Diabetic Foot Infection Guideline Team

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Diabetic Foot Infections

Patient population: Adult diabetic patients.

Objectives: Improve quality of care for diabetic foot infections by optimizing diagnosis and medical therapy, use of imaging and use of subspecialty consultation.

Key points

Definitions. Diabetic foot infection (DFI) is a soft tissue or bone infection that is often associated with neuropathy or peripheral arterial disease in diabetic patients. DFI is often, but not always, preceded by a diabetic foot ulceration (DFU). Presence of DFU alone does not imply infection.

Diagnosis. The general evaluation of a patient with a suspected diabetic foot infection is summarized in Figure 1. History should focus on acuity and severity of the infection and physical exam should assess the skin, vascular, neurological and musculoskeletal systems. *[I-C]* Grading of severity can be done using the Infectious Diseases Society of America classification scheme (Table 1). *[I-C]* Ankle Brachial Index and Toe Brachial Index (ABI/TBI) measurements should be taken to evaluate for underlying peripheral vascular disease. Perform an initial x-ray to evaluate depth of infection. *[I-C]* If a patient does not have a current A1c result available, obtain upon hospital admission.

Cultures.

Obtain post-debridement soft tissue cultures rather than superficial swabs for evaluation of infected diabetic foot ulcers. *[I-C]*

If wound swab is the only available method of obtaining a culture, perform it after debriding and cleaning the wound. *[II-E]*

If osteomyelitis is suspected, obtain bone culture to guide antibiotic therapy rather than soft tissue culture if clinically feasible; do not obtain superficial swabs. *[I-C]*

When obtaining bone specimens, send the specimen for both histopathology and culture, as either can make the diagnosis of osteomyelitis. *[I-D]*

Imaging (Table 2).

Obtain foot radiographs for initial evaluation of suspected non-superficial soft tissue infection or osteomyelitis. *[I-C]*

Perform MRI as the next imaging test if soft tissue abscess is suspected. *[II-E]*

If osteomyelitis is suspected despite negative or equivocal radiograph, or if additional imaging is needed to evaluate the extent of osteomyelitis, perform an MRI as the next imaging test. *[I-C]*

Obtain a triple-phase bone scan in combination with a tagged WBC scan if MRI cannot be obtained but further evaluation of osteomyelitis is needed. *[I-C]*

Treatment.

Delay antibiotic initiation until after soft tissue cultures are obtained in patients with mild and moderate wound infections and without evidence of active cellulitis (Table 1). *[II-E]*

Consult the appropriate surgical service for all moderate and severe infections (Figure 1). *[II-E]*

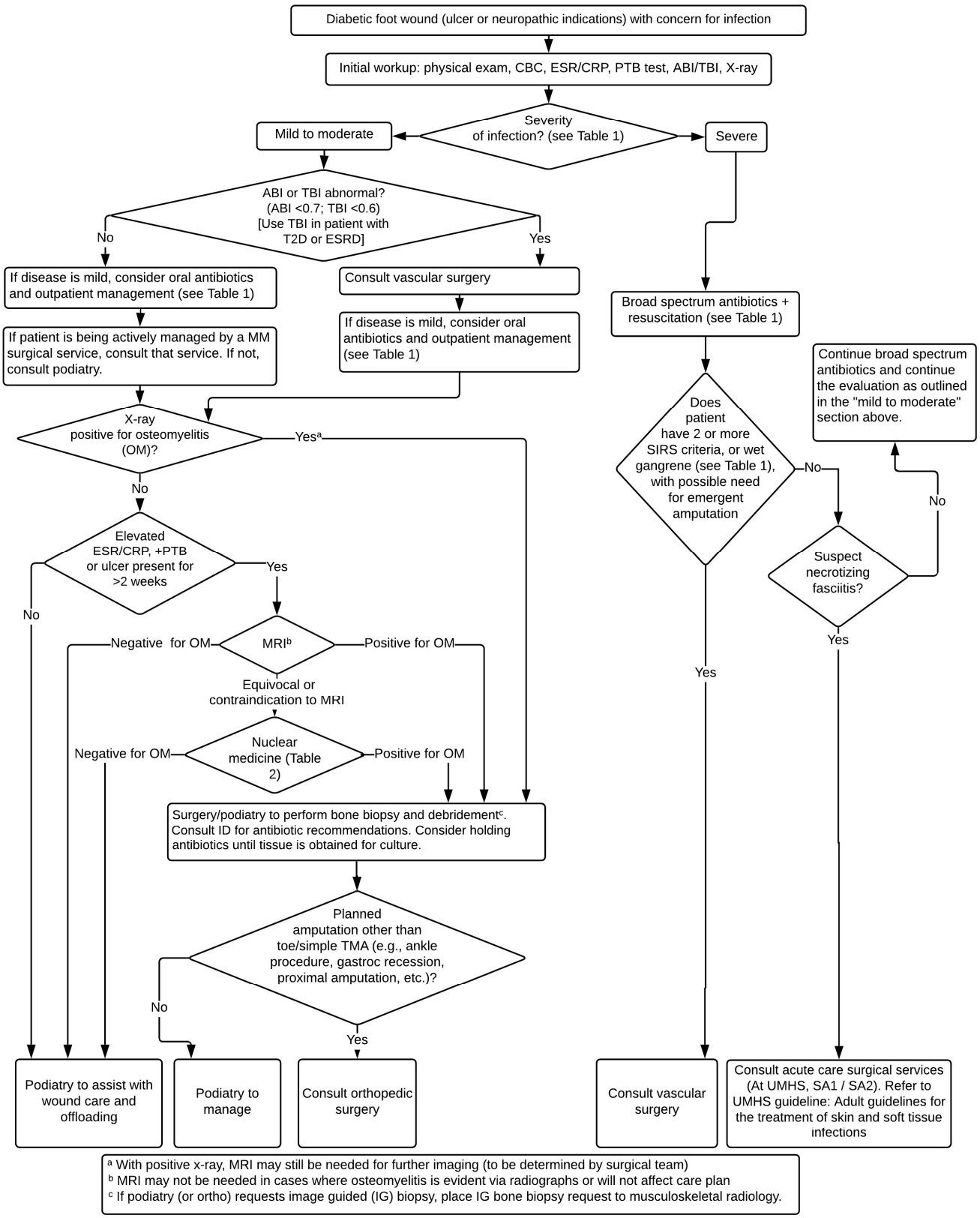
Wound care, including debridement when necessary, as well as off-loading wound pressure are key components to effective healing. *[I-C]*

