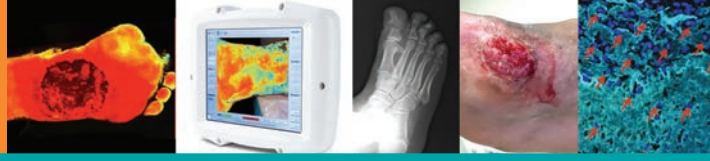

Diagnosis and Treatment of Diabetic Foot Osteomyelitis

New technologies show promise in managing this challenging condition.

BY CHALEN YANG, MS AND STEPHANIE WU, DPM, MSC

Introduction

A report from the Center for Disease Control in 2018 shows that more than 100 million U.S. adults are now living with diabetes or pre-diabetes.[1] This devastating disease kills more Americans than acquired immune deficiency syndrome (AIDS) and breast cancer combined.[2] This report confirms that the rate of new diabetes diagnosis remains steady, with nearly one in four adults living with diabetes unaware of their condition.[1]

Diabetes is the seventh leading cause of death in the United States in 2015[3] and continues to climb due to increasing obesity, sedentary lifestyles, and an aging population.[4] One in four patients with diabetes will develop a foot ulcer during their lifetime, and during the course of treatment, 60% of these ulcers are complicated by soft tissue infections with bone involvement affecting one in five infected ulcers.[5]

Osteomyelitis

Osteomyelitis is described as a broad group of infectious diseases that involves the bone and/or bone marrow.[6] It can arise hematogenously via extension from a contiguous infection, or by direct inoculation during surgery or trauma.[6,7] Patients with soft tissue infections or skin ulcerations that have been present for more than a week, especially if located over a bony prominence, are at risk for contiguous bone involvement.[8]

Osteomyelitis in patients with diabetes is largely a consequence of several complications of the disease, including neuropathy, vasculopathy, and defects in immunity and wound healing.[8] Osteomyelitis can be categorized as acute or chronic based on histopathologic results.[7]

Acute osteomyelitis secondary to hematogenous spread or direct inoculation causes bacteria to proliferate within the bone and induces an acute response within the medullary cavity, leading to increased intramedullary pressure and vascular congestion.[7,9] Acute infection if inadequately treated will progress to chronic osteomyelitis, resulting in osteonecrosis that is caused by a disruption of the intraosseous and periosteal blood supply during the acute stage.[9]

Osteomyelitis is a leading cause of hospitalization and lower limb amputation worldwide, costing well above $40,000 per event.[4,10] Although diabetic foot osteomyelitis has been well-described for over 25 years, optimal treatment, be it conservative or surgical, the optimal route of antibiotic delivery, and the optimal duration of antibiotic therapy remain unclear.[11] This article will discuss some of the current updates in the treatment and diagnosis of diabetic foot osteomyelitis with a specific focus on advanced imaging modalities in terms of current evidence as well as emerging technological advances.

Treatment

Surgical resection of infected bone and tissues is typically the traditional approach for diabetic foot infection and osteomyelitis.[7] Surgery is rapidly effective in reducing the bacterial load at the infected site and can remove necrotic tissues that cannot be reached by antibiotics; however, this procedure is extremely invasive, leaves the patient's foot disfigured, and can potentially introduce new bacteria to the wound.[12] Moreover, recurrence of diabetic foot osteomyelitis has been noted in about 20% to 50% of the cases despite the use of surgical debridement and long-term antibiotic therapy.[11,13]

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In the modern management of diabetic foot osteomyelitis that was published in January of this year, key opinion leaders in infectious disease recommended that "Antibiotic therapy, preferably with oral agents guided by results of bone culture, for a duration of no more than 6 weeks,

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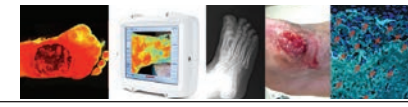

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appears to be as safe and effective as surgery in cases of uncomplicated forefoot diabetic foot osteomyelitis."[14]

