Diabetic foot infection: an update

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Article points

1. Diabetic foot infections commonly occur in the presence of pedal ulcer, barefoot walking, skin scratching and inadvertent trauma.
2. Timely and appropriate diagnosis can be limb- and life-saving.
3. Assigning depth and/or severity of infection is helpful in guiding medical and surgical management.
4. An appropriate culture specimen after debridement must be obtained from all infected diabetic foot ulcers.
5. Commencing empirical antibiotics should not await culture reports.
6. Regional and national pathogen diaspora from diabetic foot infections is helpful for an early institution of appropriate antibiotic regimen.

Key words

- Antibiotic therapy
- Diabetic foot ulcers
- Infection

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Diabetic foot infection (DFI) is a common reason for hospitalisation of people with diabetes. DFI usually occurs as a consequence of foot ulceration and requires attention to assess the severity of infection and initiating appropriate treatment. Recent guidelines from the International Working Group on the Diabetic Foot recommendations have elaborated upon the management of DFI. However, the knowledge of causative pathogens in the local milieu is necessary to initiate empirical antibiotics pending culture reports. The present review highlights the classification, severity assessment, role of serological and radiological tests and the antibiotic choices for the management of DFI.

Diabetic foot infection (DFI) is a condition triggered by invasion of a microorganism, and the resultant inflammation in any tissue below the malleoli in a person with diabetes. DFI does not limit its purview to diabetic foot ulcers (DFUs) or wounds, as earlier believed, but inflammation of any part of the foot, with or without systemic inflammatory response syndrome (SIRS).

The rising age of people with diabetes has contributed to the global burden of DFI consequent to DFUs (Bhansali and Rastogi, 2016). The annual incidence of DFUs is 2% (Abbott et al, 2002). DFI is a frequent cause of increased morbidity, economic burden and mortality (Boulton et al, 2015; Al-Rubeaan et al, 2017; Kerr et al, 2019). It is the most common cause of hospitalisation and lower-extremity amputation in people with diabetes (Lavery et al, 2006; Ghanassia et al, 2008; Wukich et al, 2015; Tan et al, 2019). In the following sections, we discuss various aspects of DFI, with an emphasis on diagnosis and treatment for primary care physicians.

Risk factors

People with diabetes are predisposed to develop a DFI when they have an ulcer or pre-ulcerative lesion (fissures, blisters and subcutaneous haemorrhage), trauma (trivial or major), foot deformity, previous lower extremity amputation or healed ulcer, chronic kidney disease (CKD), peripheral arterial disease and chronic hyperglycaemia. A study has shown increased risk of infection in neuropathic ulcers, especially in ulcers where healing was delayed beyond 3 months (Jia et al, 2017). Additional risk factors, namely barefoot walking, inadvertent scratching of skin at the lower shin and foot, and dermatophytosis (nail/interdigital), are common forerunners of DFI.

How to recognise DFI?

A timely and appropriate identification of clinical infection in people with diabetes can be limb-sparing. Although most ulcers are colonised with bacteria, not all DFUs develop clinical infection. Thus, such individuals can be spared unnecessary treatment with antibiotics, their side-effects, high costs and possible risk of selection of drug-resistant microorganisms (Lipsky et al, 2012; 2020).

Diagnosis of a DFI is based on a thorough assessment of the ulcer and foot for signs of inflammation, systemic symptoms and supportive biochemical and radiological investigations. The foot should also be examined for loss of protective sensation, pedal pulses, deformities and venous

insufficiency.

Clinical features and investigations indicating the presence of SIRS may not be seen in DFIs, but when present suggest a limb- or life-threatening infection, requiring hospitalisation and surgical intervention (Wukich et al, 2015). Local swelling or induration, erythema around the ulcer, tenderness, warmth and purulent discharge, some of which may be present even in the absence of an ulcer, are signs of active infection. Since these findings can be altered in a neuropathic foot, ulcer with undermined edges, friable granulation tissue and foul odour can be taken as evidence of infection (Boulton et al, 2020). Differentiation of deep infection (abscess and osteomyelitis) from Charcot neuropathic osteoarthropathy can be challenging.