Regardless of disease severity, all patients should receive coverage for *Staph aureus* and *Strep spp.* Patients with severe disease should receive antibiotics that include coverage for MRSA and *Pseudomonas aeruginosa* (Table 1). *[II-E]*

Empiric treatment should also target known pathogens from patient's previous microbiology results. *[I-D]*

***Strength of recommendation:**
I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.
Level of evidence supporting a diagnostic method or an intervention:
A = systematic reviews of randomized controlled trials with or without meta-analysis, B = randomized controlled trials, C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control), D = individual observation studies (case study/case series), E = expert opinion regarding benefits and harm

Figure 1. Approach to the patient with a diabetic foot infection



ABI: ankle/brachial index; TBI: toe/brachial index; CBC: complete blood count; ESR/CRP: Erythrocyte sedimentation rate and C-reactive protein; ESRD: end-stage renal disease; PTB: probe to bone; OM: osteomyelitis, SA1 and SA2: acute care surgery teams; TMA: Transmetatarsal amputation

Table 1. Empiric Antibiotic Therapy Stratified by IDSA Disease Severity and Risk Factors for MRSA and Gram-negative Bacilli

Disease Severity	Risk Factors Considerations	Empiric Antibiotic Treatment[a-c]
Minor Infection Infection present with 2 or more of: Local swelling or induration Erythema <2cm around ulcer Local tenderness or pain Local warmth Purulent discharge Local infection involving skin and subcutaneous tissue only without systemic signs. Other causes of inflammatory response should be excluded (gout, trauma, Charcot arthropathy, fracture, thrombosis, venous stasis)	Empiric Oral antibiotic therapy is appropriate if patient doesn't meet criteria for moderate or severe infection	Preferred option: Cephalexin 500mg PO QID Previous MRSA infection: Add trimethoprim/sulfamethoxazole DS 1-tab PO BID-TID. (Consider higher dosing if patient is greater than 80 kg or has extensive disease.) Alternative for cephalosporin allergy: Linezolid 600 mg PO BID
Moderate Infection Local infection with erythema >2 cm or involving deeper structures and no systemic inflammatory response	Hemodynamically stable patient presenting with acute diabetic foot infection, without relapse or reinfection, or risk factor for Gram-negative/*Pseudomonal* infection (see below)	Consider holding antibiotics until tissue is obtained for culture. Preferred option: vancomycin
	Anti-pseudomonal gram-negative coverage is indicated if: • recurrent or relapsed diabetic foot infection • previously isolated gram-negative pathogen • patient received broad-spectrum antibiotic therapy in the previous 90 days • recent hospitalization >2 days in the previous 90 days • wound was exposed to fresh water (i.e. lake or river)	Preferred option: Piperacillin/tazobactam Alternative option for patients with non-life threatening penicillin allergy: Cefepime Alternative option for patients with life threatening penicillin allergy: Aztreonam
Severe Infection (including necrotizing fasciitis, or wet gangrene) Local infection with signs of SIRS with ≥2 of: • Temperature >38C or <36C • HR >90 bpm • RR >20 breaths/min or PaCO2 <32 mmHg • WBC >12000 or <4000 or >10% band forms		Preferred option: Piperacillin/tazobactam + vancomycin Alternative option for patients with non-life threatening penicillin allergy: Cefepime + Vancomycin + Metronidazole Alternative option for patients with life threatening penicillin allergy: Aztreonam + Vancomycin + Metronidazole *If necrotizing fasciitis is suspected, add clindamycin 900 mg IV q 8 hours, for its anti-toxin activity.

