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## **Short duration of post-amputation antibiotic therapy in diabetic foot patients with total resection of osteomyelitis**

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## **ABSTRACT**

**Background.** Short duration of post-amputation antibiotic therapy (2-5 days) is recommended in patients with diabetic foot osteomyelitis after total resection of infected bone tissue.

**Objective.** To evaluate the long-term effectiveness of short-duration post-amputation antibiotic therapy in diabetic patients with total resection of osteomyelitis assessed by sterile bone bacteriological samples obtained from the resection margin.

**Methods.** The endpoint was the absence of osteomyelitis relapse at 6 months, defined as recurrence of osteomyelitis with the need for surgical revision and/or new bone antibiotic therapy.

**Results.** Among 15 patients included, 12 (80%) were cured without recurrence of osteomyelitis at 6 months, with a mean duration of antibiotic therapy of  $8.3 \pm 5.9$  days post surgery. This result is comparable to literature data, while all of them reported longer duration of antibiotic therapy and/or shorter follow-up.

**Conclusion.** Short duration of post-amputation antibiotic therapy in diabetic patients with sterile bacteriological samples obtained from resection margin seems effective.

Professional societies for infectious diseases in America and France recommend a short duration of post-amputation antibiotic therapy (2-5 days) in patients with diabetic foot osteomyelitis after total resection of infected bone tissue [1,2]. In case of residual infected bone, they recommend prolongation of antibiotic therapy (4-6 weeks) [1,2]. However, these recommendations have a low level of evidence, because of the limited number of clinical studies [1,2]. In addition, how residual osteomyelitis should be evaluated is not defined.

We conducted a prospective study to evaluate the long-term effectiveness of short-duration post-amputation antibiotic therapy in diabetic patients with total resection of osteomyelitis, as assessed by sterile bone bacteriological samples obtained from the resection margin.

## **METHODS**

We performed a prospective, observational study between June 2015 and May 2017 at the university hospital of Reims, France. Inclusion criteria were adults (>18 years of age) with type 1 or type 2 diabetes who underwent surgical amputation for foot osteomyelitis. Bone biopsies in a “macroscopically” healthy zone had to be performed and bacterial cultures had to be sterile on the fifth day. Foot osteomyelitis was determined by positive probe to bone test and imaging data on plain X-rays and/or bone scans.

All patients’ observations were discussed at a multidisciplinary meeting on bone and joint infection at Reims university hospital and the indication for both surgical resection and antibiotic therapy was jointly decided.

The endpoint was the absence of osteomyelitis relapse at 6 months, defined as recurrence of osteomyelitis with the need for surgical revision and/or new bone antibiotic therapy.

Patients were systematically seen in consultation at 1, 3, and 6 months postoperatively, with clinical reassessment of the foot, and x-ray. All events occurring during follow-up, particularly infections, were recorded.

Demographic variables, and data on all diabetes-related disorders were collected, including duration of diabetes, presence of hypertension, chronic renal failure, occlusive arterial disease of the lower limb, and peripheral neuropathy. Doppler ultrasound explorations with transcutaneous measurement of oxygen pressure (TcPO<sub>2</sub>) were performed in case of clinical abnormalities. Revascularization procedures were performed before amputation if necessary. Microbiological data was also recorded.

Qualitative variables are described as number (percentage) and quantitative variables as mean  $\pm$  standard deviation.

## **RESULTS**

Between June 2015 and May 2017, a total of 50 patients with type 1 or type 2 diabetes underwent surgical amputation for foot osteomyelitis in our hospital. Among these, a total of 15 patients (30%) with sterile biopsies in macroscopically healthy zone were included. The characteristics of the study population are reported in Table 1. Mean age was  $68\pm 11$  years. Most were men (73%) and had type 2 diabetes (93%). The mean duration of diabetes was  $14.9\pm 9.8$  years. Comorbidities included hypertension (60%), chronic renal failure with glomerular filtration rate between 30 and 59 mL/min/1.73m<sup>2</sup> (40%), and peripheral neuropathy (80%). Occlusive arterial disease of the lower limb was present in eight patients (53%), two of whom had already been treated by surgery. Previous lower limb amputation was reported in eight patients (53%); for osteomyelitis in seven cases (47%) and for occlusive arterial disease in one case.