Role of serological tests for DFI

White blood cell (WBC) count, erythrocyte sedimentation rate (ESR), procalcitonin and/or C-reactive protein (CRP) are helpful in diagnosing and monitoring DFI (Uzun et al, 2007; Massara et al, 2017). However, WBC count may be normal in 50% of patients with DFI, and there is little correlation with infection severity. Similarly, ESR and procalcitonin are higher in DFIs compared to non-infected DFUs.

Nevertheless, there can be other causes of high ESR in a given patient, including anaemia and chronic kidney disease, and little correlation exists between the procalcitonin values and infection severity. A high ESR (>70mm/h) has been shown to be more commonly associated with bone infection than superficial soft tissue DFI. In turn, CRP rises earlier in DFI than other serological markers, and also falls quickly at resolution of infection. Overall, procalcitonin and CRP have better diagnostic accuracy than ESR or WBC count for the diagnosis of DFI. These serological tests are widely available and relatively inexpensive, even in resource-constrained settings.

Role of thermography in DFI

Infrared thermography and photographic foot imaging have been used for diagnosing and monitoring DFI. Few studies suggest their usefulness in remote assessment of DFI, but their correlation with clinical assessment and diagnosis of DFI is far from perfect. The recent IWGDF guidelines do not suggest thermographic monitoring for either the diagnosis or follow-up of DFI (Lipsky et al, 2020).

Probe-to-bone test for osteomyelitis

Presence of a positive probe-to-bone (PTB) test is an easy and simple way to assess bone involvement in DFI, as it requires a sterile blunt metal probe, is inexpensive and harmless. It can be easily performed at the bedside. However, the physicians' experience may be a limiting factor for diagnosing osteomyelitis with PTB. Overall, PTB has a sensitivity of 87% and specificity of 83% (Lipsky et al, 2020).

Radiological evaluation for DFI

A radiograph is often considered in combination with clinical examination and serological tests for DFI, especially to establish osteomyelitis. In fact, guidelines do suggest that if a plain X-ray of the foot on clinical and laboratory examination suggests osteomyelitis, no further advanced imaging modalities should be performed. However, magnetic resonance imaging (MRI) should be considered if doubt persists and to ascertain deep infections and osteomyelitis. MRI has an overall sensitivity of 90% and specificity of 80% for diagnosing bone involvement in DFI (Barwell et al, 2017). Newer imaging modalities like FDG PET/CT and leukocyte scintigraphy have also been used for complicated DFI but have a limited role because of availability and costs. Our group has shown the utility of leucocyte-labelled ^{18}F-FDG-PET/CT for diagnosis of osteomyelitis in the presence of Charcot neuropathic osteoarthropathy (Rastogi et al, 2016).

Depth and classification

DFI can be characterised on the basis of depth as superficial (cellulitis, paronychia, ulcer) or deep (ulcer, abscess, myositis, septic arthritis, osteomyelitis, tenosynovitis or necrotising fasciitis) infection. Initial classification is important because depth guides the antimicrobial prescription (oral versus intravenous), duration (1–2 weeks in superficial/mild ulcers), surgical intervention (gas gangrene) and prognosis of DFI (osteomyelitis is an independent predictor of lower extremity amputation) and consideration for hospitalisation (Pickwell et al, 2015). Deep ulcers can usually involve muscle, fascia and tendon. Knowing this

Table 1. Empirical antibiotic therapy for DFI.			
Severity	**Additional factors**	**Pathogen(s)**	**Empirical therapy**
Mild (oral therapy)	Antibiotic naïve	GPC	Cloxacillin
	Previous antibiotic use	GPC	Co-amoxiclav, clindamycin, cefuroxime
	Penicillin allergy	GPC	Clindamycin
	Duration >2 weeks	GNB>GPC	Cefuroxime, levofloxacin, faropenem
	MRSA	GPC	Clindamycin, linezolid
Moderate (oral/ parenteral therapy) to severe (parenteral therapy)	Antibiotic naïve	GPC>GNB	Co-amoxiclav, cefuroxime
	Previous antibiotic use	GNB ± GPC	Piperacillin/tazobactam + clindamycin
	Maceration, greenish pus	*Pseudomonas* or GNB ± anaerobes	Piperacillin/tazobactam + metronidazole, imipenem, meropenem
	Ischaemic foot	GNB ± GPC or anaerobes	Piperacillin/tazobactam + clindamycin, imipenem, meropenem
	Duration >2 weeks	GNB ± anaerobes	Piperacillin/tazobactam + clindamycin or metronidazole
	MRSA	GPC	Vancomycin, teicoplanin, linezolid
	HAI	MDR *Acinetobacter*	Colistin
	Sepsis/SIRS	GNB ± GPC	Piperacillin/tazobactam + vancomycin or teicoplanin

