2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections[a]

Benjamin A. Lipsky,[1] Anthony R. Berendt,[2] Paul B. Cornia,[3] James C. Pile,[4] Edgar J. G. Peters,[5] David G. Armstrong,[6] H. Gunner Deery,[7] John M. Embil,[8] Warren S. Joseph,[9] Adolf W. Karchmer,[10] Michael S. Pinzur,[11] and Eric Senneville[12]

[1]Department of Medicine, University of Washington, Veterans Affairs Puget Sound Health Care System, Seattle; [2]Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford; [3]Department of Medicine, University of Washington, Veteran Affairs Puget Sound Health Care System, Seattle; [4]Divisions of Hospital Medicine and Infectious Diseases, MetroHealth Medical Center, Cleveland, Ohio; [5]Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands; [6]Southern Arizona Limb Salvage Alliance, Department of Surgery, University of Arizona, Tucson; [7]Northern Michigan Infectious Diseases, Petoskey; [8]Department of Medicine, University of Manitoba, Winnipeg, Canada; [9]Division of Podiatric Surgery, Department of Surgery, Roxborough Memorial Hospital, Philadelphia, Pennsylvania; [10]Department of Medicine, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [11]Department of Orthopaedic Surgery and Rehabilitation, Loyola University Medical Center, Maywood, Illinois; and [12]Department of Infectious Diseases, Dron Hospital, Tourcoing, France

Foot infections are a common and serious problem in persons with diabetes. Diabetic foot infections (DFIs) typically begin in a wound, most often a neuropathic ulceration. While all wounds are colonized with microorganisms, the presence of infection is defined by ≥2 classic findings of inflammation or purulence. Infections are then classified into mild (superficial and limited in size and depth), moderate (deeper or more extensive), or severe (accompanied by systemic signs or metabolic perturbations). This classification system, along with a vascular assessment, helps determine which patients should be hospitalized, which may require special imaging procedures or surgical interventions, and which will require amputation. Most DFIs are polymicrobial, with aerobic gram-positive cocci (GPC), and especially staphylococci, the most common causative organisms. Aerobic gram-negative bacilli are frequently copathogens in infections that are chronic or follow antibiotic treatment, and obligate anaerobes may be copathogens in ischemic or necrotic wounds.

Wounds without evidence of soft tissue or bone infection do not require antibiotic therapy. For infected wounds, obtain a post-debridement specimen (preferably of tissue) for aerobic and anaerobic culture. Empiric antibiotic therapy can be narrowly targeted at GPC in many acutely infected patients, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections usually require broader spectrum regimens. Imaging is helpful in most DFIs; plain radiographs may be sufficient, but magnetic resonance imaging is far more sensitive and specific. Osteomyelitis occurs in many diabetic patients with a foot wound and can be difficult to diagnose (optimally defined by bone culture and histology) and treat (often requiring surgical debridement or resection, and/or prolonged antibiotic therapy). Most DFIs require some surgical intervention, ranging from minor (debridement) to major (resection, amputation). Wounds must also be properly dressed and off-loaded of pressure, and patients need regular follow-up. An ischemic foot may require revascularization, and some nonresponding patients may benefit from selected adjunctive measures. Employing multidisciplinary foot teams improves outcomes. Clinicians and healthcare organizations should attempt to monitor, and thereby improve, their outcomes and processes in caring for DFIs.

Received 21 March 2012; accepted 22 March 2012.

[a]It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Correspondence: Benjamin A. Lipsky, MD, University of Washington, VA Puget Sound Health Care System, 1660 S Columbian Way, Seattle, WA 98108 (balipsky@uw.edu).

Clinical Infectious Diseases 2012;54(12):132–173
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2012.
DOI: 10.1093/cid/cis346

EXECUTIVE SUMMARY

Diabetic foot infections (DFIs) are a frequent clinical problem. Properly managed, most can be cured, but many patients needlessly undergo amputations because of improper diagnostic and therapeutic approaches. Infection in foot wounds should be defined clinically by the presence of inflammation or purulence, and then classified by severity. This approach helps clinicians make decisions about which patients to hospitalize or to send for imaging procedures or for whom to recommend surgical interventions. Many organisms, alone or in combinations, can cause DFI, but gram-positive cocci (GPC), especially staphylococci, are the most common.

Although clinically uninfected wounds do not require antibiotic therapy, infected wounds do. Empiric antibiotic regimens must be based on available clinical and epidemiologic data, but definitive therapy should be based on cultures of infected tissue. Imaging is especially helpful when seeking evidence of underlying osteomyelitis, which is often difficult to diagnose and treat. Surgical interventions of various types are often needed and proper wound care is important for successful cure of the infection and healing of the wound. Patients with a DFI should be evaluated for an ischemic foot, and employing multidisciplinary foot teams improves outcomes.

Summarized below are the recommendations made in the new guidelines for diabetic foot infections. The expert panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [1–6] (Table 1). A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found online in the full text of the guidelines.

RECOMMENDATIONS FOR MANAGING DIABETIC FOOT INFECTIONS

I. In which diabetic patients with a foot wound should I suspect infection, and how should I classify it?

Recommendations

1. Clinicians should consider the possibility of infection occurring in any foot wound in a patient with diabetes (strong, low). Evidence of infection generally includes classic signs of inflammation (redness, warmth, swelling, tenderness, or pain) or purulent secretions, but may also include additional or secondary signs (eg, nonpurulent secretions, friable or discolored granulation tissue, undermining of wound edges, foul odor) (strong, low).
2. Clinicians should be aware of factors that increase the risk for DFI and especially consider infection when these factors are present; these include a wound for which the probe-to-bone (PTB) test is positive; an ulceration present for >30 days; a history of recurrent foot ulcers; a traumatic foot wound; the presence of peripheral vascular disease in the affected limb; a previous lower extremity amputation; loss of protective sensation; the presence of renal insufficiency; or a history of walking barefoot (strong, low).
3. Clinicians should select and routinely use a validated classification system, such as that developed by the International Working Group on the Diabetic Foot (IWGDF) (abbreviated with the acronym PEDIS) or IDSA (see below), to classify infections and to help define the mix of types and severity of their cases and their outcomes (strong, high). The DFI Wound Score may provide additional quantitative discrimination for research purposes (weak, low). Other validated diabetic foot classification schemes have limited value for infection, as they describe only its presence or absence (moderate, low).

II. How should I assess a diabetic patient presenting with a foot infection?

Recommendations

4. Clinicians should evaluate a diabetic patient presenting with a foot wound at 3 levels: the patient as a whole, the affected foot or limb, and the infected wound (strong, low).
5. Clinicians should diagnose infection based on the presence of at least 2 classic symptoms or signs of inflammation (erythema, warmth, tenderness, pain, or induration) or purulent secretions. They should then document and classify the severity of the infection based on its extent and depth and the presence of any systemic findings of infection (strong, low).
6. We recommend assessing the affected limb and foot for arterial ischemia (strong, moderate), venous insufficiency, presence of protective sensation, and biomechanical problems (strong, low).
7. Clinicians should debride any wound that has necrotic tissue or surrounding callus; the required procedure may range from minor to extensive (strong, low).

III. When and from whom should I request a consultation for a patient with a diabetic foot infection?

Recommendations

8. For both outpatients and inpatients with a DFI, clinicians should attempt to provide a well-coordinated approach by those with expertise in a variety of specialties, preferably by a multidisciplinary diabetic foot care team (strong, moderate). Where such a team is not yet available, the primary treating clinician should try to coordinate care among consulting specialists.

Table 1. Strength of Recommendations and Quality of the Evidence

Strength of Recommendation and Quality of Evidence	Clarity of Balance Between Desirable and Undesirable Effects	Methodological Quality of Supporting Evidence (Examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Strong recommendation, very low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect for at least 1 critical outcome is very uncertain
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low-quality evidence	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws, or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Weak recommendation, very low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects or may be closely balanced	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain

Abbreviation: RCT, randomized controlled trial.

9. Diabetic foot care teams can include (or should have ready access to) specialists in various fields; patients with a DFI may especially benefit from consultation with an infectious disease or clinical microbiology specialist and a surgeon with experience and interest in managing DFIs (strong, low).

10. Clinicians without adequate training in wound debridement should seek consultation from those more qualified for this task, especially when extensive procedures are required (strong, low).

11. If there is clinical or imaging evidence of significant ischemia in an infected limb, we recommend the clinician

consult a vascular surgeon for consideration of revascularization (strong, moderate).

12. We recommend that clinicians unfamiliar with pressure off-loading or special dressing techniques consult foot or wound care specialists when these are required (strong, low).

13. Providers working in communities with inadequate access to consultation from specialists might consider devising systems (eg, telemedicine) to ensure expert input on managing their patients (strong, low).

IV. Which patients with a diabetic foot infection should I hospitalize, and what criteria should they meet before I discharge them?

Recommendations

14. We recommend that all patients with a severe infection, selected patients with a moderate infection with complicating features (eg, severe peripheral arterial disease [PAD] or lack of home support), and any patient unable to comply with the required outpatient treatment regimen for psychological or social reasons be hospitalized initially. Patients who do not meet any of these criteria, but are failing to improve with outpatient therapy, may also need to be hospitalized (strong, low).

15. We recommend that prior to being discharged, a patient with a DFI should be clinically stable; have had any urgently needed surgery performed; have achieved acceptable glycemic control; be able to manage (on his/her own or with help) at the designated discharge location; and have a well-defined plan that includes an appropriate antibiotic regimen to which he/she will adhere, an off-loading scheme (if needed), specific wound care instructions, and appropriate outpatient follow-up (strong, low).

V. When and how should I obtain specimen(s) for culture from a patient with a diabetic foot wound?

Recommendations

16. For clinically uninfected wounds, we recommend not collecting a specimen for culture (strong, low).

17. For infected wounds, we recommend that clinicians send appropriately obtained specimens for culture prior to starting empiric antibiotic therapy, if possible. Cultures may be unnecessary for a mild infection in a patient who has not recently received antibiotic therapy (strong, low).

18. We recommend sending a specimen for culture that is from deep tissue, obtained by biopsy or curettage after the wound has been cleansed and debrided. We suggest avoiding swab specimens, especially of inadequately debrided wounds, as they provide less accurate results (strong, moderate).

VI. How should I initially select, and when should I modify, an antibiotic regimen for a diabetic foot infection? (See question VIII for recommendations for antibiotic treatment of osteomyelitis)

Recommendations

19. We recommend that clinically uninfected wounds not be treated with antibiotic therapy (strong, low).

20. We recommend prescribing antibiotic therapy for all infected wounds, but caution that this is often insufficient unless combined with appropriate wound care (strong, low).

21. We recommend that clinicians select an empiric antibiotic regimen on the basis of the severity of the infection and the likely etiologic agent(s) (strong, low).

    a. For mild to moderate infections in patients who have not recently received antibiotic treatment, we suggest that therapy just targeting aerobic GPC is sufficient (weak, low).

    b. For most severe infections, we recommend starting broad-spectrum empiric antibiotic therapy, pending culture results and antibiotic susceptibility data (strong, low).

    c. Empiric therapy directed at *Pseudomonas aeruginosa* is usually unnecessary except for patients with risk factors for true infection with this organism (strong, low).

    d. Consider providing empiric therapy directed against methicillin-resistant *Staphylococcus aureus* (MRSA) in a patient with a prior history of MRSA infection; when the local prevalence of MRSA colonization or infection is high; or if the infection is clinically severe (weak, low).

22. We recommend that definitive therapy be based on the results of an appropriately obtained culture and sensitivity testing of a wound specimen as well as the patient's clinical response to the empiric regimen (strong, low).

23. We suggest basing the route of therapy largely on infection severity. We prefer parenteral therapy for all severe, and some moderate, DFIs, at least initially (weak, low), with a switch to oral agents when the patient is systemically well and culture results are available. Clinicians can probably use highly bioavailable oral antibiotics alone in most mild, and in many moderate, infections and topical therapy for selected mild superficial infections (strong, moderate).

24. We suggest continuing antibiotic therapy until, but not beyond, resolution of findings of infection, but not through complete healing of the wound (weak, low). We suggest an initial antibiotic course for a soft tissue infection of about 1–2 weeks for mild infections and 2–3 weeks for moderate to severe infections (weak, low).

VII. When should I consider imaging studies to evaluate a diabetic foot infection, and which should I select?

Recommendations

25. We recommend that all patients presenting with a new DFI have plain radiographs of the affected foot to look for bony abnormalities (deformity, destruction) as well as for soft tissue gas and radio-opaque foreign bodies (strong, moderate).

26. We recommend using magnetic resonance imaging (MRI) as the study of choice for patients who require further (ie, more sensitive or specific) imaging, particularly when soft tissue abscess is suspected or the diagnosis of osteomyelitis remains uncertain (strong, moderate).

27. When MRI is unavailable or contraindicated, clinicians might consider the combination of a radionuclide bone scan and a labeled white blood cell scan as the best alternative (weak, low).

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

Recommendations

28. Clinicians should consider osteomyelitis as a potential complication of any infected, deep, or large foot ulcer, especially one that is chronic or overlies a bony prominence (strong, moderate).

29. We suggest doing a PTB test for any DFI with an open wound. When properly conducted and interpreted, it can help to diagnose (when the likelihood is high) or exclude (when the likelihood is low) diabetic foot osteomyelitis (DFO) (strong, moderate).

30. We suggest obtaining plain radiographs of the foot, but they have relatively low sensitivity and specificity for confirming or excluding osteomyelitis (weak, moderate). Clinicians might consider using serial plain radiographs to diagnose or monitor suspected DFO (weak, low).

31. For a diagnostic imaging test for DFO, we recommend using MRI (strong, moderate). However, MRI is not always necessary for diagnosing or managing DFO (strong, low).

32. If MRI is unavailable or contraindicated, clinicians might consider a leukocyte or antigranulocyte scan, preferably combined with a bone scan (weak, moderate). We do not recommend any other type of nuclear medicine investigations (weak, moderate).

33. We suggest that the most definitive way to diagnose DFO is by the combined findings on bone culture and histology (strong, moderate). When bone is debrided to treat osteomyelitis, we suggest sending a sample for culture and histology (strong, low).

34. For patients not undergoing bone debridement, we suggest that clinicians consider obtaining a diagnostic bone biopsy when faced with specific circumstances, eg, diagnostic uncertainty, inadequate culture information, failure of response to empiric treatment (weak, low).

35. Clinicians can consider using either primarily surgical or primarily medical strategies for treating DFO in properly selected patients (weak, moderate). In noncomparative studies each approach has successfully arrested infection in most patients.

36. When a radical resection leaves no remaining infected tissue, we suggest prescribing antibiotic therapy for only a short duration (2–5 days) (weak, low). When there is persistent infected or necrotic bone, we suggest prolonged (≥4 weeks) antibiotic treatment (weak, low).

37. For specifically treating DFO, we do not currently support using adjunctive treatments such as hyperbaric oxygen therapy, growth factors (including granulocyte colony-stimulating factor), maggots (larvae), or topical negative pressure therapy (eg, vacuum-assisted closure) (weak, low).

IX. In which patients with a diabetic foot infection should I consider surgical intervention, and what type of procedure may be appropriate?

Recommendations

38. We suggest that nonsurgical clinicians consider requesting an assessment by a surgeon for patients with a moderate or severe DFI (weak, low).

39. We recommend urgent surgical intervention for most foot infections accompanied by gas in the deeper tissues, an abscess, or necrotizing fasciitis, and less urgent surgery for wounds with substantial nonviable tissue or extensive bone or joint involvement (strong, low).

40. We recommend involving a vascular surgeon early on to consider revascularization whenever ischemia complicates a DFI, but especially in any patient with a critically ischemic limb (strong, moderate).

41. Although most qualified surgeons can perform an urgently needed debridement or drainage, we recommend that in DFI cases requiring more complex or reconstructive procedures, the surgeon should have experience with these problems and adequate knowledge of the anatomy of the foot (strong, low).

X. What types of wound care techniques and dressings are appropriate for diabetic foot wounds?

Recommendations

42. Diabetic patients with a foot wound should receive appropriate wound care, which usually consists of the following:

a. Debridement, aimed at removing debris, eschar, and surrounding callus (strong, moderate). Sharp (or surgical) methods are generally best (strong, low), but mechanical, autolytic, or larval debridement techniques may be appropriate for some wounds (weak, low).

b. Redistribution of pressure off the wound to the entire weight-bearing surface of the foot ("off-loading").

While particularly important for plantar wounds, this is also necessary to relieve pressure caused by dressings, footwear, or ambulation to any surface of the wound (strong, high).

c. Selection of dressings that allow for moist wound healing and control excess exudation. The choice of dressing should be based on the size, depth, and nature of the ulcer (eg, dry, exudative, purulent) (strong, low).

43. We do not advocate using topical antimicrobials for treating most clinically uninfected wounds.

44. No adjunctive therapy has been proven to improve resolution of infection, but for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents (weak, moderate), growth factors (weak, moderate), granulocyte colony-stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low).

INTRODUCTION

Foot infections in persons with diabetes are an increasingly common problem and are associated with potentially serious sequelae. The continued rise in incidence of diabetes in developed, and to an even greater degree in many lesser-developed, countries, the increasing body weight of many diabetic patients, and their greater longevity all contribute to the growth of this problem. Diabetic foot infections (DFIs) usually arise either in a skin ulceration that occurs as a consequence of peripheral (sensory and motor) neuropathy or in a wound caused by some form of trauma. Various microorganisms inevitably colonize the wound; in some patients 1 or more species of organisms proliferate in the wound, which may lead to tissue damage, followed by a host response accompanied by inflammation, that is, clinical infection. These infections can then spread contiguously, including into deeper tissues, often reaching bone. Even when DFIs are acute and relatively mild, they usually cause major morbidity, including physical and emotional distress and lost mobility, as well as substantial direct and indirect financial costs.

If the infection progresses, many patients require hospitalization and, all too often, surgical resections or an amputation. Diabetic foot complications continue to be the main reason for diabetes-related hospitalization and lower extremity amputations. The most recent data from the US Centers for Disease Control and Prevention (CDC) show that the annual number of hospitalizations for diabetic foot "ulcer/infection/inflammation" continued to rise steadily from 1980 to 2003, when it exceeded 111 000, thereby surpassing the number attributed to peripheral arterial disease (PAD) [7]. Not surprisingly, the annual number of hospital discharges for nontraumatic lower extremity amputations also increased steadily in the early 1990s, but fortunately have recently leveled off to 71 000 in 2005 [8]. The additional good news is that the annual rate of amputations in the United States has almost halved in the past decade, to 4.6 per 1000 persons with diabetes, and most of this decrease has been in major (above the ankle) amputations [9]. These findings differ, however, from those in a more recent study from the United Kingdom, which found that between 1996 and 2005, while the number of amputations in patients with type 1 diabetes decreased substantially, in those with type 2 diabetes the number of minor amputations almost doubled and major amputations increased >40% [10]. Unfortunately, many diabetic patients who undergo a lower extremity amputation have a very poor quality of life and have a 5-year mortality rate similar to that of some of the most deadly cancers [11].

Since the publication of the initial DFI guidelines in 2004, we have learned a good deal about this complex problem. The Thomson Reuters ISI Web of Science for 2010 exemplifies the steadily increasing number of published reports on DFIs; the yearly number of published items rose from <than 20 in the 1990s to about 100 in the past few years (http://pcs.isiknowledge.com/). Two series of prospective observations from Europe exemplify the rigorous approach that is now beginning to provide the evidence we need to better manage DFIs. In 2010 the Observational Study of the Infected Diabetic Foot reported its findings on 291 evaluable consecutively enrolled patients hospitalized with a DFI at any of 38 specialized hospital centers [12]. Among their findings were the following: almost all of the patients had peripheral neuropathy; more than half had PAD; and nearly half had evidence of osteomyelitis. In the year prior to hospitalization, 40% had a history of an infected foot ulcer (perhaps implying inadequate outpatient care); most infections involved the toes (45%) or forefoot (34%) and were of moderate severity (by Infectious Diseases Society of America [IDSA] criteria). Clinicians performed cultures on 86% of patients (usually by swabbing the wound) and initiated antibiotic therapy for all patients (half of whom had received antibiotic therapy in the preceding 3 months) with a total of 62 combinations of agents. Highly noteworthy is that in 56% of patients the initial antibiotic regimen was changed, mainly because of a mismatch with the culture susceptibility results. The median duration of hospitalization was 3 weeks and 35% of patients underwent some type of lower extremity amputation. Overall, 48% of patients had an unfavorable outcome of hospitalization. Worse, in follow-up a year after discharge, an additional 19% of patients had had an amputation and 21% of the nonamputated patients had persistent or recurrent infection of the site, meaning that <30% of the enrolled patients had a healed wound. The presence of PAD was

significantly associated with a poor outcome, yet it was often not addressed by the treating clinicians.

Another enlightening series of investigations conducted in the past decade by the Eurodiale study group, a consortium of 14 centers of expertise in the field of diabetic foot disease, has greatly increased our knowledge on the epidemiology of this problem. During one year (2003–2004), 1229 consecutive patients presenting with a new foot ulcer, 27% of whom were hospitalized, were enrolled in an observational, prospective data collection study. At enrollment, more than one-quarter of the patients had been treated for >3 months before being referred to a foot clinic and more than three-quarters had not had adequate wound off-loading. Half of the patients had PAD and 58% of the foot ulcers were clinically infected; the one-third of patients with both neuropathy and PAD had more severe infections and underlying comorbidities [13]. After 1 year of follow-up, 23% of the patients had not healed their foot ulcer; among independent baseline predictors of nonhealing, PAD was key, and infection was a predictor only in patients with PAD [14]. Infection was also 1 of 4 independent predictors of minor amputation in these patients [15]. The highest costs per patient were those for hospitalization, antibiotic therapy, and surgery, and these increased with the severity of disease. The total cost per patient was >4 times higher for patients with infection and PAD than for those with neither [16]. Based on other recent studies and the collective experience of the panel members, we believe that the following conclusions of the Eurodiale investigators apply to all parts of the world: treatment of many DFI patients is not in line with current guidelines; there are great variations in management among different countries and centers; currently available guidelines are too general, lacking specific guidance; and, healthcare organizational barriers and personal beliefs result in underuse of recommended therapies [17].

Can we do better? Unquestionably. For >20 years, studies in many settings have reported improvements in outcomes with DFIs (especially reduced major amputation rates) when patients are cared for in specialty diabetic foot clinics or by specialized inpatient foot teams. A key factor in this success has been the multidisciplinary nature of the care. A decade ago Denmark established a multidisciplinary wound healing center and integrated diabetic foot care as an expert function in their national healthcare organization. They found that the center broadly enhanced the knowledge and understanding of wound problems, improved healing rates in patients with leg ulcers, and decreased rates of major amputations [18]. We agree with their conclusion that this model, with minor adjustments for local conditions, is applicable for most industrialized and developing countries. More recently, a report from one city in Germany showed a 37% reduction in the incidence of nontraumatic lower limb amputations (mostly in diabetic patients) when comparing data from 1990–1991 to those from 1994–2005, likely as a consequence of introducing a network of specialized physicians and defined clinical pathways for diabetic foot wound treatment and metabolic control [19].

One UK hospital reduced the total incidence of amputations by 40% and major amputations by 62% over an 11-year period following improvements (including multidisciplinary team work) in foot care services [20]. They made the important observation that when they lost financial support for the multidisciplinary team the rates of amputation rose, but they fell again with renewed support. Recent studies have shown that adopting even relatively simple protocols with no increase in staffing can lead to improved outcomes and lower costs [21]. Hospitals in small or underdeveloped areas have also shown statistically significant improvements in outcomes of DFI after adopting systems of education and applying multidisciplinary protocols [22]. We agree with the conclusions of the authors of a study that used a risk-based Markov analysis of data from Dutch studies that "management of the diabetic foot according to guideline-based care improves survival, reduces diabetic foot complications, and is cost-effective and even cost saving compared with standard care" [23].

Recently, the UK National Institute for Clinical Excellence (NICE) Guideline Development group published guidance for inpatient management of diabetic foot problems on the basis of a systematic review of published data [24]. We largely agree with their recommendations and offer this brief summary. Each hospital should have a care pathway for inpatients with a diabetic foot problem, including any break in the skin, inflammation, swelling, gangrene, or signs of infection. Optimally, a multidisciplinary foot care team comprised of professionals with the needed specialist skills should evaluate the patient's response to medical, surgical, and diabetes management within 24 hours of the initial examination. This evaluation will include determining the need for specialist wound care, debridement, pressure off-loading, or any other vascular or surgical interventions; reviewing the treatment of any infection (with antibiotic therapy based on guidelines established by each hospital); and assessing the need for interventions to prevent other foot deformities or recurrent foot problems [24]. The foot care team should also help to arrange discharge planning for both primary (and/or community) and specialist care.

