Diabetic Foot Infections and Empirical Antimicrobial Guidelines

Introduction:

Diabetes is the most common cause of nontraumatic limb amputation, with foot ulcers preceding more than 80% of cases.

Clinicians should consider the possibility of infection occurring in any foot wound in a patient with diabetes. It is important therefore that patients have their feet examined carefully at each hospital or outpatient encounter.

The term “diabetic foot infection” is an inclusive term for:

- An infected diabetic foot ulcer
- Cellulitis
- Abscesses
- Necrotising fasciitis
- Osteomyelitis

Infection must be diagnosed clinically based on the presence of:

- At least 2 classic signs or symptoms of inflammation, ie induration, erythema, warmth, tenderness, pain

OR

- Purulent secretions.

Severity of infection can be classed as mild, moderate or severe based on the:

- Extent and depth of wound
- Presence of any systemic findings of infection.

Remember that not all ulcers are infected.

Collection of Specimens:

Properly obtained wound cultures guide antibiotic therapy, especially in patients with chronic infections or in those who have been already treated with antibiotics.

Optimal samples include purulent secretions (pus), deep tissue specimens and bone curettage/biopsy specimens.
Samples should be placed in separate sterile containers so that they can be sent to both Microbiology and Histology.

- Wounds should be cleansed and debrided before sampling.
- Appropriate specimens should be sent from clinically infected wounds.
- Do not culture a clinically uninfected wound as they rarely warrant antibiotic treatment.
- Do not send superficial wound swabs as they are often contaminated with colonising flora. They do not yield deep tissue pathogens and are less likely to grow anaerobic or difficult to grow pathogens.

**Microbiology of Diabetic Foot Wounds:**

Chronic wounds are often polymicrobial due to complex colonising flora and likely previous exposure to prolonged / broad spectrum antibiotic therapy.

Cultures from such wounds generally yield 3-5 different bacterial types. The pathogenic role of each is often unclear.

**Commonly isolated bacteria:**

- *S. aureus*
- Enterobacteriaceae (*E.coli, Klebsiella pneumoniae, Proteus species*)
- β haemolytic Streptococci Groups A,B,C,G
- *Staphylococcus epidermidis*
- Low virulence colonisers such as Coagulase negative staphylococci (CoNS) and *Corynebacterium* species (“diphtheroids”) may assume a pathogenic role around necrotic soft tissue or bone.
- Multiresistant bacteria (eg MRSA, ESBL, VRE, CPE) are increasing in prevalence due to prolonged and broad spectrum antibiotic therapy.
- Anaerobes play an important role where there is extensive necrosis and gangrene (foetid foot).

**Imaging Studies in Diabetic Foot Infections :**

**Plain Xray:**

Patients should have a plain Xray to look for bony abnormalities (deformity, destruction) as well as for soft tissue gas.

Radiographic changes in infected bone generally take at least 2 weeks to be evident.

When the presence of bone infection is in doubt and the patient is stable, repeating a plain radiograph in a couple of weeks is recommended.
MRI:
When X-ray findings are equivocal for osteomyelitis an MRI is recommended because it provides the greatest accuracy for the detection of bone infection and optimal definition of soft tissue infection including sinus tracts, deep tissue necrosis and abscesses.

Management of Diabetic Foot Infections:

Route of therapy:
The key to successful antibiotic therapy is achieving adequate serum levels and a therapeutic drug concentration at the site of infection.

Intravenous antibiotics are indicated for patients who:
■ Are systemically ill
■ Have a severe infection and are unable to tolerate oral agents
■ Have known or suspected pathogens that are not susceptible to available oral agents.

Most patients can subsequently have their treatment switched to oral therapy with high bioavailability agents.

Please note that when peripheral vascular disease is present, therapeutic antibiotic concentrations are often not achieved in the infected tissues, even when serum levels are adequate.

Empirical Choice of Antibiotic:
■ Usually selected based on the severity of infection with the aim of covering the most common pathogens.

We do not recommend antibiotic therapy for clinically uninfected wounds as a means of enhancing wound healing or as prophylaxis against infection.