GPC = Gram-positive cocci, GNB = Gram-negative bacilli; HAI = hospital-acquired infection; MDR = multi-drug resistant; SIRS = systemic inflammatory response syndrome.

is important because a severe DFI can be missed when mild superficial signs in a DFU mask the deep-seated and proximally spread infection, owing to the inter-communicating compartments, fascia and tendons in the foot. Hence, a meticulous debridement is necessary not only to remove as much dead and devitalised tissue as possible but for proper culture specimen retrieval, to ensure correct ulcer grading.

The infection burden and the depth of DFUs can be categorised using the University of Texas Wound Classification System (UTWCS), SINBAD or the recently updated International Working Group on the Diabetic Foot (IWGDF) classification system (Lavery et al, 1996; Ince et al, 2008; Lipsky et al, 2020). The IWGDF classification is preferred to report DFI, because it has been validated in various populations; is easy to use, even in community settings, as it requires only a clinical examination and simple blood tests and imaging; helps in decision-making regarding treatment regimen; and is presently the most widely accepted of all classification systems.

Culture specimens and microbiology

As stated previously, local non-spreading cellulitis and clinically uninfected DFUs do not require tissue culture specimen. Appropriate culture specimen is essential for deeper DFI in order to identify the causative pathogen and recognise the antimicrobial sensitivity pattern. Deep soft tissue culture can be less revealing or different to the bone tissue culture in the presence of osteomyelitis (Boulton et al, 2020). Therefore, for osteomyelitis, percutaneous bone biopsy with 10–12 G biopsy needle, open wound biopsy or bone scrapings should be taken (Uzun et al, 2007).

Since clinically infected DFU are often polymicrobial, a thorough debridement is necessary to obtain a proper culture specimen. Debridement is helpful in taking off the slough and biofilm that may shield the pathogenic microorganisms and lead to polymicrobial colonisation. A recent microbiome study of DFUs showed that bystander contaminants like *Corynebacterium* and *Alcaligenes* species delay ulcer healing and worsen the severity, by imparting antibiotic resistance to the actual pathogen by forming a biofilm (Kalan et al, 2019).

Post-debridement, deep tissue culture (base of ulcer or as close as possible to the bone) should be obtained through curettage or biopsy (Malone et al, 2013; Rastogi et al, 2017). Bone biopsy must be analysed histologically to ascertain necrosis and inflammation in the bone. Pus or wound swab cultures are least sensitive and should not be encouraged (Lipsky et al, 2020). Acutely infected foot ulcers (<2 weeks) are usually colonised by Gram-positive bacteria (*Staphylococcus* and Streptococcus species), whereas, chronic DFIs are colonised by Gram-negative (*Enterobacteriaceae* and *Pseudomonas* species) and anaerobic bacteria (*Bacteroides*, *Peptostreptococcus* and *Clostridium* species). Anaerobic bacteria are frequently found in necrotic/ischaemic tissues (Jude and Unsworth, 2004).

Experts have noticed a shift in microbiology of DFI, with Gram-positive organisms common in Europe and America, and Gram-negative organisms common in south-east Asia, Brazil, China and Africa (Boulton et al, 2020). Thus, a list of most likely organisms causing DFI at regional or national centres, as well as antimicrobial sensitivity pattern, would help to expedite treatment, as often the initial treatment is empirical. Clinically infected DFUs in individuals previously treated with antibiotics or in-patient, have predominantly gram-negative and multi-drug resistant organisms causing the DFI (Rastogi et al, 2017).