Given advances in the diagnosis and treatment of diabetic foot osteomyelitis, expert recommendations are that most cases can be managed via a conservative approach by treating either with antibiotics alone or with surgery removing as little bone and soft tissue as necessary in cases of deep abscess, necrotizing fasciitis, gangrene, or when the infection is not responding either clinically or radiographically to apparently appropriate antibiotic therapy.[14]

Whether osteomyelitis can be treated with or without the removal of chronically infected bone is still debated due to the low success rates reported in previous studies using antimicrobial therapy alone.[12] One potential explanation for the high recurrence rate of diabetic foot osteomyelitis may be the existence of biofilms in the bone. Johani and colleagues obtained intraoperative bone specimens from 20 consecutive subjects with suspected diabetic foot osteomyelitis.[15] Of the 20 subjects, 19 had an infected diabetic foot ulcer.

The authors analyzed the bone specimens via next-generation DNA sequencing, scanning electron microscopy, and peptide nucleic acid fluorescent in situ hybridization with confocal microscopy, and identified microbial aggregates in biofilms in 80% of the bone specimens.[15] The findings may be indirectly supported by a single-center retrospective cohort survey of recurrent diabetic foot infections.

Lebowitz and co-workers followed 482 subjects for a median of 3.3 years after the first occurrence of diabetic foot infections and noted 2,257 total episodes of infection with a median of 7.6 months interval between recurrent episodes.[16] The causative pathogens was noted to be the same as in previous episodes in 43% of recurrent cases with no significant increase in the incidence of antibiotic resistance over the episodes.[16]

The authors concluded that previous diabetic foot infection episodes did not predict a greater likelihood of antibiotic-resistant isolate in subsequent episodes, and broadening the spectrum of empiric antibiotic therapy for recurrent episodes of diabetic foot infections did not appear necessary.[16] Needless to say, larger studies are needed to confirm or refute these findings.

Diagnosis

A suspected pedal bone infection in diabetic patients should be considered a medical alert since early diagnosis plays a key role in decreasing morbidity, mortality, and amputation rate of patients.[17] Early diagnosis of osteomyelitis can significantly improve the success of medical therapy, decrease the rate and degree of complications, and reduce the need for amputation.[18-20] Diabetic foot osteomyelitis is generally diagnosed by a combination of clinical evaluation, serum inflammatory markers, and plain radiographs.[14]

Abnormal findings on plain radiographs typically show soft tissue changes, muscle swelling, and blurring of the soft tissue planes.[20] However, in patients with osteomyelitis, radiographic changes may be less sensitive as they require several weeks to be visualized and may be non-specific because of commonly co-existing osseous distortions.[21] Radiographic abnormalities associated with osteomyelitis may not become visible until 10 to 21 days after onset.[22] Moreover, it typically takes about 30%-50% of bone density loss before radiographs can detect the disease.[22,23]

Radiographs are not a sensitive indicator of acute bone infections and are therefore often supplemented with advanced imaging modalities and bone biopsies when necessary. Currently available advanced imaging techniques with various associated advantages and disadvantages offer a complementary approach to diagnosing diabetic foot osteomyelitis. In general, these modalities require that the patient be injected with a radiopharmaceutical or contrast agent prior to imaging with the specified modality. Appropriate imaging selection may therefore vary depending on circumstances of the patient, on-site equipment and expertise availability, and of course cost.[24]

Magnetic Resonance Imaging

Of the advanced imaging modalities, magnetic resonance imaging or MRI has long been recognized as an accurate technique for detecting osteomyelitis and is one of the most commonly utilized advanced imaging techniques in the United States.[25,26] MRI has excellent bone and soft tissue contrast which aids the assessment of infectious bone and soft tissue involvement; however, MRI does have its limitations.[18]

MRI changes can be detected in any process that results in bone marrow replacement or infiltration.

