Progress in a pedestrian problem: A review of the revised Infectious Diseases Society of America diabetic foot infection guidelines

Benjamin A Lipsky

Citation: Lipsky BA (2013) Progress in a pedestrian problem: The revised Infectious Diseases Society of America diabetic foot infection guidelines. *The Diabetic Foot Journal* **16**: 56–62

Article points

1. Consider infection in all patients with a diabetic foot wound and if present classify it by the clinical severity.
2. Seek consultation from appropriate specialists for complex problems, particular from a multidisciplinary team and / or an experienced surgeon for deep or severe infections.
3. Treat most patients in an outpatient setting, but consider hospitalising those with a severe infection or complex problems.
4. Send specimens for culture after cleansing and debriding the wound; send tissue samples rather than swabs.
5. Base empiric antibiotic therapy for infected wounds on the likelihood of various pathogens then modify based on the results of cultures.
6. Osteomyelitis can be difficult to diagnose and treat; the guidelines provide suggestions for doing both.

Key words

- Guidance
- Infection
- Osteomyelitis

Author

Author details can be found on the last page of this article.

Foot infections are among the most common and severe complications of diabetes, and the usual final step leading to lower-extremity amputation. In 2004, the Infectious Diseases Society of America (IDSA) empaneled a multidisciplinary committee of experts to draft guidelines on the diagnosis and management of diabetic foot infections. Given the accelerating development of knowledge in this field the guidelines were updated in 2012 and have 14 tables, 1 figure, and 345 references, most published in the past decade. This review provides an update on infection for the diabetic foot practitioner.

Foot infections are now among the most common, and potentially devastating, complications of diabetes. Most diabetic foot infections (DFIs) start in a foot wound, usually one that results from the consequences of peripheral neuropathy (sensory, motor, autonomic), often with peripheral vascular disease in the background.

Infection occurs when organisms, usually the aerobic Gram-positive cocci colonising the surrounding skin, proliferate and cause a host response. This is manifest as signs and symptoms of inflammation, followed by tissue destruction. Unchecked, infection can progress contiguously to involve more of the superficial, and often the deeper, soft tissues. Ultimately, underlying bone becomes infected in about 20% of DFIs (Lipsky and Berendt, 2008).

Diabetic foot infection guidelines have been published by an expert panel selected by the Infectious Diseases Society of America (IDSA; Lipsky et al, 2012a) and the International Working Group on the Diabetic Foot (Lipsky et al, 2012b), and represent updates of guidelines published by each of these groups in 2004. The format of the new IDSA DFI guidelines largely consists of posing questions, answering them, and providing and grading the evidence used for the answers. The 10 questions can be summarised as follows:

1. In which patients with diabetes and a foot wound should I suspect infection, and how should I classify foot wounds?

Consider the possibility of infection in any foot wound in a person with diabetes; those with neuropathy, a previous foot wound or amputation, peripheral arterial disease, or renal insufficiency are at increased risk. Clinicians should be attuned to the signs and symptoms of life- or limb-threatening DFI, which are summarised in *Box 1*.

Classify wounds using a validated system; for infection, this includes the IDSA definitions of uninfected and mild, moderate, and severe infection (*Box 2*; *Table 1*). Using a validated wound scoring system may be helpful to follow progress during treatment (Lipsky et al, 2009).

2. How should I assess the patient with diabetes presenting with a foot infection?

Evaluate the patient at three levels: the whole patient, the affected limb, and the wound. Diagnose infection by the presence of classic signs of local infection (*Box 2*), and occasionally by the presence of various secondary findings (e.g. undermining, poor-quality granulation tissue) in the wound.

Assess the patient for evidence of clinically significant peripheral ischemia, which may require revascularisation. Assess the need to debride any necrotic tissue or surrounding callus.

3. When should I request a consultation for a patient with a DFI, and from whom?

Attempt to provide a well-coordinated approach to management for both outpatients and inpatients with DFIs, including the involvement of appropriate specialists (e.g. podiatrists, orthopaedic or vascular surgeons, infectious diseases specialist) when needed. This is best accomplished within the setting of a multidisciplinary foot team, but otherwise should be coordinated by a designated clinician. Seek expertise in providing optimal pressure offloading of the wound, if needed.

