Antibiotics Versus Conservative Surgery for Treating Diabetic Foot Osteomyelitis: A Randomized Comparative Trial

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OBJECTIVE

No prospective trials have been carried out comparing antibiotic treatment alone with primarily surgical treatment in patients with diabetes and foot osteomyelitis. The aim of the current study was to compare the outcomes of the treatment of diabetic foot osteomyelitis in patients treated exclusively with antibiotics versus patients who underwent conservative surgery, following up the patients for a period of 12 weeks after healing.

RESEARCH DESIGN AND METHODS

Between 1 January 2010 and 31 December 2012, a prospective randomized comparative trial (clinical trial reg. no. NCT01137903, clinicaltrials.gov) of patients with diabetes who had received a diagnosis of neuropathic foot ulcers complicated by osteomyelitis was carried out at the Diabetic Foot Unit at the Complutense University of Madrid. Patients were randomized into the following two groups: the antibiotics group (AG) and the surgical group (SG). Antibiotics were given for a period of 90 days in the AG. Patients in the SG received conservative surgery with postoperative antibiotic treatment for 10 days.

RESULTS

Eighteen patients (75%) achieved primary healing in the AG, and 19 (86.3%) in the SG (P = 0.33). The median time to healing was 7 weeks (quartile [Q] 1 to Q5, Q3–Q8) in the AG and 6 weeks (Q1–Q3, Q3–Q9) in the SG (P = 0.72). The conditions of four patients from the AG worsened (16.6%), and they underwent surgery. Three patients from the SG required reoperation. No difference was found between the two groups regarding minor amputations (P = 0.336).

CONCLUSIONS

Antibiotic therapy and surgical treatment had similar outcomes in terms of healing rates, time to healing, and short-term complications in patients with neuropathic forefoot ulcers complicated by osteomyelitis without ischemia or necrotizing soft tissue infections.

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Osteomyelitis in the feet of patients with diabetes is one of the most controversial issues when dealing with diabetic foot syndrome (1). It is generally accepted that bacteria reach the bone by first involving soft tissue and then involving cortical bone and/or the bone marrow (2). The diagnosis can be a challenge and may require advanced imaging studies in some cases (3). However, definitive diagnosis requires removing bone samples for both microbiological and histopathological studies.

The choice of treatment is based on the anatomical site of infection, the local vascular supply, the extent of soft tissue and bone destruction, the presence of necrosis, systemic signs of infection, and the clinician's and patient's preferences (4). The optimum approach is currently being debated, and the definitive role of surgery and antibiotic treatment is not sufficiently well clarified.

Several retrospective studies have reported good results when treating diabetic foot osteomyelitis (DFO) exclusively with antibiotics for a variable period (5–8). However, these studies have been criticized because the remission of inflammatory signs, "apparent remission," or limb salvage are not appropriate end points for demonstrating that the bone infection has actually been eradicated (9). Additionally, previous studies have been criticized because DFO was not diagnosed by bone biopsy, there was no comparator group, or long-term follow-up was lacking in most patients.

The main advantage of treating DFO with antibiotics is that it reduces the biomechanical changes that occur in the feet after surgical procedures (7), and avoids the financial cost and potential medical/surgical complications of surgical procedures (7), although it remains to be demonstrated that using primarily nonsurgical treatment is a more cost-effective approach. However, studies using antibiotics exclusively have failed to demonstrate this because short-term and mid-term follow-up was not carried out (9). On the other hand, the biomechanical disturbance that was the cause of the index ulcer would remain as it was, becoming a risk zone after successful antibiotic treatment (9).

Finally, when antibiotic therapy alone is chosen to treat DFO, one cannot predict with certainty the patients in whom medical therapy will fail (10), and failure could be associated with a more proximal level of amputation (9).

Surgery has been used for many years and is the mainstay of treatment of DFO. Several authors have reported the efficacy of surgical treatment of osteomyelitis (11–15). Furthermore, the development of conservative surgery to remove the bone infection while avoiding amputation is an attractive option (9,12,14). However, surgery, including conservative procedures, leads to biomechanical changes and reulceration due to pressure transfer syndrome (16), even though removing a bone deformity could have a prophylactic effect (9). According to a recent report, conservative surgery could also reduce the period of antibiotic therapy with a high rate of limb salvage (13).

