Guidelines for the Medical management of Diabetic Foot Infection

Introduction and summary points

- Foot infections in diabetic patients usually begin with skin ulceration
- However, skin wounds with no associated signs of infection do not require antibiotic treatment
- While most infections are superficial, approximately 25% spread contiguous to involve deeper subcutaneous tissues which may include bone
- The choice, route of administration, and duration of antibiotic treatment, depend upon an assessment of severity and of the most likely aetiological agents. Acute infections in previously untreated patients are often monomicrobial and caused by Staphylococci or Streptococci. Chronic wounds develop complex flora.
- Determining the microbial aetiology of a wound infection will assist subsequent management. Deep tissue samples obtained aseptically at surgery are the most likely to yield the true pathogens; tissue from the base of a debrided ulcer is preferable to a wound swab.
- Antibiotic therapy is very likely to be ineffective without adequate attention to wound care (e.g. debridement, dressing changes, pressure off-loading), glycaemic control, and accompanying peripheral vascular disease.

Diagnosis, Clinical Presentation and Severity Assessment

- Infection must be diagnosed clinically, not on the basis of positive microbiological culture results.
- Both local and systemic signs of infection may be masked, and the severity of diabetic foot infection may therefore be underestimated
- Local signs of infection include purulence or ≥2 signs of inflammation (warmth, redness, pain, induration). Delayed healing, abnormal colouration, friability or foul odour may be additional signs of infection in the context of chronic ulcers. However, local signs of infection may be absent, or difficult to distinguish from underlying rubor in patients with limb ischaemia.
- Many patients do not report pain.
- Systemic signs (e.g. fever, chills, leucocytosis) should also be sought but are frequently absent.
- Inflammatory markers (WCC, CRP) are not a reliable guide to severity, and should not replace clinical judgment

Severity Assessment (table 1):

- Assessing the severity of infection is essential to selecting an appropriate antibiotic regime, for guiding the need for hospitalisation, and for determining the potential necessity and timing of surgery
- The wound should be carefully explored to look for foreign or necrotic material, and probed with a sterile metal instrument.
- Examination should include overall assessment of the patient’s status (for example whether there is evidence of systemic response to infection), and of the limb, rather than just of the wound alone.

### Table 1: Clinical features of foot ulcers that help to define severity

<table>
<thead>
<tr>
<th>Clinical features that help to define severity</th>
<th>Mild infection</th>
<th>Severe infection</th>
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<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>slowly progressive</td>
<td>Acute or rapidly progressive</td>
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<tr>
<td><strong>Ulceration</strong></td>
<td>involves only skin</td>
<td>penetrates to subcutaneous tissues</td>
</tr>
<tr>
<td><strong>Tissues involved</strong></td>
<td>epidermis, dermis</td>
<td>fascia, muscle, joint, bone</td>
</tr>
<tr>
<td><strong>Cellulitis</strong></td>
<td>minimal (&lt;2cm around wound)</td>
<td>extensive, or distant from site of ulcer</td>
</tr>
<tr>
<td><strong>Local signs</strong></td>
<td>limited inflammation</td>
<td>severe inflammation, crepitus, bullae, necrosis, gangrene</td>
</tr>
<tr>
<td><strong>Systemic signs</strong></td>
<td>none / minimal</td>
<td>fever, chills, hypotension, confusion, volume depletion, leukocytosis</td>
</tr>
<tr>
<td><strong>Metabolic control</strong></td>
<td>mildly abnormal (e.g. hyperglycaemia)</td>
<td>severe hyperglycaemia, acidosis, electrolyte abnormalities, hyperosmolar states</td>
</tr>
<tr>
<td><strong>Foot vasculature</strong></td>
<td>minimally impaired</td>
<td>absent pulses, reduced ABPI</td>
</tr>
<tr>
<td><strong>Complicating features</strong></td>
<td>none / minimal</td>
<td>eschar, foreign body, puncture wound, abscess, marked oedema, implanted metalwork or other prosthesis</td>
</tr>
</tbody>
</table>

*Note that peripheral arterial disease may mask both local and systemic signs of infection, resulting in the severity of infection being underestimated*

### Out-patient treatment versus hospitalisation:

- Patients with serious infection should be admitted to hospital for possible surgical intervention, fluid resuscitation, and control of metabolic derangement.
- Hospitalisation should also be considered if the patient is unable or unlikely to comply with wound care, offloading or antibiotic treatment, or if parenteral treatment or close monitoring are required.
- Most other patients can be managed outside hospital, with frequent re-evaluation.

