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ORIGINAL ARTICLE

Discordant isolates in bone specimens from patients with recurrent foot osteomyelitis

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Abstract

We compared paired operative bone cultures (initial operation and reoperation) for 35 patients who experienced foot osteomyelitis treatment failure at a single hospital. Concordance was poor (kappa = 0.180). *Staphylococcus aureus*, gram negatives, and anaerobes were the most common discordant bacteria seen at reoperation, while *Enterococcus* was the most persistent.

Keywords Diabetic foot infection · Osteomyelitis · Bone biopsy

Introduction

Contemporary management of foot osteomyelitis typically results in treatment failure in 20–30% of cases [1–3]. Recent studies utilizing 16S RNA analysis demonstrating a wide variety of organisms present in diabetic foot ulcers and in diabetic foot osteomyelitis bone specimens [4, 5] raise the possibility that pathogenic organisms present but not identified at the time of the initial diagnosis of foot osteomyelitis may be at least partly responsible for the high rate of treatment failure. Many of the organisms identified in these 16S RNA studies are anaerobes; difficulty in growing anaerobic organisms in culture may be partly responsible for the low rates for anaerobes typically reported from clinical series reporting bone culture results [3, 4]. On the other hand, some findings suggest that the microbiome of foot ulcers changes over time, perhaps in association with the process of wound healing [6] and the effects of antibiotic regimens. Herein, we describe findings from paired bone cultures from patients with foot osteomyelitis who experienced treatment failure after initial management that included surgical intervention and an appropriate antibiotic course.

Methodology

We identified treatment failure among all cases of probable or definite osteomyelitis [7] at the Michael E. DeBakey Veterans Affairs Medical Center between 2011 and 2016. In 183 of 184 cases (99.5%), the diagnosis of probable or definite osteomyelitis was based on histopathology and/or microbiology cultures from surgical bone specimens. This identification was done using a comprehensive database of all patients treated for foot osteomyelitis during a time period when the treatment of foot osteomyelitis was primarily directed by a single surgical service in consultation with the infectious disease team. Treatment failure was defined as either: (1) unplanned resection of additional bone contiguous the previously treated area or (2) leg (above-ankle) amputation.

We use a multimodal approach to foot osteomyelitis at our institution, generally consisting of surgical resection of grossly affected bone followed by 2–12 weeks of antibiotic therapy selected based on bone culture results [3]. In the operating room, the skin of the foot is sterilized using a two-step iodine-based preparation solution. Samples from surgical bone specimens resected in the operating room are submitted to the microbiology laboratory for cultures and to the pathology laboratory for histopathology. Specimens submitted for culture are sent in a small volume of sterile saline to prevent desiccation prior to processing. Intraoperative antibiotics are given only after surgical specimens have been

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obtained. Antibiotics—preferentially oral but occasionally parenteral—are chosen organisms identified in operative bone cultures. Findings from these cultures at our center have previously been reported as 61% gram positive, 23% gram negative, 13% anaerobic, and 2% fungal. The most commonly isolated species is *Staphylococcus aureus* (18.4% of isolates), followed by *Enterococcus* species (10.9%), streptococcal species (10.6%), and *Staphylococcus epidermidis* (5.9%) [3].

Cases of treatment failure were included in this study if paired bone cultures were obtained—that is, bone cultures from the initial operation and from a reoperation for treatment failure. Cohen's kappa was calculated to estimate concordance between isolates seen at the initial operation and reoperation. RStudio version 1.0.143 was used for all statistical analyses. A p value of < 0.05 was considered statistically significant.