It is very difficult to compare a series treating patients with antibiotics with a series consisting of surgically treated patients for several reasons: different end points were used; the characteristics of patients included in the series differed; the studies were carried out in different clinical settings; and histopathological confirmation of bone infection is not usually carried out.

The aim of the current study was to compare the outcomes of the treatment of DFO in patients treated exclusively with antibiotics to those of patients who underwent conservative surgery, following up the patients for a period of 12 weeks after healing.

RESEARCH DESIGN AND METHODS

Between 1 January 2010 and 31 December 2012, a prospective randomized comparative trial of patients with diabetes in whom foot osteomyelitis had been diagnosed was carried out at the Diabetic Foot Unit at the Complutense University of Madrid. The diagnosis of DFO was established on the basis of a combination of probing-to-bone test and plain X-ray, as previously published (17). The probe-to-bone test was performed using a metal forceps (Halsted mosquito forceps), and the result was considered positive when a hard or gritty surface was felt by the researcher. We considered the plain X-rays (two standard views) "positive" for osteomyelitis if they showed cortical disruption, periosteal elevation, a sequestrum or involucrum, or gross bone destruction.

Inclusion criteria were as follows: age >18 years; neuropathic ulcers complicated by osteomyelitis; ability to attend the appointments during the follow-up period; and written consent for inclusion in the study.

Exclusion criteria were as follows: patients with severe infections according to Infectious Diseases Society of America classification (18); necrotizing soft tissue infections accompanying osteomyelitis (19); peripheral arterial disease; Charcot foot; glycated hemoglobin >10% (86 mmol/mol); bone exposed at the bottom of the ulcer; pregnancy; antibiotic allergies; creatinine values >98 μmol/L in women and >106 μmol/L in men; hepatic insufficiency; and patients who did not understand the purpose of the study or refused to be included.

The neurological examination was undertaken using Semmes-Weinstein 5.07/10 g monofilaments (Novalab Ibérica, Alcalá de Henares, Madrid, Spain) and using Horwell's Biotensiometer (Novalab Ibérica). Neuropathy was diagnosed in patients who did not feel one of the two tests (20). Peripheral arterial disease was diagnosed if the patient met the following criteria: absence of both distal pulses and/or ankle brachial index <0.9 (21). Wounds were photographed and measured by means of planimetry (VISITRAK; Smith & Nephew, Hull, U.K.).

After agreeing to be included in the study and before randomization, therapy with antibiotics was ceased for 2 weeks. Patients were evaluated every 48 h during this period in order to detect any complication. They also received instructions to phone our department if any alarming signs were detected. After the period of antibiotic clearance, a deep soft tissue sample from the bottom of the ulcer was taken in every patient and was sent to a microbiological laboratory (22).

A computer-generated random number table was used to carry out a simple randomization of the patients into the following two groups: the antibiotics group (AG) and the surgical group (SG).

The AG Protocol

Antibiotic treatment was initially empiric, according to the clinician's preference, and consisted of the following three regimens: ciprofloxacin 500 mg b.i.d.; amoxicillin/clavulanic acid 875/125 mg b.i.d.; or trimethoprim 160 mg/sulfamethoxazole 800 mg b.i.d. The antibiotic regimen was modified according to the results of an antibiogram. Antibiotic treatment lasted 90 days, according to the study protocol. Therapy with antibiotics was discontinued in patients in whom healing occurred before 90 days. After this period, if the patients did not heal and had a positive probe-to-bone test result and/or progressive radiological bone destruction, surgery was carried out in the same fashion as for the SG.

The SG Protocol

Patients in the SG received conservative surgery, as previously described by our group (13), consisting of removal of the infected bone without performing amputation of any part of the foot. Bone samples were sent for microbiology and pathology studies. All surgical procedures were performed by the first author (J.L.L.-M.). All patients received postoperative empiric antibiotic treatment, which was modified according to the results of an antibiogram, for 10 days.

