Diagnosis and Treatment of Diabetic Foot Infections (DFI)

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INFECTIOUS DISEASES

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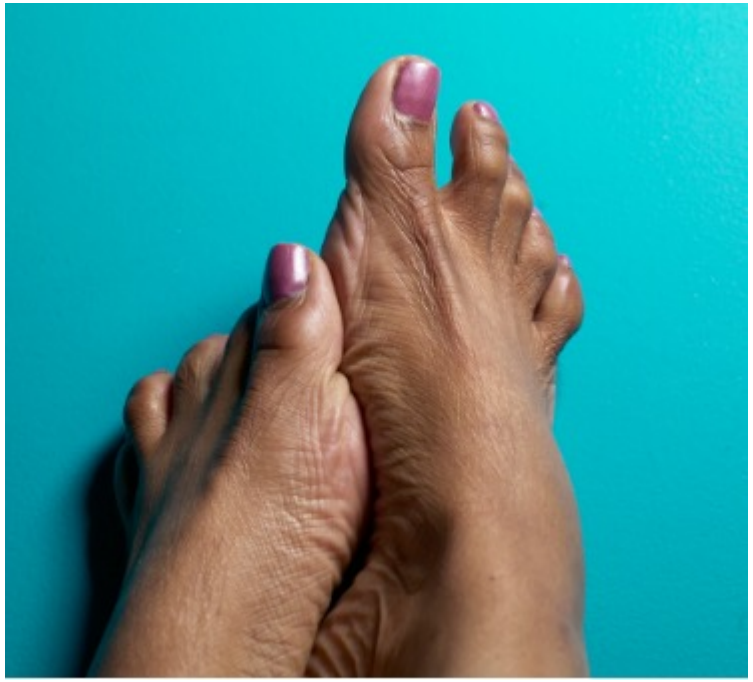
Background

- Around one third of patients with diabetes develop a diabetic foot problem over the course of their lives.

- More than 15% of patients with DFIs will die within one year of diagnosis and 17% will undergo major amputation.

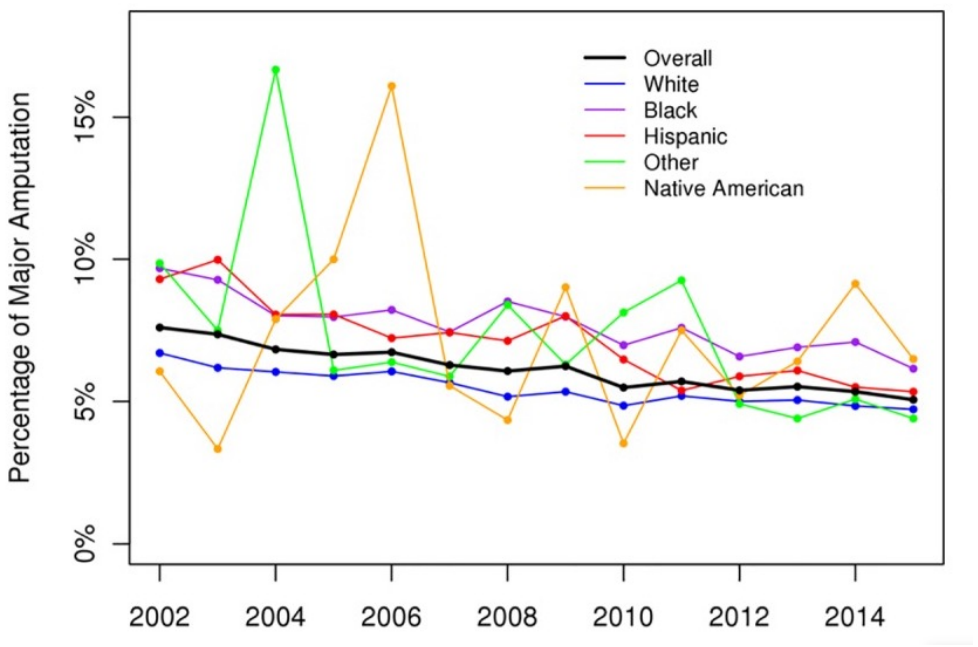


Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med*. 2017;376(24):2367–75. 10.1056/NEJMra1615439

Background

- In a 2019 study on disparities in DFI outcomes, the risks for major amputation were significantly higher (OR 1.5, 95%CI 1.2,1.8) for Native American patients with DFIs compared to White patients.