Another logical way of improving care would be to further empower those with most at stake—persons with diabetes. Although we know a good deal about how to prevent diabetic foot wounds [25], few studies have investigated the value of educating diabetic patients. In one prospective controlled

study, providing patients with computerized information on preventive measures (including foot care) improved the use of screening tests by their providers [26]. We think we now have the knowledge to dramatically improve outcomes in patients presenting with a DFI. What we most need is the administrative will and support to ensure that various types of clinicians are educated about their respective roles, that clinicians and healthcare institutions assess and attempt to improve their outcomes, and that patients have ready access to appropriate care.

Most of the information contained in the previous DFI guideline is still applicable. Having produced an extensive and heavily referenced work in 2004, our goal with this revision of the guideline was to reformat it in the new IDSA style and make it a companion to the previous work that not only updates our recommendations on the basis of recent data, but to make them relatively simple and, we hope, clear. We elected to address 10 clinical questions in the current guideline:

(I) In which diabetic patients with a foot wound should I suspect infection, and how should I classify it?
(II) How should I assess a diabetic patient presenting with a foot infection?
(III) When and from whom should I request a consultation for a patient with a diabetic foot infection?
(IV) Which patients with a diabetic foot infection should I hospitalize, and what criteria should they meet before I discharge them?
(V) When and how should I obtain specimen(s) for culture from a patient with a diabetic foot wound?
(VI) How should I initially select, and when should I modify, an antibiotic regimen for a diabetic foot infection?
(VII) When should I consider imaging studies to evaluate a diabetic foot infection, and which should I select?
(VIII) How should I diagnose and treat osteomyelitis of the foot in a patient with diabetes?
(IX) In which patients with a diabetic foot infection should I consider surgical intervention, and what type of procedure may be appropriate?
(X) What types of wound care techniques and dressings are appropriate for diabetic foot wounds?

PRACTICE GUIDELINES

"Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate healthcare for specific clinical circumstances" [27]. Attributes of high-quality guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [27].

METHODS

Panel Composition

We convened a panel of 12 experts, including specialists in infectious diseases, primary care/general internal medicine, hospital medicine, wound care, podiatry, and orthopedic surgery. The panel included physicians with a predominantly academic position, those who are mainly clinicians, and those working in varied inpatient and outpatient settings. Among the 12 panel members, 6 had been on the previous DFI guideline panel, and 4 are based outside the United States.

Literature Review and Analysis

Following the IDSA format, the panel selected the questions to address and assigned each member to draft a response to at least 1 question in collaboration with another panel member. Panel members thoroughly reviewed the literature pertinent to the selected field. In addition, the panel chair searched all available literature, including PubMed/Medline, Cochrane Library, EBSCO, CINAHL, Google Scholar, the National Guidelines Clearinghouse, ClinicalTrials.gov, references in published articles, pertinent Web sites, textbooks, and abstracts of original research and review articles in any language on foot infections in persons with diabetes. For the past 8 years the chair has also conducted a prospective systematic literature search, using a strategy developed with the help of a medical librarian, for a weekly literature review for updates on any aspect of DFIs in all languages.

The panel chair also searched publications listed in PubMed from 1964 to January 2011 to find articles that assessed diabetic patients for risk factors for developing a foot infection using the following query: ("diabetic foot" [MeSH Terms] OR ("diabetic" [All Fields] AND "foot" [All Fields]) OR "diabetic foot" [All Fields]) AND ("infection" [MeSH Terms] OR "infection" [All Fields] OR "communicable diseases" [MeSH Terms] OR ("communicable" [All Fields] AND "diseases" [All Fields]) OR "communicable diseases" [All Fields]) AND ("risk factors" [MeSH Terms] OR ("risk" [All Fields] AND "factors" [All Fields]) OR "risk factors" [All Fields]).

Process Overview

In updating this guideline the panel followed the newly created Grading of Recommendations Assessment, Development and Evaluation (GRADE) system recommended by IDSA [1, 3–6]. This included systematically weighting the quality of the available evidence and grading our recommendations. To evaluate evidence, the panel followed a process consistent with other IDSA guidelines, including a systematic weighting of the quality of the evidence and the grade of recommendation (Table 1) [1–6, 28, 29]. High-quality evidence does not necessarily lead to strong recommendations; conversely, strong

recommendations can arise from low-quality evidence if one can be confident that the desired benefits clearly outweigh the undesirable consequences. The main advantages of the GRADE approach are the detailed and explicit criteria for grading the quality of evidence and the transparent process for making recommendations [1–6, 28, 29].

This system requires that the assigned strength of a recommendation be either "strong" or "weak." The main criterion for assigning a "strong" recommendation is that the potential benefits clearly outweigh the potential risks. The panel chair and vice-chair reviewed all the recommendation gradings and then worked with the panel to achieve consensus via teleconference and e-mail.

Consensus Development Based on Evidence

Most of the panel members met in person twice, at the time of the 2007 and 2008 IDSA annual meetings. They also held 2 teleconferences and frequently corresponded electronically. The chair presented a preliminary version of the guidelines at the 2009 IDSA annual meeting and sought feedback by distributing a questionnaire to those attending the lecture. All members of the panel participated in the preparation of questions for the draft guideline, which were then collated and revised by the chair and vice-chair, and this draft was disseminated for review by the entire panel. The guideline was reviewed and endorsed by the Society of Hospital Medicine and the American Podiatric Medical Association. We also sought and received extensive feedback from several external reviewers, and the guideline manuscript was reviewed and approved by the IDSA Standards and Practice Guidelines Committee (SPGC) and by the IDSA Board of Directors.

Guidelines and Conflicts of Interest

All members of the expert panel complied with the IDSA policy regarding conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the expert panel were provided a conflicts of interest disclosure statement from IDSA and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. The statement requested information regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel was instructed to make decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict, but no limiting conflicts were identified.

Revision Dates

At annual intervals, the panel chair, the liaison advisor, and the chair of the SPGC will determine the need for revisions to the updated guideline based on an examination of current literature. If necessary, the entire panel will reconvene to discuss potential changes. When appropriate, the panel will recommend full revision of the guideline to the IDSA SPGC and the board for review and approval.

RECOMMENDATIONS FOR MANAGING DIABETIC FOOT INFECTIONS

I. In which diabetic patients with a foot wound should I suspect infection, and how should I classify it?

Recommendations

1. Clinicians should consider the possibility of infection occurring in any foot wound in a patient with diabetes (strong, low). Evidence of infection generally includes classic signs of inflammation (redness, warmth, swelling, tenderness, or pain) or purulent secretions but may also include additional or secondary signs (eg, nonpurulent secretions, friable or discolored granulation tissue, undermining of wound edges, foul odor) (strong, low).
2. Clinicians should be aware of factors that increase the risk for DFI and especially consider infection when these factors are present; these include a wound for which the probe-to-bone (PTB) test is positive; an ulceration present for >30 days; a history of recurrent foot ulcers; a traumatic foot wound; the presence of peripheral vascular disease in the affected limb; a previous lower extremity amputation; loss of protective sensation; the presence of renal insufficiency; or a history of walking barefoot (strong, low).
3. Clinicians should select and routinely use a validated classification system, such as that developed by the International Working Group on the Diabetic Foot (IWGDF) (abbreviated with the acronym PEDIS) or IDSA (see below), to classify infections and to help define the mix of types and severity of their cases and their outcomes (strong, high). The DFI Wound Score may provide additional quantitative discrimination for research purposes (weak, low). Other validated diabetic foot classification schemes have limited value for infection, as they describe only its presence or absence (moderate, low).

Evidence Summary

When to Suspect Infection. Any foot wound in a patient with diabetes may become infected. Traditional inflammatory signs of infection are redness (erythema or rubor), warmth (calor), swelling or induration (tumor), tenderness and pain (dolor), and purulent secretions. Some infected patients may not manifest these findings, especially those who have peripheral neuropathy (leading to an absence of pain or tenderness) or limb ischemia (decreasing erythema, warmth, and possibly induration). In this situation, some evidence supports the

correlation of additional or secondary findings, for example, nonpurulent secretions, friable or discolored granulation tissue, undermining of the wound edges, or a foul odor, with evidence of infection [30]. However, none of these findings, either alone or in combination, correlate with a high colony count of bacteria in a wound biopsy [31]. Since the original IDSA DFI guidelines, we have advocated using the presence of ≥2 of the classic findings of inflammation to characterize a wound as infected. Although this definition is based only on expert consensus opinion, it has been used as the diagnostic criterion in many studies of DFI, including some used by the US Food and Drug Administration (FDA) to approve specific antibiotic agents for treating DFIs.

During the systematic review of the literature (see Introduction) we found 177 studies that identified risk factors for developing a foot infection in persons with diabetes. Identification of risk factors for DFI was the objective in only 2 studies [32, 33]. In one instance, factors that were significantly associated (by multivariate analysis) with developing a foot infection included having a wound that extended to bone (based on a positive PTB test; odds ratio [OR], 6.7); a foot ulcer with a duration >30 days (OR, 4.7); a history of recurrent foot ulcers (OR, 2.4); a wound of traumatic etiology (OR, 2.4); or peripheral vascular disease, defined as absent peripheral arterial pulsations or an ankle-brachial index (ABI) of <0.9 (OR, 1.9) [32]. Among 199 episodes of DFI, only 1 infection occurred in a patient without a previous or concomitant foot ulcer. In the second study, a retrospective review of 112 patients with a severe DFI, multivariate analysis identified 3 factors that were associated with developing a foot infection: a previous amputation (OR, 19.9); peripheral vascular disease, defined as any missing pedal pulsation or an ABI of <0.8 (OR, 5.5); or loss of protective sensation (OR, 3.4). Psychological and economic factors did not contribute significantly to infection [33].

Several other studies examined the association between a specific medical condition and various diabetic foot complications, including infections. These types of studies lack a control group of patients without foot infection and are therefore subject to selection bias. Some studies, each of which was retrospective and reported only a small number of cases, have suggested an association between renal failure and DFI [34–36]. Finally, a report from Sri Lanka found that, compared to patients who wore shoes, those who walked barefoot for >10 hours per day had more web space and nail infections (14% vs 40%, respectively, $P < .01$) [37].

How to Classify Infection. In most published classification schemes, assessing infection is a subsection of a broader wound classification. These classification systems each have somewhat different purposes, and there is no consensus on which to use [38, 39]. Some classifications, including the Meggitt-Wagner [40] and SINBAD (site, ischemia, neuropathy, bacterial infection, and death) [41], subjectively categorize infection only dichotomously, that is, as present or absent, and without clear definitions. We briefly summarize the key features of commonly used diabetic foot classification schemes and wound scoring systems.

IWGDF (PEDIS) and IDSA. IWGDF developed a system for classifying diabetic foot wounds that uses the acronym PEDIS, which stands for perfusion, extent (size), depth (tissue loss), infection, sensation (neuropathy). While originally developed as a research tool [39], it offers a semiquantitative gradation for the severity of each of the categories. The infection part of the classification differs only in small details from the classification developed by IDSA, and the 2 classifications are shown in Table 2. Major advantages of both classifications are clear definitions and a relatively small number of categories, making them more user-friendly for clinicians having less experience with diabetic foot management. Importantly, the IDSA classification has been prospectively validated [13, 42, 43] as predicting the need for hospitalization (in one study, 0 for no infection, 4% for mild, 52% for moderate, and 89% for severe infection) and for limb amputation (3% for no infection, 3% for mild, 46% for moderate, and 70% for severe infection) [42].

Other Diabetic Foot Wound Classification Schemes.

- Wagner—Wagner, in collaboration with Meggitt, developed perhaps the first, and still among the most widely used, classification schemes for diabetic foot wounds [40, 44]. It assesses ulcer depth and the presence of infection and gangrene with grades ranging from 0 (pre- or postulcerative) to 5 (gangrene of the entire foot). The system only deals explicitly with infections of all types (deep wound abscess, joint sepsis, or osteomyelitis) in grade 3.
- S(AD)/SAD—This is an acronym for 5 key points of foot ulcers: size, (area, depth), sepsis (infection), arteriopathy, and denervation [45]. Each point has 4 grades, thus creating a semiquantative scale. Infection is graded as none, surface only, cellulitis, and osteomyelitis; these are not further defined. One study reported good interobserver agreement [45]. Unlike the other key points, studies have not shown infection to be related to outcome of the foot ulcer [45, 46]. The SINBAD ulcer classification is a simplified version of the S(AD)/SAD system with a decreased number of grades of infection (present or absent) [41].
- University of Texas (UT) ulcer classification [47]—This system has a combined matrix of 4 grades (related to the depth of the wound) and 4 stages (related to the presence or absence of infection or ischemia). The classification successfully predicted a correlation of the likelihood of complications in patients with higher

Table 2. Infectious Diseases Society of America and International Working Group on the Diabetic Foot Classifications of Diabetic Foot Infection

Clinical Manifestation of Infection	PEDIS Grade	IDSA Infection Severity
No symptoms or signs of infection	1	Uninfected
Infection present, as defined by the presence of at least 2 of the following items: • Local swelling or induration • Erythema • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white or sanguineous secretion)		
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 (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis).	2	Mild
Local infection (as described above) with erythema > 2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis), **and** No systemic inflammatory response signs (as described below)	3	Moderate
Local infection (as described above) with the signs of 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 $PaCO_2$ <32 mm Hg • White blood cell count >12 000 or <4000 cells/μL or ≥10% immature (band) forms	4	Severe[a]

Abbreviations: IDSA, Infectious Diseases Society of America; $PaCO_2$, partial pressure of arterial carbon dioxide; PEDIS, perfusion, extent/size, depth/tissue loss, infection, and sensation; SIRS, systemic inflammatory response syndrome.

[a] Ischemia may increase the severity of any infection, and the presence of critical ischemia 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 hyperglycemia, and new-onset azotemia [29, 43, 44].

stages and grades and a significantly higher amputation rate in wounds deeper than superficial ulcers [47]. A study in Brazil compared the UT and the S(AD)SAD and SINBAD systems and found that all 3 predicted the outcomes of diabetic foot ulcers; the association of outcome with infection was stronger than that reported from the centers in Europe or North America [48].

- Ulcer Severity Index [49]—This index measures 20 clinical parameters and allows determination of an infection score by combining the scores for erythema, edema, and purulence, while counting exposed bone separately. In 1 study, presence or absence of infection in this index was not associated with a difference in wound healing [49].
- Diabetic Ulcer Severity Score (DUSS) and MAID [50, 51]—These scoring systems are based on specific wound characteristics associated with stages of wound repair. Studies have found no significant correlation between soft tissue infection and wound healing, although there was a trend toward more infection in the higher-risk groups [50, 51].
- DFI Wound Score [52]—Lipsky et al developed this 10-item scoring system to measure outcomes in studies of various antimicrobial treatments for DFIs (Table 3). The score consists of a semiquantitative assessment of the presence of signs of inflammation, combined with measurements of wound size and depth. Explicit definitions allow numerical scoring of wound parameters. An evaluation of the wound score calculated for 371 patients with DFI demonstrated that it significantly correlated with the clinical response and that scores demonstrated good internal consistency [52]. Patients with more severe wounds had higher scores; clinical response was favorable at the follow-up assessment in 94.8% with a baseline score <12 compared with 77.0% with a score >19. Surprisingly, excluding scores for wound discharge (purulent and nonpurulent), leaving an 8-item score, provided better measurement statistics [52]. The DFI Wound Score appears to be a useful tool for predicting clinical outcomes in treatment trials, but its complexity requires clinicians to use a scoring sheet [52].

Comparison of Classifications in the Literature. Each of these classifications may be used in clinical practice, but they have not been compared in a large prospective trial. The PEDIS, IDSA, UT, and S(AD)SAD classification systems are fairly simple to use and appear to help predict outcomes. The DFI and DUSS wound scores are relatively complex, but each has been validated in large research trials (Table 2) [52, 53].

Table 3. Diabetic Foot Infection Wound Score (Items Comprising the Diabetic Foot Infection Wound Score Wound Parameters and Wound Measurements and the Method for Scoring Each)

Item	Assessment	Scoring
Wound parameters[a]		
Purulent discharge	Absent	0
	Present	3
Other signs and symptoms of inflammation[a]	Absent	0
Nonpurulent discharge	Mild	1
Erythema	Moderate	2
Induration		
Tenderness		
Pain	Severe	3
Local warmth		
Range of wound parameters (10-item) subtotal		0–21
Range of wound parameters (8-item) subtotal		0–15
Wound measurements[a]		
Size (cm^2)	<1	0
	1–2	1
	>2–5	3
	>5–10	6
	>10–30	8
	>30	10
Depth (mm)	<5	0
	5–9	3
	10–20	7
	>20	10
Undermining (mm)	<2	3
	2–5	5
	>5	8
Range of wound measurements subtotal		3–28
Range of total 10-item[b] DFI wound score		3–49
Range of total 8-item[b] DFI wound score		3–43

The 10-item score: purulent discharge, nonpurulent discharge, erythema, induration, tenderness, pain, warmth, size, depth, undermining. The 8-item score leaves out purulent and nonpurulent secretions.

Abbreviation: DFI, diabetic foot infection.

[a] Definitions for wound parameters and wound measurement can be found in the original article [52].

[b] Each assessed and placed in one of the preassigned categories.

II. How should I assess a diabetic patient presenting with a foot infection?

Recommendations

4. Clinicians should evaluate a diabetic patient presenting with a foot wound at 3 levels: the patient as a whole, the affected foot or limb, and the infected wound (strong, low).

5. Clinicians should diagnose infection based on the presence of at least 2 classic symptoms or signs of inflammation (erythema, warmth, tenderness, pain, or induration) or purulent secretions. They should then document and classify the severity of the infection based on its extent and depth and the presence of any systemic findings of infection (strong, low).

6. We recommend assessing the affected limb and foot for arterial ischemia (strong, moderate), venous insufficiency, presence of protective sensation, and biomechanical problems (strong, low).

7. Clinicians should debride any wound that has necrotic tissue or surrounding callus; the required procedure may range from minor to extensive (strong, low).

Evidence Summary

The evaluation of a DFI should occur at 3 levels: first the patient as a whole, then the affected foot and limb, and finally the wound. The goal is to determine the extent of infection (local and systemic), its microbial etiology, the pathogenesis of the wound, and the presence of any contributing biomechanical, vascular, or neurological abnormalities [54]. Most DFIs start in a skin ulceration [53]. Risk factors for these ulcers include complications of diabetes, for example, the presence of peripheral neuropathy (motor, sensory, or autonomic), peripheral vascular disease, neuro-osteoarthropathy, and impaired wound healing, as well as various patient comorbidities (eg, retinopathy or nephropathy) and maladaptive behaviors [53]. Diabetes also is associated with immunological perturbations, especially reduced polymorphonuclear leukocyte function, but also impaired humoral and cell-mediated immunity [55]. Importantly, local and systemic inflammatory responses to infection may be diminished in patients with peripheral neuropathy or arterial insufficiency. Because of the complex nature of DFI and the potential for rapid worsening (sometimes within hours), the clinician must assess the patient promptly, methodically, and repeatedly. The initial assessment should also include an evaluation of the patient's social situation and psychological state, which may influence his or her ability to comply with recommendations and appear to influence wound healing [43, 56, 57].

Systemic symptoms and signs of infection include fever, chills, delirium, diaphoresis, anorexia, hemodynamic instability (eg, tachycardia, hypotension), and metabolic derangements (eg, acidosis, dysglycemia, electrolyte abnormalities, worsening azotemia). Laboratory markers suggesting systemic infection include leukocytosis, a left-shifted leukocyte differential, and elevated inflammatory markers (eg, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]). An elevated level of procalcitonin has recently been found to be a useful adjunct to diagnosing various bacterial infections, including DFI. Two prospective studies [43, 57] of patients with a diabetic foot ulcer have shown that procalcitonin levels (using reported cutoff values of 17 mg/L and 0.08 ng/mL, respectively) correlate more accurately with clinical evidence of infection (using the IDSA criteria) than levels of white blood cells, ESR, or CRP. Levels of CRP and procalcitonin, especially when these values were combined, accurately distinguished clinically uninfected ulcers from those with mild or moderate infections [43]. We would welcome additional large studies of this biomarker in DFIs.

The presence of systemic signs or symptoms generally signifies severe infection with extensive tissue involvement or more virulent pathogens. Unfortunately, elevations of temperature, white blood cell count, or sedimentation rate are absent in up to one-half of patients, even with severe DFI. When present, however, elevated inflammatory markers have been shown to predict worse clinical outcomes of treatment [58]. Importantly, inflammatory markers may also have value in helping to determine when a DFI has resolved, therefore allowing discontinuation of antibiotic therapy. A larger prospective observational study noted that an elevation of CRP levels (by 1 standard deviation) a week after a patient with a DFI finished treatment was the only independent factor that predicted the need for a lower extremity amputation [59].

Next, examine the limb and foot, especially looking for proximal spread of infection (eg, to contiguous skin, lymphatic channels, or regional lymph nodes) and evaluate the foot for deformities such as Charcot arthropathy, claw or hammer toes, bunions, or callosities. Altered biomechanics may both predispose to foot wounds and impair wound healing. Assessing the vascular supply is crucial. PAD is present in 20%–30% of persons with diabetes [13, 60, 61] and in up to 40% of those with a DFI [14]. In contrast to atherosclerosis in nondiabetic patients, which usually involves the aortoiliofemoral vessels, diabetes-associated PAD most often affects the femoral-popliteal and tibial arteries with sparing of the foot vessels. Although the presence of normal femoral, popliteal, and pedal pulses reduces the likelihood that a patient has moderate to severe PAD, this finding may be less reliable in persons with diabetes. The absence of pedal pulses suggests PAD, but this method of assessment of arterial perfusion is often unreliable, especially in persons with diabetes. Determining the ratio of systolic blood pressure in the ankle to the systolic blood pressure in the brachial artery (ABI) using sphygmomanometers and a hand-held Doppler machine (if available) is a simple, reliable, noninvasive, bedside procedure to assess for PAD [60]; clinicians should attempt to document this in patients with a DFI, especially if pedal pulses are absent or diminished on palpation (Table 4). Venous insufficiency may cause edema, which in turn may impede wound healing. Finally, assess for neuropathy, especially the loss of protective sensation. While there are several methods for doing this, using a 10-g nylon monofilament (Semmes-Weinstein 5.07) is perhaps the easiest and best validated [25].

Following the above assessments, evaluate the wound. Because microorganisms colonize all wounds, infection must be diagnosed clinically (see question I) rather than microbiologically. Key factors deciding the outcome of a DFI are the wound depth and the foot tissues involved. Assessing these requires first debriding any necrotic material or callus, then gently probing the wound to uncover any abscesses, sinus tracts, foreign bodies, or evidence of bone or joint involvement. The wound size and depth should be documented, along with the extent of cellulitis and the quality and quantity of any secretions present. Occasionally, defining the extent of infection requires an imaging study (see question VII) or surgical exploration. If there is any concern for necrotizing deep space infection, request that an experienced surgeon promptly evaluate the patient. Regardless of the location of the wound, palpate the plantar arch for the presence of pain or fullness, which may indicate a deep plantar space abscess. Explore the wound with a blunt metal probe (including doing a PTB test, as described in question VIII). Properly obtained wound cultures (see question V) are useful for guiding antibiotic therapy in DFI, particularly in patients with a chronic infection or who have recently been treated with antibiotics.

Table 4. Interpretation of the Results of Ankle-Brachial Index Measurement

ABI[a]	Interpretation
>1.30	Poorly compressible vessels, arterial calcification
0.90–1.30	Normal
0.60–0.89	Mild arterial obstruction
0.40–0.59	Moderate obstruction
<0.40	Severe obstruction

Abbreviation: ABI, ankle-brachial index.

[a] Obtained by measuring the systolic blood pressure (using a properly sized sphygmomanometer) in the ankle divided by that in the brachial artery. The presence of arterial calcification can lead to an overestimate in the index.