Osteomyelitis was located in the forefoot (metatarsal and/or toe involvement) in 13 cases (87%), extended to the tarsal bones in one case and was located only in the calcaneus bone in

one case. Vascular investigations were necessary in 11 patients (73%). Doppler ultrasound was performed in 10 patients (67%) and TcPO<sub>2</sub> measurement in 10 patients (67%). Two patients (20%) had a pathological TcPO<sub>2</sub> measurement (<35 mmHg), but only one patient required thromboendarterectomy and stenting prior to orthopedic surgery.

Before amputation, antibiotic therapy was initiated for concomitant skin and soft infections in 12 patients (80%), averaging  $9.7 \pm 5.4$  days before surgery. Most patients (n=9) received amoxicillin-clavulanic acid. Two patients discontinued the antibiotic therapy on respectively Day 8 and 28 before surgery.

Nine patients (60%) required transmetatarsal resection and five patients (33%) minor resection (arthroplasty resection). One patient had major amputation (transtibial amputation). The mean number of bone biopsies in macroscopically healthy zones was  $1.6 \pm 0.83$ . On average, the duration of postoperative antibiotic therapy was  $8.3 \pm 5.9$  days.

A bacterial culture of resected bone was available in seven patients, which was positive in all cases. The median number of bacteria types was three (range 1-3). Among the eight other patients, the bacterial culture of deep tissue sample obtained before intervention was positive for *Staphylococcus aureus* in six cases, streptococci in two cases, *Proteus mirabilis* or *vulgaris* in three cases, and anaerobes in two cases. The median number of bacteria types was two (range 1-4).

Twelve patients (80%) did not experience recurrence of osteomyelitis during the six-month postoperative follow-up. Among the remaining three patients, one required antibiotic therapy to be resumed in the 3<sup>rd</sup> month due to soft tissue infection, and subsequently required surgical revision at 6 months due to radiological osteomyelitis in relation to the adjacent bone tissues. The second patient was successfully treated one month postoperatively with two weeks of antibiotic therapy alone for persisting purulent flow from the scar with positive microbiological samples for the same pathogens that caused the osteomyelitis. The third

patient was lost to follow-up from the 3<sup>rd</sup> month of follow-up, and outcome at six months was unknown, although it should be noted that up to one month of follow-up, no recurrence of osteomyelitis was observed.

## **DISCUSSION**

To the best of our knowledge, this is the first prospective study aimed at evaluating the recommendations of a short duration of antibiotic therapy in patients with diabetic foot osteomyelitis and no residual infected bone after amputation. The absence of residual bone infection was defined as sterile bone biopsies (after a culture of five days) obtained from the resection margin. A high rate of residual osteomyelitis, ranging from 35% to 63% based on bone margin culture, has indeed been reported after amputation in the literature [3–5]. Residual osteomyelitis was also observed in 70% of cases over the study period. Furthermore, bacteriological culture of bone biopsy from resection margins, in patients with total surgical resection of infected bone tissue, has been shown to be predictive of osteomyelitis recurrence [3,4]. In a retrospective cohort of 111 patients with surgically treated diabetic foot osteomyelitis, 39 (35.1%) had pathologically confirmed positive margins for residual osteomyelitis. The median duration of antibiotic therapy was 19 days (10–134) in patients with positive margins and 14 days (2–63) in patients with negative margins. Patients with positive margins had a significantly higher rate of re-amputation compared with patients with negative margins (43.6% vs 15.3%) [3]. In another study including 27 diabetic patients who underwent partial foot amputation, patients with a positive bone margin had a significantly higher rate of poor outcome than patients with negative bone margin (82% versus 25%;  $p=0.0063$ ) [4].