- Native American patients with DFI were less likely to receive a revascularization procedure (OR 0.6, 95%CI 0.3, 0.9, p = 0.03) than Whites.



Tan TW, Shih CD, Concha-Moore KC, Diri MM, Hu B, Marrero D, Zhou W, Armstrong DG. Disparities in outcomes of patients admitted with diabetic foot infections. PLoS One. 2019 Feb 4;14(2):e0211481. doi: 10.1371/journal.pone.0211481. Erratum in: PLoS One. 2019 Apr 11;14(4):e0215532. PMID: 30716108; PMCID: PMC6361439.

IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections

Published by IDSA, 10/2/2023

Clinical Infectious Diseases, ciad527, https://doi.org/10.1093/cid/ciad527

Published: 02 October 2023

Image source: Preventing Diabetes-Related Amputations | CDC

Diagnosis

- A clinician seeing a patient with diabetes and a foot ulcer should always assess for the presence of an infection and, if present, classify the infection's severity.

- IWDGF/IDSA guidelines define a DFI based on the presence of evidence of (a) inflammation of any part of the foot, not just of an ulcer, or (b) findings of Systemic Inflammatory Response Syndrome (SIRS).

- Because of the important diagnostic, therapeutic, and prognostic implications of osteomyelitis, the guidelines separate it out by indicating the presence of bone infection with “(O)” after the grade number (3 or 4).

Table 1.

The classification system for defining the presence and severity of foot infection in a person with diabetes.[a]

Clinical classification of infection, definitions	IWGDF/IDSA classification
No systemic or local symptoms or signs of infection	1/Uninfected
Infected: At least two of these items are present: Local swelling or induration Erythema >0.5 but <2 cm[b] around the wound Local tenderness or pain Local increased warmth Purulent discharge	2/Mild
And, no other cause of an inflammatory response of the skin (e.g., trauma, gout, acute charcot neuro-arthropathy, fracture, thrombosis, or venous stasis)	
Infection with no systemic manifestations and involving: Erythema extending ≥2 cm[b] from the wound margin, *and/or* Tissue deeper than skin and subcutaneous tissues (e.g., tendon, muscle, joint, and bone)[c]	3/Moderate
Infection involving bone (osteomyelitis)	Add "(O)"
Any foot infection with associated systemic manifestations (of the systemic inflammatory response syndrome [SIRS]), as manifested by ≥2 of the following: Temperature, > 38°C or <36°C Heart rate, > 90 beats/min Respiratory rate, > 20 breaths/min, *or* PaCO2 < 4.3 kPa (32 mmHg) White blood cell count >12,000/mm^3, *or* < 4G/L, *or* >10% immature (band) forms	4/Severe
- Infection involving bone (osteomyelitis)	Add "(O)"

The presence of clinically significant foot ischaemia makes both diagnosis and treatment of infection considerably more difficult.

a infection refers to any part of the foot.

b in any direction, from the rim of the wound.

c if osteomyelitis is demonstrated in the absence of ≥2 signs/symptoms of local or systemic inflammation, classify the foot as either grade 3(O) (if <2 SIRS criteria) or grade 4(O) if ≥2 SIRS criteria) (see text).

Which patients with DFI need hospitalization?

- The guidelines recommend considering hospitalization for all patients with severe infection or a moderate infection which is associated with key relevant morbidities (particularly peripheral arterial disease).

- "Of note, the presence of osteomyelitis does not necessarily require hospitalization, since many of these patients are clinically stable and can be treated with oral antibiotic agents."

