Antimicrobial management of diabetic foot infection

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Article points

1. Diabetic foot infections are the most frequent diabetes-related complication requiring hospitalisation
2. Osteomyelitis is present in 44–68% of patients admitted into hospital with diabetic foot infections.
3. Diabetic foot infections (DFIs) account for 60% of lower extremity amputations in developed countries.
4. Diagnosis of DFIs should be based upon the presence of local and systemic signs and symptoms.
5. The management and outcome for a DFI is superior if there is the involvement of a multidisciplinary team.

Key words

- Antimicrobials
- Diabetic foot infections
- Diagnosis
- Management

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Diabetic foot infections (DFIs) are a frequent and costly complication associated with diabetes mellitus. Osteomyelitis is present in 44-68% of patients admitted to hospital DFI and DFIs account for 60% of lower extremity amputations in developed countries. Diagnosis of DFIs should be based upon the presence of local and systemic signs and symptoms, and the management and outcomes of DFIs are superior through the involvement of a multidisciplinary team. This article presents an overview of the current evidence for diagnosis and management of DFIs in practice.

The prevalence of diabetes mellitus has increased dramatically in recent decades, as have the complications associated with the disease (Lipsky et al, 2016). Chronic hyperglycaemia associated with diabetes mellitus is known to have a detrimental effect on human immune function; specifically cellular immunity and polymorphonuclear leukocytes are affected, and phagocytosis is impaired (Akkus et al, 2016). Thus, people with diabetes are at increased risk of diabetic foot infections (DFIs). According to Peters (2016) the incidence of foot infections in people with diabetes ranges from an overall lifetime risk of 4% to a yearly risk of 7%. DFIs usually occur when pathogens enter the foot through a break in the skin's integrity, for instance via a neuropathic or neuroischaemic foot ulceration (Peters, 2016). DFIs are associated with significant morbidity and mortality; infection can spread rapidly in the diabetic foot. If infection spreads to deeper structures, including the underlying bone, diabetic foot osteomyelitis (DFO) develops. DFIs are the most frequent diabetes-related complication requiring hospitalisation and DFO is present in 44–68% of patients admitted into hospital with DFIs (Lipsky et al, 2016; Peters, 2016). Furthermore, DFIs account for 60% of lower extremity amputations in developed countries (Peters, 2016). Prompt identification, rapid diagnosis, timely referral for specialist review and appropriate management strategies are all vital steps in the quest to minimise the adverse outcomes associated with DFIs, including limb-threatening infections and amputations.

Establishing the diagnosis

Peters (2016) stresses the importance of an initial diagnosis of DFI being made based upon clinical signs and symptoms, as the reliance on bloods, microbiological and radiological studies could lead to a delay in diagnosis. However, he also debates the challenges faced by clinicians when using clinical judgement. It is possible that the signs and symptoms of infection are less prevalent in people with diabetes. This may be due to the presence of foot ischaemia, neuropathy and immunopathy which could, theoretically, reduce the inflammatory response and mask the classic signs of infection (Peters, 2016). Though as Peters highlights, this theory is not proven. The Infectious Diseases Society of America (IDSA) and the International Working

Group on the Diabetic Foot (IWGDF) both concur that the diagnosis of DFIs should be based on the presence of local and systemic signs and symptoms, and also on the symptoms of inflammation. Furthermore, the severity of DFIs should be classified using the IDSA and IWGDF classification scheme (Lipsky et al, 2015) (*Table 1*).

NICE (2016) have also published specific guidance in relation to the diagnosis of DFIs, which include recommendations for diagnostic imaging:

- If DFI is suspected and ulceration is present, send a soft tissue or bone sample from the base of the debrided wound for microbiological examination. If this cannot be obtained, take a deep swab because it may provide useful information on the choice of antibiotic treatment
- Consider an X-ray of the person's affected foot (or feet) to determine the extent of the diabetic foot problem
- Consider osteomyelitis if the person with diabetes has a local infection, a deep foot wound or a chronic foot wound
- Be aware that osteomyelitis may be present in a person with diabetes, despite normal inflammatory markers, X-rays or probe-to-bone testing
- If osteomyelitis is suspected in a person with diabetes, but is not confirmed by initial X-ray, consider magnetic resonance imaging (MRI) to confirm the diagnosis.

With specific regards to osteomyelitis, Lipsky and colleagues recommend a probe-to-bone test for all open wounds. A positive test is diagnostic of DFO, while a negative test largely rules out this diagnosis (Lipsky et al, 2015). They

Table 1. Infectious Diseases Society of America and International Working Group on the diabetic foot classification of diabetic foot infection (adapted from Lipsky et al, 2012).