III. When and from whom should I request a consultation for a patient with a diabetic foot infection?

Recommendations

8. Regarding both outpatients and inpatients with a DFI, clinicians should attempt to provide a well-coordinated approach by those with expertise in a variety of specialties, preferably by a multidisciplinary diabetic foot care team (strong, moderate). Where such a team is not yet available, the primary treating clinician should try to coordinate care among consulting specialists (strong, moderate).
9. Diabetic foot care teams can include (or should have ready access to) specialists in various fields; patients with a DFI may especially benefit from consultation with an infectious disease or clinical microbiology specialist and a surgeon with experience and interest in managing DFIs (strong, low).
10. Clinicians without adequate training in wound debridement should seek consultation from more-qualified clinicians for this task, especially when extensive procedures are required (strong, low).
11. If there is clinical or imaging evidence of significant ischemia in an infected limb, we recommend that the clinician

consult a vascular surgeon for consideration of revascularization (strong, moderate).

12. We recommend that clinicians unfamiliar with pressure off-loading or special dressing techniques consult foot or wound care specialists when these are required (strong, low).

13. Providers working in communities with inadequate access to consultation from specialists might consider devising systems (eg, telemedicine) to ensure expert input on managing their patients (strong, low).

Evidence Summary

DFIs may begin as a seemingly minor problem but often progress if not managed appropriately. Depending on where the patient presents for care, primary care providers, emergency department clinicians, internists, or hospitalists are often primarily responsible for initially managing a DFI. Initial management includes deciding when and with whom to consult for issues beyond the scope of practice or comfort level of the primary clinician. Providing optimal patient care usually requires involving clinicians from a variety of specialties, which may include endocrinology, dermatology, podiatry, general surgery, vascular surgery, orthopedic surgery, plastic surgery, wound care, and sometimes psychology or social work. Specialists in infectious diseases or clinical microbiology can often make a valuable contribution, especially when the DFI is severe or complex or has been previously treated or caused by antibiotic-resistant pathogens. In light of the wide variety of causative organisms and the absence of widely accepted, evidence-based antibiotic treatment algorithms, such consultation would be especially valuable for clinicians who are relatively unfamiliar with complex antibiotic therapy.

Care provided by a well-coordinated, multidisciplinary team has been repeatedly shown to improve outcomes [17, 32, 60–65]. Two retrospective studies have shown decreased amputation rates following the establishment of multidisciplinary teams for the treatment of DFIs [66, 67]. A prospective observational study has also shown reduced rates of recurrent foot ulceration by using a multidisciplinary team approach [68]. A variant on the multidisciplinary team is the diabetic foot care rapid response team, which can potentially be comprised of an ad hoc group of clinicians who have mastered at least some of the essential skills for managing DFIs [69]. Unfortunately, even when specialist consultation is available, clinicians often do not make timely referrals to a multidisciplinary diabetic foot care team [70]. Because providers in some communities may not have ready access to specialists, they may consider consultation via electronic or telephonic arrangements (sometimes referred to as telemedicine) [71, 72]. Although using high-resolution optical equipment may be optimal [73], even standard or video telephones have allowed expert consultation from a distance [74].

Moderate DFI and severe DFI frequently require surgical procedures. Severe infections may be immediately life- or limb-threatening (Table 2) and require urgent surgical consultation [75]. The surgeon's area of specialty training is less important than his or her experience and interest in DFI and knowledge of the anatomy of the foot (see question IX). Following debridement or, when needed, a more extensive surgical procedure, the wound must be properly dressed and protected. Many types of wound dressings and off-loading devices are available (see Question X); nonspecialists who are unfamiliar with these should consult with a foot surgeon or wound care specialist.

The presence of clinically important PAD (see question II and Table 4) in a patient with a DFI should prompt most nonvascular specialists to seek consultation from a vascular surgeon [76]. Patients with mild to moderate arterial obstruction can usually be treated without an urgent revascularization procedure, but an ABI of <0.40 signifies severe or critical ischemia [60]. Severe arterial obstruction in persons with diabetes is often amenable to endovascular intervention, open vascular reconstruction, or both. Recent studies have demonstrated excellent outcomes in the hands of experienced surgeons [70, 77]. In special situations, the clinician caring for a patient with a DFI may need to consult specialists in fields not represented in the available team.

IV. Which patients with a diabetic foot infection should I hospitalize, and what criteria should they meet before I discharge them?

Recommendations

14. We recommend that all patients with a severe infection, selected patients with a moderate infection with complicating features (eg, severe PAD or lack of home support), and any patient unable to comply with an appropriate outpatient treatment regimen for psychological or social reasons be hospitalized initially. Patients who do not meet any of these criteria but are failing to improve with outpatient therapy may also need to be hospitalized (strong, low).

15. We recommend that prior to being discharged, a patient with a DFI should be clinically stable; have had any urgently needed surgery performed; have achieved acceptable glycemic control; be able to manage (on his/her own or with help) at the designated discharge location; and have a well-defined plan that includes an appropriate antibiotic regimen to which he/she will adhere, an off-loading scheme (if needed), specific wound care instructions, and appropriate outpatient follow-up (strong, low).

Evidence Summary

The main determinant of which patients with a DFI need to be hospitalized is the clinical severity of the infection. All

patients with a severe infection (as defined by the IDSA or IWGDF classification) require hospitalization, as these are often imminently limb-threatening and, in some cases, life-threatening. Conversely, the large majority of patients with a mild (IWGDF PEDIS grade 2) infection can be treated as outpatients, provided they are able to adhere to medical therapy and are closely followed to ensure they are improving and do not need urgent revascularization. Some individuals with a moderate (IWGDF PEDIS grade 3) infection may benefit from at least a brief course of inpatient treatment to more expeditiously obtain needed diagnostic studies and consultations and to initiate appropriate therapy. Outpatient therapy for a moderate infection is, however, often acceptable for reliable patients without critical ischemia, who do not have an urgent indication for surgical intervention [78, 79]. This includes many patients with osteomyelitis, which is usually a chronic infection that does not require urgent inpatient treatment (see question VIII).

Patients with deep foot infections often do not have fever, leukocytosis, or leftward shift in the white blood cell differential or markedly elevated acute phase serum markers, but absence of these findings does not necessarily exclude a potentially serious infection. Worsened glycemic control is often the only systemic evidence of a serious infection in this setting [80–82]. Hospitalization is sometimes needed for patients who are unable to follow the necessary regimen for their foot infection and who have no family or friends who can provide the needed support. For inpatients, prompt social work consultation, with particular attention to the patient's (or caregiver's) ability to comply with recommended wound care and off-loading, may help limit the duration of hospitalization and ensure the most appropriate discharge setting.

No evidence-based admission or discharge criteria have been developed for patients with a DFI. Although hospitalization is very expensive, a brief admission is often justified by the complexities of properly evaluating the patient, setting up a treatment regimen, and educating the patient and his/her caregivers. Consider discharge when all evidence of the systemic inflammatory response syndrome has resolved, the patient is metabolically stable, and any urgently needed surgery has been performed. Achieving adequate glycemic control is important, but this will usually require titration on an outpatient basis [83, 84]. The clinicians and patient should be clear on the antibiotic regimen (type, route, and duration of therapy), the wound care plans, and the off-loading regimen, as well as the most appropriate site of care (eg, home, skilled nursing facility, outpatient infusion center). Patient and family preference will frequently play a role in these decisions, but the clinician must consider patient motivation, expected adherence to therapy, availability of home support, and third-party payer issues [85]. Lastly, the patient should have appropriate outpatient follow-up appointments set up prior to discharge, and the hospital clinician should communicate with the patient's primary care provider and any consulting clinicians, as appropriate.

V. When and how should I obtain specimen(s) for culture from a patient with a diabetic foot wound?

Recommendations

16. For clinically uninfected wounds, we recommend not collecting a specimen for culture (strong, low).
17. For infected wounds, we recommend that clinicians send appropriately obtained specimens for culture prior to starting empiric antibiotic therapy, if possible. Cultures may be unnecessary for a mild infection in a patient who has not recently received antibiotic therapy (strong, low).
18. We recommend sending a specimen for culture that is from deep tissue, obtained by biopsy or curettage and after the wound has been cleansed and debrided. We suggest avoiding swab specimens, especially of inadequately debrided wounds, as they provide less accurate results (strong, moderate).

Evidence Summary

Because patients with clinically uninfected wounds rarely require antibiotic therapy, these wounds usually should not be cultured unless there is a reason to identify colonizing organisms for epidemiologic purposes. In patients with a clinically infected wound, however, properly obtained wound cultures provide highly useful information for guiding antibiotic therapy, particularly in those with chronic infections or who have recently been treated with antibiotics. One instance in which wound cultures may not be needed are mild infections in patients who have not recently received antibiotic therapy and who are at low risk for methicillin-resistant *Staphylococcus aureus* (MRSA) infection; these infections are predictably caused solely by staphylococci and streptococci.

Isolation of antibiotic-resistant organisms, particularly MRSA [86–89], but also extended-spectrum β-lactamase (ESBL)–producing gram-negative bacilli and highly resistant *Pseudomonas aeruginosa* [90–94], is an increasing problem with DFI in most settings. Infection with these organisms requires specifically targeted antibiotic therapy, but empiric coverage in all cases is not prudent. Thus, where multidrug-resistant organisms are possible pathogens, it is essential to obtain optimal wound cultures prior to initiating antibiotic therapy.

An approach to collecting specimens for culture is outlined in Table 5. Collect culture specimens only after the wound has been cleansed and debrided and prior to initiating antibiotic therapy. A sample obtained by curettage, the scraping of tissue from the ulcer base using a dermal curette or sterile scalpel blade, more accurately identifies pathogens than does rolling a

Table 5. Recommendations for Collection of Specimens for Culture From Diabetic Foot Wounds

Do
• Obtain an appropriate specimen for culture from almost all infected wounds • Cleanse and debride the wound before obtaining specimen(s) for culture • Obtain a tissue specimen for culture by scraping with a sterile scalpel or dermal curette (curettage) or biopsy from the base of a debrided ulcer • Aspirate any purulent secretions using a sterile needle and syringe • Promptly send specimens, in a sterile container or appropriate transport media, for aerobic and anaerobic culture (and Gram stain, if possible)
Do not
• Culture a clinically uninfected lesion, unless for specific epidemiological purposes • Obtain a specimen for culture without first cleansing or debriding the wound • Obtain a specimen for culture by swabbing the wound or wound drainage

cotton swab over a wound. Although obtaining swab specimens is more convenient, they provide less accurate results, particularly if the wound has not been properly debrided. Swabs are often contaminated with normal skin flora or colonizers (thus giving false-positive cultures); they may also fail to yield deep-tissue pathogens and are less likely to grow anaerobic, and some fastidious aerobic, organisms (thus giving false-negative cultures) [95]. Furthermore, many clinical microbiology laboratories do not process swabs as rigorously as tissue specimens but merely report "mixed cutaneous flora" or "no *S. aureus* isolated." A recent meta-analysis of studies examining the usefulness of superficial (compared with deeper) cultures in lower extremity wounds (half of which were in diabetic patients) found that their sensitivity was 49%, specificity 62%, positive likelihood ratio (LR) 1.1, and negative LR 0.67; thus, they provide minimal utility in altering pretest probabilities [96]. For clinicians who elect to use a swab for culture, some data support employing a semiquantitative technique, like that described by Levine (rotating the swab over a 1-cm square area with sufficient pressure to express fluid from within the wound tissue) [97]. Other acceptable methods of culturing wounds include aspiration (with a sterile needle and syringe) of purulent secretions or perhaps cellulitic tissue, and tissue biopsy (usually obtained with a 4–6-mm punch device at the bedside or by resection at the time of surgery). Some microbiology laboratories can determine the quantitative count of organisms per gram of tissue, but this is rarely necessary for clinical situations [98].

Specimens must be placed in an appropriate sterile transport system and promptly delivered to the laboratory, where they should be processed for aerobic and anaerobic cultures. Given that culture results are generally not available for 2–3 days, a Gram-stained smear (if available) can provide immediate information that may aid in initial antibiotic selection. When cultures yield multiple organisms, the Gram stain may also demonstrate which are predominant in the wound, thereby allowing tailored antibiotic therapy. Finally, the presence of polymorphonuclear leukocytes on the Gram-stained smear suggests that infection is present (ie, the equivalent of purulent secretions).

Recent studies have demonstrated that standard cultures identify only a small percentage of the microorganisms present in wounds, including DFIs [99]. Molecular microbiological techniques can detect more organisms and provide the results considerably faster [100]. In addition, molecular techniques can detect the presence of pathogen virulence factors and genes encoding for antibiotic resistance [101]. Preliminary evidence suggests that having this information when a patient presents for treatment may aid the clinician in selecting optimal antibiotic regimens, resulting in improved outcomes. In one retrospective study of chronic wounds, complete healing occurred significantly more often after the implementation of molecular diagnostics (298 of 479 [62.4%] vs 244 of 503 patients [48.5%]), the time to healing was significantly shorter ($P < .05$), and use of expensive "first-line" antibiotics declined in favor or targeted antibiotic therapy [102].

VI. How should I initially select, and when should I modify, an antibiotic regimen for a diabetic foot infection? (See question VIII for recommendations for antibiotic treatment of osteomyelitis)

Recommendations

19. We recommend that clinically uninfected wounds not be treated with antibiotic therapy (strong, low).

20. We recommend prescribing antibiotic therapy for all infected wounds but caution that this is often insufficient unless combined with appropriate wound care (strong, low).

21. We recommend that clinicians select an empiric antibiotic regimen on the basis of the severity of the infection and the likely etiologic agent(s) (strong, low).

    a. For mild to moderate infections in patients who have not recently received antibiotic treatment, we suggest that therapy just targeting aerobic gram-positive cocci (GPC) is sufficient (weak, low).

    b. For most severe infections, we recommend starting broad-spectrum empiric antibiotic therapy, pending culture results and antibiotic susceptibility data (strong, low).

    c. Empiric therapy directed at *P. aeruginosa* is usually unnecessary except for patients with risk factors for true infection with this organism (strong, low).

d. Consider providing empiric therapy directed against MRSA in a patient with a prior history of MRSA infection; when the local prevalence of MRSA colonization or infection is high; or if the infection is clinically severe (weak, low).

22. We recommend that definitive therapy be based on the results of an appropriately obtained culture and sensitivity testing of a wound specimen as well as the patient's clinical response to the empiric regimen (strong, low).

23. We suggest basing the route of therapy largely on infection severity. We prefer parenteral therapy for all severe, and some moderate, DFIs, at least initially (weak, low), with a switch to oral agents when the patient is systemically well and culture results are available. Clinicians can probably use highly bioavailable oral antibiotics alone in most mild, and in many moderate, infections and topical therapy for selected mild superficial infections (strong, moderate).

24. We suggest continuing antibiotic therapy until, but not beyond, resolution of findings of infection, but not through complete healing of the wound (weak, low). We suggest an initial antibiotic course for a soft tissue infection of about 1–2 weeks for mild infections and 2–3 weeks for moderate to severe infections (weak, low).

Evidence Summary

Avoidance of Prescribing Antibiotics for Clinically Uninfected Wounds. Selecting an appropriate antibiotic regimen is an important issue in treating diabetic foot infections. Table 6 provides an overview of the key elements in making this decision.

Table 6. Antibiotic Selection Overview: Questions a Clinician Should Consider

Is there clinical evidence of infection?
Do not treat clinically uninfected wounds with antibiotics
For clinically infected wounds consider the questions below:
- Is there high risk of MRSA?
Include anti-MRSA therapy in empiric regimen if the risk is high (see Table 7) or the infection is severe
- Has patient received antibiotics in the past month?
If so, include agents active against gram-negative bacilli in regimen If not, agents targeted against just aerobic gram-positive cocci may be sufficient
- Are there risk factors for *Pseudomonas* infection?[a]
If so, consider empiric antipseudomonal agent If not, empiric antipseudomonal treatment is rarely needed
- What is the infection severity status?
See Table 9 for suggested regimens for mild versus moderate/severe infections

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Such as high local prevalence of *Pseudomonas* infection, warm climate, frequent exposure of the foot to water.

The limited available evidence does not support using antibiotic therapy for treating clinically uninfected wounds, either to enhance healing or as prophylaxis against clinically overt infection [103, 104]. Furthermore, antibiotic use encourages antimicrobial resistance, incurs financial cost, and may cause drug-related adverse effects. Some wound specialists believe that diabetic foot wounds that lack clinical signs of infection may be "subclinically" infected—that is, they contain a high "bioburden" of bacteria (usually defined as $\geq 10^6$ organisms per gram of tissue) that results in "critical colonization," which might impair wound healing [105, 106]. Currently, there is little evidence to support this view. When it is difficult to decide whether a chronic wound is infected (eg, when the foot is ischemic and neuropathic), it may be appropriate to seek secondary signs of infection, such as abnormal coloration, a fetid odor, friable granulation tissue, undermining of the wound edges, an unexpected wound pain or tenderness, or failure to show healing progress despite proper treatment [31]. In these unusual cases, a brief, culture-directed course of antibiotic therapy may be appropriate.

Antibiotic Therapy of Clinically Infected Wounds. All clinically infected diabetic foot wounds require antibiotic therapy. Although this therapy is necessary, it is often insufficient. Successfully treating a DFI also requires appropriate wound care (vide infra) [85].

Choosing an Antibiotic Regimen. The initial antibiotic regimen must usually be selected empirically, and it may be modified later on the basis of availability of additional clinical and microbiological information. Selecting an empiric regimen involves making decisions about the route of therapy, spectrum of microorganisms to be covered, and specific drugs to administer. These decisions should be revisited when deciding on the definitive regimen and the appropriate duration of treatment.

Initial empiric therapy should be based on the severity of the infection and on any available microbiological data, such as recent culture results and the local prevalence of pathogens, especially antibiotic-resistant strains [107, 108]. The majority of mild, and many moderate, infections can be treated with agents that have a relatively narrow spectrum, usually covering only aerobic GPC [78]. In countries with warm climates, gram-negative isolates (especially *P. aeruginosa*) are more prevalent. Obligate anaerobic organisms are isolated from many chronic, previously treated, or severe infections [109–111]. Although they may be more common than previously suspected [112, 113], they are not major pathogens in most mild to moderate infections [78, 113]. There is little evidence to support the need for antianaerobic antibiotic agents in most adequately debrided DFIs. Treatment with oral antibiotic agents (preferably ones with high bioavailability) is often appropriate for mild to moderate infections in patients

without gastrointestinal absorption problems and for whom an oral agent with the appropriate spectrum is available. Limited data support using topical antimicrobial therapy for mildly infected open wounds with minimal cellulitis [114–116]. For severe infections, and for more extensive, chronic moderate infections, it is safest to promptly commence therapy with a broad-spectrum regimen. The agent(s) should have activity against GPC, as well as common gram-negative and obligate anaerobic organisms to ensure adequate tissue concentrations. For these more severe infections, it is usually safest to start with parenteral therapy, which can usually be switched to oral treatment within a few days when the patient is systemically well and culture results are available to guide the selection.

Clinicians should consider the results of culture and sensitivity testing in light of the clinical response of the infection to the empiric regimen. Cultures may yield organisms that are commonly considered to be contaminants (eg, coagulase-negative staphylococci, corynebacteria), but these may be true pathogens in a DFI. Because these organisms are often resistant to the prescribed antibiotic, the clinician must decide if the preponderance of clinical and microbiologic evidence suggests they are pathogens that require targeted therapy. If the patient has had a good clinical response on the empiric therapy, the regimen may be continued, or even potentially narrowed ("deescalation" therapy). However, if the patient has not adequately responded to the empiric regimen, therapy should be broadened to include all isolated organisms.

Isolating *P. aeruginosa* is a particularly problematic issue because it requires specifically targeted antibiotic coverage. Although reported in many patients, it is often a nonpathogenic colonizer when isolated from wounds. Most recent studies of complicated skin and skin structure (including diabetic foot) infections in developed (especially northern) countries have reported that *P. aeruginosa* is isolated in <10% of wounds [117, 118]. Furthermore, even when isolated, patients often improve despite therapy with antibiotics ineffective against *P. aeruginosa* [79, 90, 119–121]. Conversely, in countries where *P. aeruginosa* is a frequent isolate [122–124], or in patients who have been soaking their feet, who have failed therapy with nonpseudomonal therapy, or who have a severe infection, empiric antipseudomonal therapy may be advisable. Clinicians must also consider covering ESBL-producing gram-negative isolates, especially in countries in which they are relatively common [125].

Methicillin-Resistant S. aureus. Since publication of the previous DFI guidelines, many studies have demonstrated the increasing role of MRSA in DFI [121, 126–129]. Whereas some studies document MRSA in almost one-third of DFIs [86, 127], others report rates of little more than 10% in complicated skin infections and DFIs [118, 120, 130]. A recent review of patients enrolled in 20 studies conducted from 1993 to 2007 found that the prevalence of MRSA in DFIs ranged from 5% to 30% [131]. Factors noted to increase the risk for infection with MRSA in some, but not all studies, include prior long-term or inappropriate use of antibiotics, previous hospitalization, long duration of the foot wound, the presence of osteomyelitis, and nasal carriage of MRSA. Perhaps the most reliable predictor for MRSA as a cause of a DFI is a previous history of MRSA infection [132]. Infection with MRSA may also increase the time to wound healing, the duration of hospitalization, the need for surgical procedures (including amputations), and the likelihood of treatment failure [131]. The previously emphasized differentiation between healthcare-acquired and community-associated MRSA infections has become blurred [133]. There are few data comparing the efficacy of various antibiotic agents for treating MRSA. As with *P. aeruginosa*, some studies have shown clinical resolution of DFIs from which MRSA is cultured despite the regimen not covering this organism [79, 120]. Employing appropriate infection control measures has been shown to limit the acquisition or spread of MRSA among diabetic persons attending a foot clinic [12, 134].

On the basis of currently available evidence, we recommend that a patient presenting with a DFI be empirically treated with an antibiotic regimen that covers MRSA in the following situations:

- The patient has a history of previous MRSA infection or colonization within the past year.
- The local prevalence of MRSA (ie, percentage of all *S. aureus* clinical isolates in that locale that are methicillin-resistant) is high enough (perhaps 50% for a mild and 30% for a moderate soft tissue infection) that there is a reasonable probability of MRSA infection.
- The infection is sufficiently severe that failing to empirically cover MRSA while awaiting definitive cultures would pose an unacceptable risk of treatment failure.

For bone infections, we would recommend obtaining a specimen of bone when there is concern that MRSA is a pathogen.

Specific Antibiotic Selections. Antibiotics vary in how well they achieve therapeutic concentrations in infected diabetic foot lesions [135–145]. This is related to the pharmacodynamic properties of the specific agent and the arterial supply to the foot, rather than to diabetes per se [146]. The 2004 Diabetic Foot Guidelines document (Table 7) provides a list of published clinical trials that focused on therapy of DFIs, either exclusively or as an identified subset of a larger study. Table 7 shows the 11 studies published since that time [90, 114, 120, 147–158].

Table 7. Studies of Antibiotic Therapy for Diabetic Foot Infections Published Since 2004 (and Not Included in Previous Version of This Guideline)

Antibiotic Agent(s) (Route)	Patients Treated, No.	Study Design	Patient Group	Type/Severity of Infection	Reference
Metronidazole + ceftriaxone vs ticarcillin/clavulanate (IV)	70	Prospective open label	H	Older men, Wagner grades 1–3	Clay 2004 [150]
Ceftobiprole vs vancomycin + ceftazidime (IV)	828	RCDBT DFI subgroup	H	cSSSI	Deresinski 2008 [147]
Piperacillin/tazobactam vs ampicillin/sulbactam (IV)	314	Prospective open label	H	Moderate/severe infected DFU	Harkless 2005 [149]
Daptomycin vs vancomycin or Semisynthetic penicillin (IV)	133	RCSBT DFI subgroup	H	Gram + DFI	Lipsky 2005 [155]
Ertapenem vs piperacillin/tazobactam (IV)	586	RCDBT	H	Moderate/severe DFI	Lipsky 2005 [120]
Moxifloxacin (IV to PO) vs piperacillin/tazobactam (IV) to amoxicillin/clavulanate (PO)	78	RCDBT DFI subgroup	H	cSSSI, including DFI (not classified)	Lipsky 2007 [148]
Pexiganan (topical) vs ofloxacin (PO)	835	2 RCDBTs	O	Mildly infected DFU	Lipsky 2008 [114]
Ceftriaxone vs fluoroquinolone (IV)	180	Prospective open label	H	"Severe limb-threatening" DFI	Lobmann 2004 [151]
Moxifloxacin vs amoxicillin/clavulanate (IV to PO)	804	Prospective open label	H	cSSSI, including DFI	Vick-Fragoso 2009 [152]
Tigecycline vs ertapenem (IV)	944	RDBCT	H	Qualifying DFI± osteomyelitis	Clinicaltrials.gov 2010 [158]
Piperacillin/tazobactam vs imipenem/cilastatin (IV)	62	RCT open-label	H	Severe DFI, including osteomyelitis	Saltoglu 2010 [157]

Abbreviations: cSSSI, complicated skin and skin structure infection; DFI, diabetic foot infection; DFU, diabetic foot ulcer; H, hospitalized; O, outpatient; IV, intravenous; PO, oral; RCT, randomized controlled trial; RCDBT, randomized controlled double-blind trial; RCSBT, randomized controlled single-blind trial.