- "Hospitalization may be preferable (at least initially) in those patients who require intravenous antibiotic therapy, have substantial associated soft tissue infection, require special diagnostic testing, or require urgent surgical treatment."

Culture Collection

- In a person with suspected soft tissue DFI obtain a culture preferably by aseptically (after cleansing and debridement and trying to avoid contamination) collecting a tissue specimen (by curettage or biopsy) from the wound.

- In patients with osteomyelitis, BonE BiOPsy (BeBOP) is the only definitive way to determine the causative pathogen.

- Published studies consistently report a low correlation between bone and non-bone culture results, most <50%, with the highest correlation for Staphylococcus aureus.

Senneville EM, Lipsky BA, van Asten SAV, Peters EJ. Diagnosing diabetic foot osteomyelitis. Diab Metab Res Rev. 2020; 36(Suppl 1):e3250.

BonE BiOPsy (BeBOP)

- "BonE BiOPsy is, however, usually not performed in most cases of suspected DFO due to the absence of a health care professional adequately trained to perform the procedure and/or the fear of possible adverse effects, especially fracture or induced infection of the bone."

- "Percutaneous biopsy is generally not painful (as the majority of affected patients have sensory neuropathy, and local anaesthetics can be offered), and complications are rare. Recent studies suggest it can be performed safely at the bedside by any trained medical caregiver."

Féron F, de Ponfilly GP, Potier L, et al. Reliability and safety of bedside blind bone biopsy performed by a diabetologist for the diagnosis and treatment of diabetic foot osteomyelitis. Diabetes Care. 2021; 44(11):2480–2486.

Table 4.

Proposals for the empirical antibiotic therapy according to clinical presentation and microbiological data (from Lipsky et al.[11]).[a]

Infection severity	Additional factors	Usual pathogen(s)[b]	Potential empirical regimens[c]
Mild	No complicating features	GPC	Semisynthetic penicillinase-resistant penicillin (cloxacillin)
			1st generation cephalosporin (cephalexin)
	ß-lactam allergy or intolerance	GPC	Clindamycin; fluoroquinolone (levo/moxi-floxacin); trimethoprim-sulfamethoxazole; doxycycline
	Recent antibiotic exposure	GPC + GNR	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam)
			Fluoroquinolone (levo/moxi-floxacin); trimethoprim-sulfamethoxazole
	High risk for MRSA	MRSA	Linezolid; trimethoprim-sulfamethoxazole; clindamycin; doxycycline, fluoroquinolone (levofloxacin, moxifloxacin)
Moderate or severe[d]	No complicating features	GPC ± GNR	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam)
			2nd, 3rd generation cephalosporine (cefuroxime, cefotaxime, ceftriaxone)
	Recent antibiotics	GPC ± GNR	ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam)
			2nd, 3rd generation cephalosporine (cefuroxime, cefotaxime, ceftriaxone) group 1 carbapenem (ertapenem); (depends on prior therapy; seek advice)
	Macerated ulcer or warm climate	GNR, including *Pseudomonas* sp.	ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam) semisynthetic penicillinase-resistant penicillin (cloxacillin) + ceftazidime or ciprofloxacin group 2 carbapenem (mero/imi-penem)
	Ischaemic limb/necrosis/gas forming	GPC ± GNR ± strict anaerobes	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam) or ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam)
			Group 1 (ertapenem) or 2 (mero/imi-penem) carbapenem
			2nd (cefuroxime)/3rd (cefotaxime, ceftriaxone) generation cephalosporin + clindamycin or metronidazole
	MRSA risk factors	MRSA	Consider adding, or substituting with, glycopeptides (vancomycin, teicoplanin); llLinezolid; daptomycin; fusidic acid, trimethoprim-sulfamethoxazole; doxycycline
	Risk factors for resistant GNR	ESBL	Carbapenem (erta/mero/imi-penem); fluoroquinolone (ciprofloxacin); Aminoglycoside (amikacin); colistin

Antibiotic Treatment of Diabetic Foot Infections (DFI)

Table 5.