How to treat DFI?

Antibiotic therapy is guided by the drug efficacy, DFI severity and duration, local pathogen diversity, antibiotic sensitivity pattern, previous antimicrobial use, presence of ischaemia, chronic kidney disease and side-effect profile. For example, an ischaemic ulcer is likely to harbour anaerobes besides Gram-positive/negative bacteria, hence empirical antibiotic cover with metronidazole/carbapenems is necessary (*Table 1*).

Table 2. Primary surgery versus antibiotics in the management of diabetic foot osteomyelitis.

Primarily surgery	Primarily antibiotics
• Severe infection (gangrene, necrotising fasciitis, systemic inflammatory response syndrome) • Abscess or spreading soft-tissue infection • Severe bone necrosis or destruction • Surgically correctable deformities with osteomyelitis • Multi-drug resistant pathogens	• Bone biopsy proven uncomplicated forefoot osteomyelitis • Pre-ulcer bone biopsy proven uncomplicated osteomyelitis • High likelihood of poor-post operative biomechanics of the foot • Patient unfit for surgery

The initial antibiotic regimen may need to be broad-spectrum, until culture results are available that can help to modify and narrow the therapy. Although, Infectious Disease Society of America (IDSA) guidelines have been the cornerstone in the management of DFI, many national and regional groups have formulated antibiotic algorithms based on pathogen diversity, antimicrobial sensitivity and drug availability (Uzun et al, 2007; Lipsky et al, 2012; 2020).

The duration of antibiotic therapy is dependent on the clinical resolution of infection, and not the healing of DFUs. Generally, antibiotic duration of 1–2 weeks is sufficient for acute, mild-moderate infections, >2 weeks for chronic, deep soft tissue infections and >6 weeks for osteomyelitis. Few patients may need long duration intravenous therapy that can be managed in outpatient clinics and centres of convenience or in the domiciliary setting. Topical antibiotics like gentamicin-collagen or pexiganan have certain advantages, including ease of use, requirement of small doses at sites of ulcers, fewer adverse events and less likely to develop antibiotic resistance. However, the efficacy of topical antibiotics for mild to moderate infections has not been demonstrated in various studies.

It is important that the clinician revaluates the patient if the infection has not resolved/improved after 1–2 weeks of appropriate regimen in appropriate doses in superficial, mild infections and at 4 weeks for more severe infections and

osteomyelitis. Initial antibiotic failure is likely to be due to underlying abscess, osteomyelitis, foreign body or a predominantly ischaemic wound.

Surgical intervention for deep soft tissue infections, abscess, osteomyelitis and severe or life-threatening infection (e.g. gas gangrene) is part of the multimodality management of DFI. Surgery with antibiotics versus antibiotics alone for osteomyelitis remains a clinical conundrum, despite trial evidence suggesting safety and efficacy of antibiotic therapy alone for mild to moderate cases of uncomplicated forefoot osteomyelitis (Lázaro-Martínez et al, 2014). An expert commentary has outlined the primary use of surgery or antibiotics in osteomyelitis (*Table 2*; Boulton et al, 2020).

We believe that the decision to treat a DFI must be prompt and based at least on DFI severity and duration. The limitations of suboptimal sampling technique, non-availability of culture results, biofilm and polymicrobial infection must not delay the institution of empirical antibiotic therapy. If there is a clinical response, we suggest continuing the empirical antibiotic, even if the pathogen grown lacks susceptibility. However, it is not recommended to treat uninfected DFU with antibiotics, for the purpose of reducing susceptibility to infection or to promote ulcer healing.

Conclusion

DFI is consequent to a multitude of avoidable and unavoidable risk factors that contribute to significant morbidity and mortality in people with diabetes. Even though most DFIs occur in individuals with DFUs, not all DFUs are infected. A thorough assessment of the foot for symptoms and signs of infection, appropriate severity classification, knowledge of local pathogen diaspora and proper culture specimen retrieval (especially bone in suspected osteomyelitis), a multimodality management with empirical and culture specific antibiotics, and surgical intervention is helpful in reducing the risk of limb amputation. ■

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