MRI changes can be detected in any process that results in bone marrow replacement or infiltration. The efficacy in accurately evaluating osteomyelitis in the presence of ischemia is unclear[25] and more research is needed to fully understand the relationship between osteomyelitis and ischemia. Other complications such as bone trauma, surgery, or fracture in combination with bone infection cause localized bone marrow edema, which may persist for many months, rendering MRI unreliable for monitoring osteomyelitis resolution.[26]

Lauri and colleagues evaluated the diagnostic performance of various advanced modalities including MRI, radio-labeled white blood cell (WBC) scintigraphy (either with 99mTc-hexamethylpropyleneamineoxime (HMPAO) or 111In-oxine), and [18F]fluorodeoxyglucose positron emission tomography (18F-FDG–PET)/computed tomography in a systemic review using Cochrane criteria).[24] The authors found MRI to have a sensitivity of 93% (95% Confidence Interval 82, 97), a specificity of 75% (63, 84), a diagnostic odds ratio of

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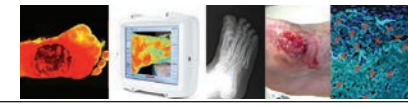

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37 (11.3, 121.3), a positive likelihood ratio of 3.66 (2.1, 6.4), and a negative likelihood ratio of 0.10 (0.04, 0.26).[24]

Findings of the systematic review and meta-analysis suggest that 99mTc-HMPAO–labeled WBC scintigraphy and 18F-FDG–PET/CT offer the highest specificity for diagnosing diabetic foot osteomyelitis while demonstrating comparable sensitivity to the other advanced imaging techniques including MRI and 111In-oxine-labeled WBC scintigraphy.

Radiolabeled White Blood Cell Scintigraphy

Radiolabeled leukocytes for infection imaging has emerged to become an effective method for diagnosing various lesions, such as osteomyelitis, cellulitis, Crohn's disease, and more.[27] WBC imaging is usually performed 18-30 hours after re-infusion of labeled cells. The uptake of isotopes depends on intact chemotaxis, number and types of cells labeled, and the cellular component of a particular inflammatory response.[6]

One of the main advantages to radiolabeled WBC scintigraphy is the marked improvement in specificity, especially in the diagnosis of osteomyelitis. Moreover, prospective studies found that WBC scintigraphy performed while the patient is under or has just completed antibiotic therapy retains a high sensitivity and specificity for osteomyelitis, perhaps even greater than for MRI for detecting residual disease.[24,26]

While WBC scintigraphy is more specific in detecting active diabetic foot infection in comparison to an MRI, it still imposes a major limitation when trying to distinguish soft tissue infection from bone involvement, with the biggest disadvantage of having low spatial resolution and sensitivity.[6,8,26] A variety of radiopharmaceuticals, including antibodies or antibody fragments against granulocytes, have been employed to better image infections.[6,22]

Of the two more commonly used radiopharmaceuticals, 99mTc-HMPAO and 111In-oxine, the 2017 systematic review and meta-analysis found 99mTc-HMPAO–labeled WBC scintigraphy to offer the highest specificity.[24] While 99mTc-HMPAO and 111In-oxine demonstrated similar sensitivity, 91% versus 92% respectively, 99mTc-HMPAO yielded significantly higher specificity at 92% as compared to 111In-oxine at 75%. The diagnostic odds ratio was also significantly higher for 99mTc-HMPAO at 118 versus 34 for 111In-oxine.

The positive likelihood ratio for 99mTc-HMPAO was 12, and for 111In-oxine 3.6. The negative likelihood ratio for both radiopharmaceuticals was the same at 0.10.[24]

Technetium-99 White Blood Cell Single-Photon Emission Computed Tomography

Metastable nuclear isomer technetium-99 white blood cell single-photon emission computed tomography (99mWBC-SPEC/CT) is a novel imaging technique that was developed to increase the anatomic localization of infection.[28] Planar scintigraphy has been used for years as standard imaging for infection, and the need for improved localization was met by SPEC/CT. This allows for more detailed 3-dimensional localization which can provide crucial information, particularly in patients with osteomyelitis.[22]