Clinical Manifestation of Infection	IDSA Infection Severity
No symptoms or signs of infection	**Uninfected**
Infection present (defined by the presence of 2 or more signs/ symptoms): • Local swelling or induration • Erythema • Local tenderness or pain • Local warmth • Purulent discharge	**Mild** Local infection involving only the skin and subcutaneous tissues. **Moderate** Local infection with erythema >2cm or involving structures deeper than skin and subcutaneous tissues (e.g. abscess, osteomyelitis, septic arthritis, fasciitis), AND no systemic inflammatory response signs (as described below). **Severe** Local infection (as described above) with the signs of SIRS, as manifested by ≥2 of the following: • Temperature >38oC or <36oC • Heart rate >90 beats/ min • Respiratory rate > 20 breaths/ min or PaCO2 <32mmHg • White blood cell count >12,000 or <4,000 cells/μL or ≥10% immature (band) forms.

also state that a probable diagnosis of DFO is reasonable if positive results are obtained on a combination of tests, including the probe-to-bone, X-ray, MRI, serum inflammatory markers or radionuclide scanning.

Choosing an appropriate antibiotic

Once the diagnosis of DFI is established, antibiotic treatment should be initiated as soon as possible. NICE (2016) guidelines state that all primary care settings should have care pathways in place for managing DFIs with specific antibiotic regimens that take into account any local issues of resistance. Antibiotic choice should be based on the likely proven caustative pathogens, the severity of the infection, evidence of efficacy for DFIs while being cognisant of cost (Lipsky et al, 2015). Furthermore, NICE recommends that the choice of antibiotic treatment may be influenced by the care setting, patient preferences, the clinical situation and the patients' medical history.

The IWGDF and NICE make specific recommendations with regards to antimicrobial therapy for DFIs dependent on severity (*Table 2*):

- For mild infections, initially offer oral antibiotics with activity against Gram-positive organisms
- A 1–2-week course of antibiotic therapy is usually sufficient for mild infections
- For moderate and severe infections, administer antibiotics with activity against Gram-positive and Gram-negative organisms, including anaerobic bacteria
- For moderate infections, offer oral or initial parental administration depending on the clinical situation and choice of antibiotic
- For severe infections, administer parental therapy with a switch to oral therapy based on the clinical situation and response to treatment
- For DFO, offer 6 weeks of antibiotic therapy for patients who do not undergo surgical resection of the infected bone, according to local protocols
- For those who have had surgical intervention and all infected bone is resected, offer no more than 1 week of antibiotic therapy (Lipsky et al, 2015; NICE, 2016).

Lipsky et al (2015) do not recommend the prophylactic treatment of clinically uninfected wounds with antimicrobial therapy and they advise against the selection of any specific type of dressing for DFI with the aim of preventing an infection or improving its outcome.

Outpatient or inpatient?

Diabetic foot clinics typically operate through an outpatient system. The management and outcome for a DFI is superior if there is the involvement of a multidisciplinary team which includes podiatrists, nurses, endocrinologists, infectious disease specialists, vascular and orthopaedic surgeons (Lipsky et al, 2012). In 2012, the IDSA published a clinical practice guideline for the diagnosis and treatment of DFIs (Lipsky et al, 2012) and in 2015, the IWGDF produced guidelines and a global evidence-based consensus

Table 2. Suggested route, setting and duration of antibiotic therapy by clinical syndrome (adapted from Lipsky et al, 2012).

Severity or extent of infection	Route of administration	Setting	Duration of therapy
Soft-tisue only			
Mild	Topical or oral	Outpatient	1–2 weeks (may extend up to 4 weeks if slow to resolve).
Moderate	Oral (or initial parenteral)	Outpatient/in patient	1–3 weeks
Severe	Initial parenteral, switch to oral when possible	Inpatient, then outpatient	2–4 weeks
Bone or Joint			
No residual infected tissue e.g. post-amputation	Parenteral or oral	Oral or initial parental administration depending on the clinical situation	2–5 days
Residual infected soft tissue but not bone	Parenteral or oral	Oral or initial parental administration depending on the clinical situation	1–3 weeks
Residual infected (but viable) bone	Initial parenteral, then consider oral switch	Oral or initial parental administration depending on the clinical situation	4–6 weeks
No surgery, or residual dead bone postoperatively.	Initial parenteral, then consider oral switch	Oral or initial parental administration depending on the clinical situation	≥ 3 months

document on the management of foot problems in diabetes (Bakker et al, 2015). Both documents provide the treating clinician with practical guidance on which specific patients require, and would benefit most from, hospitalisation. As acute hospitals are constantly under sustained pressure due to limited bed capacity, the question of continuing outpatient care or admission to hospital is of significant importance.