4. Which patients with a DFI should I hospitalise, and what criteria should they meet before being discharged?

Hospitalisation is by far the most expensive aspect of managing a DFI and is needed only in specific situations, including:

- Those with a severe infection
- Those requiring inpatient diagnostic or therapeutic procedures.
- Those with complex wound care requirements
- Those with psycho–social issues that preclude outpatient treatment.

Prior to discharge, the patient should have had any urgent procedures performed, be clinically stable, be able to manage as an outpatient, and have a well-defined treatment follow-up plan.

5. When and how should I send specimen/s for microbiological culture from a patient with a diabetic foot wound?

It is unnecessary to culture clinically uninfected wounds, but clinicians should obtain appropriate specimens from most wounds with evidence of infection. These should preferably be deep-tissue specimens, obtained by biopsy or curettage after wound cleansing and debridement, or aspirates of

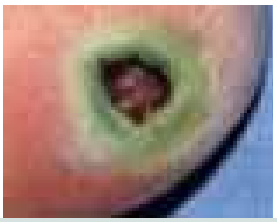
Box 1. Signs and symptoms of a possibly life- or limb-threatening infection. It should be noted that, in clinical setting with less advanced services available, lesser degrees of infection may be limb-threatening.

- Evidence of systemic inflammatory response
- Rapid progression of infection
- Extensive necrosis or gangrene
- Crepitus on examination or tissue gas on imaging
- Extensive ecchymoses or petechiae
- Bullae, especially haemorrhagic
- New onset wound anaesthesia
- Pain out of proportion to clinical findings
- Recent loss of neurologic function
- Critical limb ischaemia
- Extensive soft tissue loss
- Extensive bony destruction, especially in the mid- or hind-foot
- Failure of infection to improve with appropriate therapy

Box 2. Local infection is as defined by the presence of at least two of the following:

- Local swelling or induration
- Erythema (>0.5 cm)
- Local tenderness or pain
- Local warmth
- Purulent discharge (opaque to white or sanguineous secretion)

Table 1. Clinical manifestations of infection by severity based on the definitions of the Infectious Disease Society of America (Lipsky et al, 2009).

	Clinical manifestations of infection	
Unifected†	• No symptoms or signs of infection	
Mild infection‡	• Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below) • If erythema, must be >0.5 cm to ≤2 cm around the ulcer • Exclude other causes of an inflammatory response of the skin (e.g. trauma, gout, acute Charcot neuro-osteoarthropahy, fracture, thrombosis, venous stasis)	
Moderate infection§	• Local infection with erythema >2 cm, or involving structures deeper than the skin and subcutaneous tissues (e.g. abscess, osteomyelitis, septic arthritis, fasciitis) AND • No systemic inflammatory response signs (as described below)	
Severe infection¶,††	• Local infection with the signs of systemic inflammatory response syndrome, as manifested by ≥2 of the following: ▸ Temperature >38°C or <36°C ▸ Heart rate >90 beats/minute ▸ Respiratory rate >20 breaths/minute or $PaCO_2$ <32 mmHg ▸ White blood cell count >12 000 or <4000 cells/mm^3 or 10% immature (band) forms	

The International Working Group of the Diabetic Foot developed the PEDIS (perfusion, extent/size, depth/tissue loss, infection, sensation) grading system to classify diabetic foot ulcers (Schaper, 2004); the classifications provided here correspond to PEDIS grades 1=†, 2=‡, 3=§, 4=¶.
††Foot ischaemia may increase the severity of any infection, and the presence of critical ischaemia often makes the infection severe. Systemic infection may sometimes manifest with other clinical findings, such as hypotension, confusion, vomiting, or evidence of metabolic disturbances, such as acidosis, severe hyperglycaemia, or new-onset azotemia.

purulent secretions. Wound surface swab specimens are likely to yield colonising organisms and miss true pathogens and should be avoided.