[a] Tailor treatment to treat previously isolated pathogens in patients with recurrent diabetic foot infections
[b] Modify antibiotic therapy when culture results and sensitivities are available
[c] ID consult is recommended to help guide antibiotic treatment recommendations

Table 2. Imaging in Diabetic Foot Infections

Condition	Imaging Modality
Preferred initial imaging	Radiograph of affected foot
If radiographs are equivocal, or if results are negative, but there is a high clinical concern for osteomyelitis (eg, positive probe-to-bone test, elevated ESR/CRP, ulcer present for ≥2 months)	MRI with contrast (Group 2 gadolinium agents are used if impaired renal function)
If gadolinium contraindicated	Contrast MRI after steroid prep or MRI without contrast
If MRI contraindicated	Triple-phase bone scan in combination with a tagged WBC scan

Clinical Background

A diabetic foot infection (DFI) is a soft tissue or bone infection that is often associated with neuropathy or peripheral arterial disease in a patient with diabetes mellitus. Prevalence of this infection in the diabetic population is common, with over 30 million people in the USA with diabetes mellitus,[1] with 84 million with pre-diabetes, and an estimated 20% of people aged 65-74 diagnosed with diabetes. Age and duration of diabetes increase risk of DFI. The CDC estimated 8 in 1000 hospital discharges of patients with diabetes included DFI. Development of infection can have significant morbidity, as well as socioeconomic and quality of life impact.[2]

Clinical Problem and Management Issues

The diagnosis and treatment of diabetic foot often requires the input of a multidisciplinary team that can include Emergency Medicine, Internal Medicine, Infectious Disease, Podiatry, and other surgical services. Coordination of patient care around these specialties can be challenging due to lack of guidance around which consultant expertise is required in different clinical scenarios. This uncertainty can lead to inconsistencies and delays in appropriate management.

Rationale for Recommendations

This guideline is intended to provide a consistent set of criteria to facilitate the timely and effective treatment of DFI and to clarify how to coordinate care of the DFI patient.

Causes

Diabetic foot infections (DFI) are often associated with peripheral neuropathy and can develop with trauma, insertion of a foreign object or disruption of the skin barrier.[2] Vascular disease contributes to risk of a foot wound becoming infected.

Diagnosis

Recommendations:

- Assess all diabetic foot ulcers for presence of infection and severity (Table 1)
- Once DFI is confirmed:
  Obtain ABI/TBI
  Perform the probe-to-bone test
  Obtain initial labs, including CBC, basic profile, ESR, and CRP

History/Physical Exam

The evaluation of a patient with a DFI involves 3 steps: determining the extent and severity of the infection, identifying underlying factors that promote infection, and assessing microbial etiology.[3]

The clinical history should focus on details related to all current lesions, including duration, prior trauma to the site, and whether the lesion is sensate or has pain. Systemic symptoms, including fevers and chills should be noted, as they portend a more severe infection. Obtain history of prior foot infections or ulcerations and their treatments, including prior causative pathogens (particularly MRSA and *Pseudomonas aeruginosa*), antibiotic use (including specific agents and duration of therapy), wound care, and surgical interventions. Specific attention should be focused on factors which increase the risk for DFI, including ulceration present for more than 30 days, history of recurrent ulcerations, traumatic wounds, prior amputations, and renal insufficiency.

On physical exam, note the presence of classic signs of inflammation (redness, warmth, swelling, tenderness, pain) or purulent secretions. The presence of two or more of these signs is diagnostic of acute infection (Table 1). Other features that have also been associated with DFI include: non-purulent secretions, necrosis, friable granulation tissue, undermining of wound edges, or foul odor. Document the size and depth of any ulceration, as well as the presence or absence of surrounding erythema. Perform the probe-to-bone test on all ulcers, as positive results are predictive of osteomyelitis.[3]

Assess the severity of infection according to the size and depth of infection as well as the presence of absence of systemic signs, and grade per the Infectious Disease Society of America (IDSA) Classification of DFIs (Table 1).