Duration of antibiotic therapy according to the clinical situation.

	Route	Duration
Infection severity (skin and soft tissues)		
Class 2: Mild	Oral	1–2 weeks[a]
Class 3/4: Moderate/severe	Oral/initially iv	2–4 weeks
Bone/joint		
Resected	Oral/initially iv	2–5 days
Debrided (soft tissue infection)	Oral/initially iv	1–2 weeks
Positive culture or histology of bone margins after bone resection	Oral/initially iv	3 weeks
No surgery or dead bone	Oral/initially iv	6 weeks

Abbreviation: iv, intravenous.

a 10 days following surgical debridement.

Rationale for shortened durations and oral treatments

- "In a prospective, randomized, non-inferiority, pilot trial, patients with diabetic foot osteomyelitis (DFO) who underwent surgical debridement and received either a 3- or 6-week course of antibiotic therapy had similar outcomes and antibiotic-related adverse events"

- "Penetration of antibiotic agents from the blood into the bone is variable but most classes can attain adequate levels in infected bone. Suggest administering antibiotic agents at their upper recommended dosage range"

Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis. 2012; 54(3):393–407. https://doi.org/10.1093/cid/cir842

Gariani K, Pham T, Benjamin K, et al. Three versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: a prospective, randomized, non-inferiority pilot trial. Clin Inf Dis. 2021; 73(7):e1539–e1545. https://doi.org/10.1093/cid/ciaa1758

How do you diagnose diabetic foot osteomyelitis (DFO)?

- "Osteomyelitis may be present underlying any foot wound, especially those that have been present for many weeks or that are wide, deep, located over a bony prominence, showing visible bone, or accompanied by an erythematous, swollen ("sausage") toe"

- "In a person with diabetes, consider using a combination of probe-to-bone test, plain X-rays, and ESR, or CRP, or procalcitonin (PCT) as the initial studies to diagnose osteomyelitis of the foot."

Lázaro-Martínez JL, Tardáguila-García A, García-Klepzig JL. Diagnostic and therapeutic update on diabetic foot osteomyelitis. Endocrinol Diab 2017; 64(2):100–108.

Probe-to-bone test (PTB)

- A systematic review of the PTB test found that for detecting DFO, the sensitivity was 0.87 and specificity 0.83

- "The procedure is easy to learn and perform, requiring only a sterile blunt metal probe (gently inserted into the wound, with a positive test defined by feeling a hard, gritty structure), is inexpensive and essentially harmless, but interobserver agreement is only moderate."

Plain X-ray

- "Provides useful information, especially about the status of the underlying osteoarticular tissues, the presence of gas in deep tissues, and the presence of any radio-opaque foreign body "
- "Because plain X-rays are insensitive to acute osteomyelitis, it is often useful to repeat a normal examination in 2–3 weeks when the suspicion of osteomyelitis is still high"

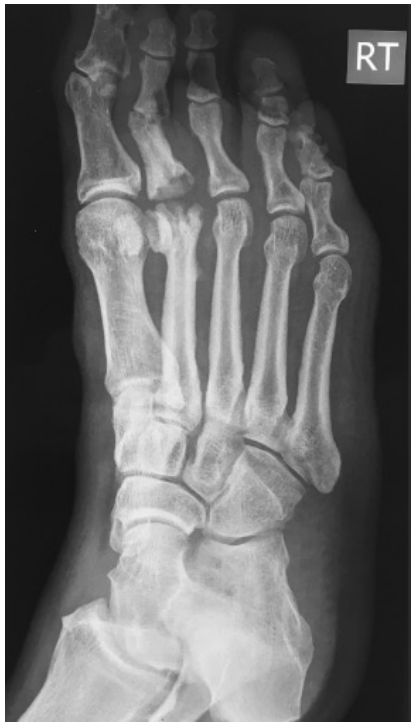


Image source: Osteomyelitis | Image | Radiopaedia.org

Serum Biomarkers

- "In a systematic review published in 2019, it was found that ESR ≥70 mm/hr had a sensitivity, specificity, and AUC of 0.81, 0.8 and 0.84, respectively"