6. How should I initially select, and when should I modify, an antibiotic regimen for a DFI?

While all foot lesions require appropriate wound care, only clinically infected wounds need antibiotic treatment. An empiric antibiotic regimen, based on the severity of the infection and the likely aetiological agent/s, should be initially selected (*Table 2; Table 3*).

For mild to moderate infections in patients who have not recently received antibiotic treatment, targeting just aerobic Gram-positive cocci (especially *Staphylococcus aureus*) is usually sufficient. For severe infections, initiate broad-spectrum empiric therapy, pending the results of culture and sensitivity testing. Empiric therapy directed at *Pseudomonas aeruginosa* is usually unnecessary, except in those patients with risk factors for true infection with this organism.

Table 2. Suggested empiric antibiotic regimens based on clinical severity and probable pathogen/s for diabetic foot infections (adapted from Lipsky et al [2012a]).

Probable pathogen/s	Antibiotic agent	Notes
Infection severity: *Mild*		
MSSA; *Streptococcus* sp.	Dicloxacillin or flucloxacillin	Requires dosing four times each day; narrow-spectrum; inexpensive
	Clindamycin†	Usually active against community-associated MRSA, but check macrolide sensitivity and consider ordering a D-test before use; inhibits protein synthesis of some bacterial toxins
	Cephalexin†§	Requires dosing four times each day; inexpensive
	Levofloxacin†	Once daily dosing; suboptimal against *Staphylococcus aureus*
	Amoxicillin / clavulanate†§	Relatively broad-spectrum oral agent that includes anaerobic coverage
MRSA	Doxycycline	Active against many MRSA and some Gram-negative sp.; uncertain against *Streptococcus* sp.
	Trimethoprim / sulfamethoxazole	Active against many MRSA and some Gram-negative sp.; uncertain against Streptococci
Infection severity: *Moderate or Severe*		
MSSA; *Streptococcus* sp.; Enterobacteriaceae obligate anaerobes	Levofloxacin†	Once daily dosing; suboptimal against *S. aureus*
	Cefoxitin†	Second generation cephalosporin with anaerobic coverage
	Ceftriaxone	Third generation cephalosporin; once daily dosing
	Ampicillin / sulbactam†§	Adequate if low suspicion of *P. aeruginosa*
	Moxifloxacin†	Once daily oral dosing; relatively broad-spectrum including most obligate anaerobic organisms
	Ertapenem†	Once daily dosing; relatively board-spectrum including anaerobes; not active against *P. aeruginosa*
	Tigecycline†	Active against MRSA; spectrum may be excessively broad; high rates of nausea and vomiting and increased mortality warning. Non-equivalent to ertapenem and vancomycin in one randomised clinical trial
	Levofloxacin† or ciprofloxacin† with clindamycin†	Limited evidence supporting clindamycin for sever *S. aureus* infections; oral and intravenous formulations for both drugs
	Imipenem / cilastatin†	Very broad-spectrum (but not against MRSA); use only when this is required; consider when ESBL-producing pathogens suspected
MRSA	Linezolid†	Expensive; increased risk of toxicities when used for >2 weeks
	Daptomycin†	Once daily dosing; requires serial monitoring of CPK
	Vancomycin†§	Vancomycin minimum inhibitory concentrations for MRSA are gradually increasing
Pseudomonas aeruginosa	Piperacillin / tazobactam†§	*P. aeruginosa* is an uncommon pathogen in DFIs except in special circumstances; dosing three to four times a day; useful for board-spectrum coverage
MRSA, Enterobacteriaceae	Vancomycin‡§ plus one of the following: ceftazidime, cefepime, piperacillin / tazobactam†, aztreonam†, or a carbapenem†	Very broad-spectrum coverage; usually only used for empiric therapy of severe infection; consideration addition of obligate anaerobe coverage if ceftazidime, cefepime, or aztreonam selected

CPK, creatine phosphokinase; DFI, diabetic foot infection; ESBL, extended-spectrum beta-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; sp., species.

†This agent has been shown to be effective in clinical trials that included patients with DFIs; ‡daptomycin or linezolid may be substituted for vancomycin; §agent commonly used as a comparator in clinical trials.