The lack of standardization among these trials, including the varied definitions of infection severity and the clinical end points used, makes it inappropriate to compare outcomes of different regimens. This fact highlights the need for a generally acceptable diabetic foot classification system. Fortunately, both the IDSA and IWGDF classifications are now widely used, allowing standardization of severity scoring in more recent DFI antibiotic trials (Table 2).

Based on the results of the available studies, no single drug or combination of agents appears to be superior to any others [129, 159]. The study with tigecycline (currently available only as an abstract) showed that it did not meet noninferiority criteria compared with ertapenem and was associated with significantly more drug discontinuations (mostly related to nausea and vomiting) [156, 158]. Since publication of the 2004 DFI guidelines, the FDA has approved 3 antibiotics (ertapenem, linezolid, and piperacillin-tazobactam) specifically for the treatment of "complicated skin and skin structure infections including DFI," but not for any accompanying osteomyelitis. Studies of several new agents have been completed and are being analyzed, are under way, or are in the planning stages. The recently released FDA draft guidance for clinical development of antimicrobials classifies what was previously called "uncomplicated and complicated skin and skin structure infection" as "acute bacterial skin and skin structure infections" [160]. Unfortunately, it states that "[T]his guidance does not address lower extremity infections in neurologically compromised patients, such as the diabetic foot infection," making it difficult for pharmaceutical companies to know how to proceed with developing new antimicrobials for DFIs.

Table 8 offers our suggestions for various empiric antibiotic regimens a clinician might consider for a DFI, based on the severity of the infection. This table differs from the one in the previous guideline in that, for simplicity, it combines moderate and severe infections in a single category. The suggested agents are derived from available published clinical trials (in particular those enrolling patients with a DFI) and our collective experience and are not meant to be inclusive of all potentially reasonable regimens (weak, low). Similar agents to those listed could be used, based on various clinical, microbiologic, epidemiologic, and financial considerations. A review of recent randomized clinical trials on antibiotic therapy of DFIs pointed out the many discrepancies among the 14 papers they included, which preclude determining the optimal regimen [161]. Prescribers should select dosages of antibiotic agents according to recommendations of the FDA (or equivalent organizations in their own

Table 8. Suggested Empiric Antibiotic Regimens Based on Clinical Severity for Diabetic Foot Infections[a]

Infection Severity	Probable Pathogen(s)	Antibiotic Agent	Comments
Mild (usually treated with oral agent[s])	*Staphylococcus aureus* (MSSA); Streptococcus spp	Dicloxacillin	Requires QID dosing; narrow-spectrum; inexpensive
		Clindamycin[b]	Usually active against community-associated MRSA, but check macrolide sensitivity and consider ordering a "D-test" before using for MRSA. Inhibits protein synthesis of some bacterial toxins
		Cephalexin[b]	Requires QID dosing; inexpensive
		Levofloxacin[b]	Once-daily dosing; suboptimal against *S. aureus*
		Amoxicillin-clavulanate[b]	Relatively broad-spectrum oral agent that includes anaerobic coverage
	Methicillin-resistant *S. aureus* (MRSA)	Doxycycline	Active against many MRSA & some gram-negatives; uncertain against streptococcus species
		Trimethoprim/ sulfamethoxazole	Active against many MRSA & some gram-negatives; uncertain activity against streptococci
Moderate (may be treated with oral or initial parenteral agent[s]) or severe (usually treated with parenteral agent[s])	MSSA; *Streptococcus* spp; Enterobacteriaceae; obligate anaerobes	Levofloxacin[b]	Once-daily dosing; suboptimal against *S. aureus*
		Cefoxitin[b]	Second-generation cephalosporin with anaerobic coverage
		Ceftriaxone	Once-daily dosing, third-generation cephalosporin
		Ampicillin-sulbactam[b]	Adequate if low suspicion of *P. aeruginosa*
		Moxifloxacin[b]	Once-daily oral dosing. Relatively broad-spectrum, including most obligate anaerobic organisms
		Ertapenem[b]	Once-daily dosing. Relatively broad-spectrum including anaerobes, but not active against *P. aeruginosa*
		Tigecycline[b]	Active against MRSA. Spectrum may be excessively broad. High rates of nausea and vomiting and increased mortality warning. Nonequivalent to ertapenem + vancomycin in 1 randomized clinical trial
		Levofloxacin[b] or ciprofloxacin[b] with clindamycin[b]	Limited evidence supporting clindamycin for severe *S. aureus* infections; PO & IV formulations for both drugs
		Imipenem-cilastatin[b]	Very broad-spectrum (but not against MRSA); use only when this is required. Consider when ESBL-producing pathogens suspected
	MRSA	*Linezolid*[b]	Expensive; increased risk of toxicities when used >2 wk
		Daptomycin[b]	Once-daily dosing. Requires serial monitoring of CPK
		Vancomycin[b]	Vancomycin MICs for MRSA are gradually increasing
	Pseudomonas aeruginosa	***Piperacillin-tazobactam***[b]	TID/QID dosing. Useful for broad-spectrum coverage. *P. aeruginosa* is an uncommon pathogen in diabetic foot infections except in special circumstances (2)

Table 8 continued.

Infection Severity	Probable Pathogen(s)	Antibiotic Agent	Comments
	MRSA, Enterobacteriacae, *Pseudomonas*, and obligate anaerobes	Vancomycin[c] plus one of the following: ceftazidime, cefepime, *piperacillin-tazobactam*[b], aztreonam,[b] or a carbapenem[b]	Very broad-spectrum coverage; usually only used for empiric therapy of severe infection. Consider addition of obligate anaerobe coverage if ceftazidime, cefepime, or aztreonam selected

Agents in boldface type are those that have been most commonly used as comparators in clinical trials (see Table 7). The only agents currently specifically FDA-approved for diabetic foot infections are shown in italics.

Narrow-spectrum agents (eg, vancomycin, linezolid, daptomycin) should be combined with other agents (eg, a fluoroquinolone) if a polymicrobial infection (especially moderate or 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 empiric regimen.

Similar agents of the same drug class can probably be substituted for suggested agents.

Some of these regimens do not have FDA approval for complicated skin and skin structure infections.

Abbreviations: CPK, creatine phosphokinase; ESBL, extended-spectrum β-lactamase; FDA, US Food and Drug Administration; IV, intravenous; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PO, oral; QID, 4 times a day; TID, 3 times a day.

[a] Agents approved for treating skin and skin structure infections on the basis of studies that excluded patients with diabetic foot infections (eg, ceftaroline, telavancin) are not included.

[b] Agents shown to be effective in clinical trials including patients with diabetic foot infections.

[c] Daptomycin or linezolid may be substituted for vancomycin.

countries), the drug's manufacturers, and their own experience; these may then need to be modified on the basis of any relevant organ (especially renal) dysfunction and other clinical factors.

Duration of Therapy. Duration of antibiotic therapy for a DFI should be based on the severity of the infection, the presence or absence of bone infection, and clinical response to therapy (Table 8). Data from aforementioned clinical trials demonstrate that most patients with just skin and soft tissue infections do well with 1–2 weeks of treatment. Routinely prescribing antibiotics for a fixed duration may result in an insufficient or, more often, unnecessarily prolonged course of therapy. This increases cost, potential for adverse drug-related events, and risk of development of antibiotic resistance. Antibiotics can usually be discontinued once the clinical signs and symptoms of infection have resolved. There is no good evidence to support continuing antibiotic therapy until the wound is healed in order to either accelerate closure or prevent subsequent infection.

VII. When should I consider imaging studies to evaluate a diabetic foot infection, and which should I select?

Recommendations

25. We recommend that all patients presenting with a new DFI have plain radiographs of the affected foot to look for bony abnormalities (deformity, destruction) as well as for soft tissue gas and radio-opaque foreign bodies (strong, moderate).

26. We recommend using magnetic resonance imaging (MRI) as the study of choice for patients who require additional (ie, more sensitive or specific) imaging, particularly when soft tissue abscess is suspected or the diagnosis of osteomyelitis remains uncertain (strong, moderate).

27. When MRI is unavailable or contraindicated, clinicians may consider the combination of a radionuclide bone scan and a labeled white blood cell scan as the best alternative (weak, low).

Evidence Summary

Imaging studies may help disclose or better define deep soft tissue purulent collections and are usually needed to detect pathological findings in bone. Plain radiographs may provide some information regarding the soft tissues in the patient with DFI, for example, the presence of radio-opaque foreign bodies, calcified arteries, or soft tissue gas. They are primarily used, however, to determine whether there are bony abnormalities. In this regard, plain radiographs have only moderately helpful performance characteristics, with a recent meta-analysis reporting pooled sensitivity of 0.54 and specificity of 0.68 for osteomyelitis [162]. They provide reasonably accurate information in the setting of established osteomyelitis [162–164]. Clinicians should consider radiologically evident bone destruction beneath a soft tissue ulcer to represent osteomyelitis unless proven otherwise [163]. If the films show classic changes suggestive of osteomyelitis (cortical erosion, periosteal reaction, mixed lucency, and sclerosis), and if there is little likelihood of neuro-osteoarthropathy, it is reasonable to initiate treatment for presumptive osteomyelitis, preferably

after obtaining appropriate specimens for culture. The major limitation of sensitivity of plain films in the diagnosis of osteomyelitis is the delayed appearance of cortical changes, with radiographic abnormalities lagging clinical disease by up to a month [165]. The continued absence of any bony abnormalities on repeat radiographs taken at least a few weeks apart probably excludes osteomyelitis. The major limitation of specificity is differentiating infection from neuro-osteoarthropathy in a patient with bony destruction, especially if the patient has peripheral neuropathy.

Among currently available imaging modalities, MRI provides the greatest accuracy (ie, combined sensitivity and specificity) for the detection of bone infection in the diabetic foot. One recent meta-analysis reported a pooled sensitivity of 90% and specificity of 79% for MRI in this setting [162], whereas a more inclusive meta-analysis calculated a specificity of 82.5% with a cut point of 90% sensitivity [166]. MRI also provides optimal definition of soft tissue infection, including detecting sinus tracts, deep tissue necrosis, abscesses, and other inflammatory changes [162, 164, 166–169]. Characteristic findings of diabetic foot osteomyelitis (DFO) on MRI include decreased signal intensity of affected bone on T1-weighted images and increased intensity on T2-weighted and postcontrast images. It is not necessary to administer gadolinium to detect bony changes, but it increases the sensitivity for detection of various soft tissue abnormalities [170]. MRI is also frequently useful to help determine the need for any type of surgical intervention [171]. MRI is usually not needed as a first-line investigation in cases of DFI, and potential limitations may include limited availability (precluding or delaying the study), high cost, and a lack of a musculoskeletal radiologist skilled in interpreting MRIs. Consider obtaining a MRI when there is suspicion of a deep abscess or when findings on plain radiography are equivocal for osteomyelitis. In this latter setting, no study has yet formally compared serial plain films with MRI. MRI is usually not needed to diagnose osteomyelitis in a patient with observable or palpable bone and plain radiographs suggestive of osteomyelitis in that location [172].

When imaging beyond the capabilities of plain radiographs is needed but MRI is unavailable or contraindicated, a nuclear medicine scan is the best alternative. These scans have good sensitivity but (especially in the case of bone scans) relatively low specificity; almost any type of inflammatory condition will cause increased uptake, and the abnormalities are slow to resolve [161, 173]. Conventional bone scans (eg, ^{99m}Tc-MDP) have little value for either screening or anatomical reference [174]. Labeled leukocyte (with either ^{99m}Tc or ^{111}In) or antigranulocyte Fab fragment (eg, sulesomab) imaging [175] are the nuclear medicine procedures of choice for investigating a DFI, with an overall accuracy of 80%–85% [174]. Combining the results of bone scanning with a labeled white blood cell scan appears to provide the best scanning accuracy but is laborious, expensive, and still less specific than MRI [176]. Although the results of one study suggested the benefit of ultrasound for diagnosing deep soft tissue infection and perhaps osteomyelitis in the diabetic foot [177], there have been no further reports. Preliminary data suggest a possible role for combined fluorodeoxyglucose–positron emission tomography/computed tomography (CT) (or MRI), although the utility and cost-effectiveness of this approach requires further study [178–180]. The same is true for using single-photon emission CT (SPECT)/CT with bone and leukocyte scanning [181]. Standard CT scanning is more sensitive than plain radiography (and in some cases MRI) in detecting cortical disruption, periosteal reaction, and sequestrae, but has relatively low specificity and plays a limited role in evaluating a DFI [182].

Distinguishing the bony changes of osteomyelitis from those of the less common entity of diabetic neuro-osteoarthropathy (Charcot foot) may be particularly challenging and requires considering clinical information in conjunction with imaging [183]. Clinical clues supporting neuro-osteoarthropathy in this context include midfoot location and absence of a soft tissue wound, whereas those favoring osteomyelitis include presence of an overlying ulcer (especially of the forefoot or heel), either alone or superimposed on Charcot changes. Findings supporting neuro-osteoarthropathy on MRI are the presence of intra-articular bodies or subchondral cysts and involvement of multiple joints; findings favoring osteomyelitis are diffuse signal enhancement involving an entire bone, replacement of fat adjacent to abnormal bone, and presence of a sinus tract [169, 170, 184]. Consultation with an experienced musculoskeletal radiologist in distinguishing between these entities is invaluable [185].

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

Recommendations

28. Clinicians should consider osteomyelitis as a potential complication of any infected, deep, or large foot ulcer, especially one that is chronic or overlies a bony prominence (strong, moderate).

29. We suggest doing a PTB test for any DFI with an open wound. When properly conducted and interpreted, it can help to diagnose (when the likelihood is high) or exclude (when the likelihood is low) DFO (strong, moderate).

30. We suggest obtaining plain radiographs of the foot, but they have relatively low sensitivity and specificity for confirming or excluding osteomyelitis (weak, moderate). Clinicians might consider using serial plain radiographs to diagnose or monitor suspected DFO (weak, low).

31. For a diagnostic imaging test for DFO, we recommend using MRI (strong, moderate). However, MRI is not always necessary for diagnosing or managing DFO (strong, low).

32. If MRI is unavailable or contraindicated, clinicians might consider a leukocyte or antigranulocyte scan, preferably combined with a bone scan (weak, moderate). We do not recommend any other type of nuclear medicine investigations (weak, moderate).

33. We suggest that the most definitive way to diagnose DFO is by the combined findings on bone culture and histology (strong, moderate). When bone is debrided to treat osteomyelitis, we suggest sending a sample for culture and histology (strong, low).

34. For patients not undergoing bone debridement, we suggest that clinicians consider obtaining a diagnostic bone biopsy when faced with specific circumstances, eg, diagnostic uncertainty, inadequate culture information, failure of response to empiric treatment (weak, low).

35. Clinicians can consider using either primarily surgical or primarily medical strategies for treating DFO in properly selected patients (weak, moderate). In noncomparative studies, each approach has successfully arrested infection in most patients.

36. When a radical resection leaves no remaining infected tissue, we suggest prescribing antibiotic therapy for only a short duration (2–5 days) (weak, low). When there is persistent infected or necrotic bone, we suggest prolonged (≥4 weeks) antibiotic treatment (weak, low).

37. For specifically treating DFO, we do not currently support using adjunctive treatments such as hyperbaric oxygen therapy, growth factors (including granulocyte colony-stimulating factor), maggots (larvae), or topical negative pressure therapy (eg, vacuum-assisted closure) (weak, low).

Evidence Summary

Dealing with osteomyelitis is one of the more difficult and controversial aspects of the management of DFIs [165, 186–190]. Its presence increases the likelihood of surgical intervention, including amputation, and the recommended duration of antibiotic therapy [186]. It impairs healing of the overlying wound and acts as a focus for recurrent infection. DFO is mostly a complication of a preexisting infected foot ulcer, arising via contiguous spread following compromise of the soft tissue envelope and the periosteum. DFO may be present in up to 20% of mild to moderate infections and in 50%–60% of severely infected wounds [191]. Noninfectious neuro-osteoarthropathy (Charcot foot) is sometimes difficult to distinguish from DFO, and they can coexist [183].

Definitions. The criterion standard for diagnosing osteomyelitis is isolation of bacteria from a reliably obtained sample of bone (using measures to minimize contamination) concomitant with histological findings of inflammatory cells and osteonecrosis. Culture of the bone specimen may be falsely negative because of sampling errors, prior antibiotic therapy, or inability to culture fastidious organisms; they may also be falsely positive because of contamination by wound-colonizing flora or skin commensals. The histomorphology of uninfected bone is normal in diabetic patients, including in those with neuropathy or vasculopathy [192]. In the absence of bone culture and histopathology, a reasonable clinical definition of osteomyelitis is the observation at surgery of purulence in bone. Recently the IWGDF proposed consensus diagnostic criteria for defining osteomyelitis in the diabetic foot, stratified into 4 categories based on the results of clinical, imaging, and bone sampling methods (ranging from unlikely [<10% posttest probability], through possible [10%–50%], probable [51%–90%], and definite [>90%]) [185]. In the absence of any validation, these are currently principally for research purposes.

History and Physical Examination. Two recent systematic reviews examined studies addressing the utility of the patient's history and clinical assessment in the diagnosis of DFO [162, 164]. Using similar methodologies, both studies concluded there was no strong evidence to suggest that historical features strongly predict active osteomyelitis. We think clinicians should suspect osteomyelitis in a patient with an adequate blood supply to the affected foot when an ulcer, especially if it is deep, does not heal after at least 6 weeks of appropriate wound care and off-loading. Both the presence of any exposed bone and ulcer area larger than 2 cm^2 increase the likelihood of osteomyelitis [193].

Neither the presence of signs of infection of the wound nor an elevated white blood cell count influences the likelihood of osteomyelitis [172, 193]. In a recent prospective cohort study, independent risk factors for osteomyelitis in a patient with infection of the foot were wounds that extended to bone or joint; previous history of a wound; and recurrent or multiple wounds [194]. Taking together clinical and laboratory findings (ulcer depth >3 mm or CRP >3.2 mg/dL, ulcer depth >3 mm or ESR >60 mm/hour) is likely to help differentiate osteomyelitis from cellulitis [195]. Although the presence of a local ulceration (toe or metatarsophalangeal joint) or a "sausage toe" (swollen, erythematous, and lacking normal contours) [196] is suggestive of the diagnosis, there is no specific clinical finding of DFO.

The true depth of an ulcer is often not clinically apparent, so explore any foot wound at each consultation with a sterile blunt metal probe (the PTB test). Any ulcer with either a positive PTB test (ie, palpable hard, gritty bone) or in which bone is visible is likely to be complicated by osteomyelitis [193]. The accuracy of the PTB test in predicting or excluding osteomyelitis is, however, directly related to the pretest likelihood (ie, the prevalence in the population under study) of osteomyelitis. Previous studies have established that in the presence of a clinically infected wound, a positive PTB test is highly suggestive of osteomyelitis, but a negative test does not exclude the diagnosis; conversely, in the case of an apparently uninfected foot wound,

a positive PTB test is not specific for osteomyelitis, but this diagnosis is unlikely if the PTB test is negative [197–202].

Microbiology. In almost all reported DFO series, *S. aureus* is the most common pathogen cultured from bone samples, followed by *Staphylococcus epidermidis* [193, 203–206]. Among the gram-negative bacilli, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus* species are the most common pathogens, followed by *P. aeruginosa*. The frequency of isolation of obligate anaerobes (mostly *Peptostreptococcus*, *Peptococcus*, and *Finegoldia magna*) is low, but depends on the method by which the bone fragments are sampled and transported to the laboratory. An increasing prevalence of multiresistant bacteria, already established for soft tissue infections of the diabetic foot, has also been reported for DFO [207].

Cultures of bone specimens provide more accurate microbiologic data for defining DFO than do those of soft tissue specimens [168, 205, 208–210]. The concordance between cultures from a soft tissue swab and bone is <50% [211]. Needle aspiration of deep soft tissue adjacent to bone is more accurate than superficial samples (swabs) [212] but does not correlate well with the results of bone biopsy cultures [213]. Unlike most previous reports, a recent nonrandomized study in patients undergoing surgery for various types of osteomyelitis found that obtaining 2 consecutive deep sinus tract cultures (after cleansing the orifice) correlated well with the results of bone culture if the infection was monomicrobial (typically staphylococci or streptococci) [214]. Although there is some debate about the value of cultures of bone, either extruded or removed from an open wound, bone biopsy using an appropriate procedure (see below) remains the recommended method for definitive diagnosis of DFO [185].

The main value of bone biopsy is to provide reliable data on the organisms responsible for the infection and to determine their profile of susceptibility to antimicrobial agents [215]. Despite this, in most reports of the medical treatment of DFO, the authors did not use bone culture to select the antibiotic regimen. A retrospective multicenter study demonstrated that patients treated with bone culture–guided antibiotic treatment had a significantly better outcome than those treated in the same center without such guidance (18 of 32 [56.3%] vs 4 of 18 [22.2%], respectively, $P = .02$) [213]. Nevertheless, some authors continue to report success rates of 75% in the empiric treatment of DFO [216].

Obtaining a bone specimen for culture (and histology, when available), is most likely to be justified [204, 208, 216–218] (Table 9) when there is

- uncertainty regarding the diagnosis of osteomyelitis despite clinical and imaging evaluations;
- an absence (or confusing mix) of culture data from soft tissue specimens;
- failure of the patient to respond to empiric antibiotic therapy; or
- a desire to use antibiotic agents that may be especially effective for osteomyelitis but have a high potential for selecting resistant organisms (eg, rifampin, fluoroquinolones).

Table 9. In Which Situations Is Diagnostic Bone Biopsy Most Recommended?

• Patient or provider prefers definitive diagnosis to justify choice of early surgery in favor of prolonged treatment
• Cultures of soft tissue or blood suggest high risk of osteomyelitis with antibiotic-resistant organism(s)
• There is progressive bony deterioration or persistently elevated inflammatory markers during empiric or culture-directed therapy (should consider surgical resection)
• Suspect bone is a planned target for insertion of orthopaedic metalware

We would make a stronger case for routinely obtaining biopsy specimens of midfoot or hindfoot lesions because they are more difficult to treat, more often lead to a high-level (ie, above the ankle) amputation, and more often yield a good bone specimen. While we think it is optimal to obtain the bone specimen at a time when the patient is not receiving systemic antibiotic therapy, recent data from a study of vertebral osteomyelitis suggest that even with antimicrobial pretreatment, at least half of the bone cultures will be positive [219]. We suggest, in the absence of data for DFO, that a 2-week antibiotic-free period is best to avoid false-negative cultures. Of course, the potential benefit in accurate cultures must be weighed against the risk of progressive infection in the absence of treatment. Any properly trained physician (eg, foot surgeon, interventional radiologist) can perform the biopsy. Although it is not always necessary, percutaneous biopsy should preferably be done under fluoroscopic or CT guidance and if possible, traversing the uninvolved skin. For patients with sensory neuropathy, providing anesthesia may be unnecessary. Using any of the various types of bone-cutting needles, such as Jamshidi (Perfectum Corporation; distributed by Propper and Sons) and Ostycut (Bard Products; distributed by Angiomed), clinicians should obtain 2–3 specimens if possible, sending at least 1 for culture and another for histological analysis [220]. With small-toe bones, it may only be possible to aspirate a few bony spicules. Complications of bone biopsy are very rare [211, 213, 221].

Even using results of previous imaging studies and real-time fluoroscopic guidance, bone biopsy may miss the area of active osteomyelitis, giving a potentially false-negative result. On the other hand, skin antisepsis will not always prevent contamination of the bone samples during the biopsy procedure, giving a potentially false-positive result. In light of

these deficiencies, bone histology (when available) can be helpful. A study comparing culture to histopathology on 44 surgically obtained bone specimens from patients with DFO found that the 2 performed similarly [222]. Clinicians should take other available clinical, radiologic, and biologic parameters into account; a diagnostic scheme incorporating combinations of findings may prove useful for diagnosing DFO [185].

