosa* intermediate to ceftazidime) and *S. lugdunensis* in one patient. Only 2 patients had the same microorganism the second time as the first, and in both cases it was *S. aureus* (one MRSA and one MSSA). Two patients initially infected by sensitive microorganisms developed a new infection with a multidrug-resistant microorganism (one MRSA and one *P. aeruginosa* intermediate for ceftazidime). Inversely, sensitive microorganisms were found during the second infection for 2 patients, although resistant microorganisms (MR- S. epidermidis and MRSA) had caused the first.

Five patients were hospitalized and all were treated with antibiotic therapy for a median duration of 96 days (43-180 days). Four patients required amputation (2 at the ray, one transmetatarsal, and one at the leg). Two had had revascularization and one surgical debridement.

**Discussion**

Prevention and management of diabetic foot osteomyelitis remains inadequate in France. Once apparent, foot osteomyelitis in patients with diabetes raises problems of early diagnosis,
multidisciplinary management, and the risk of new infectious episodes. Our population, mainly men with type 2 diabetes treated with insulin and with multiple complications, is the population identified by the American Diabetes Association as at risk of ulcers and amputation (diabetes > 10 years, male, unstable blood glucose, and cardiovascular, retinal, renal and neuropathic complications [12]). Peripheral arterial disease and infection together play a decisive role in the need for amputation.

**Serious consequences of delayed treatment**

Only one-quarter of the patients included in our study had had a swab sample taken for bacteriological testing before arriving at the hospital, even though most had had the wound for a relatively long period (median 60 days) before admission to our hospital, generally on an emergency basis (64%). This underlines the importance of early treatment of these patients in a specialized setting: general practitioners are not always at ease with this condition, which requires time and experience to treat effectively. Because of this delay but especially because of the arterial damage, which is often essential in these infections, healing required amputation at a rather high rate.

**Microorganisms involved: predominance of *S. aureus* and frequent multidrug-resistance**

According to our study, diabetic foot osteomyelitis is most often a monomicrobial infection (54%) and one third of the microorganisms are multidrug-resistant. The microorganisms most frequently involved are *S. aureus* (58%) and GNB (29%). Recent data about the microorganisms responsible for diabetic foot osteomyelitis are sparse. Most published studies (table II) [13-16] do not distinguish osteomyelitis from other foot infections. Bamberger et al. conducted a study similar to ours, but prospective from 1980 through 1984 [14]. It included 42 patients with diabetes and 51 episodes of foot osteomyelitis. Their sampling methods were fairly similar to ours (7 blood samples, 24 needle aspiration samples, 4 bone biopsies, and 20 swabs) (table II). When we compare our results to theirs, we note the increasing importance of *S. aureus* (58% compared with 43% 20 years ago) and especially the absence of anaerobic microorganisms, which were much more common in older studies [13-16]. Our 11 needle aspiration samples (23% of our samples) produced only one anaerobic culture. Moreover, in our study, 31% of the pathogenic microorganisms were multidrug-resistant, 23% of them MRSA. These results corroborate those from the literature [17-19], which indicates that MRSA has become much more prevalent in diabetic foot infections. We did not see an association between multidrug-resistance and earlier antibiotic therapy, probably because the retrospective nature of the study resulted in an information bias. Multidrug-resistance was no longer associated with poorer prognosis.

**Growing role for medical treatment?**

Data on prognosis are sparse in the literature. The study by Bamberger et al. [14] included 11 deaths (among 42 patients) and 24 amputations (15 below the knee and 9 more distal) while in ours there were 4 deaths and 19 amputations (2 below the knee and 17 more distal). The San Antonio classification, dating from 1998, assesses the risk of amputation at 92% at 6 months for patients with osteomyelitis [3]. Our practice is developing towards an approach in which surgery is not routine, is rarely radical, is increasingly conservative, and is used more often with medical treatment [20]. This strategy, more acceptable to the patient, also has the advantage of accelerating wound healing [20]. Nonetheless, prognosis remains grim and involves increasingly burdensome medical treatment: it most often requires hospitalization to impose off-loading, obtain glycemic control, plan a revascularization procedure, and administer wide-spectrum antibiotics intravenously (following the emergence of bacterial resistance), although these treatments are increasingly often continued at home. Treatment is long: a median of 30 days of hospitalization and 95 days of antibiotic therapy in our study. Failures are associated more with the