Notes: Agents approved by the US Food and Drug Administration for treating skin and skin-structure infections based on studies that excluded patients with DFIs (e.g. ceftaroline, telvancin) are not included; Narrow spectrum agents (e.g. vancomycin, linesolid, daptomycin) should be combined with other agents (e.g. a fluoroquinolone) if a polymicrobial infection (especially if moderate to severe) is suspected. Use an agent active against MRSA for patients who have a severe infection, evidence of infection or colonization with this organism elsewhere, or epidemiological risk factors for MRSA infection. Select definitive regimens after considering the results of culture and susceptibility tests from wound specimens, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted for the suggested agents.

Consider providing empiric therapy directed against methicillin-resistant *S. aureus* (MRSA) in patients with a history of MRSA infection, when the local prevalence of MRSA colonisation or infection is high, or if the infection is clinically severe.

Routes and length of antibiotic therapy are summarised in *Table 4*. Base the route of therapy largely on infection severity, with parenteral therapy for all severe, and some moderate, DFIs, at least initially, and switch to oral agents when the patient is systemically well and culture results are available. Use highly bioavailable oral antibiotics in most mild, and in many moderate, infections. Consider topical antimicrobial therapy for selected mild superficial infections.

Base definitive antibiotic therapy on the results of culture and sensitivity testing of an appropriately obtained wound specimen, as well as the patient's clinical response to the empiric regimen. Continue antibiotic therapy until, but not beyond, resolution of the infection, but not through complete healing of the wound; for soft tissue infections this will usually be approximately 1–3 weeks.

7. When should I consider imaging studies to evaluate a DFI, and which should I select?

Order plain radiographs for almost all patients presenting with a new DFI to look for bony abnormalities, soft tissue gas, and radio-opaque foreign bodies. For patients who require more sensitive or specific imaging, particularly when soft tissue abscess or osteomyelitis is suspected, magnetic resonance imaging (MRI) is the study of choice. If MRI is unavailable or contraindicated, consider the combination of a radionuclide bone scan and a labelled white blood cell scan.

8. How should I diagnose and treat osteomyelitis of the foot in a patient with diabetes?

Consider the possibility of osteomyelitis in the presence of any infected, deep, or large foot ulcer, especially one that is chronic or overlies a bony prominence. A properly performed and interpreted probe-to-bone test in a DFI with an open wound can help to diagnose diabetic foot osteomyelitis (high likelihood) or exclude it (low likelihood).

Plain X-rays have relatively low sensitivity and specificity for confirming or excluding osteomyelitis, but serial X-rays over a period of weeks may be useful. MRI is the best of the advanced diagnostic imaging studies for osteomyelitis, but is usually needed only when diagnostic uncertainty remains after clinical and plain X-ray evaluations.

The definitive diagnosis of osteomyelitis rests on bone culture, combined with histopathology. Bone biopsy is most appropriate when there is diagnostic uncertainty, inadequate culture information, or failure of response to an empiric treatment.

Table 3. Usual microbiology of diabetic foot infections based on clinical situation.

Clinical situation	Most common pathogens
Acute wound infection *[no recent antibiotic therapy or major immune dysfunction]*	Aerobic gram-positive cocci; *Staphylococcus aureus* > beta-haemolytic streptococci (especially group B); coagulase-negative staphylococci
Chronic wound *[recent antimicrobial therapy, immunopathy]*	Aerobic Gram-positive cocci often combined with aerobic Gram-negative rods (*Enterobacteriaceae* > non-fermenters); occasionally *Enterococcus* species
Wounds in hot climates, water exposure	*Pseudomonas aeruginosa*
Ischaemic or necrotic wounds	Obligate anaerobes (*Peptostreptococcus, Peptococcus, Fingoldia magna, Bacteroides* species)

Table 4. Suggested route†, and duration, of antibiotic therapy for diabetic foot infections by extent and involvement of tissue and bone.

