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BRIEF REPORT

Microbiologic and Histopathologic Features of Pedal Osteomyelitis

Julieta Madrid-Morales,[1] Marissa M. Maier,[1,2] Amy Boda,[2] Robert Bosch,[2] and Kristina L. Bajema[1,2]

[1]Department of Medicine, Division of Infectious Disease, Oregon Health & Science University, Portland, Oregon, USA, and [2]Department of Medicine, Division of Infectious Disease, Veterans Affairs Portland Health Care System, Portland, Oregon, USA

The value of microbiology and histopathology in the diagnosis of neuropathic foot osteomyelitis remains poorly understood. In this retrospective cohort study, we evaluated the concordance of microbiology and histopathology results from bone resections and found similar proportions of bacterial growth in samples with and without histopathologic evidence of osteomyelitis.

Keywords. diagnosis; histopathology; microbiology; osteomyelitis.

Diabetes mellitus (DM) is highly prevalent in the United States, affecting 15% of the adult population and disproportionately affecting veterans [1, 2]. Complications such as peripheral artery disease and neuropathy contribute to the development of diabetic foot ulcers, which can be complicated by infection in 50% to 60% of cases, with diabetic foot osteomyelitis occurring in 20% [3]. Diabetic foot ulcers are the leading cause of nontraumatic limb amputations [3, 4], with crude amputation rates of up to 6.1% per 1000 US adults with DM [1, 4]. Up to 14% of veterans engaged in care are at moderate to high risk of lower extremity amputations secondary to complications related to DM [5]. While DM is the most common cause of neuropathic foot osteomyelitis, other conditions and exposures, such as HIV and chemotherapy agents, contribute to peripheral neuropathy and neuropathic foot osteomyelitis.

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Correspondence: Julieta Madrid-Morales, MD, Department of Medicine, Division of Infectious Disease, Oregon Health and Science University, 3181 SW Sam Jackson Park Road L457, Portland, OR 97239-3098 (julietamadrid1992@gmail.com); Kristina L. Bajema, MD, MSc, Department of Medicine, Division of Infectious Disease, Veterans Affairs Portland Health Care System, Portland, OR (Kristina.Bajema@va.gov); Marissa M. Maier, MD, Department of Medicine, Division of Infectious Disease, Veterans Affairs Portland Health Care System, Portland, OR (Marissa.Maier@va.gov).

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Despite the significant impact on quality of life and mortality [4], the optimal diagnosis of neuropathic foot osteomyelitis remains poorly understood. As outlined by the Infectious Diseases Society of America and the International Working Group on the Diabetic Foot, a bone sample sent for microbiology and histopathology analysis remains the accepted standard criterion to establish the presence of osteomyelitis and is used to guide clinical care [6, 7]. However, with practice heterogeneity in sample collection, microbiology alone cannot differentiate colonization from infection [8], and culture concordance between sample collection techniques (deep ulcer swab vs bone biopsy) is low (22%–38%) [7, 9, 10]. Histopathology may be a more accurate marker for osteomyelitis, but it is also limited by interobserver variability [11]. Furthermore, agreement between microbiology and histopathology in establishing the presence of osteomyelitis is generally low (41%–56%) [12–14]. We sought to determine the proportion of veteran patients with neuropathic foot osteomyelitis, including diabetic foot osteomyelitis, who had bone samples collected for microbiology and histopathology and to describe agreement between these results.

METHODS

Design

We conducted a single-center retrospective cohort study of patients with suspected neuropathic osteomyelitis who had forefoot or midfoot bone samples obtained via amputation, debridement, or resection in the operating room, minor procedure room, or bedside as part of usual clinical care in the Veterans Affairs (VA) Portland Health Care System between 1 January 2017 and 31 December 2019. We evaluated the proportion of bone samples sent for microbiology, histopathology, or dual testing and described corresponding results, including agreement between tests.

Data Source

We extracted data from the VA Corporate Data Warehouse, a nationwide repository of clinical and procedural data. Through structured chart review, we independently verified date of sample collection, procedural or surgical technique (swab, biopsy, resection), sample type (bone), anatomic site, laterality (left vs right), culture growth, and presence or absence of osteomyelitis on histopathology. Data access and management followed the VA Office of Information Technology policy.

Study Population

We included individuals in VA care, defined as ≥2 outpatient or ≥1 inpatient encounter in the 18 months preceding the index bone sample collection, who had forefoot or midfoot

bone samples obtained as a part of clinical care for pedal infection in a VA Portland operating room, minor procedure room, or bedside between 1 January 2017 and 31 December 2019. We defined the index procedure as the first eligible bone sample obtained during the study period. We excluded individuals who had prior operative or procedural intervention on the ipsilateral foot within 1 year prior to the index procedure and any individuals with hindfoot or more proximal bone samples obtained during the index procedure.