The presence of a severe infection as defined by IDSA criteria requires emergency admission to hospital for parenteral antibiotics, assessment from a surgical specialist, and rapid access to the multidisciplinary team. Imaging studies and diagnostic tests (e.g. MRI scanning is readily accessible as an inpatient). Patients with moderate DFI with complicating features (eg, severe peripheral arterial disease, or lack of home support) or inability to comply with the required outpatient treatment regimen for psychological or social reasons should be hospitalised initially (Lipsky et al, 2012). Other factors that would result in hospitalisation include haemodynamic and metabolic stabilisation, the need for careful continuous observation, and the use of complex dressings may necessitate inpatient care. If intravenous therapy is required, but not available as an outpatient or if surgical procedures (more than minor are required) are required, then inpatient care is optimal (Bakker et al, 2015).

If a multidisciplinary team (MDT) is not available in the outpatient setting, subjects with moderate grade diabetic foot ulceration may benefit from an inpatient 'shortstay', of approximately 5 days to obtain diagnostic tests, and clinical consultations from the MDT. This approach addresses the complexities of the patient with a DFI and allows a more complete evaluation and establishment of a treatment regimen. This clinical care pathway would allow parenteral antibiotics to be administered initially with a switch to oral agents when the patient is systemically well and culture results are available. Surgical intervention maybe performed and glycaemic control would be optimised with an effective individualised discharge plan instituted.

A significant factor is the social circumstances of a patient. The considerations of distance of travel to outpatient clinics, family and caregiver support, adherence to antibiotic treatment and offloading regimens are important in the successful treatment of an infected diabetic foot ulcer and in the decision to manage patients as an inpatient or outpatient. This highlights the need for, and the importance of, an individualised treatment plan.

How long is long enough?

The optimum duration of antibiotics is of significant clinical importance, as under treatment will lead to persistence of infection with inherent risk of amputation and systemic sepsis, while overtreatment may increase the risk

of multidrug resistant organisms and antibiotic associated infections e.g. *Clostridium difficile*. The duration of antibiotic therapy for a DFI should be based on the severity of the infection, the presence or absence of bone infection, the likely or proven causative agents and the clinical response to therapy (Lipsky et al, 2012; Bakker et al, 2015). 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 (Lipsky et al, 2012).

Guidelines recommend a course of antibiotic therapy of 1–2 weeks for most mild and moderate infections (Lipsky et al, 2012). Parenteral therapy should be administered initially for severe infections and some moderate infections, with a switch to oral therapy when the infection is responding (Bakker et al, 2015). The duration of antibiotics in moderate to severe diabetic foot infection is 1–4 weeks (*Table 2*).

In non-healing diabetic foot ulceration (> 4 weeks), the presence of underlying diabetic foot osteomyelitis (DFO) should be assessed. If DFO is present there exist primarily medical or surgical treatment approaches. Both treatment approaches have demonstrated efficacy in selected patients. Antibiotic treatment alone for DFO will likely succeed with smaller ulcers, with more extensive disease requiring surgery. Resection of infected bone will cure osteomyelitis but increases the risk of altered foot biomechanics and transfer ulceration. Surgical intervention should be considered in cases of osteomyelitis accompanied by: spreading soft tissue infection; destroyed soft tissue envelope; progressive bone destruction on X-ray, or bone protruding through the ulcer (Bakker et al, 2015). The decision to institute either a primary medical or surgical approach, based on randomised clinical trial data is not strong as the diagnosis of osteomyelitis was not based on bone culture and histology in some trials.

The IWGDF guideline recommends 6 weeks of antibiotic therapy for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment if all infected bone is resected. Similar guidance is provided with the IDSA guidelines, which advise 4-6 weeks of antibiotics if there is residual infected, but viable, bone. However, the IDSA guidelines recommend greater than 3 months of antibiotic therapy if there is no surgery or residual dead bone postoperatively (*Table 2*) (Lipsky et al, 2012; Bakker et al, 2015). There is variance in the recommendation between the two guidelines, and the decision to extend antibiotic treatment beyond 6 weeks to 3 months, should be made in consultation with an infectious diseases or clinical microbiological specialist.

The optimal treatment of diabetic foot infection with DFO will be based on clinical severity, likely or proven causative agents and clinical progression. A consultation with an infectious diseases or clinical microbiological specialist and the wider MDT is recommended.

Conclusion

DFIs are a common and serious complication of diabetes. DFIs can spread rapidly to underlying tissues, including bone, and DFO is a frequent outcome. Early diagnosis of DFI and rapid initiation of antimicrobial therapy is vital to minimise the adverse patient outcomes associated with foot infections, including limb-threatening infection and amputation. The IDSA, IWGDF and NICE all offer clear guidance on appropriate antimicrobial therapy dependent on the severity of the infection, clinical situation and efficacy of the agents. ■

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