■ Consider factors such as patient allergies, renal dysfunction, recent antibiotic therapy, and known local antibiotic susceptibility patterns.

■ Always include an agent active against staphylococci and streptococci.

■ Previously treated or severe cases may need extended coverage that also include commonly isolated Gram-negative bacilli.

■ Empiric therapy directed at *Pseudomonas aeruginosa* is usually unnecessary except when there are risk factors for true infection such as a high local prevalence of *Pseudomonas* infection or a macerated foot resulting from frequent exposure to water. **Although reported in many patients, it is often a non-pathogenic coloniser of wounds.**

■ Empiric therapy against MRSA should be considered in a patient with a history of MRSA infection or colonisation within the past year or when there is an increased local prevalence of MRSA.

■ Necrotic, gangrenous, or foul-smelling wounds usually require anti-aerobic therapy.

**No single drug or combination of agents is superior to others**
Definitive Choice of Antibiotic:

- Should be based on culture and sensitivity results as well as the patient’s clinical response to the empiric regimen.

- It is not always necessary to cover all the microorganisms isolated from cultures.

- More virulent species (e.g. S. aureus and group A or B strep) should always be covered.

- In a polymicrobial infection, less virulent bacteria (e.g., coagulase-negative staphylococci, enterococci) are less important.

Duration of therapy:
Generally, therapy should continue until all local and systemic signs and symptoms of infection have resolved:

- Mild infections: 1-2 weeks.

- Moderate or severe infections: 2-4 weeks.

**Antibiotic therapy can generally be discontinued when all signs and symptoms of infection have resolved, even if the wound has not completely healed**

### Empirical Antibiotic Therapy for Management of Diabetic Foot Infections

<table>
<thead>
<tr>
<th>Severity of Skin and Soft Tissue Infection</th>
<th>Likely Organisms</th>
<th>First Line Antibiotic</th>
<th>Penicillin Allergy</th>
<th>Approximate Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uninfected</strong></td>
<td>Colonising skin flora</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td>No wound inflammation or purulence</td>
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**Mild :**

- No systemic illness

  **And**

  ≥ 2 signs of inflammation\(^1\)

  OR

  Purulent discharge

  **And**

  Cellulitis / erythema ≤ 2cm around the wound, limited to skin or superficial subcutaneous tissue

  **Monomicrobial**

  - *Staph aureus*

  **Or**

  β haemolytic *Strept Grps A, B, C, F, G*

  **If MRSA suspected:**

  Oral Doxycycline 100mg bd

  **Oral Flucloxacillin 1g QDS**

**Oral Doxycycline 100mg bd**

7-14 days

\(^1\) Signs of inflammation = induration, erythema, warmth, tenderness, pain.

**CONSIDER REFERRAL TO DIABETIC / ENDOCRINOLOGY OR VASCULAR TEAMS FOR REVIEW AS APPROPRIATE.**
### Empirical Antibiotic Therapy for Management of Diabetic Foot Infections ctd

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<tr>
<td>Moderate:</td>
<td>If no previous antibiotic treatment: Most likely monomicrobial with <em>Staph aureus</em> or <em>β haemolytic Strep G</em>rp A, B, C, F, G</td>
<td>OUTPATIENT SETTING Oral Rx: PO Coamoxiclav 625mg tds</td>
<td>OUTPATIENT SETTING Oral Rx: PO Clindamycin ² 300 - 450mg qds PLUS PO Ciprofloxacin ³ 500mg bd</td>
<td>14-28 days</td>
</tr>
<tr>
<td></td>
<td>If previous antibiotic therapy: Likely polymicrobial with Gram negative organisms in addition to <em>Staph</em> and <em>Strep</em> as above.</td>
<td>OUTPATIENT SETTING Oral Rx: PO Coamoxiclav 625mg tds</td>
<td>OUTPATIENT SETTING Oral Rx: PO Clindamycin ² 300 - 450mg qds PLUS PO Ciprofloxacin ³ 500mg bd</td>
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<tr>
<td></td>
<td>If MRSA Positive: Add PO Doxycycline 100mg bd</td>
<td>INPATIENT SETTING Intravenous Rx: IV Coamoxiclav 1.2g tds</td>
<td>INPATIENT SETTING Intravenous Rx: IV Teicoplanin (dosing as per Trust Antibiotic Guidelines) PLUS IV Ciprofloxacin 400mg bd or PO Ciprofloxacin ³ 500 mg bd PLUS IV Metronidazole 400mg tds or PO Metronidazole 500mg tds</td>
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² If diarrhoea develops, stop Clindamycin as it is associated with ↑ risk of *C.difficile* infection.