- "A more recent systematic review and meta-analysis published in 2022 found that procalcitonin had the highest diagnostic test accuracy when compared to that of ESR, WBC and CRP with sensitivity, specificity, and AUC of 0.85, 0.67 and 0.844 at a cut-off value of 0.33 ng/mL"

Van Asten SA, Nichols A, La Fontaine J, Bhavan K, Peters EJ, Lavery LA. The value of inflammatory markers to diagnose and monitor diabetic foot osteomyelitis. Int Wound J. 2017; 14(1):40–45.
Sharma H, Sharma S, Krishnan A, et al. The efficacy of inflammatory markers in diagnosing infected diabetic foot ulcers and diabetic foot osteomyelitis: systematic review and meta-analysis. PLoS One. 2022

When to get an MRI

- "Perform MRI when the diagnosis of diabetes-related osteomyelitis of the foot remains in doubt despite clinical, plain X-rays and laboratory findings."

- Besides being used as a (very sensitive) diagnostic tool, MRI gives a good overview of the anatomy of soft tissues as well as bones and joints, which can be of aid for detecting pre-operatively any purulent collections or the extent of bone involvement.

- It is important to note that the presence of reactive bone marrow edema from non-infectious pathologies, such as trauma, previous foot surgery or Charcot neuroarthropathy, lowers its specificity and positive predictive value.

Chatha DS, Cunningham PM, Schweitzer ME. MR imaging of the diabetic foot: diagnostic challenges. Radiol Clin North Am. 2005; 43(4):747–759. ix

When is surgery indicated?

- "Urgent surgical consultation should be obtained in cases of severe infection or moderate DFI complicated by extensive gangrene, necrotizing infection, signs suggesting deep (below the fascia) abscess, compartment syndrome, or severe lower limb ischemia"

- "Consider performing early (within 24–48 h) surgery combined with antibiotics for moderate and severe DFIs to remove the infected and necrotic tissue."

- Retrospective studies comparing early surgery (variously defined, but usually within 72 h of presentation) versus delayed surgery (3–6 days after admission) in hospitalized patients with a severe, deep DFI, with or without osteomyelitis have reported lower rates of major lower extremity amputation and higher rates of wound healing.

Zhou S, Schmidt BM, Henig O, Kaye KS. Deferring amputation in diabetic foot osteomyelitis: doing more harm than good? Open Forum Infect Dis. 2021; 8(7):ofab184.

When is surgery indicated for DFO?

- "Consider performing surgical resection of infected bone combined with systemic antibiotics in a person with diabetes-related osteomyelitis of the foot. "
- "Consider antibiotic treatment without surgery in case of (i) forefoot osteomyelitis without an immediate need for incision and drainage to control infection, (ii) without PAD, and (iii) without exposed bone."
- If perfusion is severely compromised, revascularization should always be performed (either before or after any soft tissue/bone resection).

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):789–795.

What about adjunctive wound healing therapies?

Recommendation 23:

a. We suggest not using the following treatments to address DFIs: (a) adjunctive G-CSF treatment or (b) topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative-pressure wound therapy (with or without instillation). Conditional; Low.

Recommendation 25:

a. We suggest not using HBO therapy or topical oxygen therapy as an adjunctive treatment for the sole indication of treating a DFI. (Conditional; Low).

PAD Management

- All patients with DFI should be assessed for the presence and severity of PAD. As clinical assessment is often unreliable, it is important to also perform non-invasive tests, for example, Doppler waveform analysis combined with ankle pressure measurement, as well as toe pressure measurements.

- Based on the assessment of the wound and the amount of tissue loss, the results of non-invasive tests, and the IWGDF/IDSA infection severity score, all patients should be classified according to the WIfI classification scheme.