Local treatment of the ulcer was the same for both groups. Antimicrobial dressing was used for 2 weeks (Actisorb Plus 25; Systagenix, Cardiff, U.K.), after which the patients were treated according to the wound care protocol of our department.

Offloading was carried out using felted padding and a removable cast walker. Patients were evaluated every 48–72 h to change the dressings and felted paddings.

The main end points were the primary healing rate and time to healing. Secondary end points were as follows: the need for surgery in the AG; the need for reoperation in the SG; amputation rate and recurrence; and reulceration and death during the follow-up period. Patients were followed up for 12 weeks after healing.

We measured inflammatory markers in blood samples from the patients in both groups at the beginning of the study (day 0) and 12 weeks after primary healing. Inflammatory markers were defined as follows: leukocytosis was defined as a white blood cell count $>11 \times 10^9$/L; elevated erythrocyte sedimentation rate (ESR) was defined as an ESR >20 mm/h; and elevated C-reactive protein (CRP) was defined as a CRP level >28.5 nmol/L.

We used the outcome definitions given below, based on our previous experience (12). Primary healing was defined in the AG as healing achieved exclusively with antibiotic treatment. It was defined in the SG as healing achieved after the first surgical procedure.

Healing was defined as the complete epithelialization of the ulcer and/or the surgical wound that was created while treating the infection. Time to healing was defined as the time in weeks from the date on which osteomyelitis was diagnosed to the date of healing.

Complication during follow-up was defined as any event in the AG requiring surgical treatment (i.e., necrosis, exposed bone, and signs of systemic toxicity) and the need for reoperation in the SG. Healing after surgery for complications was not considered to be primary healing.

Recurrence of osteomyelitis was defined as the appearance of bone infections at the same or an adjacent site after healing of both the ulcer that was the point of entry of the infection and the surgical wound. In cases of recurrence, the ray, bone, and/or joint affected had to be the same as that operated on in the first attempt.

Reulceration was defined as any ulcer, whatever depth, appearing during follow-up at the same or other sites including the contralateral foot. A new episode of osteomyelitis was defined in cases in which the new ulcer was complicated by bone infection.

Statistical Methods

For descriptive purposes, we used the median and quartile (Q) 1 and Q3 for nonnormally distributed continuous variables and percentages for discrete variables. Using univariate analysis, we compared discrete variables using the χ^2 test and Fisher test when indicated; for continuous variables, we used the nonparametric Mann-Whitney *U* test. A *P* value <0.05 was fixed as the threshold of statistical significance. We performed statistical analyses using SPSS version 20.0 for Macintosh (SPSS, Chicago, IL).

The current study was approved by the local ethics committee of the Clínico San Carlos Hospital of Madrid on 18 November 2009 with the internal code number 09/346, and was recorded in the international trial registry (http://clinicaltrials.gov/; clinical trial reg. no. NCT01137903). All patients gave written informed consent for surgery, for photographs to be taken of their wounds, to be included in our computer database, and for their anonymized case data to be included in a publication. The authors declare that they have conformed to the Declaration of Helsinki code of ethics.

RESULTS

One hundred fifty-six patients with diabetes received a diagnosis of foot osteomyelitis in our center during the period of study. The main reasons for exclusion were the presence of peripheral arterial disease, exposed bone at the bottom of the ulcer, and patients' refusal to participate in the study. Fifty-two patients (33.3%) met the inclusion criteria of the study. Twenty-five patients (48.1%) were randomized to the AG, and 27 (51.9%) to the SG. One patient belonging to the AG and five patients belonging to the SG dropped out of the study because of difficulties attending follow-up appointments or personal reasons for abandoning the study (Fig. 1).