Imaging Studies. When considering osteomyelitis, we recommend obtaining plain radiographs of the foot, as they are widely available and relatively inexpensive (see question VII). It may take weeks after the onset of bone disease for osteomyelitis to become evident on plain radiographs [163, 177, 193]. Progressive changes seen on serial plain radiographs repeated after 2–4 weeks may have greater sensitivity and specificity [200]. Radioisotope scans are more sensitive than radiographs for detecting early osteomyelitis, but unfortunately they are rather nonspecific [223]. MRI is the most accurate imaging study for defining bone infection [166, 188, 224, 225], but accurately interpreting images requires a well-trained and experienced reader. MRI is not always needed to diagnose osteomyelitis (eg, when there is exposed grossly infected bone). The UK NICE guidelines [24] suggest that when osteomyelitis is suspected but not confirmed by initial radiography, clinicians should use MRI or, if MRI is unavailable or contraindicated, white blood cell scanning. The NICE guidelines offer receiver operating characteristic curves and Forrest plots relevant to the diagnosis of osteomyelitis. In preliminary studies, fluorodeoxyglucose positron emission tomography (or MRI) has better accuracy for confirming or excluding the diagnosis of chronic osteomyelitis than plain MRI, but its role in diabetic patients is not yet established [225].

Management of Diabetic Patients With Osteomyelitis of the Foot. If MRI is unavailable, contraindicated, or otherwise difficult to justify, we think the following protocol should suffice:

- If the plain radiograph has changes suggestive of osteomyelitis (cortical erosion, active periosteal reaction, mixed lucency, and sclerosis), treat for presumptive osteomyelitis, preferably after obtaining appropriate specimens for culture (consider obtaining bone biopsy, if available).
- If the radiographs show no evidence of osteomyelitis, treat the patient with antibiotics for up to 2 weeks if there is soft tissue infection, in association with optimal care of the wound and off-loading. Perform repeat radiographs of the foot 2–4 weeks after the initial radiographs.
- If these repeat bone radiographs remain normal but suspicion of osteomyelitis remains:
    - Where the depth of the wound is decreasing and the PTB test is negative, osteomyelitis is unlikely.
    - Where the wound is not improving or the PTB test is positive, 1 of the following choices should be considered:
        - Additional imaging studies, preferably MRI. If results are negative, osteomyelitis is unlikely.
        - Bone biopsy for culture and histology.
        - Empiric treatment: Provide antibiotic therapy (based on any available culture results, and always covering at least for *S. aureus*) for another 2–4 weeks and then perform radiography again.

Choosing Between Medical and Surgical Therapy. Bone resection has been considered essential for curing chronic osteomyelitis [186, 218], but this belief has been challenged by recent reports of cure with antibiotic therapy alone [165]. Definitive surgical solutions to osteomyelitis, such as ray and transmetatarsal amputations, may risk architectural reorganization of the foot, resulting in altered biomechanics and additional cycles of "transfer ulceration," that is, skin breakdown at a new high-pressure site. Neuropathy and attenuated systemic manifestations of infection may render osteomyelitis tolerable for the diabetic patient and may also mask progressive bone destruction. Delayed or inadequate surgery may impair control of infection and allow additional bone or soft tissue necrosis. No studies directly compare primarily surgical and primarily medical strategies, but nonsurgical treatment with a prolonged (3–6 months) course of antibiotics has a reported clinical success rate of 65%–80% [81, 189, 221, 226–236]. Unfortunately, these data from nonrandomized case series often fail to specify a definition of osteomyelitis, how patients were selected, and how much nonoperative debridement of bone was performed. At the clinical extremes (ie, minimal or massive bone involvement), trained clinicians may find it easy to decide whether the patient requires surgical debridement of the infected bone or amputation. In the majority of cases, however, a didactic approach to management is not supported by strong evidence.

There are 4 situations in which nonsurgical management of osteomyelitis might be considered [185, 189, 221, 234]:

1. There is no acceptable surgical target (ie, radical cure of the infection would cause unacceptable loss of function).
2. The patient has limb ischemia caused by unreconstructable vascular disease but wishes to avoid amputation.
3. Infection is confined to the forefoot, and there is minimal soft tissue loss.
4. The patient and healthcare professional agree that surgical management carries excessive risk or is otherwise not appropriate or desirable.

When therapy for osteomyelitis fails, clinicians should consider several possible reasons:

1. Was the original diagnosis correct?
2. Is there residual necrotic or infected bone or surgical hardware that should be resected or removed?
3. Did the selected antibiotic regimen likely cover the causative organism(s) and achieve adequate levels in bone, and was it administered for a sufficient duration?
4. Are noninfectious complications (eg, inadequate offloading of the wound or insufficient blood supply to the foot), rather than failure to eradicate bone infection, the real problem?

Each case needs an individualized approach (Table 10), preferably in consultation with a multidisciplinary team. Selected patients may benefit from implanted antibiotic carriers (eg, poly[methyl methacrylate] beads or calcium sulfate pellets) [237–242], or from revascularization, whereas others may elect long-term or intermittent antibiotic suppression or, in some cases, amputation. There is no persuasive evidence that the use of adjunctive treatments, such as hyperbaric oxygen therapy, growth factors (including granulocyte colony-stimulating factor), maggots (larvae), or topical negative pressure therapy (eg, vacuum-assisted closure) are beneficial in the management of DFO [185].

Selecting an Antibiotic Regimen. A recent systematic review demonstrated the poor evidence base for making any recommendation on antibiotic therapy for DFO [185]. No data support the superiority of any specific antibiotic agent or treatment strategy, route, or duration of therapy. The results of one retrospective study of patients with DFO suggest that antibiotic therapy directed by culture of bone (compared with empiric therapy) is associated with a significantly higher rate of resolution of the bone infection without surgery after a mean of 12 months' follow-up [221].

The most appropriate duration of therapy for any type of DFI is not well defined [149]. It is important to consider the presence and amount of any residual dead or infected bone and the state of the soft tissues. When a radical resection leaves no remaining infected tissue, only a short duration of antibiotic therapy is needed. Alternatively, if infected bone remains despite surgery, we advise prolonged treatment. For osteomyelitis, some initial parenteral antibiotic therapy may be beneficial, especially if an agent with suboptimal bioavailability is selected, but predominantly oral therapy with a highly bioavailable agent is probably adequate. Parenteral therapy may be delivered in the outpatient setting, where this service is available [241, 243, 244]. Recommendations for duration of therapy are based on the clinical syndrome and are summarized in Table 11. Although there are no tests that have been proven to correlate with long-term resolution of osteomyelitis, the consensus of the panel is that the following are suggestive of a response: a decrease in previously elevated inflammatory markers (especially the ESR); resolution of any overlying soft tissue infection; healing of any wound; and evolution of radiographic changes that suggest healing.

Table 10. Approach to Treating a Patient With Diabetic Foot Osteomyelitis

When to consider a trial of nonsurgical treatment
• No persisting sepsis (after 48–72 h if on treatment) • Patient can receive and tolerate appropriate antibiotic therapy • Degree of bony destruction has not caused irretrievable compromise to mechanics of foot (bearing in mind potential for bony reconstitution) • Patient prefers to avoid surgery • Patient comorbidities confer high risk to surgery • No contraindications to prolonged antibiotic therapy (eg, high risk for *C. difficile* infection) • Surgery not otherwise required to deal with adjacent soft tissue infection or necrosis
When to consider bone resection
• Persistent sepsis syndrome with no other explanation • Inability to deliver or patient to tolerate appropriate antibiotic therapy • Progressive bony deterioration despite appropriate therapy • Degree of bony destruction irretrievably compromises mechanics of foot • Patient prefers to avoid prolonged antibiotics or to hasten wound healing • To achieve a manageable soft tissue wound or primary closure • Prolonged antibiotic therapy is relatively contraindicated or is not likely to be effective (eg, presence of renal failure)

IX. In which patients with a diabetic foot infection should I consider surgical intervention, and what type of procedure may be appropriate?

Recommendations

38. We suggest that nonsurgical clinicians consider requesting assessment by a surgeon for patients with a moderate or severe DFI (weak, low).
39. We recommend urgent surgical intervention for most foot infections accompanied by gas in the deeper tissues, an abscess, or necrotizing fasciitis, and less urgent surgery for wounds with substantial nonviable tissue or extensive bone or joint involvement (strong, low).
40. We recommend involving a vascular surgeon early on to consider revascularization whenever ischemia complicates a DFI, but especially in any patient with a critically ischemic limb (strong, moderate).
41. Although most qualified surgeons can perform an urgently needed debridement or drainage, we recommend that in DFI cases requiring more complex or reconstructive procedures, the surgeon should have experience with these problem and adequate knowledge of the anatomy of the foot (strong, low).

Table 11. Suggested Route, Setting, and Duration of Antibiotic Therapy, by Clinical Syndrome

Site of Infection, by Severity or Extent	Route of Administration	Setting	Duration of Therapy
Soft-tissue only			
Mild	Topical or oral	Outpatient	1–2 wk; may extend up to 4 wk if slow to resolve
Moderate	Oral (or initial parenteral)	Outpatient/ inpatient	1–3 wk
Severe	Initial parenteral, switch to oral when possible	Inpatient, then outpatient	2–4 wk
Bone or joint			
No residual infected tissue (eg, postamputation)	Parenteral or oral	…	2–5 d
Residual infected soft tissue (but not bone)	Parenteral or oral	…	1–3 wk
Residual infected (but viable) bone	Initial parenteral, then consider oral switch	…	4–6 wk
No surgery, or residual dead bone postoperatively	Initial parenteral, then consider oral switch	…	≥3 mo

Table 12. Signs of a Possibly Imminently Limb-Threatening Infection

- 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 hemorrhagic
- New onset wound anesthesia
- Pain out of proportion to clinical findings
- Recent loss of neurologic function
- Critical limb ischemia
- Extensive soft tissue loss
- Extensive bony destruction, especially midfoot/hindfoot
- Failure of infection to improve with appropriate therapy

In clinical settings with less advanced healthcare available, lesser degrees of infection severity may make an infection limb-threatening.

Evidence Summary

Determining the Need for Surgery. Many infections require surgical procedures, ranging from minor (eg, drainage and excision of infected and necrotic tissues) to major (eg, reconstruction of soft tissue or bony defects, revascularization of the lower extremity, and lower limb amputation) [245–249]. Clinicians should seek urgent surgical consultation for patients presenting with clinical evidence of a life- or limb-threatening infection (Table 12), or if the involved limb is critically ischemic (Table 4) [250, 251]. A surgical specialist should also evaluate any patient who has unexplained persistent foot pain or tenderness or evidence of a deep-space infection or abscess.

The absence of fever or leukocytosis should not dissuade the clinician from considering surgical exploration of a DFI [252, 253]. The most common site for a severe foot infection is the plantar surface. A plantar wound accompanied by dorsal erythema or fluctuance suggests that the infection has passed through fascial compartments, likely requiring surgical drainage (Figure 1). Prompt and adequate surgical debridement, including limited resections or amputations, may decrease the likelihood that a more extensive amputation is needed [227, 254]. The progressive development of an abscess within the foot, especially in the presence of ischemia, can rapidly lead to irreparable tissue damage.

Various publications suggest that there are between 4 and 7 compartments in the foot; the 4 in the plantar aspect are medial, lateral, and central plantar and deep plantar (Figure 1) [255, 256]. The key element of any surgical approach is to reach the appropriate foot compartment(s) and extend the exploration and debridement to healthy tissue [257]. Appropriate planning, careful tissue dissection, [257] and using longitudinal skin incisions respecting the specific compartments can lead to a durable, weight-bearing, and often nonpainful plantar surface [255]. An example of a well-tolerated plantar incision is one that begins posterior to the medial malleolus and extends laterally and distally toward the midline, then distally to end between the metatarsal heads. This incision can be modified to end medially or laterally, depending on the involved compartments or anatomic location of the infection. If required, this incision can also be modified to include a partial ray (metatarsal) amputation or extended more proximally to resect all toes (transmetatarsal amputation) or to undertake a midfoot/rearfoot amputation.

For patients with an early, evolving infection, it may be best to delay surgery in an attempt to avoid the consequent scarring and deformity. In those with a nonsevere infection, carefully observing the effectiveness of medical therapy and the demarcation line between necrotic and viable tissue before operating may be prudent [255, 258]. If clinical findings worsen, surgical intervention is usually needed. The surgeon must

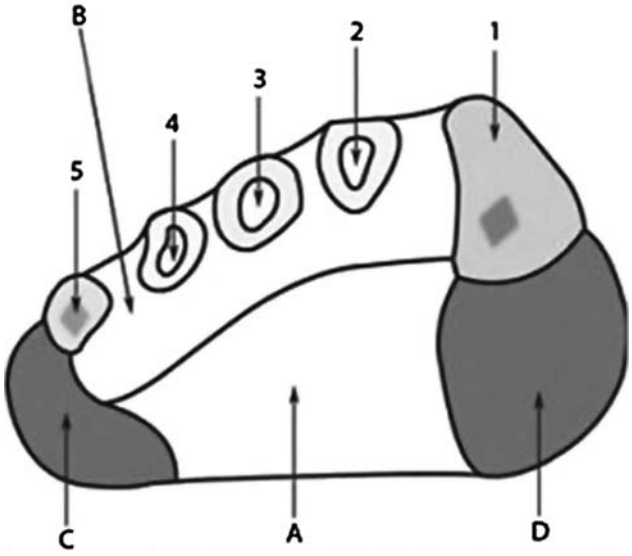

Figure 1. Schematic diagram of cross-section of the foot. Numbers 1–5 indicate metatarsal bones. *A*, central plantar space; *B*, deep interosseous space; *C*, lateral plantar space; *D*, medial plantar space [255, 256].

determine the adequacy of the blood supply to apparently viable tissues, consider common operative pitfalls (eg, infection spreading among foot compartments, to the deep plantar space, or along the tendon sheaths), and formulate a strategy for eventual soft tissue cover (eg, closure that is primary, delayed primary closure, by secondary intention, or by tissue transfer) [259–261]. The surgical approach should optimize the likelihood for healing while attempting to preserve the integrity of the walking surface of the foot [66, 262].

In addition to being knowledgeable about foot anatomy and the pathophysiology of DFI, the surgeon should optimally have experience with and enthusiasm for the field [66]. In most instances, the surgeon should continue to observe the patient until the infection is under control and the wound is healing. In some cases, unfortunately, amputation is the best option [63, 250, 263]. Urgent amputation is rarely required except when there is extensive necrosis or life-threatening infection [264] (Table 12). Elective amputation may be considered for the patient who has recurrent ulceration (despite maximal preventive measures), has irreversible loss of foot function, or would require unacceptably prolonged or intensive hospital care [265, 266]. The surgeon must consider vascular, reconstructive, and rehabilitation issues in selecting the level of amputation [267, 268]. Generally, the surgeon should attempt to save as much of the limb as possible [269]. However, a higher-level amputation that results in a more functional residual stump (even if a prosthesis is required) may be a better choice than preserving a foot that is mechanically unsound, unlikely to heal, or prone to future ulceration. When all or part of a foot has dry gangrene, it may be preferable (especially for a patient who is a poor surgical candidate) to let the necrotic portions auto-amputate. It may also be best to leave adherent eschar in place, especially on the heel, until it softens enough to be more easily removed, provided that there does not appear to be an underlying focus of infection [270, 271].

If the infected limb appears to be ischemic, the patient should be referred to a surgeon with vascular expertise [272]. In most cases, ischemia is secondary to larger-vessel atherosclerosis, rather than to "small-vessel disease" [273]. Because vessels above the knee and below the ankle tend to be relatively spared, lower extremity atherosclerosis may be amenable to angioplasty or vascular bypass [70]. Patients with noncritical ischemia (eg, those with an ABI of 0.4–0.9) can in some cases be successfully treated without a vascular procedure. The clinician should rarely use just a single invasive or noninvasive technique to determine whether to undertake a vascular intervention without taking into account other clinical parameters [60]. For more severe vascular disease of the foot in patients with diabetes, many centers have reported successful use of both aggressive endovascular intervention and distal bypass procedures [70, 77, 274, 275]. For a patient with a severely infected ischemic foot, it is usually preferable to perform any needed revascularization early rather than to delay this procedure in favor of prolonged (and potentially ineffective) antibiotic therapy [276, 277]. On the other hand, careful debridement of necrotic infected material should not be delayed while awaiting revascularization. Optimal surgical management may require combined (multispecialty), multiple, or staged procedures [278].

X. What types of wound care techniques and dressings are appropriate for diabetic foot wounds?

Recommendations

42. Diabetic patients with a foot wound should receive appropriate wound care, which usually consists of the following:
    a. Debridement, aimed at removing debris, eschar, and surrounding callus (strong, moderate). Sharp (or surgical) methods are generally best (strong, low), but mechanical, autolytic, or larval debridement techniques may be appropriate for some wounds (weak, low).
    b. Redistribution of pressure off the wound to the entire weight-bearing surface of the foot ("off-loading"). While particularly important for plantar wounds, this is also necessary to relieve pressure caused by dressings, footwear, or ambulation to any surface of the wound (strong, high).
    c. Selection of dressings that allow for moist wound healing, and control excess exudation. The choice of

dressing should be based on the size, depth, and nature of the ulcer (eg, dry, exudative, purulent) (strong, low).

43. We do not advocate using topical antimicrobials for treating most clinically uninfected wounds (strong, low).

44. No adjunctive therapy has been proven to improve resolution of infection, but for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents (weak, moderate), growth factors (weak, moderate,) granulocyte colony-stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low).

Evidence Summary

Available data to support the use of the different dressings and adjunctive measures for the management of diabetic foot wounds are weak [279–282]. The fundamental problem with studies supporting the benefits of various measures is that they are small in size and suboptimal in design and execution [279–286]. In light of the complex pathophysiology of diabetic foot wounds, most are unlikely to be healed by any single treatment. This makes it difficult to demonstrate the effectiveness of any one intervention in studies that measure wound healing as the primary end point [283]. Extensive clinical experience, and at least some studies, support several basic principles for managing diabetic foot wounds, often called "standard/good wound care." These include sharp debridement of callus and other wound debris or eschar, moist wound healing, and pressure or weight displacement off the affected area of the foot [278, 287, 288]. Other factors that are important in healing a wound include ensuring adequate arterial perfusion to the site and controlling any concomitant infection.

Wound Dressings. The principal function of a wound dressing is to help achieve an optimal healing environment. Many types of dressings have been designed to serve various functions, such as protecting the wound, encouraging wound healing, and preventing or treating infection. Because diabetic foot wounds are heterogeneous, no single dressing is suitable for all types. Clinicians should base dressing selections on the wound's location, size, and depth, amount of exudate, presence of infection or necrosis, and the condition of the surrounding tissue. The goal is to create a moist wound environment to promote granulation (new tissue containing all the cellular components for epithelialization), autolytic processes (wherein host generated enzymes help break down devitalized tissues), angiogenesis (new blood vessel formation), and more rapid migration of epidermal cells across the wound base [289, 290]. Selection of wound dressing should be based on the wound bed characteristics: if dry, it should be hydrated; if draining, the exudate should be absorbed; if necrotic, it should be debrided. Commonly used dressing types include:

- Continuously moistened saline gauze: for dry or necrotic wounds
- Hydrogels: for dry and or necrotic wounds and to facilitate autolysis
- Films: occlusive or semiocclusive, for moistening dry wounds
- Alginates: for drying exudative wounds
- Hydrocolloids: for absorbing exudate and to facilitate autolysis
- Foams: for exudative wounds

Currently, there is insufficient evidence to recommend one specific dressing type over another, but some data support the effectiveness of hydrogels [283, 291–293].

Topical Antimicrobials. The controversial concept of excess wound bioburden has led to the increasing use of antimicrobials, particularly topical antiseptics (eg, cadexomer-iodine) and silver-based dressings, despite little evidence substantiating any benefit of these dressings over conventional therapy [115, 282–285]. In addition to their expense and potential for causing local adverse effects, use of these antimicrobials may further promote the emergence of bacterial resistance [294–296]. With these theoretical risks, and a lack of evidence of any advantages, we do not advocate using topical antimicrobials for most clinically uninfected wounds [115]. Furthermore, the available evidence does not support any benefit to using silver-based dressings for clinically infected wounds [281, 282, 297, 298].

Debridement. Debridement involves removing necrotic or nonviable tissue, slough, or foreign material from the wound, as well as trimming any surrounding hyperkeratosis (callus). This process also removes colonizing bacteria, aids granulation tissue formation and reepithelialization, reduces pressure at callused sites, facilitates the collection of appropriate specimens for culture, and permits examination for the presence of deep tissue (especially bone) involvement [84, 270, 271, 292, 299]. The goal is to enable wound healing and to remove a reservoir of potential pathogens [291, 292, 300, 301]. The patient should be forewarned that bleeding is likely and that the wound will appear larger after the procedure, when its full extent is exposed. Debridement can usually be undertaken as a clinic or bedside procedure and without anesthesia, although patients who do not have a loss of protective sensation may require local anesthesia. If the wound is extensive, there is adherent eschar, the clinician's time is limited, or the patient finds the procedure too painful, it may be best to stop and to conduct additional debriding sessions over several days. Wounds needing deeper or more extensive debridement, however, may require surgery in an operative suite. Debridement may be relatively contraindicated in wounds that are primarily ischemic [301].

We generally prefer sharp debridement (with scalpel, scissors, or tissue nippers) to other techniques that are less definitive and controllable and may require prolonged and repeated applications [301, 302]. Although sharp debridement has been proven to be efficacious in clinical trials [278, 303], a systematic review found little strong evidence of the effectiveness of either sharp debridement or topical debriding agents [283]. Debridement should be repeated as often as needed if nonviable tissue continues to form [304]. Other methods of debridement include autolytic dressings and biological debridement with maggots (ie, larvae of *Lucilia sericata* [green-bottle fly]). The exact mechanism of maggot biotherapy is not yet known, but it appears to be useful for carefully selected necrotic and infected wounds [305–308]. Limited evidence supports the use of hydrosurgery systems, an emerging technology that simultaneously cuts and aspirates soft tissue, but they are relatively expensive [309, 310]. Following debridement, measure and record the wound size, the extent of any surrounding cellulitis, and the quality and quantity of any drainage (including color, lucency, and odor); taking photographs is helpful in this regard. Bear in mind when documenting treatment that >1 clinician will treat most patients during the healing process.

Off-loading Pressure. Relieving pressure from a diabetic foot wound (off-loading) is a vital part of wound care [311]. The choice of off-loading modality should be based on the wound's location, the presence of any associated PAD, the presence and severity of infection, and the physical characteristics of the patient and their psychological and social situation. The total contact cast, often considered the "gold standard" device, redistributes pressure to the entire weight-bearing surface to accelerate healing of a neuropathic ulcer [299, 312, 313]. Its main advantage may be that it is irremovable, leading to the development of other devices, such as the instant total contact cast [314], that are easier to apply, less expensive, and equally efficacious. The total contact cast should only be used with caution in patients with severe PAD or active infection, as it precludes viewing the wound [315]. There are many types of removable off-loading devices from which to choose [316–318], but patients often remove them, especially when they are at home.

Studies over the past 2 decades have established that the majority of diabetic foot ulcers take at least 20 weeks to heal [319, 320]. If a diabetic foot wound fails to heal despite good wound care, the clinician should initiate a reevaluation of management (Table 13). This should include ensuring that perfusion of the limb is adequate and that any infection (especially osteomyelitis) has been adequately addressed. Consider obtaining a biopsy of a recalcitrant or atypical wound, as a lesion that appears to be a diabetic foot ulcer may on occasion be a malignancy (eg, a melanoma or Kaposi sarcoma). After addressing these issues, the clinician should consider using adjunctive treatments to promote wound healing. None of these measures, however, have been shown to improve resolution of infection; moreover, they are expensive, not universally available, and may require consultation with experts, and the reports supporting their utility are mostly flawed.

Table 13. Questions to Ask When Dealing With Nonresponse or Recurrence

Is there a failure of wound healing?
• Is the patient adhering to the wound care regimen?
• Has the wound been adequately debrided?
• Has the wound been appropriately dressed?
• Has the wound been adequately off-loaded?
• Is there unidentified or untreated ischemia?
• Is the lesion malignant?
• Is there undiagnosed or improperly treated infection?
Is there a failure of infection to respond?
• Is there unidentified or untreated limb ischemia?
• Is there unidentified necrotic soft tissue or bone?
• Is there an undrained abscess?
• Has the wound been adequately debrided?
• Is there osteomyelitis that has not yet responded?
• Is there an untreated or an unidentified pathogen?
• Is there an antibiotic delivery problem?
• Is there an antibiotic nonadherence issue?
• Have all metabolic aberrations been corrected?