The number of bone biopsies which had to be performed in macroscopically healthy zones to eliminate the risk of residual infection is not defined. In our study, the mean number of bone biopsies in macroscopically healthy zones was  $1.6 \pm 0.8$ , because it is usually difficult to perform more than one bone biopsy in patients with minor resection (arthroplasty resection). Most of our patients (80%) had received preoperative antibiotics for concomitant skin and soft tissue infections for a mean of  $9.7 \pm 5.4$  days. Although the Infectious Diseases Society of America (IDSA) recommends a 2-week antibiotic-free period to avoid false-negative cultures in the absence of data in patients with diabetic foot osteomyelitis, only two of our patients had discontinued antibiotics on Day 28 and 8 before surgery, while three patients did not receive any antibiotics before surgery [1]. We cannot exclude false-negative culture results in other patients, but it has been shown that culture of bone specimens remains largely positive despite antibiotic therapy [6–8]. In a study of 80 patients with diabetic foot osteomyelitis, culture of per-wound bone specimens was positive in 96% of patients, although half of patients received a course of antimicrobials within 14 days of bone specimen collection [6]. In another cohort study of 165 patients with diabetic foot osteomyelitis, in whom 83% were given antibiotics (mean duration of exposure,  $6.2 \pm 4.1$  weeks; amoxicillin-clavulanic acid was the most frequently prescribed antibiotic), antibiotics did not have any negative impact on microbiologic culture of surgical bone biopsy results (87.8% in patients exposed to antibiotics versus 61.8% in antibiotic-naïve patients ( $p < .001$ )) [7]. In a cohort study of 60 adults with vertebral osteomyelitis who had biopsy performed because of previous antibiotic exposure  $\leq 14$  days (median duration 4 days; 1–37 days), only 17 (28%) had potentially false-negative culture results because of the empirical antibiotic treatment. The rate of negative culture was also very low in patients with open surgical bone biopsy compared with percutaneous bone biopsy (5% versus 41%) [8].



Among the 15 patients included in our study, 80% were cured without recurrence of osteomyelitis at 6 months with antibiotic therapy of a mean duration of  $8.3 \pm 5.9$  days post-surgery. The antibiotic therapy duration was slightly higher than the 3-5 days recommended because discontinuation of therapy had to be validated at our weekly multidisciplinary consultation meeting, and bone bacterial cultures had to be sterile on Day 5. Among the three patients who experienced treatment failures, one was lost to follow-up, although without recurrence during the first month of follow-up. The two others included one case of recurrent clinical and radiological osteomyelitis requiring surgical revision, and one case of persistent purulent flow from the scar successfully treated with two weeks of antibiotic treatment alone. Our cure rate (80%), with less than 10 days of post-amputation antibiotic therapy and six months of follow-up, is comparable to literature data, although most other authors reported a longer duration of antibiotic therapy (above 10 days) and/or shorter follow-up [9–14]. However, some of them included patients with surgical debridement but not amputation [13]. In addition, the duration of antibiotic therapy was not determined by the results of bone biopsies from resection margins. Furthermore, the primary objective of these studies was the comparison of antibiotics [9,10,12,14].

## **Conclusion**

In a small, real-life population of diabetic patients undergoing surgical amputation for osteomyelitis, our study shows that a short duration of post-amputation antibiotic therapy in patients with sterile bacteriological samples on Day 5 obtained from resection margins, is effective and supports the French and American guidelines. This approach should be validated in a larger cohort.

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**Disclosure of interest**

The authors declare no conflict of interest.

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**ETHICAL STATEMENT**

The work has not been submitted elsewhere for publication, in whole or in part. The article is not currently being considered for publication in another journal. All the authors listed have approved the article that is enclosed.

**Authors' contributions**

All authors cared for the patients. FBS, MF, and SD were responsible for the overall supervision of the study. JG, SD, and FBS wrote the first draft of the article. All authors critically reviewed the article and gave final approval.

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**Table 1.** Demographic, clinical, and biological characteristics of the 15 patients

<b>Variable</b>	<b>All patients (N=15)</b>
Age (years)	68 ±11
Male sex	11 (73%)
Type II diabetes	14 (93%)
Duration of diabetes (years)	14.9 ±9.8
Mean HbA1C (%)	7.6 ±1.6
High blood pressure	9 (60%)
Chronic renal failure (Cr Cl 30-60 mL/min/1.73 m <sup>2</sup> )	6 (40%)
Peripheral neuropathy	12 (80%)
Occlusive arterial disease of the lower limbs	8 (53%)
History of amputation	8 (53%)
Preoperative antibiotic therapy	12 (80%)
Duration of preoperative antibiotic therapy	9.7 ±5.4 days
Mean number of margin bone biopsies	1.6 ±0.8
Duration of post-amputation antibiotic therapy	8.3 ±5.9 days
Absence of recurrent osteomyelitis at 6 months	12 (80%)