The demographic and clinical characteristics of the study population are shown in Table 1. No differences were found in the size of ulcers (AG: median 0.7 cm^2; Q1 0.56 cm^2; Q3 0.85 cm^2; SG: median 0.8 cm^2; Q1 0.6 cm^2; Q3 1.15 cm^2; *P* = 0.155) or the duration of the ulcers (AG: median 13 weeks; Q1 3 weeks; Q3 10 weeks; SG: median 14 weeks; Q1 5 weeks; Q3 52 weeks; *P* = 0.192). Every

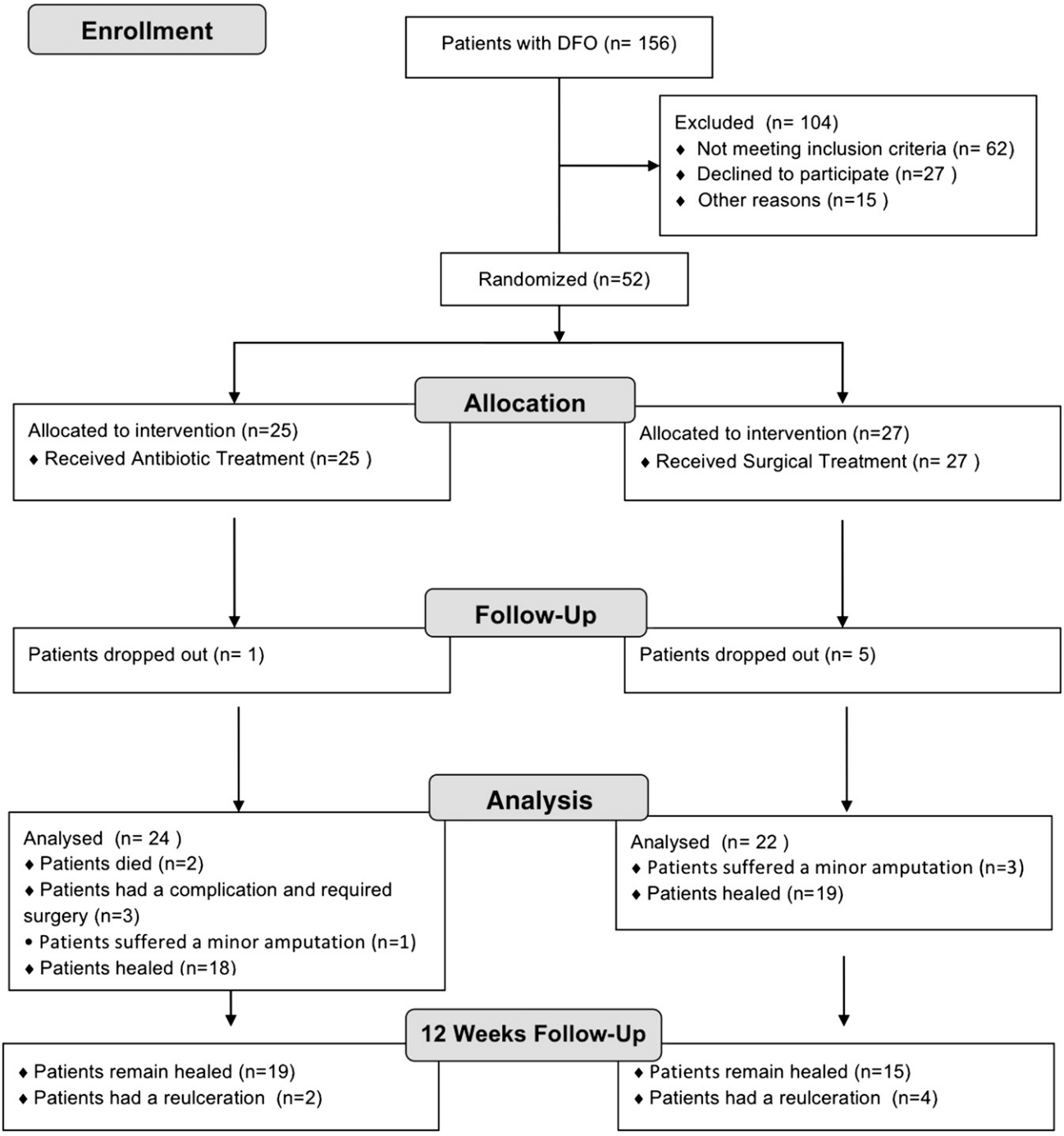

Figure 1—Flow chart of the patients included in the study.

ulcer included in the study was located in the forefoot (Table 2).