- Hyperbaric oxygen therapy: A limited number of randomized controlled trials are available to support its use for wound healing (but not resolving infection) [321–324].
- Platelet-derived growth factors: Although an initial study demonstrated benefit, subsequent investigations have not shown these treatments to improve healing, or they have been conducted in a fashion where the data cannot be interpreted in the context of routine care [287, 325, 326].
- Granulocyte colony-stimulating factor (G-CSF): Based on results of 5 randomized clinical trials using various preparations and protocols, adding G-CSF did not significantly affect the likelihood of resolution of infection or wound healing but was associated with a significantly reduced likelihood of lower extremity surgical interventions (including amputation) and reduced duration of hospital stay, but not duration of systemic antibiotic therapy. The available data are not sufficiently robust to support the routine use of this therapy [327–333].
- Bioengineered skin equivalents: The data supporting the effectiveness of these products are not of sufficient quality or robustness to support their use [334–336].

- Topical negative pressure: Although some studies have demonstrated that this widely used treatment may safely improve healing of a diabetic foot ulcer, especially after a surgical procedure (eg, wide debridement or partial amputation) [337–339], there is limited high-level evidence to support widespread utilization, especially in an infected wound [280, 340].

Only additional randomized clinical trials can establish when, for whom, and with what protocols these expensive adjunctive therapies might be used in the treatment of the diabetic foot ulcer.

Limitations of the Literature and Future Studies. By mid-2011, >1800 papers had been published on some aspect of foot infections in persons with diabetes. We know a great deal about why diabetic patients develop foot infections, we have learned much about their epidemiology and pathophysiology, we know the usual causative organisms, we understand the role of surgical interventions, and we have demonstrated the effectiveness of many antimicrobial agents. And yet, the care of patients with this devastating problem is suboptimal in almost all settings. The main problem currently is less our lack of full understanding of the problem as our failure to apply what we know works. Based on the results of studies carried out in several settings in different countries, we know that about half of foot amputations can be avoided by improved care of a diabetic foot ulceration or infection. Mainly, this means applying the basic principles outlined in this guideline (and those of other organizations). Clearly, the best way to ensure that these principles are applied is for the patient to be seen by some type of a multidisciplinary foot care team.

What, then, are the limitations of the literature? Before the past decade we did not have a common language, so it was difficult to know what kinds of patients had been studied in a published report. In this regard, using one of several classification schemes, and specifically the IDSA or IWGDF infection severity classification, has helped. A major problem with studies of the microbiology of DFIs has been their failure to require optimal (ie, tissue) specimens for culture, and to some degree, the failure to properly culture for obligate anaerobes. In studies of antimicrobial therapy, the limitation has been the paucity, until the past decade, of randomized controlled trials. Unfortunately, these trials almost always exclude patients with bone infection or an ischemic limb, leaving us with little evidence-based information on how to treat these patients. Finally, many of the studies of treatments for DFIs, as with other conditions, are sponsored by industry, raising concerns about potential bias in which products are tested, by what methods, and how the results are reported.

Recommendations From the Panel for Future Work in This Field. Listed below are several areas related to DFI that the panel members think are in most need of further research, technological and commercial development, or improved educational methods that may lead to better outcomes when treating DFIs.

Implementation.

1. Deploying a multidisciplinary team reduces the likelihood and extent of lower extremity amputations in diabetic patients with a foot infection. Medical institutions, insurance companies, and other healthcare systems should encourage the development of the following:
   a. Rapid-response or "hot" teams that can provide appropriate initial evaluation and recommendations for care.
   b. Diabetic foot specialty teams or centers of excellence to which patients can later be referred for further consultation, if necessary. These teams should be composed of experienced medical, surgical, or nursing providers, working with specified, evidence-based procedures. Optimally they should include a foot specialist, a vascular surgeon, and a wound care specialist; they should also include or have access to specialists in infectious diseases or clinical microbiology and other disciplines (eg, diabetes, pharmacy).
   c. In communities where this is not practical, providers should seek telemedicine consultations from experts, or at least attempt to develop formal or informal consulting relationships, to ensure prompt evaluation and treatment by appropriate specialists, when needed.
2. We encourage healthcare organizations to develop systems to regularly audit various aspects of their processes and key outcomes of care for patients with DFIs who are treated in their institutions. Organizations should then use the results of these audits to improve care and better outcomes.
3. Healthcare organizations should ensure that providers who evaluate and manage patients with DFIs have ready access to the required diagnostic and therapeutic equipment (including a monofilament, scalpel, sterile metal probe, forceps, tissue scissors), as well as advanced imaging and vascular diagnostic equipment and specialists.
4. Healthcare organizations should ensure implementation of measures to prevent spread of multidrug-resistant organisms in both inpatient and outpatient settings, and we encourage providers to monitor bacterial resistance patterns of diabetic foot isolates.

Regulatory Changes.

1. The FDA previously had a specific pathway for manufacturers of new and approved antibiotics to apply for approval for treatment of "complicated skin and skin structure infections including DFIs." Their recently issued draft guidance for acute bacterial skin and skin structure infections specifically excludes patients with DFIs from enrollment in clinical trials, suggesting that sponsors wishing to develop a drug for this

indication consult with the FDA [160]. We encourage the FDA (and similar agencies in other countries) to clarify its requirements for studying DFIs, and the pharmaceutical companies to invest in testing for antimicrobial agents for the DFI designation.

2. Many DFIs are complicated by bone involvement, yet there are no specific guidelines for conducting studies of treatment of this problem. Thus, we encourage the FDA (and similar agencies in other countries) to develop "Guidance for Industry" on conducting studies of antibiotic agents for treating osteomyelitis.

3. We encourage regulatory and oversight agencies, both local and national, to encourage (and ultimately require) healthcare organizations to tabulate and evaluate rates of foot complications in their diabetic population, to compare them to other sites, and to strive to improve outcomes.

4. We encourage various agencies that fund research programs to invest in studies of this large and growing problem, including developing calls for proposals on the most needed subjects of research.

Research Questions.

1. In an era of increasing antibiotic resistance, we must address several questions concerning the most appropriate antibiotic therapy for various types of DFIs:
   a. Is there a role for treating clinically uninfected foot wounds with antimicrobials, either to prevent active infection or hasten wound healing?
   b. For which, if any, wounds are topical antimicrobial agents appropriate therapy?
   c. In which situations, and for how long, is parenteral (rather than oral) antibiotic therapy needed for a DFI?
   d. What total duration of antibiotic therapy (topical, oral, or parenteral) is needed for various types of DFIs?
   e. Is it necessary to select an antibiotic regimen that covers all proven or suspected pathogens in a DFI? Is narrow-spectrum therapy safe and effective for selected types of infections?
2. Managing proven or presumed osteomyelitis is the most contentious aspect of treatment of DFIs. We encourage research that addresses these issues:
   a. What are the best clinical and imaging criteria (alone or in combinations) to diagnose bone infection?
   b. When is it appropriate to obtain a specimen of bone for culture (and histology, if possible) in a patient with suspected osteomyelitis? What are the best methods to obtain such a specimen, and how can we persuade reluctant specialists to perform the procedure?
   c. When is surgical resection of infected or necrotic bone most appropriate?
   d. What is the required duration of antimicrobial treatment of osteomyelitis, both in patients who have, and have not, undergone surgical resection of infected or necrotic bone?
   e. What diagnostic studies can help determine when osteomyelitis has been arrested after treatment?
3. Various types of adjunctive therapies (eg, antibiotic loaded poly[methyl methacrylate] beads, hyperbaric oxygen, and G-CSF) may have some benefit in selected patients; we need to define for which, if any, patients these treatments are cost-effective.
4. Biofilm appears to play an important role in increasing the difficulty of treating DFIs. What are the best ways to try to eliminate biofilm or make bacteria in biofilm easier to eradicate?

PERFORMANCE MEASURES

Clinicians caring for patients with a DFI, and their patients, need assurance that the care they are providing (or receiving) is of acceptable quality. For this reason, and to drive service improvement, clinicians and organizations should undertake measures of both outcome and process, and make them available for review, benchmarking, and action planning (Table 14). Currently, there is considerable variability in care pathways and processes, even within similar organizations, but particularly across different types of healthcare systems. We think clinicians should attempt to compare their key outcomes to those of

Table 14. Potential Performance Measures for Managing Diabetic Foot Infection

Outcomes of Treatment
• What percentage of treated patients had their infection eradicated?
• What percentage of treated patients underwent an amputation (and at what level) or other substantial surgical procedure (eg, bone resection)?
• What percentage of patients suffered clinically significant adverse effects from their treatment?
• What percentage of patients were alive; antibiotic free; ulcer free at various intervals (and at least 12 mo after treatment)?
Process of management
• Did appropriate clinicians evaluate the patient (eg, foot surgeon, vascular surgeon, infectious diseases or clinical microbiology specialist, wound care specialist)?
• How long did it take before the patient was seen by a foot specialist or team?
• Were appropriate specimens taken for culture from infected wounds?
• Was the selected antibiotic regimen appropriate (empiric and definitive choices, changes in regimen when needed, duration of treatment)?
• Was appropriate outpatient follow-up arranged after acute care?
• Does the service have protocols to assist and define the functioning of the multidisciplinary team, the process of antibiotic selection, and antibiotic duration in different situations?

others (at least in similar situations) and should strive to achieve better outcomes as they examine their processes.

Recently, Fincke et al developed a classification system for patients with DFI designed for use with large, computerized, *International Classification of Diseases, Ninth Revision, Clinical Modification*–coded administrative medical databases [341]. This system provides a model for a framework for conducting observational studies to examine treatment variation and patient outcomes, including the effect of new management strategies, implementation of practice guidelines, and quality improvement initiatives. Using this system on a database of patients treated at US Veterans Affairs medical centers, they demonstrated that their severity ranking showed a monotonic relationship to hospital length of stay, amputation rate, transition to long-term care, and mortality. They also found that the range of variation in these parameters, as well as in the spectrum of the antibiotic regimens across facilities, was substantially greater than that across the categories of foot infection. The large variations in regimens appear to reflect differences in facility practice styles rather than case mix [342].

Another recent example of the benefits of auditing followed by process change concerned the microbiologic assessment of a DFI. After implementing recommendations from international guidelines, Sotto et al demonstrated significant and dramatic decreases in the median number of bacteria species per sample, multidrug-resistant organisms, and colonizing (nonpathogenic) organisms over a 5-year period in their hospital [343]. In parallel, there was an associated cost savings of €14 914 related to a reduced microbiology laboratory workload and another €109 305 due to reduced prescribing of extended-spectrum antibiotic agents. Thus, this simple intervention saved >$200 000, while improving antibiotic stewardship.

Activities of this sort are essential to drive quality improvement, but the measures must be chosen with care. At first glance the most meaningful outcome measure would be success in eradicating signs and symptoms of infection. However, infection is of particular significance in the diabetic foot because of its close relationship to the need for amputation [343]. Therefore, in addition to collecting data on resolution of infection, multidisciplinary teams managing DFI should also know the service's minor and major amputation rates, and ideally other patient-related outcomes, such as survival, ulcer-free duration, and antibiotic-free days [344]. Administering antibiotics effectively is of little value if the rest of the patient pathway is not also organized so that the ulcer can heal and an amputation is avoided.

Performance measures might include:

- The composition and meeting frequency of multidisciplinary teams
- The percentage of patients with DFI in an institution seen by a multidisciplinary team
- Waiting times for initial evaluation of a DFI and for referral to the specialist foot care team
- Time intervals between key milestones in management, such as clinical assessment to appropriate imaging to initiation of treatment, or recommendation for surgical procedure to when it is completed
- Average and median length of hospital stay for a DFI
- Frequency of providing appropriate foot care services on discharge from the hospital, or as part of a primary care consultation
- Existence and use of locally agreed protocols for referral, antibiotic regimens, and evidence of audit of compliance to these protocols

These measures should be reviewed as part of ongoing audits of care. This will allow any site (or individual practitioner) to compare his or her results to those made public by others, as well as to track performance at a single site over time. Poor or worsening performance measures should trigger more detailed review (using, eg, the Plan-Do-Check-Act cycle or other "lean methodologies") to determine and address the cause(s) [345]. These performance measures may be able to be done in conjunction with other ongoing evaluations, such as antibiotic stewardship reviews and adverse medical or surgical outcome reviews.

Notes

Acknowledgments. The panel members thank Drs Thomas File, Mark Kosinski, and Brad Spellberg for their thoughtful reviews of earlier drafts of the guideline, and Dr James Horton (IDSA SGPC liaison), Jennifer Padberg, and Vita Washington for overall guidance and coordination in all aspects of the development of this guideline.

Financial support. Support for these guidelines was provided by the Infectious Diseases Society of America.

Potential conflicts of interest. The following list is a reflection of what has been reported to the IDSA. In order to provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. B. L. has served as a consultant to Merck, Pfizer, Cubist, Innocoll, TaiGen, KCI, and Dipexium. E. S. has served on the board of and consulted for Novartis. H. G. D. has served on the speakers' bureau for Merck and Sanofi. J. P. has served as a consultant to Pfizer and Ortho McNeil. M. P. has served as a consultant for Orthopedic Implants for Deputy Orthopedics and Small Bone Innovation. W. J. has served as a consultant for Merck, Pfizer, Cerexa, and Dipexium and has served on the speakers' bureaus of Merck and Pfizer. A. W. K. is on the boards of Pfizer and Merck and the speakers' bureau for Astella, and consults for Novartis. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ **2008**; 336:924–6.

2. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. BMJ **2008**; 336:1049–51.
3. Jaeschke R, Guyatt GH, Dellinger P, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. BMJ **2008**; 337:a744.
4. Kish MA. Guide to development of practice guidelines. Clin Infect Dis **2001**; 32:851–4.
5. Schunemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ **2008**; 336:1106–10.
6. Guyatt GH, Oxman AD, Kunz R, et al. Incorporating considerations of resources use into grading recommendations. BMJ **2008**; 336:1170–3.
7. Centers for Disease Control and Prevention. Number (in thousands) of hospital discharges with ulcer/inflammation/infection (ULCER) as first-listed diagnosis and diabetes as any-listed diagnosis, 1980–2003. **2010**. Available at: http://www.cdc.gov/diabetes/statistics/hosplea/diabetes_complications/fig5.htm.
8. Centers for Disease Control and Prevention. Number (in thousands) of hospital discharges for non-traumatic lower extremity amputation with diabetes as a listed diagnosis, 1988–2006. CDC, **2010**. Available at: http://www.cdc.gov/diabetes/statistics/lea/fig1.htm.
9. Prevention. Age-adjusted hospital discharge rates for non-traumatic lower extremity amputation per 1,000 diabetic population, by level of amputation. CDC, **2010**. Available at: http://www.cdc.gov/diabetes/statistics/lealevel/fig8.htm.
10. Vamos EP, Bottle A, Majeed A, Millett C. Trends in lower extremity amputations in people with and without diabetes in England, 1996–2005. Diabetes Res Clin Pract **2010**; 87:275–82.
11. Armstrong DG, Wrobel J, Robbins JM. Guest editorial: are diabetes-related wounds and amputations worse than cancer? Int Wound J **2007**; 4:286–7.
12. Richard JL, Lavigne JP, Got I, et al. Management of patients hospitalized for diabetic foot infection: results of the French OPIDIA study. Diabetes Metab **2010**; 37:208–15.
13. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia **2007**; 50:18–25.
14. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia **2008**; 51:747–55.
15. van Battum P, Schaper N, Prompers L, et al. Differences in minor amputation rate in diabetic foot disease throughout Europe are in part explained by differences in disease severity at presentation. Diabet Med **2011**; 28:199–205.
16. Prompers L, Huijberts M, Schaper N, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale study. Diabetologia **2008**; 51:1826–34.
17. Prompers L, Huijberts M, Apelqvist J, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale study, a prospective cohort study. Diabet Med **2008**; 25:700–7.
18. Gottrup F, Holstein P, Jorgensen B, Lohmann M, Karlsmar T. A new concept of a multidisciplinary wound healing center and a national expert function of wound healing. Arch Surg **2001**; 136:765–72.
19. Trautner C, Haastert B, Mauckner P, Gatcke LM, Giani G. Reduced incidence of lower-limb amputations in the diabetic population of a German city, 1990–2005: results of the Leverkusen Amputation Reduction Study (LARS). Diabetes Care **2007**; 30:2633–7.
20. Krishnan S, Nash F, Baker N, Fowler D, Rayman G. Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit. Diabetes Care **2008**; 31:99–101.
21. Hellingman AA, Smeets HJ. Efficacy and efficiency of a streamlined multidisciplinary foot ulcer service. J Wound Care **2008**; 17:541–4.
22. Rerkasem K, Kosachunhanun N, Tongprasert S, et al. Reducing lower extremity amputations due to diabetes: the application of diabetic-foot protocol in Chiang Mai University Hospital. Int J low Extrem Wounds **2008**; 7:88–92.
23. Ortegon MM, Redekop WK, Niessen LW. Cost-effectiveness of prevention and treatment of the diabetic foot: a Markov analysis. Diabetes Care **2004**; 27:901–7.
24. Tan T, Shaw EJ, Siddiqui F, Kandaswamy P, Barry PW, Baker M. Inpatient management of diabetic foot problems: summary of NICE guidance. BMJ **2011**; 342:d1280.
25. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA **2005**; 293:217–28.
26. Haller NA, Gil KM, Gardner WG, Whittier FC. Patient computer use to prompt doctor adherence to diabetes management guidelines. J Eval Clin Pract **2009**; 15:1118–24.
27. Field MJ, Lohr KN; Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines. Clinical Practice Guidelines: directions for a new program. Washington, DC: National Academies Press, **1990**:52–77.
28. Guyatt GH, Cook DJ, Jaeschke R, Pauker SG, Schunemann HJ. Grades of recommendation for antithrombotic agents: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest **2008**; 133:123S–31S.
29. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ **2008**; 336:995–8.
30. Cutting KF, White R. Defined and refined: criteria for identifying wound infection revisited. Br J Community Nurs **2004**; 9:S6–15.
31. Gardner SE, Hillis SL, Frantz RA. Clinical signs of infection in diabetic foot ulcers with high microbial load. Biol Res Nurs **2009**; 11:119–28.
32. Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. Diabetes Care **2006**; 29:1288–93.
33. Peters EJ, Lavery LA, Armstrong DG. Diabetic lower extremity infection: influence of physical, psychological, and social factors. J Diabetes Complications **2005**; 19:107–12.
34. Bartos V, Jirkovska A, Koznarova R. [Risk factors for diabetic foot in recipients of renal and pancreatic transplants]. Cas Lek Cesk **1997**; 136:527–9.
35. George RK, Verma AK, Agarwal A, Agarwal G, Mishra SK. An audit of foot infections in patients with diabetes mellitus following renal transplantation. Int J low Extrem Wounds **2004**; 3:157–60.
36. Hill MN, Feldman HI, Hilton SC, Holechek MJ, Ylitalo M, Benedict GW. Risk of foot complications in long-term diabetic patients with and without ESRD: a preliminary study. ANNA J **1996**; 23:381–6; discussion 87–8.
37. Jayasinghe SA, Atukorala I, Gunethilleke B, Siriwardena V, Herath SC, De Abrew K. Is walking barefoot a risk factor for diabetic foot disease in developing countries? Rural Remote Health **2007**; 7:692.
38. Karthikesalingam A, Holt PJ, Moxey P, Jones KG, Thompson MM, Hinchliffe RJ. A systematic review of scoring systems for diabetic foot ulcers. Diabet Med **2010**; 27:544–9.
39. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes Metab Res Rev **2004**; 20(Suppl 1):S90–5.
40. Meggitt B. Surgical management of the diabetic foot. Br J Hosp Med **1976**; 16:227–332.
41. Ince P, Abbas ZG, Lutale JK, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care **2008**; 31:964–7.
42. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis **2007**; 44:562–5.
43. Jeandrot A, Richard JL, Combescure C, et al. Serum procalcitonin and C-reactive protein concentrations to distinguish mildly infected

from non-infected diabetic foot ulcers: a pilot study. Diabetologia **2008**; 51:347–52.
44. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle **1981**; 2:64–122.
45. Treece KA, Macfarlane RM, Pound N, Game FL, Jeffcoate WJ. Validation of a system of foot ulcer classification in diabetes mellitus. Diabet Med **2004**; 21:987–91.
46. Ince P, Kendrick D, Game F, Jeffcoate W. The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes. Diabet Med **2007**; 24:977–81.
47. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care **1998**; 21:855–9.
48. Parisi MC, Zantut-Wittmann DE, Pavin EJ, Machado H, Nery M, Jeffcoate WJ. Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. Eur J Endocrinol **2008**; 159:417–22.
49. Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL. Classification and treatment of chronic nonhealing wounds. Successful treatment with autologous platelet-derived wound healing factors (PDWHF). Ann Surg **1986**; 204:322–30.
50. Beckert S, Witte M, Wicke C, Konigsrainer A, Coerper S. A new wound-based severity score for diabetic foot ulcers: a prospective analysis of 1,000 patients. Diabetes Care **2006**; 29:988–92.
51. Beckert S, Pietsch AM, Kuper M, et al. M.A.I.D.: a prognostic score estimating probability of healing in chronic lower extremity wounds. Ann Surg **2009**; 249:677–81.
52. Lipsky BA, Polis AB, Lantz KC, Norquist JM, Abramson MA. The value of a wound score for diabetic foot infections in predicting treatment outcome: a prospective analysis from the SIDESTEP trial. Wound Repair Regen **2009**; 17:671–7.
53. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis **2004**; 39:885–910.
54. Schaper NC, Apelqvist J, Bakker K. The international consensus and practical guidelines on the management and prevention of the diabetic foot. Curr Diab Rep **2003**; 3:475–9.
55. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care **2003**; 26:510–3.
56. Vedhara K, Miles JN, Wetherell MA, et al. Coping style and depression influence the healing of diabetic foot ulcers: observational and mechanistic evidence. Diabetologia **2010**; 53:1590–8.
57. Uzun G, Solmazgul E, Curuksulu H, et al. Procalcitonin as a diagnostic aid in diabetic foot infections. Tohoku J Exp Med **2007**; 213:305–12.
58. Lipsky BA, Sheehan P, Armstrong DG, Tice AD, Polis AB, Abramson MA. Clinical predictors of treatment failure for diabetic foot infections: data from a prospective trial. Int Wound J **2007**; 4:30–8.
59. Akinci B, Yener S, Yesil S, Yapar N, Kucukyavas Y, Bayraktar F. Acute phase reactants predict the risk of amputation in diabetic foot infection. J Am Podiatr Med Assoc **2011**; 101:1–6.
60. Peripheral arterial disease in people with diabetes. Diabetes Care **2003**; 26:3333–41.
61. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation **2006**; 113: e463–654.
62. van Baal JG. Surgical treatment of the infected diabetic foot. Clin Infect Dis **2004**; 39(Suppl 2):S123–8.
63. Pinzur MS, Pinto MA, Schon LC, Smith DG. Controversies in amputation surgery. Instr Course Lect **2003**; 52:445–51.
64. Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? JAMA **2006**; 295:536–46.
65. Wilson JF, Laine C, Goldmann D. In the clinic. Peripheral arterial disease. Ann Intern Med **2007**; 146:ITC3-1–ITC3-16.
66. Crane M, Werber B. Critical pathway approach to diabetic pedal infections in a multidisciplinary setting. J Foot Ankle Surg **1999**; 38:30–3; discussion 82–3.
67. Larsson J, Apelqvist J, Agardh CD, Stenstrom A. Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? Diabet Med **1995**; 12:770–6.
68. Dargis V, Pantelejeva O, Jonushaite A, Vileikyte L, Boulton AJ. Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. Diabetes Care **1999**; 22:1428–31.
69. Fitzgerald RH, Mills JL, Joseph W, Armstrong DG. The diabetic rapid response acute foot team: 7 essential skills for targeted limb salvage. Eplasty **2009**; 9:e15.
70. Gibbons GW. Lower extremity bypass in patients with diabetic foot ulcers. Surg Clin North Am **2003**; 83:659–69.
71. Bus SA, Hazenberg CE, Klein M, Van Baal JG. Assessment of foot disease in the home environment of diabetic patients using a new photographic foot imaging device. J Med Eng Technol **2010**; 34:43–50.
72. Clemensen J, Larsen SB, Ejskjaer N. Telemedical treatment at home of diabetic foot ulcers. J Telemed Telecare **2005**; 11(Suppl 2):S14–6.
73. Bowling FL, King L, Paterson JA, et al. Remote assessment of diabetic foot ulcers using a novel wound imaging system. Wound Repair Regen **2011**; 19:25–30.
74. Wilbright WA, Birke JA, Patout CA, Varnado M, Horswell R. The use of telemedicine in the management of diabetes-related foot ulceration: a pilot study. Adv Skin Wound Care **2004**; 17:232–8.
75. Aragon-Sanchez J. Seminar review: a review of the basis of surgical treatment of diabetic foot infections. Int J Low Extrem Wounds **2011**; 10:33–65.
76. Sumpio BE, Armstrong DG, Lavery LA, Andros G. The role of interdisciplinary team approach in the management of the diabetic foot: a joint statement from the Society for Vascular Surgery and the American Podiatric Medical Association. J Vasc Surg **2010**; 51:1504–6.
77. Akbari CM, Pomposelli FB Jr, Gibbons GW, et al. Lower extremity revascularization in diabetes: late observations. Arch Surg **2000**; 135:452–6.
78. Lipsky BA, Pecoraro RE, Larson SA, Hanley ME, Ahroni JH. Outpatient management of uncomplicated lower-extremity infections in diabetic patients. Arch Intern Med **1990**; 150:790–7.
79. Lipsky BA, Itani K, Norden C. Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate. Clin Infect Dis **2004**; 38:17–24.
80. Armstrong DG, Lavery LA, Sariaya M, Ashry H. Leukocytosis is a poor indicator of acute osteomyelitis of the foot in diabetes mellitus. J Foot Ankle Surg **1996**; 35:280–3.
81. Eneroth M, Larsson J, Apelqvist J. Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. J Diabetes Complications **1999**; 13:254–63.
82. Frykberg RG. An evidence-based approach to diabetic foot infections. Am J Surg **2003**; 186:44S–54S; discussion 61S–64S.
83. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. N Engl J Med **1994**; 331:854–60.