Patient Characteristics

We evaluated demographic data (birth sex, death date, age, race, and ethnicity), laboratory data (hemoglobin A_{1c}), and procedural data: sample collection date and location (operating room, minor procedure room, bedside), sample type (swab, biopsy, resection), specimen collected (phalanx, toe, foot), laterality, microbiology, and histopathology results. Index procedure bone samples were defined as having positive microbiology based on any bacterial growth and positive histopathology based on pathologist assessment of acute or chronic osteomyelitis.

Analysis

We calculated the proportion of individuals with microbiology and histopathology results available vs microbiology or histopathology results alone, the proportion of microbiology and histopathology samples with positive results, and intertest agreement using the Cohen κ coefficient. In sensitivity analysis, we excluded samples with isolated growth of *Corynebacterium* spp or coagulase-negative staphylococci other than *Staphylococcus lugdunensis*, which may be considered nonpathogenic in the appropriate clinical setting. Results were also stratified by whether antibiotics were received within 7 days prior to the index sampling.

RESULTS

Between 1 January 2017 and 31 December 2019, there were 672 bone resections performed among 393 individuals. We excluded 62 hindfoot or more proximal resections, 233 ipsilateral resections occurring in the year prior to the index procedure, and 3 resections among individuals not in VA care, yielding 379 eligible resections among 342 patients. The cohort was 97% male (n = 333) with a median age of 69 years; 82% (n = 281) were White and 92% (n = 315) were non-Hispanic. Most patients (63%, n = 217) had a hemoglobin A_{1c} >6.5%, and 24% (n = 82) died within 2 years of the index procedure.

Of the 379 resections, 44% (n = 167) had microbiology and histopathology results, 11% (n = 44) had microbiology alone, and 45% (n = 172) had histopathology alone. Of resections with microbiology and histopathology results, 86% (144/167) had bacterial growth and 58% (97/167) had osteomyelitis on histopathology; bacterial growth was present in 91% and 80% of specimens with and without osteomyelitis on histopathology, respectively (Table 1). Positive histopathology was present in 61% and 39% of specimens with and without bacterial growth. The corresponding κ was 0.12. Of those with microbiology alone, 93% (41/44) had bacterial growth. Of those with histopathology alone, 50% (87/172) had osteomyelitis.

After exclusion of 21 samples with isolated growth of *Corynebacterium* spp or coagulase-negative staphylococci from resections with microbiology and histopathology results, 84% (123/146) had bacterial growth and 60% (87/146) had osteomyelitis on histopathology; bacterial growth was present in 90% (78/87) and 76% (45/59) of specimens with and without osteomyelitis on histopathology, respectively, and positive histopathology results were present in 63% (78/123) and 39% (9/23) of specimens with and without bacterial growth. The corresponding κ was 0.15.

Antibiotics were administered within 7 days prior to sampling in 124 of 167 (74%) specimens with microbiology and histopathology results (Table 2). Among 43 specimens not collected after antibiotics, bacterial growth was present in 95% (19/20) and 83% (19/23) with and without histopathologic evidence of osteomyelitis, respectively. The corresponding κ was 0.12.

DISCUSSION

In this single-center 3-year cohort of veterans receiving care for pedal infection, similar proportions of bone specimens were

Table 1. Patterns of Osteomyelitis and Bacterial Growth Among Bone Samples With Histopathology and Microbiology Results

	Microbiology					
	All Eligible Specimens (n = 167)			Specimens With Exclusions (n = 146)[a]		
	Bacterial Growth	No Bacterial Growth	Proportion With Bacterial Growth, %	Bacterial Growth	No Bacterial Growth	Proportion With Bacterial Growth, %
Histopathology						
Osteomyelitis	88	9	91	78	9	90
No osteomyelitis	56	14	80	45	14	76
Proportion with osteomyelitis, %	61	39		63	39	

Data are presented as frequency unless noted otherwise.

[a]Specimens with isolated growth of *Corynebacterium* spp and coagulase-negative staphylococci were excluded.