The following surgical procedures were performed: 2 arthroplasties (8.6%); 2 sesamoidectomies (8.6%); 4 bone curettages (18.3%); and 14 metatarsal head resections (63.6%).

Previous antibiotic therapy before the period of clearance of antibiotics in the AG was as follows: amoxicillin/clavulanic acid 875/125 mg b.i.d. in 20 patients (80%); and ciprofloxacin 500 mg b.i.d. in 4 patients (20%). Previous antibiotic therapy before the period of clearance of antibiotics in the SG was as follows: amoxicillin/clavulanic acid 875/125 mg b.i.d. in 10 patients (45.5%); ciprofloxacin 500 mg b.i.d. in 3 patients (13.6%); trimethoprim 160 mg/sulfamethoxazole 800 mg b.i.d. in 1 patient (4.5%); clindamycin 300 mg b.i.d. in 2 patients (9.1%); ciprofloxacin 500 mg b.i.d. plus clindamycin 300 mg in 2 patients (9.1%); levofloxacin 500 mg b.i.d. in 2 patients (9.1%); and tetracycline 250 mg b.i.d. in 2 patients (9.1%).

After culture results, treatment was modified according to the antibiogram in eight patients as follows: amoxicillin/clavulanic acid 875/125 mg b.i.d. in 12

Table 1—Demographic and clinical characteristics of the study population

Variables	AG (n = 24)	SG (n = 22)	P value
Age (years)[a]	75 (72–78)	62 (50–67.2)	<0.001
Male sex	14 (58.3)	19 (86.4)	0.035
Diabetes type			0.446
Type 1	4 (16.7)	2 (9.1)	
Type 2	24 (83.3)	20 (90.9)	
Diabetes treatment			0.451
OHA	6 (25)	8 (36.4)	
Insulin	12 (50)	7 (31.8)	
OHA + insulin	6 (25)	7 (31.8)	
BMI (kg/cm^2)	26 (22–28)	28.3 (26–30)	0.05
Glycemia, % (mmol/L)	7.60 (5.88–8.05)	7.74 (6.74–11.90)	0.172
HbA_{1c} (% [mmol/mol])	5.7 [39] (5.3 [34]–9.1 [76])	6.2 [44] (4.7 [28]–8.3 [67])	0.502
Hypertension	16 (66.7)	15 (68.2)	0.913
High cholesterol levels	16 (66.7)	12 (54.5)	0.400
Coronary heart disease	11 (45.8)	4 (18.2)	0.046
Smoking	6 (25)	2 (9.1)	0.165
Alcohol abuse	—	2 (9.1)	0.131
Nephropathy	14 (58.3)	14 (63.6)	0.713
Retinopathy	12 (50)	5 (22.7)	0.05
Antiplatelet treatment	24 (100)	15 (68.2)	0.003
Previous antibiotic treatment	22 (91.7)	20 (90.9)	0.927
Antibiotic treatment duration (days)	3.5 (0–14)	7 (0–21)	0.144
Previous ulcer	16 (66.7)	16 (72.7)	0.655
Previous amputation	10 (41.7)	10 (45.5)	0.796
S-W 5.07/10 g monofilament	20 (83.3)	17 (77.3)	0.605
Vibration threshold determined by biotensiometer	20 (83.3)	19 (86.4)	0.775
Ankle/brachial index	1.2 (1.07–1.29)	1.06 (0.87–1.34)	0.332
Toe/brachial index	0.74 (0.55–0.98)	0.66 (0.54–0.94)	0.498
$tcPo_2$ (mmHg)	40 (35–43)	38.5 (31–44.5)	0.238

Data are n (%) or median (Q1–Q3) unless otherwise stated. OHA, oral hypoglycemic agents; S-W, Semmes-Weinstein; $tcPo_2$, transcutaneous oxygen pressure. [a]Data are n (range).

patients (50%); ciprofloxacin 500 mg b.i.d. in 10 patients (41.6%); and trimethoprim 160 mg/sulfamethoxazole 800 mg b.i.d. in 2 patients (8.4%). No side effects of antibiotherapy were found in the study.