### Urgent surgical intervention:

- Urgent surgical referral should be made if there is life- or limb-threatening infection (e.g. abscess, progressive or extensive gangrene, necrotising fasciitis, critical ischaemia, or systemic toxicity).
Assessment for osteomyelitis:

- Underlying osteomyelitis and deep space infections may occur in the presence of few superficial signs. Approximately 50-60% of serious foot infections, and 10-20% of mild/moderate infections, are complicated by osteomyelitis.
- Consider possible osteomyelitis as a complication of any deep or extensive ulcer, particularly if chronic and overlying a bony prominence, or if the ulcer fails to heal despite apparently appropriate measures. Swelling of the foot or a toe (including “sausage-toe” appearance) associated with a history of ulceration, with or without elevation of inflammatory markers, should also arouse suspicion of osteomyelitis. Note that finding that inflammatory markers are within the normal range does not exclude osteomyelitis.
- Ulcers should be explored and probed by an appropriately trained person such as a podiatrist. If bone is visible or can be palpated with a blunt probe then osteomyelitis is likely (positive predictive value almost 90%).
- Plain radiographs should be obtained for most patients with diabetic foot infections. Radiographic changes generally take at least 2 weeks to become evident.
- When there is a high suspicion of osteomyelitis and plain radiographs are normal, MRI is the radiological investigation of choice for detecting and accurately delineating bone involvement. MRI is not always necessary however, particularly in cases of early osteomyelitis which are managed conservatively.
- When the presence of osteomyelitis is in doubt and the patient is stable, repeating plain radiographs after 2 weeks may be a reasonable alternative to MRI.
- Definitive diagnosis of osteomyelitis, and identification of the infecting agent(s), may in some cases require open or percutaneous bone biopsy.

Microbiological investigation:

- Determining the microbial aetiology of an infected wound greatly assists subsequent antibiotic treatment, and may help to reduce the use of unnecessarily broad-spectrum agents. Culture of deep tissues is the gold standard, and superficial wound swabs should only be sent when this is impossible.
- Appropriate microbiological samples should be obtained before antibiotic treatment is commenced.
- Patients who are systemically unwell due to severe infection should have blood cultures taken before antibiotic treatment. However the initiation of antibiotic treatment should not be delayed in septic patients pending sampling from the infected ulcer.
- Deep tissue samples obtained aseptically at surgery, are most likely to identify the true pathogens. Bone sequestra should also be sent for microbiological investigation.
- Alternatively, a soft tissue sample from the base of the debrided wound should be sent when surgery is not intended, and bone biopsy should be considered if osteomyelitis is suspected, provided this does not result in a delay in initiating antibiotic therapy.
- Superficial wound swabs should be sent if deep samples cannot be obtained. However it must be recognised that these may fail to identify the infecting pathogen, while conversely yielding colonising organisms, resulting in ineffective or inappropriately broad-spectrum antibiotic treatment. The interpretation of bacterial culture results depends on the clinical context.
- Empirical antibiotic treatment may be initiated pending culture and sensitivity results becoming available, and should be adjusted accordingly