Assessment of peripheral perfusion via ankle/brachial index and toe brachial index (ABI/TBI) should be performed as it guides further management strategies.[4] ABI does not provide reliable results in patients with non-compressible vessels, such as diabetics and patients with renal insufficiency, so TBI is needed as well. Finally, assess presence of peripheral neuropathy, for example, monofilament examination for pressure sensation.

Initial laboratory studies can establish severity of infection and serve as a mechanism for monitoring subsequent response to therapy. Standard evaluation includes CBC, blood glucose, electrolytes, and renal function. Inflammatory markers such as ESR and CRP should be obtained if there is suspicion for osteomyelitis.[3] Use of procalcitonin to aid in clinical decision making in DFI is not currently recommended.

How to Obtain Cultures

Recommendations:

- Obtain soft tissue cultures rather than superficial swabs for evaluation of infected diabetic foot ulcers.
- If wound swab is the only available method of obtaining a culture, perform it after debriding and cleaning the wound.[5,6]
- If osteomyelitis is suspected, obtain bone culture to guide antibiotic therapy rather than soft tissue culture, if clinically feasible. Do not obtain superficial swabs.
- When obtaining bone specimens, send the specimen for both histopathology and culture.

The optimal method of obtaining cultures is by curettage of the base of a debrided ulcer with a curette or scalpel. Deep tissue cultures offer a higher yield than surface swabs and reduce the likelihood of culturing colonizing organisms. If wound swab is the only available method of obtaining a culture, perform it after debriding and cleaning the wound. Tissue cultures generally provide more accurate results than superficial swabs; deep tissue cultures are more likely to identify true pathogenic organisms and are less likely to identify superficial colonizing organisms than superficial swabs.[7] Current guidelines state deep tissue cultures should be preferentially obtained over superficial swabs in patients with infected diabetic foot ulcers.[5,6]

If osteomyelitis is suspected, obtain bone culture to guide antibiotic therapy rather than soft tissue culture if clinically feasible; do not obtain superficial swabs. Complete concordance between soft tissue and bone cultures was found to be only approximately 49%, and 11% of cases had no common pathogens[8] and was worse between swab and bone cultures.[9,10]One retrospective cohort study found that patients managed with bone culture-based therapy were significantly more likely to be in remission at follow-up than patients managed with swab culture-based therapy (56% vs. 22%).[11] Current guidelines are in agreement that superficial swab cultures do not reliably predict bone microorganisms.[2] Bone biopsy may be obtained surgically (usually during debridement) or percutaneously. If the bone biopsy is not obtained surgically, either Podiatry or Orthopaedic Surgery should contact Musculoskeletal Radiology to discuss the approach for percutaneous biopsy, which is typically via CT guidance. Ideally, a bone biopsy should be obtained prior to antibiotic treatment to increase diagnostic yield, or discontinue antibiotics at least 24 hours prior to biopsy when safe to do so.[12]

Bone biopsy is favored if any of the following are present:
- Uncertainty regarding the diagnosis of osteomyelitis
- Lack of reliably obtained soft tissue cultures
- Lack of improvement on current antibiotic therapy
- Prior infection or colonization with multidrug-resistant bacteria
- Lesions involving the midfoot or hindfoot

When obtaining bone specimens, send the specimen for both histopathology and culture, as a positive result in either test can be used to make the diagnosis of osteomyelitis in the right clinical context. Histology has been considered the gold standard for the diagnosis of osteomyelitis, but a positive culture result can help confirm the diagnosis of osteomyelitis and identify potentially causative organisms that can guide treatment. If there is doubt regarding the diagnosis based on culture or histology results (eg, a culture positive for a commensal organism with negative histology) or a culture or histology result discordant with the patient's clinical presentation, consultation with infectious diseases regarding the results is encouraged.

Imaging

Recommendations:

- Obtain foot radiographs for initial evaluation of suspected non-superficial soft tissue infection or osteomyelitis.
- If soft tissue abscess is suspected, perform MRI as the next imaging test.
- If osteomyelitis is suspected despite a negative or equivocal radiograph, or if additional imaging is needed to evaluate the extent of osteomyelitis, perform a MRI as the next imaging test.
- If MRI cannot be obtained but further evaluation of osteomyelitis is needed, obtain a triple-phase bone scan in combination with a tagged WBC scan.

Obtain foot radiographs for initial evaluation of suspected non-superficial soft tissue diabetic foot infection or osteomyelitis. Evidence in support of radiography is inconclusive and support for this recommendation rests mainly on expert opinion. Sensitivity and specificity of radiography for diagnosis of osteomyelitis range from below 60% to values greater than 90%.[13-16] Despite this, radiography is routinely performed in the initial evaluation of non-superficial diabetic foot infection as it is inexpensive and low-risk, and may show important features (gas, radiopaque foreign body, post-surgical changes, vessel calcifications, etc.). Findings on radiography greatly complement the interpretation of MRI. Radiography is recommended for initial evaluation of non-superficial soft tissue infection by the IDSA guidelines.[2,3,17] Although sensitivity for diagnosing osteomyelitis with foot radiographs is lower earlier in the disease course, it is recommended at any stage.