Table 2—Ulcer location

Locations	AG (n = 24)	SG (n = 22)	P value
Hallux	3 (12.5)	5 (22.7)	<0.001
First metatarsal	1 (4.2)	5 (22.7)	<0.001
Lesser metatarsal	14 (58.3)	11 (50)	0.571
Lesser toes	6 (25)	1 (4.5)	<0.001

Values are given as n (%), unless otherwise stated.

Bacterial isolates from deep culture from both groups and bone culture in the SG are shown in Table 3. Eighteen patients (75%) achieved primary healing in the AG, and 19 patients (86.3%) in the SG (P = 0.33). The median time to healing was 7 weeks (Q1 5 weeks; Q3 8 weeks) in the AG, and 6 weeks (Q1 3 weeks; Q3 9 weeks) in the SG (P = 0.72).

The levels of inflammatory markers measured on day 0 and 12 weeks after primary healing are shown in Table 4.

Two patients from the AG died unhealed during the follow-up period, one from myocardial infarction and the other from stroke. No patient from the SG died (P = 0.490). The deaths were not related to infection. The conditions of four patients from the AG worsened (16.6%), and they underwent surgery (one had minor amputation and three had conservative surgery). Three patients from the SG required reintervention, and minor amputation was performed in all three. No difference in minor amputations was found between the two groups (P = 0.336). All patients in both groups healed after reoperation or minor amputation.

Two reulcerations were detected in the AG (9.5%), and four (21%) in the SG during the period of follow-up after healing (P = 0.670). No recurrence was found in either group.

CONCLUSIONS

The current study is the first reported attempt in the medical literature to compare the treatment of DFO with antibiotic therapy exclusively to treatment with surgery followed by a short postoperative period of antibiotic therapy. No differences were found between the two types of treatment in healing rate and time to achieve healing in our trial. Complications were similar in both groups, and no differences in minor amputations as a result of complications were found.

Previous studies dealing with the antibiotic treatment of DFO have reported several remission criteria other than healing rates and time to healing. Embil et al. (5), using the resolution of clinical findings as the evaluated outcome, reported an 80.5% remission rate in a mean time of 35 ± 27 weeks. Another group reported 64% remission, 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 (6). Patient survival with the limb intact was used to define remission by another group, which reported an 82.3% remission rate (7). Only Lesens et al. (23) used an end point similar to ours; they reported that 81% of patients achieved complete healing of the wound with no signs of infection. Eighty-three percent of our patients achieved healing within 7 weeks exclusively with antibiotics. These rates are similar, although they used bone biopsy samples through the ulcer and we used deep soft tissue samples.

Table 3—Bacterial isolates from deep culture from both groups and bone culture in SG

Microorganisms	Deep culture in AG	Deep culture in SG	Bone culture in SG
Staphylococcus aureus	13	10	4
Staphylococcus epidermidis	5	2	7
Methicillin-resistant S. aureus	—	1	—
Streptococcus viridans	—	2	1
Streptococcus agalactiae	—	—	1
Streptococcus species	—	—	2
Streptococcus anginosus	—	1	—
Pseudomonas aeruginosa	2	2	2
Proteus mirabilis	4	2	1
Corynebacterium species	—	3	2
Escherichia coli	—	1	1
Alcaligenes species	—	1	—
Enterobacter cloacae	—	—	1
Citrobacter koseri	—	—	1

In the current study, the diagnosis of DFO was established on the basis of a combination of a probing-to-bone test and a plain X-ray, which has a high predictive value, as previously reported (17). However, a definitive confirmation of osteomyelitis in the AG could not be achieved because bone samples were not obtained. No previous studies dealing with antibiotic treatment of DFO confirmed osteomyelitis by means of histopathological study of bone samples. This is a limitation of our study because some patients may had have radiological changes as a result of neuroarthropathy rather than a bone infection (24).