99mWBC-SPEC/CT has the ability to detect abnormalities within a few hours after injection and is capable of producing high-resolution images.[6] The combination of SPEC/CT, localization of labeled WBC, and high-resolution diagnostic images improves both the assessment of local WBC scinitigraphic intensity and depicts cortical bone destruction caused by the infection.[26] This technique provides semi-quantitative grading of WBC, a characteristic that is not discernible by clinical examination, and has significantly improved diagnostic accuracy over some of the other scintigraphy procedures.[21,29]

Prior studies found 99mWBC SPEC/CT imaging to be 88-90% sensitive, 56-71% specific, with a 70% positive predictive value (PPV), and a 83% negative predictive value (NPV) in diagnosing diabetic foot infections;[26,28] however, pre-existing fractures or hardware can adversely affect the specificity, dramatically decreasing it down to 35%.[6,22]

99mWBC-SPEC/CT has the ability to detect abnormalities within a few hours after injection and is capable of producing high-resolution images.

Not only is WBC SPEC/CT useful in diagnosing bone infections, but it potentially has other uses depending on which SPEC agents are intravenously injected. For example, gallium-67 (67Ga) citrate binds to transferrin in the plasma and specifically monitors musculoskeletal infection by the uptake of granulocyte or bacteria.[6,8] However, 99mTC diphosphonate is taken up into the calcium moiety of bone mineral matrix and monitors osteoblast activity, not bone infection.[6,22]

Because mesenchymal cells and osteoblasts work concomitantly with osteoclasts to degrade the extracellular matrix in times of inflammation,[6] bone scanning is only helpful in determining osteomyelitis in the absence of other pathology that may cause bone remodeling to occur.[8]

99mWBC-SPEC/CT may also be helpful in predicting recurrences of diabetic foot infections. The International Working Group on the Diabetic Foot (IWGDF) guidelines consider the best way to define treatment success is the absence of infection recurrence for 12 months after cessation of treatment.[13]

Vouillarmet, et al. found that WBC-SPEC/CT could predict osteomyelitis remission at the end of antibiotic therapy with a NPV of 100%. The main drawbacks for 99mWBC-SPEC/CT imaging include the laborious preparation, the need for specialized equipment, and handling of potentially infectious blood.[22] Because the test is time-consuming and not widely available, it is not recom-

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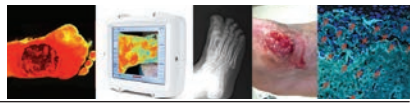

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mended for routine care.[13]

Nuclear medicine agents are also unstable and have a short half-life,[6] which makes it difficult for continual infection monitoring in prolonged durations. Nevertheless, the development of hybrid imaging in nuclear medicine is a significant advancement in early diagnosis of patients suspected of having diabetic foot infections.

Emerging Modalities

One of the emerging technological advances is the use of high-resolution spectral analysis to help identify bacterial signature in infected diabetic foot ulcers in real time, without any contact with the wound. High-resolution spectroscopy analyzes changes in the spectrum of the reflected visual light from the wound center and peri-wound area with estimated multispectral signature of bacteria to identify the presence of bacteria in wound infections.[30] Poosapadi Arjunan and colleagues conducted a prospective pilot study and found that spectral coefficients directly correlated with results from the wound swab with 100% sensitivity, with 100% NPV to identify the presence of the bacteria that caused the infection in the wound.[30] While further studies are needed, this technology may provide objective real time evaluation of wound infection status to help with clinical assessment of diabetic foot infections.

Timely actions along with meticulous evaluations of various parameters are paramount to decreasing morbidity, mortality, and the amputation rate of patients.

Conclusion

Diabetic foot osteomyelitis is difficult to diagnose and treat, and is often associated with a high rate of recidivism and limb loss. The management of diabetic foot infections and osteomyelitis remains challenging and requires inter-professional collaboration from various specialties including cooperation from the patient and caretakers. Timely actions along with meticulous evaluations of various parameters are paramount to decreasing morbidity, mortality, and the amputation rate of patients. New imaging technologies and novel molecular techniques show promise in improving the diagnosis and treatment of diabetic foot infections. **PM**

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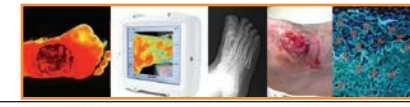

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