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Long-term antibiotic therapy is just as effective as amputation for foot osteomyelitis in diabetics without peripheral arterial disease

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ABSTRACT A critical appraisal and clinical application of Lázaro-Martínez JL, Aragón-Sánchez J, García-Morales E. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. *Diabetes Care.* 2014;37(3):789-95. doi: 10.2337/dc13-1526.

Keywords: *Diabetic, foot, osteomyelitis, antibiotics, surgery*

Clinical Context

A 69-year-old man with type II Diabetes treated compliantly with metformin presented to the emergency department with complaints of a right first metatarsal ulcer that had not healed in the last two weeks. He reported no pain, but stated that he had a left first metatarsal amputation due to osteomyelitis several years ago. Physical exam revealed a left first metatarsal amputation and a 2x2 cm stage 3 Wagner classification ulcer (deep ulcer with bone involvement) overlying the right plantar metatarsal area. The ulcer was non-purulent with an erythematous border and had a positive bone to probe test. The ER physician ordered an MRI that was suggestive of right first metatarsal osteomyelitis. The patient was admitted to the hospital to start broad-spectrum antibiotics including Piperacillin-Tazobactam and Vancomycin for osteomyelitis. Since the patient was in no acute distress, the medicine team decided to order cultures of the ulcer and do a bone biopsy to check for signs of osteomyelitis. The cultures of the ulcer showed E. coli and Pseudomonas aeruginosa with possible bone involvement. Medicine also ordered an Ankle-brachial index (ABI), which was 0.91 (normal range: 0.90 to 1.20) in his right left lower extremity indicating no peripheral arterial disease. Surgery was consulted to evaluate for amputation of the right first metatarsal bone.

At this point, the patient asked if it was possible to prevent the amputation by taking antibiotics because he didn't want another amputation for fear it would destabilize his gait.

Clinical Question

Is long-term antibiotic therapy equally efficacious compared to amputation for foot osteomyelitis in diabetic patients without peripheral arterial disease?

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Research Article

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Related Literature

PubMED Database was used to search for keywords “osteomyelitis”, “foot”, “diabetic”, and “antibiotics”. Many of the articles assessed the efficacy of specific antibiotics for diabetic foot infections in patients with peripheral arterial disease; the patient in question had no evidence of peripheral arterial disease in the affected limb as confirmed by ABI > .90 and thus, these studies fail to assess the potential for successful treatment in this patient.

Surgery is usually the first line treatment for diabetic foot osteomyelitis due to the efficacy of removing the entire infection with clean non-infected margins. Surgical treatment of diabetic foot osteomyelitis is reported to have increased efficacy when compared to antibiotic therapy alone.[1,2] In Ha Van et al (1996), conservative surgery involving just the bone infected was shown to be superior to antibiotic therapy alone with the primary measure of outcome being time to healing; the average time to healing for only antibiotics was 462 days versus 181 days for surgery. Secondary surgical treatment was required in 40% of the antibiotic group; whereas, only 9.4% of primary surgical patients required the same correction.[2] However, 54% of the antibiotic group and 47% of the surgical group presented with concurrent peripheral vascular disease. This earlier study’s results could be confounded by the small sample size (67 patients) and the effect of peripheral arterial disease.

The International Working Group on the Diabetic Foot and Infectious Disease Society of America leave the choice of surgery or antibiotic treatment up to the clinician because many comparative studies do not exist that would encompass all diabetic patients that are seen.[3,4]

In 2008, Game et al published a retrospective case series on the effects of antibiotic therapy alone in patients without limb-threatening osteomyelitis of the foot in diabetics at a single center over a five year period.[5] This study was limited by a sample size of only 147 patients, but in the 113 patients who received only antibiotics, 93 patients attained complete healing with only that intervention (82.8%).[5] This study showed that stable patients without a limb threatening infection could receive antibiotics and successfully heal.

The article chosen for this critical appraisal and clinical application was a prospective randomized single-center comparative trial of 46 patients that only included diabetic patients with forefoot osteomyelitis. This study’s design is the gold standard for evaluating the efficacy difference between two therapeutic interventions through randomization protocols to limit selection bias and two clinical arms that differ only in intervention utilized.[6] The main benefit of this study is that it was the only study with an exclusion of all diabetic patients who had peripheral arterial disease allowing a focus on the subset of diabetics that the patient fits; therefore, this study by Lázaro-Martínez et al best fits the clinical question and context.

Critical Appraisal

The article by Lázaro-Martínez et al was a prospective randomized single-center comparative trial that took place from 2010 to 2012 at Madrid’s Complutense University Diabetic Foot Unit with follow-up after healing for 12 weeks.[7] The study compared the outcomes of the treatment of diabetic foot osteomyelitis secondary to neuropathic ulcers in patients who were treated exclusively with antibiotics versus patients who underwent conservative surgery. The study is the first of its kind to directly compare surgical and antibiotic therapy in diabetic patients with foot osteomyelitis and no peripheral arterial disease.

156 patients were selected on basis of the presence of a diabetic foot ulcer with underlying osteomyelitis. This step avoided a potential selection bias as all patients with foot osteomyelitis at the single hospital were considered initially. Next, patients were excluded or included based on study criteria. 52 patients were successfully computer-randomized into two similar groups: an antibiotic group and a surgical group. The only significant demographic difference between the groups was the average age: 75 and 62 in the antibiotic and surgical groups respectively. The age difference could introduce a confounding error as the younger surgical patients might be more likely to heal faster than the older patients in the antibiotic group.