Regarding the SG, the healing rates and time to healing are similar to previous reports (11,12). However, patients included in the present series differ from those in other studies for the following several reasons: only patients with forefoot osteomyelitis without necrosis, ischemia, or soft tissue infections were included. It should be noted that it is precisely these factors that are related to the failure of conservative surgery and the need for amputation, and that increased the time to healing in previous studies (12,13).

ESR and CRP were the inflammatory markers that displayed abnormal values on day 0, and only two patients from the SG had leukocytosis (8.3%). After 12 weeks of follow-up, no patients in the AG presented abnormal values of any inflammatory markers, and only two patients in the SG had leukocytosis and elevated CRP levels 12 weeks after healing. However, neither of these patients had any signs of recurrence or complication. The combination of wound healing and normalization of inflammatory marker levels after 12 weeks suggests that DFO could be considered arrested after both treatments.

Complications during the treatment were similar in both groups. Four patients required surgery in the AG (three underwent conservative surgery, and one minor amputation), and three patients required revision surgery, consisting of minor amputations in the SG (P = 0.336). No patient required a major amputation during the study. An historical series dealing with antibiotic treatment of osteomyelitis reported major amputation rates >30% (25). Previous studies on the surgical treatment of osteomyelitis, including patients with advanced cases with ischemia and soft tissue infection, have reported a major amputation rate of 6.3% and a minor amputation rate of 11.7%, showing a good prognosis in >80% of the cases (12). In a more recent series, the major amputation rate was reduced to 1.2% (13). Aragón-Sánchez (26) reported 100% successful conservative surgery outcomes in patients with osteomyelitis without soft tissue infection or ischemia.

Table 4—Frequency and percentage of patients with inflammatory markers determined at day 0 of study and after 12 weeks of healing in both groups

Variables	ESR elevated at day 0	ESR elevated after 12 weeks of healing	CRP elevated at day 0	CRP elevated after 12 weeks of healing	Leukocytosis at day 0	Leukocytosis after 12 weeks of healing
AG	19 (79.1)	0	5 (20.8)	0	0	0
SG	14 (63.6)	2 (9)	6 (27.2)	2 (9)	2 (8.3)	2 (8.3)
P value	0.098	0.146	0.423	0.146	0.131	0.131

Values are given as *n* (%), unless otherwise indicated.

There were no statistical differences in reulceration rates during the 12-week follow-up after healing (two patients in the AG vs. four patients in the SG; P = 0.670). There was no recurrence after healing in either group. Even though surgery has been described as a risk factor for the development of ulcers due to pressure transfer syndrome (16), no differences were found between the two groups. Although 12 weeks could be considered a short-term follow-up, a previous study reported that recurrence usually occurred earlier than this (13).

The main limitations of our study were as follows: the possibility of a type 2 error given the small sample size; not having diagnostic confirmation of DFO by histopathological studies in the AG, even though we were certain that the patients had osteomyelitis because the combination of the probe-to-bone test followed by X-ray has a positive predictive value of 97% (17). All lesions were located in the forefoot; the follow-up period was only 12 weeks; we could not analyze the mid- and long-term complications including late recurrences; and, finally, differences in the locations of the ulcers between the two groups may have influenced the outcomes.

The strengths of this study are that surgery was performed by the same surgeon, thus minimizing the possibility

of bias, and it was performed in an experienced center exclusively dedicated to treating diabetic foot problems.

In conclusion, antibiotic and surgical treatment had similar outcomes in terms of healing rates, time to healing, and short-term complications for patients with neuropathic forefoot ulcers complicated by osteomyelitis without ischemia, necrosis, or soft tissue infections.