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**Table II**

<table>
<thead>
<tr>
<th>Studies [reference]</th>
<th>*S. aureus (%)</th>
<th>Staph. coag. negative (%)</th>
<th>Streptococci (%)</th>
<th>Enterococci (%)</th>
<th>GNB (%)</th>
<th>Anaerobic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study by Wheat*, 1986 [13]</td>
<td>64</td>
<td>30</td>
<td>26</td>
<td>50</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Study by Bamberger**, 1987 [14]</td>
<td>43</td>
<td>37</td>
<td>17</td>
<td>45</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>Our study</td>
<td>58</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>29</td>
<td>0</td>
</tr>
</tbody>
</table>

GNB: Gram-negative bacilli
* Microorganisms found in reliable specimens (aspirations of deep wounds, surgical biopsies) (n = 54) from 131 diabetic ulcers.
** Microorganisms found in specimens (7 blood samples, 24 needle samples, 4 bone biopsies, 20 swabs) of 51 cases of diabetic foot osteomyelitis.
*** Microorganisms involved (reliable specimens) in grade 3 and 4 diabetic foot infections (meta-analyses of 9 validated studies).
**** Microorganisms found in diabetic foot osteomyelitis (meta-analysis of 5 studies).
Emergence of monomicrobial methicillin-resistant *Staphylococcus aureus* infections in diabetic foot osteomyelitis

wound site, in particular calcaneal osteomyelitis, and with the extent of lower limb peripheral arterial disease than with the particular microorganisms involved.

**Prognosis darkened by the high rate of new infections**

While the development is globally favorable (recovery in 83% of cases in our study), the rate of subsequent re-infection at another site and most often with a different microorganism is high (45% of the initially recovered patients). These are not relapses but new infectious episodes, distinct from the previous ones. These re-infections may result from failure to comply with basic rules (walking barefoot or with inappropriate shoes, neglecting a wound, etc.), from localized excess pressure due to a foot deformation (Charcot foot, amputation, supplementary pressure on the foot not initially infected). Above all, improved prognosis for these infections requires prevention (systematic foot examination, screening for arterial disease, early treatment of wound, proper shoes, and patient education).

**Identifying the microorganisms involved from a reliable sample is essential**

Taking and interpreting samples in these patients is always delicate. To the extent that an infected wound very frequently precedes osteomyelitis, patients (56% of those in our study) have often already received antibiotic treatment before coming to the hospital; this may distort the result of samples taken at the hospital. In this case, it is necessary to rely on samples taken by private general practitioners or laboratories, but these were relatively rare (25% of the cases in our study). The needle aspiration samples are most reliable [21, 22] but are sometimes difficult to take (especially in the case of advanced arterial disease) or are distorted by previous antibiotic therapy. In our study, needle samples enabled us to identify microorganisms in 23% of cases. The most reliable sample was always a bone biopsy [10], but it was not always possible (lack of exposed bone, surgeon availability, severe arterial disease). It helped diagnose 17% of our cases. Blood work-ups were useful in 6% of cases. The proportion of patients (54%) for whom diagnosis was based on swab samples is therefore relatively elevated and constitutes a limitation of our results.

In 5 cases, we must point out, an unfavorable course led us to repeat sampling and change the antibiotic therapy (recovery followed in all cases). For these patients, it is likely that the microorganism shown in the second sample was present initially and that it was “unmasked” by antibiotic therapy directed at the initially predominant microorganism. It is therefore necessary to avoid the needless multiplication of samples (a factor that must always be taken into account) but also to be able to take new samples in the case of failure to respond to efficacious antibiotic therapy.

**Conflicts of interest:** none

**References**