MRI is not indicated if any of the following are present:
- Proven osteomyelitis by bone biopsy/culture
- Recent MRI without substantive interim clinical change
- Clear radiographic changes of osteomyelitis without concern for soft tissue abscess
- Exposed necrotic bone
- MRI unlikely to change treatment plan

When further evaluation of non-superficial soft-tissue infection following radiography is desired (eg, when soft tissue abscess is suspected), perform MRI as the next imaging test. The role of further imaging in diagnosing non-superficial soft tissue infection in the diabetic foot is less well studied than in diagnosing osteomyelitis, and support for MRI in this setting comes primarily from guideline recommendations. In the absence of soft tissue ulcer or

penetrating injury, osteomyelitis is extremely unlikely, meaning that MRI performed in this setting is done to evaluate soft tissue infection rather than osteomyelitis and may be of low yield.[17] MRI is believed to provide optimal definition of soft tissue infection and is recommended by expert opinion especially when there is concern for soft tissue abscess.[3] The addition of intravenous gadolinium with the MRI significantly improves sensitivity in the diagnosis of soft tissue abscess.[18]

To diagnose suspected osteomyelitis following a negative or equivocal radiograph, or to evaluate the extent of osteomyelitis, perform a MRI as the next imaging test. Evidence showing the utility of MRI in diabetic foot infections with suspected osteomyelitis is robust and comes from several meta-analyses that suggest good sensitivity (80-90%) and fair specificity (70-80%) and favorable comparison to radiography, tagged WBC scan (fair sensitivity and specificity), and bone scan (good sensitivity but poor specificity).[14,15,19] The preferential use of MRI over nuclear medicine studies in diagnosing osteomyelitis is also supported by various guideline recommendations.[2,3,17]

If clinical suspicion for osteomyelitis is high and diagnostic testing is suggestive of osteomyelitis (eg. ESR >70, ulcer size >2cm^2, positive radiographic findings or probe-to-bone test), MRI does not necessarily need to be obtained solely to make the diagnosis of osteomyelitis.[16] In this situation, MRI can be useful to show extent of infection for surgical planning, and decisions regarding its use should be made in conjunction with the surgical team. In one retrospective study of diabetic patients undergoing first ray amputation, pre-surgical MRI was found to have significant mortality benefit (4-year survival rate 100% versus 73% among patients who did not receive pre-surgical MRI), though it should be noted that there were several confounding factors that may have affected results.[20] If image-guided bone biopsy is being considered and MRI has not been obtained, the decision regarding obtaining MRI to assist in biopsy planning should be made in conjunction with a musculoskeletal radiologist.

Intravenous gadolinium contrast is not required for diagnosis of acute osteomyelitis using MRI, but may add valuable information by diagnosing abscess and other soft tissue fluid collections, as well as delineating sinus tracts. It is also useful for determining extent of infection and necrosis, as well as vascularity and perfusion.[17] If a patient has had a prior allergic-type reaction to gadolinium contrast, premedication with corticosteroids is required. In patients with impaired renal function (eGFR<30), a specific type of Gadolinium (Group II) can be used, although one should refer to the current institutional contrast guidelines. *An inability to use gadolinium should not preclude non-contrast MRI from being performed to evaluate suspected osteomyelitis.*

If MRI cannot be obtained but further evaluation of osteomyelitis is needed, obtain a triple-phase bone scan in combination with a tagged WBC scan. If MRI is equivocal for osteomyelitis, nuclear medicine studies may be considered to further evaluate for osteomyelitis. Obtaining both nuclear medicine studies rather than one alone is supported by IDSA guidelines and is favored at our institution to help localize radiotracer uptake. Newer guidelines suggest a potential role for SPECT/CT and PET/CT.[2,21,22] At our institution, bone and WBC scans routinely include SPECT (single-photon emission computed tomography), and conventional CT is sometimes added at the discretion of the nuclear medicine physician to further delineate anatomy and pathologic findings. Conventional CT alone is of less value in the diagnosis of acute osteomyelitis and is not recommended to complement or replace MRI in this setting.[17] In chronic osteomyelitis, CT can add value by delineating a sequestrum (dead bone occurring within osteomyelitis) and is used in surgical planning.