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References

1. Lipsky BA, Berendt AR, Deery HG, et al.; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004;39:885–910
2. Jeffcoate WJ, Lipsky BA. Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. Clin Infect Dis 2004;39 (Suppl. 2):S115–S122
3. Lipsky BA, Berendt AR, Cornia PB, et al.; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:e132–e173
4. Lipsky BA, Peters EJ, Senneville E, et al. Expert opinion on the management of infections in the diabetic foot. Diabetes Metab Res Rev 2012;28(Suppl. 1):163–178
5. Embil JM, Rose G, Trepman E, et al. Oral antimicrobial therapy for diabetic foot osteomyelitis. Foot Ankle Int. 2006;27:771–779
6. Senneville E, Lombart A, Beltrand E, et al. Outcome of diabetic foot osteomyelitis treated nonsurgically: a retrospective cohort study. Diabetes Care 2008;31:637–642
7. Game FL, Jeffcoate WJ. Primarily non-surgical management of osteomyelitis of the foot in diabetes. Diabetologia 2008;51: 962–967
8. Valabhji J, Oliver N, Samarasinghe D, Mali T, Gibbs RG, Gedroyc WM. Conservative management of diabetic forefoot ulceration complicated by underlying osteomyelitis: the benefits of magnetic resonance imaging. Diabet Med 2009;26: 1127–1134
9. Aragón-Sánchez J. Treatment of diabetic foot osteomyelitis: a surgical critique. Int J Low Extrem Wounds 2010;9:37–59
10. Berendt AR, Peters EJ, Bakker K, et al. Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. Diabetes Metab Res Rev 2008;24(Suppl. 1):S145–S161
11. Karchmer AW, Gibbons GW. Foot infections in diabetes: evaluation and management. Curr Clin Top Infect Dis 1994;14:1–22
12. Aragón-Sánchez FJ, Cabrera-Galván JJ, Quintana-Marrero Y, et al. Outcomes of surgical treatment of diabetic foot osteomyelitis: a series of 185 patients with histopathological confirmation of bone involvement. Diabetologia 2008;51:1962–1970
13. Aragón-Sánchez J, Lázaro-Martínez JL, Hernández-Herrero C, et al. Does osteomyelitis in the feet of patients with diabetes really recur after surgical treatment? Natural history of a surgical series. Diabet Med 2012;29:813–818
14. Ha Van G, Siney H, Danan JP, Sachon C, Grimaldi A. Treatment of osteomyelitis in the diabetic foot. Contribution of conservative surgery. Diabetes Care 1996; 19:1257–1260
15. Henke PK, Blackburn SA, Wainess RW, et al. Osteomyelitis of the foot and toe in adults is a surgical disease: conservative management worsens lower extremity salvage. Ann Surg 2005;241:885-892
16. Molines-Barroso RJ, Lázaro-Martínez JL, Aragón-Sánchez J, García-Morales E, Beneit-Montesinos JV, Alvaro-Afonso FJ. Analysis of transfer lesions in patients who underwent surgery for diabetic foot ulcers located on the plantar aspect of the metatarsal heads. Diabet Med 2013;30: 973–976
17. Aragón-Sánchez J, Lipsky BA, Lázaro-Martínez JL. Diagnosing diabetic foot osteomyelitis: is the combination of probe-to-bone test and plain radiography sufficient for high-risk inpatients? Diabet Med 2011;28:191–194
18. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis 2007;44:562–565
19. Aragón-Sánchez J, Quintana-Marrero Y, Lázaro-Martínez JL, et al. Necrotizing soft-tissue infections in the feet of patients with diabetes: outcome of surgical treatment and factors associated with limb loss and mortality. Int J Low Extrem Wounds 2009;8: 141–146
20. Feldman EL, Stevens MJ. Clinical testing in diabetic peripheral neuropathy. Can J Neurol Sci 1994;21:S3–S7
21. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 (Suppl. S):S5–S67
22. Malone M, Bowling FL, Gannass A, Jude EB, Boulton AJ. Deep wound cultures and bone biopsy in diabetic foot osteomyelitis. Diabetes Metab Res Rev 2013;29:546–550
23. Lesens O, Desbiez F, Vidal M, et al. Culture of per-wound bone specimens: a simplified approach for the medical management of diabetic foot osteomyelitis. Clin Microbiol Infect 2011;17:285–291
24. Rogers LC, Bevilacqua NJ. The diagnosis of Charcot foot. Clin Podiatr Med Surg 2008; 25:43–51, vi
25. 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 1987;83:653–660
26. Aragón-Sánchez J. Clinical-pathological characterization of diabetic foot infections: grading the severity of osteomyelitis. Int J Low Extrem Wounds 2012;11:107–112