84. No authors listed. Consensus Development Conference on Diabetic Foot Wound Care: 7–8 April 1999, Boston, Massachusetts. American Diabetes Association. Diabetes Care **1999**; 22:1354–60.
85. Rao N, Lipsky BA. Optimising antimicrobial therapy in diabetic foot infections. Drugs **2007**; 67:195–214.
86. Dang CN, Prasad YD, Boulton AJ, Jude EB. Methicillin-resistant *Staphylococcus aureus* in the diabetic foot clinic: a worsening problem. Diabet Med **2003**; 20:159–61.
87. Stanaway S, Johnson D, Moulik P, Gill G. Methicillin-resistant *Staphylococcus aureus* (MRSA) isolation from diabetic foot ulcers correlates with nasal MRSA carriage. Diabetes Res Clin Pract **2007**; 75:47–50.
88. Carvalho CB, Neto RM, Aragao LP, Oliveira MM, Nogueira MB, Forti AC. [Diabetic foot infection. Bacteriologic analysis of 141 patients]. Arq Bras Endocrinol Metabol **2004**; 48:398–405.
89. Shankar EM, Mohan V, Premalatha G, Srinivasan RS, Usha AR. Bacterial etiology of diabetic foot infections in South India. Eur J Intern Med **2005**; 16:567–70.
90. Tascini C, Gemignani G, Palumbo F, et al. Clinical and microbiological efficacy of colistin therapy alone or in combination as treatment for multidrug resistant *Pseudomonas aeruginosa* diabetic foot infections with or without osteomyelitis. J Chemother **2006**; 18:648–51.
91. Kandemir O, Akbay E, Sahin E, Milcan A, Gen R. Risk factors for infection of the diabetic foot with multi-antibiotic resistant microorganisms. J Infect **2007**; 54:439–45.
92. Gadepalli R, Dhawan B, Sreenivas V, Kapil A, Ammini AC, Chaudhry R. A clinico-microbiological study of diabetic foot ulcers in an Indian tertiary care hospital. Diabetes Care **2006**; 29:1727–32.
93. Edmonds M. Infection in the neuroischemic foot. Int J low Extrem Wounds **2005**; 4:145–53.
94. Richard JL, Sotto A, Jourdan N, et al. Risk factors and healing impact of multidrug-resistant bacteria in diabetic foot ulcers. Diabetes Metab **2008**; 34:363–9.
95. Sotto A, Richard JL, Jourdan N, Combescure C, Bouziges N, Lavigne JP. Miniaturized oligonucleotide arrays: a new tool for discriminating colonization from infection due to *Staphylococcus aureus* in diabetic foot ulcers. Diabetes Care **2007**; 30:2051–6.
96. Chakraborti C, Le C, Yanofsky A. Sensitivity of superficial cultures in lower extremity wounds. J Hosp Med **2010**; 5:415–20.
97. Gardner SE, Frantz RA, Saltzman CL, Hillis SL, Park H, Scherubel M. Diagnostic validity of three swab techniques for identifying chronic wound infection. Wound Repair Regen **2006**; 14:548–57.
98. Nelson EA, O'Meara S, Craig D, et al. A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers. Health Technol Assess **2006**; 10:iii–iv, ix–x, 1–221.
99. Singh SK, Gupta K, Tiwari S, et al. Detecting aerobic bacterial diversity in patients with diabetic foot wounds using ERIC-PCR: a preliminary communication. Int J Low Extrem Wounds **2009**; 8:203–8.
100. Fisher TK, Wolcott R, Wolk DM, Bharara M, Kimbriel HR, Armstrong DG. Diabetic foot infections: a need for innovative assessments. Int J Low Extrem Wounds **2010**; 9:31–6.
101. Sotto A, Lina G, Richard JL, et al. Virulence potential of *Staphylococcus aureus* strains isolated from diabetic foot ulcers: a new paradigm. Diabetes Care **2008**; 31:2318–24.
102. Wolcott RD, Cox SB, Dowd SE. Healing and healing rates of chronic wounds in the age of molecular pathogen diagnostics. J Wound Care **2010**; 19:272–8, 80–1.
103. Hirschl M, Hirschl AM. Bacterial flora in mal perforant and antimicrobial treatment with ceftriaxone. Chemotherapy **1992**; 38:275–80.
104. Chantelau E, Tanudjaja T, Altenhofer F, Ersanli Z, Lacigova S, Metzger C. Antibiotic treatment for uncomplicated neuropathic forefoot ulcers in diabetes: a controlled trial. Diabet Med **1996**; 13:156–9.
105. Edmonds M, Foster A. The use of antibiotics in the diabetic foot. Am J Surg **2004**; 187:25S–28S.
106. Gardner SE, Frantz RA. Wound bioburden and infection-related complications in diabetic foot ulcers. Biol Res Nurs **2008**; 10:44–53.
107. Ramakant P, Verma AK, Misra R, et al. Changing microbiological profile of pathogenic bacteria in diabetic foot infections: time for a rethink on which empirical therapy to choose? Diabetologia **2011**; 54:58–64.
108. Lipsky BA. Empirical therapy for diabetic foot infections: are there clinical clues to guide antibiotic selection? Clin Microbiol Infect **2007**; 13:351–3.
109. Wheat LJ, Allen SD, Henry M, et al. Diabetic foot infections. Bacteriologic analysis. Arch Intern Med **1986**; 146:1935–40.
110. Krikava K, Pospisil M. [The diabetic foot syndrome—antibiotic therapy]. Rozhl Chir **1999**; 78:295–8.
111. Ng LS, Kwang LL, Yeow SC, Tan TY. Anaerobic culture of diabetic foot infections: organisms and antimicrobial susceptibilities. Ann Acad Med Singapore **2008**; 37:936–9.
112. Dowd SE, Wolcott RD, Sun Y, McKeehan T, Smith E, Rhoads D. Polymicrobial nature of chronic diabetic foot ulcer biofilm infections determined using bacterial tag encoded FLX amplicon pyrosequencing (bTEFAP). PLoS One **2008**; 3:e3326.
113. Armstrong DG, Liswood PJ, Todd WF, William J. Stickel Bronze Award. Prevalence of mixed infections in the diabetic pedal wound. A retrospective review of 112 infections. J Am Podiatr Med Assoc **1995**; 85:533–7.
114. Lipsky BA, Holroyd KJ, Zasloff M. Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. Clin Infect Dis **2008**; 47:1537–45.
115. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis **2009**; 49:1541–9.
116. Lipsky BA, McDonald D, Litka P. Treatment of infected diabetic foot ulcers: topical MSI-78 vs. oral ofloxacin. Diabetologia **1997**; 40:482.
117. Noel GJ, Strauss RS, Amsler K, Heep M, Pypstra R, Solomkin JS. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. Antimicrob Agents Chemother **2008**; 52:37–44.
118. Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clin Infect Dis **2008**; 46:647–55.
119. Graham DR, Lucasti C, Malafaia O, et al. Ertapenem once daily versus piperacillin-tazobactam 4 times per day for treatment of complicated skin and skin-structure infections in adults: results of a prospective, randomized, double-blind multicenter study. Clin Infect Dis **2002**; 34:1460–8.
120. Lipsky BA, Armstrong DG, Citron DM, Tice AD, Morgenstern DE, Abramson MA. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. Lancet **2005**; 366:1695–703.
121. Ertugrul MB, Baktiroglu S, Salman S, et al. Pathogens isolated from deep soft tissue and bone in patients with diabetic foot infections. J Am Podiatr Med Assoc **2008**; 98:290–5.
122. Martinez-Gomez Dde A, Ramirez-Almagro C, Campillo-Soto A, Morales-Cuenca G, Pagan-Ortiz J, Aguayo-Albasini JL. [Diabetic foot infections. Prevalence and antibiotic sensitivity of the causative microorganisms]. Enferm Infecc Microbiol Clin **2009**; 27:317–21.
123. Bansal E, Garg A, Bhatia S, Attri AK, Chander J. Spectrum of microbial flora in diabetic foot ulcers. Indian J Pathol Microbiol **2008**; 51:204–8.
124. Yoga R, Khairul A, Sunita K, Suresh C. Bacteriology of diabetic foot lesions. Med J Malaysia **2006**; 61(Suppl A):14–6.
125. Shakil S, Khan AU. Infected foot ulcers in male and female diabetic patients: a clinico-bioinformative study. Ann Clin Microbiol Antimicrob **2010**; 9:2.
126. Wang SH, Sun ZL, Guo YJ, et al. Meticillin-resistant *Staphylococcus aureus* isolated from foot ulcers in diabetic patients in a Chinese care

hospital: risk factors for infection and prevalence. J Med Microbiol **2010**; 59:1219–24.
127. Tentolouris N, Petrikkos G, Vallianou N, et al. Prevalence of methicillin-resistant *Staphylococcus aureus* in infected and uninfected diabetic foot ulcers. Clin Microbiol Infect **2006**; 12:186–9.
128. Yates C, May K, Hale T, et al. Wound chronicity, inpatient care, and chronic kidney disease predispose to MRSA infection in diabetic foot ulcers. Diabetes Care **2009**; 32:1907–9.
129. Vardakas KZ, Horianopoulou M, Falagas ME. Factors associated with treatment failure in patients with diabetic foot infections: an analysis of data from randomized controlled trials. Diabetes Res Clin Pract **2008**; 80:344–51.
130. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis **2004**; 38:1673–81.
131. Eleftheriadou I, Tentolouris N, Argiana V, Jude E, Boulton AJ. Methicillin-resistant *Staphylococcus aureus* in diabetic foot infections. Drugs **2010**; 70:1785–97.
132. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis **2011**; 52:e18–55.
133. David MZ, Glikman D, Crawford SE, et al. What is community-associated methicillin-resistant *Staphylococcus aureus*? J Infect Dis **2008**; 197:1235–43.
134. Lagace-Wiens PR, Ormiston D, Nicolle LE, Hilderman T, Embil J. The diabetic foot clinic: not a significant source for acquisition of methicillin-resistant *Staphylococcus aureus*. Am J Infect Control **2009**; 37:587–9.
135. Raymakers JT, Schaper NC, van der Heyden JJ, Tordoir JH, Kitslaar PJ. Penetration of ceftazidime into bone from severely ischaemic limbs. J Antimicrob Chemother **1998**; 42:543–5.
136. Seabrook GR, Edmiston CE, Schmitt DD, Krepel C, Bandyk DF, Towne JB. Comparison of serum and tissue antibiotic levels in diabetes-related foot infections. Surgery **1991**; 110:671–6; discussion 76–7.
137. Duckworth C, Fisher JF, Carter SA, et al. Tissue penetration of clindamycin in diabetic foot infections. J Antimicrob Chemother **1993**; 31:581–4.
138. Legat FJ, Maier A, Dittrich P, et al. Penetration of fosfomycin into inflammatory lesions in patients with cellulitis or diabetic foot syndrome. Antimicrob Agents Chemother **2003**; 47:371–4.
139. Muller M, Brunner M, Hollenstein U, et al. Penetration of ciprofloxacin into the interstitial space of inflamed foot lesions in non-insulin-dependent diabetes mellitus patients. Antimicrob Agents Chemother **1999**; 43:2056–8.
140. Kuck EM, Bouter KP, Hoekstra JB, Conemans JM, Diepersloot RJ. Tissue concentrations after a single-dose, orally administered ofloxacin in patients with diabetic foot infections. Foot Ankle Int **1998**; 19: 38–40.
141. Mueller-Buehl U, Diehm C, Gutzler F, Adam D. Tissue concentrations of ofloxacin in necrotic foot lesions of diabetic and non-diabetic patients with peripheral arterial occlusive disease. Vasa **1991**; 20:17–21.
142. Traunmuller F, Schintler MV, Metzler J, et al. Soft tissue and bone penetration abilities of daptomycin in diabetic patients with bacterial foot infections. J Antimicrob Chemother **2010**; 65:1252–7.
143. Schintler MV, Traunmuller F, Metzler J, et al. High fosfomycin concentrations in bone and peripheral soft tissue in diabetic patients presenting with bacterial foot infection. J Antimicrob Chemother **2009**; 64:574–8.
144. Majcher-Peszynska J, Haase G, Sass M, et al. Pharmacokinetics and penetration of linezolid into inflamed soft tissue in diabetic foot infections. Eur J Clin Pharmacol **2008**; 64:1093–100.
145. Nicolau DP, Stein GE. Therapeutic options for diabetic foot infections: a review with an emphasis on tissue penetration characteristics. J Am Podiatr Med Assoc **2010**; 100:52–63.
146. Raymakers JT, Houben AJ, van der Heyden JJ, Tordoir JH, Kitslaar PJSchaper NC. The effect of diabetes and severe ischaemia on the penetration of ceftazidime into tissues of the limb. Diabet Med **2001**; 18:229–34.
147. Deresinski SC. The efficacy and safety of ceftobiprole in the treatment of complicated skin and skin structure infections: evidence from 2 clinical trials. Diagn Microbiol Infect Dis **2008**; 61:103–9.
148. Lipsky BA, Giordano P, Choudhri S, Song J. Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-clavulanate. J Antimicrob Chemother **2007**; 60:370–6.
149. Harkless L, Boghossian J, Pollak R, et al. An open-label, randomized study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. Surg Infect (Larchmt) **2005**; 6:27–40.
150. Clay PG, Graham MR, Lindsey CC, Lamp KC, Freeman C, Glaros A. Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males. Am J Geriatr Pharmacother **2004**; 2:181–9.
151. Lobmann R, Ambrosch A, Seewald M, et al. Antibiotic therapy for diabetic foot infections: comparison of cephalosporines with chinolones. Diabetes Nutr Metab **2004**; 17:156–62.
152. Vick-Fragoso R, Hernandez-Oliva G, Cruz-Alcazar J, et al. Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. Infection **2009**; 37:407–17.
153. Griffis CD, Metcalfe S, Bowling FL, Boulton AJ, Armstrong DG. The use of gentamycin-impregnated foam in the management of diabetic foot infections: a promising delivery system? Expert Opin Drug Deliv **2009**; 6:639–42.
154. Salgami EV, Bowling FL, Whitehouse RW, Boulton AJ. Use of tobramycin-impregnated calcium sulphate pellets in addition to oral antibiotics: an alternative treatment to minor amputation in a case of diabetic foot osteomyelitis. Diabetes Care **2007**; 30:181–2.
155. Lipsky BA, Stoutenburgh U. Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. J Antimicrob Chemother **2005**; 55:240–5.
156. Sabol M. Phase 3 study: evaluating the safety and efficacy of a once-daily dose of tigecycline and ertapenem in diabetic foot infections with a substudy in patients with diabetic foot infections complicated by osteomyelitis. **2009**; Clinical Trials Identifier Number: NCT00366249.
157. Saltoglu N, Dalkiran A, Tetiker T, et al. Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital. Clin Microbiol Infect **2010**; 16:1252–7.
158. No authors listed. Study evaluating the safety and efficacy of a once-daily dose of tigecycline vs ertapenem in diabetic foot infections (DFI) with a substudy in patients with diabetic foot infections complicated by osteomyelitis. **2010**.
159. Lipsky BA. Evidence-based antibiotic therapy of diabetic foot infections. FEMS Immunol Med Microbiol **1999**; 26:267–76.
160. No authors listed. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment DRAFT GUIDANCE. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2010; Docket Number HFA-305:1–35.
161. Crouzet J, Lavigne JP, Richard JL, Sotto A. Diabetic foot infection: a critical review of recent randomized clinical trials on antibiotic therapy. Int J Infect Dis **2011**; 15:e601–10.
162. Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. Clin Infect Dis **2008**; 47:519–27.

163. Shults DW, Hunter GC, McIntyre KE, Parent FN, Piotrowski JJ, Bernhard VM. Value of radiographs and bone scans in determining the need for therapy in diabetic patients with foot ulcers. Am J Surg **1989**; 158:525–9; discussion 29–30.
164. Butalia S, Palda VA, Sargeant RJ, Detsky AS, Mourad O. Does this patient with diabetes have osteomyelitis of the lower extremity? JAMA **2008**; 299:806–13.
165. Jeffcoate WJ, Lipsky BA. Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. Clin Infect Dis **2004**; 39(Suppl 2):S115–22.
166. Kapoor A, Page S, Lavalley M, Gale DR, Felson DT. Magnetic resonance imaging for diagnosing foot osteomyelitis: a meta-analysis. Arch Intern Med **2007**; 167:125–32.
167. Ledermann HP, Morrison WB, Schweitzer ME. Pedal abscesses in patients suspected of having pedal osteomyelitis: analysis with MR imaging. Radiology **2002**; 224:649–55.
168. Ledermann HP, Schweitzer ME, Morrison WB. Nonenhancing tissue on MR imaging of pedal infection: characterization of necrotic tissue and associated limitations for diagnosis of osteomyelitis and abscess. AJR Am J Roentgenol **2002**; 178:215–22.
169. Schweitzer ME, Morrison WB. MR imaging of the diabetic foot. Radiol Clin North Am **2004**; 42:61–71, vi.
170. Tan PL, Teh J. MRI of the diabetic foot: differentiation of infection from neuropathic change. Br J Radiol **2007**; 80:939–48.
171. Tomas MB, Patel M, Marwin SE, Palestro CJ. The diabetic foot. Br J Radiol **2000**; 73:443–50.
172. Armstrong DG, Harkless LB. Outcomes of preventative care in a diabetic foot specialty clinic. J Foot Ankle Surg **1998**; 37:460–6.
173. Becker W. Imaging osteomyelitis and the diabetic foot. Q J Nucl Med **1999**; 43:9–20.
174. Palestro CJ, Love C. Nuclear medicine and diabetic foot infections. Semin Nucl Med **2009**; 39:52–65.
175. Delcourt A, Huglo D, Prangere T, et al. Comparison between Leukoscan (Sulesomab) and Gallium-67 for the diagnosis of osteomyelitis in the diabetic foot. Diabetes Metab **2005**; 31:125–33.
176. Schweitzer ME, Daffner RH, Weissman BN, et al. ACR Appropriateness criteria on suspected osteomyelitis in patients with diabetes mellitus. J Am Coll Radiol **2008**; 5:881–6.
177. Enderle MD, Coerper S, Schweizer HP, et al. Correlation of imaging techniques to histopathology in patients with diabetic foot syndrome and clinical suspicion of chronic osteomyelitis. The role of high-resolution ultrasound. Diabetes Care **1999**; 22:294–9.
178. Keidar Z, Militianu D, Melamed E, Bar-Shalom R, Israel O. The diabetic foot: initial experience with 18F-FDG PET/CT. J Nucl Med **2005**; 46:444–9.
179. Basu S, Chryssikos T, Houseni M, et al. Potential role of FDG PET in the setting of diabetic neuro-osteoarthropathy: can it differentiate uncomplicated Charcot's neuroarthropathy from osteomyelitis and soft-tissue infection? Nucl Med Commun **2007**; 28:465–72.
180. Nawaz A, Torigian DA, Siegelman ES, Basu S, Chryssikos T, Alavi A. Diagnostic performance of FDG-PET, MRI, and plain film radiography (PFR) for the diagnosis of osteomyelitis in the diabetic foot. Mol Imaging Biol **2010**; 12:335–42.
181. Heiba SI, Kolker D, Mocherla B. The optimized evaluation of diabetic foot infection by dual isotope SPECT/CT imaging protocol. J Foot Ankle Surg **2010**; 49:529–36.
182. Sella EJ. Current concepts review: diagnostic imaging of the diabetic foot. Foot Ankle Int **2009**; 30:568–76.
183. Berendt AR, Lipsky B. Is this bone infected or not? Differentiating neuro-osteoarthropathy from osteomyelitis in the diabetic foot. Curr Diab Rep **2004**; 4:424–9.
184. Ahmadi ME, Morrison WB, Carrino JA, Schweitzer ME, Raikin SM, Ledermann HP. Neuropathic arthropathy of the foot with and without superimposed osteomyelitis: MR imaging characteristics. Radiology **2006**; 238:622–31.
185. Berendt AR, Peters EJ, Bakker K, et al. Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. Diabetes Metab Res Rev **2008**; 24(Suppl 1):S145–61.
186. Lipsky BA. Osteomyelitis of the foot in diabetic patients. Clin Infect Dis **1997**; 25:1318–26.
187. Snyder RJ, Cohen MM, Sun C, Livingston J. Osteomyelitis in the diabetic patient: diagnosis and treatment. Part 2: medical, surgical, and alternative treatments. Ostomy Wound Manage **2001**; 47:24–30, 32–41; quiz 42–3.
188. Snyder RJ, Cohen MM, Sun C, Livingston J. Osteomyelitis in the diabetic patient: diagnosis and treatment. Part 1: overview, diagnosis, and microbiology. Ostomy Wound Manage **2001**; 47:18–22, 25–30; quiz 31–2.
189. Embil JM. The management of diabetic foot osteomyelitis. The Diabetic Foot **2000**; 3:76–84.
190. Eckman MH, Greenfield S, Mackey WC, et al. Foot infections in diabetic patients. Decision and cost-effectiveness analyses. JAMA **1995**; 273:712–20.
191. Lipsky BA. A report from the international consensus on diagnosing and treating the infected diabetic foot. Diabetes Metab Res Rev **2004**; 20(Suppl 1):S68–77.
192. Chantelau E, Wolf A, Ozdemir S, Hachmoller A, Ramp U. Bone histomorphology may be unremarkable in diabetes mellitus. Med Klin (Munich) **2007**; 102:429–33.
193. Newman LG, Waller J, Palestro CJ, et al. Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. JAMA **1991**; 266:1246–51.
194. Lavery LA, Peters EJ, Armstrong DG, Wendel CS, Murdoch DP, Lipsky BA. Risk factors for developing osteomyelitis in patients with diabetic foot wounds. Diabetes Res Clin Pract **2009**; 83:347–52.
195. Fleischer AE, Didyk AA, Woods JB, Burns SE, Wrobel JS, Armstrong DG. Combined clinical and laboratory testing improves diagnostic accuracy for osteomyelitis in the diabetic foot. J Foot Ankle Surg **2009**; 48:39–46.
196. Rajbhandari SM, Sutton M, Davies C, Tesfaye S, Ward JD. 'Sausage toe': a reliable sign of underlying osteomyelitis. Diabet Med **2000**; 17:74–7.
197. Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA **1995**; 273:721–3.
198. Shone A, Burnside J, Chipchase S, Game F, Jeffcoate W. Probing the validity of the probe-to-bone test in the diagnosis of osteomyelitis of the foot in diabetes. Diabetes Care **2006**; 29:945.
199. Lavery LA, Armstrong DG, Peters EJ, Lipsky BA. Probe-to-bone test for diagnosing diabetic foot osteomyelitis: reliable or relic? Diabetes Care **2007**; 30:270–4.
200. Hartemann-Heurtier A, Senneville E. Diabetic foot osteomyelitis. Diabetes Metab **2008**; 34:87–95.
201. Aragon-Sanchez J, Lipsky BA, Lazaro-Martinez JL. Diagnosing diabetic foot osteomyelitis: is the combination of probe-to-bone test and plain radiography sufficient for high-risk inpatients? Diabet Med **2011**; 28:191–4.
202. Morales Lozano R, Gonzalez Fernandez ML, Martinez Hernandez D, Beneit Montesinos JV, Guisado Jimenez S, Gonzalez Jurado MA. Validating the probe-to-bone and other tests for diagnosing chronic osteomyelitis in the diabetic foot. Diabetes Care **2010**; 33:2140–45.
203. Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. J Foot Ankle Surg **1996**; 35:528–31.
204. Wheat J. Diagnostic strategies in osteomyelitis. Am J Med **1985**; 78:218–24.
205. Senneville E, Melliez H, Beltrand E, et al. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. Clin Infect Dis **2006**; 42:57–62.
206. Lesens O, Desbiez F, Vidal M, et al. Culture of per-wound bone specimens: a simplified approach for the medical management of diabetic foot osteomyelitis. Clin Microbiol Infect **2011**; 17:285–91.