Fitridge R, Chuter V, Mills J, et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in people with diabetes mellitus and a foot ulcer. Diab Metab Res Rev 2023

The Wound, Ischemia, and Foot Infection (WIfI) classification system consists of 3 components graded separately from 0 (none) to 3 (severe).

One component may be dominant but the specific combination of scores is used to estimate the risk of limb amputation at 1 year and the need for or benefit of revascularization.[a]

Wound (W)

Grade	Ulcer	Gangrene
0	None	None
1	Small, shallow	None
2	Deep with exposed bone, joint, or tendon	Limited to digits
3	Extensive, deep, and involving forefoot and/or midfoot with or without calcaneal involvement	Extensive and involving forefoot and/or midfoot Full thickness heel necrosis with or without calcaneal involvement

Ischemia (I)

Grade	Ankle-brachial index Ankle systolic pressure	Toe pressure or transcutaneous oximetry
0	≥0.80 >100 mm Hg	≥60 mm Hg
1	0.60-0.79 70-100 mm Hg	40-59 mm Hg
2	0.40-0.59 50-69 mm Hg	30-39 mm Hg
3	≤0.39 <50 mm Hg	<30 mm Hg

Foot infection (fI)

Grade	Clinical manifestation
0	No symptoms or signs of infection
1	Infection indicated by ≥2 of the following: • Local swelling or induration • Erythema 0.5-2.0 cm around ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous)
2	Infection as described above with: • Erythema >2 cm around ulcer • Involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis) • No signs of systemic inflammatory response (see below)
3	Infection as described above with ≥2 signs of systemic inflammatory response syndrome: • Temperature >38 °C or <36 °C • Heart rate >90/min • Respiratory rate >20/min or $Paco_2$ <32 mm Hg • White blood cell count >12 000/μL or <4000/μL or 10% immature forms

	Low	Moderate	High
What is the risk of major lower extremity amputation?	Nearly all classifications with a sum of scores ≤3[a]	Society for Vascular Surgery's WIfI (Wound, Ischemia, Foot Infection) classifications that do not fit the low- or high-risk criteria shown	Nearly all classifications with a foot infection score of 3 (extensive local and systemic infection) OR a sum of scores ≥5[b]
What is the likelihood that revascularization would be beneficial if the infection can be controlled first?	All classifications with: • Ischemia scores of 0 • Ischemia scores of 1 with no wound and no more than local infection • Ischemia scores of 2 with no wound and no more than limited local infection	Most other classifications with an ischemia score of 1	Most other classifications with an ischemia score ≥2

Glycemic Control

- HbA1c values ≥8.0% and correlating fasting blood glucose of ≥126 mg/dL are associated with increased lower extremity amputation risk among patients with DFI, and HbA1c control between 7% and 8% was associated with optimal DFI healing at 1 year in observational studies.

- Drug considerations:
  - SGLT-2 inhibitors – increased risk of amputation with canagliflozin in the CANVAS trial (not identified in the respective RCTs of other SGLT2i)
  - GLP-1 inhibitors – cardiovascular and glycemic benefit; considerations of timing with surgical interventions

Yin X, Zhu W, Liu C, et al. Association of continuous glucose monitoring-derived time in range with major amputation risk in diabetic foot osteomyelitis patients undergoing amputation. *Ther Adv Endocrinol Metabn* 2022

Multidisciplinary Care Coordination

- Gallup Indian Medical Center Preventing adverse Outcomes in Diabetic foot infections (POD) Squad
- Founded: July 2023, modeled closely on the VA PAVE Program
- Members: Podiatry, Diabetes Clinic, Infectious Diseases, Cardiology, Behavioral Health, Podiatry Nursing, Podiatry Case Management
- Meet weekly to discuss an iCare list of patients with current diabetic foot infections to coordinate care
- Current projects: developing an inpatient care pathway for DFI, obtaining equipment (non-invasive vascular studies, MRI), improving general PAD care and access to diabetic shoes, improving culture collection techniques by frontline providers in ED/walk in clinic