Treatment

Recommendations:

- Consult a surgical service for all cases of moderate and severe DFIs. (Table 1, Figure 1)
- All patients with mild, moderate or severe disease should receive coverage for *Staph aureus* and *Strep spp*., and patients with severe or life-threatening disease should receive antibiotics that include coverage for MRSA and *Pseudomonas aeruginosa* (Table 1).
- If a patient does not have a current A1c result available, obtain upon hospital admission.

Surgery

Consult a surgical service for all cases of moderate and severe DFIs. Table 1 defines criteria for severity of infection, and Figure 1 guides clinicians to the appropriate surgical service based on clinical parameters, history of treatment by a surgical service, and location of infection. Many DFIs require surgical intervention, varying from local incision and debridement to high-level amputation, depending on the severity of infection and degree of peripheral vascular disease. The goal of surgery is to control the infection while preserving maximal function and quality of life[23] and the level of amputation is determined by the extent and severity of the infection.[24]

Indications for surgical consult.

Urgent surgical consultation should be obtained for:

- Life/limb threatening infection
- Critical limb ischemia
- Gas in deep tissues
- Necrotizing fasciitis
- Compartment syndrome
- Deep soft tissue abscess

Surgical consultation should also be obtained for:

- Wounds with substantial non-viable tissue
- Wounds with bone or joint involvement (includes positive probe-to-bone test)
- Ulceration with drainage, erythema, or fluctuance
- Unexplained persistent foot pain or tenderness
- Progressive bone destruction on imaging

Determining the appropriate surgical service.

Consult vascular surgery for all patients with known critical limb ischemia or PAD (defined as ABI <0.7 or TBI <0.6). For all other patients who do not have a pre-existing relationship with a surgical service, consult podiatry. Involvement of orthopedic or plastic surgery will be determined by the podiatry service.

Determining whether to pursue amputation versus medical therapy alone or combined with local incision and debridement is complex and should be made on an individual case-by-case basis, considering the site and severity of infection as well as patient preferences. Factors favoring amputation include persistent sepsis syndrome with no alternative explanation, bony destruction that compromises foot mechanics or progressive bone destruction despite adequate antibiotic therapy.[3]

Predictors of amputation are presence of periwound or pretibial edema, deep ulcers, positive probe-to-bone test, CRP three times upper limit of normal, large ulcer size, and presence of peripheral vascular disease. A prospective multicenter cohort study of 575 infected diabetic ulcers demonstrated that there was an increased incidence of amputation with increased severity of infection.[25]

Wound Care

The wound bed should be managed to promote healing. In addition to debridement (if indicated), strategies include inspection, cleansing, surface debris removal, and wound protection.[26]

Wound debridement should be used to remove non-viable tissue in the wound bed and stimulate a granular wound bed. Types of wound debridement include sharp/surgical debridement, mechanical debridement (wet-to-dry dressings), and enzymatic debridement (collagenase/Santyl)

Wound debridement may not be necessary in circumstance where:

- A granular wound bed is present
- There is severe peripheral vascular disease without clinical infection signs and vascular workup is pending
- A dry stable eschar
- There is scheduled surgical intervention such as a pending amputation[27].

Dressings should be selected that provide a moist wound bed, control exudate, and prevent maceration.[4] Wound bed healing following surgical debridement of DFI can be facilitated by use of negative pressure.[28] Decisions regarding wound dressing should be at the discretion of the surgical team. There is insufficient data to support routine use of G-CSF for wound healing at this time.

Wound care does not need to be consulted if podiatry and/or surgery has evaluated the ulcer and made wound care recommendations. If there are other wounds that need to be addressed, or if podiatry and surgery will not be consulted, it is recommended that wound care be consulted.

Offloading.

The podiatry or surgical service will typically make recommendations for activity-level and offloading devices. In general, for the plantar forefoot ulcer, a wedge (half) shoe may be more effective than wound care alone.[29] Caution should be taken in the acute setting where gait instability and risk of falls should be carefully considered. For non-plantar wounds, surgical shoe and heel relief boot/shoe are recommended.[4] For long-term management, therapeutic shoes with offloading foot orthoses can prevent recurrence of DFU.[29]

If the patient has a total contact cast and it has been recommended to be removed for wound inspection, consult physical therapy for cast removal. For plantar DFU, total contact casts (TCC) and irremovable fixed ankle boot promote the best healing rates.[4] In the acute DFI setting, the use of TCC may be limited. TCC have limited use in the setting of acute osteomyelitis because the cast typically stays on the patient 3-7 days. It is most appropriate to use TCC in the subacute or chronic wound treatment when infection has been properly managed.

Alternative off-loading modalities to TCC when managing acute osteomyelitis include wound healing shoes, Darco wedge shoes and CROW devices. Podiatry should be consulted to make specific offloading device recommendations based on wound location and deformity.

Antibiotic treatment.