207. Game F, Jeffcoate W. MRSA and osteomyelitis of the foot in diabetes. Diabet Med **2004**; 21(Suppl 4):16–9.
208. Khatri G, Wagner DK, Sohnle PG. Effect of bone biopsy in guiding antimicrobial therapy for osteomyelitis complicating open wounds. Am J Med Sci **2001**; 321:367–71.
209. Slater RA, Lazarovitch T, Boldur I, et al. Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone. Diabet Med **2004**; 21:705–9.
210. Zuluaga AF, Galvis W, Jaimes F, Vesga O. Lack of microbiological concordance between bone and non-bone specimens in chronic osteomyelitis: an observational study. BMC Infect Dis **2002**; 2:8.
211. Elamurugan TP, Jagdish S, Kate V, Chandra Parija S. Role of bone biopsy specimen culture in the management of diabetic foot osteomyelitis. Int J Surg **2011**; 9:214–6.
212. Kessler L, Piemont Y, Ortega F, et al. Comparison of microbiological results of needle puncture vs. superficial swab in infected diabetic foot ulcer with osteomyelitis. Diabet Med **2006**; 23:99–102.
213. Senneville E, Morant H, Descamps D, et al. Needle puncture and transcutaneous bone biopsy cultures are inconsistent in patients with diabetes and suspected osteomyelitis of the foot. Clin Infect Dis **2009**; 48:888–93.
214. Bernard L, Uckay I, Vuagnat A, et al. Two consecutive deep sinus tract cultures predict the pathogen of osteomyelitis. Int J Infect Dis **2010**; 14:e390–3.
215. Ertugrul MB, Baktiroglu S, Salman S, et al. The diagnosis of osteomyelitis of the foot in diabetes: microbiological examination vs. magnetic resonance imaging and labelled leucocyte scanning. Diabet Med **2006**; 23:649–53.
216. Howard CB, Einhorn M, Dagan R, Yagupski P, Porat S. Fine-needle bone biopsy to diagnose osteomyelitis. J Bone Joint Surg Br **1994**; 76:311–4.
217. Tan JS, File TM Jr. Diagnosis and treatment of diabetic foot infections. Baillieres Best Pract Res Clin Rheumatol **1999**; 13:149–61.
218. Mader JT, Ortiz M, Calhoun JH. Update on the diagnosis and management of osteomyelitis. Clin Podiatr Med Surg **1996**; 13:701–24.
219. Marschall J, Bhavan KP, Olsen MA, Fraser VJ, Wright NM, Warren DK. The impact of prebiopsy antibiotics on pathogen recovery in hematogenous vertebral osteomyelitis. Clin Infect Dis **2011**; 52:867–72.
220. White LM, Schweitzer ME, Deely DM, Gannon F. Study of osteomyelitis: utility of combined histologic and microbiologic evaluation of percutaneous biopsy samples. Radiology **1995**; 197:840–2.
221. Senneville E, Lombart A, Beltrand E, et al. Outcome of diabetic foot osteomyelitis treated nonsurgically: a retrospective cohort study. Diabetes Care **2008**; 31:637–42.
222. Weiner RD, Viselli SJ, Fulkert KA, Accetta P. Histology versus microbiology for accuracy in identification of osteomyelitis in the diabetic foot. J Foot Ankle Surg **2011**; 50:197–200.
223. Sella EJ, Grosser DM. Imaging modalities of the diabetic foot. Clin Podiatr Med Surg **2003**; 20:729–40.
224. Chatha DS, Cunningham PM, Schweitzer ME. MR imaging of the diabetic foot: diagnostic challenges. Radiol Clin North Am **2005**; 43:747–59, ix.
225. Termaat MF, Raijmakers PG, Scholten HJ, Bakker FC, Patka P, Haarman HJ. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. J Bone Joint Surg Am **2005**; 87:2464–71.
226. Peterson LR, Lissack LM, Canter K, Fasching CE, Clabots C, Gerding DN. Therapy of lower extremity infections with ciprofloxacin in patients with diabetes mellitus, peripheral vascular disease, or both. Am J Med **1989**; 86:801–8.
227. Ha Van G, Siney H, Danan JP, Sachon C, Grimaldi A. Treatment of osteomyelitis in the diabetic foot. Contribution of conservative surgery. Diabetes Care **1996**; 19:1257–60.
228. Venkatesan P, Lawn S, Macfarlane RM, Fletcher EM, Finch RG, Jeffcoate WJ. Conservative management of osteomyelitis in the feet of diabetic patients. Diabet Med **1997**; 14:487–90.
229. Senneville E, Yazdanpanah Y, Cazaubiel M, et al. Rifampicin-ofloxacin oral regimen for the treatment of mild to moderate diabetic foot osteomyelitis. J Antimicrob Chemother **2001**; 48:927–30.
230. Pittet D, Wyssa B, Herter-Clavel C, Kursteiner K, Vaucher J, Lew PD. Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up. Arch Intern Med **1999**; 159:851–6.
231. Yadlapalli N, Vaishnar A, Sheehan P. Conservative management of diabetic foot ulcers complicated by osteomyelitis. Wounds **2002**; 14:31–5.
232. Bamberger DM, Daus GP, Gerding DN. Osteomyelitis in the feet of diabetic patients. Long-term results, prognostic factors, and the role of antimicrobial and surgical therapy. Am J Med **1987**; 83:653–60.
233. Nix DE, Cumbo TJ, Kuritzky P, DeVito JM, Schentag JJ. Oral ciprofloxacin in the treatment of serious soft tissue and bone infections. Efficacy, safety, and pharmacokinetics. Am J Med **1987**; 82:146–53.
234. Embil JM, Rose G, Trepman E, et al. Oral antimicrobial therapy for diabetic foot osteomyelitis. Foot Ankle Int **2006**; 27:771–9.
235. Yamaguchi Y, Yoshida S, Sumikawa Y, et al. Rapid healing of intractable diabetic foot ulcers with exposed bones following a novel therapy of exposing bone marrow cells and then grafting epidermal sheets. Br J Dermatol **2004**; 151:1019–28.
236. Game FL, Jeffcoate WJ. Primarily non-surgical management of osteomyelitis of the foot in diabetes. Diabetologia **2008**; 51:962–7.
237. Roeder B, Van Gils CC, Maling S. Antibiotic beads in the treatment of diabetic pedal osteomyelitis. J Foot Ankle Surg **2000**; 39:124–30.
238. Wininger DA, Fass RJ. Antibiotic-impregnated cement and beads for orthopedic infections. Antimicrob Agents Chemother **1996**; 40:2675–9.
239. Yamashita Y, Uchida A, Yamakawa T, Shinto Y, Araki N, Kato K. Treatment of chronic osteomyelitis using calcium hydroxyapatite ceramic implants impregnated with antibiotic. Int Orthop **1998**; 22:247–51.
240. Jacobs AM, Seifert AM, Kirisits TJ, Protzel HR. Use of antibiotic-loaded bone cement in the management of common infections of the foot and ankle. Clin Podiatr Med Surg **1990**; 7:523–44.
241. Marvaso A, Esposito S, Noviello S, et al. [Outpatient parenteral antibiotic therapy (OPAT) of diabetic foot infections with piperacillin/tazobactam]. Infez Med **2002**; 10:230–5.
242. Barth RE, Vogely HC, Hoepelman AI, Peters EJ. 'To bead or not to bead?' Treatment of osteomyelitis and prosthetic joint-associated infections with gentamicin bead chains. Int J Antimicrob Agents **2011**; 38:371–5.
243. Fox HR, Karchmer AW. Management of diabetic foot infections, including the use of home intravenous antibiotic therapy. Clin Podiatr Med Surg **1996**; 13:671–82.
244. Tice AD, Hoaglund PA, Shoultz DA. Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. Am J Med **2003**; 114:723–8.
245. Steffen C, O'Rourke S. Surgical management of diabetic foot complications: the Far North Queensland profile. Aust N Z J Surg **1998**; 68:258–60.
246. Giurini JM, Rosenblum BI. The role of foot surgery in patients with diabetes. Clin Podiatr Med Surg **1995**; 12:119–27.
247. Bridges RM Jr, Deitch EA. Diabetic foot infections. Pathophysiology and treatment. Surg Clin North Am **1994**; 74:537–55.
248. Gill LH. Foot surgery in the patient with diabetes. J South Orthop Assoc **1994**; 3:261–7.
249. Chaytor ER. Surgical treatment of the diabetic foot. Diabetes Metab Res Rev **2000**; 16(Suppl 1):S66–9.
250. Scher KS, Steele FJ. The septic foot in patients with diabetes. Surgery **1988**; 104:661–6.
251. Pinzur MS, Sage R, Abraham M, Osterman H. Limb salvage in infected lower extremity gangrene. Foot Ankle **1988**; 8:212–5.
252. Armstrong DG, Perales TA, Murff RT, Edelson GW, Welchon JG. Value of white blood cell count with differential in the acute diabetic foot infection. J Am Podiatr Med Assoc **1996**; 86:224–7.

253. Lavery LA, Armstrong DG, Quebedeaux TL, Walker SC. Puncture wounds: normal laboratory values in the face of severe infection in diabetics and non-diabetics. Am J Med **1996**; 101:521–5.
254. Tan JS, Friedman NM, Hazelton-Miller C, Flanagan JP, File TM Jr. Can aggressive treatment of diabetic foot infections reduce the need for above-ankle amputation? Clin Infect Dis **1996**; 23:286–91.
255. Armstrong DG, Lipsky BA. Diabetic foot infections: stepwise medical and surgical management. Int Wound J **2004**; 1:123–32.
256. Grodinsky M. A study of the fascial spaces of the foot and their bearing on infections. **1929**:737–43.
257. Loeffler RD Jr, Ballard A. Plantar fascial spaces of the foot and a proposed surgical approach. Foot Ankle **1980**; 1:11–4.
258. Piaggesi A, Schipani E, Campi F, et al. Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. Diabet Med **1998**; 15:412–7.
259. Bose K. A surgical approach for the infected diabetic foot. Int Orthop **1979**; 3:177–81.
260. Brodsky JW, Schneidler C. Diabetic foot infections. Orthop Clin North Am **1991**; 22:473–89.
261. Connolly JE, Wrobel JS, Anderson RF. Primary closure of infected diabetic foot wounds. A report of closed instillation in 30 cases. J Am Podiatr Med Assoc **2000**; 90:175–82.
262. Pinzur MS. Amputation level selection in the diabetic foot. Clin Orthop Relat Res **1993**:68–70.
263. Armstrong DG, Lavery LA, Frykberg RG, Wu SC, Boulton AJ. Validation of a diabetic foot surgery classification. Int Wound J **2006**; 3:240–6.
264. Durham JR, McCoy DM, Sawchuk AP, et al. Open transmetatarsal amputation in the treatment of severe foot infections. Am J Surg **1989**; 158:127–30.
265. Benton GS, Kerstein MD. Cost effectiveness of early digit amputation in the patient with diabetes. Surg Gynecol Obstet **1985**; 161:523–4.
266. Field CK, Kerstein MD. Cost-benefit analysis of lower-extremity amputation: ethical considerations. Wounds **1993**; 5:10–3.
267. Van Damme H, Rorive M, Martens De Noorthout BM, Quaniers J, Scheen A, Limet R. Amputations in diabetic patients: a plea for foot-sparing surgery. Acta Chir Belg **2001**; 101:123–9.
268. Khammash MR, Obeidat KA. Prevalence of ischemia in diabetic foot infection. World J Surg **2003**; 27:797–9.
269. Wrobel JS, Robbins J, Armstrong DG. The high-low amputation ratio: a deeper insight into diabetic foot care? J Foot Ankle Surg **2006**; 45:375–9.
270. Jones V. Debridement of diabetic foot lesions. The Diabetic Foot **1998**; 1:88–94.
271. Rauwerda JA. Foot debridement: anatomic knowledge is mandatory. Diabetes Metab Res Rev **2000**; 16(Suppl 1):S23–6.
272. Lepantalo M, Biancari F, Tukiainen E. Never amputate without consultation of a vascular surgeon. Diabetes Metab Res Rev **2000**; 16 (Suppl 1):S27–32.
273. LoGerfo FW, Coffman JD. Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. N Engl J Med **1984**; 311:1615–9.
274. Holstein PE, Sorensen S. Limb salvage experience in a multidisciplinary diabetic foot unit. Diabetes Care **1999**; 22(Suppl 2):B97–103.
275. Estes JM, Pomposelli FB Jr. Lower extremity arterial reconstruction in patients with diabetes mellitus. Diabet Med **1996**; 13(Suppl 1): S43–7.
276. Chang BB, Darling RC 3rd, Paty PS, Lloyd WE, Shah DM, Leather RP. Expeditious management of ischemic invasive foot infections. Cardiovasc Surg **1996**; 4:792–5.
277. Taylor LM Jr, Porter JM. The clinical course of diabetics who require emergent foot surgery because of infection or ischemia. J Vasc Surg **1987**; 6:454–9.
278. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group. J Am Coll Surg **1996**; 183:61–4.
279. Vermeulen H, Ubbink D, Goossens A, de Vos R, Legemate D. Dressings and topical agents for surgical wounds healing by secondary intention. Cochrane Database Syst Rev **2004**; 2:CD003554.
280. Ubbink DT, Westerbos SJ, Evans D, Land L, Vermeulen H. Topical negative pressure for treating chronic wounds. Cochrane Database Syst Rev **2008**; 3:CD001898.
281. Vermeulen H, van Hattem JM, Storm-Versloot MN, Ubbink DT. Topical silver for treating infected wounds. Cochrane Database Syst Rev **2007**; 1:CD005486.
282. Bergin SM, Wraight P. Silver based wound dressings and topical agents for treating diabetic foot ulcers. Cochrane Database Syst Rev **2006**; 1:CD005082.
283. Hinchliffe RJ, Valk GD, Apelqvist J, et al. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Rev **2008**; 24 (Suppl 1):S119–44.
284. Hilton JR, Williams DT, Beuker B, Miller DR, Harding KG. Wound dressings in diabetic foot disease. Clin Infect Dis **2004**; 39(Suppl 2): S100–3.
285. Nelson EA, O'Meara S, Golder S, Dalton J, Craig D, Iglesias C. Systematic review of antimicrobial treatments for diabetic foot ulcers. Diabet Med **2006**; 23:348–59.
286. O'Meara SM, Cullum NA, Majid M, Sheldon TA. Systematic review of antimicrobial agents used for chronic wounds. Br J Surg **2001**; 88:4–21.
287. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plast Reconstr Surg **2006**; 117:143S–149S; discussion 50S–51S.
288. Apelqvist J, Bakker K, van Houtum WH, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot: based upon the International Consensus on the Diabetic Foot (2007) Prepared by the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev **2008**; 24(Suppl 1):S181–7.
289. Driver VR. Treating the macro and micro wound environment of the diabetic patient: managing the whole patient, not the hole in the patient. **2004**:49–56.
290. Svensjo T, Pomahac B, Yao F, Slama J, Eriksson E. Accelerated healing of full-thickness skin wounds in a wet environment. Plast Reconstr Surg **2000**; 106:602–12; discussion 13–4.
291. Smith J, Thow J. Is debridement effective for diabetic foot ulcers? A systematic review: 2. The Diabetic Foot **2001**; 4:77–80.
292. Smith J. Is debridement effective for diabetic foot ulcer? A systematic review: 1. The Diabetic Foot **2001**; 1:10–4.
293. Eldor R, Raz I, Ben Yehuda A, Boulton AJ. New and experimental approaches to treatment of diabetic foot ulcers: a comprehensive review of emerging treatment strategies. Diabet Med **2004**; 21:1161–73.
294. Cutting K, White R, Edmonds M. The safety and efficacy of dressings with silver—addressing clinical concerns. Int Wound J **2007**; 4:177–84.
295. Chopra I. The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern? J Antimicrob Chemother **2007**; 59:587–90.
296. Percival SL, Woods E, Nutekpor M, Bowler P, Radford A, Cochrane C. Prevalence of silver resistance in bacteria isolated from diabetic foot ulcers and efficacy of silver-containing wound dressings. Ostomy Wound Manage **2008**; 54:30–40.
297. Silver dressings for the treatment of patients with infected wounds: a review of clinical and cost-effectiveness. Health Technology Inquiry Service, **2010**.
298. Storm-Versloot MN, Vos CG, Ubbink DT, Vermeulen H. Topical silver for preventing wound infection. Cochrane Database Syst Rev **2010**; 3:CD006478.
299. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care **2001**; 24:1019–22.
300. Lewis R, Whiting P, ter Riet G, O'Meara S, Galanville J. A rapid systematic review of the clinical effectiveness and cost effectiveness of

debriding agents in treating surgical wounds healing by secondary intention. NHS HTA Programme, the National Institute of Clinical Excellence, NHS Centre for Reviews and Dissemination: University of York, **2000**:1–8.
301. Armstrong DG, Lavery LA, Vazquez JR, Nixon BP, Boulton AJ. How and why to surgically debride neuropathic diabetic foot wounds. J Am Podiatr Med Assoc **2002**; 92:402–4.
302. Singhal A, Reis ED, Kerstein MD. Options for nonsurgical debridement of necrotic wounds. Adv Skin Wound Care **2001**; 14:96–100; quiz 02–3.
303. Attinger CE, Janis JE, Steinberg J, Schwartz J, Al-Attar A, Couch K. Clinical approach to wounds: debridement and wound bed preparation including the use of dressings and wound-healing adjuvants. Plast Reconstr Surg **2006**; 117:72S–109S.
304. Attinger CE, Bulan E, Blume PA. Surgical debridement. The key to successful wound healing and reconstruction. Clin Podiatr Med Surg **2000**; 17:599–630.
305. Tantawi TI, Gohar YM, Kotb MM, Beshara FM, El-Naggar MM. Clinical and microbiological efficacy of MDT in the treatment of diabetic foot ulcers. J Wound Care **2007**; 16:379–83.
306. Paul AG, Ahmad NW, Lee HL, et al. Maggot debridement therapy with *Lucilia cuprina*: a comparison with conventional debridement in diabetic foot ulcers. Int Wound J **2009**; 6:39–46.
307. Lodge A, Jones M, Thomas S. Maggots 'n' chips: a novel approach to the treatment of diabetic ulcers. Br J Community Nurs **2006**; 11 (Suppl):23–6.
308. Edwards J, Stapley S. Debridement of diabetic foot ulcers. Cochrane Database Syst Rev **2010**; 4:CD003556.
309. Sainsbury DC. Evaluation of the quality and cost-effectiveness of Versajet hydrosurgery. Int Wound J **2009**; 6:24–9.
310. Caputo WJ, Beggs DJ, DeFede JL, Simm L, Dharma H. A prospective randomised controlled clinical trial comparing hydrosurgery debridement with conventional surgical debridement in lower extremity ulcers. Int Wound J **2008**; 5:288–94.
311. Cavanagh PR. Therapeutic footwear for people with diabetes. Diabetes Metab Res Rev **2004**; 20(Suppl 1):S51–5.
312. Mueller MJ, Diamond JE, Sinacore DR, et al. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care **1989**; 12:384–8.
313. Bus SA, Valk GD, van Deursen RW, et al. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. Diabetes Metab Res Rev **2008**; 24(Suppl 1):S162–80.
314. Katz IA, Harlan A, Miranda-Palma B, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care **2005**; 28:555–9.
315. Nabuurs-Franssen MH, Sleegers R, Huijberts MS, et al. Total contact casting of the diabetic foot in daily practice: a prospective follow-up study. Diabetes Care **2005**; 28:243–7.
316. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision). J Foot Ankle Surg **2006**; 45:S1–66.
317. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet **2005**; 366:1725–35.
318. Spencer S. Pressure relieving interventions for preventing and treating diabetic foot ulcers. Cochrane Database Syst Rev **2000**; 3:CD002302.
319. Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen **2008**; 16:19–22.
320. Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. Diabetes Care **2007**; 30:660–3.
321. Chuck AW, Hailey D, Jacobs P, Perry DC. Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. Int J Technol Assess Health Care **2008**; 24:178–83.
322. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. PM R **2009**; 1:471–89.
323. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev **2004**; 2:CD004123.
324. Lipsky BA, Berendt AR. Hyperbaric oxygen therapy for diabetic foot wounds: has hope hurdled hype? Diabetes Care **2010**; 33:1143–5.
325. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes Care **1998**; 21:822–7.
326. Robson M. Integrating the results of phase IV (postmarketing) clinical trial with four previous trials reinforces the position of Regranex (becaplermin) gel 0.01% is an effective adjunct to the treatment of diabetic foot ulcer. J Appl Res **2005**; 5:35–45.
327. Viswanathan V, Mahesh U, Jayaraman M, Shina K, Ramachandram A. Beneficial role of granulocyte colony stimulating factor in foot infection in diabetic patients. J Assoc Physicians India **2003**; 51:90–1.
328. Gough A, Clapperton M, Rolando N, Foster AV, Philpott-Howard J, Edmonds ME. Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection. Lancet **1997**; 350:855–9.
329. de Lalla F, Pellizzer G, Strazzabosco M, et al. Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limb-threatening diabetic foot infection. Antimicrob Agents Chemother **2001**; 45:1094–8.
330. Yonem A, Cakir B, Guler S, Azal OO, Corakci A. Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. Diabetes Obes Metab **2001**; 3:332–7.
331. Kastenbauer T, Hornlein B, Sokol G, Irsigler K. Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers. Diabetologia **2003**; 46:27–30.
332. Huang P, Li S, Han M, Xiao Z, Yang R, Han ZC. Autologous transplantation of granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells improves critical limb ischemia in diabetes. Diabetes Care **2005**; 28:2155–60.
333. Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database Syst Rev **2009**; 3:CD006810.
334. Gentzkow GD, Iwasaki SD, Hershon KS, et al. Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes Care **1996**; 19:350–4.
335. Naughton G, Mansbridge J, Gentzkow G. A metabolically active human dermal replacement for the treatment of diabetic foot ulcers. Artif Organs **1997**; 21:1203–10.
336. Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. Diabetes Care **2003**; 26:1701–5.
337. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care **2008**; 31:631–6.
338. Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet **2005**; 366:1704–10.
339. Wu SC, Marston W, Armstrong DG. Wound care: the role of advanced wound-healing technologies. J Am Podiatr Med Assoc **2010**; 100:385–94.
340. Gregor S, Maegele M, Sauerland S, Krahn JF, Peinemann F, Lange S. Negative pressure wound therapy: a vacuum of evidence? Arch Surg **2008**; 143:189–96.
341. Fincke BG, Miller DR, Turpin R. A classification of diabetic foot infections using ICD-9-CM codes: application to a large computerized medical database. BMC Health Serv Res **2010**; 10:192.

342. Fincke BG, Miller DR, Christiansen CL, Turpin RS. Variation in antibiotic treatment for diabetic patients with serious foot infections: a retrospective observational study. BMC Health Serv Res **2010**; 10:193.
343. Sotto A, Richard JL, Combescure C, et al. Beneficial effects of implementing guidelines on microbiology and costs of infected diabetic foot ulcers. Diabetologia **2010**; 53:2249–55.
344. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care **2006**; 29: 1784–7.
345. Kimsey DB. Lean methodology in health care. AORN J **2010**; 92:53–60.