**Antibiotic treatment (Tables 2 and 3):**

- Patients with clinically uninfected ulcers should not be treated with antibiotics
- The most likely infecting organism(s) depends on factors such as chronicity, prior antibiotic exposure, and the presence or absence of ulceration, local ischaemia or necrosis. Chronically infected ulcers are more likely to be polymicrobial. Deep or ischaemic ulcers are more likely to be infected by anaerobes.
- In mild and previously untreated cases, empirical treatment may be appropriate without sampling
- Initial choice of antibiotic regimen (table 2) should take into account a severity assessment and any available microbiological data such as past culture results. Narrow-spectrum agents may be appropriate for empirical treatment of mild infections, but severe infection warrants broad-spectrum treatment.
- An empirical antibiotic regimen should always include an agent active against Staphylococci and Streptococci.
- Patients with necrotic, gangrenous or foul-smelling lesions should also receive anti-anaerobic therapy.
- Intravenous antibiotics are indicated for patients who are systemically unwell, have a severe infection, are unable to tolerate oral agents, or who are known or suspected to carry pathogens that are resistant to oral agents.
- Antibiotics should be adjusted according to clinical progress, and culture and sensitivity results when these become available.
- Consider the need for surgical intervention if the infection is worsening despite appropriate antibiotic therapy.
- Treatment should be continued until there is evidence that the infection has resolved, but not necessarily until the wound has healed. Treatment durations in Table 2 are given as a guide only, and will depend on individual factors such as adequacy of surgical debridement, if applicable, and clinical response to treatment.
- Bacteraemia, particularly due to S. aureus, often necessitates more prolonged therapy.
- Early IV-to-PO switch will often be appropriate.
- Consider home intravenous antibiotic therapy for patients requiring prolonged IV treatment.
<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Severity (IDSA grade)</th>
<th>Suggested empirical antibiotics (adapt if necessary based on microbiology results / recent antibiotic treatment)</th>
<th>Suggested duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No purulence or manifestations of inflammation</td>
<td>Uninfected</td>
<td>No antibiotic treatment</td>
<td>-</td>
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</tbody>
</table>
| Presence of ≥2 of purulence/erythema/pain/tenderness/warmth/induration, but cellulitis extends ≤2cm, only skin/superficial soft tissues involved, no local complications, not systemically unwell | mild | Antibiotic naïve and infection of recent (<3 weeks) onset:  
Flucloxacillin 1g QDS (consider adding metronidazole if anaerobic infection suspected),  
or  
Clindamycin 450mg QDS PO (If Penicillin allergic)  
If MRSA-positive: Doxycycline 100mg BD (consider adding metronidazole if anaerobic infection suspected) | 1-2 weeks |
| Infection as above and systemically well but cellulitis extends >2cm, lymphangitis, spread beyond superficial fascia, gangrene, involvement of muscle/tendon/joint/bone | Moderate [may be limb-threatening] | Antibiotic naïve and recent (<3 weeks) onset: (consider adding metronidazole if anaerobic infection suspected),  
Flucloxacillin 1g QDS, or  
If Penicillin-allergic: Clindamycin 450/600mg QDS PO/IV  
Not antibiotic naïve, or chronically infected:  
Co-amoxyclov (1.2g TDS IV or 625mg TDS PO), or  
Clindamycin 450/600mg QDS PO/IV plus  
Ciprofloxacin 750/400mg PO/IV BD  
For more extensive infection, and infections in MRSA-carriers:  
treat as severe | 2-4 weeks (see also “diabetic foot osteomyelitis”) |
| Systemic toxicity or metabolic instability | Severe [may be life-threatening] | IV Piperacillin/tazobactam (Tazocin) 4.5g TDS (Add Teicoplanin if known colonisation with MRSA, and consider a single dose of Gentamicin 5mg/kg if there is evidence of systemic upset due to sepsis), or  
If Penicillin-allergic: IV Teicoplanin (or Vancomycin) plus Ciprofloxacin 400/750mg IV/PO BD, plus IV/PO Metronidazole. Consider single dose of Gentamicin 5mg/kg in addition, if systemic upset due to sepsis | 2-4 weeks |

Table 2 – Empirical antibiotic choices for the treatment of Diabetic foot infection without osteomyelitis

Notes: Clindamycin and Ciprofloxacin have excellent oral bioavailability and should be given by the oral route if possible.  
Oral step down for moderate to severe infections should be discussed with Microbiology and based on culture/susceptibility results where possible.
Antibiotic treatment of Diabetic Foot Infection associated with osteomyelitis:

- Deep tissue sampling (whether biopsy or intra-operative), before the initiation of antibiotic therapy, may be helpful in guiding later antibiotic choice, but must not result in an unreasonable delay in initiating treatment.
- Percutaneous bone biopsy should be considered, particularly:
  - if the diagnosis remains in doubt after imaging
  - when there has been a failure to respond to prior courses of antibiotic therapy
- It may be reasonable to consider empirical antibiotic treatment without first obtaining deep tissue samples, if any of the following apply:
  - very mild/early onset infection, previously untreated, and with no systemic upset
  - osteomyelitis associated with a rapidly spreading cellulitis
  - systemically unwell patient with evidence of sepsis
- Empirical antibiotic treatment may be commenced after sampling, before culture and sensitivity results become available, and later adjusted accordingly.
- Medical therapy, without surgery, is usual practice unless there is a clear indication for surgery (e.g. unviable toes, critical ischaemia, abscess requiring drainage etc – see “urgent surgical intervention”, above).
- Initial antibiotic treatment will usually be given by the intravenous route to hospitalised patients with osteomyelitis. - Urgent surgical intervention may be required, however this is often because of infection of the surrounding soft tissues rather than bone. Whether there is an indication for early surgical intervention should by discussed by a multidisciplinary team.
- Treatment should be rationalised once culture results are available.

Duration of treatment for osteomyelitis:

- Where surgical debridement has been performed, it is advisable for the duration of treatment to be agreed with the surgeon concerned.
- For incomplete or uncertain excision a minimum of six weeks’ treatment is recommended; more prolonged courses (e.g. 3-6 months) are often needed.
- A shorter treatment duration (e.g. 2 weeks) may be adequate if the infected bone has been completely excised.
- There is a lack of evidence regarding the efficacy of oral as opposed to intravenous antibiotic therapy for osteomyelitis. An early switch to oral antibiotics may be considered in patients who are systemically well, particularly when pathogens are identified which are susceptible to agents with good oral bioavailability. Patients at the Royal Liverpool University and Broadgreen Hospitals may be eligible for recruitment to the OVIVA study of oral versus intravenous antibiotic therapy.
1. *Onset in the community* and no prior antibiotic treatment and no systemic upset due to sepsis:

- **Flucloxacillin 2g QDS (IV)**

  - If **penicillin allergic**: Clindamycin 450mg TDS (PO) or 600mg QDS (IV)

2. *Onset in hospital* or failure of prior antibiotic therapy or known or suspected colonization with antibiotic-resistant organisms

- IV Piperacillin/tazobactam (Tazocin) 4.5g TDS. (Add Teicoplanin/vancomycin if known colonisation with MRSA)

- Clindamycin 450mg TDS (PO) or 600mg QDS (IV) plus Ciprofloxacin 400/750mg IV/PO BD

3. *Acutely unwell patients with systemic upset due to sepsis*  
   (Send blood cultures and do not delay initiation of antibiotic treatment pending tissue sampling)

- IV Piperacillin/tazobactam (Tazocin) 4.5g TDS plus a single dose of Gentamicin 5mg/kg  
  (Add Teicoplanin/Vancomycin if known colonisation with MRSA)

- If **Penicillin-allergic**: IV Teicoplanin/Vancomycin plus Ciprofloxacin 400/750mg IV/PO BD, plus IV or PO Metronidazole. Consider single dose of Gentamicin 5mg/kg IV in addition, in severely unwell patients

| Table 3: Empirical antibiotic choices for patients with osteomyelitis associated with diabetic foot infection |

**Note**: The subsequent choice of antibiotics, after initiation of empirical therapy, should be discussed with a Microbiologist in all cases
References and Acknowledgements:


Lipsky, BA. Medical Treatment of diabetic foot infections (2004). Clinical Infectious Diseases, 39:S104-14


www.nice.org.uk/guidance/CG119


In compiling this document, use was made of antibiotic guidelines already in place at University Hospital Aintree (authors S. Benbow, R. Cooke, E. Hughes), Countess of Chester Hospital (authors D. Ewins, K. Patel, N. Goenka, F. Joseph, R. Worth and A. Cater), and the Royal Liverpool and Broadgreen University Hospitals (authors M. Taegtmeyer, J. Folb).

Recommendations for empirical antibiotic treatment are based on expert opinion (see references) and existing local guidelines. There is no evidence to suggest superior efficacy for any regimen in particular, and it is anticipated that specific antibiotic recommendations will be adapted to reflect resistance rates and local preference at individual hospitals.

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