	Topical	Oral	Parenteral	Initial parenteral, switch to oral when appropriate	Duration
Soft tissue infection					
Mild	✓	✓			1–2 weeks‡
Moderate				✓	1–3 weeks
Severe				✓	2–4 weeks
Bone infection					
No residual infected bone (e.g. postamputation)		✓	✓		2–5 days
Residual infected soft tissue (but not bone)		✓	✓		1–3 weeks
Residual infected, but viable, bone				✓	4–6 weeks
No surgery, or residual postoperative nonviable bone				✓	≥3 months

†Agents can be given by more than one route, either sequentially or simultaneously; ‡up to 4 weeks if resolution is slow.

"The evidence base for managing diabetic foot infections is now robust enough to allow good outcomes – especially the avoidance of major amputations – in the majority of patients."

Consider using either primarily surgical or primarily medical strategies for treating diabetic foot osteomyelitis in properly selected patients. The duration of antibiotic therapy can be short (2–5 days) when surgical resection leaves no remaining infected tissue, but should be more prolonged (≥4 weeks) when there is persistent infected or necrotic bone.

9. In which patients with a DFI should I consider surgical intervention and what procedures may be appropriate?

Consider urgent surgical intervention for DFIs accompanied by gas in the deeper tissues, an abscess, or evidence of necrotizing fasciitis, and less urgent surgery for wounds with substantial nonviable tissue, or extensive bone or joint involvement in the infection. The surgeon should have experience managing patients with DFIs and knowledge about foot anatomy.

10. What type of wound care techniques and dressings should I use for a patient with a diabetic foot wound?

Key aspects of wound care include adequate cleansing, debridement of callus and necrotic tissue, selecting an appropriate dressing that will allow for moist wound healing while controlling excess exudate, and pressure offloading. When an infected wound is unresponsive to treatment, consider whether the problem is a failure of the infection to respond (due to untreated ischemia, inadequate drainage or debridement, pathogens that are resistant to the prescribed therapy, or lack patient adherence to the antibiotic regimen) or failure of the wound to heal (because of lack of adherence to the dressing regimen or offloading device, misdiagnosis of the cause of the wound, or inadequate blood flow).

Among adjunctive measures, hyperbaric oxygen therapy may help heal wounds more quickly, but has not been shown to improve infection outcomes, and granulocyte-colony stimulating factors may reduce the need for various surgical interventions, but do not appear to improve other infectious outcomes.

Conclusions

The IDSA expert panel recommend several areas that would be most useful to investigate to improve the management of DFIs in the future. They include those related to implementation of available guidelines (e.g. deploying multidisciplinary teams, developing audit systems for both the process and outcomes of treatment, and encouraging clinicians and healthcare providers to assess and improve their outcomes) and those related to regulatory changes (e.g. developing guidance for studies of new agents for treating DFIs that will lead to marketing approval, including for osteomyelitis). Helpful future studies would elucidate the role of biofilm in DFIs and how best to manage it, and the potential usefulness of molecular microbiological techniques in DFI management.

In the past decade there has been an enormous increase in studies examining the epidemiology, pathophysiology, treatment, and outcome of DFIs. The evidence base for managing DFIs is now robust enough to allow good outcomes – especially the avoidance of major amputations – in the majority of patients. Efforts now must focus on the implementation of what we know works, while continuing to find better ways to manage this complex and potentially devastating problem. ■

Benjamin A Lipsky, Deputy Director, Graduate Education Course, University of Oxford Division of Medical Sciences, Oxford; Visiting Professor of Medicine, University of Geneva, Division of Infectious Diseases, Geneva, Switzerland; Emeritus Professor, University of Washington School of Medicine, Seattle, WA, USA

Lipsky BA, Berendt AR (2008) *The Diabetic Foot: Essentials of Managing Infectious Complications*. Springer, London

Lipsky BA, Polis, A, Lantz KC (2009) The value of a wound score for diabetic foot infections in predicting treatment outcome: a prospective analysis from the SIDESTEP trial. *Wound Repair Regen* **17**: 671–7

Lipsky BA, Berendt AR, Cornia PB et al (2012) Executive summary: 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* **54**: 1679–84

Lipsky BA, Peters EJ, Berendt AR et al (2012) Specific guidelines for the treatment of diabetic foot infections 2011. *Diabetes Metab Res Rev* **28**(Suppl 1): 234–5

Schaper NC (2004) Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev* **20**(Suppl 1): S90–5