³ If diarrhoea develops stop Ciprofloxacin as it is associated with ↑ risk of *C.difficile* infection. A patient stool sample should be sent for culture as soon as practical. If sample is *C.difficile* toxin negative and diarrhoea continues, can send a repeat sample if diarrhoea does not resolve. If *C. difficile* positive, treat as for *C.difficile*. Contact ASPh microbiology for advice at any time.

**CONSIDER REFERRAL TO DIABETIC / ENDOCRINOLOGY OR VASCULAR TEAMS FOR REVIEW.**

Ratified by NW Surrey CCG Medicines Optimisation Group, Feb 2106

Review Feb 2019
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<th>Severity of Skin and Soft Tissue Infection</th>
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<th>First Line Antibiotic Therapy</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Severe:</td>
<td>Staph, Strep, Gram neg rods Anaerobes</td>
<td>IV Piperacillin/Tazobactam (Tazocin) 4.5g tds (reduce to 4.5g bd only if eGFR &lt;10mls/min)</td>
<td>IV Teicoplanin (dosing as per Trust Antibiotic Guidelines) PLUS IV Ciprofloxacin³ 400mg bd PLUS IV Metronidazole 500mg tds</td>
<td>14 – 28 days</td>
</tr>
<tr>
<td>Moderate infection findings as above</td>
<td></td>
<td></td>
<td></td>
<td>PO switch when</td>
</tr>
<tr>
<td><strong>PLANS</strong></td>
<td></td>
<td></td>
<td></td>
<td>■ clinically appropriate</td>
</tr>
<tr>
<td>⁴Signs of systemic toxicity, ⁵metabolic instability</td>
<td></td>
<td></td>
<td></td>
<td><strong>PLUS</strong></td>
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<tr>
<td>Or</td>
<td></td>
<td></td>
<td></td>
<td>■ as guided by culture &amp; sensitivity results</td>
</tr>
<tr>
<td>Presence of critical foot ischaemia with infection</td>
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³ If diarrhoea develops stop Ciprofloxacin as it is associated with ↑ risk of C.difficile infection. A stool sample should be sent for culture as soon as practical. If sample is C.difficile toxin negative and diarrhoea continues, can send a repeat sample if diarrhoea does not resolve. If C. difficile positive, treat as for C. difficile. Contact ASPH microbiology for advice at any time.

⁴ Systemic toxicity: fever, chills, tachycardia, hypotension, confusion, leukocytosis

⁵ Metabolic instability: acidosis, severe hyperglycemia, uraemia

**CONSIDER REFERRAL TO DIABETIC / ENDOCRINOLOGY OR VASCULAR TEAMS FOR REVIEW.**
Diabetic Foot Osteomyelitis (DFO):

Osteomyelitis is a frequent complication of a pre-existing infected diabetic foot ulcer as a result of contiguous spread of a deep soft tissue infection through the bone cortex (osteitis) to the marrow (myelitis). Its presence increases the likelihood of surgical interventions including amputation.

Diabetic patients can have destructive bone changes caused by peripheral neuropathy. Charcot foot (noninfectious neuro-osteoarthropathy) can be difficult to distinguish from a diabetic foot osteomyelitis and they can coexist.

Risk factors:

- Long standing foot ulcers (>4 weeks) which are not healing after at least 6 weeks of care.
- Large (>2 cm) and deep (>3 mm) ulcers.
- Visible bone or a positive “probe to bone test”

Definitive diagnosis and identification of the aetiologic agent(s):

A two week antibiotic free period before a biopsy is recommended, if patient is stable, in order to avoid false negative cultures.