All patients with DFI, regardless of disease severity, should receive coverage for *Staph aureus* and *Strep spp.*, and patients with severe or life-threatening disease should receive antibiotics that include additional coverage for MRSA and *Pseudomonas aeruginosa* (Table 1). The IDSA guidelines for the treatment of DFIs stratify treatment recommendations by disease severity, risk factors for MRSA and *Pseudomonas,* and patient history. There are several studies that have identified risk factors for multi-drug resistant pathogens, which include repeated hospitalizations for the same ulcers; previous antibiotic utilization; duration of previous antibiotic therapy; severity of wound; and osteomyelitis.

There is limited data evaluating efficacy of empiric gram-negative coverage for DFIs. A number of Phase III randomized controlled trials have evaluated the efficacy of antibiotic regimens for complex skin and skin structure infections, and 10-38% of patients presented with DFIs .[3,30] All published randomized controlled trials have evaluated antibiotics that cover only gram-positive pathogens. Trials evaluating the efficacy of newer antibiotics including dalbavancin, oritavancin, daptomycin, linezolid, tedizolid, tigecycline have demonstrated non-inferior activity compared to nafcillin, dicloxacillin, cloxacillin, flucloaxacillin, and vancomycin.

IDSA guidelines generally recommend covering *Enterobacteriaceae*, *Pseudomonas aeruginosa*, MRSA and anaerobes for severe infections. For patients with moderate infections, spectrum of coverage should target a minimum of

MSSA and streptococci, and can expand to include gram-negative pathogens and anaerobes in select circumstances (Table 1). Patient with mild diabetic foot infections can be treated with oral antibiotics (Table 1).

In addition to disease severity treatment, the IDSA guidelines recommend treatment based on patient's previous infection and treatment history, in addition to risk factors for MRSA and *Pseudomonas*. Patients should be empirically covered for MRSA if risk factors are present: previous MRSA infection, high local prevalence of MRSA, and failure of current therapy. UMHS is considered an area of high local MRSA prevalence. Additionally, patients should be covered for *Pseudomonas* if infection develops following frequent exposure of foot ulcer to water, for residents in warm climates, and high local prevalence of *Pseudomonas* infections (Table 1). A recent study of the microbiology of DFIs at the University of Michigan revealed very low rates of *P. aeruginosa* (5%).

Antibiotic initiation should be delayed until after deep cultures are obtained in patients with mild or moderate wound infections that are clinically stable and deep tissue cultures are scheduled within the next 24-48 hours. Once culture results are obtained, antibiotics should be tailored to target isolated pathogens. Duration of therapy is usually 1-2 weeks for skin and soft tissue infection, and at least 4 weeks if osteomyelitis is present. Infectious Diseases consultation is recommended to help guide antibiotic therapy and evaluate response to therapy.

Indications for Inpatient Infectious Disease Consult

- All severe DFIs
- Moderate DFIs with confirmed or suspected osteomyelitis
- Any DFI in patients with a history of prior infection or colonization with multidrug-resistant organisms

Choosing the optimal antibiotic regimen can be challenging and requires thorough knowledge of the microbiology of DFIs, local antimicrobial resistance rates, and limitations of various culture techniques. Infectious diseases consultation can help tailor antibiotics appropriately and limit the use of overly broad-spectrum agents, as well as provide monitoring of parental antibiotics after discharge and determine duration of treatment.

Glycemic Control

Glucose management is a key component to managing patients with DFIs.

The hemoglobin A1c (HbA1c) can aid with determining the effectiveness of the patient's current medical regimen. If a patient does not have a current A1c result available (eg. within the last 3 months), one should be obtained upon hospital admission. The standard for medical management in most patients with diabetes is an HbA1c value of <7%, which correlates to average blood glucose readings of 150 mg/dL. If blood glucose averages are >180 mg/dL or the HbA1c is over 8%, the patient is considered to have uncontrolled diabetes. Chronic hyperglycemia is negatively associated with endothelial-dependent vasodilatation, which may contribute to the development of ischemic foot ulcers.[31] High HbA1c levels have been shown to be an important risk factor for lower extremity amputation in patients with diabetes.[32] Achieving adequate glycemic control should be part of the management of DFIs.

Glycemic management recommendations for patients with DFIs include the following:

Aim for preprandial glycemic levels of 100-140 mg/dL and postprandial levels of <180 mg/dL for most hospitalized patients.

Any patient with a HbA1c level >8.5% should be considered for intensification of their diabetes medical regimen.

Insulin is the preferred agent for reducing glucose levels in hospitalized patients.

For additional recommendations on inpatient glycemic control, please see the Michigan Medicine Inpatient Glycemic Management Guideline.

The Endocrinology Service is available for consultation to assist in the management of patients with poor glycemic control.