Table 2. Patterns of Osteomyelitis and Bacterial Growth According to Prior Receipt of Antibiotics

	Microbiology					
	Any Antibiotic Prescribed (n = 124)			No Antibiotics Prescribed (n = 43)		
	Bacterial Growth	No Bacterial Growth	Proportion With Bacterial Growth, %	Bacterial Growth	No Bacterial Growth	Proportion With Bacterial Growth, %
Histopathology						
Osteomyelitis	69	8	90	19	1	95
No osteomyelitis	37	10	79	19	4	83
Proportion with osteomyelitis, %	65	44		50	20	

Prior receipt of antibiotics within 7 days before bone specimen collection. Data are presented as frequency unless noted otherwise.

sent for histopathology alone and both microbiology and histopathology, while only a small proportion was sent for microbiology alone. In the group with microbiology and histopathology results, the proportion with bacterial growth among those with histopathologic evidence of osteomyelitis was only slightly higher than the corresponding proportion among those without histopathologic evidence of osteomyelitis, even after accounting for potential nonpathogenic bacteria and prior receipt of antibiotics. Intertest agreement between microbiology and histopathology results was low.

Consistent with other studies, our findings suggest that positive microbiology may overcall the diagnosis of osteomyelitis [8, 14], although there is no gold standard or consensus definition between microbiology and histopathology [6]. While culture data may be useful to inform antibiotic selection, there remains uncertainty to whether it should be relied on solely to guide the decision to use antibiotics after surgical debridement or resection.

Limitations of our study include a single-institution setting, practice variation in sample collection technique and testing, a lack of information on the type of procedure performed (resection vs bone biopsy), and the absence of complete data on whether resection bone specimens were from proximal (clean) margins. Histopathology slides were reviewed by multiple pathologists during the study period, which may have affected interrater reliability of histopathology and, in turn, concordance with microbiology results.

To build on these findings, we plan to extend the evaluation over a longer study period and determine whether concordance of microbiology and histopathology results is associated with infection progression, resulting in subsequent resection or amputation, as well as infection-related hospital readmission.

Notes

Disclaimer. The contents of this article do not necessarily represent the views of the US Department of Veterans Affairs or the US government.

Patient consent statement. The present study does not include factors necessitating patient consent.

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References

1. Centers for Disease Control and Prevention. National diabetes statistics report, 2022. Atlanta, GA: US Department of Health and Human Services, **2022**.
2. Liu Y, Sayam S, Shao X, et al. Prevalence of and trends in diabetes among veterans, United States, 2005–2014. Prev Chronic Dis **2017**; 14:170230.
3. Edmonds M, Manu C, Vas P. The current burden of diabetic foot disease. J Clin Orthop Trauma **2021**; 17:88–93.
4. Brownrigg JR, Davey J, Holt PJ, et al. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. Diabetologia **2012**; 55:2906–12.
5. Veterans Health Administration. Amputation risk (PAVE) cube—pyramid. VHA Support Service Center. Updated 9 June 2024. Available at: https://vssc.med.va.gov/VSSCMainApp/products.aspx?PgmArea=55. Accessed 13 June 2024.
6. Senneville É, Albalawi Z, van Asten SA, et al. IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDSA 2023). Diabetes Metab Res Rev **2024**; 40:e3687.
7. Uçkay I, Gariani K, Pataky Z, Lipsky BA. Diabetic foot infections: state-of-the-art. Diabetes Obes Metab **2014**; 16:305–16.
8. Mijuskovic B, Kuehl R, Widmer AF, et al. Culture of bone biopsy specimens overestimates rate of residual osteomyelitis after toe or forefoot amputation. J Bone Joint Surg Am **2018**; 100:1448–54.
9. Elamurugan TP, Jagdish S, Kate V, Chandra Parija S. Role of bone biopsy specimen culture in the management of diabetic foot osteomyelitis. Int J Surg **2011**; 9:214–6.
10. Senneville E, Melliez H, Beltrand E, et al. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. Clin Infect Dis **2006**; 42:57–62.
11. Meyr AJ, Singh S, Zhang X, et al. Statistical reliability of bone biopsy for the diagnosis of diabetic foot osteomyelitis. J Foot Ankle Surg **2011**; 50:663–7.
12. Bonnet E, Maulin L, Senneville E, et al. Clinical practice recommendations for infectious disease management of diabetic foot infection (DFI)—2023 SPILF. Infect Dis Now **2024**; 54:104832.
13. Meyr AJ, Seo K, Khurana JS, Choksi R, Chakraborty B. Level of agreement with a multi-test approach to the diagnosis of diabetic foot osteomyelitis. J Foot Ankle Surg **2018**; 57:1137–9.
14. Jin LJ, Chia RX, Neilson W, et al. Evaluation of routine proximal bone analysis for microbiology and histopathology in diabetes-related foot infections and osteomyelitis. ANZ J Surg **2024**; 94:445–50.