- Bone biopsy remains the gold standard method for the definitive diagnosis of osteomyelitis.
- At least 2-3 samples should be obtained and sent separately for microbiological culture and histological analysis.
- Patients who are receiving antibiotic therapy may have a negative culture result, but histopathologic findings (inflammatory cells and osteonecrosis) can help diagnose infection.

Treatment of Diabetic Foot Osteomyelitis:

- Antibiotic choices should optimally be based on results of the bone culture, especially in view of the need for a prolonged duration of therapy.
- Antibiotics may not penetrate well into infected bone. Therefore pending culture results, treatment is often started parenterally. Oral antibiotics with good bioavailability may be an option for most, if not all, of the therapy.
- Empirical therapy should always cover S. aureus with coverage broadened as necessary.

Duration of antibiotic therapy:
Generally at least 6 weeks, but see table below.

OPAT (Outpatient Antimicrobial Therapy): Once patient is deemed fit for discharge by the Diabetic / Endocrinology team, but still thought to require IV antibiotic therapy, please contact Microbiology Consultant to discuss suitability for home IV antibiotic(s) through Hospital at Home (formerly known as Medihome).
**Empirical Antibiotic Therapy for Management of Diabetic Foot Osteomyelitis:**

<table>
<thead>
<tr>
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<th>Approximate Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Osteomyelitis</strong></td>
<td>Predominantly <em>Staph aureus</em></td>
<td>IV Flucloxacillin 2g qds</td>
<td>IV Teicoplanin (dosing as per Trust Antibiotic Guidelines)</td>
<td>6 weeks (At least 2wks IV)</td>
</tr>
<tr>
<td>Remember to obtain blood culture before starting antibiotic(s).</td>
<td>If High Risk for MRSA: IV Teicoplanin (dosing as per Trust Antibiotic Guidelines)</td>
<td>PLUS PO Rifampicin⁶ 300-450mg bd (if Staph and sensitive)</td>
<td>PLUS</td>
<td>POSSIBLE ORAL SWITCH, PER CULTURE RESULTS: PO Ciprofloxacin³ 750mg bd</td>
</tr>
<tr>
<td><strong>Chronic Osteomyelitis</strong></td>
<td>Polymicrobial</td>
<td>EMPIRIC THERAPY NOT INDICATED: <strong>Debride ulcer and send tissue/bone for histology and culture</strong></td>
<td>EMPIRIC THERAPY NOT INDICATED: <strong>If patient acutely unwell:</strong> Treat as severe diabetic foot infection (see above)</td>
<td>Generally at least 6-12 wks with initial 2 weeks IV</td>
</tr>
<tr>
<td><strong>Debride ulcer and send tissue/bone for histology and culture</strong></td>
<td><strong>If patient acutely unwell:</strong> Treat as severe diabetic foot infection (see above)</td>
<td>BE GUIDED BY CULTURE RESULTS</td>
<td>See below for duration recommendations based on extent of debridement / amputation.</td>
<td></td>
</tr>
</tbody>
</table>

- No residual infected tissue (eg post amputation) Be guided by culture results 2-5 days
- Residual infected soft tissue but not bone Be guided by culture results 2-4 weeks (IV +PO)
- Residual infected but viable bone Be guided by culture results 4-6 weeks (IV +PO)
- No surgery or Residual dead bone postop Be guided by culture results > 3months (IV +PO)

³ If diarrhoea develops stop Ciprofloxacin as it is associated with ↑ risk of C.difficile infection. A stool sample should be sent for culture as soon as practical. If sample is C.difficile toxin negative and diarrhoea continues, can send a repeat sample if diarrhoea does not resolve. If C. difficile positive, treat as for C.difficile. Contact ASPH microbiology for advice at any time.

⁶ With Rifampicin, monitor baseline and weekly LFTs. Also check for any drug interactions.

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References:

1) NICE Guideline: Diabetic foot problems: prevention and management 26 August 2015