At the University of Michigan, the endocrinology service has two different teams covering the hospital. The Hospital Intensive Insulin Program (HIIP) covers patients on the Vascular Surgery Service (SVA) who are located in the Cardiovascular Center levels 4 or 5, and University Hospital patients located on 4C or 7C. The Endocrine Consult Service (pager 7185) manages all other medical/surgical services located in the University Hospital.

Discharge Coordination

Many patients will be able to be transitioned to oral therapy upon discharge. If the patient requires parenteral antibiotics upon discharge, the infectious disease team should be consulted. Outpatient follow-up should be arranged with the primary surgical team before discharge and with primary care or endocrinology as glycemic control is a priority in the outpatient setting. Before discharge, the patient should receive education in wound care, dressing placement and how to use any offloading prosthetic. Many of these patients will be discharged with a need for ongoing wound care. At Michigan Medicine, that care can be provided via the Comprehensive Wound Care Clinic. Of note, that clinic can also provide hyperbaric oxygen treatment, which may be indicated for patients with diabetic foot ulcers with osteomyelitis (Wagner grade 3+), if standard wound care/antibiotic treatment is not effective.

Guideline Creation Process and Considerations

Related National Guidelines

The UMHS Clinical Guideline on Diabetic Foot Infections is consistent with:

Lipsky BA, Aragon-Sanchez J, Diggle M, et al. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev. 2016;32 Suppl 1:45-74.

Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12): e132-73

Related National Performance Measures

There are no national performance measures associated with diabetic foot infections.

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Guideline Development Team and Disclosures

The multidisciplinary guideline development team consisted of:

- The medical team: Stephanie M Burdick, MD, Internal Medicine; Aaron E Silver, MD, Internal Medicine, Eric Broekhuizen, Orthotics & Prosthetics; Christina DeGeorge, PA-C, Endocrinology; Katherine A Gallagher, MD, Vascular Surgery; Steven C Haase, MD, Plastic Surgery; Crystal M Holmes, DPM, Podiatry; Jon A Jacobson, MD Radiology; John P Mills, MD, Infectious Diseases; Jerod Nagel, PharmD, Pharmacy; Payal Patel, MD, Infectious Disease; David M Somand, MD, Emergency Medicine; Paul G Talusan, MD, Orthopaedic Surgery; Jeffrey Wensman, Orthotics & Prosthetics; James S Wrobel, DPM, Podiatry
- A guideline development methodologist: F. Jacob Seagull, PhD, Learning Health Sciences
- Literature search services were provided by informationists at the Taubman Health Sciences Library, University of Michigan Medical School.

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

No relevant personal financial relationships with commercial entities: Eric Broekhuizen; Stephanie M Burdick, MD; Christina DeGeorge, PA-C; Katherine A Gallagher, MD; Steven C Haase, MD; Crystal M Holmes, DPM; Jon A Jacobson, MD; John P Mills, MD; Jerod L Nagel, PharmD; Payal Patel, MD; F. Jacob Seagull, PhD; Aaron E Silver, MD; David M Somand, MD; Paul G Talusan, MD; Jeffrey Wensman; James S Wrobel, DPM

Strategy for Literature Search

Within the Medline (Ovid) database, the following search strategy was used for most of the search topics. The search below is identified as Main in the search strategies document. The appropriate indexing terms either do not exist or were applied inconsistently, so the main search uses keywords in addition to MeSH terms to arrive at the following main strategy.

Results were limited to: English, and 2014 to present. The Main search retrieved 1,023 references. When the search hedges for Guidelines, Clinical Trials, and Cohort Studies were added, the base results are as follow:

Diabetic Foot Infection-Guidelines, total results were 25
Diabetic Foot Infection-Clinical Trials, total results were 146
Diabetic Foot Infection-Cohort Studies, total results were 198

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

Level of evidence supporting a diagnostic method or an intervention:
A = systematic reviews of randomized controlled trials with or without meta-analysis,
B = randomized controlled trials,
C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control),
D = individual observation studies (case study/case series),
E = expert opinion regarding benefits and harm

Search details and evidence tables available at http://www.uofmhealth.org/provider/clinical-care-guidelines.

Recommendations

Guideline recommendations were based on prospective randomized controlled trials if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size. The "strength of recommendation" for key aspects of care was determined by expert opinion.

The strength of recommendations regarding care were categorized as:

I = Generally should be performed
II = May be reasonable to perform
III = Generally should not be performed

Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, Orthopaedic Surgery, Plastic Surgery, Vascular Surgery, Infectious Diseases Division, Gastroenterology Division, Endocrinology Division, Podiatry Division, Department of Emergency Medicine, Radiology Department and Orthotics & Prosthetics Division. The final version of this guideline was endorsed by the Clinical Practice Committee of the University of Michigan Medical Group and by the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

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