Results

Two hundred eight cases of definite or probable foot osteomyelitis were reviewed. Treatment failure occurred in 55 cases (26%), 35 of which had microbiology results from paired bone specimens. Initial cultures identified 70 bacterial and 1 fungal isolates, cultures at recurrence identified 77 bacterial and 3 fungal isolates. Overall concordance was poor (kappa = 0.180). Species and group-specific concordance ranged from poor to moderate (Table 1). *Enterococcus* species were among the most common isolates and was the most frequent organisms to be cultured at the initial operation and to remain at reoperation. In contrast, *Staphylococcus aureus*, gram negatives, and anaerobes more frequently were isolated for the first time at reoperation. *Streptococcal* species were frequently retrieved from cultures at initial intervention but rarely seen at reoperation.

Discussion

Investigators of a recent trial of antibiotics for soft tissue infection [8] have urged caution in drawing conclusions from expert opinion and/or observational series. Findings of their large trial were different from those of other smaller trials that may have been underpowered. The state of research on foot osteomyelitis is even more basic still. Guidelines on the management of diabetic foot infections [9], for example, suggest that an antibiotic regimen directed to organisms identified on conventional bone cultures may be more effective than an empiric regimen, citing a single observational series of 50 patients distributed in nine centers [10]. Many centers—including our own—opt for such directed antibiotic regimens as recommended by the guidelines rather than empiric regimens when treating foot osteomyelitis.

Our analysis suggests that among patients who experience foot osteomyelitis treatment failure after appropriate surgical and medical management, the organisms seen with conventional microbiology cultures at reoperation differ frequently from those seen at initial operation. This may have various meanings. First, organisms involved in pathogenesis may not be consistently identified by conventional cultures—an idea supported by 16S RNA analysis [4]. This may be related to the relative preponderance of various bacteria or to their propensity to grow in culture plates. Additionally, it is possible that the relative preponderance of organisms may fluctuate during treatment, and 16S RNA analysis of foot ulcers suggest that this is common.

These findings suggest the need to improve our understanding of the foot osteomyelitis on a very fundamental level. Further 16S RNA studies will help clarify whether fastidious organisms and organisms typically considered non-pathogens (such as fungal species [11]) play a role in the initial pathogenesis of osteomyelitis or in treatment failure. Large randomized trials, such as the recently initiated Veterans Health Administration trial evaluating the addition of empiric

Table 1 The frequency (and relative proportion) of various bacterial species seen at the initial operation and at reoperation for patients who experienced treatment failure for foot osteomyelitis

Isolate	Present at either operation	Seen only at initial operation	Seen at both operations	Seen only reoperation	Absent in both	Kappa
Staphylococcus aureus	14	4 (29)	3 (21)	7 (50)	21	0.154
Other *Staphylococcus* spp.	9	4 (44)	2 (22)	3 (33)	26	0.246
Streptococci	9	7 (78)	2 (22)	0 (0)	26	0.298
Enterococcus spp.	12	4 (33)	5 (42)	3 (25)	23	0.457
Corynebacterium spp.	10	3 (30)	3 (30)	4 (40)	25	0.340
Pseudomonas spp.	5	1 (20)	1 (20)	3 (60)	30	0.278
Escherichia coli	9	4 (44)	1 (11)	4 (44)	26	0.067
Other gram negatives	14	7 (50)	1 (7)	6 (43)	21	− 0.102
Anaerobes	11	6 (55)	0 (0)	5 (45)	24	− 0.185

rifampin therapy, will be a critical complement to microbiological analyses. These findings may also suggest that, in patients who experience treatment failure, further antibiotic therapy should cover *Staphylococcus aureus*, gram negative bacteria (including *Pseudomonas aeruginosa*), and anaerobic bacteria. Clinicians that typically pursue primary antibiotic therapy for foot osteomyelitis should reconsider surgical resection of bone for cases in which *Enterococcus* species are identified by percutaneous bone biopsy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This project was approved by the Baylor College of Medicine Institutional Review Board (protocol H-34858) and by the Michael E. DeBakey Veterans Affairs Medical Center Research Committee (protocol 15A12.HB). All research was consistent with principles outlined in the Helsinki Declaration.

Informed consent Individual consent was not obtained for this study, as it was a retrospective review.

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