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In the antibiotic group, antibiotics were given for up to 90 days or until the patient completed healing if earlier. In the surgical group, the same surgeon was used in all cases to remove the infected bone. The specimen was sent for pathology studies after which, the patient received 10 days of empiric antibiotics modified by bone culture biopsy results. The inclusion criteria for this study were an age of 18 years or older, neuropathic ulcer history with underlying osteomyelitis, and ability to attend follow-up appointments. The patients also had to agree to have current antibiotic therapy ceased for two weeks prior to randomization. The most significant exclusion criteria was the presence of peripheral arterial disease. The patient in question met the criteria to be included in this study.

The main primary outcomes were primary healing achieved exclusively with initially the same empiric or later targeted antibiotics in the antibiotic group and with the first surgical procedure in the surgical group. Primary healing was defined as complete epithelialization of the ulcer or the surgical wound. If reoperation happened after surgery or the antibiotics, that patient failed primary healing. Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) levels were utilized to track resolution of underlying osteomyelitis. No harms were associated with either group.

The study utilized a per protocol analysis as one antibiotic patient and five surgical patients who were randomized dropped out and were excluded from analysis. This analysis introduces an attrition bias since not all study participants were analyzed in groups to which they were originally assigned. The final analysis compared 24 antibiotic group patients to 22 surgical group patients. Blinding of patients and caretakers was not possible in this study due to foot differences apparent after surgery. Outcome assessors were not blinded. 75.0% of antibiotic patients achieved primary healing and 86.3% of surgical patients achieved primary healing (P=0.33). The time to healing was 7 weeks with antibiotics versus 6 weeks with surgery (P=0.72). These p-values indicate that a patient who meets the criteria of inclusion will have similar outcomes with surgery or antibiotic use for osteomyelitis of the diabetic foot.

There are three main limitations of this trial. Firstly, osteomyelitis was identified with a positive probe to bone test and x-ray. The gold standard for identifying osteomyelitis is a bone biopsy and culture.[8] The antibiotic group did not receive a confirmatory bone biopsy for osteomyelitis, so ulcer resolution not secondary to antibiotics could confound results. Secondly, not having intention to treat protocol limits the study as well. Dr. Lipsky notes in his 2014 review article for the Lázaro-Martínez et al study, “Treating Diabetic Foot Osteomyelitis Primarily with Surgery or Antibiotics: Have We Answered the Question?,” the intention to treat analysis including the six patients not currently analyzed would make a more compelling comparison of similarities in treatments; 72.0% of antibiotic protocol patients would show success versus 70.4% of surgical patients.[9] Finally, the power of the study is low due to the small sample size of the population which could cause a true difference between the treatments to be missed (a possible type II error). The study’s strengths are the deep tissue biopsy method for microbial sample obtainment, the cessation of all antibiotics two weeks prior to randomization, post-surgical antibiotic modification informed by cultures, and one surgeon performing all surgeries. There was no funding or publishing conflict reported.

Current Clinical Guidelines for the treatment of diabetic foot osteomyelitis give clinicians the choice of deciding surgical or medical management appropriateness.3-4 In this critical appraisal, there is limited Grade 2B evidence from a prospective controlled study as determined by the SORT Taxonomy to suggest that in a subset of diabetics with no peripheral arterial disease, similar outcomes can be expected with surgery or up to 90 days of antibiotics.[6] This evidence level means that although a randomized trial was completed, due to a small sample size, benefits and risks must be balanced with each other and both physician and patient preferences must be strongly considered.[6]

Clinical Application

The patient of interest fit the criteria of the Lázaro-Martínez et al trial. He was a male with a diabetic forefoot ulcer, suspected osteomyelitis, and no peripheral arterial disease in his injured limb. The patient’s age of 69 sits in the middle between the two average group ages of 75 and 62 for the antibiotic and surgical interventions respectively. Taking into account the Lázaro-Martínez et al results, this patient is just as likely to see similar results from long-term antibiotic use as from conservative surgery on his first metatarsal. This patient’s preference to avoid surgery can be upheld here, as no extra benefit would be derived provisionally from surgery over antibiotics. However, since the data set is so small, to increase the statistical power of the data, larger multicenter trials would be necessary to confirm the results across more patient populations with diabetic foot osteomyelitis in the absence of peripheral arterial disease. Performing such a large study however may prove difficult though as type II diabetes and peripheral arterial disease commonly co-occur. Additionally, long-term antibiotics would not be

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without risk as they could cause gastrointestinal disturbances or acute kidney injury, so appropriate monitoring of those two organ systems would be necessary when treating this patient.

Learning points:

1. Surgical and Long-term antibiotic use of up to 90 days have similar outcomes in diabetic patients with foot osteomyelitis and no peripheral arterial disease.
2. Tailoring antibiotics to a specific microbe informed by bone biopsy and culture can lead to better clinical outcomes in diabetic foot osteomyelitis.
3. Provider perception of surgery as more definitive for infection control and healing might play into clinical decision making such that surgery with clean margins is seen as the only absolute treatment.

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